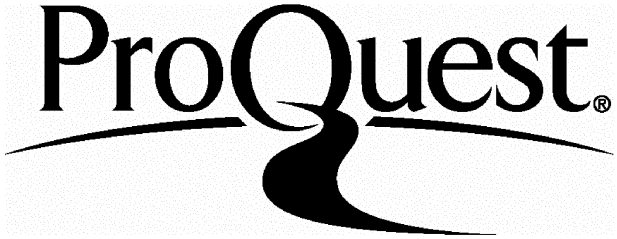
Synthesis of Conformationally Restricted Melatonin Analogues

by

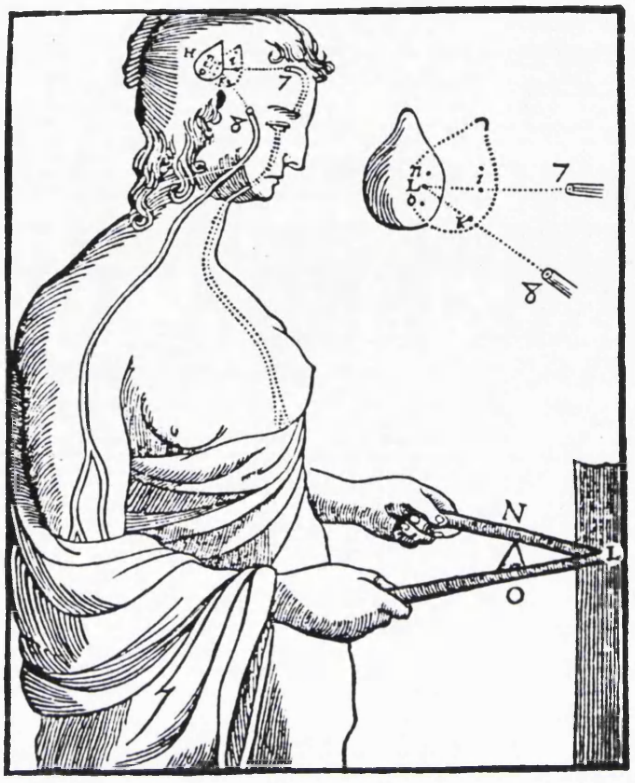
Stefan Vonhoff

A Thesis presented to the University of London in partial fulfilment of the requirements for the Doctor of Philosophy

Department of Chemistry
University College London
October 1994



Dedicated with love to
my parents,
Bettina and Christian



Descartes, L'Homme, 1647

La partie du corps en laquelle l'âme exerce immédiatement ses fonctions... est seulement la plus intérieure de ses parties, qui est une certaine glande fort petite, siuée dans le milieu de sa substance...

The part of the body in which the soul directly exercises its function...is rather the innermost part of the brain, which is a certain very small gland [the pineal gland] situated in the middle of the brain's substance...

R. Descartes, Les passions de l'âme

Das schönste Glück des denkenden Menschen ist, das Erforschliche erforscht zu haben und das Unerforschliche ruhig zu verehren.

The greatest fortune of thinking mankind is, to have investigated the researchable, whilst gracefully respecting the unresearchable.

Johann Wolfgang von Goethe,
Maximen und Reflexionen Nr. 718

Acknowledgements

I wish to thank my "Doktorvater" Prof Peter Garratt for suggesting this research project, for his enthusiasm, encouragment and friendship throughout my time at UCL. Thanks to all the technical staff for their excellent support, help and advice, especially Jill Maxwell, David Knapp, Steve Corker and Alan Stones. I am grateful to Dr David Sugden, King's College London, for performing the biological assays and Dr John Davies, Sandoz Institute of Medical Research, London, for carrying out molecular modelling studies. Thanks also to Dr Derek Tocher, UCL, for the crystal structure analyses. Special thanks to Chris Cooksey for introducing me to new nmr-techniques on sunday mornings and to Peter Leighton for his help in switching off the overnight experiments. I am indebted to UCL for the award of a Provost's Studentship and the financial support to visit the Conference of the European Pineal Society in Copenhagen.

To all my friends in the Chemistry Department especially the Garratt group - Peter, Rob, Ashley, Najeeb and Sundrum - thanks for all the good times.

Finally, I wish to thank my family and friends for their encouragement and support over the last three years.

Abstract

The pineal hormone melatonin plays a major role in the regulation of seasonal cycles and the control of circadian rhythms in mammals, reptiles and birds. The emerging potential of melatonin in the therapy of human rhythm disorders (i.e. SAD and shift-work syndrome) and its application in agriculture (control of reproductive cycles in farm-animals such as sheep and horses) has caused a dramatic upsurge of interest in synthesising melatonin agonists and antagonists.

As part of a programme to examine the three-dimensional structure of the melatonin receptor the synthesis and biological activity of several structural melatonin analogues with conformationally restricted N-acyl-3-ethanamine side-chain was investigated. The tricyclic analogue N-butanoyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetra-hydrocarbazole showed the highest affinity in the 2-[^{125}I]-iodomelatonin radioligand binding assay in chick brain membranes (K_i=378 pM, melatonin K_i=580 pM). Displacement of the 6-methoxy moiety effected a change from agonistic to antagonistic properties in the pigment aggregation response test involving melanophores obtained from the neural crest of *Xenopus laevis* embryos. β-Alkylated melatonin analogues were prepared by Bischler methodology and showed, as well as 4-bromo-melatonin, a retention in binding potency. Several synthetic routes towards N-acyl-nortryptamines, 2-substituted cyclopent[b]- and 9-substituted cyclohept[b]-indoles were investigated.

Biological results were evaluated by correlating the binding affinity of the melatonin analogues with the conformation of the side chain, the nature of the N-acylating group, and the spatial distance between the methoxy and amide pharmacophores.

Contents

Experimental Part

VII Biological Assays

VIII Chemical Syntheses

Appendix

Glossary

Ag	agonist
Ant	antagonist
APT	attached proton test
aq	aqueous
cAMP	cyclic adenosin monophosphate
CC	column chromatography
DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
EC_{50}	effective concentration for achieving 50% of the maximal response
EGTA	ethyleneglycoltetraacetate
EI	electron impact
eq	equivalent
FAB	fast atom bombardment
HMPT	hexamethylphosphoric triamide
HPG	hypothalamic-pituitary-gonadal
HPLC	high performance liquid chromatography
INEPT	insensitive nuclei enhancement by polarization transfer
ir	infra red
K_d	dissociation constant
K_i	inhibition constant
L:D	light : dark
LHRH	luteinizing hormone releasing hormone
ML-1, ML-2	melatonin receptor subtypes
MS	mass spectroscopy
MSH	melanocyte stimulating hormone
NBS	N-bromo-succinimide
NE	not effective
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NT	not tested
part Ag	partial agonist
PD	pars distalis
PMSF	phenylmethylsulphonylfluoride
ppm	parts per million
PT	pars tuberalis

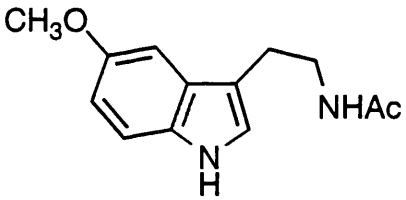
pyr	pyridine
SAD	seasonal affective disorder
SCN	suprachiasmatic nuclei
SPC	spinning plate chromatography
THF	tetrahydrofuran
TLC	thin layer chromatography
Tris	tris(hydroxymethyl)aminomethane

Introduction

I Physiological Activity and Pharmaceutical Potential of the Pineal Hormone Melatonin

In the last decade it has been generally acknowledged that depressive and chronobiological disorders such as SAD (seasonal affective disorder), jet-lag and shift-work syndrome are examples of disturbed circadian rhythms. The increasing prevalence of these diseases has evoked considerable interest in a therapy resetting the endogenous "human clock" to the external daily cycle of light and darkness[1,2].

The most important compound in controlling physiological responses of mammals, reptiles and birds to the circadian light-dark rhythm and to the annual changes in day-length is the hormone melatonin (**1**). In 1958 melatonin was first isolated from bovine pineal tissue by Lerner *et al.* [3], who identified the structure of the indoleamine as N-acetyl-5-methoxytryptamine.



1

Five years later Quay, Wurtman and Axelrod[4-6] discovered the biosynthetic activity of the pineal gland, which produces and releases the melatonin during the hours of darkness. The important discovery of a photoperiod-dependent melatonin level emerged in the examination of the endocrine capability of the pinealocyte by Hoffman and Reiter in 1965[7].

Today the role of the pineal gland and its hormone melatonin in the process of synchronising circadian and annual cycles in vertebrates is well established and the number of melatonin-controlled endocrinological, neurophysiological and behavioural functions has increased dramatically[8,9]. Endogenous melatonin has been implicated in the regulation of reproduction[10], body weight[11,12] and temperature[13], metabolism[14], hibernation[15] and coat colour[16] in photoperiodic mammals.

Although the exact role of melatonin in humans is less explicit, recent research demonstrated its therapeutic potential in a number of patho/physiological conditions, such as SAD[17], regulation of sleep-wake cycles[18] and jet-lag[19].

I.1 Regulation of Melatonin Biosynthesis in the Pineal Gland

Pineal melatonin synthesis is primarily stimulated by neural signals which originate in the hypothalamic suprachiasmatic nuclei (SCN). The SCN are situated above the crossing of the optical nerves and function as autonomous, central, circadian oscillators or "clocks", that establish rhythms with an approximately 24 hours periodicity. In the presence of the solar cycle of day and night these endogenous rhythms are entrained to a 24 hours period. In addition to synchronising the SCN to the environmental light:dark cycle, light also inhibits the transmission of neural signals to the pineal, restricting melatonin synthesis to the hours of darkness[20]. Recently, specialised pineal cells have been shown to be sensitive to other environmental stimuli such as magnetic fields[21], ultrasound waves[22] and temperature[23], all of which are thought to modulate the light-controlled pineal melatonin synthesis to a small extent.

The SCN receive the required photoperiodic information from the retina via the retino-hypothalamic tract and indirectly via the retino-geniculo-suprachiasmatic pathway (RGSP)[24] (figure 1). From the SCN the nerve impulses are transmitted to the paraventricular nucleus (PVN). Via fibres in the medial forebrain bundle and reticular formation the impulses reach the intermediolateral nucleus of the spinal cord. From there they traverse preganglionic adrenergic fibres of the sympathetic nervous system, which conduct them via the superior cervical ganglia (SCG) to the pineal[20].

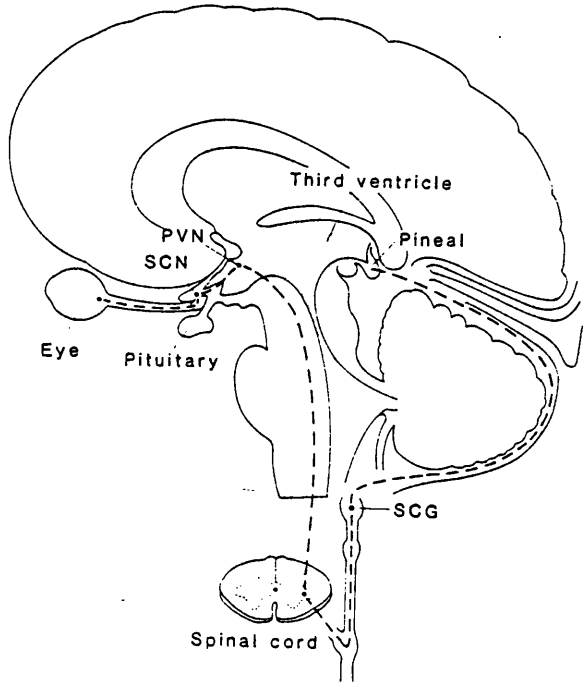


Figure 1: Diagram of the human brain (midsaggital section), showing the neural pathway (dashed line) from the eye to the pineal gland[20]

The conversion of the neuronal input emitted from the SCN into the endocrine output by the pineal gland is initiated by the release of the neurotransmitter noradrenaline from sympathetic nerve fibres[25,26]. Noradrenaline is subsequently bound by pineal membrane β_1-adrenergic receptors, the cyclic nucleotide system is activated, enzymes in the melatonin pathway are activated (N-acetyltransferase (NAT); hydroxyindole-O-methyltransferase (cf. I.2)) and the synthesis of melatonin follows[22,27]. In turn the SCN is reading the circulating level of melatonin to ensure pineal function by a feedback mechanism (figure 2).

Apart from β_1-adrenoceptors, pre- and postsynaptic pineal α-adrenoceptors have been characterised in many mammalian species[28]. In rat pineal glands activation of α_1-adrenoceptor by the α_1-agonist phenylephrine potentiates and prolongs the effect of NAT stimulation by the β_1-agonist isoproterenol[29], whereas the α_2-adrenergic agonist clonidine reduces NAT activity in rats; this effect is blocked by the α_2-adrenergic antagonist yohimbine[30]. In contrast to β_1-adrenergic receptors, the α-adrenoceptors initiate the inositol lipid signalling pathway leading to a secondary messenger duet, diacylglycerol and inositol 1,4,5-triphosphate, the former activating protein kinase C and the later mobilising calcium from intracellular stores[25].

Complementary to the main pineal neurotransmitter noradrenaline several other transmitters play a role in the fine-tuning of mammalian pineal function. Both pineal muscarinic and nicotinic acetylcholine receptors have been characterised[31,32]. By employing radioligand binding techniques, pineal binding sites for a number of neurotransmitters, such as γ-aminobutyric acid (GABA), benzodiazepine (BZP), dopamine (D2)[33], vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY), have been identified; however, a demonstration of their receptor nature and transmitter function is still lacking in many cases. It has been established that BZP[34] and GABA[22] decrease the nocturnal rise of melatonin, whereas VIP[35] exhibits a potent stimulating effect on mammalian melatonin synthesis. NPY appears to exert a dual effect on melatonin synthesis by increasing NAT activity in rats during daytime but damping its night time rise[36]. Recently interferon-γ was reported to increase melatonin production, indicating a possible immunological role for the pineal gland[37].

It has been suggested that circulating hormones such as oestrogen, progesterone, testosterone, prolactin and melatonin itself, could perform the role of amplitude modulators in pineal melatonin synthesis[25]. Physiological concentrations of several adenohypophysial hormones, such as luteinising hormone (LH), thyroid-stimulating hormone (TSH) and growth hormone (GH), elevated daily nocturnal melatonin levels by enhancing NAT activity[38].

In summary, the pineal gland can be characterised as a SCN-controlled neuroendocrine transducer, signalling important environmental information to the organism.

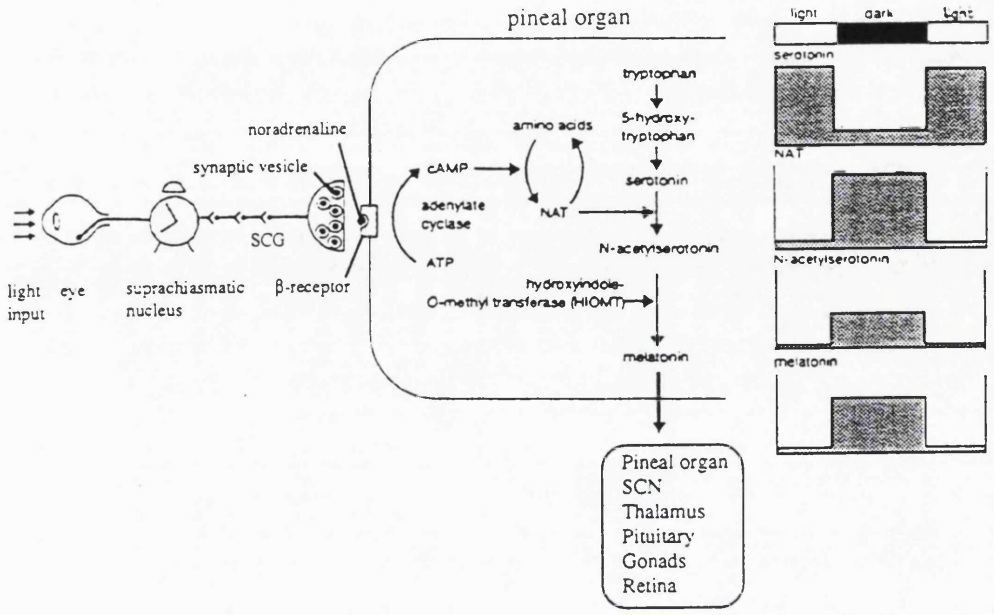


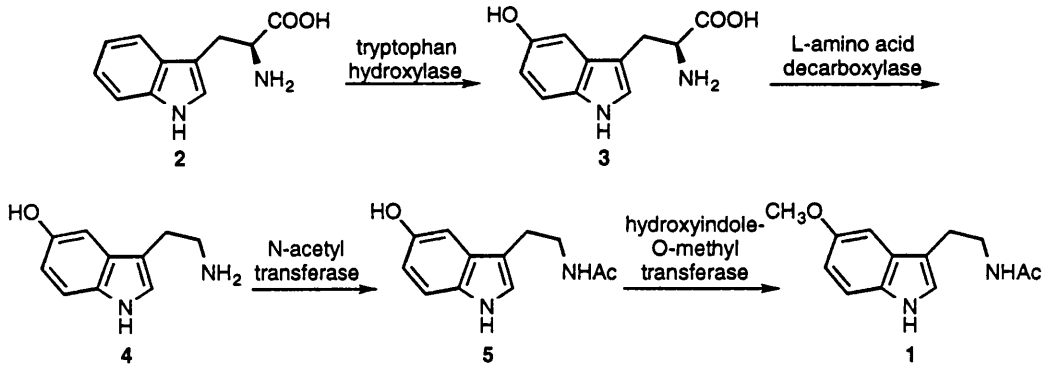
Figure 2: Noradrenergic innervation of pineal melatonin biosynthesis

I.2 Biosynthesis, Secretion and Metabolism of Melatonin

The first step in the biosynthesis of melatonin is the enzyme-catalysed oxidation of the amino acid L-tryptophan (**2**) at C5 of the indole ring. The resulting 5-hydroxy-tryptophan (**3**) is subsequently decarboxylated to 5-hydroxytryptamine (**4**) (5-HT or serotonin). Melatonin is synthesised from serotonin through the action of two enzymes - N-acetyl transferase (NAT) and hydroxyindole-O-methyl transferase (HIOMT). The later catalyses the transfer of a methyl group from S-adenosyl-methionine to N-acetylserotonin (**5**). As previously mentioned, acetylation by NAT and the alkylation by HIOMT are the rate-limiting steps in the melatonin biosynthesis. The night-time increase of pineal melatonin concentration is caused by the large nocturnal increase in NAT activity of the pineal, which shifts the oxidative metabolism of serotonin by monoamine oxidase (MAO) to the N-acetylation of serotonin[39]. In contrast to NAT, the enzyme HIOMT reveals no significant diurnal activity rhythm[40].

The secretion of the synthesised melatonin from the pineal is possibly under neural control, but simple diffusion of the highly-lipophilic hormone into the surrounding vasculature and ventricular system can not be excluded[20]. A part of the produced melatonin might also be stored in the pineal, which led to the assumption that there are a readily releasable and a bound pool of melatonin[41].

After melatonin is secreted from the pineal gland it is to some extent reversibly bound to the plasma protein albumin, whereas the other part circulates freely in blood and cerebrospinal fluid[42]. There is evidence for placental transfer of melatonin, which led to its role as a maternal-foetal synchroniser[43].



Scheme 1: Biosynthesis of melatonin (**1**) in the pineal gland

Apart from the pineal, biosynthetic activity for melatonin is also found in morphological and developmental similar tissues such as retina and harderian gland[44,45] and in enterochromaffin cells in the gastrointestinal tract[46,47].

The major metabolic site for melatonin is the liver where the hormone is C6-hydroxylated and subsequently conjugated as water soluble sulphate or glucoronide[48]. Another metabolic pathway is the oxidative cleavage of the melatonin C2-C3 pyrrole bond in brain tissue by indoleamine-2,3-dioxygenase[49]. The resulting kynurenamines are claimed to possess some melatonin like action such as antigonadotrophic and phase advancing activities[50].

I.3 Physiological Role of Melatonin

Several endocrinological, neurophysiological and behavioural functions in lower vertebrates, birds, mammals and humans are controlled by the circulating level of melatonin[8,20,51,52]. Responses to endogenous melatonin extend from the simple lightening of frog skin in darkness to the elaborate control of reproduction in photoperiodic animals. For photoperiodic animals the pineal melatonin signal provides information about the external light-dark cycle and has consequently the potential for synchronising complex physiological processes in which daily and seasonal coordination is crucial. In general, this mechanism developed during evolution to optimise the efficiency of biological systems by preparing an organism to foresee and

to cope with alterations in the environment (i.e. winter fur, fat reserves for the winter, hibernation).

One of the most important physiological roles of the pineal gland and its hormone melatonin is the mediation of environmental impulses regulating reproduction. The annual breeding cycles of many mammalian species from temperate and polar latitudes ensure that offspring are produced at a time that is optimal for survival. Seasonal mammals are generally classified as "long-day breeders" (e.g. hamsters, ferrets, voles) or "short-day breeders" (e.g. sheep, mink, deer) depending on whether the species is fertile as day length increases or decreases. The short- and long-term cycles in reproduction activity are determined by periodical variations in activity of the primary hypothalamic-pituitary-gonadal (HPG) axis, which are accompanied by changes in the pineal rhythm of melatonin secretion. The photoperiodic information about the day-length is coded as the duration of the pineal melatonin signal (long = winter; short = summer). Investigations of the melatonin level in man revealed that apart from a daily and seasonal rhythm (lowest level in April, highest level in June) there is also a secretion pattern that is related to the ovarian cycle[39].

There is experimental evidence that the rhythm of melatonin production relays photoperiodic information of day length on the HPG-axis; it is, however, still uncertain whether this effect is due to melatonin's influence on the CNS or its direct action on the peripheral organs themselves. In several seasonal breeders the parameters of the melatonin rhythm (phase, duration, amplitude) and therefore their reproductive behaviour were altered by exogenous administration of the hormone and/or changes in photoperiod[53]. Alterations were also achieved by interfering with the neural system controlling the melatonin biosynthesis (e.g. interruptions of the neural pathways anywhere between the retina and the pineal gland, blinded or pinealectomised animals)[54] or blocking of the melatonin receptor sites in the target tissues by antagonists[14]. However, it is still difficult to say which features of the melatonin profile account for effects of photoperiod on reproduction.

Because patterns of melatonin production can be similar in short- and long-day breeders, it is unlikely that melatonin is an exclusively antigonadal hormone - an early claim that was based on the assumption that long-day breeders undergo gonadal regression during short days due to prolonged melatonin secretion[54]. In fact melatonin plays a dual role in influencing the activity of the HPG-axis. Beside the antigonadotropic effect of continual exogenous melatonin exposure on hamsters (long-day breeder), the normal reproduction cycle in blind hamsters can be restored by administration of melatonin, which is accounted for by its counter-antigonadotropic effect[55]. Lesions of the visual pathways leave the SCN without the required photoperiodic information to entrain the circadian rhythm. The lack of a light signal in blind hamsters is

interpreted by the SCN as continual darkness and therefore the melatonin secretion is on an unperiodical high level, inhibiting reproduction. Administration of exogenous melatonin entrains and synchronises the disturbed circadian rhythm.

Abolition of the periodic melatonin biosynthesis either by interrupting the neural pathways between the SCN and the pineal or by pinealectomy renders many mammalian species unable to alter their reproductive behaviour. For example, the gonads of pinealectomised hamsters remain permanently active (low level of melatonin) and pinealectomised ferrets exhibit periods of estrus at infrequent, non-synchronised intervals proving that the pineal is essential for coordinating the reproductive system with photoperiod[56]. It was concluded that the different response to pinealectomy (permanent versus periodical reproductive activity) may reflect the variety in reproductive strategies required by species having different life-spans[56].

Although the influence of the day-night rhythm on the melatonin biosynthesis in man is not as important as in photoperiodic animals, the hormone is involved in the coordination of several physiological and physiopathological events. These processes are mainly controlled by the CNS and include sleep, seasonal affective disorder (SAD), depression, anxiety, mania and dementia[57,58].

The age-dependent calcification of the pineal gland causes a significant change in melatonin blood level and rhythm. Supported by the finding that melatonin is a potent hydroxyl radical scavenger, which protects cells from oxidative stress[59], it has been suggested, that decreasing melatonin levels are involved in the process of ageing[60]. Additionally, melatonin's potential as radical scavenger led to its proposed application as radioprotective agent[61].

Melatonin effects sexual maturation by inducing changes in secretion of adrenal, thyroid, gonadal and hypothalamic hormones[62,63]. The production of testosterone is reduced by its effect on Leydig cells and by its inhibition of hypothalamic biosynthesis and secretion of LHRH (luteinising hormone releasing hormone) at the level of the central nervous system[64]. However, it is not certain that melatonin directly exerts the effects on reproduction, as several peptides that appear to modulate gonadotropin secretion in vivo have been isolated from the pineal. It has been suggested that melatonin might serve as a local hormone regulating the release of one or more of these peptides[65].

Altered levels of melatonin are found in humans suffering from multiple-sclerosis[66], Alzheimer's[67] and Parkinson's disease[68] and breast cancer[69,70], suggesting the considerable pharmaceutical potential of melatonin agonists and antagonists.

I.4 Present and Future Applications of Exogenous Melatonin

The finding that durational changes in the melatonin level are sufficient to drive seasonal changes in reproduction of sheep led to the first application of the hormone in animal breeding[11,71]. The extension of the daily signal of melatonin by either an artificial shorter photoperiod or the administration of the hormone itself causes an increase in short-day breeders' gonadal activity. Under this aspect the exogenous donation of melatonin brings about winter changes during the summer, what is now a practical method of inducing farm animals (e.g. sheep) to breed out of season. There is, however, no current method of inducing summer changes during the winter.

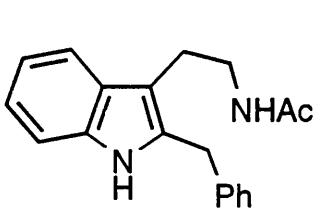
It should be possible to mimic longer photoperiods in the winter by preventing the action of endogenous melatonin on the SCN. This effect can be realised by application of an antagonist that competes with melatonin for the receptor without triggering the melatonin reaction. Therefore the SCN read a short-term melatonin signal, which is interpreted as a long photoperiod (summer).

Principally all melatonin controlled physiological processes can be influenced either by alteration of the photoperiod or by administration of either exogenous melatonin or its antagonist. For example, administration of melatonin advances the seasonal onset of prewinter fattening and storage of substantial energy reserves in red deers by several days[72] and causes behavioural effects in mammals, including decreased locomotor activity and rearing, increased grooming and sniffing[73] and the induction of sleep[74,75].

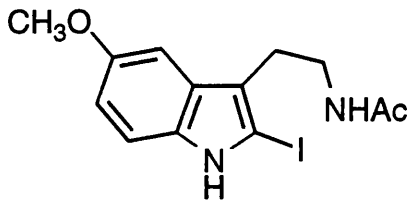
The leading application of exogenous melatonin in humans is its use as chronobiotic. In 1967 Halberg supposed that depressed patients have circadian rhythms that are desynchronised from the 24 hours natural environment[76]. Proceeding on this hypothesis, several psychiatric and sleep disorders due to depression, sexual maturation, shift work or jet-lag are believed to be examples of disturbed circadian rhythms that are related to alterations in melatonin levels and rhythmicity[77,78]. As mentioned previously the administration of melatonin at scheduled times appears to be effective in synchronising disturbed circadian rhythms and is therefore employed to treat sleep disorders[78,79].

Conversely, exposure to bright light is now being used experimentally to treat chronobiological mood and sleep disorders which are characterised by altered circadian patterns of melatonin secretion[80]. It is supposed that the high melatonin levels which are found in humans suffering from SAD or depression can be reduced by the suppressive effect of light on melatonin biosynthesis. Artificial illumination is also used to entrain the disturbed circadian rhythm of patients suffering from time-shifts due to jet-lag or shift work[80].

The same "light-like" effect can be achieved by the application of a melatonin antagonist. It is reported that the putative antagonist luzindole (**6**) exerts antidepressant-like activity by blocking the effects of endogenous melatonin at target receptor sites within the central nervous system[81].



6



7

Possible future applications of melatonin agonists include the therapy of cancer (melatonin exhibits an oncostatic and cytotoxic effect in animal models of human MCF-7 breast cancer cells[69]) and hypertonia (melatonin is effective in normalising pinealectomy induced hypertonia[82]). It has been reported that melatonin increases the immune reactivity of T-lymphocytes in AIDS patients, which indicates its potential in the treatment of viral and parasitic infections[83]. Like benzodiazepines, melatonin enhances GABA binding in the CNS, which leads to its anticonvulsant activity and a possible application in the therapy of epilepsy[84].

Administrating melatonin for the therapy of any of the above mentioned diseases might be contraindicated by its antigonadotropic action[57]. However, this effect on the HPG-axis may be utilised in contraception and the treatment of premenstrual syndrome[85,86].

I.5 Melatonin Binding Sites

As mentioned in the previous paragraphs, melatonin is involved in the control of several distinct physiological processes. The diversity of these various activities suggest a widespread distribution of melatonin target sites, which have been recently located in the brain and peripheral tissues[87,88].

A major advance in identifying melatonin binding sites has been the discovery that 2-iodomelatonin (**7**) binds more strongly than melatonin itself to the melatonin binding site. Since 1987 *in vitro* autoradiographic localisation and characterisation of melatonin binding sites with radioiodinated 2-[^{125}I]iodomelatonin[89,90] has verified and extended the earlier ambiguous results obtained with tritiated [^{3}H]melatonin[91,92].

Sites of melatonin binding have been localised in a wide range of brain sites and peripheral tissues. In lower vertebrates, specific melatonin binding sites are widely distributed throughout the brain. Consistent with melatonin's role in transducing

photoperiodic information, receptors have been identified in the retina and retinorecipient structures of the hypothalamus and thalamus of chicken and goldfish[93,94].

By contrast, the distribution of melatonin receptors in the mammalian brain is less widespread than in lower vertebrates and reveals a considerable species dependence. The only region which shows saturable and reversible 2-[^{125}I]iodomelatonin labelling in all so far studied mammals is the pars tuberalis (PT) of the pituitary gland, which is consistent with a role of the PT in seasonal behaviour. The SCN of the hypothalamus is a second area which is labelled in many species but not in sheep, goat and deer. Other important central sites for melatonin receptors include the pineal gland, thalamic PVN and pars distalis (PD) of the pituitary[87].

Peripheral melatonin binding sites have been localised in the duck spleen, kidney, thymus and jejunum[95-98]. The identification of melatonin binding sites in the duck thymus gland might support the hypothesis of melatonin's modulatory action on the immune system. Melatonin binding sites have also been found in the rat caudal arteries which are thought to be involved in thermoregulation[99]. Whereas the later studies still await detailed autoradiographic localisation of the cell type(s) expressing melatonin binding, the receptor causing the melatonin-induced melanin aggregation in dermal melanophores of amphibians[100] has recently be cloned from *Xenopus laevis* dermal melanophores[101]. A similar effect of melatonin-induced pigment aggregation has been observed in the Australian pencil fish[102]

The profound effect of melatonin on the seasonal reproduction of photoperiodic mammals is primarily mediated via the hypothalamic-pituitary axis. However, melatonin binding sites have also been identified in chicken ovaries and testes[103] and human spermatozoa[104]. The presence of melatonin binding sites in the gonads of males is consistent with the earlier finding that melatonin acts on isolated Leydig cells to inhibit luteinizing hormone- or forskolin-stimulated testosterone production[105].

A summary evaluating recent advances in the characterisation of central and peripheral melatonin binding sites is given in a review by Morgan *et al.*[87].

I.6 Pharmacology of the Melatonin Receptor

All of the described melatonin binding sites exhibit high affinity for melatonin with a K_d in the low picomolar range (40-400 pM). These membrane-bound ML-1 receptors are generally coupled to a guanine nucleotide binding protein (G-protein) and have been shown to inhibit cAMP in such different histological formations as the PT and PD of the pituitary, the amphibian melanophore and the vertebrate retina.

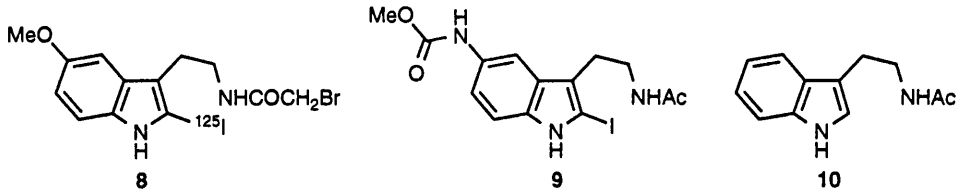
As for other membrane-bound receptors which utilise heterotrimeric G-proteins, the ML-1 receptor can exist in two affinity states: the first, G-protein-coupled state has a high affinity of ~40 pM; the second, G-protein-uncoupled state, in which the melatonin binding site and the G-protein have dissociated, has an affinity of ~400 pM[88]. In the pars distalis the melatonin signal is also transduced by the inhibition of calcium influx, thereby altering the membrane potential. However, for most of the identified receptor tissues a demonstration of the mediated biochemical and cellular responses is still lacking.

An early attempt to isolate and characterise the melatonin receptor protein by means of affinity labelling utilised N-bromoacetyl-2-[^{125}I]iodo-5-methoxytryptamine (**8**), which has been proposed to be a selective irreversible ligand for the melatonin binding site. Studies by Zisapel *et al.* on rat and hamster brain synaptosomes indicated that this agent labelled 3 proteins with apparent molecular weights of 45, 55 and 92 kDa [106,107]. However, it was later reported by Sugden that the melatonin analogue **8** unselectively labels numerous proteins in chicken brain membrane and that the labelling was not blocked by co-incubation with melatonin[88].

A breakthrough in the molecular characterisation of the melatonin binding site was the recent cloning of a high-affinity ML-1 receptor from *Xenopus* dermal melanophores[101]. Reppert and co-workers reported that the isolated cDNA encodes a protein of 420 amino acids which is a novel member of the G protein-coupled receptor family. The cloned receptor exhibited an identical pharmacological profile to the previously characterised ML-1 receptors in chicken retina, chicken brain, wallaby brain and sheep pars tuberalis. In these tissues specific 2-[^{125}I]iodomelatonin binding was inhibited in the order 2-iodomelatonin > melatonin > 6-methoxymelatonin > N-acetylserotonin >>> 5-hydroxytryptamine[108-111]. The significant correlation of the binding affinity constants (K_i) for a number of melatonin analogues in sheep PT, chicken brain, chicken retina and wallaby brain suggests that there is a great conservation of melatonin binding site affinity and pharmacology across a wide variety of tissues and species.

However, a low-affinity melatonin receptor (ML-2) has now also been identified in hamster and guinea-pig brain, where the binding site exhibits distinct binding kinetics and a different pharmacology from the high affinity receptor ML-1[112]. The rank order of specific 2-[^{125}I]iodomelatonin binding inhibition is 2-iodomelatonin > 6-methoxymelatonin > N-acetylserotonin ≥ melatonin > 5-hydroxytryptamine. In contrast to the ML-1 receptor the biosynthetic precursor N-acetylserotonin and 6-methoxymelatonin show a higher affinity than melatonin. Recently specific ML-2 melatonin receptor ligands, 5-methoxycarbonylamino-N-acetyltryptamine and the 2-

iodinated analogue **9**, have been developed to further characterise this new receptor subtype[113]. However, until now the ML-2 receptor has not been shown to mediate any particular biological response[88].



I.7 Structure-Affinity and Structure-Activity Relationships of Melatonin Analogues

Early examinations of the structure-activity relationship of melatonin and related indoleamines were carried out using the melatonin-induced pigment aggregation assay in amphibian dermal melanophores[114,115]. Heward and Hadley demonstrated on frog skin that N-acetyltryptamine can block the activity of melatonin, but has no intrinsic activity on its own[114]. Studying several putative melatonin analogues they found a relative potency series in which melatonin » 5-methoxytryptamine > 5-methoxyindole > serotonin. They concluded that the 5-methoxy substituent triggers the biological response of the receptor, whereas the affinity for the receptor binding site is primarily determined by the 3-(N-acetyl-ethaneamine) group.

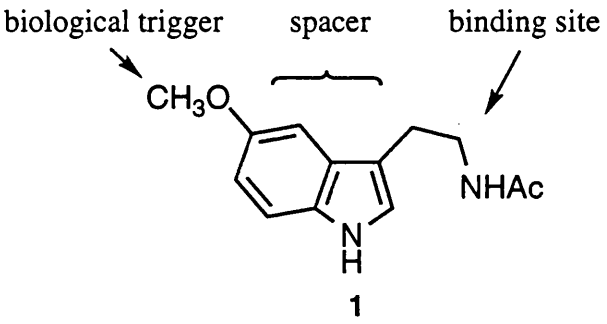


Figure 3: Suggested pharmacophores in melatonin (Heward and Hadley, 1975)[114]

The importance of the 5-methoxy group for intrinsic activity of melatonin is emphasised by studies in which it is substituted by other alkoxy groups, alkyl groups or halogens. Exchange of the 5-methoxy group by fluorine, but not by bromine leads to a loss of biological activity in the melatonin-induced delay of puberty in male rats[116]. Similarly the ovulation-blocking effect of melatonin is lost in melatonin analogues with acetyl, ethyl or phenyl substitution at C5[117] and a reduced activity is

observed in the pencil fish pigment aggregation assay for 5-ethoxy and 5-propyloxy derivatives[118]. However, in all of the three studies the melatonin analogues were not tested for their binding affinity. A possible biological activity might not have been observed because of the dramatic loss of binding affinity, which was recently reported for various 5-aryloxy and 5-cycloalkyloxy analogues[119].

The dual role of the 5-methoxy group in biological activity and binding affinity of melatonin has recently been established by Sugden and Chong who showed in chicken brain that N-acetyltryptamine (**10**), an analogue lacking the 5-methoxy group, has a K_i of 530 nM, which is more than 1000-fold less than melatonin (K_i 508 pM)[109]. N-Acetyltryptamine was also shown to exhibit concentration dependent mixed agonist-antagonist effects in an electrophysiological bioassay measuring the firing of melatonin-sensitive hamster SCN neurones[12].

Recently, the theory that the 5-methoxy group is not essential for conferring biological activity was further developed by Garratt *et al.*, who synthesised various 2-bromo- and 2-phenyl-N-acyltryptamines without a C5 substituent. These indole-derived melatonin analogues showed a slightly reduced binding affinity in chicken brain (K_i~100 nM) and were melatonin agonists in the *Xenopus* melanophore assay[120].

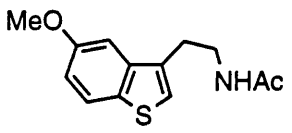
Other modifications of the melatonin molecule include increasing the length of the N-acyl side-chain and substitution on C2 and/or C6 of the indole nucleus. Variations of the N-acyl group of the essential amide function led to an optimal binding affinity for the N-butanoyl analogue of melatonin in both chicken brain and sheep PT membranes[109,121]. Further increase of the chain-length resulted in a progressive loss of affinity. A reduced affinity was also observed for analogues in which the amide group was exchanged for a urea, thiourea or carbamate functionality[119].

The C2 position of melatonin was initially substituted by a methyl group to block *in vivo* enzymatic degradation by pyrrolases[122]. Halogenation of C2 enhances the binding affinity (2-chloroMT: K_i 24 pM[123], 2-bromoMT: K_i 45 pM (rabbit parietal cortex)[124], 2-iodoMT: K_i 58 pM[123]) in chicken brain membrane. Stankov *et al.* reported that in a series of 2-alkyl and 2-phenyl-substituted melatonin analogues 2-phenylmelatonin showed the highest binding affinity (K_i 24 pM compared to K_i 1.1 nM for melatonin) in quail brain suggesting a vicinal lipophilic pocket of the receptor site[125].

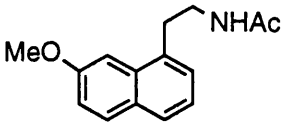
Substituents at C6 of melatonin were initially introduced to block metabolic degradation by 6-hydroxylation and to increase their *in vivo* half lifes[117]. Whereas C6 halogenation retained the affinity to the chicken brain membrane binding site (i.e. 6-chloromelatonin K_i 0.58 nM[123]), introduction of 6-OH or 6-OMe resulted in a slight decrease in binding affinity (K_i 6.3 nM and K_i 31.7 nM, respectively[123]).

Another possibility to prelong the half life of melatonin analogues is to exchange the indole nucleus, which is apparently not required for binding nor activation, for sterically similar spacers like benzo[b]thiophene[126], benzo[b]furans[127], benzimidazole[127], naphthalene[128], tetralin[129,130] or chroman[131].

The binding affinity of N-acetyl-3-ethaneamine-5-methoxy-benzo[b]thiophene (**11**) in chicken brain (K_i 5.2 nM)[123] and of N-acetyl-1-ethaneamine-7-methoxy-naphthalene (S20098, **12**) in ovine pars tuberalis (K_i 100 pM)[128] are comparable to the affinity of melatonin in the same tissue preparations (K_i 508 pM and 92 pM, respectively). A loss of binding affinity was only observed for the benzimidazole analogue[119].

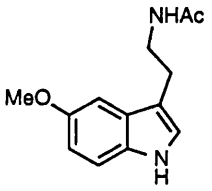


11

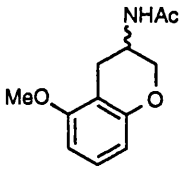


12

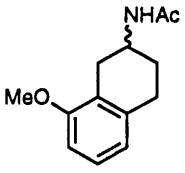
Whereas the benzo[b]thiophene and naphthalene analogues can be regarded as bioisosters of melatonin with flexible N-acyl-3-ethaneamine side chains the relative position of the pharmacophores in the series of chromans and tetralins is fixed by incorporating the side chain into a pyran or cyclohexane ring.



1



13



14

15

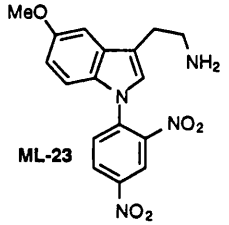
N-Acetyl-3-amino-5-methoxychroman (**13**) exhibits only weak binding affinity in chicken brain (K_i 8.4 µM) and shows no response in the *Xenopus* melanophore assay[131]. The binding affinity and biological activity of the carboxylic series of tetralins determined in chicken and rabbit retina, respectively[129], was found to be 100-times weaker than for melatonin (**14** K_i 46.3 nM). As for the series of naphthalene and chroman analogues of melatonin binding is optimal for N-butanoyl amides. N-Acetyl-2-amino-tetralins with a methoxy group on C7 (K_i 121 nM), C5 (K_i 2 µM) or C6 (not active) showed a reduced affinity. The conformationally restricted melatonin analogue **15** also showed a reduced binding affinity on chicken brain membrane (K_i 184 nM)[123]. Although racemic mixtures were used in these studies it can be concluded that the relative orientation of the melatonin pharmacophores in the receptor-melatonin complex must be different from the one allowed in the above series of chromans and tetralins.

Melatonin Antagonists

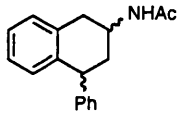
Several compounds have been reported to block the effects of melatonin *in vivo* and *in vitro*. In keeping with Heward and Hadley's initial theory of melatonin SARs the melatonin precursor N-acetyl-5-hydroxytryptamine (**5**) was reported to be an antagonist blocking the melatonin-induced inhibition of calcium-dependent release of [^{3}H]dopamine from rabbit retina[132]. However, in other functional assays **5** showed a dose-dependent mixed activity of a partial agonist[121,133].

In 1988 Dubocovich designed the first reported melatonin antagonist, luzindole (**6**)[14]. Luzindole successfully blocked the effect of melatonin in the rabbit retina and *Xenopus* melanophore assay[134]. It also showed antidepressant-like activity in the mouse behavioural despair test where the anti-immobility effect of luzindole was prevented by the administration of melatonin[81]. These results were in accord with Heward and Hadley's theory that melatonin analogues lacking the 5-methoxy functionality bind to the receptor without triggering a biological action.

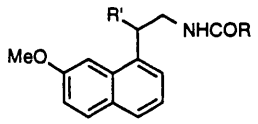
However, the antagonistic activity of luzindole is not universal as it has low affinity for the chicken brain (K_i 1050 nM)[123] and ovine PT receptor. Additionally it failed to block melatonin-induced inhibition of forskolin stimulated cAMP production in ovine PT cells, which might reflect differences between the melatonin receptors[133].



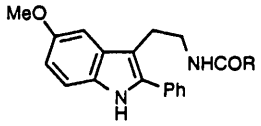
ML-23



16



17 a R' = H, R = CH_2CH_2Ph
b R' = H, R = c-C_4H_7
c R' = COOMe, R = c-C_3H_5



18 a R = CH_3
b R = c-C_3H_5

Mixed effects were also observed for N-(2,4-dinitrophenyl)-5-methoxytryptamine (ML-23), which was reported to inhibit melatonin mediated processes of sexual maturation in rats *in vivo*[135]. However ML-23 has only weak affinity for the melatonin receptor in ovine PT and shows no effect to block melatonin on *Xenopus* melanophore or chicken retina[134,136].

Combining the binding affinity of the tetralin series with the antagonistic activity of luzindole Dubocovich *et al.* recently designed a novel compound, 4-phenyl-acetamidotetralin (**16**), which was reported to be a competitive ML-1 receptor antagonist in rabbit retina[137].

The problem of decreased binding affinity in melatonin antagonists lacking the 5-methoxy group was recently solved by the design of analogues with modified acyl moieties. In the series of naphthalenic analogues **17** a gradual change from agonistic

to antagonistic properties was observed with increasing size of the cycloalkyl or alkylphenyl substituent; the analogues **17 a,b** are potent antagonists in the chicken retina and the ovine PT assay (**17 b**: K_i 100 nM). The binding affinity of the antagonists can be improved by introducing a methoxycarbonyl moiety in β-position to the amide group and reducing the size of the cycloalkyl ring (**17 c**: K_i 29 nM)[119].

Antagonists in the 5-methoxy tryptamine series were synthesised by introducing a 2-phenyl moiety in the indole nucleus[125]. Both the acetyl and the cyclopropanoyl analogue **18 a,b** exhibit high binding affinity in quail brain (K_i 57 pM, 240 pM, respectively; melatonin K_i 1.1 nM) and are antagonists in the syrian hamster gonadal regression model. However, the efficacy of all recently reported antagonists awaits assessment in other systems.

I.8 Melatonin Receptor Model

The observed SARs of melatonin analogues underline the importance of methoxy and amide group for binding affinity, suggesting the possibility of hydrogen bonding between the two pharmacophores and the receptor protein. Based on thermodynamic studies of the melatonin-receptor complex[123] and electrostatic potential energy calculations[138] a pentapeptide sequence (Ser Trp Ile Asn Ile) has been suggested as a model for the melatonin binding site. This sequence is modified from a model for the 5-HT_{1c} receptor, which accommodates the serotonin ligand (Ser Trp Ile Asp Ile). Following interactions are postulated between complementary residues of the receptor binding site and melatonin:

- van der Waals interaction between the tryptophan residue and the indole ring
- hydrogen bond formation between the serine residue and the 5-methoxy group
- hydrogen bond formation between the asparagine residue and the amide group.

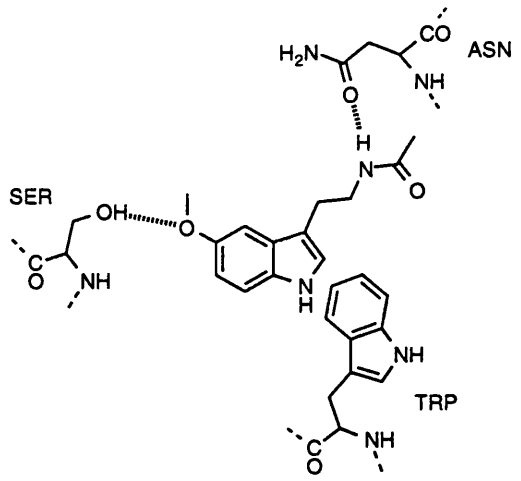


Fig. 4: Interaction between melatonin and the receptor binding site[123]

Quantitative Structure-Activity Relationship (QSAR) analysis for 12 melatonin analogues demonstrated that the binding affinity at the chicken brain ML-1 receptor is correlated to ΔE, the energy difference between HOMO and LUMO, and Q_NH, the electron density of the amide nitrogen[123].

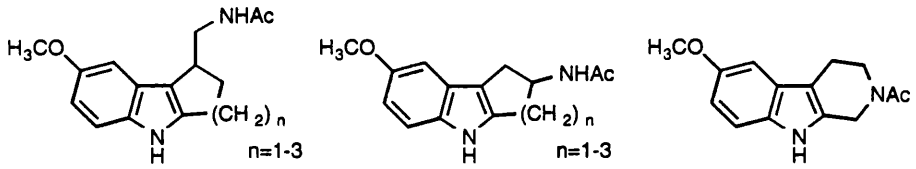
$$pK_i = 777\ \Delta E^{-1} + 50\ Q_NH - 59$$

Combined with the recently cloned melatonin receptor in *Xenopus* dermal melanophores this receptor model and the described SARs might help to elucidate the 3 dimensional structure of the melatonin binding site and to design further melatonin agonists and antagonists.

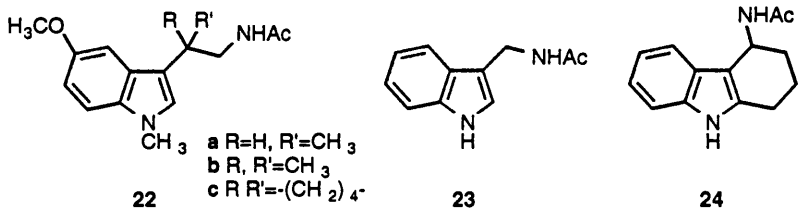
I.9 Objectives of this Thesis

Although several melatonin receptor ligands have been developed further structurally diverse analogues are necessary to understand the pharmacology of the receptor both in terms of the improvement of existing SAR theories and for the definition of emerging receptor subtypes.

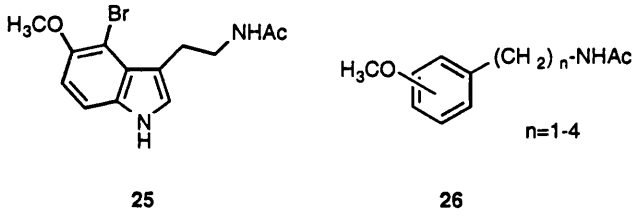
The major aim of the presented thesis is to examine the spatial and electronic requirements of melatonin analogues necessary for conferring binding affinity and biological activity. In the line of previous investigations of dopamine[139] and 5-HT[140] receptor ligands the syntheses of novel classes of melatonin analogues **19-21** with the C3 amidoethane side chain incorporated in a carbocyclic or heterocyclic ring are targeted. To test existing SAR theories these tricyclic analogues are also prepared without a 5-methoxy group and/or a modified N-acyl group.



The effect of β-alkyl branching of the amidoethane side chain is examined in the new melatonin receptor ligands **22**. Apart from reducing the conformational flexibility of the side chain the cyclopentane analogue **22 c** provides information about the size of the receptor pocket accommodating the side chain. The amidoethane side chain is also shortened in a series of nortryptamine derivatives (**23, 24**).



To investigate the steric requirements around C4 of the indole nucleus the first melatonin analogue with a substituent at this position - 4-bromomelatonin (**25**) - is prepared.



Another parameter influencing binding affinity to the melatonin receptor is the spatial distance between methoxy and amide group. In a series of benzene analogues (**26**) the length of the amidoalkane chain and the substitution pattern of the benzene ring is varied. These analogues might also be useful as model compounds to investigate the effect of substituting the 5-methoxy group by various other functionalities (i.e. halogen, alkyl etc.).

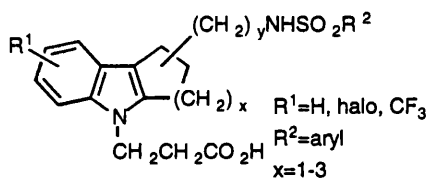
Theoretical Part

II Syntheses of tricyclic Melatonin Analogues

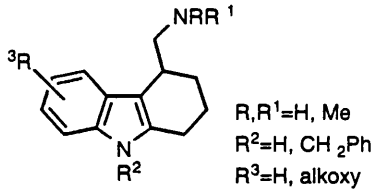
II.1 N-Acyl-aminomethyl-cycloalkan[b]indoles

II.1.1 Introduction

Substituted cycloalkan[b]indoles of the general structural formulae **27** and **28** have been patented as thromboxane A_2 antagonists[141] and antibacterial agents[142], respectively.

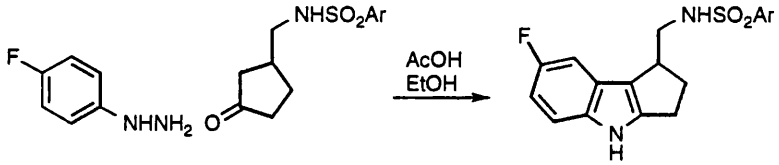


27



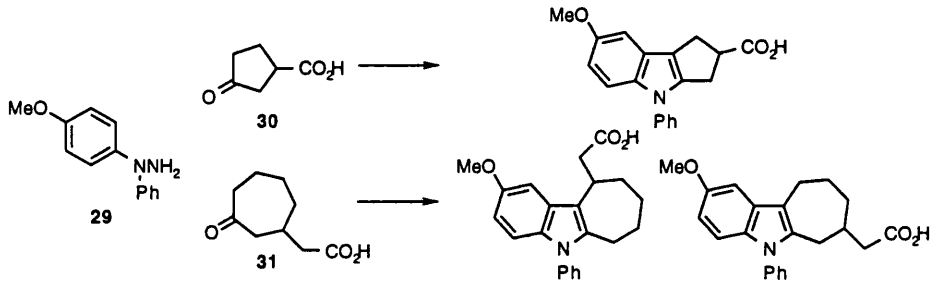
28

Two different strategies have been employed for the preparation of these indole-based heterocycles. The Fischer indole methodology is used in a convergent approach condensing fully functionalised phenylhydrazine and cycloalkanone derivatives on the last step of the synthesis (scheme 2).



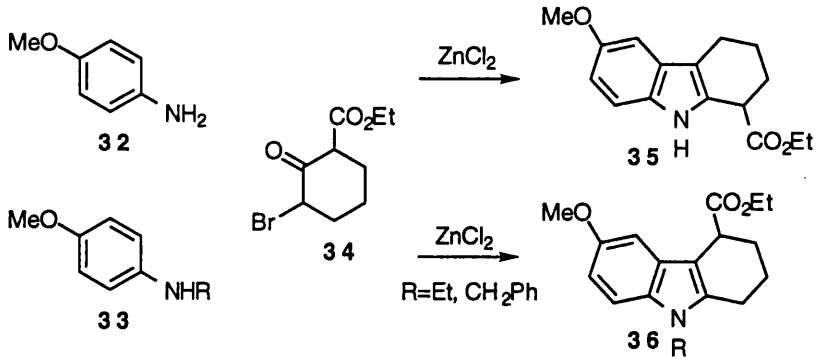
Scheme 2: Fischer synthesis of a cyclopent[b]indole[141]

However, the preparation of the functionalised cycloalkanone usually involves several steps and the reported yields of the final Fischer reaction are low to moderate (around 10% for the 5-membered ring and 50% for the 6-membered ring)[141]. Another problem of the Fischer synthesis is the drop in regioselectivity with increasing ring size of the substituted cycloalkanone. While only one product is observed in the reaction of N-phenyl-*p*-methoxyphenylhydrazine (**29**) with cyclopentanone-3-carboxylic acid (**30**)[143] a 1:1 mixture of both isomers is isolated when cyclo-heptanone-3-acetic acid (**31**)[144] is used (scheme 3).



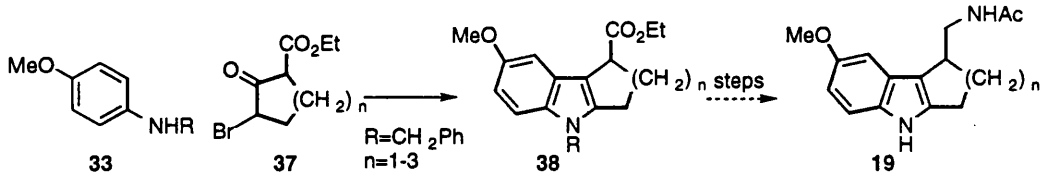
Scheme 3: Fischer synthesis of cyclopent[b]indolecarboxylic acid and cyclohept-[b]indoleacetic acid

The regioselectivity on the indole formation step can be controlled in the alternative Bischler synthesis, which has been employed in the synthesis of several 1,2,3,4-tetrahydrocarbazoles derivatives[142,145]. According to Julia *et al.* N-alkylanilines **33** react with 2-bromo-6-carbethoxycyclohexanone (**34**) to give exclusively the 4-substituted tetrahydrocarbazoles **36**, whereas the reaction with aniline **32** yields the 1-substituted regioisomer **35** (scheme 4)[146]. The same regioselectivity is observed for acyclic α-bromoketones (cf. chap. III)[147].



Scheme 4: Bischler synthesis of 1,2,3,4-tetrahydrocarbazoles

Considering the targeted melatonin analogues **19**, it was planned to extend the regioselective Bischler synthesis of tetrahydrocarbazoles **36** to the general structure of ethyl N-benzyl-cycloalkan[b]indole-carboxylates (**38**).



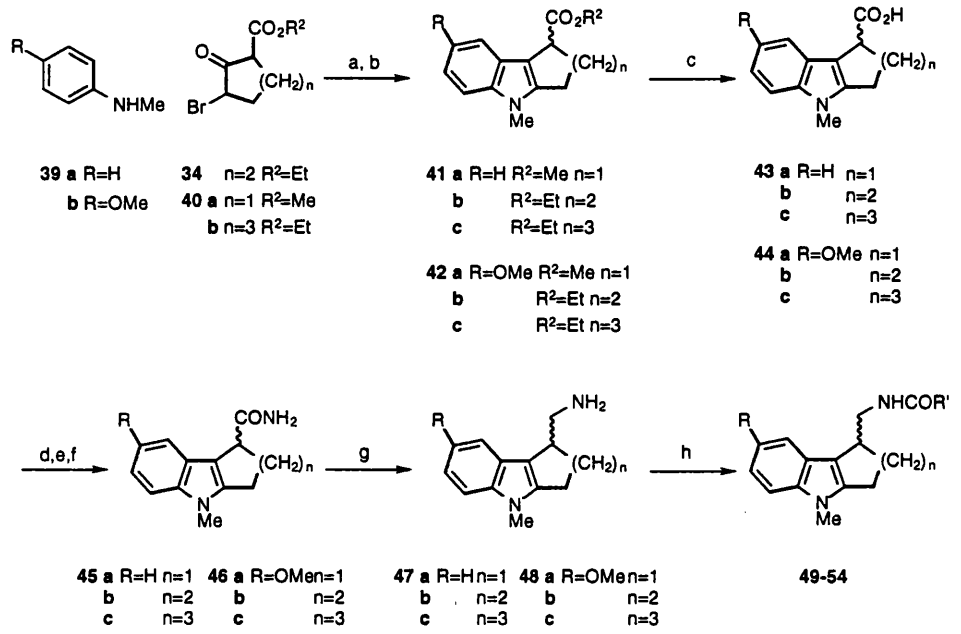
Scheme 5: Planned synthesis of N-acetyl-aminomethyl-cycloalkane[b]indoles **19**

The interconversion of the carboxyclic ester into the aminomethyl group has been accomplished by two different synthetic sequences. In a four step synthesis the ester is initially reduced and the resulting alcohol is converted into a tosylate/mesylate, which is then substituted by azide and finally reduced to the amine (cf. chap. II.2)[145]. The method of choice is the saponification of the ester and the generation of an acetamide which is finally reduced to the aminomethyl functionality[148].

Initially it was planned to remove the directing benzyl group in a later stage of the synthesis. However, the attempted debenzylation of the acyclic N-benzylindole (**183b**) by catalytic hydrogenation or treatment with sodium in ammonia was unsuccessful (cf. chap. III). Therefore, the directing effect of the smallest alkyl moiety was used in N-methylanilines, knowing that the additional N-methyl group of the final tricyclic melatonin analogues would be tolerated at the melatonin binding site. In comparison to melatonin the naphthalene analogue **12** and N-methylmelatonin (**199**) exhibit the same or slightly reduced binding affinities (cf. chap. I.7 and III).

II.1.2 Synthesis

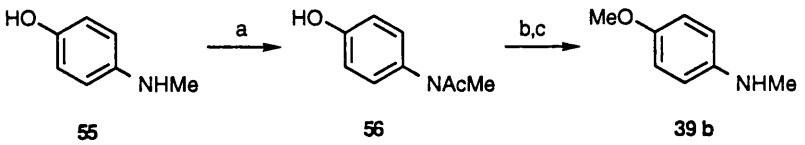
The synthesis of the various N-acetyl-aminomethyl-cycloalkan[b]indoles (**49-54**) is outlined in scheme 6.



Scheme 6: Synthesis of N-acetyl-aminomethyl-cycloalkan[b]indoles

a 50 °C, 3 h; b $ZnCl_2$, propane-2-ol, Δ, 16 h; c NaOH, H_2O, EtOH, Δ, 6 h; d Et_3N, CH_2Cl_2, 0 °C, 10 min; e $ClCO_2Me$, CH_2Cl_2, 0 °C, 4 h; f NH_3, 20 °C, 16 h; g THF, BH_3-THF or $LiAlH_4$, Δ, 4 h; h R'COCl or $(R'CO)_2O$, Et_3N, CH_2Cl_2, 20 °C, 4 h.

For the preparation of putative melatonin antagonists **49-51** commercially available N-methylaniline (**39 a**) is used, whereas compounds containing a methoxy group required *p*-methoxy-N-methylaniline (**39 b**) as one building block. *p*-Methoxy-N-methylaniline is prepared on a 100 g scale and in good yield using a method reported by Julia and Bagot[147]. Starting from N-methyl-4-amino-phenol (**55**) the amine group is protected as amide. In a one-pot procedure the phenol is alkylated with dimethyl sulphate and the amide is saponified. The product *p*-methoxy-N-methylaniline (**39 b**) is purified by vacuum distillation and solidifies at 0 °C.

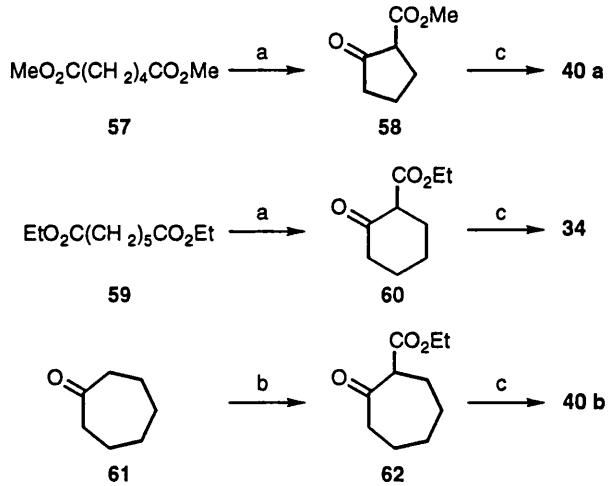


Scheme 7: Preparation of 4-methoxy-N-methylaniline (**39 b**)

a Ac_2O, 90 °C, 15 min; b $(MeO)_2SO_2$, 25 °C, 4 h; c NaOH, Δ, 16 h.

The building block in the size of the annelated carbocylic ring is synthesised by bromination of the appropriate ethyl or methyl 2-oxocycloalkanecarboxylate[149]. The heat labile α-bromoketones **34** and **40 a,b** are used without purification for the following Bischler condensation.

Whereas methyl 2-oxocyclopentanecarboxylate (**58**) and ethyl 2-oxocyclohexane-carboxylate (**60**) can be prepared by Dieckmann cyclisation of dimethyl adipate (**57**)[150] and diethyl pimelate (**59**), respectively, the cyclisation to the 7-membered ring proceeds in low yield. Two methods are reported for the synthesis of ethyl 2-oxocycloheptanecarboxylate (**62**). Prelog and Hinden reacted the sodium enolate of cycloheptanone (**61**) with diethyl oxalate at - 10 °C and eliminated carbon monoxide from the intermediate by heating with a catalytic amount of boric acid[151]. However, only decomposition and polymerisation products were obtained in the attempt to purify the crude product. Alternatively, the enolate was reacted with diethyl carbonate at 60 °C to yield the product **62** in moderate yield[152].



Scheme 8: Synthesis of 3-bromo-2-oxo-cycloalkanecarboxylates

a Na, xylene, 110 °C, 5 h; b KO^{t}Bu, $(EtO)_2CO$, Δ,7 h; c Br_2, 0 °C, 16 h

The Bischler reaction between anilines and α-halogenoketones has been extensively studied by Julia and co-workers (cf. scheme 4)[146,147,153-156]. Modifying Julia's procedure, 2 equivalents of N-methylaniline were treated with 1 equivalent of α-bromoketone in the absence of any solvent. In some cases the exothermic alkylation did not proceed immediately and the mixture was heated under nitrogen at 50 °C for 3 h. In the next step the reaction mixture containing the α-anilinoketone was dissolved in 2-propanol and cyclised to the indole in the presence of dry zinc chloride. Usually the resulting indole ester was not purified but saponified directly. In contrast to the highly viscous esters the acids are crystalline solids which can be easily precipitated by acidifying an ice-cold solution of their salts.

For the esters and acids of the tetrahydrocarbazoles and cyclohept[b]indoles only one set of ^{1}H nmr signals was observed, indicating the presence of only one regioisomer. However, the ^{1}H nmr spectra of the cyclopent[b]indoles **41 a, 42 a, 43 a** and **44 a** showed a doubling of signals with a product ratio of 4:1. Using this mixture for the amidification, only one product having the desired regiochemistry is isolated. The regiochemistry of the products was established during the course of the synthesis by means of INEPT experiments (cf. chp II.1.3). Crystal structure analysis of **53 g** also showed the presence of the 4-substituted tetrahydrocarbazole (Fig. 5), thus confirming the earlier results by Julia and co-workers and providing substantiation for the INEPT experimental results.

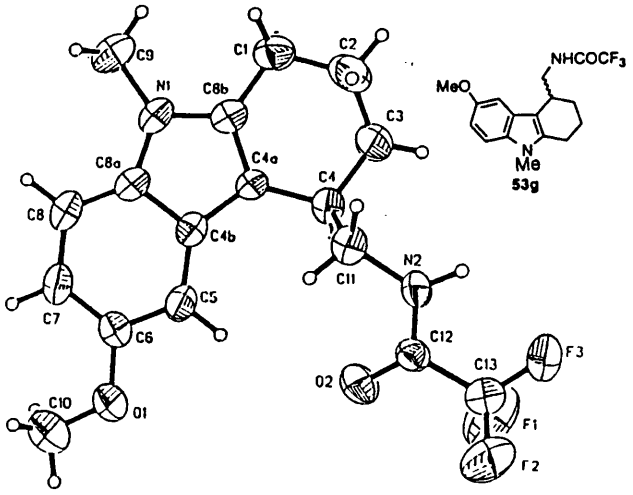
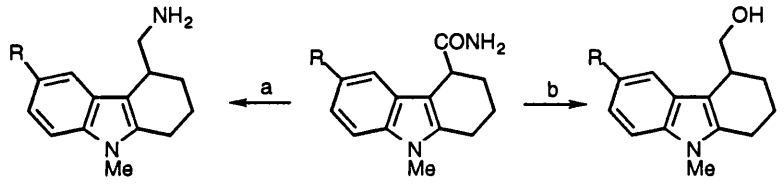


Figure 5: X-ray crystal structure of one enantiomer of **53 g**, 50 % probability thermal ellipsoids

The amides **45** and **46** were prepared by ammonolysis of mixed anhydride which were generated by reacting the deprotonated carboxylic acid with ethyl or methyl chloroformate[157]; alternatively the acid **43b** was heated with excess urea[158]. However, under the vigorous reaction conditions the amide is obtained in low yield (11 %). Julia *et al.* reported decarboxylation as the major reaction pathway[157]. Characteristic for the amides is the carbonyl absorption in the ir spectrum and the two broad signals between 5 and 6.5 ppm in the ^1H nmr spectra (cf. fig. 13, appendix).

Reduction of the amides was accomplished in good yield with lithium aluminium hydride. Because of the low solubility of the amides in ether, THF was used as solvent. Interestingly the reduction of the tetrahydrocarbazole amides **45b** and **46b** gave predominately neutral products. These were identical with the products of lithium aluminium hydride reduction of the esters **41b** and **42b** and were identified as the corresponding alcohols **63** and **64** (scheme 9). Reduction of the amides under milder conditions using borane resulted the targeted amines **47b** and **48b**.



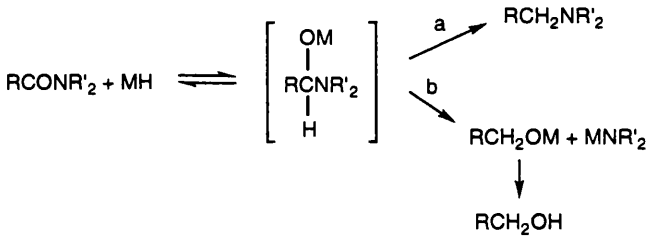
47 b R=H
48 b R=OMe

45 b R=H
46 b R=OMe

63 R=H
64 R=OMe

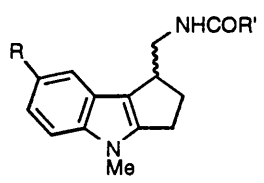
Scheme 9: Reduction of 4-carboxamide-9-methyl-1,2,3,4-tetrahydrocarbazoles **45b** and **46b** a) BH_3-THF, 20 °C, 16 h and b) $LiAlH_4$, THF, Δ, 2 h.

The unexpected product formation in the lithium aluminium hydride reduction of the tetrahydrocarbazoleamides is difficult to explain, because of the clean conversion of the homologues cyclopent[b] and cyclohept[b]indoleamides into the amines under the same reaction conditions. In all three annelated indoles the carboxamide group should be in equatorial orientation to minimise diaxial interaction. The reduction of hindered tertiary amides by lithium aluminium hydride to alcohols is well precedented in the literature. According to Brown and Heim the intermediate amide-metal hydride complex undergoes C-O or C-N bond cleavage in dependence of the steric characteristics of the amide and the reactivity of the reducing agent[159]. They reported that hindered tertiary amides are cleanly converted to amines by reduction with borane. For other, but unknown reasons, the same reactivity of lithium aluminium hydride and borane was observed for the above reduction of the tetrahydrocarbazoleamides.



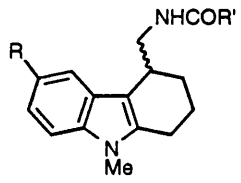
Scheme 10: Reduction of amides by metal hydrides[159]

Finally the amines **47** and **48** were acylated by standard methods. In general the milder condition of the acylation with carboxylic acid anhydrides produced the amides in higher yield and purity than the method using acyl chlorides. However the valeroyl, cyclopropancarbonyl and cyclobutancarbonyl moiety are commercially only available as acyl chlorides. The trifluoroacetyl group is introduced by stirring the amine in methanol with ethyl trifluoroacetate and evaporating the volatile components *in vacuo* at 30 °C.



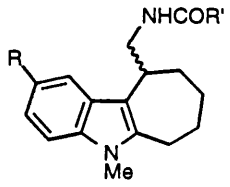
49a R=H, R'=Me
49b R=H, R'=Et
49c R=H, R'=n-prop
49d R=H, R'=n-but
49e R=H, R'=cyclo-C_3H_5
49f R=H, R'=cyclo-C_4H_7
49g R=H, R'=CF_3

52a R=OMe, R'=Me
52b R=OMe, R'=Et
52c R=OMe, R'=n-prop
52e R=OMe, R'=cyclo-C_3H_5



50a R=H, R'=Me
50b R=H, R'=Et
50c R=H, R'=n-prop
50d R=H, R'=n-but
50e R=H, R'=cyclo-C_3H_5
50g R=H, R'=CF_3

53a R=OMe, R'=Me
53b R=OMe, R'=Et
53c R=OMe, R'=n-prop
53d R=OMe, R'=n-but
53e R=OMe, R'=cyclo-C_3H_5
53f R=OMe, R'=cyclo-C_4H_7
53g R=OMe, R'=CF_3



51a R=H, R'=Me
51b R=H, R'=Et
51c R=H, R'=n-prop
51d R=H, R'=n-but
51e R=H, R'=cyclo-C_3H_5
51f R=H, R'=cyclo-C_4H_7
51g R=H, R'=CF_3

54a R=OMe, R'=Me
54b R=OMe, R'=Et
54c R=OMe, R'=n-prop
54d R=OMe, R'=n-but
54e R=OMe, R'=cyclo-C_3H_5
54f R=OMe, R'=cyclo-C_4H_7

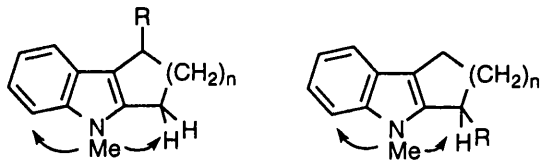
The amides **49** - **54** were purified by spinning plate chromatography on silica gel and were identified by means of nmr, ir and mass spectroscopy. The racemic mixture of the melatonin analogue **53 a** was resolved on a chiral analytical HPLC column. Although the amount of separated amide (0.001 g) was large enough for biological testing the absolute configuration could not be established. Attempts to separate the enantiomers on a larger scale by forming a diastereomeric salt of the amines **47** or **48** with D-camphorsulphonic acid or D-mandelic acid were not successful due to the

small quantities of compounds (0.5 g) involved which caused problems in recrystallising the salts.

II.1.3 Structure Elucidation of the Cycloalkan[b]indoles

Empirically the regiochemistry of the Bischler products is dictated by the N-methyl group of the anilines which should direct the ester group to the opposite side of the pyrrole ring to form the tricyclic esters **41** and **42**. Although crystal structure analysis of **53g** revealed that the substituent orientation of the annelated cycloalkane ring was as predicted it was crucial to verify the structure of all six classes of melatonin analogues (**49-54**)

Initially an attempt was made to establish the regiochemistry of the Bischler product by NOE-experiments, irradiating the N-methyl group of the pyrrole ring.



65 **66**

Figure 6: Expected NOE interaction for the tricyclic Bischler products **65** and **66**

In the case of the targeted substitution pattern depicted in the general structure **65**, irradiation of the N-methyl group should enhance the signal of the adjacent methylene protons whereas regioisomers **66** were expected to show an NOE effect of the adjacent methine proton. NOE experiments were carried with compounds showing distinct ^1H nmr signals for the protons in question. Figure 12 (Appendix) shows a typical NOE experiment carried out with the amide **45a**. The signals for methylene (δ=2.95 ppm), methine (δ=3.98 ppm) and methyl protons (δ=3.69 ppm) are well separated and not overlaid with other signals. However, no NOE effect was observed between the methyl group and aliphatic protons under various experimental conditions. Only the adjacent aromatic proton at δ=7.26 ppm showed some enhancement, allowing the assignment of the individual doublets of the typical aromatic signal pattern.

The aromatic protons of all compounds unsubstituted on the benzene ring give rise to a pair of doublets and to two doublets of doublets, overlapping to give a triplet. In

some cases a small ^4J coupling of ~1Hz was observed. Compounds with a methoxy substituent show three distinct aromatic signals (cf. fig. 13, appendix): a doublet with ^3J~8.5 Hz for H5, a doublet with ^4J~1.2 Hz for H8 and a doublet of doublets with both coupling constants for H6. ^1H nmr spectra of compounds **54a** and **50e** are included in the appendix to illustrate the coupling patterns of the benzylic and diastereotopic protons of the methylamino moiety (cf. fig. 14 and 15).

Since the adjacent N-methyl and methylene protons could not be connected through space by means of NOE experiments, different nmr techniques utilising connection through bonds between nuclei of the pyrrole ring and the methine or methylene group of the annelated carbocyclic ring were employed.

Initially a ^{13}C proton coupled spectrum of the amide **49c** was recorded to detect CH coupling between the nuclei C4a/H4 and C9a/H1 (fig. 7, R'=Me, R=$CH_2NHCOC_3H_7$, n=1). The signals for C4a (117.6 ppm) and C9a (147.2 ppm) were assigned by comparison with other 2,3-disubstituted indoles such as 1,2,3,4-tetrahydrocarbazole and by INEPT experiments[160]. However, the coupling pattern was too complex to extract a doublet for C4a (coupling to H4) and a triplet for C9a (coupling to H1) which would have established the position of the aminomethyl substituent.

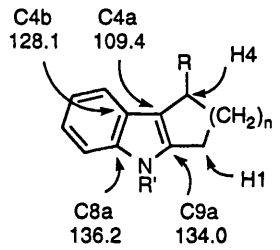


Figure 7: ^{13}C chemical shifts for 1,2,3,4-tetrahydrocarbazole (R, R'=H, n=2)[160]

The position of the substituent R in **49c** was finally established by a series of line sensitive INEPT experiments, in which the ^{13}C spins were labelled with ^1H polarisation and by J_{CH}. Irradiation at the frequency of the N-methyl group (3.66 ppm) with J=1.8 Hz labelled C8a and C9a (141.5 and 147.2 ppm), whereas irradiation at the frequency of the overlaid signal of methine and methylene proton (3.52 ppm) with J=8.0 Hz resulted in a large nmr signal for C4a (117.6 ppm) and a smaller signal for C9a (fig. 16, appendix). Combination of both INEPT experiments and comparison with reported ^{13}C nmr data of 2,3-disubstituted indoles[160] not only allowed the assignment of ^{13}C nmr signals to the individual carbon atoms of the

pyrrole ring but also established that the orientation of the aminomethyl side chain was in the desired position. For the alternative regioisomer an inverted peak intensity in the second INEPT experiment is expected.

For all of the six series of melatonin analogues INEPT experiments showed the presence of the targeted regioisomer. The INEPT spectra are depicted in the appendix (fig. 16 to fig. 21) and a few details are briefly discussed in the following paragraph.

In an attempt to avoid irradiation at frequencies of overlaid ^1H nmr signals the carboxamides **45c** and **46a-c** were used for the INEPT experiments. Irradiating at the frequency of the methine proton of **46b** at various coupling constants (J = 4-12 Hz) labelled only the adjacent C4a atom at δ 106 ppm (fig. 17, appendix).

A different result was obtained for the amide **45c** (fig. 18, appendix). At J = 4 Hz the distant carbon atoms C4b (127.6 ppm) and C9a (139.8 ppm) were labelled. With increasing coupling constant the signal for C4a (110.6 ppm) built up, whereas the signals for C4b and C9a decreased in intensity until they disappeared at J = 11 Hz. A similar result was obtained in the INEPT experiments of **46a** and **46c**, which at J = 8 Hz showed labelling for C4a and to a lesser extent for C9a (fig. 19 and fig. 20, appendix). In general, the signal for C4a was always enhanced at J > 8 Hz.

For the trifluoroacetamide **50g**, the electron withdrawing effect of the trifluoroacetyl moiety moves the chemical shift of the methylene group sufficiently to lower field to give a distinct signal which is not overlaid by the methine group. Irradiation at the frequency of the methylene group (3.83 ppm) labelled C4a (108.2 ppm) as the only carbon atom of the pyrrole ring (fig. 21, appendix). Additionally, the carbonyl C-atom at 157.4 ppm with the characteristic $^2J_{CF}$ coupling (37 Hz) was enhanced. The trifluoromethyl group gave a quartet at δ=117.3 ppm with $^1J_{CF}$=288 Hz.

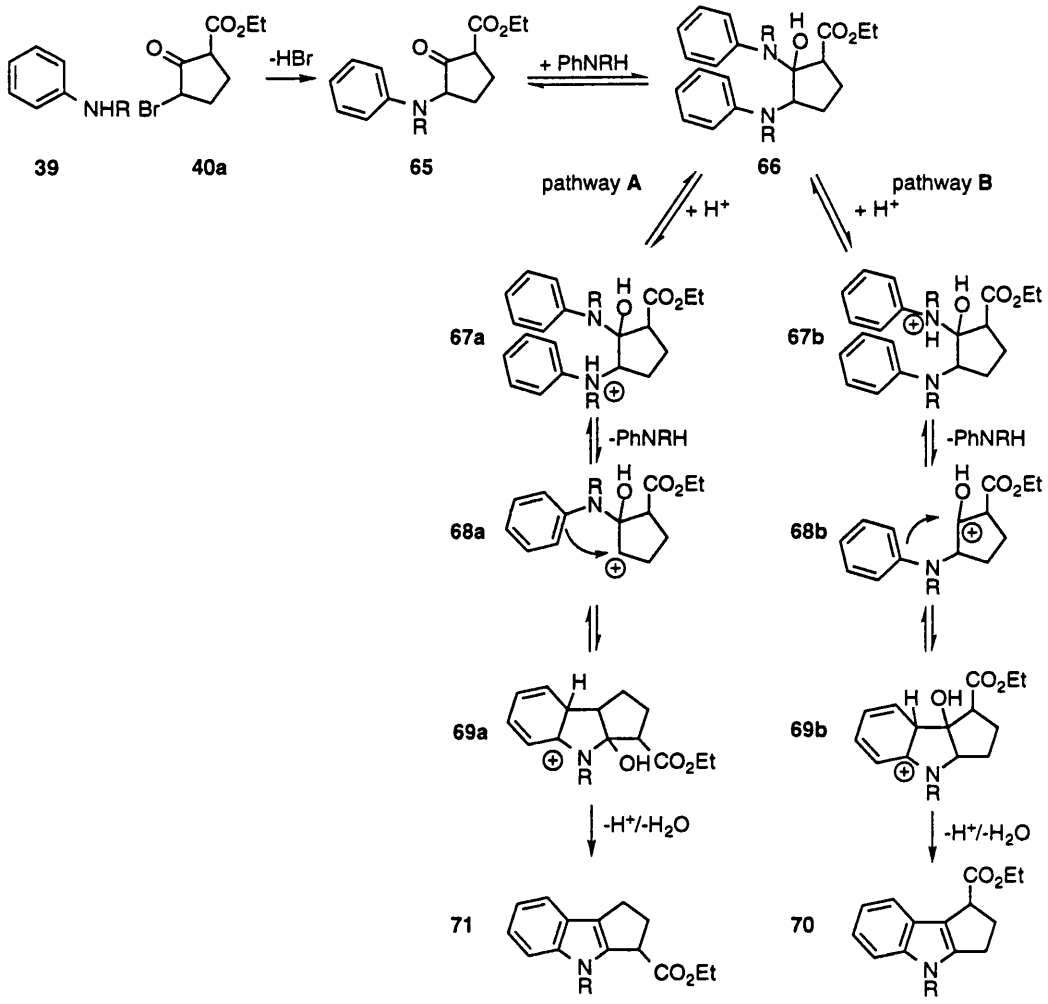
Some of the INEPT experiments also showed labelling of carbon atoms in the carbocyclic ring, but these were not further investigated (i.e. **50g**, fig. 21, appendix).

It is interesting to note that the variation of chemical shifts for carbon atoms in the pyrrole ring was minute in comparison to structural alterations of the heterocyclic system (i.e. additional 6-MeO moiety and various sizes of the carbocyclic ring). Only the chemical shift of C4a in the carboxamides **46a-c** exhibited a dependence from the ring size (120.0, 106.0 and 110.2 with increasing ring size), possibly caused by the different orientations of the anisotropic carbonyl group.

II.1.4 Mechanism of the Bischler Reaction

Various mechanisms for the Bischler reaction have been proposed and are summarised by the reaction between the aniline derivative **39** and 2-bromo-5-ethoxycarbonylcyclopentanone (**40 a**) (scheme 11)[161-164]. The initial α-anilinoketone **65** reacts with another molecule of the aniline component **39**, the latter having either been added in a catalytic amount or produced by the acid-catalysed cleavage of **65**. By radioactive marking, Weygand and Richter[164] confirmed earlier results obtained from cross-over experiments with differently substituted anilines that, under acid catalysis, the distribution of the aniline moiety equilibrates between the intermediates **68a** and **68b**, possibly via the dianiline **66**. It is usually observed that cyclisation of N-alkyl-α-anilino-ketones (**65**, R=alkyl) proceeds without apparent rearrangement via pathway **B**, whereas unsubstituted α-anilino-ketones (**65**, R=H) give rise to products resulting from apparent rearrangement via pathway **A**. A possible explanation for this observation might be the steric interaction between the N-alkyl group and a substituent such as the ethoxycarbonyl moiety. In order to reduce this interaction the intermediates **68b** and **69b** are favoured and result eventually the cyclisation product **70**. For R=H the steric interaction is minimal and the reaction proceeds via pathway **A**, possibly because of hydrogen bond formation between NH and the adjacent carbonyl group. The reactive intermediates **68** are cyclised to the indole ring by electrophilic attack of the carbocation at the ortho position of the aniline ring and subsequent aromatisation.

This mechanism accounts for the observed directing effect of the N-methyl group in the synthesis of tetrahydrocarbazoles, cyclohept[b]indoles and indole-3-acetic acids (cf. chp. III). The formation of **71** as a by-product in the synthesis of ethyl 4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indol-1-carboxylates (**41a** and **42a**) can be explained by the slightly reduced interaction between the N-methyl group and the substituents of the cyclopentane ring which causes a shift of the equilibrium towards the intermediate **68a** and **69a**.

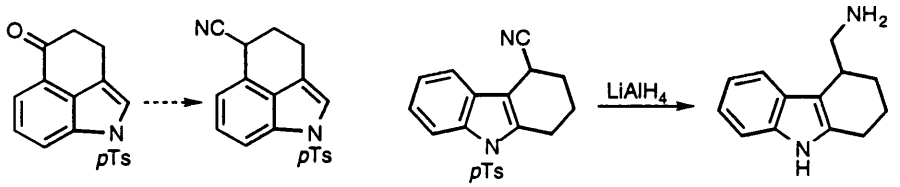


Scheme 11: Proposed mechanism for the Bischler reaction

II.1.5 Attempted alternative Synthesis of 1,2,3,4-Tetrahydrocarbazoles

All of the synthesised aminomethyl-cycloalkan[b]indoles **49-54** possess a N-methyl group which was essential to effect the regioselectivity of the cyclisation in the Bischler reaction. Since melatonin is not N-alkylated, an alternative synthesis of 1,2,3,4-tetrahydrocarbazoles which utilises a N-protecting group that can be easily removed towards the end of the reaction sequence was attempted.

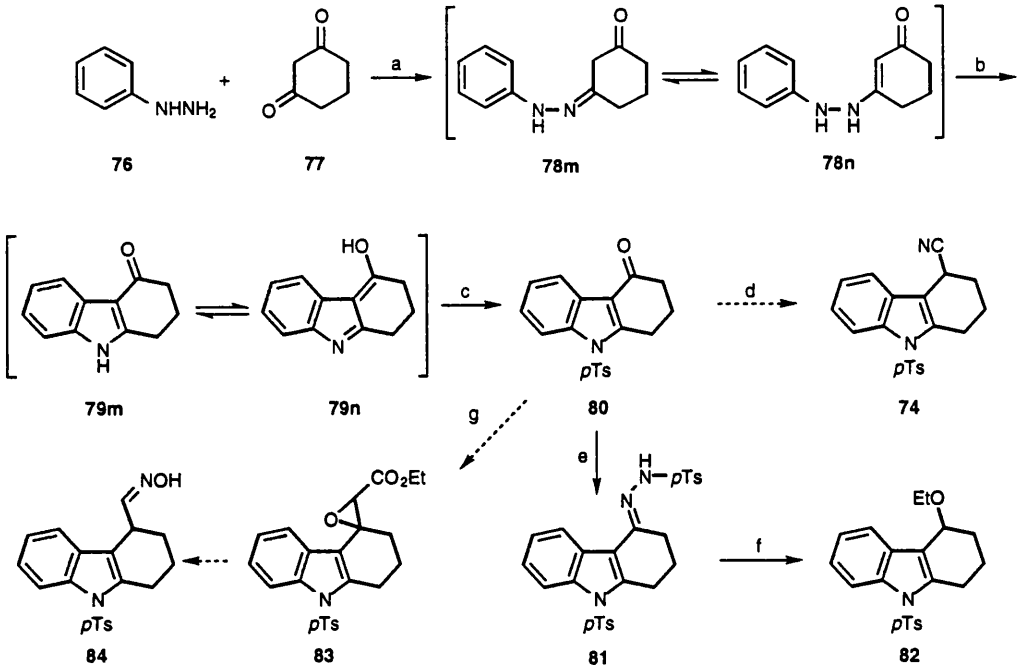
Based on the synthesis of 1,3,4,5-tetrahydro-1-(*p*-tolylsulphonyl)benz[cd]indole-5-carbonitrile (**73**), which has been reported by Guyett and co-workers[165], the synthesis of the analogous nitrile **74** was investigated. Reduction of the nitrile with lithium aluminium hydride should simultaneously install the targeted 4-aminomethyl moiety and remove the *p*-tolylsulphonyl protecting group.



72 **73** **74** **75**

In analogy to the synthesis of Guyett *et al.*, which commenced from the ketone **72**, 2,3-dihydrocarbazol-4(1H)-one (**79**) had to be prepared. Following a method reported by Clemo and Felton phenylhydrazine (**76**) was condensed with 1,3-cyclohexandione (**77**) to give the monophenylhydrazone (**78**)[166]. This monohydrazone is in equilibrium with the enamine **78n** and a conjugated imine-enol which renders the second carbonyl group unreactive towards phenylhydrazine. The presence of an enamine/enol is indicated by nmr spectra which show signals for a sp^2 non-aromatic CH group (δ=4.68 ppm (s); δ=95.8 ppm (d)). Further, this tautomerism explains the regioselectivity of the subsequent Fischer reaction, in which the monohydrazone was cyclised with 40% sulphuric acid to result 2,3-dihydrocarbazol-4(1H)-one (**79**). The ketone is predominantly tautomerised to the enol **79n**, which is indicated by the absence of a carbonyl absorption in the ir-spectrum. To prevent this enolisation which renders the carbonyl group unreactive towards its conversion into a nitrile functionality, **79** was protected as N-tosyl derivative[167]. Because of the increased acidity of the indolic NH-proton the N-tosyl derivative **80** was obtained in good yield by reacting the parent ketone with *p*-toluenesulphonyl chloride in the presence of potassium carbonate. The ir-spectrum of the tosylate shows the expected vinylogous carbonyl absorption at 1655 cm^{-1}.

Three different synthetic routes were employed in an attempt to convert the carbonyl group into the side chain. Firstly, an attempt was made to install the nitrile moiety by a one-step synthesis using tosylmethyl-isocyanide (TosMIC)[168]. It was hoped that the mildly alkaline conditions of this method would not deprotect the indole; however, since no reaction was observed at 25 °C after 3 days, the reaction mixture was stirred at 45 °C for further 3 days. After this time the tosyl group was completed saponified and the only isolated product was the ketone **79**.



Scheme 12: Attempted synthesis of 4-carbonitrile-1,2,3,4-tetrahydro-9-*p*-tolylsulphonyl-carbazole (**74**)

a 10% aq HOAc, 50 °C, 10 min; b 40% H_2SO_4, 100 °C, 90 min;

c *p*TsCl, K_2CO_3, Δ, 4 h; d *p*$TsCH_2NC$, KO^tBu, MeOH, 45 °C, 65 h;

e $C_7H_7NHNH_2$, *p*TsOH, THF, Δ, 3 h; f KCN, EtOH, Δ, 24 h;

g $ClCH_2COOEt$, KO^tBu, benzene, Δ, 1 h

In the second synthesis, the carbonyl group was converted into a tosylhydrazone in order to increase its reactivity towards attack by cyanide[169]. Under acid catalysis the hydrazone **81** was obtained in good yield. Reaction with potassium cyanide in refluxing ethanol yielded the ethylether **82**, rather than the desired cyanide, via formation of an intermediate carbene. Analysis of the unexpected product by mass spectroscopy showed the fragmentation products due to loss of ethoxy and tosyl group. Additionally, the nmr spectra exhibited the typically signal pattern for 4-substituted 1,2,3,4-tetrahydrocarbazoles which had been previously observed for compounds **45b** or **50**. Instead of being displaced by the nucleophilic nitrile the hydrazone was deprotonated and subsequently generated a carbene as in the Stevens-Bamford procedure. This carbene reacted with ethanol to give a N-tosyl derivative which was not saponified under the basic reaction conditions. Apparently, the carbonyl moiety in **80** has an activating effect on the deprotection of the tosyl group under basic conditions.

The third attempt to synthesise the oxime **84** followed the method reported by Guyett *et al.* who converted the ketone **72** into a spiro-oxirane under conditions of the Darzens condensation. In the reported procedure the oxirane was then reacted with hydroxylamine to give an oxime, which was finally dehydrated to the nitrile **73**. Even after prolonged reaction times no formation of the spiroester **83** was observed. Instead the tosyl group was saponified to yield the ketone **79**.

II.1.6 Biological Results

The binding affinity of the synthesised cycloalkan[b]indole analogues of melatonin (**49-54**) was determined in a 2-[^{125}I]iodomelatonin radioligand binding assay in chick brain membranes (cf. chp. VIII). For a few compounds the biological activity was also assessed in the *Xenopus* dermal melanophore assay (cf. chp. VIII). With the exception of the tetrahydrocarbazole **53a**, racemic mixtures were used for testing.

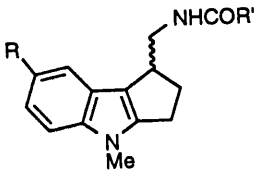
Structure	No	R	R'	K_i/nM	Act.
	**49a**	H	CH_3	516±33	NT
	49b	H	C_2H_5	272±33	NT
	49c	H	n-C_3H_7	239±24	NT
	49d	H	n-C_4H_9	11200±1000	NT
	49e	H	c-C_3H_5	5100±500	NT
	49f	H	c-C_4H_7	5700±600	NT
	49g	H	CF_3	>10000	NT
	52a	OMe	CH_3	161±20	NT
	52b	OMe	C_2H_5	16±2.2	NT
	52c	OMe	n-C_3H_7	23±3.6	NT
	52e	OMe	c-C_3H_5	459±46	NT

Table 1: Binding affinity and biological activity of N-acyl-1-aminomethyl-1,2,3,4-tetrahydro-cyclopent[b]indoles **49** and **52**

NT = not tested

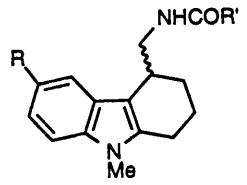
Structure	No	R	R'	K_i/nM	Act.
	**50a**	H	CH_3	227±39	Ant
	50b	H	C_2H_5	204±34	Ant
	50c	H	n-C_3H_7	215±33	Ant
	50d	H	n-C_4H_9	>10000	NT
	50e	H	c-C_3H_5	4460±710	NT
	50g	H	CF_3	>10000	NT
	53a	OMe	CH_3	0.97±0.20	Ag
	53b	OMe	C_2H_5	1.44±0.18	NT
	53c	OMe	n-C_3H_7	0.378±0.056	Ag
	53d	OMe	n-C_4H_9	82±11	NT
	53e	OMe	c-C_3H_5	30±3.7	NT
	53f	OMe	c-C_4H_7	271±9	Ag
	53g	OMe	CF_3	1.98±0.38	NT

Table 2: Binding affinity and biological activity of N-acyl-4-aminomethyl-1,2,3,4-tetrahydrocarbazoles **50** and **53**

Ant = antagonist, NT = not tested, Ag = agonist

Comparison of the binding affinities of the melatonin analogues **52a** (K_i 161 nM), **53a** (K_i 0.97 nM) and **54a** (K_i 24 nM) clearly indicates that the conformation of the flexible N-acetyl-aminoethyl side chain of melatonin in the receptor complex is best represented by its partly restricted conformation in the tetrahydrocarbazoles (cf. fig. 8). Interestingly the individual enantiomers of the amide **53a** showed a considerable difference in binding affinity (K_i 37.1±6 nM and 484±42 pM) indicating that the receptor site can discriminate between chiral ligands, although melatonin is achiral.

Taking into account that the additional N-methyl group reduces the affinity to the melatonin binding site (Melatonin: K_i 0.58 nM; N-methylmelatonin: K_i 25±4 nM, cf. tab. 5, appendix), the binding affinities might be improved 50-fold by testing analogues lacking a N-alkyl group. In the line of earlier SAR studies most of these cycloalkan[b]indole analogues show a maximum binding affinity for the n-butanoyl group. A drastic improvement in binding affinity was observed from N-acetyl- to N-butanoyl-cyclohept[b]indole **51a** to **51c** (K_i 424±36 nM and 84±9 nM, respectively). However, in some cases, such as the tetrahydrocarbazoles **50a** to **50c** and **53a** to **53c**, the binding affinities for the N-acetyl to N-butanoyl derivative are comparable

within experimental error. Further increase of the N-acyl group results in a sharp drop of affinity for the N-pentanoyl and the cyclobutancarbonyl moiety.

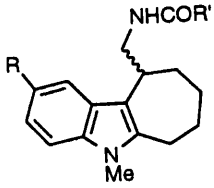
Structure	No	R	R'	K_i/nM	Act.
	**51a**	H	CH_3	424±36	NT
	51b	H	C_2H_5	129±12	NT
	51c	H	n-C_3H_7	84±9	NT
	51d	H	n-C_4H_9	8300±700	NT
	51e	H	c-C_3H_5	1220±180	NT
	51f	H	c-C_4H_7	1690±340	NT
	51g	H	CF_3	15800±700	NT
	54a	OMe	CH_3	24±3.5	NT
	54b	OMe	C_2H_5	7±0.8	NT
	54c	OMe	n-C_3H_7	10.3±1.6	NT
	54d	OMe	n-C_4H_9	471±92	NT
	54e	OMe	c-C_3H_5	44.7±6.9	NT
	54f	OMe	c-C_4H_7	144.8±23.9	NT

Table 3: Binding affinity and biological activity of N-acyl-10-aminomethyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indoles **51** and **54**

NT = not tested

The importance of the methoxy group for binding and biological activity is confirmed for these tricyclic analogues. It is interesting to note that the methoxy group increases the binding affinity for the tetrahydrocarbazole analogues **53** about 200-fold, whereas the increase for the cyclopent[b]indoles **52** and cyclohept[b]indoles **54** is smaller, 5-15 fold and 10-30 fold, respectively. So far, only a few of these novel melatonin analogues have been tested for their biological activity. The results for the tetrahydrocarbazoles **50** and **53** indicate that compounds lacking the methoxy group act as antagonists in the *Xenopus* dermal melanophore assay. The N-propanoyl derivative **50b** exhibits the best binding affinity (K_i=204 nM) and is therefore a valuable lead compound for the design of further melatonin antagonists. It is tempting to suggest that the binding affinity of the derivative of **50b** lacking the N-methyl group will be 50-fold improved.

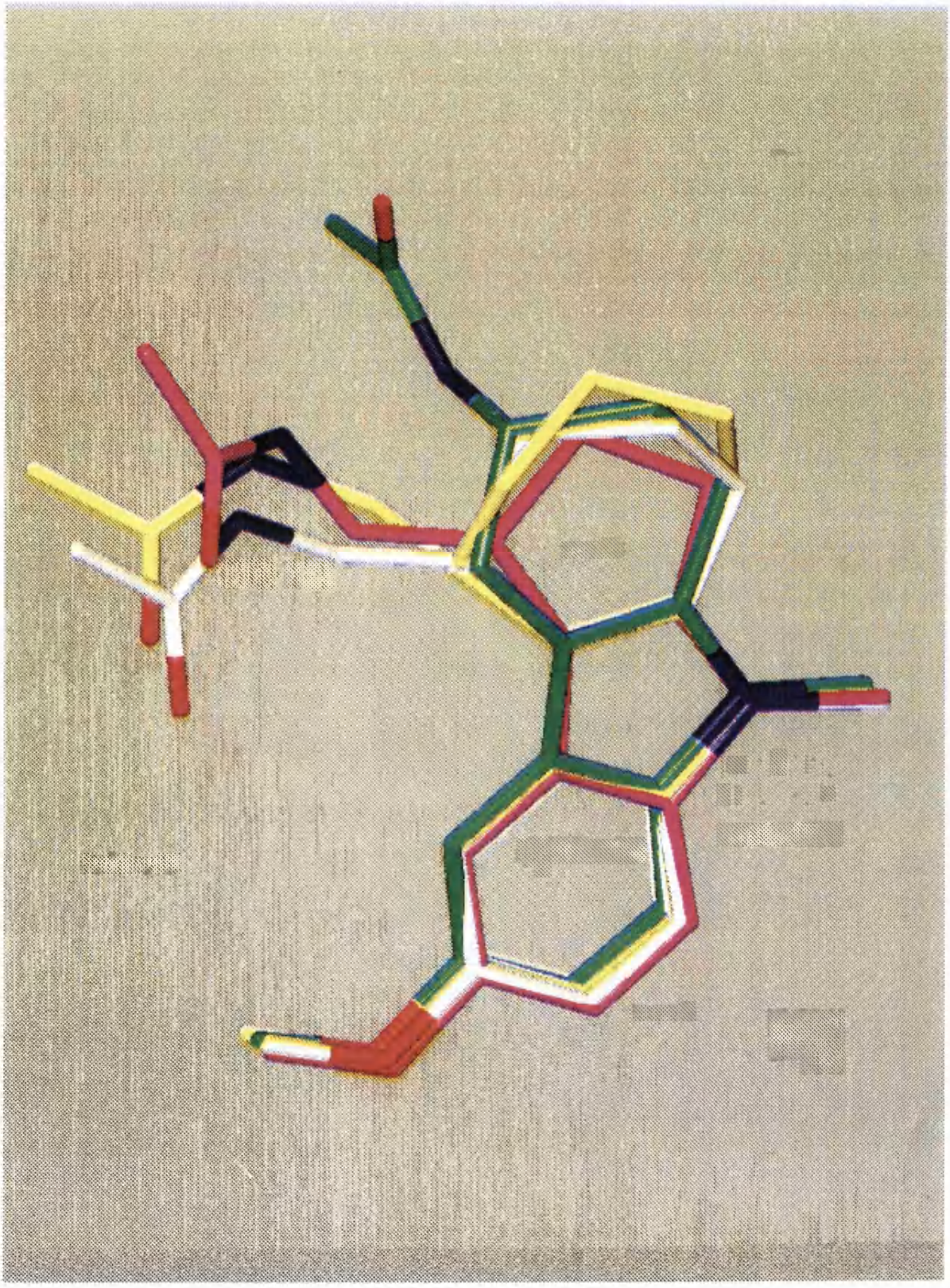
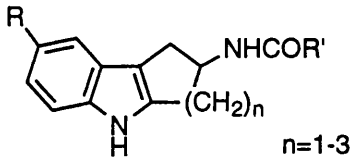


Figure 8: Energy minimised structures of N-acetyl-aminomethyl-cycloalkan[b]indoles **52a** (purple), **53a** (white), **54a** (yellow) and N-acetyl-3-amine-6-methoxy-1,2,3,4-tetrahydrocarbazole (**107a**, green)

II.2 N-Acylamine-cycloalkan[b]indoles

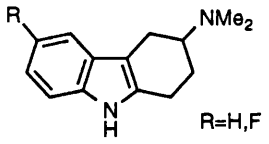
II.2.1 Introduction

In comparison to the previously discussed N-acyl-aminomethyl-cycloalkan-[b]indoles **19**, the conformation of the amidoethane side chain in N-acylamine-cycloalkan[b]indoles **20** is more restricted and the distance between the putative pharmacophores of melatonin is increased.

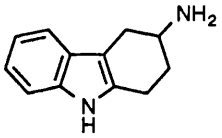


20 R=OMe, R'=Me

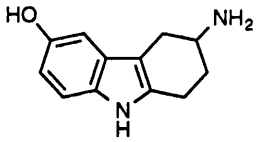
Several 3-amino-1,2,3,4-tetrahydrocarbazole derivatives have been described in the literature as dopamine agonists (**85**)[170], thromboxane A2-antagonist (**86**)[171] and inhibitors of serotonin uptake into hypothalamic synaptosomes (**87**)[172]. The functional diversity is achieved by alkylation of the amino moiety and/or substitution of the indolic benzene ring.



85

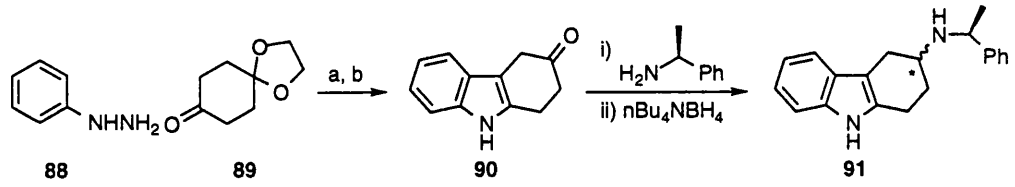


86



87

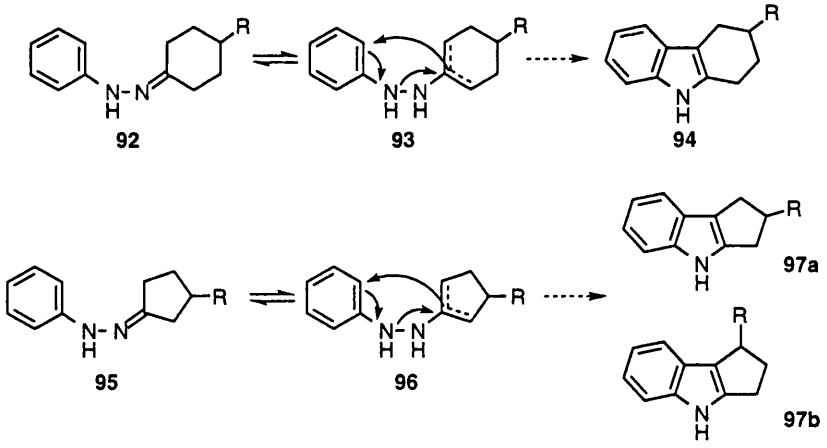
Generally, the syntheses are accomplished by applying Fischer methodology, reacting *para*-substituted phenylhydrazine with an appropriately 4-substituted cyclohexanone derivative. The substituent of the cyclohexanone building block is either a protected amine, such as an amide[142], a protected ketone[173] or an acetoxy moiety[174,175]; the latter two functionalities require subsequent transformation into the amine group. An interesting synthesis was patented by Alexander and Mooradian who combined the elaboration of the amine functionality with the resolution of the racemic mixture (scheme 13). In the last step the secondary amine **91** was debenzylated by catalytical hydrogenation[142]. Alternatively, the amines were resolved by forming diastereomeric salts with various enantiomerical pure chiral acids, such as D-camphorsulphonic acid and D-mandelic acid.



Scheme 13: Synthesis of 3-amine-1,2,3,4-tetrahydrocarbazoles

a ZnCl, benzene, Δ, 90 min; b *p*TsOH, H_2O, acetone, Δ, 4h

Whereas several methods exist for the preparation of the tetrahydrocarbazolamine **86**, no syntheses for 2-amino-1,2,3,4-tetrahydro-cyclopent- or 9-amino-5,6,7,8,9,10-hexahydro-cyclohept[b]indole and derivatives such as **20** (n=1 and n=3) have so far been reported. The synthesis of theses latter amines is complicated by the desired substitution pattern. In the case of the tetrahydrocarbazole, the intermediate hydrazone **92** is symmetrically substituted; consequently, cyclisation of the enamine **93** in either direction results in the same product (scheme 14).



Scheme 14: Comparison of the Fischer syntheses of tetrahydrocarbazole and cyclopent[b]indole derivatives

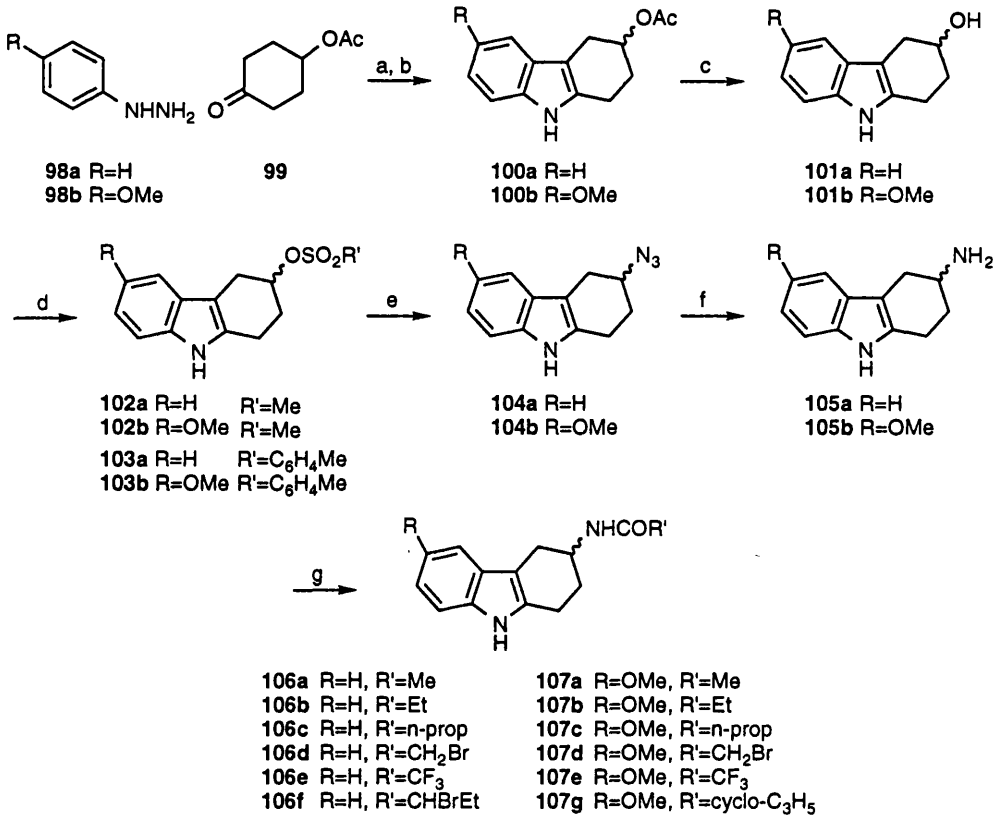
In contrast to the tetrahydrocarbazole intermediates, the hydrazones and enamines formed in the Fischer synthesis of cyclopent- and cyclohept[b]indoles possess an unsymmetrical substitution pattern in the carbocyclic ring which theoretically yields a mixture of regioisomers (scheme 14). The enamine formation has been controlled by using electron withdrawing groups such as carboxylic acids, which leads to the

selective generation of 1,2,3,4-tetrahydro-cyclopent[b]indole-2-carboxylic acid (**97a**, R=COOH)[176].

II.2.2 Synthesis of N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles

The synthesis of the 3-amine-1,2,3,4-tetrahydrocarbazoles **105**, which were subsequently acetylated to the melatonin analogues, was carried out as reported by Bird and Wee[175]. In their approach the heterocyclic system is constructed by Fischer indole synthesis to give 3-acetoxy-1,2,3,4-tetrahydrocarbazoles. The functionality at position 3 of the carbazole ring is subsequently modified to the amine group.

Alternatively, the amines can be obtained by lithium aluminium hydride reduction of the oxime obtained from ketones such as **90**.



98a R=H
98b R=OMe

99

100a R=H
100b R=OMe

101a R=H
101b R=OMe

102a R=H R'=Me
102b R=OMe R'=Me
103a R=H R'=C_6H_4Me
103b R=OMe R'=C_6H_4Me

104a R=H
104b R=OMe

105a R=H
105b R=OMe

106a R=H, R'=Me
106b R=H, R'=Et
106c R=H, R'=n-prop
106d R=H, R'=CH_2Br
106e R=H, R'=CF_3
106f R=H, R'=CHBrEt

107a R=OMe, R'=Me
107b R=OMe, R'=Et
107c R=OMe, R'=n-prop
107d R=OMe, R'=CH_2Br
107e R=OMe, R'=CF_3
107g R=OMe, R'=cyclo-C_3H_5

Scheme 15: Synthesis of N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles

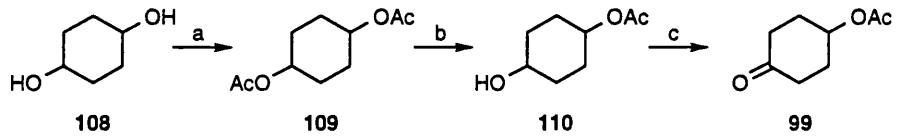
a HOAc, EtOH, Δ, 20 min; b HOAc, Δ, 4 h; c NaOH, aq. EtOH, Δ, 6 h;

d $MeSO_2Cl$ or $MeC_6H_4SO_2Cl$, pyr., 20 °C, 24 h; e NaN_3, EtOH, H_2O, Δ, 12 h;

f $LiAlH_4$, THF, 20 °C, 24 h;

g R'COCl or $(R'CO)_2O$, Et_3N, CH_2Cl_2, 20 °C, 4 h

The *para*-substituted phenylhydrazines **98** are commercially available while 4-acetoxycyclohexanone (**99**) was synthesised from 1,4-cyclohexanediol (**108**) in three step. Initially the diol **108** was quantitatively esterified by acetic anhydride to the diacetate **109**, which was saponified with 0.9 equivalents of potassium hydroxide to give a mixture of monoacetate **110** and diacetate **109**[177]. This mixture was easily separated, since the diacetate crystallised in the cold, whereas the monoacetate was a liquid. The oxidation of 4-acetoxy-cyclohexanol to the ketone **99** was achieved in good yield according to a method reported by Sondheimer and Jones, who reacted 4-benzoate-cyclohexanol with chromium trioxide in acetic acid[178].



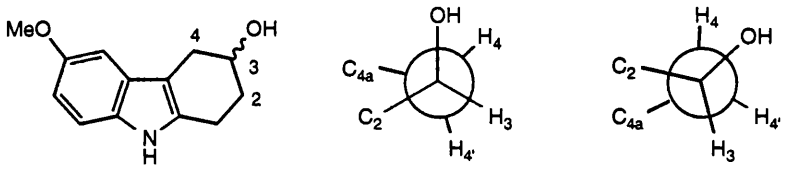
108 **109** **110** **99**

Scheme 16: Synthesis of 4-acetoxycyclohexanone (**99**)

a Ac_2O, Δ, 1 h; b KOH, aq. EtOH, 50 °C, 30 min; c CrO_3, HOAc, 25 °C, 18 h

On the first step of the Fischer synthesis 4-acetoxycyclohexanone (**99**) was condensed with the phenylhydrazines to give hydrazones, which were not isolated but directly converted into the tetrahydrocarbazole acetates **100a** and **100b**. The Fischer cyclisation products were identified by mass spectroscopy and the characteristic ^1H nmr signal pattern for the aromatic protons of the indole ring. After saponification of the acetate moiety under standard conditions, the crude alcohols **101** were converted into the mesylate **102** or tosylate **103**. For the parent compound **101a** the yield of the mesylate formation was higher than for the tosylate (85% versus 66%). In the case of 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (**101b**) the mesylate was formed in only 49 % and no tosylate was obtained. The product of the attempted tosylation and the by-product of the mesylation showed mass and ir spectra identical to those of the starting material. However, a considerable change in the chemical shift of C3 (δ = 67.5 to 56.7 ppm) and H3 (δ = 4.22 to 4.52 ppm) is observed, [redacted]. The conformation of the cyclohexene ring is determined by coupling constant analysis of the ^1H nmr signal for the diastereotopic H4 protons coupling to H3, which give rise to two doublets of doublets (cf. fig. 6 and fig. 22, appendix). In detail, a small coupling constant of ^3J = 4.8 Hz (dd at 3.31 ppm) is observed for H4' coupling to H3, which in both conformers enclose a dihedral angle of $\phi \sim 60°$. The larger coupling constant of 6.8 Hz

(dd at 3.05 ppm) represents the mean value of coupling constants for H4 in the axial ($\phi \sim 60°$, J ~ 4 Hz) and the equatorial alcohol ($\phi \sim 180°$, J ~ 10 Hz), which indicates a rapid equilibrium between both conformers.



101b axial alcohol equatorial alcohol

Figure 6: Possible orientation of the hydroxy group in 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (**101b**)

In a modification of the synthesis of Bird and Wee, the mesylates **102** were converted into 3-azide-1,2,3,4-tetrahydrocarbazoles (**104**) by the reaction with sodium azide in aqueous ethanol[175]. Optimal results for the nucleophilic displacement were obtained on a smaller scale of 3.5 mmol of mesylate. The crude azides showed the characteristic azide absorption band in the ir spectrum at $\nu = 2020\ cm^{-1}$.

In contrast to the original method, where the azide is hydrogenated in the presence of palladium-on-charcoal[175], the amines **105** were obtained by lithium aluminium hydride reduction of the azide. As previously described the amines were isolated via their hydrochloride salts and were directly acylated by standard procedures with various carboxylic acid anhydrides or acyl chlorides. Both amines were characterised by the strong NH_2 absorption band in the ir spectrum.

The amides **106** and **107** were purified by spinning plate chromatography on silica gel and were identified by means of nmr, ir and mass spectroscopy.

In the ^1H nmr spectrum the 6-methoxy-carbazoles **107** show the previously discussed coupling pattern for the aromatic protons (cf. chp. II.1.3). Generally, the signal for H5 at 6.8 ppm is a doublet (^4J = 2.5 Hz) resulting from the long-range coupling with H7 at 6.7 ppm (^4J = 2.5 Hz, ^3J = 8.7 Hz). The proton H7 is also coupled to H8 at 7.2 ppm (^3J = 8.6 Hz) to give a doublet of doublets (cf. fig. 23, appendix). In contrast to the N-acyl-aminomethyl amides, which gave a broad triplet for the amide proton, the N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles show a broad doublet at 5.5 - 6.5 ppm reflecting the coupling of the amide proton with H3. The signal for H3 is usually a multiplet at $\delta \sim 4.5$ ppm.

All the 3-substituted carbazoles synthesised show two doublets of doublets at about 2.5 ppm and 3.0 ppm, representing the protons H4. As has been shown for the alcohol **101b**, the protons at C4 give rise to two doublets of doublets with a large geminal coupling constant of 15.0 Hz and a smaller vicinal coupling to H3 (cf. fig. 23, appendix). It is interesting to note that, for the series of 6-methoxy-tetrahydrocarbazoles **107**, the vicinal coupling constant for H4 at 2.5 ppm increases gradually with the size of the amide group (R = Me, J = 6.3 Hz; R = C_3H_7, J = 6.6 Hz; R = CH_2Br, J = 6.8 Hz). The larger amide group shifts the conformational equilibrium towards the equatorial amide, which results an increased mean dihedral angle between H4 and H3 and therefore an increased coupling constant.

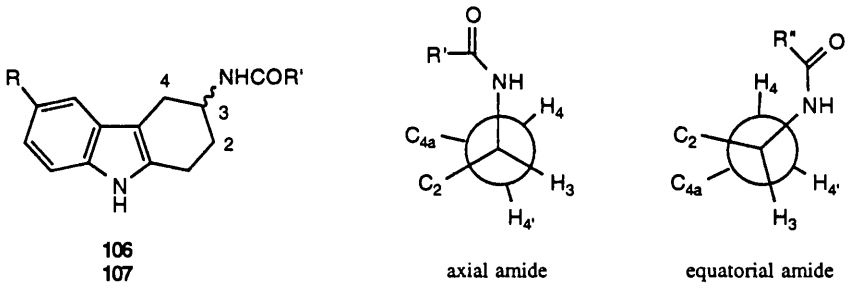


Figure 7: Possible conformations of the tetrahydrocarbazoles **106** and **107**

Mass spectra of the amides **106** and **107** show the common fragmentation of the amide group (NHCOR), which gives rise to the most intense peak at m/z = 169 and 199 for the parent carbazole and the 6-methoxy derivative, respectively. The same fragmentation pattern was also observed for N-acyl-aminomethyl-cyclopent[b]indoles (**19**), the only exception being N-trifluoroacetyl amides, such as **49g**, which lost the trifluoroacetyl group ($COCF_3$).

II.2.3 Biological Results

Racemic mixtures of the tetrahydrocarbazole analogues of melatonin **106** and **107** were tested for their binding affinity for the melatonin binding site in chick brain and their biological activity in the *Xenopus* dermal melanophore assay (cf. chp. VIII). In the 2-[^{125}I]iodomelatonin radioligand binding assay the melatonin analogue N-acetyl-3-amine-6-methoxy-1,2,3,4-tetrahydrocarbazole (**107a**, K_i 219 nM) shows a 300 times smaller binding activity than melatonin and is therefore slightly less active than the cyclopent[b]indole analogue **52a**. Obviously the conformational restriction of the

N-acyl-ethaneamine side chain into the tetrahydrocarbazole system moved the amide pharmacophore further away from the receptor pocket. The ester analogue **100b** showed no binding affinity (K_i > 10 μM) emphasising the importance of the amide group for conveying affinity to the receptor (cf. tab. 23, appendix).

Similar to the cycloalkan[b]indole analogues binding affinity is increased by elongating the amide side chain. However, optimal binding affinity is reached with the N-propanoyl and not the N-butanoyl group. The decreased binding activity can also be counterbalanced by introducing the reactive N-bromoacetyl group (K_i 8.3±1.3 nM), which has been used for alkylation of the receptor proteine[107] (cf. chp. I.6). In analogy to the cycloalkan[b]analogues of melatonin, carbazoles with a 6-methoxy group bind about 50 times more strongly to the receptor than compounds lacking this functionality.

In the *Xenopus* melanophore assay tetrahydrocarbazoles lacking the 6-methoxy group showed little (**106b** and **106d**, EC_{50} >> 10 μM) or no (**106c**) agonist activity, although the propanoyl (**106b**) and bromoacetyl (**106d**) derivatives having affinities for the chick brain receptor of < 1μM. By contrast, the compounds with the 6-methoxy group (**107a**, **107c**, **107d**) gave significant pigment aggregation (cf. fig. 8). Interestingly, the bromoacetyl derivative **107d** (K_i 8.3 nM) aggregated pigment at low concentration (10^{-10} - 10^{-7} M) and dispersed it at high concentration (10^{-6} - 10^{-5} M) (cf. fig. 8). This unusual observation may have a number of explanations. First, since this analogue is chiral one enantiomer may act as an agonist at the receptor site and the other as an antagonist. The analogues **107a** and **107c**, however, showed a normal aggregation response. Second, the reversal of response may relate to the previously reported reactivity of the bromoacetyl side chain. High concentrations of the compound may non-specifically alkylate intracellular melanophore proteins essential in physically transporting pigment granules. This might also explain why the bromoacetyl analogue **106d**, which showed little agonist activity, significantly reversed the aggregation action of melatonin despite its low binding affinity to the receptor (K_i 740 nM). Another reason for the divergence between binding potency and biological activity might be an emerging difference between the melatonin receptor in chick brain and *Xenopus* melanophore. Comparison between the binding affinities and biological activities in the 6-methoxy series (**107**) and the 6-H series (**106**) reveals, that the methoxy group is important for binding and agonistic activity in this class of melatonin analogues. This finding is in accord with the Heward and Hadley hypothesis[114].

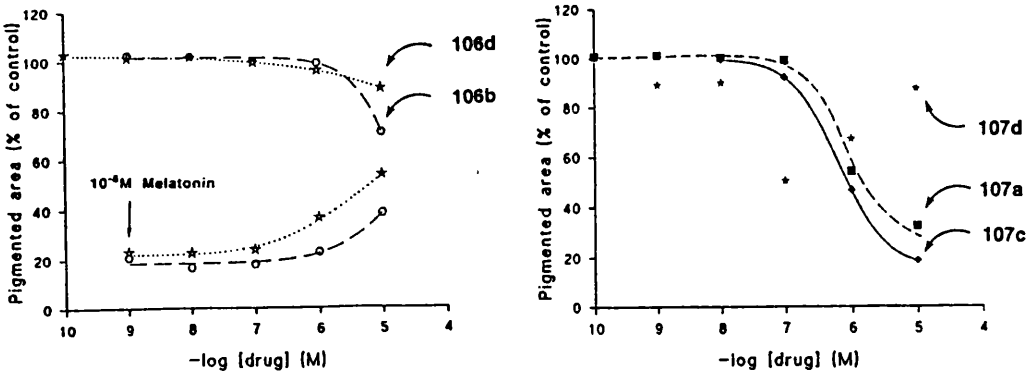


Figure 8: Pigment aggregation response for the tetrahydrocarbazoles **106b,d** and **107a,c,d**

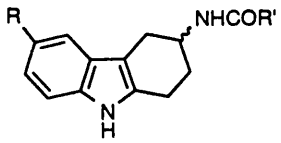
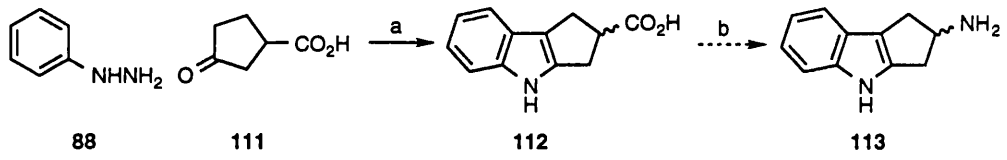
Structure	No	R	R'	K_i/nM	Act.
	**106a**	H	CH_3	5350±810	NT
	106b	H	C_2H_5	436±105	part Ag
	106c	H	n-C_3H_7	1060±160	NE
	106d	H	CH_2Br	740±150	part Ag
	106e	H	CF_3	4630±1080	NT
	106f	H	$CHBrC_2H_5$	>10000	NT
	107a	OMe	CH_3	219±50	Ag
	107b	OMe	C_2H_5	41±6	NT
	107c	OMe	n-C_3H_7	560±110	Ag
	107d	OMe	CH_2Br	8.3±1.3	(Ag)
	107e	OMe	CF_3	102±22	NT
	107g	OMe	c-C_3H_5	570±112	NT

Table 4: Binding affinity and biological activity of N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles **106** and **107**

NT = not tested, NE = not effective at 10 μM, part Ag = partial agonist

II.2.4 Attempted Syntheses of 2-Amine-1,2,3,4-tetrahydro-cyclopent[b]indole

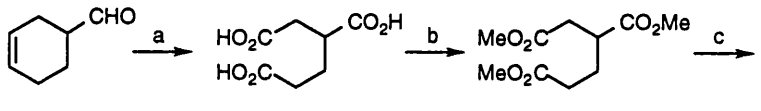
As mentioned in the introduction to this chapter, the Fischer reaction is usually of limited value for the synthesis of 2-substituted 1,2,3,4-tetrahydro-cyclopent[b]indoles, as there is little regioselectivity on the cyclisation step, which leads to a mixture of 2- and 1-substituted isomers. One exception is, however, the regioselective synthesis of 1,2,3,4-tetrahydro-cyclopent[b]indole-2-carboxylic acid (**112**), in which phenylhydrazine (**88**) was condensed with 3-carboxy-cyclopentanone (**111**). The intermediate hydrazone was reacted *in situ* to give the tricyclic acid[176]. Since the acid was obtained in good yield, it was planned to extend this synthesis and to convert the carboxyl functionality into an amine group by one carbon degradation methods, such as the Curtius reaction.



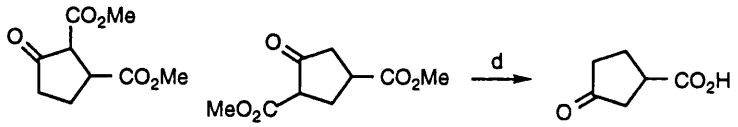
88 111 112 113

Scheme 17: Planned synthesis of 2-amine-1,2,3,4-tetrahydro-cyclopent[b]indole (**113**) a HOAc, MeOH, Δ, 4 h; b Schmidt reaction: NaN_3, H_2SO_4

The required 3-carboxyl-cyclopentanone (**111**) was obtained from commercially available 1,2,3,6-tetrahydrobenzaldehyde (**114**) in a 4-step reaction sequence (scheme 18).



114 115 116



117 111

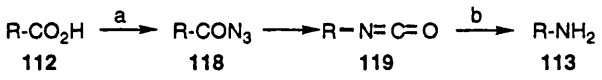
Scheme 18: Synthesis of 3-carboxyl-cyclopentanone (**111**)

a aq. HNO_3, $(NH_4)_3VO_4$, Cu, 55 °C, 4 h; b MeOH, H_2SO_4, ClC_2H_4Cl, Δ, 6h;
c NaH, toluene, 80 °C, 1h; d 2N H_2SO_4, Δ, 2h

In analogy to the reported oxidation of methyl cyclohex-3-ene-carboxylate, 1,2,3,6-tetrahydrobenzaldehyde was oxidised with nitric acid in the presence of ammonium vanadate and cuprous nitrate[179]. The temperature of the exothermic reaction has to be carefully controlled to avoid overheating and decomposition. The crude tricarboxylic acid showed the reported melting point and was converted into the trimethylester **116** by extractive esterification in 1,2-dichloroethane[179].

Earlier attempts to obtain this ester by condensing ethyl chloropropionate with diethyl succinate in the presence of various equivalents of base, such as sodium hydride, yielded either the starting materials or the elimination product ethyl acrylate. No reaction was also observed for the Michael addition of methyl acrylate and succinic anhydride or diethyl succinate in the presence of sodium methanolate.

Dieckmann condensation of the triester **116** gave a 3:2 mixture of isomers, which were not separated, since the subsequent acid-catalysed decarboxylation yielded the same product, 3-carboxyl-cyclopentanone (**111**)[180]. The ketone **111** was reacted with phenylhydrazine hydrochloride according to a method reported by Lacoume *et al.* to give the desired 1,2,3,4-tetrahydro-cyclopent[b]indole-2-carboxylic acid (**112**), which spectral information was identical to the reported data[176].



Scheme 19: Attempted conversion of the carboxylic acid **112** into the amine **113**

The first attempt to convert the carboxyl group into an amine moiety was made by using the Schmidt reaction, in which hydrazoic acid is added to the carboxylic acid **112**. Under catalyses of sulphuric acid a carbonylazide (**118**) is formed, which thermally rearranges to an isocyanate (**119**). On the last step of the reaction sequence the isocyanate is hydrolysed to yield the targeted amine **113**. However, the acid was insoluble in chloroform, which is normally used for the Schmidt reaction, and even after prolonged reaction times and elevated temperatures of 50 °C, no reaction was observed.

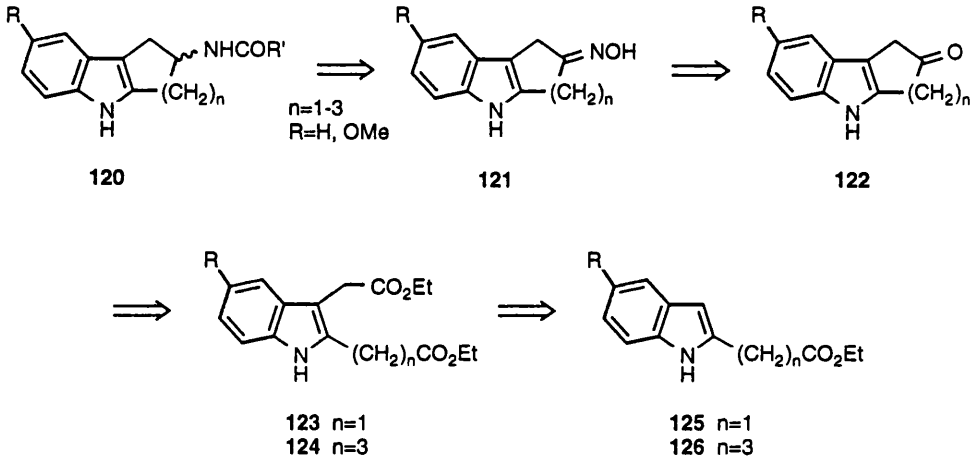
Since the acid **112** was found to be insoluble in most organic solvents and only slightly soluble in DMSO, an attempt was made to convert it into the carboxylate anion by neutralisation with triethylamine in acetone. Following a method reported by Weinstock, it was planned to react the carboxylate with methyl chloroformate to produce a mixed anhydride, which is then converted to the azide **118** by reaction with

sodium azide[181]. Again, the acid was not soluble under the reaction conditions, and the starting material was recovered. An attempt to form the anion by reaction with n-butyl lithium in THF was also unsuccessful.

In analogy to the method described for the synthesis of the amide **45b**, the conversion of the carboxylic acid **112** into an amide under more vigorous reaction conditions seemed possible[158]. The amide can subsequently be converted into the amine **113** by Hofmann rearrangement (cf. chp. VI). However, heating the carboxylic acid with urea at 180 °C for 2 h gave only insoluble decomposition products. Primary amides are also accessible by treatment of the appropriate acyl chloride with ammonia. The attempt to prepare the acyl chloride of 1,2,3,4-tetrahydro-cyclopent[b]indole (**112**) by treatment with thionyl chloride in chloroform at 70 °C gave decomposition products. At lower temperatures no reaction was observed.

Because of the problems encountered in converting the carboxyl group, it might be necessary to employ already functionalised cyclopentanone derivative, such as N-acyl-3-amine-cyclopentanones in the Fischer synthesis of 2-amine-1,2,3,4-tetrahydro-cyclopent[b]indole (**113**). However, the 1- and 2-substituted regioisomers might be obtained in the cyclisation step.

In a second alternative method for the preparation of 2-amine-1,2,3,4-tetrahydro-cyclopent[b]indoles (**120**) a general synthesis was explored, which would also allow the preparation of the 7-membered ring analogues (scheme 20).



120 **121** **122**

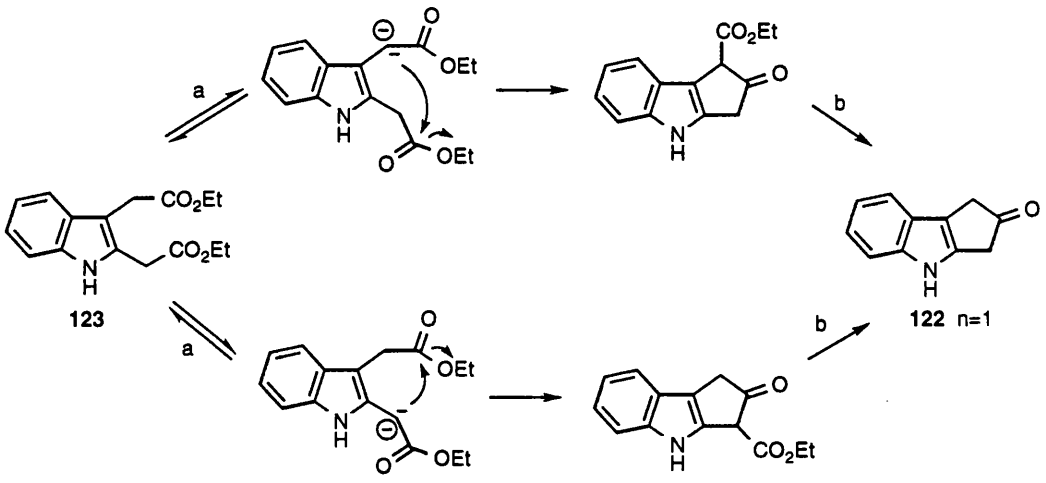
123 n=1
124 n=3

125 n=1
126 n=3

Scheme 20: Retrosynthesis of N-acylamine-cycloalkan[b]indoles (**120**)

The amides **120** can be obtained by standard acylation of the appropriate amines, which are produced by reduction of the oximes **121**. Key-step of the synthesis is the

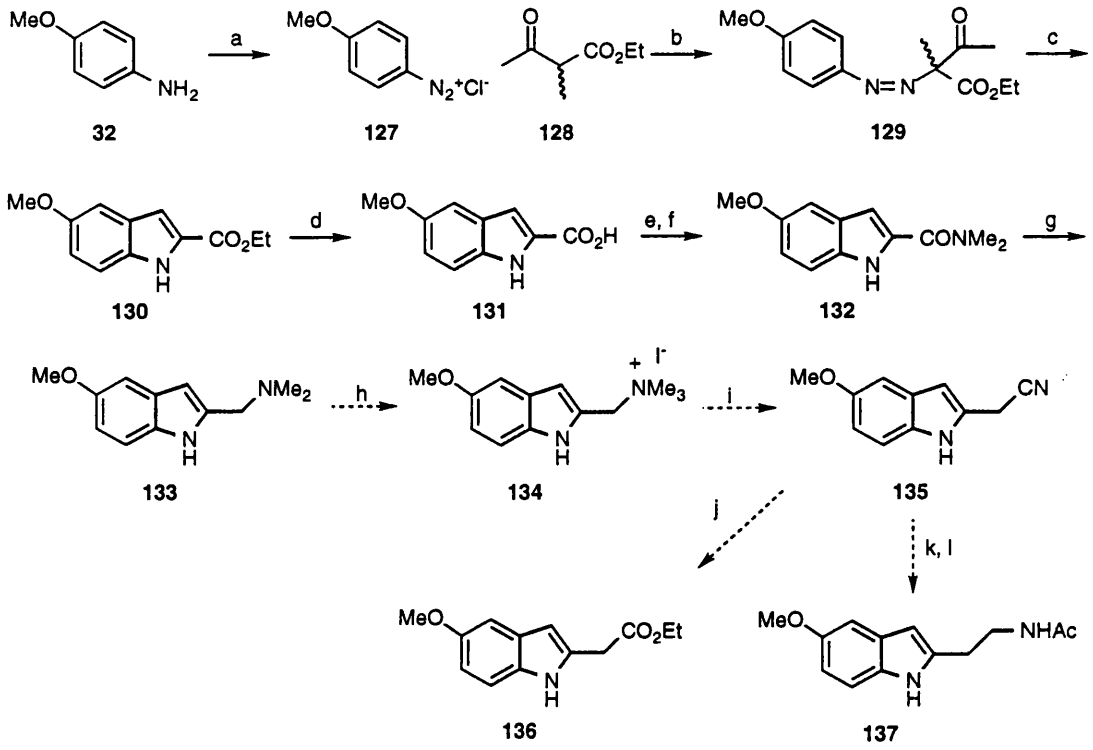
construction of the annelated carbocyclic ring by Dieckmann condensation of the diesters **123** and **124**, which after decarboxylation should result the five and seven-membered ring ketones **122** (n=1 or 3). The cyclisation direction of the Dieckmann reaction is unimportant, since both β-ketoesters should be decarboxylated to the same ketone (scheme 21).



Scheme 21: Dieckmann condensation and subsequent decarboxylation to 3,4-dihydrocyclopent[b]indol-2(1H)-one (**122**) a base; b 2N HCl

The synthesis of the diesters **123** and **124** was envisaged to commence from the monoesters **125** and **126**, which functionalisation to the ethyl indole-3-acetates should be achieved following the known conversions of indole and 4-nitro-2-phenylindole[182,183]. While several syntheses for ethyl indole-2-acetate (**125**) and its derivatives have been reported[184-187], the ω-butyric acid ester **126** should be accessible in analogy to Julia's synthesis of ethyl indole-2-propionate[147].

The first attempt to synthesise ethyl 5-methoxy-indole-2-acetate (**136**) followed Schindler's protocol, who homologated ethyl indole-2-carboxylate in a 6-step reaction sequence[184,185]. This reaction was selected, since the intermediate 2-acetonitrile-5-methoxy-indole (**135**) can also be converted into the melatonin isomer **137**.



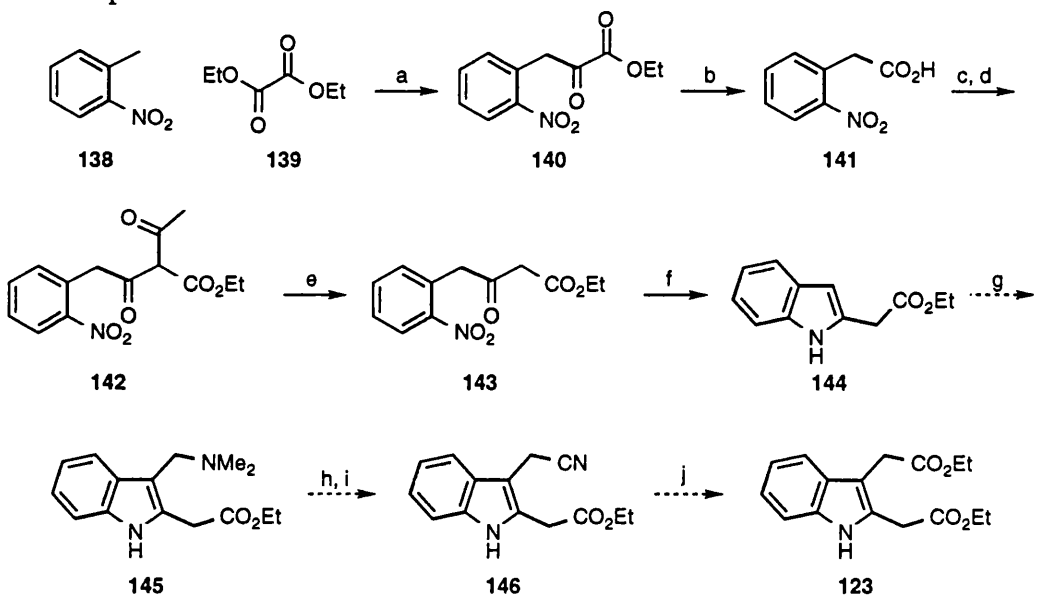
Scheme 22: Attempted synthesis of ethyl 5-methoxy-indole-2-acetate (**136**) and N-acetyl-2-aminoethyl-5-methoxy-indole (**137**)

a $NaNO_2$, HCl, H_2O, 0 °C, 15 min; b NaOAc, H_2O, pH 5.5, 0 °C, 4 h;
c EtOH, $HCl_{(g)}$, Δ, 20 min; d aq. MeOH, NaOH, Δ, 30 min;
e $SOCl_2$, C_6H_6, 45 °C, 90 min; f $NHMe_2$, C_6H_6, 25 °C, 10 min;
g $LiAlH_4$, THF, Δ, 6 h; h MeI, EtOAc, 25 °C, 10 min;
i KCN, EtOH, DMF, Δ, 16 h; j Et_2O, EtOH, $HCl_{(g)}$, 0 °C, 8 d;
k $LiAlH_4$, THF, Δ, 4 h; Ac_2O, Et_3N, CH_2Cl_2, 25 °C, 30 min

Ethyl 5-methoxy-indole-2-carboxylate (**130**) was obtained by Japp-Klingemann reaction of the diazonium salt of *p*-anisidine (**32**) with ethyl 2-methyl-3-oxo-butyric acid ester (**128**) and following acid-catalysed Fischer cyclisation[188]. The synthesis of the β-ketoester **128** is described in chp. III. After saponification of the ester **130**, the acid was reacted with thionyl chloride and the resulting acyl chloride was converted *in situ* to the dimethylcarboxamide **132**. The ^1H nmr spectrum of the amide showed broad signals for the N-methyl groups, which is an indication for their restricted rotation. The amide was reduced with lithium aluminium hydride to yield the tertiary amine **133**, which is subsequently reacted with methyl iodide to yield an amorphous solid, which was insoluble in water and only slightly soluble in DMSO. In contrast to the reported quaternisation of the parent 2-dimethylaminomethyl-indole[184] the analogous reaction of the 5-methoxy derivative gave polymerisation products possibly

via elimination of trimethylamine and generation of a reactive benzylic cation (cf. chp. IV). In summary, 5-methoxy-indole-2-carboxylic acid (**131**) was obtained in good yield by the method reported by Heath-Brown and Philpot[188]. However the functionalisation of the side chain, which was previously reported for the unsubstituted parent indole[184], was laborious and yielded polymerisation products on the quaternisation step.

Therefore, ethyl indole-2-acetate (**144**) was synthesised by utilising a different method, which has also been reported for the preparation of the analogous 5-methoxy derivative **136**[187]. This method is based on the Reissert indole synthesis, in which the activated methyl group of an *ortho*-nitrotoluene is reacted with diethyl oxalate and the resulting nitroketone is reductively cyclised to yield the indole nucleus (scheme 23). The construction of the 3-acetate moiety was envisaged to proceed via Mannich base **145** and indole-3-acetonitrile **146**[182]. Conversion of the nitrile into the carboxylate group should be achieved by hydrolysis of the iminoether-hydrochloride, produced by reacting nitrile **146** with ethanol and hydrogen chloride. This method was chosen in order to avoid the reported decarboxylation of the 2-acetate under conditions of alkaline saponification[185].



Scheme 23: Reissert synthesis of ethyl indole-2-acetate (**144**)

a NaH, THF, Δ, 10 h; b H_2O_2, NaOH, 25 °C; c $SOCl_2$, toluene, 50 °C;
d NaH, ethyl acetoacetate, THF, 25 °C, 16 h; e MeOH, NH_4OH, 25 °C, 1 h;
f $Na_2S_2O_4$, MeOH, H_2O, Δ, 20 min; g $HNMe_2$, HCHO, dioxane, HOAc, 25 °C, 16 h; h MeI, EtOAc, 25 °C, 10 min; i KCN, EtOH, DMF, Δ, 16 h;
j Et_2O, EtOH, $HCl_{(g)}$, 0 °C, 8 d;

In detail, commercially available *o*-nitrotoluene (**138**) was treated with diethyl oxalate and sodium hydride to give the pyruvate ester **141**, which was not isolated but directly oxidised with hydrogen peroxide in sodium hydroxide solution. After acidification, *o*-nitrophenylacetic acid (**141**) was obtained in 63 % yield. Treatment of the acid with thionyl chloride resulted the intermediate acid chloride, which was condensed with the enolate, prepared from ethyl acetoacetate and sodium hydride, to furnish the β-keto ester **142** in low yield. Nmr spectroscopy indicates, that the ester is completely enolised as no signal for a methine proton is observed and the APT shows an olefinic singlet at 108.1 ppm. Ammonolysis of **142** gave quantitatively the β-keto ester **143**, which was not separated from the by-product, acetamide, since the reductive cyclisation with sodium dithionite gave the desired ethyl indole-2-acetate (**144**) in good yield. The deacetylated β-keto ester **143** was identified by nmr spectroscopy, which showed the loss of the acetyl group. The olefinic ^{13}C-signal at 108.1 ppm was also absent. Initially an attempt was made to reduce the crude nitro-ketone **143** following the reported method using ammonium formate and palladium-on-charcoal[187]; however, the mixture of starting materials was recovered even after prolonged reaction time and higher temperature. The product of the reduction with sodium dithionate showed the characteristic ^1H nmr signals for a 2-substituted indole with the singlet at 6.36 ppm being assigned for H3.

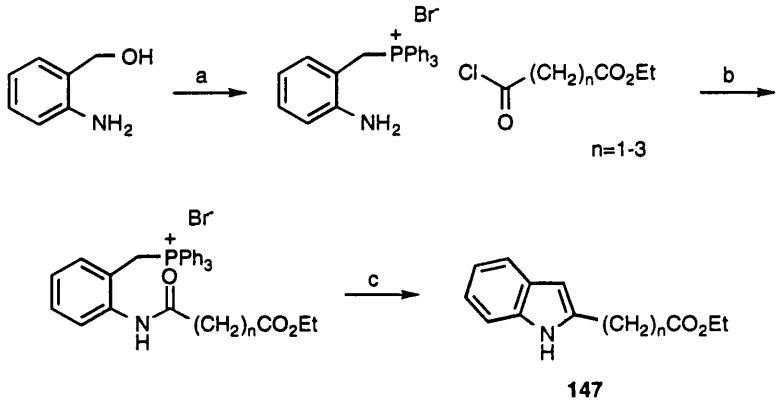
The attempted Mannich reaction of ethyl indole-2-acetate yielded an unidentified neutral product, which ^1H nmr spectrum does not show the expected ethyl ester and dimethylamine group. However, the proton H3 is substituted, as the ^1H nmr signal at 6.36 ppm has disappeared and only 4 aromatic CH groups were detected by the APT experiment. Since the Mannich reaction was successfully employed for the synthesis of 3-(N,N-dimethylaminomethyl)-5-methoxyindole (**230**, cf. chp. V), the 2-acetate functionality must interfere with the product formation, possibly after the electrophilic substitution has occurred.

Although the Reissert synthesis gives access to the targeted intermediate ethyl indole-2-acetate (**144**), the planned functionalisation to the diacetate **123** was unsuccessful. To investigate, if the interference of the 2-acetate moiety is caused by its benzylic position, an attempt was made to synthesise ethyl 4-(2-indole)-butyrate (**126**), which is the precursor for the cyclohept[b]alkanone **122** (R=H, n=3).

II.2.5 Attempted Syntheses of 9-Amino-5,6,7,8,9,10-hexahydro-cyclohept[b]indole

As outlined in the retrosynthetic analysis for N-acylamine-cycloalkan[b]indoles (scheme 20), the preparation of the annelated cycloheptane indoles (**120**, n=3) commences from 4-(2-indole)-butyrates (**126**). These butyric acid esters should be available by two different synthetic methods.

In a general method for the preparation of indole-2-carboxylic acid esters, which was not examined within this study, an intramolecular Wittig reaction is employed to generate the indole nucleus with the required functionality[186] (scheme 24). This reaction might also improve the yield of ethyl indole-2-acetate obtained by the Reissert synthesis.

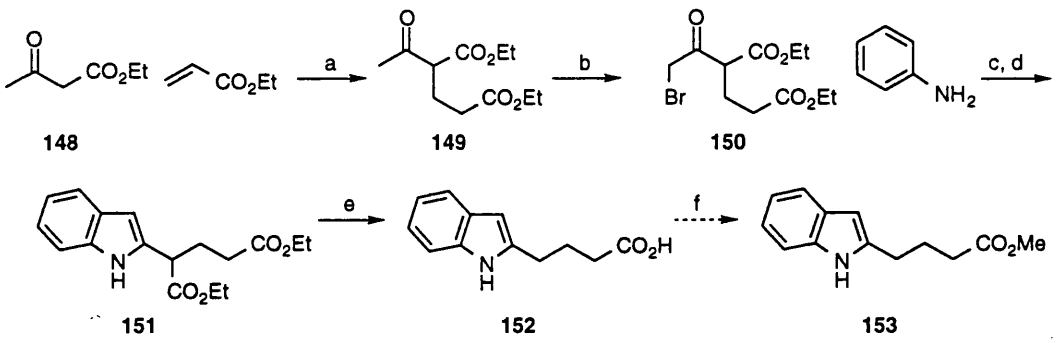


147

Scheme 24: Synthesis of ethyl ω-(2-indole)-carboxylic acids (**148**)[186,189]

a PPh_3HBr, CH_3CN; b CH_2Cl_2; c NaO^{tert}-pentylate, toluene

Julia and Bagot reported the synthesis of 3-(2-indole)-propionic acid by Bischler reaction of aniline with ethyl γ-bromoacetyl-succinate and subsequent decarboxylation[147]. As mentioned in chapter II, the Bischler reaction of unalkylated aniline with α-bromoketone derivatives results the 2-substituted indole. Modifying Julia's synthesis, diethyl 2-bromoacetyl-glutarate (**150**) was reacted with aniline to yield the homologous diester (**151**) (scheme 25). An attempt to prepare ethyl indole-2-acetate (**144**) by condensing aniline with γ-bromoacetoacetate under analogous reaction conditions gave unextractable products.



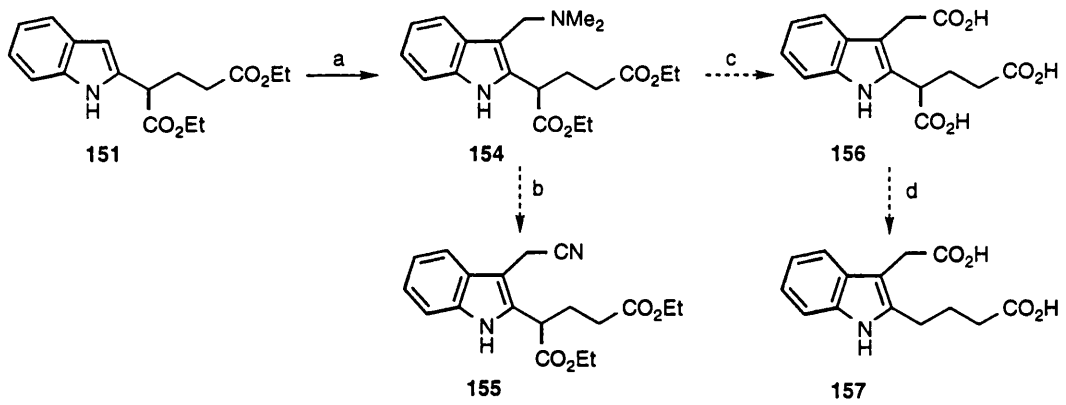
Scheme 25: Synthesis of 4-(2-indole)-butyric acid (**152**)

a KOH, EtOH, 100 °C; b Br_2, ether, 0 °C, 16 h; c 50 °C, 3 h;
d $ZnCl_2$, propan-2-ol, Δ,16 h; e MeOH, H_2O, Δ, 6h; f MeOH, H_2SO_4, Δ,5 h

The required diethyl 2-bromoacetyl-glutarate (**150**) was prepared by Michael-addition of ethyl acrylate to ethyl acetoacetate (**148**)[190] and subsequent bromination of the β-ketoester with bromine in ether. As in the cyclic α-bromoketones **34** and **40**, the bromination occurs at the least substituted carbon atom. The Bischler reaction produced the targeted 2-substituted indole **151** as indicated by the ^1H nmr spectrum showing a singlet for H3 at 6.36 ppm. In comparison to ethyl indole-2-acetate (**144**) the ^{13}C nmr signal for the benzylic proton is shifted to lower field from 33.9 to 41.2 ppm. The nmr signals for the non-equivalent ethyl ester groups are doubled in both the ^1H and the ^{13}C nmr spectrum. Saponification of the diethyl ester and simultaneous decarboxylation of the benzylic carboxyl moiety gave the expected mono acid **152** in 48 % yield. The attempted esterification of the acid with methanol and catalytic amounts of concentrated sulphuric acid resulted polymerisation products, possibly via acid-catalysed electrophilic substitution at the reactive C3-atom of the indole nucleus.

Therefore, an alternative synthesis for 4-(2-indole-3-acetic acid)-butyric acid (**157**) was attempted, in which the Mannich reaction was applied prior to the saponification/decarboxylation step (scheme 26).

In contrast to ethyl 2-indole-acetate the diester **151** produced the Mannich addition product diethyl 2-(2-(3-dimethylaminomethyl)indole)glutarate (**154**), although in low yield of 17 %. The ^1H nmr spectrum shows the additional signals for the dimethylaminomethyl group at 2.22 and 3.67 ppm. Additionally, the characteristic singlet for H3 at 6.36 ppm has disappeared, indicating the 2,3-disubstitution of the indole nucleus.

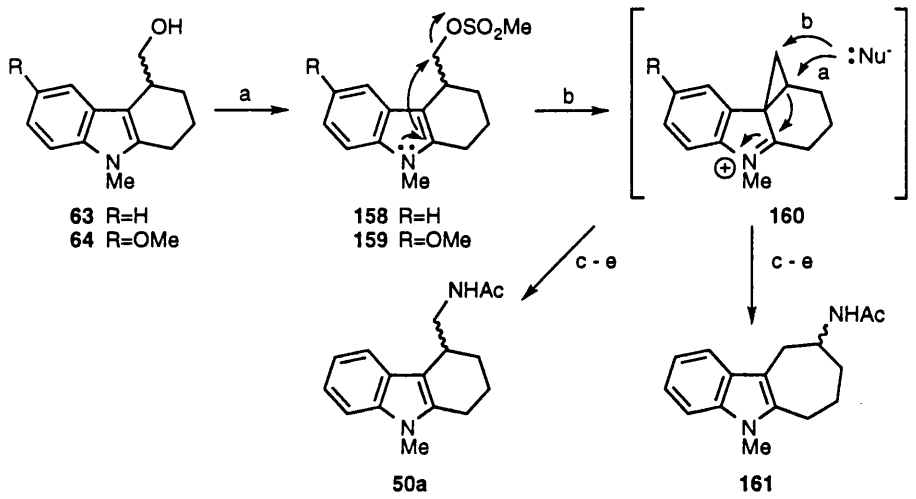


Scheme 26: Attempted synthesis of 4-(2-indole-3-acetic acid)-butyric acid (**157**)
a $HNMe_2$, HCHO, dioxane, HOAc, 25 °C, 2 h; b MeI, KCN, MeOH, DMF, 50 °C, 5 d; c NaCN, aq. EtOH, Δ, 3 d; d KOH, MeOH, Δ, 5 h

The attempted conversion of the gramine derivative **154** into the nitrile **155** under conditions, successfully employed for the synthesis of 3-acetonitrile-5-methoxy-indole (**216**, cf. chp. V), resulted an acidic unidentified product, which shows olefinic signals in the ^1H nmr spectrum. In a modified procedure[182] the nitrile is immediately saponified under the reaction condition and the same product was obtained. Since the product could not be sufficiently purified by chromatography, esterification with methanol was attempted. However, no product could be extracted from the reaction mixture.

In summary, the synthesis of the targeted 4-(2-indole)butyric acid (**152**) was achieved by Bischler reaction. However, the functionalisation at C3 of the indole nucleus by Mannich reaction resulted insoluble products.

An alternative synthesis for 9-substituted cyclohept[b]indoles **120** (n=3) was reported by Julia and Lenzi, who explained the formation of 9-hydroxy-5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole from alcohol **63** by the rearrangement of the tosylate via the intermediate **160** (scheme 27)[155]. The ring expansion was also effected by solvolysis of the alcohol with silver oxide in water/ether or by treatment of the analogous bromo derivative with formalin and sodium formate and subsequent saponification. In all cases a mixture of the cyclohexyl derivative, formed by attack of the nucleophile at position b (**160**), and rearranged product (attack at position a) was observed.



Scheme 27: Synthesis of N-acetyl-9-amine-5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole (**161**) by rearrangement of the mesylate **158**

a $MeSO_2Cl$, pyr., 20 °C, 24 h; b NaN_3, EtOH, H_2O, Δ, 12 h;

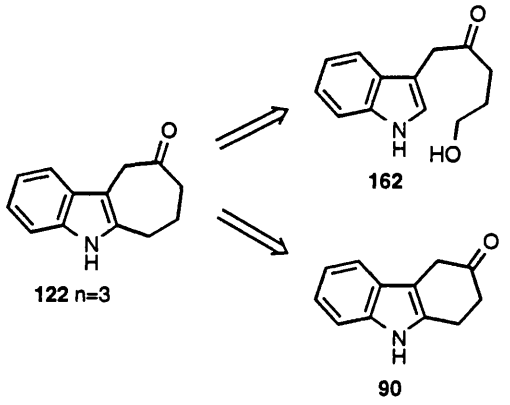
c $LiAlH_4$, THF, 20 °C, 24 h; d Ac_2O, Et_3N, CH_2Cl_2, 20 °C, 4 h

Adopting this method for the synthesis of the melatonin analogue **161** and its 2-methoxy derivative, the previously prepared alcohol **63** was converted into the mesylates **158**. In analogy to the difficulties encountered in preparing the mesylate of 3-hydroxy-1,2,3,4-tetrahydrocarbazole (**101b**), the reaction of the 6-methoxy carbazole **64** and methanesulphonyl chloride in pyridine or in THF with sodium hydride gave a product, which shows no ^1H nmr signal for the methanesulphonyl protons. Compared to the starting material the only difference in the ^1H nmr spectrum of the starting material was a new doublet of doublets at δ=4.16 ppm. Possibly the mesylate was formed as an intermediate, effected the rearrangement and was finally hydrolysed, to result a mixture of starting material and rearranged alcohol, which could not be separated by chromatography.

4-Methanesulphonyloxymethyl-1,2,3,4-tetrahydrocarbazole (**158**) was converted into the amide by the procedure described for the synthesis of N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles (**106**). The intermediate azide and amine were not isolated. Acetylation of the amine gave 47 µg of an amide mixture, which could not be separated by spinning plate chromatography using various solvent systems. In the ^1H nmr spectrum a doubling of the singlets for N-methyl and acetyl group is observed. Interestingly, the ^1H nmr signals for the amide proton show different coupling patterns. For the minor product, which might be the amide **50a**, the signal is a broad triplet at 5.82 ppm, whereas the major product, shows a broad doublet at 5.64 ppm,

which has also been observed for N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles (**106**). It is tempting to conclude that the N-acylamine group is directly attached to the carbocyclic ring, which is in agreement with structure **161**. Therefore, the nucleophilic substitution of mesylate by sodium azide might have been partly effected the rearrangement to the 7-membered ring. However, the fact, that the product mixture could not be separated, made a further structure determination of the latter product impossible.

Retrosynthetic analysis of the 9-substituted 5,6,7,8,9,10-hexahydro-cyclohept-[b]indole (**122**, n=3) reveals two further synthetic routes, namely the intramolecular acid-catalysed cyclisation of the alcohol **162** and the ring expansion of 1,2-dihydrocarbazol-3(4H)-one (**90**) (scheme 28).

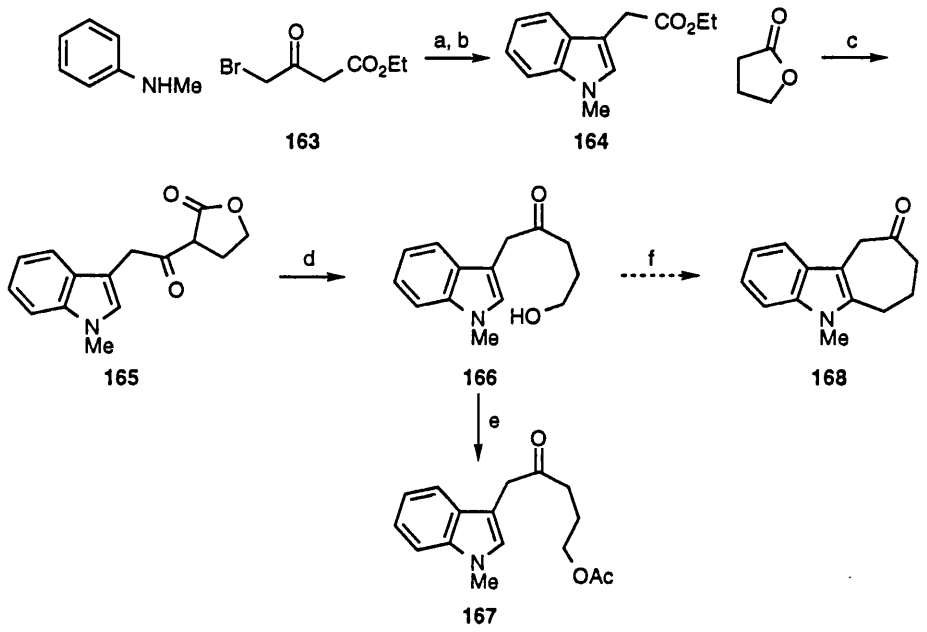


Scheme 28: Retrosynthesis of 5,6,7,8-tetrahydro-cyclohept[b]indol-9(10H)-one (**122** n=3)

Jackson *et al.*[191] reported the BF_3-catalysed cyclisation of 3-(3-indole)butanol to 1,2,3,4-tetrahydrocarbazole. In modification of this procedure, the cyclisation of 5-(3-N-methylindole)-4-oxo-pentanol (**166**) to 5-methyl-5,6,7,8-hexahydro-cyclohept-[b]indol-9(10H)-one (**168**) was attempted (Scheme 29).

The alcohol **166** was obtained by a synthesis commencing from ethyl N-methylindole-3-acetate (**164**), produced by Bischler reaction of commercially available N-methylaniline with γ-bromo-acetoacetate (**163**)[157]. In analogy to the cyclic α-bromoketones **34** and **40**, the latter was prepared by bromination of acetoacetate[192]. As expected, the Bischler reaction of the N-alkylated aniline derivative gave exclusively the 3-substituted indole **164**, as shown by the ^1H nmr signal for H2 (δ=7.07 ppm). It is interesting to note, that the same reaction, employing aniline as amine component, produced instead of the expected 2-substituted indoleacetate

unextractable compounds. Claisen condensation between ethyl indole-3-acetate (**164**) and γ-butyrolactone gave only the β-keto ester **165**, which is the product of enolate formation of the butyrolactone. The product of enolate formation of ethyl indole-3-acetate was not observed.



Scheme 29: Attempted synthesis of **168** by cyclisation of 5-(3-(N-methylindole))-4-oxo-pentanol (**166**)

a 50 °C, 3 h; b $ZnCl_2$, propan-2-ol, Δ,16 h; c NaOMe, 1,4-dioxane, Δ, 2 d; d 2N NaOH, 1,4-dioxane, Δ,16 h; e HOAc, 25 °C, 4 h; f BF_3-Et_2O, Δ, 1 h

From the various investigated reaction conditions for the Claisen condensation the one employed by Martin and Moody, who reacted ethyl indole-2-carboxylate with γ-butyrolactone and sodium methanolate in 1,4-dioxane, gave optimal results, when 4 equivalents of butyrolactone were used[193]. The condensation product **165** was identified by the nmr signals of the chiral methine group, α to both carbonyl moieties, which gave rise to a triplet (δ=3.85 ppm) and to a doublet (δ=49.8 ppm) in the ^1H and ^{13}C nmr spectra, respectively. Simultaneous saponification of the lactone and decarboxylation of the resulting β-keto acid with 2N sodium hydroxide solution in dioxane gave the δ-keto alcohol **166**, which was identified by the absence of the nmr signals for the methine group. Further, the ir spectrum shows strong hydroxy and carbonyl group absorption and the characteristic loss of a water molecule from the alcohol is observed in the FAB mass spectrum. The alternative saponification with

sodium hydroxide in aqueous methanol resulted in unidentified decomposition products.

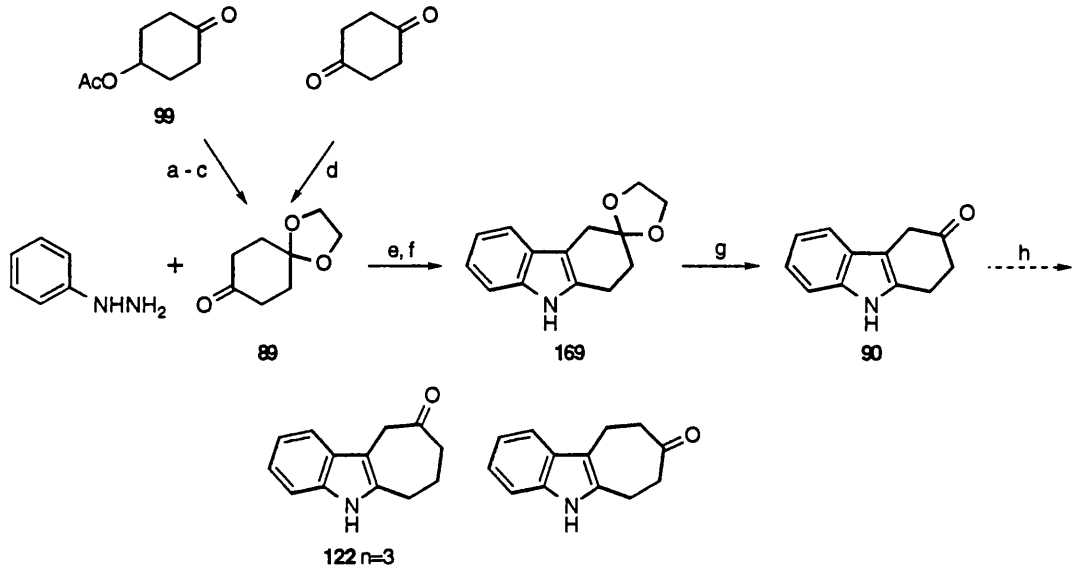
An attempt was then made to effect cyclisation of the alcohol **166** to the cyclohept[b]indole **168**. Using the reported reaction conditions with BF_3 etherate in refluxing ether[191] insoluble decomposition products were obtained, suggesting, that the carbonyl moiety might interfere with the Lewis acid-catalysed ring closure. After 5 days at 25 °C no reaction was observed and the starting material was recovered. Although no reaction occurred when the alcohol was refluxed with aqueous acetic acid, the acetate **167** was obtained when the alcohol was treated with glacial acetic acid at 25 °C. The ester **167** was identified by the nmr signals for the acetyl group (^1H nmr singlet at 1.95 ppm and ^{13}C nmr signal at 170.8 ppm) and the shift of the ^1H nmr signal for the methylene group adjacent to oxygen from 3.53 to 3.98 ppm. Stirring the alcohol at 50 °C with glacial acetic acid or with trifluoracetic acid at 25 °C gave insoluble solids. The reaction with dioxane and a catalytic amount of hydrochloric acid at 50 °C gave a mixture of starting material and polymerised products, suggesting that the intermediate carbocation does not cyclise in an intramolecular electrophilic substitution, but reacts intermolecular.

The alternative synthesis of 5,6,7,8-tetrahydro-cyclohept[b]indol-9(10H)-one (**122** n=3) by ring expansion required the preparation of 1,2-dihydro-carbazol-3(4H)-one (**90**). Attempts to prepare the ketone from the bisphenylhydrazone of cyclohexane-1,4-dione, did not give any of the desired product[194]. In an alternative approach the ketone was obtained from the analogous alcohol **101a** by means of an Oppenauer oxidation with aluminium isopropoxide and cyclohexanone in refluxing toluene[174]. However, earlier reported attempts to oxidise the alcohol were unsuccessful[194,195]. Therefore, 1,2-dihydro-carbazol-3(4H)-one (**90**) was prepared following the method reported by Britten and Lockwood, who applied the Fischer reaction between phenylhydrazine and 4,4-ethylenedioxycyclohexanone (**89**)[173].

Several syntheses exist for the commercially available 4,4-ethylenedioxy-cyclohexanone (**89**)[173,196,197]. Commencing from the already synthesised 4-acetoxycyclohexanone (**99**) the mono-protected diketone **89** was obtained in a three-step synthesis in 40 % yield[173]. Alternatively, cyclohexan-1,4-dione was reacted with 1.2 equivalents of ethanediol to give 4,4-ethylenedioxycyclohexanone in one-step and 11 % yield. Zinc chloride-catalysed Fischer reaction between phenylhydrazine and monoketal **89** gave the protected 1,2-dihydro-carbazol-3(4H)-one, which was

deprotected with refluxing aqueous acetone in the presence of *p*-toluenesulphonic acid. The overall yield of 1,2-dihydro-carbazol-3(4H)-one (**90**) was 12 %.

The planned ring expansion with diazomethane, which might be generated *in situ* from *p*-toluenesulphonylmethylnitrosamide[198], remains to be investigated.



Scheme 30: Synthesis of 1,2-dihydro-carbazol-3(4H)-one (**90**)

a $(CH_2OH)_2$, benzene, *p*TsOH, Δ, 8 h; b MeOH, H_2O, NaOH, Δ, 5 h;

c CrO_3, CH_2Cl_2, py., 0 °C, 20 min; d $(CH_2OH)_2$, benzene, *p*TsOH, Δ, 8 h;

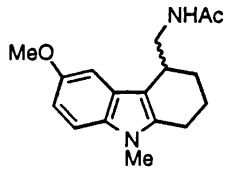
e H_2O, 100 °C, 20 min; f benzene, $ZnCl_2$, Δ, 4 h;

g acetone, H_2O, *p*TsOH, Δ, 4 h; h "CH_2N_2"

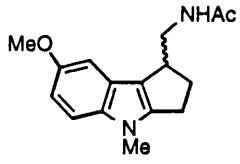
II.3 N-Acetyl-tetrahydro-β-carbolines

II.3.1 Introduction

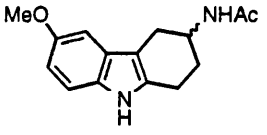
Considering the gradual decrease in binding affinity to the melatonin receptor in the series N-acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**53a**, K_i 0.97 nM), N-acetyl-1-aminomethyl-7-methoxy-4-methyl-1,2,3,4-cyclopent-[b]indole (**52a**, K_i 161 nM) and N-acetyl-3-amine-6-methoxy-1,2,3,4-tetrahydro-carbazole (**107a**, K_i 219 nM), a further reduction of K_i is expected for the N-acetylated tetrahydro-β-carboline **21**, in which the melatonin amidoethane side chain is completely incorporated in a heterocyclic ring. In fact, the tetrahydro-β-carboline analogue of **21** lacking the methoxy group showed no binding affinity in the chicken brain assay[123].



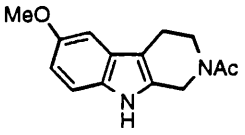
53a



52a

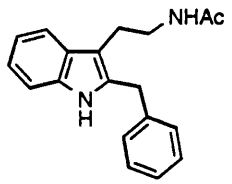


107a

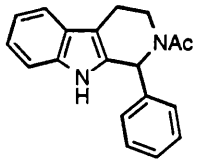


21

Based on the reported antagonist luzindole (**6**) as lead compound[81], an attempt was made, to design a melatonin antagonist using the tetrahydro-β-carboline structure. In the line of the high binding affinity of 2-phenylindole analogues of melatonin[120,125], it seemed likely that the phenyl ring in 3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**) might also increase the binding affinity by ππ-interaction with a putative tryptophan residue in the receptor protein[123].



6

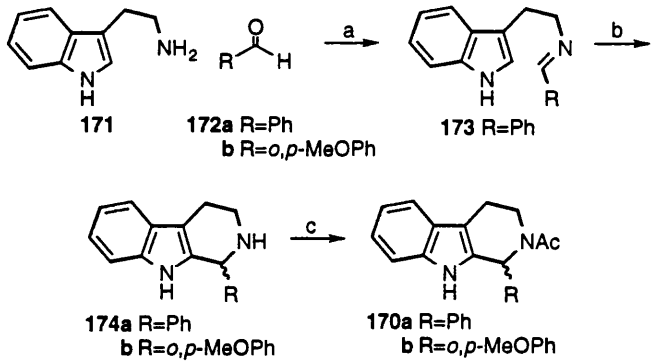


170a

II.3.2 Synthesis

Tetrahydro-β-carbolines are easily prepared by a modified Pictet-Spengler synthesis, which was originally applied for the synthesis of tetrahydroisoquinolines[199,200]. In detail, condensation of tryptamine (**171**) with the

aldehydes **172** yields the intermediate imine **173** which, in analogy to the Mannich reaction, reacts in an acid-catalysed electrophilic substitution at C2 of the indole ring to give the tetrahydro-β-carbolines as intramolecular cyclisation products[201].



Scheme 31: Preparation of the tetrahydro-β-carbolines **170** by a modified Pictet-Spengler synthesis

a EtOH, 25 °C; b aq. HCl, EtOH, 60 °C, 1 h;

c Ac_2O, Et_3N, CH_2Cl_2, 20 °C, 4 h

Although Wieland *et al.* were not able to detect the imine **173** by chromatographic means in the case of tetrahydrobenzaldehyde[201], the same reaction with benzaldehyde yielded quantitatively N-benzylidenetryptamine (**173**), a compound which was first synthesised by Hoshino *et al.* in 1935[202]. N-Benzylidene-tryptamine (**173**) was identified by the characteristic ir absorption bands at ν = 1640 and 3140 cm^{-1} reflecting the C=N and NH bond, respectively. Moreover the reported melting point and the ^1H nmr data correspond with the reported experimental values[203]. The proton nmr signal for H2 at δ = 6.88 ppm is clearly identified by a decoupling experiment. Irradiation of this doublet ($^3J_{2,1}$ = 2.2 Hz) results in sharpening of the broad signal for H1. According to Jackson *et al.* the imine proton H11 gives a low field signal at δ = 8.12 ppm[203].

A number of problems occurred in this synthetic sequence. In contrast to N-benzylidenetryptamine (**173**), the condensation product of tryptamine and 2,4-dimethoxybenzaldehyde was not isolated but immediately cyclised on addition of hydrochloric acid. Reacting tryptamine hydrochloride with aldehydes **172** gave only decomposition products. The amines obtained by the Pictet-Spengler reaction were unstable in air and decomposed rapidly in solution. Therefore, no nmr spectra could be obtained and 3-phenyl-3,4,5,6-tetrahydro-β-carboline (**174a**) was identified by mass spectroscopy.

Acetylation of the crude amines **174** by acetic anhydride in dichloromethane gave racemic mixtures of the chiral N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**) and N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**).

While N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**) is insoluble in ether, ethanol, water, chloroform and tetrachloromethane, the analogous compound **170b**, substituted with two methoxy groups on the phenyl ring, is soluble in ethanol and chloroform, which facilitates biological testing. Both amides **170a** and **170b** show characteristic ir absorption bands at ν = 1620 and 1560 cm^{-1} and ν = 1640 and 1560 cm^{-1}, respectively. The 2,4-dimethoxyphenyl derivative also exhibits absorption bands at ν = 1260 and 1210 cm^{-1}, which are assigned to the two methoxy groups.

The molecular structure of both amides was determined by X-ray diffraction experiments carried out with single crystals obtained by recrystallisation. Subsequently dissolving the crystals **170a** in d_6-DMSO and the crystals **170b** in $CDCl_3$ gave solutions from which nmr spectra were obtained.

Crystal structure analysis of **170a** and **170b** reveals a shortening of the nitrogen-carbon bond N2-C16 (1.325 Å, [1.365 Å for **170b**]) reflecting the partial double bond character of the amide functionality (cf. fig. 27 and 28, tab 12-19, appendix). The nitrogen atom N2 can be considered as almost sp^2-hybridized, since the atoms C1, N2, C3 and C16 lay in a plane (max. dev. 0.03 Å of N2); the bond angles are ∠ C1-N2-C3 = 113.8° [113.5°], ∠ C1-N2-C16 = 120.0° [124.5°] and ∠ C3-N2-C16 = 126.0° [120.7°].

The substitution of the phenyl ring in **170b** effects a significant elongation of the bonds between N2-C1 (1.468 Å [1.508 Å]) and C1-C9a (1.482 Å [1.514 Å]), whereas the bond length C1-C10 is maintained (1.522 Å [1.530 Å]). Therefore the geometry of the six-membered ring is slightly altered (fig. 9). Reported structural data of melatonin (**1**)[204-206] coincide partly with the found structures. The geometry of the indole ring and the bonds C4a-C4, C4-C3, C3-N2, N2-C16, C16-C17 and C16-O1 can be regarded as equivalent, whereas the bond C3-N2 is elongated (1.474 Å in **170a**, 1.476 Å in **170b**, 1.445 Å in **1**[206]).

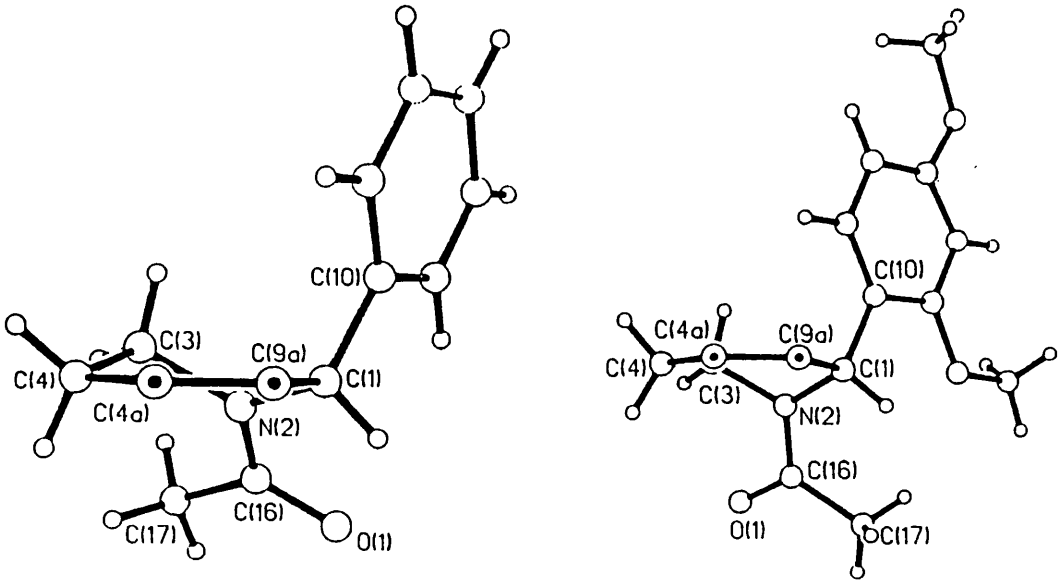
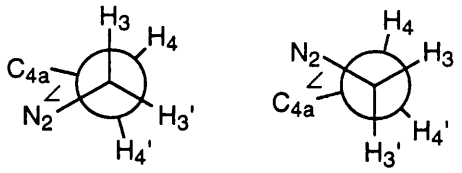


Figure 9: Molecular structure of **170a** and **170b** seen from the indole plane (idealised position of hydrogen atoms)

As the nmr spectra of the amides **170a** and **170b** were recorded in different solvents (d_6-DMSO and $CDCl_3$, respectively), they are only roughly comparable (cf. fig. 24 and 25, appendix). However, in both ^1H nmr spectra the signal of the benzylic proton H1 appears at a position (**170a**, δ=6.86 ppm; **170b**, δ=6.28 ppm) which is consistent with the reported chemical shifts of H1 in other 3-phenyl-3,4,5,6-tetrahydro-β-carbolines such as 2-(ethoxycarbonyl)-3-phenyl-3,4,5,6-tetrahydro-β-carboline (δ = 6.39 ppm)[207]. The ^1H nmr spectrum of **170a** shows the expected coupling pattern of the indole protons and the signal of the acetyl protons H11.

Both amides exhibit two 'doublets of doublets' and two 'triplets of doublets' for the diastereotopic equatorial and axial protons in the six-membered heterocyclic ring. To assign the peaks, coupling constants were calculated by the Karplus equation using the dihedral angle N2-C3-C4-C4a obtained by X-ray crystallography. Even if this angle is maintained in solution, the calculations are probably only accurate to ±1 Hz. The dihedral angles for the tetrahydro-β-carbolines **170a** and **170b** are 45.5° and 38.6°, respectively.

The two possible conformations of the 6-membered ring are represented by the structures depicted in figure 10. Conformer I is found by the crystal structure analysis.



conformer I conformer II

Figure 10: Conformers of **170a** and **170b**

Therefore, the dihedral angles between the vicinal protons in the conformer I are

dihedral angle	**170a**	**170b**
∠ H3-C3-C4-H4 ∠ H3'-C3-C4-H4'	45.5°	38.6°
∠ H3-C3-C4-H4'	165.5°	158.6°
∠ H3'-C3-C4-H4	74.5°	81.4°

The coupling constant ^3J is calculated using the Karplus equation

$$^3J = (9.4 \cos^2\Theta - 1.4 \cos \Theta + 1.6)\ Hz$$

For the conformers I and II the calculated coupling constants ^3J are

coupling constant	conformer I		conformer II	
	170a	**170b**	**170a**	**170b**
$^3J_{3,4} = {}^3J_{3',4'}$	5.2 Hz	6.2 Hz	5.2 Hz	6.2 Hz
$^3J_{3,4'}$	11.8 Hz	11.1 Hz	1.9 Hz	1.6 Hz
$^3J_{3',4}$	1.9 Hz	1.6 Hz	11.8 Hz	11.1 Hz

If both conformers are equally populated the coupling constants are averaged.

average coupling constant	**170a**	**170b**
$<{}^3J_{3,4}> = <{}^3J_{3',4'}>$	5.2 Hz	6.2 Hz
$<{}^3J_{3,4'}> = <{}^3J_{3',4}>$	6.9 Hz	6.4 Hz

For both conformers the geminal coupling constant ^2J will be about 11-15 Hz.

The measured vicinal coupling constants are between 3.1 and 4.6 Hz, suggesting a rapid equilibration between both conformers at room temperature. For each methylene group one doublet of doublets and one triplet of doublets is observed. The difference of the chemical shift between the protons of one methylene group can be explained by the anisotropic effect of the adjacent amide group, which influences the near protons at C3 more than those at C4. Idealised positions of the hydrogen atoms were calculated to find their deviation from the plane defined by the amide group, which is 0.12 Å (H3'), 0.59 Å (H3) for **170a** and 0.08 Å (H3'), 0.43 Å (H3) for **170b** (cf. fig. 9). While H3' lays in the plane of the amide group and its signal is therefore shifted towards lower field (δ = 3.96 ppm (**170a**); δ = 4.96 ppm (**170b**)), H3 is above the plane and its signal is shifted to higher field (δ = 3.23 ppm (**170a**); δ = 3.1 ppm (**170b**)).

It is interesting to note that two signal sets are observed in ^{1}H and ^{13}C nmr spectrum of N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**). Integration of the ^{1}H nmr signals reflects a ratio of major to minor isomer of 2.3 : 1 (cf. fig. 25 and 26, appendix). In the nmr spectra of the unsubstituted β-carboline **170a** very little of a second isomer is observed, which suggests that the signals arise from the additional substituents on the phenyl group. One explanation might be the restricted rotation of the phenyl ring, which is hindered by the interaction of the *o*-methoxy group with the indole H9 proton and the amide group. Therefore, the *o*-methoxy group in one conformer is situated above and in the other conformer beneath the indole plane. The energy barrier between the two rotational conformers is too high to interconvert the isomers at room temperature. The different environment of the *o*-methoxy group in both conformers is reflected by the chemical shifts of H18 (δ = 3.95 ppm for the major conformer, δ = 3.86 ppm for the minor conformer). Chemical shifts of the acyl and *p*-methoxy protons are unchanged in both conformers.

Since the rotation of the unsubstituted phenyl ring around the C1-C12 bond in **170a** is more or less unhindered, the ^{1}H nmr shows only small secondary peaks for the indole proton H9 (δ = 10.9 ppm), for the benzylic proton H1 (δ = 6.2 ppm) and for the H3' proton (δ = 4.7 ppm). The same effect is observed in the ^{13}C nmr spectrum of **170a**.

A similar peak doubling was observed by Ungemach *et al.*[208], who examined the ^{13}C nmr spectra of diastereomeric 3,5-disubstituted tetrahydro-β-carbolines and proposed that the difference in the chemical shifts between identical carbon atoms in the diastereomers is greatest for those carbon atoms which are asymmetrically substituted. It is interesting to note that, although **170b** possesses only one chiral centre, the largest chemical shift differences are found in the same centres as in

Ungemach's study, suggesting that the orientation of the adjacent amide group influences the chemical shift of C3 and C5 (fig. 11).

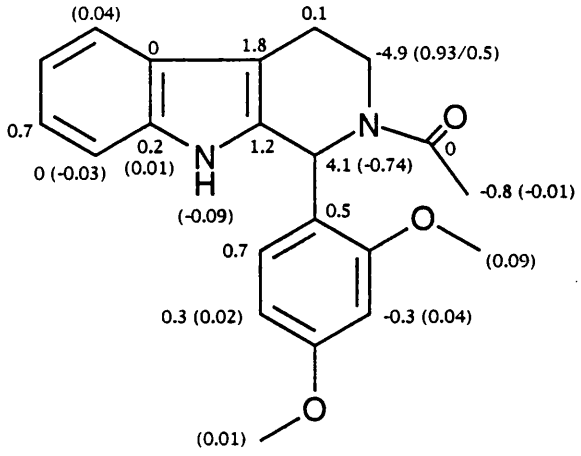


Figure 11: $\Delta\delta$ values in ppm for the ^{13}C and ^{1}H nmr spectra of **170b** (^{1}H nmr data in brackets; $\Delta\delta = \delta_{\text{major con.}} - \delta_{\text{minor con.}}$)

The ^{1}H and ^{13}C nmr signals of the aromatic protons were assigned by comparison with reported data[160,208] and from the interpretation of the coupling pattern.

II.3.3 Biological Results

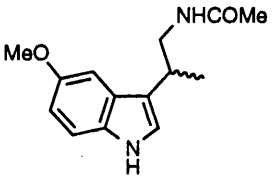
Both melatonin analogues **170a** and **170b** showed no binding affinity to the chicken brain binding site at $c=10^{-5}$ M. This might be caused by the lack of the methoxy group and the orientation of the amide group, which should produce a further decrease in binding affinity in relation to the N-acyl-3-amine-1,2,3,4-tetrahydrocarbazole derivatives **106** and **107**. The expected increase of K_i, caused by $\pi\pi$-interaction between phenyl ring and the putative tryptophan residue in the receptor protein, was not observed. Possibly the phenyl ring is locked in a conformation, which is unfavourable for a parallel alignment of both respective planes. In the crystal structure the angle between the indole-ring plane and the phenyl ring is 96.5° for **170a** and 101.5° for **170b**. A decrease in binding affinity might also be caused by size and orientation of the phenyl ring, which might be too large to be accommodated by the receptor pocket. Additionally, the amide proton, which might be essential for hydrogen bonding to the receptor protein, is lost by incorporating the amide nitrogen into the 6-membered heterocyclic ring.

Because of the restricted conformation of the N-acetyl-ethaneamine moiety, the observed crystal structures of **170a** and **170b** might provide valuable information for future molecular modelling studies.

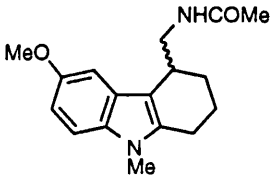
III Synthesis of β-branched Melatonin Analogues

III.1 Introduction

Branching the 3-ethaneamine functionality of melatonin restricts the rotation and increases the steric demand of the side chain, thus providing information about the geometry of the receptor pocket. The methyl group in β-alkyl branched melatonin analogues such as **175** effects an increasing in the population of the desired conformation of the side chain, which is similar to the one found in N-acetyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydro-carbazole (**53a**).

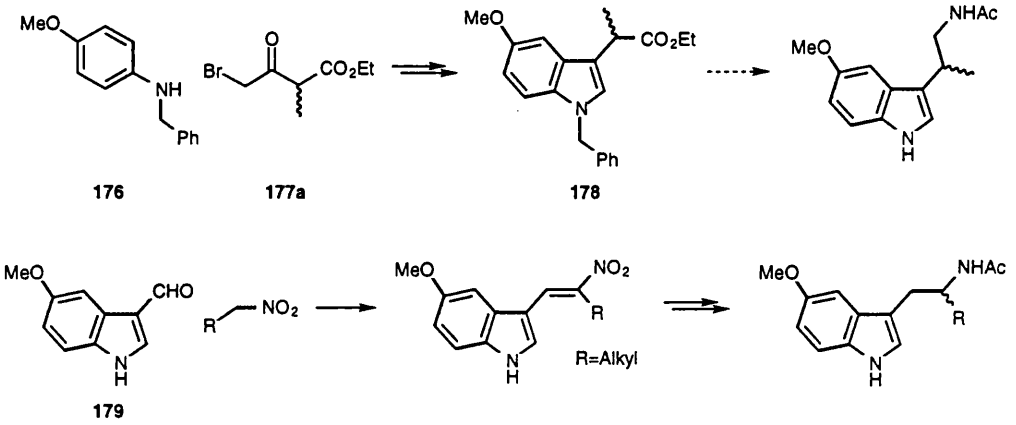


175



53a

Precursors of these β-alkyl branched analogues such as **178** have been synthesised by Julia *et al.*, who utilised the Bischler synthesis between N-alkylated *p*-anisidine (i.e. **174**) and β-alkylated γ-bromoacetoacetates such as **177a** to establish the desired substitution of the indole ring (scheme 32)[148,154,157]. Alternatively, the melatonin side chain can be branched in α position to the amide moiety by condensing 5-methoxy-indole-3-carbaldehydes **179** with nitroalkanes in a Henry reaction[209]. Since, these alkyl groups are less effective in restricting the rotation of the side chain, these melatonin analogues were not investigated in this study.

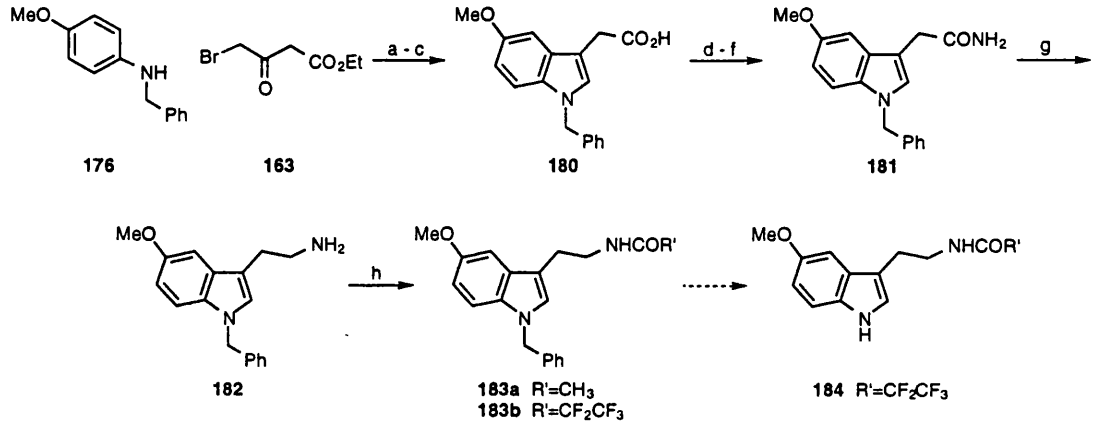


176 **177a** **178** **179**

Scheme 32: Synthesis of α- and β-alkyl branched precursors of melatonin

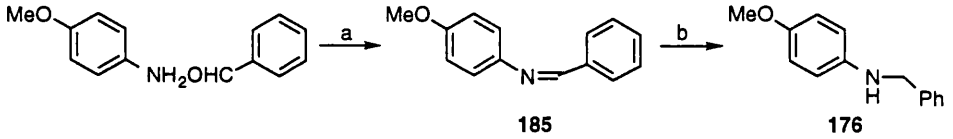
III.2 Synthesis

In analogy to the tricyclic melatonin analogues such as **53a**, the β-alkyl branched derivatives are accessible by Bischler reaction between N-alkylated *p*-anisidine and β-alkylated γ-bromo-acetoacetates[148,154,157]. Whereas the indole nitrogen in melatonin is not substituted, the products of this Bischler synthesis are N-substituted indoles. To closer mimic the structure of melatonin it would be advantageous to remove the directing N-alkyl group on a later stage of the synthesis. Therefore, an attempt was made in a model reaction to synthesise and debenzylate N'-benzyl-5-methoxy-N-acetyl-tryptamine (**183a**) and its N-pentafluoropropanoyl analogue **183b** (scheme 33).



Scheme 33: Synthesis of N'-benzyl-5-methoxy-N-acetyl-tryptamine (**183a**)
a 50 °C, 3 h; b $ZnCl_2$, propan-2-ol, Δ,16 h; c NaOH, aq. EtOH, Δ, 6 h;
d Et_3N, CH_2Cl_2, 0 °C, 10 min; e $ClCO_2Me$, CH_2Cl_2, 0 °C, 4 h;
f NH_3, 20 °C, 16 h; g $LiAlH_4$, THF, Δ, 4h; h Ac_2O, Et_3N, CH_2Cl_2, 20 °C, 4 h
or $C_2F_5CO_2Et$, MeOH, 20 °C, 4 h

According to the reported Bischler reaction between N-benzyl-*p*-anisidine (**176**) and γ-bromo-acetoacetate (**163**) gave the desired ethyl N-benzyl-5-methoxy-3-acetate, which was saponified to the acid **180**[157]. N-Benzyl-*p*-anisidine was prepared by sodium borohydride reduction of N-benzylidene-4-methoxy-aniline **185**, obtained by condensing benzaldehyde with *p*-methoxyaniline[210,211].

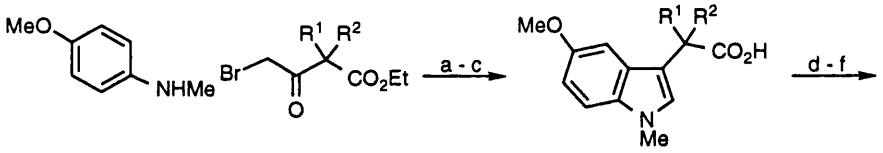


Scheme 34: Synthesis of N-benzyl-*p*-anisidine (**176**)
a 100 °C, 30 min; c $NaBH_4$, MeOH, Δ, 1h

The ^1H nmr spectrum of N-benzyl-5-methoxy-3-acetic acid (**180**) shows a singlet at 5.25 ppm, which is characteristic for the methylene protons of the benzyl group. Furthermore, the signal at 7.05 ppm for H2 indicates that the Bischler reaction gave the desired 3-substituted indole acetate. The signal for H3 of the 2-substituted indole acetate is usually shifted to higher field at around 6.5 ppm (cf. ethyl indole-2-acetate (**144**) δ=6.36 ppm). Conversion of the acid into the amide **181** was achieved under standard conditions by the mixed anhydride method[157]. After lithium aluminium hydride reduction the crude amine **182** was directly acylated with acetic anhydride and ethyl pentafluoropropionate. The amides **183a** and **183b** were identified by nmr, ir and mass spectroscopy. Attempts to debenzylate **183b** by catalytic hydrogenation or treatment with aluminium trichloride failed, as also did the usually successful reduction with sodium in liquid ammonia[212-214]. The crude product still showed the characteristic singlet for the benzylic protons (δ=5.26 ppm).

Since the benzyl group could not be removed by standard debenzylation procedures, N-methyl-*p*-anisidine (**39b**) was used in the Bischler reaction to generate the desired indole-3-acetates. Changing the structure of melatonin by introducing two additional groups, the β-alkyl and the N-methyl moiety, it was important to synthesise N-methyl-melatonin (**199**), in order to evaluate the biological activities of the β-branched melatonin analogues.

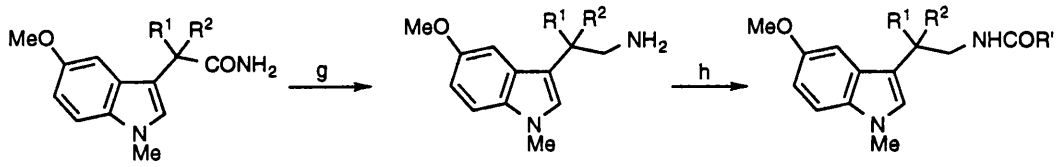
As with the synthesis of N-benzyl-5-methoxy-indole-3-acetic acid (**180**), the N-methyl analogues **187** were obtained in moderate yield after Bischler reaction and subsequent saponification (scheme 35). The products were purified and identified at the stage of the crystalline acid, since purification of the intermediate, viscous ethyl esters was difficult by distillation or chromatography. Ammonolysis of the mixed anhydrides, prepared by reacting the acids **187b-d** with methyl chloroformate, gave the acetamides **188b-d**, which were reduced to the respective amines by lithium aluminium hydride.



39b

163 R^1=H R^2=H
186a R^1=H R^2=Me
186b R^1=Me R^2=Me
186c R^1R^2=-$(CH_2)_4$-
186d R^1R^2=-$(CH_2)_2$-

187a R^1=H R^2=H
187b R^1=H R^2=Me
187c R^1=Me R^2=Me
187d R^1R^2=-$(CH_2)_4$-
187e R^1R^2=-$(CH_2)_2$-



188a R^1=H R^2=H
188b R^1=H R^2=Me
188c R^1=Me R^2=Me
188d R^1R^2=-$(CH_2)_4$-

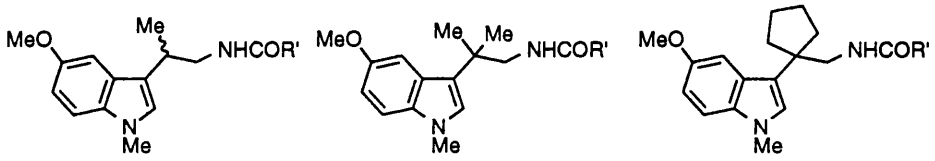
189a R^1=H R^2=Me
189b R^1=Me R^2=Me
189c R^1R^2=-$(CH_2)_4$-

190 R^1=H R^2=Me
191 R^1=Me R^2=Me
192 R^1R^2=-$(CH_2)_4$-

Scheme 35: Synthesis of β-branched melatonin analogues **190 - 192**

a 50 °C, 3 h; b $ZnCl_2$, propan-2-ol, Δ,16 h; c NaOH, aq. EtOH, Δ, 6 h;
d Et_3N, CH_2Cl_2, 0 °C, 10 min; e $ClCO_2Me$, CH_2Cl_2, 0 °C, 4 h;
f NH_3, 20 °C, 16 h; g $LiAlH_4$, THF, Δ, 4h;
h $(R'CO)_2O$ or R'COCl, Et_3N, CH_2Cl_2, 20 °C, 4 h

Acylation of the β-branched 5-methoxy-tryptamines gave the amides **190-192**, which were characterised by nmr, ir and mass spectroscopy. The amides **190** were obtained as racemic mixtures.

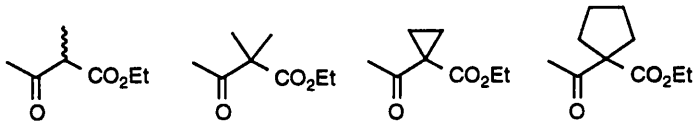


190a R'=Me
190b R'=Et
190c R'=n-prop

191a R'=Me
191b R'=Et
191c R'=n-prop
191e R'=cyclo-but

192a R'=Me
192b R'=Et
192c R'=n-prop
192d R'=cyclo-prop
192e R'=cyclo-but

γ-Brominated ethyl acetoacetates (**186a-d**) were obtained by bromination of the β-alkylated acetates **128** and **193 - 195**.

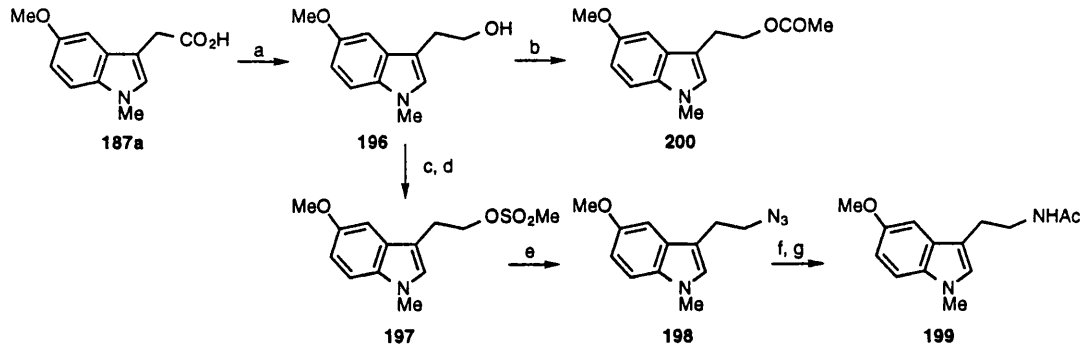


128 **193** **194** **195**

Alkylation of ethyl α-methyl-acetoacetate (**128**) with dimethyl sulphate and sodium hydride gave ethyl α,α-dimethyl-acetoacetate (**193**)[215], which was also obtained by dimethylation of ethyl acetoacetate (**148**). The cyclopropyl- and cyclopentyl derivatives **194** and **195** are obtained by alkylation of ethyl acetoacetate with dibromoethane and dibromobutane[216], respectively.

Bischler reaction of N-methyl-*p*-anisidine with ethyl 1-bromoacetyl-cyclopropane-1-carboxylate (**186d**) gave decomposition products, due to acid-catalysed opening of the cyclopropane ring. With the exception of 5-methoxy-N-methyl-indole-3-acetic acid (**187a**) all indole-3-acetic acids were cleanly converted into their acetamides via the mixed-anhydride method[157]. The amides were obtained as amorphous solids, which decomposed on recrystallisation from ethanol or ethyl acetate. Attempts to prepare 5-methoxy-N-methyl-indole-3-acetamide (**188a**) by heating the acid with urea failed, as did also an attempt to generate the mixed anhydride by using sodium hydride instead of triethylamine as base.

Therefore, N-methyl-melatonin (**199**) was prepared in analogy to the synthesis of N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles **107**. Reduction of 5-methoxy-N-methyl-indole-3-carboxylic acid (**187a**) with lithium aluminium hydride gave the tryptophol **196**, which is converted into its mesylate by treatment with sodium hydride and methanesulphonyl chloride. Using pyridine as base, no reaction was observed. Nucleophilic displacement of the mesylate by sodium azide and following reduction of the azide **198** gave 5-methoxy-N-methyl-tryptamine, which was acetylated with acetic acid anhydride to yield N-methyl-melatonin. The latter might also be obtained by N-alkylation of melatonin. 5-Methoxy-N-methyl-indole-3-ethanol (**196**) was also converted into the acetate **200**, which is the ester analogue of N-methyl-melatonin (**199**). Both melatonin analogues were obtained as yellow oils, which were identified by nmr, ir and mass spectroscopy.



Scheme 36: Synthesis of N-methyl-melatonin (**199**)

a $LiAlH_4$, THF, Δ, 2 h; b Ac_2O, CH_2Cl_2,, 25 °C, 16 h;

c NaH, THF, 20 °C, 30 min; d $MeSO_2Cl$, 25 °C, 4 h;

e NaN_3, EtOH, H_2O, Δ, 12 h; f $LiAlH_4$, THF, 20 °C, 24 h;

g Ac_2O, Et_3N, CH_2Cl_2, 20 °C, 4 h

III.3 Biological Results

Comparison of the binding inhibition constants of N-alkyl-melatonin analogues **183** and **199** shows a decrease in binding affinity with increasing size of the alkyl moiety (tab. 5), indicating that additional substituents at the indole nitrogen of melatonin interfere with binding to the receptor protein. The binding affinity of N-methyl-melatonin (**199**, K_i = 25 nM) is 40 times less than for melatonin (**1**, K_i = 0.58 nM) but 35 times higher than for the N-benzyl analogue **183a** (K_i = 897 nM). All N-alkyl melatonin derivatives await screening for biological activity.

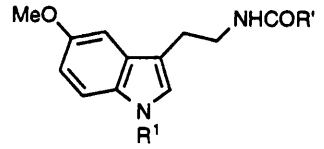
Structure	No	R^1	R'	K_i/nM
	**1**	H	CH_3	0.58
	199	CH_3	CH_3	25±4
	183a	Bn	CH_3	897±199
	183b	Bn	C_2F_5	>10000

Table 5: Binding affinity and biological activity of N-alkyl melatonin analogues
Ag = agonist, NT = not tested

Using the binding affinity of N-methyl-melatonin (**199**), the K_i values for the β-branched melatonin analogues can be compared to melatonin, assuming a cumulative and independent effect of both additional substituents (table 6).

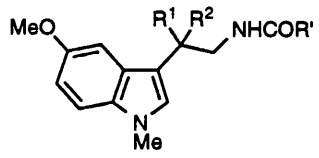
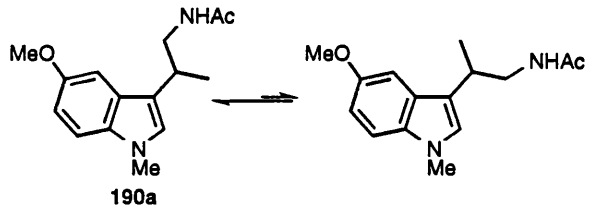
Structure	No	R^1	R^2	R'	K_i/nM
	**199**	H	H	CH_3	25±4
	190a	CH_3	H	CH_3	15.4±2.2
	190b	CH_3	H	C_2H_5	8.0±1.1
	190c	CH_3	H	n-C_3H_7	3.0±0.4
	191a	CH_3	CH_3	CH_3	5.8±0.7
	191b	CH_3	CH_3	C_2H_5	2.3±0.4
	191c	CH_3	CH_3	n-C_3H_7	1.2±0.26
	191e	CH_3	CH_3	c-C_4H_7	70.2±12.9
	192a	-$(CH_2)_4$-		CH_3	182±37
	192b	-$(CH_2)_4$-		C_2H_5	168±33
	192c	-$(CH_2)_4$-		n-C_3H_7	288±51
	192d	-$(CH_2)_4$-		c-C_3H_5	616±85
	192e	-$(CH_2)_4$-		c-C_4H_7	1810±220

Table 6: Binding affinity and biological activity of β-branched melatonin analogues. NT = not tested

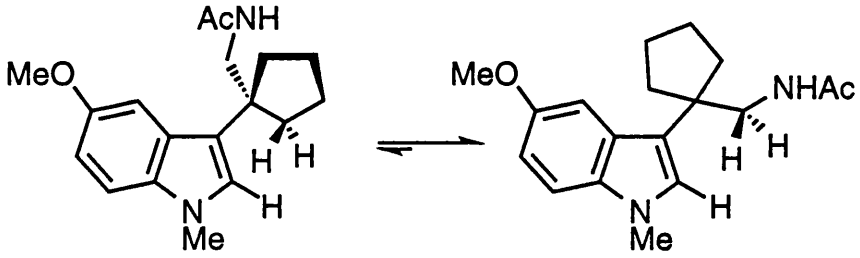
With the exception of the cyclopentane derivative **192c** the three sets of β-branched melatonin analogues, show an increase in binding affinities from the N-acetyl to the N-butanoyl moiety, which is in line with the reported data for N-acyl-5-methoxy-tryptamines (table 5, appendix)[123]. A further increase in size of the acyl group to the cyclopropylcarbonyl or cyclobutylcarbonyl derivatives **192d** and **192e** leads to a drop in binding affinity. Comparison with the binding affinity of N-methyl-melatonin (**199**, K_i = 25 nM) shows a slight increase of the binding inhibition constant by adding one or two methyl groups in β-position to the amide functionality (**190a**, K_i = 15.4 nM; **191a**, K_i = 5.8 nM). However, the increase in binding affinity does not compensate for the decrease of the K_i-value caused by introducing the N-methyl group.

Whereas two β-methyl groups improved the binding affinity to the melatonin receptor, introduction of the cyclopentane ring leads to a reduced affinity (**192a**, K_i = 182 nM). This might be caused by the increased steric demand of the cyclopentane ring or by a different orientation of the amide group. In contrast to the β-methyl analogues of melatonin the side chain in **192a** might adopt the orientation as in

conformer A, because of the greater interaction between protons of the cyclopentane and the pyrrole ring. Therefore, the amide group would be in a position similar to the one in N-acetyl-3-amine-5-methoxy-1,2,3,4-tetrahydrocarbazole (**107a**), which is reflected by their comparable binding affinities (**192a**, K_i = 182 nM; **107a**, K_i = 219 nM).



190a



192a

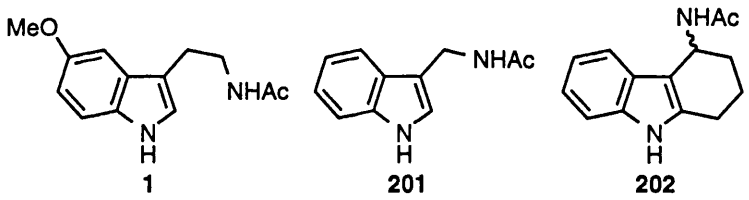
conformer A conformer B

The orientation of the amide group of the β-methyl analogues **190** and **191** mirrors the one found in N-acetyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydro-carbazole (**53a**). However, the greater flexibility of the side chain leads to a loss of binding affinity (**53a**, K_i = 0.97 nM; **190a**, K_i = 15.4 nM; **191a**, K_i = 5.8 nM).

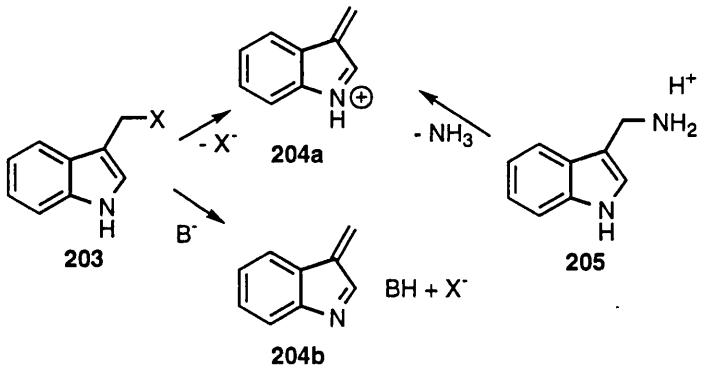
IV Synthesis of Nortryptamines

IV.1 Introduction

In contrast to the multitude of existing syntheses of tryptamine derivatives, reflecting their importance as serotonin analogues, nortryptamines have received less attention[217] and only a few synthetic routes for the preparation of N-acetyl-nortryptamines have been reported[218,219]. Additional to the screening of the flexible benzene analogues of melatonin (cf. chap. VI) the nortryptamines **201** and **202** provide valuable information about the importance of the side chain length in melatonin for conveying binding affinity to the receptor. Furthermore, the side chain in N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**) is fixed by incorporation into a cyclohexene ring.



Generally, nortryptamines are obtained by reduction of indole-3-carbaldehyde oximes or 3-cyano-indoles. Reducing agents include Raney-nickel, lithium aluminium hydride and sodium[220,221]. However, only little spectroscopic data for the parent 3-aminomethylindole have been submitted so far, emphasising the instability of the benzylic amine, which is easily dimerised by an elimination addition process via the reactive 3-indolyl-carbinyl cation (**204a**) (scheme 37).

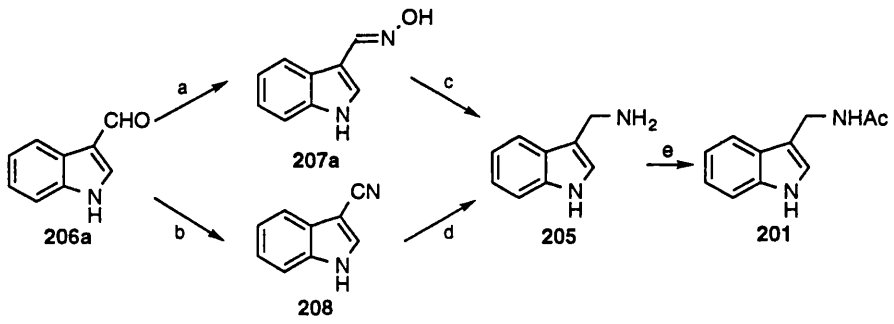


Scheme 37: Generation of the 3-indolyl-carbinyl cation (**204a**)

In contrast to indole-3-alkoxymethyl ethers (**203**, X=OAlk) and 3-halomethyl-indoles (**203**, X=halogen), which are labile under basic and neutral conditions[222], 3-aminomethylindole (**205, 203**, X=NH_2) also generates the reactive carbinyl cation **204a** under acidic conditions. To prevent this decomposition, nortryptamine is best derivatised directly after reduction of the nitrile or oxime precursor[218].

IV.2 Synthesis

Initially an attempt was made to synthesise nortryptamine (**205**) by reduction of the oxime **207a** under basic conditions in the presence of Devarda's alloy[223]. The oxime **207a** was prepared from indole-3-carbaldehyde (**206a**), which was obtained by Vilsmeier formylation of indole. Although the reduction with Devarda's alloy was successfully employed by Schallenberg and Meyer, the acylation of the crude amine under a variety of conditions did not yield the desired product, but a brown polymer.



Scheme 38: Attempted synthesis of N-acetyl-nortryptamine (**201**)
a EtOH, H_2NOH, 70 °C, 30 min; b DMF, H_2NOH, Δ, 10 min;
c, d Reduction; e Acetylation

Since Gower and Leete reported the dimerisation of 3-methaneamine-indole (**205**) under basic conditions at 80 °C, it is possible that the reduction with Devarda's alloy in the presence of sodium hydroxide at about 40 °C already lead to an intermolecular reaction of the amine[219]. To prevent this reaction the reduction with Devarda's alloy was also carried out under cooling with ice. The reaction proceeded slowly (hydrogen evolution ceased after 5 hours) and a yellow oil was isolated after extraction with ether. Attempts to purify the pale yellow crude amine by recrystallisation from benzene or by converting it into the hydrochloride or hydrooxalate salts[224] were unsuccessful.

The ^{1}H-nmr spectrum of the crude amine in d_6-DMSO shows the expected signals for a 3-substituted indole (two doublets of doublets for H5 and H6, singlet for H2,

two doublets for H4 and H7 and a broad signal at δ = 11 ppm) as well as a singlet at δ = 3.95 ppm for the methylene protons and a broad signal between δ = 3-4 ppm for the amine protons. However, Schallenberg and Meyer observed the signal for the methylene protons of nortryptamine at δ = 4.82 ppm in d_4-methanol.

Although the product of the reduction with Devarda's alloy could not be purified, the acetylation of the crude amine was attempted. Gower *et al.* reported the acetylation of 3-methaneamine-indole (**205**) with a solution of sodium acetate in acetic anhydride at 0 °C[219]. However, the acetylated amine was not obtained under the same reaction conditions.

Better results were achieved by acetylation in dichloromethane and triethylamine with acetyl chloride. The crude product was obtained after adsorptive filtration over silica and precipitation from a DMF solution. Although N-acetyl-nortryptamine (**201**) has been recrystallised from benzene[219], the crude product decomposed in contact with other solvents such as chloroform, ether, ethanol or benzene. The ir and ^{1}H nmr spectra showed an intensive carbonyl absorption band and peaks at δ=4.5 ppm (d, methylene protons) and δ=2.0 ppm (s, methyl protons), indicating the presence of the amide, which could not be purified.

Since the acetylation of the crude amine obtained by reduction of the oxime with Devarda's alloy produced an amide, which could not be purified, other syntheses of 3-methaneamine-indole based on the reduction of 3-cyano-indole (**208**) were examined.

3-Cyano-indole was prepared by a method reported by Liebscher and Hartmann[225], who reacted indole-3-carbaldehyde (**206a**) with hydroxylamine hydrochloride. Due to the high temperature of refluxing DMF the intermediate oxime spontaneously dehydrates to give the nitrile. This reaction was easily performed, if the hydroxylamine hydrochloride was added in small portions; otherwise the dehydration was not complete (a mass spectrum of the recrystallised product obtained by rapid addition of hydroxylamine hydrochloride shows peaks for the molecular ions of the oxime (m/z=160) and the nitrile (m/z=142)). The nitrile, which was characterised by ir-spectroscopy (ν = 2224 cm^{-1} (s, CN)) and elemental analysis, was obtained in about 90 % yield.

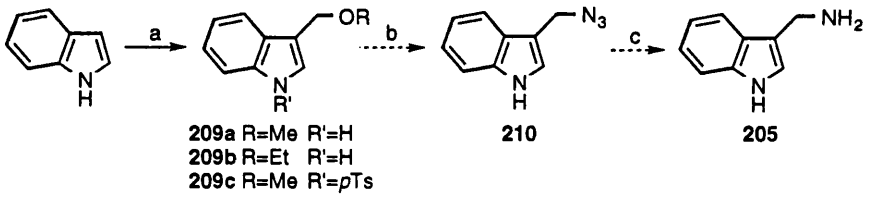
The hydrogenation of 3-cyano-indole with palladium-on-charcoal in the presence of ammonia (48 h, 20 °C; no higher temperature was applied to prevent the possible decomposition of the amine) or hydrochloric acid (24 h, 50 °C) was not successful. Both methods are standard procedures for the reduction of nitriles to primary amines. Whereas no reaction was observed in the case of ammonia, the reduction in the

presence of hydrochloric acid gave a water soluble product, which was precipitated by neutralisation with dilute sodium hydroxide solution. However, this precipitate was insoluble in methylene chloride, ether or ethyl acetate.

Gower *et al.* reduced the nitrile by hydrogenation in the presence of ammonia and Raney nickel-W-2[219]. After the reduction the characteristic ir-absorption band at ν = 2224 cm^{-1} disappeared, but the reported absorptions at 3325 and 3300 cm^{-1} were not observed.

In contrast to Gower and Leete, Somei *et al.* reported the successful reduction of the nitrile **208** by lithium aluminium hydride in THF[226]. Though an excess of the reducing reagent was used, no reaction was observed after 1 day at 25 °C and the nitrile was recovered from the reaction mixture.

Based on the reduction of 3-azido-1,2,3,4-tetrahydrocarbazole (**104**) to 3-amine-1,2,3,4-tetrahydrocarbazole (**105**) (cf. chap. II.2), the analogous conversion of 3-azidomethylindole (**210**) to nortryptamine (**205**) was envisaged (scheme 39).



Scheme 39: Attempted synthesis of 3-azidomethyl-indole (**210**)
a HCHO, NaOMe, MeOH, Δ, 10 h; b NaN_3, NaOMe, MeOH, Δ, 2 d;
c reduction

Initially, the synthesis of 3-azidomethylindole (**210**) was planned to commence from indole-3-methanol, which hydroxy group was then converted into a better leaving group, such as tosylate, which is finally displaced in a nucleophilic substitution with sodium azide. However, the attempted preparation of 3-methanol-indole, which was carried out according to the method reported by Runti[227], gave 3-methoxymethyl-indole (**209a**) instead of the alcohol. The ether **209a** was characterised by mass spectroscopy (m/z=130 for the molecular ion), elemental analysis and ^1H- (δCH_3=3.40 ppm, δCH_2=4.67 ppm) and ^{13}C nmr spectroscopy (δCH_3=57.5 ppm, δCH_2=66.4 ppm).

The reactivity of the benzylic methoxy group in **209a** was examined by heating 3-methoxymethyl-indole with sodium methanolate in ethanol, which resulted in an

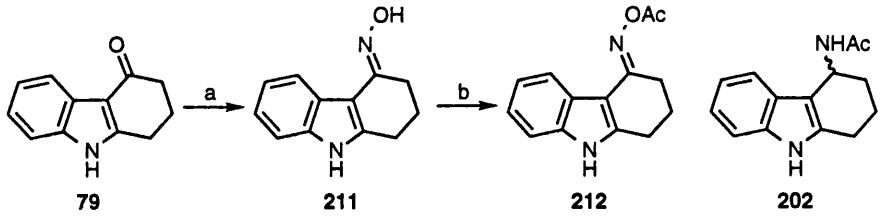
exchange of the methoxy group to give 3-ethoxymethyl-indole (**209b**). The ^1H nmr spectrum showed signals for the ethoxymethyl group at δ=1.47 ppm (t), δ=3.83 ppm (q) and δ=4.91 ppm (s).

The nucleophilic substitution confirms earlier results by Runti[227], who obtained 3-N-piperidinemethylindole by reacting piperidine with, as he believed, 3-methanol-indole in the presence of one equivalent of sodium ethanolate. Under base catalysis the indolic proton is abstracted and the aromatic pyrrole system rearranges under loss of the hydroxy- or alkoxygroup to give the intermediate diene **204b** (scheme 37). Nucleophilic attack at the benzylic carbon atom finally restores the indole system. This mechanism suggests that, under base catalysis, the methoxy group can be directly substituted by the azide group, using an excess of sodium azide.

However, no substitution for azide occurred under neutral conditions in DMSO or basic conditions in THF. The strong ir absorption at ν = 2130 cm^{-1}, which results from the asymmetric stretching of the azide group, was not observed in any crude product. Reacting 3-methoxymethyl-indole (**209a**) in ethanol with a catalytic amount of sodium methanolate the ethoxy ether **209b** was obtained.

Since the azide ion was not nucleophilic enough to effect the substitution under a variety of reaction conditions, an attempt was made to introduce a better leaving group such as in 3-(*p*-tosyloxymethyl)indole. Treating 3-methoxymethylindole (**209a**) with *para*-toluenesulphonyl chloride in the presence of one equivalent of pyridine a red polymer was obtained. This result confirmed Runti's observation, that 3-methanol-indole decomposed under acidic conditions and under treatment with acid chlorides in pyridine[227]. In an alternative procedure 3-methoxymethyl-indole (**209a**) was reacted with excess sodium hydride and the intermediate anion was subsequently treated with *para*-toluenesulphonyl chloride. However, the N-tosylate **209c** was obtained instead of the expected 3-methyltosylindole. This finding can be explained by the formation of an ionpair in the aprotic solvent THF, which prevents the rearrangement to the proposed diene **204b**. The N-tosylated indole **209c** was identified by ^1H and ^{13}C nmr spectroscopy; the ir spectrum showed no characteristic NH absorption at about ν = 3100 cm^{-1}.

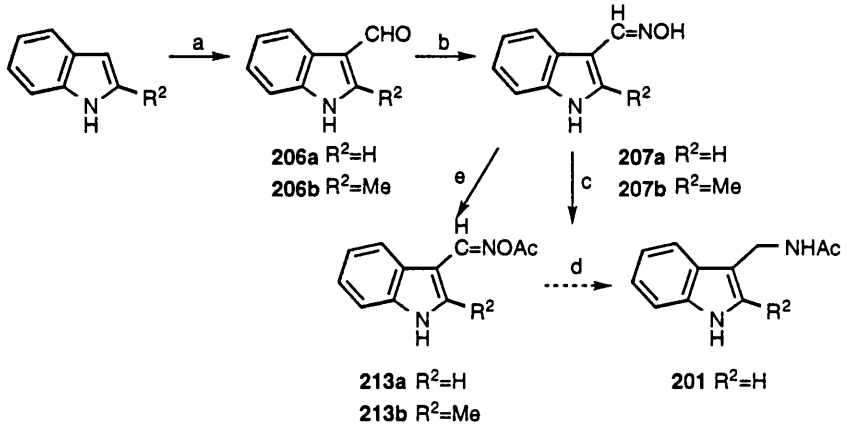
N-Acetyl-nortryptamine was finally prepared by a procedure reported for the synthesis of N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**)[218]. Fritz and co-workers obtained a mixture of O-acetylated oxime **212** and N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**) by platinum oxide catalysed hydrogenation of the tricyclic oxime **211**.



Scheme 40: Synthesis of N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**)
a H_2NOH, py., Δ, 3h; b Ac_2O, PtO_2, H_2, 25 °C, 7 d

Because of the enolisation of the ketone **79** (cf. chap. II.1.5) a prolonged reaction time and higher temperature was required for the oxime formation[228]. Catalytic reduction of the oxime with platinum(IV)-oxide in acetic anhydride gave N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**). The crude product was purified by column chromatography with benzene/ethyl acetate (1:1) and N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**) was identified by ir, nmr and mass spectroscopy. Characteristic is the coupling of the benzylic proton H4 with the amide proton and the adjacent aliphatic methylene protons. In contrast to the reported method, the formation of the O-acetyl oxime **212** could not be observed at the smaller scale of 2 mmol (original scale 5 mmol) and the amide **202** was the only product in 90 % yield[218].

After the successful synthesis of N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**) the preparation of the open chain analogue N-acetyl-3-methaneamineindole (**201**) was attempted under the same reaction conditions. The advantage of this procedure is, that reduction and immediate acetylation prevents decomposition of the intermediate amine (**205**).



Scheme 41: Synthesis of N-acetyl-nortryptamine (**201**)
a $POCl_3$, DMF, 35 °C, 90 min; b H_2NOH, py., Δ, 3h;
c, d Ac_2O, PtO_2, H_2, 25 °C, 7 d; e AcCl, Et_3N, CH_2Cl_2, 20 °C, 2 d

Reduction of the oxime **207a** in acetic anhydride gave a 1:1 mixture of the N-acetylated nortryptamine **201** and the O-acetylated oxime **213a**, which was separated by column chromatography (eluent: benzene/ethyl acetate 1:1). Both compounds gave distinct ^1H nmr spectra. Whereas the O-acetylated oxime **213a** shows a characteristic singlet for the imine proton, the reduced amine **201** shows a doublet at δ=4.59 ppm for the methylene protons coupling with the amide proton.

An attempt to convert the O-acetylated oximes **213** into the N-acetylated amines under the same reductive conditions of catalytic hydrogenation with platinum oxide in acetic anhydride failed. O-Acetylation and hydrogenation of the oxime are therefore competing processes. O-Acetyl 2-methyl-indole-3-carbaldehyde (**213b**), which was obtained by acetylation of the oxime **207b** in dichloromethane, crystallised in colourless plates, which allowed a X-ray crystal structure analysis (cf. fig. 29, appendix).

IV.3 Biological Results

The binding inhibition constant of both melatonin analogues, N-acetyl-nortryptamine (**201**) and N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**), is greater 10μM, which is considerable lower than the one for N-acetyltryptamine (**10**, K_i=730 nM). The marked loss of binding potency can only be explained by the shorter side chain. The effect of the conformational fixation of the side chain in N-acetyl-4-amine-1,2,3,4-tetrahydrocarbazole (**202**) on K_i could not be determined, since the binding affinity was too low. O-Acetyl-2-methyl-3-carbiminoxyindole (**213b**) also showed no binding affinity (K_i>10 μM) to the melatonin binding site in chicken brain.

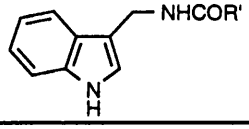
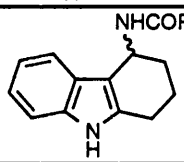
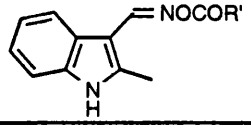
Structure	No	R'	K_i/nM
	**201**	CH_3	>10000
	**202**	CH_3	>10000
	**213b**	CH_3	>10000

Table 7: Binding affinity of various nortryptamines

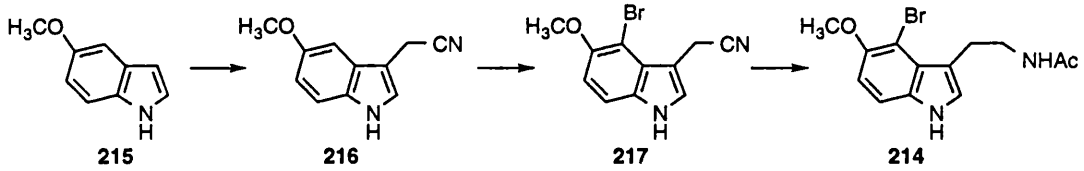
NT=not tested

V Synthesis of 4-Bromomelatonin

V.1 Introduction

Whereas melatonin analogues with substituents at C2 or C6 of the indole nucleus are well investigated[120,123,125], the effect of substituents at C4 on binding affinity and biological activity of melatonin has not been examined. Therefore, 4-bromomelatonin (**214**) was prepared to study the steric requirement around C4 of the melatonin molecule.

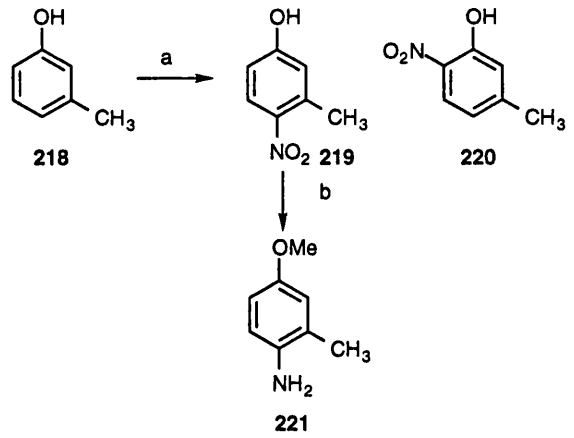
Recently, the bromination of melatonin by N-bromo-succinimide in acetic acid was reported to give 2-bromo-melatonin[124]. Consequently, the indole ring must be brominated selectively at C4 before the N-acylamine side chain is installed. Electrophilic substitution reactions of 5-alkoxyindoles suggest, that the alkoxy group directs the substituent to C4. Examples include the regioselective C4 nitration of 5-benzyloxygramine[229], the C4 bromination of 5-methoxygramine (**230**)[230] and the regiospecific Claisen rearrangement of 5-allyloxyindole to the 4-position[231]. A possible synthetic route towards 4-bromomelatonin (**214**) is therefore, the functionalisation of 5-methoxy-indole (**215**) to the 3-cyanomethyl derivative **216**, subsequent bromination, reduction of the nitrile **217** and finally acetylation.



Scheme 42: Planned synthesis of 4-bromomelatonin (**214**)

V.2 Synthesis

Two different syntheses for 5-methoxyindole (**215**) were investigated. Both commenced from 3-methyl-4-nitroanisole (**221**), which was prepared in two steps from *m*-cresol (**218**).



Scheme 43: Synthesis of 3-methyl-4-nitroanisol (**221**)
a HOAc, HNO_3, 5 °C, 90 min; b $(MeO)_2SO_2$, K_2CO_3, toluene, Δ

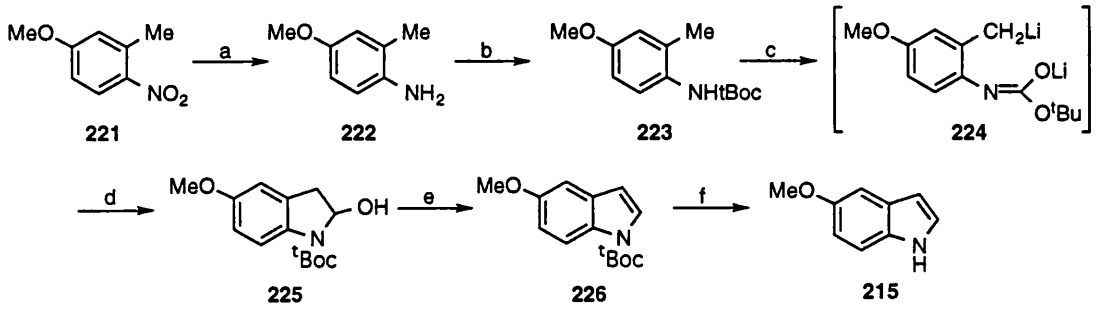
The nitration of *m*-cresol, was performed on a large scale (1.3 mol) and gave 3-methyl-4-nitrophenol (**219**) in 52 % yield[232]. However, the separation and purification of the isomeric mixture of 5-methyl-2-nitrophenol (**220**, yield 24 %) and 3-methyl-4-nitrophenol (**219**, yield 52 %) by steam distillation and sublimation is time consuming. The isomers can be distinguished by nmr spectroscopy. The ^1H nmr spectrum of 5-methyl-2-nitrophenol (**220**) showed an intramolecular hydrogen bond between the phenolic proton and the nitro group (δ_{OH}=10.59 ppm), whereas the phenolic proton in **219** has a chemical shift of δ_{OH}=6.2 ppm.

The crude 3-methyl-4-nitrophenol (**219**) was alkylated with dimethyl sulphate in 94 % yield to give 3-methyl-4-nitroanisole (**221**).

In the first synthesis of 5-methoxyindole (**215**), which was reported by Clark *et al.*, the ^{t}BOC derivative of 3-methyl-4-aminoanisole (**222**) was reacted with two equivalents *s*-butyl lithium[233]. The resulting dianion **224** was condensed with dimethylformamide and the intermediate alcohol **225** was dehydrated to the indole **226** under acid conditions. In the final step the protecting group was readily removed by alkaline hydrolysis.

For the reduction of 3-methyl-4-nitroanisole (**221**) three different methods were examined. On a large scale the reduction with tin(II) chloride was not favourable, because of the heterogeneous reaction mixture and the purification by steam distillation. The catalytic reduction with palladium-on-charcoal in 20 % aq. hydrochloric acid or Raney-nickel in ethanol produced the aniline **222** in good yield (85 %). Although the Raney-nickel catalyst had to be freshly prepared and the reduction took one day instead of 3 hours, this method was superior to the use of

palladium-on-charcoal, because of the applied moderate conditions. The liquid aniline **222** is easily purified via the hydrochloric salt and following distillation in high vacuum.



Scheme 44: Synthesis of 5-methoxy-indole (**215**)

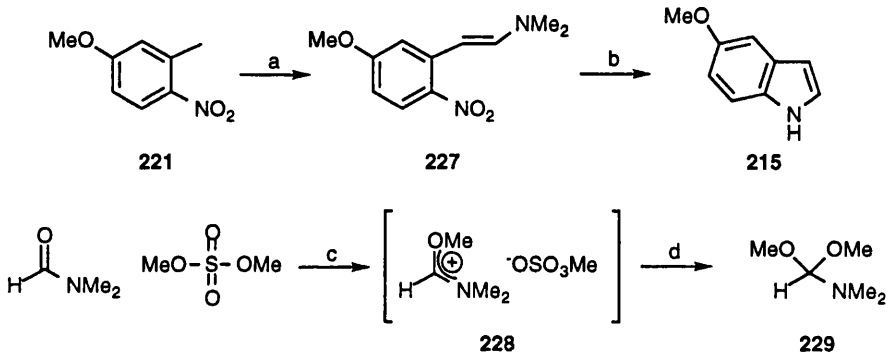
a Raney-nickel, H_2; b $O[CO_2{}^tBu]_2$, THF, Δ, 2 h; c 2eq. s-BuLi, THF, -40 °C;
d DMF, THF, -40 °C; e cat. conc. HCl, THF, 20 °C, 15 min;
f NaOH, EtOH, Δ, 30 min

Although the Clark synthesis gave 5-methoxyindole in 81 % overall yield, this method was only useful for the preparation of about 1 g 5-methoxyindole (**215**). Considering the projected functionalisation at position 3 of the indole ring, a more efficient synthesis for 5-methoxyindole was required. An attempt to synthesise larger amounts, failed due to the uncompleted heterogeneous dilithiation reaction and the difficulties in controlling the temperature of the reaction. At temperatures below -40 °C only monolithiation was observed. However, the presence of the readily removable t-Boc protecting group in the indole **226** is useful for the functionalisation of position 2 of the indole ring via lithiation with *t*-BuLi[234].

Larger amounts of 5-methoxyindole (**215**) were prepared by the application of the synthesis reported by Batcho and Leimgruber[235], which also starts from 3-methyl-4-nitroanisole (**221**).

In the first step of the Leimgruber-Batcho synthesis, 3-methyl-4-nitroanisole (**221**) was condensed with N,N-dimethylformamide diketal (**229**), which was prepared by a procedure reported by Bredereck *et al.* [236]. O-Alkylation of N,N-dimethylformamide gave the intermediate salt **228** as a viscous oil, which was added to a solution of sodium methanolate in methanol. Final distillation over a Vigreux-column afforded the moisture-sensitive diketal **229** in moderate yield. The main fraction of dimethylformamide diketal contained about 10% unreacted dimethylformamide, as

indicated by the ^1H nmr spectrum. However, the impurity was not removed, since DMF was the solvent in the condensation of ketal **229** with 3-methyl-4-nitroanisole (**221**). The condensation to the deeply red-coloured dimethylamino-2-nitrostyrene **227** went to completion on a scale of 80 mmol *o*-nitrotoluene. On a larger scale of 0.2 mol the product contained about 50 % of the starting material **221**, as indicated by the ^1H-nmr spectrum. Better yields were achieved by removing the produced methanol from the reaction mixture by distillation over a Vigreux column attached to a reflux variable head. This procedure displaced the equilibrium of the reaction towards the desired styrene **227**.



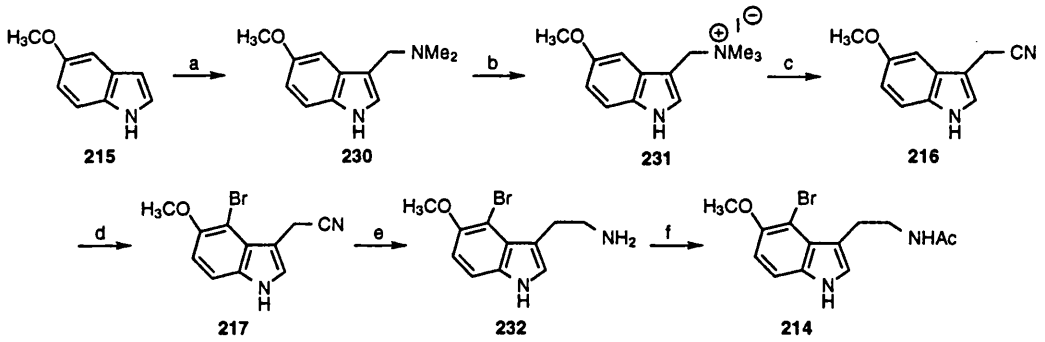
Scheme 45: Leimgruber-Batcho synthesis of 5-methoxyindole (**215**)
a DMF, DMF-diketal **229**, Δ, 22 h; b benzene, Pd/C, 90 min;
c 20 °C, 2 h; d NaOMe, MeOH, 20 °C, 12 h

The second step of the Leimgruber-Batcho method was the reductive cyclisation of the dimethylamino-2-nitrostyrene **227** to the indole nucleus, for which several conditions have been reported[237-239]. Synthesising 5-methoxyindole (**215**) optimal results were obtained by the catalytic hydrogenation with 10% palladium-on-charcoal. The presence of small amounts of unreacted 3-methyl-4-nitroanisole (**221**) led to formation of an unidentified product. It was, therefore, important to ensure that the condensation to the dimethylamino-2-nitrostyrene **227** went to completion.

Following the synthesis of 5-methoxyindole the ethaneamine side chain at C3 of the indole nucleus was installed. Because of the importance of tryptamine derivatives as analogues of serotonin, several distinct methods such as the reaction of indole with oxalyl chloride[240], the Henry reaction of nitroalkanes with indole-3-carbaldehydes[209]

and the reaction of indole magnesium bromide with aziridine[241] have been reported to achieve this synthetic modification of the indole ring.

Two syntheses can be envisaged for preparing the desired 3-cyanomethylindole derivative **216**. Majima and Hoshino reported the alkylation of indole magnesium bromide with chloroacetonitrile[242]. However, the yields of this method are generally low, because of competing polymerisation reactions. Therefore, an alternative approach was used for the synthesis of 3-cyanomethyl-5-methoxyindole (**216**).



Scheme 46: Synthesis of 4-bromomelatonin (**214**)

a HOAc, HCHO, $HNMe_2$, dioxane, 0 °C, 2 h; b MeI, EtOH, 0 °C, 30 min;
c KCN, H_2O, Δ, 4 h; d silica gel, NBS, CH_2Cl_2, 20 °C, 90 min;
e $LiAlH_4$, ether, 20 °C, 16 h; f AcCl, Et_3N, CH_2Cl_2, 20 °C, 1 h

In the first step of the synthesis 5-methoxyindole (**215**) was converted to the gramine derivative **230** by treatment with formaldehyde and dimethylamine[182,234]. The Mannich reaction proceeded in 83 % yield, and the product was identified by the ^1H nmr signals of the dimethylaminomethyl group (singlets at 2.31 and 3.61 ppm). To activate the gramine derivative for the nucleophilic substitution with cyanide the tertiary amine was converted into the intermediate trimethylammonium salt **231** by treatment with iodomethane. The ammonium salt was reacted *in situ* with potassium cyanide, which was either added together with iodomethane or after the quaternisation was completed[243]. Several polar solvent systems such as methanol/water/DMF and ethanol/water[243] were investigated for this nucleophilic substitution. Yields in both procedures were satisfactory, 56 % and 44 %, respectively. In the ^1H nmr spectrum the benzylic protons of the nitrile gave a singlet at 3.77 ppm.

Bromination of 3-cyanomethyl-5-methoxyindole (**216**) utilised a method published by Mistry *et al.*, who brominated 3-cyanomethylindole with one equivalent of N-bromo-succinimide in the presence of silica gel, to obtain 2-bromo-3-cyanomethylindole[244]. As expected, the directing effect of the 5-methoxy group gave,

under these mild bromination conditions, 3-cyanomethyl-4-bromo-5-methoxyindole. Subsequent reduction with lithium aluminium hydride was carried out at 20 °C to avoid possible reductive elimination of the bromine substituent. The amine was purified as its hydrochloride salt and identified by ir spectroscopy, which showed no nitrile absorption at $\nu = 2251$ cm^{-1} but a new broad band at $\nu = 3405$ cm^{-1}. Finally, acetylation of the amine **232** with acetyl chloride in dichloromethane and triethylamine gave the desired 4-bromomelatonin (**214**), which showed similar nmr and mass spectra to those reported for 2-bromomelatonin[124]. The chemical shifts of the ^{1}H nmr signals were identical; however, the usually observed coupling pattern for H4, H6 and H7 of the 5-substituted indole derivatives such as **46a** (cf. NMRB, appendix) had changed slightly, because of the missing small coupling to H4. Therefore, only two doublets with $^3J = 9.1$ and 8.7 Hz were observed for H6 and H7. The proton H2 showed a broad singlet at $\delta = 7.01$ ppm, possibly coupling to the NH proton.

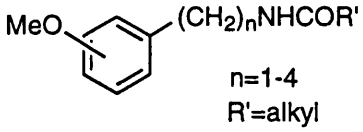
V.3 Biological Results

The binding inhibition constant of N-acetyl-4-bromo-5-methoxytryptamine (4-bromomelatonin, **214**) was found to be $K_i = 1.1 \pm 0.1$ nM, which is twice the K_i-value for melatonin. Therefore, sterically demanding substituents, such as bromine, are tolerated at C4. The biological activity of this novel melatonin analogue is awaited. Whereas 4-bromomelatonin showed a slight decrease in binding affinity, halogens bound at C6, such as 6-fluoromelatonin (K_i=0.36) and 6-chloromelatonin (K_i=0.41) exhibited a similar binding as melatonin (K_i=0.58)[123].

VI Synthesis of Benzene Analogues of Melatonin

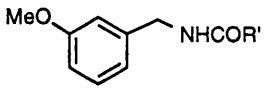
VI.1 Introduction

The nortryptamine analogues of melatonin showed a dramatic loss in binding affinity to the chick brain binding site (cf. chap. IV). To further investigate the dependence of binding affinity on the spatial distance between the methoxy and the amide pharmacophore, a series of benzene analogues with various side chain lengths was synthesised. Furthermore, the position of the methoxy substituent in the benzene ring was varied to examine the influence of the substitution pattern on binding affinity.

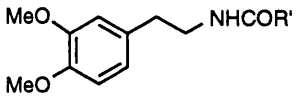


VI.2 Synthesis

N-Acyl-1-aminomethyl-3-methoxybenzenes (**233**) and N-Acyl-1-aminoethyl-3,4-dimethoxybenzenes (**234**) were prepared by standard acylation of the commercially available amines.

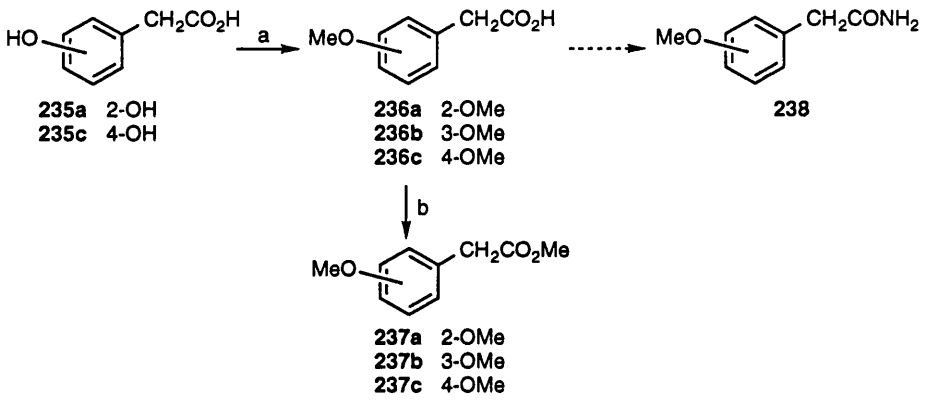


233a R'=Me
233b R'=Et
233c R'=n-prop



234a R'=Me
234b R'=Et
234c R'=n-prop

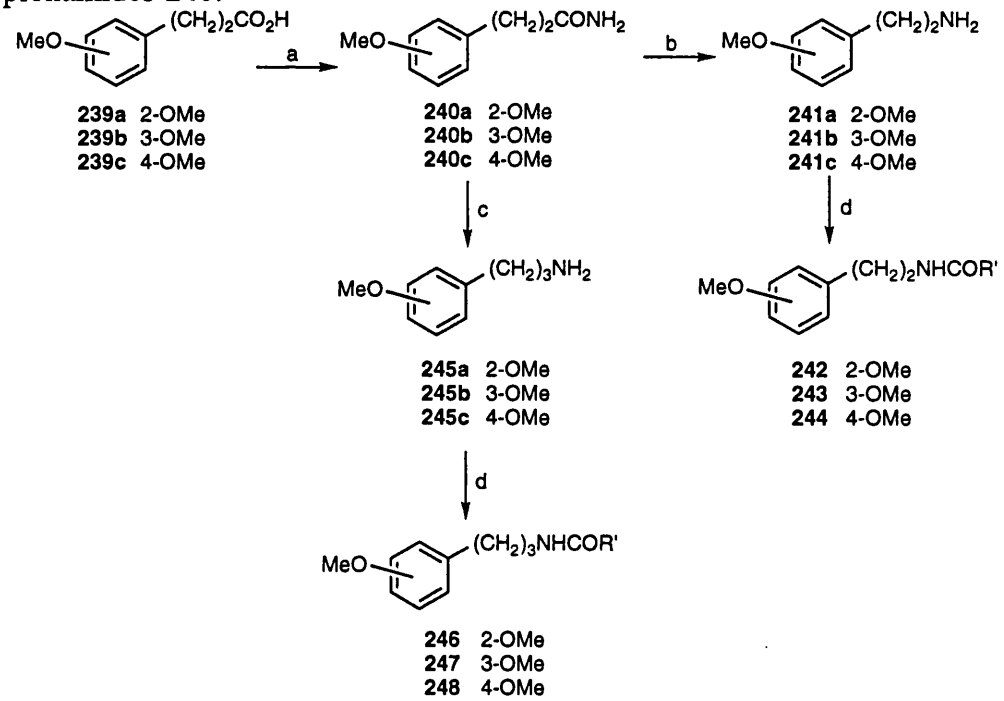
Initially an attempt was made to synthesise N-acyl-methoxyphenylethaneamines **242 - 244** by acylation of the amines **241a-c**, which can be obtained by reduction of the amides **238**. However, the usually successfully employed conversion of carboxylic acids to amides via ammonolysis of mixed anhydrides failed for all three investigated methoxy-phenylacetic acids and the acetates **237** were obtained rather than the desired amides **238** (scheme 46). Methoxyphenylacetic acids were produced by dimethyl sulphate alkylation of the parent phenols **235**. Treating the acid chloride of 2-methoxyphenylacetic acid (**236a**) with ammonium hydroxide solution resulted only in the recovery of the starting material.



Scheme 46: Attempted synthesis of methoxyphenylacetamides (**238**)

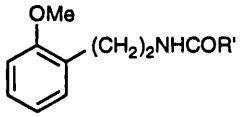
a $(MeO)_2SO_2$, aq. NaOH, 25 °C; b Et_3N, CH_2Cl_2, 0 °C, 10 min; $ClCO_2Me$, CH_2Cl_2, 0 °C, 4 h; NH_3, 20 °C, 16 h

In contrast to methoxyphenylacetic acids **236**, the homologous 3-(methoxyphenyl)propionic acids **239** were cleanly converted to their amides (**240**) by reaction of the carboxylate anion with methyl chloroformate and subsequent treatment of the mixed anhydride with ammonia. Therefore, the desired 2-(methoxyphenyl)-ethanamines **241** were prepared by Hofmann degradation of 3-(methoxyphenyl)-propionamides **240**.

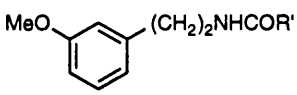


Scheme 47: Synthesis of N-acyl-ω-(methoxyphenyl)alkanamides

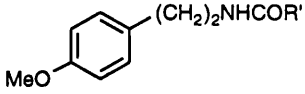
a Et_3N, CH_2Cl_2, 0 °C, 10 min; $ClCO_2Me$, CH_2Cl_2, 0 °C, 4 h; NH_3, 20 °C, 16 h; b NaOBr, NaOH, 60 °C, 30 min; c $LiAlH_4$, THF, Δ, 2h; d $(R'O)_2O$ or R'OCl, CH_2Cl_2, Et_3N, 20 °C, 1 h



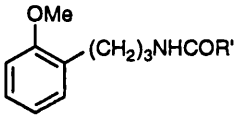
242a R'=Me
242b R'=Et
242c R'=n-prop
242d R'=n-but



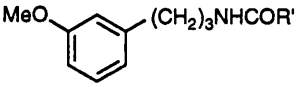
243a R'=Me
243b R'=Et
243c R'=n-prop
243d R'=n-but



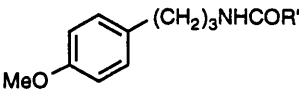
244a R'=Me
244b R'=Et
244c R'=n-prop
244d R'=n-but



246a R'=Me
246b R'=Et
246c R'=n-prop
246d R'=n-but



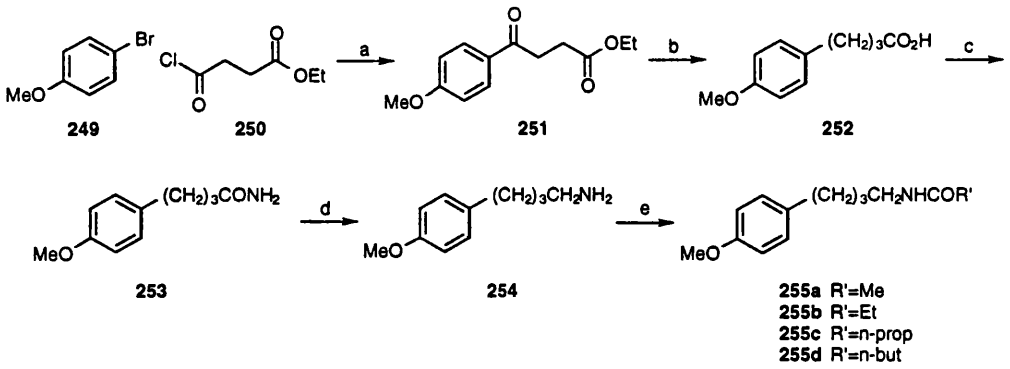
247a R'=Me
247b R'=Et
247c R'=n-prop



248a R'=Me
248b R'=Et
248c R'=n-prop

For the synthesis of N-acyl-4-(4-methoxyphenyl)butanamines (**255**) a general method was investigated, by which the 2- and the 3-methoxyphenyl analogues should also be accessible[245]. In a modified Reformatski reaction 4-methoxyphenyl magnesium bromide was reacted with cadmium chloride. The cadmium organic compound was then treated with ethyl 4-chloro-4-oxo-butanoate (**250**), which was obtained by treatment of succinic anhydride with ethanol[246] and subsequent reaction of the monoester with thionyl chloride. The keto ester **251** was reduced and saponified by applying the Huang-Minlon modification of the Wolff-Kishner reduction, which gave 4-(4-methoxyphenyl)butanoic acid (**252**)[245]. In contrast to the reported cleavage of the methoxy ether of the analogous ethyl 4-oxo-4-(4-methoxyphenyl)butanoate[245] no dealkylation was observed under identical reaction conditions and the carboxylic acid **252** was converted into the amide **253** under standard conditions. Lithium aluminium hydride reduction and subsequent acylation in dichloromethane/triethylamine yielded the desired N-acyl-4-(4-methoxyphenyl)butanamines **255**.

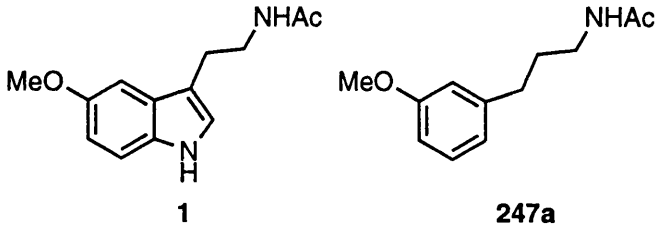
All of these benzene analogues of melatonin were characterised by nmr, ir and mass spectroscopy.



Scheme 48: Synthesis of N-acyl-4-(4-methoxy-phenyl)butanamines (**255**)
a Mg, ether, C_6H_6, 25 °C, 30 min; $CdCl_2$, Δ, 30 min; **250**, Δ, 1 h;
b KOH, N_2H_4, Δ, 6h; c Et_3N, CH_2Cl_2, 0 °C, 10 min;
$ClCO_2Me$, CH_2Cl_2, 0 °C, 4 h; NH_3, 20 °C, 16 h;
d $LiAlH_4$, THF, Δ, 2h; e $(R'O)_2O$ or R'OCl, CH_2Cl_2, Et_3N, 20 °C, 1 h

VI.3 Biological Results

The binding affinities of the benzene analogues of melatonin for the chicken brain binding site are listed in table 8. Optimal binding affinity was observed for analogues **247**, which mimic the structure of melatonin as they have the identical number of C atoms between the methoxy and amide pharmacophore and the *meta* methoxy group is in equivalent position as the 5-methoxy group in melatonin. Surprisingly, only a 100-fold loss in binding affinity was determined for these very flexible analogues of melatonin and the N-propanoyl and N-butanoyl derivative (**247b, c**) showed a considerable K_i-value of 5 nM. This finding provides more evidence for the theory, that the pyrrole ring serves as a rigid spacer rather than a binding site via the indole NH group. Therefore, melatonin analogues which are using similar spacers, such as naphthalene and benzo[b]thiophenes derivatives, retain binding affinity.



1 **247a**

The position of the methoxy group is, however, of major importance for the melatonin-like affinity of these flexible benzene analogues. A dramatic drop in binding affinity was observed, when the methoxy group was moved into *ortho* or *para* position (compounds **246** and **248**). This finding contrasts results obtained for the 4- and 6-methoxy analogue of melatonin, which only exhibit a slightly reduced K_i-value[123].

In analogy to the N-acyl-propanamines **246-248**, the N-acyl-ethanamines **242-244** show optimal binding affinity for the *meta*-methoxy derivatives, with the differences between the 2- and 3-methoxy derivatives being less striking. However, reducing the distance between the pharmacophores by one methylene spacer resulted in an overall lower affinity for the melatonin binding site. Copinga *et al.*, who investigated the binding affinity of **242a** (K_i=420 nM), **243a** (K_i=581 nM) and **244a** (K_i>10 μM) to the melatonin receptor in chicken retina (melatonin, **1**, K_i= 0.57 nM), observed similar binding affinities[129]. It is interesting to note that for all benzene analogues an increase in affinity was observed on going from N-acetyl to N-butanoyl derivatives, which is in analogy to the series of melatonin analogues (cf. tab. 5, appendix) but contradicts the earlier finding by Copinga *et al.*, who reported a loss in affinity for **242b** (K_i=789 nM) in their assay[129]. The N-pentanoyl derivatives generally showed no affinity to the melatonin binding site. Adding a second methoxy group to the benzene ring retained the K_i-value in the series of N-acyl-2-(3,4-dimethoxyphenyl)ethanamines (**234**). Compounds with one or four methylene spacer (**233** and **255**) showed no binding affinity; however, the effect of varying the position of the methoxy group on the benzene ring has not been examined, so far.

For the future design of melatonin analogues the N-acyl-3-(3-methoxy-phenyl)propanamines (**247**) provide an excellent model, which is easily modified. Evaluating binding affinity and biological activity of benzene derivatives with various substituents other than the methoxy group, might lead to the synthesis of novel 5-substituted melatonin analogues.

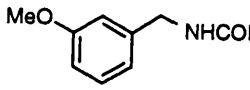
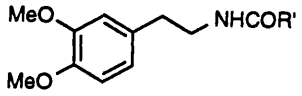
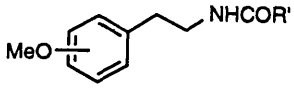
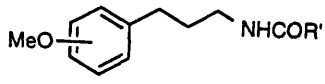
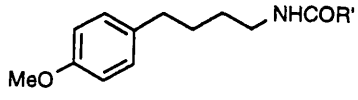
Structure	No	R	R'	K_i/nM
	**233a**		CH_3	NE at 10000
	233b		C_2H_5	>10000
	233c		n-C_3H_7	>10000
	**234a**		CH_3	870±130
	234b		C_2H_5	130±20.5
	234c		n-C_3H_7	59.1±9.2
	**242a**	2-OMe	CH_3	573±68
	242b	2-OMe	C_2H_5	135±21
	242c	2-OMe	n-C_3H_7	69±12
	242d	2-OMe	n-C_4H_9	16000±1600
	243a	3-OMe	CH_3	958±108
	243b	3-OMe	C_2H_5	62±7
	243c	3-OMe	n-C_3H_7	39.9±6.4
	243d	3-OMe	n-C_4H_9	741±63
	244a	4-OMe	CH_3	133±75.4 µM
	244b	4-OMe	C_2H_5	19.2±5.1 µM
	244c	4-OMe	n-C_3H_7	17.9±5.2 µM
	244d	4-OMe	n-C_4H_9	70.8±41 µM
	**246a**	2-OMe	CH_3	1430±310
	246b	2-OMe	C_2H_5	374±80
	246c	2-OMe	n-C_3H_7	442±122
	246d	2-OMe	n-C_4H_9	>10000
	247a	3-OMe	CH_3	63.4±4.0
	247b	3-OMe	C_2H_5	5.6±1.7
	247c	3-OMe	n-C_3H_7	5.5±1.8
	248a	4-OMe	CH_3	>10000
	248b	4-OMe	C_2H_5	2900±800
	248c	4-OMe	n-C_3H_7	860±210
	**255a**		CH_3	7300±1300
	255b		C_2H_5	1400±300
	255c		n-C_3H_7	822±192
	255d		n-C_4H_9	7000±1100

Table 8: Binding affinity of N-acyl-ω-aminoalkyl-anisidines

Experimental Part

VII Biological assays

The *in vitro* screening of the synthesised melatonin analogues for binding affinity in chick brain and biological activity in *Xenopus* dermal melanophores was carried out by Dr D Sugden, King's College, London.

VII.1 Binding Affinity of Melatonin Analogues

Binding affinities are reported as inhibition constants (K_i) indicating the ability of the melatonin analogues, to displace the radioligand 2-[^{125}I]iodomelatonin from receptors in chick brain membranes[109].

- Animals

Chicken (*Gallus domesticus*, white leghorn) were obtained from Orchard Farms (Buckinghamshire, UK) at 1-day of age and were housed under a diurnal lighting cycle (12:12 h L:D, lights on at 06.00 h) in a temperature-controlled (28±2.4 °C) room. All animals were killed between 13.00 and 15.00 h.

- Membrane preparation

At 2 weeks of age chickens were killed by decapitation and the whole brain was rapidly removed and immediately frozen in liquid nitrogen and stored at -70 °C until used. Brain tissue was homogenised in 20 vols. of Tris-HCl (50 mM, pH 7.4) containing PMSF (1 mM), leupeptin (50 µg/ml) and EGTA (1 mM). Homogenates were centrifuged (35.000 g, 30 min, 4 °C), then the pellets were re-homogenised in the same buffer and centrifuged for a second time. The final membrane pellet, at a concentration of approximately 1.0 to 2.0 mg of protein/ml, was resuspended in Tris-HCl and aliquots were stored at -70 °C until used.

- Membrane binding assays

30 µl Aliquots of membranes (approximately 30 to 50 µg of protein) and 20 µl of buffer were incubated at 25 °C for 60 min with 50 µl 2-[^{125}I]iodomelatonin (30-60 pM in 50 mM Tris-HCl, pH 7.4). 10-Fold serial dilutions of stock solutions of the melatonin analogues (0.01 M in methanol or DMSO) were made in buffer just before use. 10 µl Aliquots were added to the membrane solution. The binding assays were terminated by the addition of 2 ml ice-cold Tris-HCl buffer and immediate filtration through glass fibre filters. After washing the filter twice with 5 ml of buffer, it was counted on a LKB 1282 Compugamma CS counter. Aliquots (2x10 µl) of 2-

[^{125}I]iodomelatonin were counted in order to calculate the concentration of radiolabel actually added. All assays were done in dublicate.

- Data analysis

The inhibition constant (K_i) was calculated using the Cheng-Prusoff equation $K_i = IC_{50}/(1+[ligand]/K_d)$, where IC_{50} = concentration of competing drug which reduces specific binding by 50 % and K_d = dissociation constant obtained from kinetic experiments[247].

Errors given for the binding inhibition constants are the standard errors of the computer estimates obtained from fitting a single competition curve.

VII.2 Biological Activity of Melatonin Analogues

The biological activity was qualitatively studied by the pigment aggregation assay in *Xenopus laevis* dermal melanophores[121,134].

- Introduction

Dermal melanophores are pigmented cells which are prevalent in amphibians and fish. The contribution of the black pigment, which is contained in granules called melanosomes, affects the appearance of the cell. Thus when the melanosomes are dispersed the cell will appear black, whereas when the granules are aggregated the cell appears blanched or white. This lightening and darkening of skin colour in amphibians is modulated by melatonin - melatonin agonists cause pigment aggregation whereas antagonist reverse the melatonin-induced pigment aggregation[248].

- Tissue culture

Xenopus laevis embryos were produced from adult frogs induced to lay by injection of human chorionic gonadotrophin. The neural plate from stage 20 embryos was dissected out and dispersed into small aggregates. After 2-3 days of culture melanophores were visible among many nerve, muscle and undifferentiated cells. Melanophores were grown in medium containing NaCl (100 mM), KCl (2.5 mM), CaCl (2 mM), $MgCl_2$ (2 mM), $NaHCO_3$ (5 mM), 10 % foetal calf serum, penicillin (100 iu/ml), streptomycin (100 µg/ml), amphotericin B (2.5 µg/ml) and α-melanocyte stimulating hormone (α-MSH, 30 nM). Addition of α-MSH to the cultures resulted in proliferation of melanophores and the full dispersion of pigment granules throughout the cell. Aggregation experiments were done between 7 and 12 days of culture.

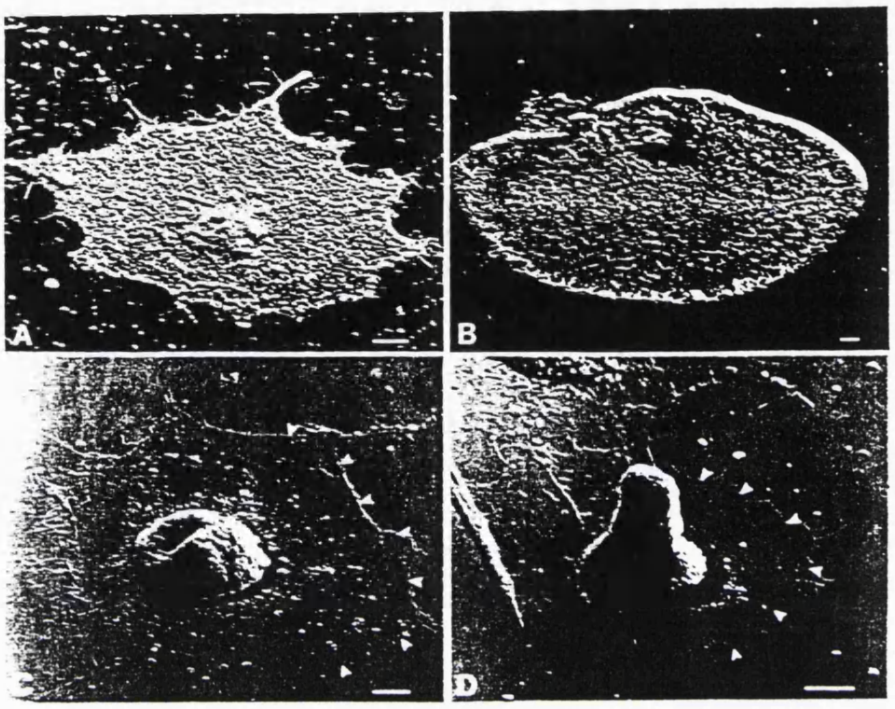


Figure: Scanning electron micrographs of dispersed and aggregated melanophores with increasing concentrations of melatonin from frame A to D. The arrowheads in frames C and D mark the peripheral edge of the cytoplasm. The white bars are 10 µm in length[248].

- Aggregation assay

Melanophores were washed twice with fresh culture medium. A 10 mM stock solution of the melatonin analogue in methanol was diluted before use with deionised water. The maximal concentration of methanol added (0.1 %) did not induce pigment aggregation. 10 Min. after the drug was added, the area covered by pigment was related to the initial pigmented area.

Antagonists were tested by first adding melatonin (10 nM), which induced full pigment aggregation to 15 and 25 % of the initial area. Then increasing concentrations of each putative antagonist were added and the aggregated area was remeasured after 30 min. In this way cumulative dose-response curves of melatonin agonists and antagonists were constructed.

VIII Chemical Syntheses

VIII.1 General

Chemical reagents were purchased from Aldrich Chemical Co., Lancaster, Fisons and BDH. Solvents were purified by standard methodologies[249]. All experiments using water sensitive reagents were carried out under an atmosphere of dry nitrogen or argon.

Microanalysis samples were prepared by drying *in vacuo* at room temperature over silica gel. The analyses were carried out by the Microanalytical Section of the Chemistry Department, University College London, with a Perkin-Elmer 2400 CHN Elemental Analyser.

Melting points were determined on a Reichert melting point apparatus. Both, melting and boiling points are uncorrected.

Infra-red (IR) spectra were recorded on a Perkin-Elmer PE-983 or Perkin-Elmer 1605 FTIR spectrometer using potassium bromide pellets unless stated otherwise. Main absorption bands are reported with wavenumber ν in cm^{-1} and intensity (s, strong; m, medium; w, weak; br, broad).

Proton nuclear magnetic resonance (^{1}H-nmr) spectra were recorded on a Varian VXR-400 (400 MHz) or VXR-200 (200 MHz) spectrometer. Chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz, respectively. The spectra were recorded in deuterochloroform ($CDCl_3$) or dimethylsulphoxide-d_6 (d_6-DMSO) solution. Residual protic solvent ie. $CHCl_3$ (δ_H 7.26 ppm) or CD_3SOCD_2H (δ_H 2.52 ppm) was used as internal reference. The following abbreviations are used in signal assignments: s (singlet), d (doublet), t (triplet), q (quartet), qi (quintet), se (sextet), h (heptet), m (multiplet) and br (broad). Carbon nuclear magnetic resonance (^{13}C-nmr) spectra were recorded at 100 MHz on a Varian VXR-400 spectrometer. Signals are reported as δ values, using the resonances of $CDCl_3$ (δ_C 77.0 ppm, t) or $(CD_3)_2SO$ (δ_C 39.7 ppm, h) as reference. The signal multiplicity was determined by an APT pulse sequence.

Mass spectra were recorded on a VG7070H mass spectrometer with Finnigan Incos II data system at University College London, or on a VG ZAB-2F (EIMS) or VG12-250 (CI) mass spectrometer at the London School of Pharmacy.

Crystal structures were obtained by using an automated four-circle diffractometer (Nicolet R3mV) equipped with Mo-Kα radiation (λ=0.71073 Å). The structure solution used the SHELXTL PLUS program package on a microVax II computer.

For analytical thin layer chromatography (TLC) Merck Kieselgel 60 F_{254} plates were used. Compounds were visualised by ultra-violet light or by heat development using a *p*-anisaldehyde [350 ml 95 % EtOH, 12 ml conc. H_2SO_4, 8 ml *p*-anisaldehyde, 6 ml glacial acetic acid] or an acidic ammonium molybdate(VI) [250 ml conc. H_2SO_4, $(NH_4)_2MoO_4$ 4 H_2O, 2.25 l H_2O] based staining preparation. Column chromatography (CC) was performed using Merck flash silica gel 60 (200-400 mesh) or Sorbsil C60-A (40-60 µm) flash silica. Spinning plate chromatography (SPC) was carried out using Merck silica gel 60 PF_{254} with calcium sulphate.

Apart from the numbering used for assignment of nmr signals the naming and numbering of compounds throughout the experimental section adheres to Chemical Abstract nomenclature.

VIII.2 General Procedures

VIII.2.1 Preparation of α-Bromoketones

At 0 °C bromine (1.1 eq) is added dropwise to a solution of the ketone (1 eq) in ether (150 ml for 0.05 mol). The mixture is stirred for 16 h at 25 °C. The organic layer is washed with water (2x200 ml) and sat. sodium bicarbonate solution (200 ml). After drying over calcium chloride the solvent is evaporated at room temp. to yield the crude α-bromoketone which is of sufficient purity for the Bischler synthesis.

VIII.2.2 Bischler Reaction

A mixture of the N-methylaniline (2 eq) and the α-bromoketone (1 eq) is stirred under nitrogen at 50 °C for 3 h. The dark viscous mixture is dissolved in 2-propanol (100 ml/0.1 mol of aniline) and treated with 3 eq of zinc chloride, which was previously dried at 25 °C/1 mmHg for 2 d. This mixture is refluxed under nitrogen for 16 h. Then the solvent is removed by evaporation and the product is extracted by addition of 2N hydrochloric acid and ethyl acetate (3x100/150 ml). The red organic layer is washed with water (2x100 ml) and sat. sodium carbonate solution (2x100 ml) and dried over magnesium sulphate. Evaporation of the solvent yields the crude product which is of sufficient purity for the subsequent reaction.

VIII.2.3 Saponification of Esters obtained by Bischler Reaction

The crude product of the Bischler reaction is dissolved in hot 90 % aqueous methanol or ethanol. 10 Eq. sodium hydroxide is added and the brown reaction mixture is refluxed for 6 h. Then the alcohol is removed by evaporation *in vacuo* and the alkaline solution is washed twice with dichloromethane. The product is precipitated by pouring the solution into an excess of ice-cold 10 % hydrochloric acid. After filtration under suction and washing with water the acid is dried at 25 °C/1 mm Hg.

VIII.2.4 Synthesis of Primary Amides

The carboxylic acid (1 eq) is dissolved in CH_2Cl_2 (10 ml/g). Triethylamine (1.1 eq) is added and the mixture is cooled to 0 °C. After 10 min methyl chloroformate or ethyl chloroformate (1.1 eq) is added dropwise to the stirred mixture. In some experiments a solid precipitates which is dissolved by addition of dichloromethane. Stirring is continued for 30 min at room temp. and then ammonia is bubbled through the solution for 2 min. A white solid precipitates.

After 1 h the reaction mixture is poured into a separatory funnel and washed with H_2O (20 ml), 2N HCl (2x20 ml) and 2N NaOH (2x20 ml). After drying over $MgSO_4$ the solvent is removed by evaporation to leave the crude amide which is of sufficient purity for the subsequent reduction with borane or $LiAlH_4$.

VIII.2.5 Reduction of Primary Amides

Two different reagents, $LiAlH_4$ (procedure A) and BH_3THF (procedure B) are employed for reducing primary amides to the corresponding amines.

- Procedure A

A solution of the amide (1 eq) in anhydrous THF (10 ml/g) is added dropwise to a suspension of lithium aluminium hydride (10 eq) in anhydrous THF (20 ml/g). After the addition is completed the reaction mixture is refluxed for 2 h. Excess lithium aluminium hydride is decomposed by careful addition of water (2 ml). The reaction mixture is filtered under suction and the filter cake is washed with ethyl acetate.

After washing the filtrate with water (20 ml) the product is extracted with dil. hydrochloric acid (2x20 ml). The aqueous layer is washed with ethyl acetate (20 ml). 2N Sodium hydroxide solution is then added to the aqueous layer to liberate the amine and the product is extracted with ethyl acetate (2x20 ml). After drying over magnesium

sulphate and evaporation of the solvent the amine is obtained as colourless oil in sufficient purity for the acylation.

- Procedure B

To a solution of the amide (1 eq) in anhydrous THF (10 ml/g) is added dropwise a 1M solution of borane-THF (2 eq). After the addition is completed the reaction is stirred for 16 h at 25 °C. Then excess borane is decomposed by careful addition of water (2 ml). The further work-up of the amine is described in procedure A.

VIII.2.6 Synthesis of Secondary Amides

Apart from trifluoroacetamides the secondary amides are prepared by acylation of the amine with either the appropriate anhydride (procedure A) or the acid chloride (procedure B) in dichloromethane and triethylamine.

- Procedure A

The required amount of amine is dissolved in CH_2Cl_2 (20 ml) and NEt_3 (5 ml). To this stirred solution is added the anhydride (1.1 equiv.). After 1 hr at room temp., the reaction mixture is poured into a separatory funnel; ether (20 ml) is added and the yellow organic layer is washed with H_2O (20 ml), 2N HCl (2x20 ml), sat. aqueous $NaHCO_3$ (2x20 ml) and brine (20 ml). After drying over $MgSO_4$ the solvent is evaporated to give the crude product, which is purified by spinning plate chromatography.

- Procedure B

The required amount of amine is dissolved in CH_2Cl_2 (20 ml) and NEt_3 (5 ml). A solution of the acid chloride (1.1 equiv.) in CH_2Cl_2 (10 ml) is added dropwise under stirring. After 30 min at room temp. the reaction mixture is worked-up following procedure A.

- Trifluoroacetamides

The required amount of amine is dissolved in methanol (20 ml) and ethyl trifluoroacetate (5 eq). The mixture is stirred at room temp. for 3 h, the solvent is evaporated to give the crude product, which is purified by spinning plate chromatography.

VIII.2.7 Fischer Reaction

A solution of 4-acetoxycyclohexanone (3.12 g, 20 mmol) and 20 mmol of the hydrazine in ethanol (20 ml) containing 2 drops of acetic acid is refluxed for 15 min. The solvent is removed by evaporation *in vacuo* and 20 ml of acetic acid is added to the oily residue. The mixture is then refluxed under nitrogen for 4 h, the solvent is evaporated and 2N sodium hydroxide solution (20 ml) is added. The product is extracted with methylene chloride (3x20 ml) and purified by spinning plate chromatography using the same solvent.

VIII.2.8 Saponification of Acetates

A solution of the acetate (16 mmol) and sodium hydroxide (1.3 g, 32 mmol) in aq. ethanol (15 ml water, 220 ml ethanol) is refluxed for 6 h under nitrogen. The ethanol is removed by evaporation *in vacuo* and the precipitated solid is removed by filtration.

VIII.2.9 Tosylation and Mesylation of Alcohols

Under nitrogen 1.2 eq. of *para*-toluenesulphonyl chloride or methanesulphonyl chloride are added to a cooled solution of the alcohol (1 eq.) in pyridine (10 ml/g). The mixture is stirred at 20 °C for 24 h, the pyridine is then removed by evaporation *in vacuo* and the oily residue is dissolved in methylene chloride. The organic layer is washed with dil. hydrochloric acid and water. After removing the solvent by evaporation, the crude product is purified by spinning plate chromatography (eluent: dichloromethane).

VIII.2.10 Reaction of Tosylates or Mesylates with Sodium Azide

A suspension of the tosylate or mesylate (1 eq.) and sodium azide (2 eq.) in aq. 90 % EtOH (40 ml/g) is refluxed for 12 h. The cooled mixture is poured into water and the product is extracted with ether (4x150 ml). The ethereal extracts are washed with brine and the solvent is removed by evaporation *in vacuo* to give the crude azide, which is of sufficient purity for the following reduction.

VIII.2.11 Reduction of Azides

- Procedure A

A solution of the crude azide (2.5 mmol) in methanol (40 ml) is hydrogenated at 40 psi hydrogen pressure in the presence of 10 % palladium-on-charcoal for 24 h. The mixture is filtered and the solvent is removed by evaporation *in vacuo* to give the amine as a pale brown solid. The product is purified by washing a solution of the amine in dichloromethane with water (20 ml). The amine is then extracted with dil. hydrochloric acid (2x20 ml), the aqueous layer is washed with ethyl acetate (20 ml) and 2N sodium hydroxide solution is added to liberate the amine. Finally the product is extracted with ethyl acetate (2x20 ml). After drying over magnesium sulphate and evaporation of the solvent the amine is obtained in sufficient purity for the acylation.

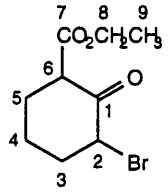
- Procedure B

A solution of the azide (2.5 mmol) in anhydrous THF (40 ml/g) is added dropwise to a suspension of lithium aluminium hydride (10 eq) in anhydrous THF (20 ml/g). After the addition is over the reaction mixture is stirred at 25 °C for 24 h. Excess lithium aluminium hydride is decomposed by careful addition of water (2 ml). The reaction mixture is filtered under suction, the filter cake is washed with ethyl acetate and the product is purified as described for procedure A.

VIII.3 Syntheses and Spectroscopic Data

2-Bromo-6-ethoxycarbonylcyclohexanone (34)

Ethyl 2-oxocyclohexanecarboxylate (25.0 g, 0.15 mol) and bromine (29.9 g, 0.19 mol) are reacted in 200 ml of ether according to the method described in VIII.2.1. Distillation at 92-106 °C/0.3 mmHg gives the product in 96 % yield (0.14 mol, 35.9 g).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{H,H}$=8.7 Hz; 3H, H9),
1.71-2.46 (m; 7H, H2, H3, H4, H5),
4.19 (m; 2H, H8),
4.65 (t; 1H, H6).

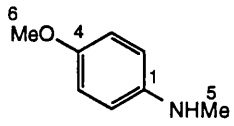
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.13, 17.7, 22.2, 32.10 (C3, C4, C5, C9), 45.93 (C8), 60.89 (C2), 99.83 (C6), 166.38, 172.23 (C1, C7).

Ir (film): ν = 1730 cm^{-1} (s; CO), 1710 (s), 1650 (s), 1610 (s).

Ms (EI, 70 eV): m/z (%) = 248, 250 (10, M^+), 202, 204 (15, M^+-EtOH), 169 (35, M^+-Br), 123 (80, M^+-Br-EtOH), 95 (100), 67 (70), 55 (65).

4-Methoxy-N-methylaniline (39b)

To a mechanically stirred solution of sodium ethoxide, prepared from sodium (26 g, 1.1 mol) in ethanol (1 l), is added N-acetyl-N-methyl-4-aminophenol (185 g, 1.1 mol). The resulting black solution is treated with dimethyl sulphate (143 g, 1.1 mol) at 20 °C. After 4 h, 300 ml of the solvent is evaporated *in vacuo*, then sodium (52 g, 2.2 mol), water (50 ml) and ethanol (200 ml) are carefully added and the mixture is refluxed for 16 h. The mixture is poured onto ice and the product is extracted with dichloromethane (5x150 ml). The combined organic layers are washed with brine. After drying over magnesium sulphate the solvent is evaporated and the product is distilled at 130 °C/15 mmHg.
Yield: 120 g (0.92 mol, 84 %); mp. 30 °C



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.79 (s; 3H, H5),
3.75 (s; 3H, H6),
3.30 (s, br; 1H, NH),
6.58 (d, ^{3}J=6.6 Hz; 2H, H2 or H3),
6.79 (d, ^{3}J=6.6 Hz; 2H, H2 or H3).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 31.5 (q, C5), 55.7 (q, C6), 113.5 (d), 114.8 (d), 143.6 (s), 152.0 (s).

2-Bromo-5-methoxycarbonylcyclopentanone (40a)

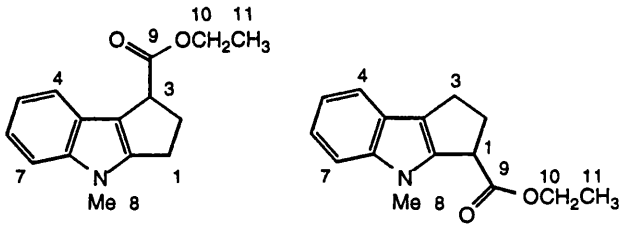
Methyl 2-oxocyclopentanecarboxylate (25.4 g, 0.16 mol) and bromine (26.0 g, 0.16 mol) are reacted in 200 ml of ether according to the method described in VIII.2.1. The viscous crude product is obtained in 85 % yield.

2-Bromo-7-ethoxycarbonylcycloheptanone (40b)

Ethyl 2-oxocycloheptanecarboxylate (18.6 g, 0.1 mol) and bromine (16.1 g, 0.1 mol) are reacted in 150 ml of ether according to the method described in VIII.2.1. The product is obtained as viscous oil in 92 % yield .

Ethyl 4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-1-carboxylate (41a) and
Ethyl 4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-3-carboxylate

N-Methylaniline (10.7 g, 0.1 mol) and 2-bromo-5-ethoxycarbonylcyclopentanone (11.8 g, 0.05 mol) are treated with 20 g of zinc chloride in 100 ml 2-propanol as described under VIII.2.2 to yield 9.1 g (38 mmol, 75 %) of an orange oil.

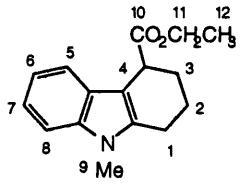


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.20 - 1.40 (m; 3H, H11),
2.28 - 2.35 (m; 1H, H2 major isomer),
2.71 - 3.09 (m; 3H, H2, H1 major, H3 minor),
3.67 (s; 3H, H8 major),
3.73 (s; 3H, H8 minor),
4.06 - 4.08 (m; 1H, H3 major),
4.13 (q, ^{3}J=7.3 Hz; 2H, H10 minor),
4.19 (q, ^{3}J=7.2 Hz; 2H, H10 major),
5.04 - 5.07 (m; 1H, H1 minor),
7.05 - 7.12 (ddd; 1H, H6 or H7),
7.12 - 7.20 (ddd; 1H, H6 or H7),
7.23 - 7.28 (d; 1H, H7),
7.47 (d, $^3J_{4,5}$=7.9 Hz; 1H, H4 major).
7.58 (d, $^3J_{4,5}$=7.5 Hz; 1H, H4 minor).

Ir (film): ν = 2945 cm^{-1} (m), 1719 (s, CO), 1483 (m), 1244 (s), 746 (s).

Ethyl 9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (41 b)

N-Methylaniline (10.7 g, 0.1 mol) and 2-bromo-6-ethoxycarbonylcyclohexanone (12.4 g, 0.05 mol) are treated with 20 g of zinc chloride in 100 ml 2-propanol as described under VIII.2.2 to yield 8.7 g (34 mmol, 68 %) of a yellow oil. An analytical sample is recrystallized from benzene/petroleum spirit 1:10 to give a solid (mp=78-80 °C, lit. 81-83 °C[145], 86 °C[146]).



^{1}H-nmr (200 MHz, $CDCl_3$): δ = 1.24 (t, $^3J_{12,11}$=9 Hz; 3H, H12),
1.8-2.0 (m; 2H, H2),
2.7-2.8 (m; 4H, H1, H3),
3.6 (s; 3H, H9),
4.12 (m; 2H, H11),
4.45 (m; 1H, H4),
7.10-7.22 (m; 2H, H6, H7),
7.3 (d, ^{3}J=8 Hz; 1H, H5 or H8),
7.52 (d, ^{3}J=8 Hz; 1H, H5 or H8).

Ir (KBr): ν = 2932 cm^{-1} (m), 1725 (s, CO), 1468 (m), 1381 (m), 1248 (m), 1174 (m), 1154 (m), 744 (s).

MS (NH_3 EI, 70 eV): m/z = 258 (M^++1, 100), 184 (95), 172 (30).

CHN $C_{16}H_{19}NO_2$ calc. C 74.68 H 7.44 N 5.44
found C 73.58 H 7.30 N 5.16

Ethyl 5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxylate (41c)

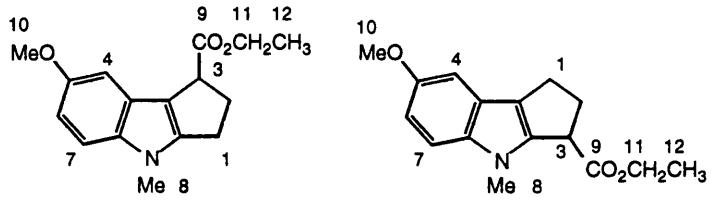
N-Methylaniline (12.0 g, 0.11 mol) and 2-bromo-7-ethoxycarbonylcycloheptanone (14.6 g, 0.06 mol) are treated with 25 g of zinc chloride in 120 ml 2-propanol as described under VIII.2.2 to yield 10.4 g (41 mmol, 69 %) of an orange solid, which is directly saponified.

Ir (KBr): ν = 2943 cm^{-1} (m), 1729 (s, CO), 1247 (s), 746 (s).

Ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-1-carboxylate (42a) and

ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-3-carboxylate

4-Methoxy-N-methylaniline (29.3 g, 0.21 mol) and 2-bromo-5-ethoxycarbonyl-cyclopentanone (25.1 g, 0.11 mol) are treated with 45 g of zinc chloride in 200 ml 2-propanol as described under VIII.2.2 to yield 20.1 g (74 mmol, 67 %) of an orange oil.

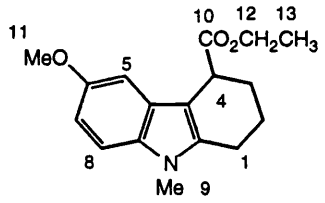


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.29 (t, $^3J_{12.11}$=7.7 Hz; 3H, H12),
2.51 - 2.54 (m; 2H, H2),
2.81 - 2.86 (m; 2H, H1),
3.62 (s; 3H, H8),
3.85 (s; 3H, H10),
3.93 - 3.95 (m; 1H, H3 major isomer),
4.04 - 4.12 (m; 1H, H3 minor isomer),
4.19 (q, $^3J_{11.12}$=7.0 Hz; 2H, H11),
6.79 (dd,$^4J_{6.4}$=2.3 Hz,$^3J_{6.7}$=8.9 Hz; 1H, H6 major),
6.82 (dd,$^4J_{6.4}$=2.5 Hz,$^3J_{6.7}$=9.0 Hz; 1H, H6 minor),
6.93 (d,$^4J_{4.6}$=2.5 Hz; 1H, H4 major),
7.00 (d,$^4J_{4.6}$=2.5 Hz; 1H, H4 minor),
7.11 (d, $^3J_{7.6}$=8.8 Hz; 1H, H7 major),
7.14 (d, $^3J_{7.6}$=8.7 Hz; 1H, H7 minor).

Ir (KBr): ν = 2930 (m), 1721 (s, C=O), 1473 (s), 1163 (s), 769 (m).

Ethyl 6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate(42b)

4-Methoxy-N-methylaniline (13.7 g, 0.1 mol) and 2-bromo-6-ethoxycarbonyl-cyclohexanone (12.4 g, 50 mmol) are treated with 15 g of zinc chloride in 100 ml 2-propanol as described under VIII.2.2 to yield 10.2 g (36 mmol, 71 %) of a yellow oil, which is directly saponified. An analytical sample with mp. 69-70 °C is prepared by filtration over a short silica gel column with dichloromethane.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{13,12}$=7.2 Hz; 3H, H13),
1.90 - 1.97 (m; 2H, H2),
2.18 - 2.34 (m; 2H, H1 or H3),
2.66 - 2.74 (m; 2H, H1 or H3),
3.57 (s; 3H, H9),
3.84 (s; 3H, H11),
4.16 - 4.21 (m; 1H, H4, H12),
6.81 (dd,$^4J_{7,5}$=2.5 Hz,$^3J_{7,8}$=8.8 Hz; 1H, H7),
7.03 (d,$^4J_{5,7}$=2.4 Hz; 1H, H5),
7.14 (d, $^3J_{8,7}$=8.7 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.4 (q, C13), 20.4 (t), 21.8 (t), 26.4 (t), 29.1 (q, C9), 38.5 (d, C4), 55.9 (q, C11), 60.5 (t, C12), 101.0 (d), 105.7 (s, C4a), 109.2 (d), 110.5 (d), 128.3 (s, C4b), 132.1 (s, C8a), 137.3 (s, C9a), 153.7 (s, C6), 175.0 (s, C10).

MS (NH_3 EI, 70 eV): m/z = 288 (M^++1, 100), 198 (32), 171 (70).

Ir (KBr): ν = 2931 (m), 1718 (s, C=O), 1478 (s), 1158 (s), 807 (m).

CHN	$C_{17}H_{21}NO_3$		
		calc.	C 71.65 H 7.37 N 4.88
		found	C 71.03 H 7.34 N 4.60

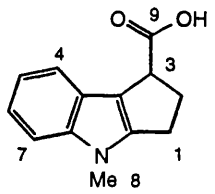
Ethyl 2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxylate (42c)

4-Methoxy-N-methylaniline (9.9 g, 72 mmol) and 2-bromo-7-ethoxycarbonyl-cycloheptanone (9.5 g, 36 mmol) are treated with 15 g of zinc chloride in 100 ml 2-propanol as described under VIII.2.2 to yield 6.8 g (23 mmol, 63 %) of an orange oil, which is directly saponified.

Ir (film): ν = 2929 (m), 1709 (s, C=O), 1474 (s), 1163 (s), 779 (m).

4-Methyl-1,2,3,4-tetrahydrocyclopent[b]indole-1-carboxylic acid (43a) and 4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole-3-carboxylic acid

The crude mixture of ethyl 4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-1-carboxylate and ethyl 4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-3-carboxylate (9.1 g, 37 mmol) is saponified with sodium hydroxide (15 g, 0.37 mol) as described previously (cf. VIII.2.3) to yield a mixture of two products (5.1 g, 24 mmol, 64 %).



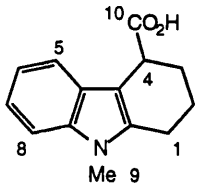
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.73 - 2.80 (m; 1H, H2),
2.81 - 2.90 (m; 2H, H1, H2),
3.00 - 3.04 (m; 2H, H1),
3.69 (s; 3H, H8),
4.04 (m; 1H, H3),
7.11 (ddd, ^4J=1.1Hz, ^3J=7.1Hz, ^3J=7.9Hz; 1H, H6 or H7),
7.17 (ddd, ^4J=1.2Hz, ^3J=7.0Hz, ^3J=8.2Hz; 1H, H6 or H7),
7.28 (d, $^3J_{7,6}$=8.1 Hz; 1H, H7),
7.50 (d, $^3J_{4,5}$=7.5 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.0 (t, C2), 30.0 (q, C8), 30.8 (t, C1), 42.5 (d, C3), 108.4 (d), 114.0 (s, C4a), 117.8 (d), 118.1 (d), 119.2 (d), 122.7 (s), 140.3 (s), 145.8 (s), 175.4 (s, C9).

Ir (KBr): ν = 3120 (m, br, OH), 2937 (s), 1690 (s, C=O), 1235 (m), 743 (m).

9-Methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid (43b)

The crude ethyl 9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (7.3 g, 28 mmol) is saponified with sodium hydroxide (11.3 g, 0.28 mol) as described previously (cf. VIII.2.3) to yield 5.14 g (22 mmol, 80 %) of the acid with mp. 174-177 °C (lit. 180-181 °C[146]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.98 - 2.06 (m; 2H, H2 and H3),
2.16 - 2.21 (m; 1H, H2 or H3),
2.27 - 2.31 (m; 1H, H2 or H3),
2.70 (ddd, $^3J_{1.2}$=6.1 Hz, $^3J_{1.2}$=8.5 Hz; 1H, H1),
2.81 (ddd, ^2J=16.3Hz, $^3J_{1.2}$=5.0Hz, $^3J_{1.2}$=5.0 Hz;1H,H1),
3.64 (s; 3H, H9),
3.97 (t, $^3J_{4.3}$=4.9 Hz, $^3J_{4.3}$=5.2 Hz; 1H, H4),
7.11 (dd, ^3J=7.0 Hz, ^3J=7.8 Hz; 1H, H6 or H7),
7.20 (dd, ^3J=7.0 Hz, ^3J=8.1 Hz; 1H, H6 or H7),
7.29 (d, $^3J_{8.7}$=8.0 Hz; 1H, H8),
7.58 (d, $^3J_{5.6}$=7.8 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.3 (t), 21.7 (t), 26.4 (t), 29.0 (q, C9), 38.2 (d, C4), 105.3 (s, C4a), 108.7 (d), 118.5 (d), 119.2 (d), 120.9 (d), 126.4 (s), 136.8 (s), 136.9 (s), 181.1 (s, C10).

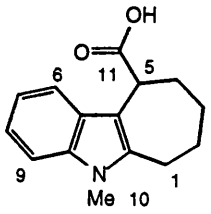
MS (EI, 70 eV): m/z = 229 (M^+, 81), 184 (M^+-COOH, 100), 156 (40), 90 (41).

Ir (KBr): ν = 3100 (m, br, OH), 2932 (s), 1692 (s, C=O), 1221 (m), 740 (m).

CHN $C_{14}H_{15}NO_2$ calc. C 73.33 H 6.59 N 6.11
found C 73.90 H 6.78 N 5.83

5-Methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxylic acid (43c)

The crude ethyl 5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole-10-carboxylate (10.4 g, 48 mmol) is saponified with sodium hydroxide (19 g, 0.48 mol) as described previously (cf. VIII.2.3) to yield 9.7 g (40 mmol, 83 %) of the acid with mp. 190-193 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.53 - 1.65 (m; 1H, H2, H3 or H4),
1.79 - 1.92 (m; 2H, H2, H3 or H4),
1.93 - 2.03 (m; 2H, H2, H3, H4),
2.46 - 2.49 (m; 1H, H4),
2.82 - 2.92 (m; 2H, H1),
3.65 (s; 3H, H10),
4.23 (t, $^3J_{5,4}$=4.2 Hz; 1H, H5),
7.06 (dd, ^{3}J=7.1 Hz, ^{3}J=7.8 Hz; 1H, H7 or H8),
7.13 (dd, ^{3}J=7.6 Hz, ^{3}J=7.6 Hz; 1H, H7 or H8),
7.22 (d, $^3J_{9,8}$=8.1 Hz; 1H, H9),
7.43 (d, $^3J_{6,7}$=7.8 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 25.7, 26.8, 26.9 (t, C2, C3, C4), 29.6 (q, C10), 30.5 (t, C1), 40.7 (d, C5), 109.1 (d, C9), 110.6 (s, C5a), 117.2 (d, C6), 119.3 (d, C7), 120.8 (d, C8), 127.6 (s, C5b), 135.9 (s, C9a), 140.3 (s, C9b).

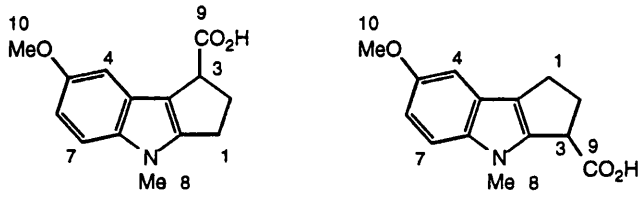
MS (EI, 70 eV): m/z = 243 (M^+, 95), 198 (M^+-COOH, 100), 170 (48), 107 (50), 84 (59).

Ir (KBr): ν = 3410 (m, br, OH), 2932 (s), 1701 (s, C=O), 1216 (s), 735 (s).

CHN	$C_{15}H_{17}NO_2$	calc.	C 74.05	H 7.04	N 5.76
		found	C 73.50	H 6.96	N 5.21

7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-1-carboxylic acid (44a) and 7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indol-3-carboxylic acid

The crude mixture of ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indol-1-carboxylate and ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indol-3-carboxylate (12.4 g, 45 mmol) is saponified with sodium hydroxide (18 g, 0.45 mol) as described previously (cf. VIII.2.3) to yield 9.0 g (36 mmol, 81 %) of a mixture of two products.



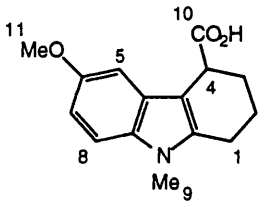
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.40 - 2.50 (m; 2H, H2),
2.81 - 2.86 (m; 2H, H1),
3.64 (s; 3H, H8),
3.86 (s; 3H, H10),
3.96 - 3.99 (m; 1H, H3 major isomer),
4.10 - 4.15 (m; 1H, H3 minor isomer),
6.80 (dd, $^4J_{6.4}$=2.3 Hz, $^3J_{6.7}$=9.0 Hz; 1H, H6 major),
6.82 (dd, $^4J_{6.4}$=2.5 Hz, $^3J_{6.7}$=9.0 Hz; 1H, H6 minor),
6.93 (d, $^4J_{4.6}$=2.4 Hz; 1H, H4 major),
7.07 (d, $^4J_{4.6}$=2.5 Hz; 1H, H4 minor),
7.12 (d, $^3J_{7.6}$=8.8 Hz; 1H, H7 major),
7.13 (d, $^3J_{7.6}$=8.8 Hz; 1H, H7 minor).

MS (EI, 70 eV): m/z = 245 (M^+, 30), 200 (M^+-COOH, 100), 106 (26), 78 (43), 48 (52).

Ir (KBr): ν = 3430 (m, br, OH), 2932 (m), 1692 (s, C=O), 1216 (m, C-O).

6-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid (44b)

The crude ethyl 6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (8.8 g, 31 mmol) is saponified with sodium hydroxide (12.4 g, 0.31 mol) as described previously (cf. VIII.2.3) to yield 7.5 g (29 mmol, 93 %) of the acid with mp. 177-178 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.91 - 1.98 (m; 2H, H2 and H3),
2.11 (m; 1H, H2 or H3),
2.22 - 2.24 (m; 1H, H2 or H3),
2.62 (ddd, $^3J_{1.2}$=6.6 Hz; 1H, H1),
2.75 (ddd, $^3J_{1.2}$=4.9 Hz; 1H, H1),
3.57 (s; 3H, H9),
3.79 (s; 3H, H11),
3.89 (t, $^3J_{4.3}$=4.8 Hz, $^3J_{4.3}$=5.3 Hz; 1H, H4),
6.80 (dd,$^4J_{7.5}$=2.5 Hz,$^3J_{7.8}$=8.8 Hz; 1H, H7),
7.00 (d,$^4J_{5.7}$=2.2 Hz; 1H, H5),
7.12 (d, $^3J_{8.7}$=8.9 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.3 (t), 21.8 (t), 26.4 (t), 29.1 (q, C9), 38.2 (d, C4), 55.9 (q, C11), 100.8 (d), 104.9 (s, C4a), 109.4 (d), 110.7 (d), 126.7 (s), 132.1 (s), 137.6 (s), 153.9 (s), 180.7 (s, C10).

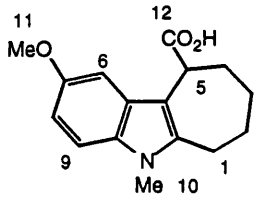
MS (EI, 70 eV): m/z = 259 (M^+, 35), 214 (M^+-COOH, 100), 120 (38), 80 (57), 49 (62).

Ir (KBr): ν = 3413 (m, br, OH), 2932 (m), 1695 (s, C=O), 1218 (m, C-O).

CHN $C_{15}H_{17}NO_3$ calc. C 69.48 H 6.61 N 5.40
found C 69.17 H 6.87 N 5.09

2-Methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxylic acid (44c)

The crude ethyl 2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxylate (3.6 g, 12 mmol) is saponified with sodium hydroxide (4.8 g, 0.12 mol) as described previously (cf. VIII.2.3) to yield 3.0 g (11 mmol, 91 %) of the acid with mp. 190-192 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.54 - 1.68 (m; 1H, H2, H3 or H4),
1.77 - 1.94 (m; 2H, H2, H3 or H4),
1.93 - 2.05 (m; 2H, H2, H3, H4),
2.42 - 2.48 (m; 1H, H4),
2.83 - 2.90 (m; 2H, H1),
3.65 (s; 3H, H10),
3.81 (s; 3H, H11),
4.20 (t, $^3J_{5,4}$=4.1 Hz; 1H, H5),
6.85 (dd,$^4J_{8,6}$=2.3 Hz,$^3J_{8,9}$=8.6 Hz; 1H, H8),
6.89 (d,$^4J_{6,8}$=2.2 Hz; 1H, H6),
7.15 (d, $^3J_{9,8}$=8.7 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 25.4, 26.7, 26.7 (t, C2, C3, C4), 29.7 (q, C10), 30.8 (t, C1), 40.8 (d, C5), 55.6 (q, C11), 99.7 (d), 105.6 (s, C5a), 109.7 (d), 111.0 (d), 127.5 (s), 131.8 (s), 138.9 (s), 154.3 (s, C7), 182.1 (s, C12).

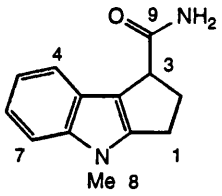
MS (EI, 70 eV): m/z = 273 (M^+, 26), 228 (M^+-COOH, 100), 122 (44), 84 (36), 49 (65).

Ir (KBr): ν = 3457 (s, br, OH), 2927 (m), 1616 (m, C=O), 1226 (m, C-O).

CHN $C_{16}H_{19}NO_3$ calc. C 70.31 H 7.01 N 5.12
found C 69.17 H 7.07 N 4.79

4-Methyl-1,2,3,4-tetrahydrocyclopent[b]indole-1-carboxamide (45a)

Following the method described in VIII.2.4, a mixture of 4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole-1- and 3-carboxylic acid (11.9, 55 mmol) is reacted with triethylamine (5.6 g, 60 mmol) and ethyl chloroformate (6.1 g, 60 mmol) in THF. A colourless solid (8.5 g, 40 mmol, 72 %) with mp. 221-223 °C is obtained.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.68 - 2.73 (m; 1H, H2),
2.84 - 2.90 (m; 1H, H2),
2.95 - 3.03 (m; 2H, H1),
3.69 (s; 3H, H8),
3.98 (m; 1H, H3),
5.28 (s, br; 1H, NH),
5.80 (s, br; 1H, NH),
7.11 (ddd, ^4J=1.1Hz, ^3J=7.1Hz, ^3J=7.7Hz; 1H, H6 or H7),
7.17 (ddd, ^4J=1.1Hz, ^3J=7.0Hz, ^3J=8.2Hz; 1H, H6 or H7),
7.26 (d, $^3J_{7,6}$=8.0 Hz; 1H, H7),
7.45 (d, $^3J_{4,5}$=7.6 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 24.0 (t, C2), 31.0 (q, C8), 34.3 (t, C1), 45.3 (d, C3), 109.8 (d), 114.5 (s, C3a), 118.1 (d), 119.9 (d), 120.8 (d), 123.3 (s, C3b), 141.7 (s, C7a), 148.4 (s, C8a), 177.9 (s, C9).

MS (EI, 70 eV): m/z = 214 (M^+, 37), 170 (M^+-$CONH_2$, 100), 142 (60), 63 (27), 42 (25).

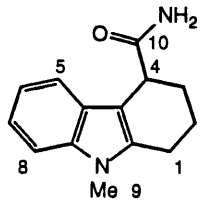
Ir (KBr): ν = 3359 (s, NH), 2931 (m), 1693 (s, C=O), 742 (m).

CHN $C_{13}H_{14}N_2O$ calc. C 72.87 H 6.59 N 13.07
found C 72.01 H 6.16 N 13.32

9-Methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (45b)

Following the method described in VIII.2.4, 9-methyl-1,2,3,4-tetrahydro-carbazole-4-carboxylic acid (12.6, 55 mmol) is reacted with triethylamine (5.6 g, 60 mmol) and ethyl chloroformate (6.1 g, 60 mmol) in dichloromethane. A colourless solid (8.5 g, 37 mmol, 68 %) with mp. 218-219 °C is obtained.

Alternatively, the acid (1.8 g, 7.9 mmol) is heated under nitrogen with urea (6.0 g). After 4 h at 200 °C, the mixture is cooled to 25 °C and 5 % sodium carbonate solution (20 ml) is added. The product is extracted with dichloromethane (2x20 ml). After drying over magnesium sulphate the solvent is evaporated and the product is purified by SPC (CH_2Cl_2 with 1% MeOH) to yield 0.2 g (0.9 mmol, 11 %) of the amide.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.90 - 2.02 (m; 3H, H2 and H3),
2.33 - 2.38 (m; 1H, H2 or H3),
2.66 - 2.72 (m; 1H, H1),
2.78 (ddd, ^2J=14.6Hz, $^3J_{1.2}$=4.8Hz, $^3J_{1.2}$=4.0 Hz; 1H, H1),
3.64 (s; 3H, H9),
3.75 (m; 1H, H4),
5.55 (s, br; 1H, NH),
5.75 (s, br; 1H, NH),
7.09 (dd, ^3J=6.9 Hz, ^3J=8.0 Hz; 1H, H6 or H7),
7.18 (dd, ^3J=7.2 Hz, ^3J=8.1 Hz; 1H, H6 or H7),
7.28 (d, $^3J_{8.7}$=8.2 Hz; 1H, H8),
7.46 (d, $^3J_{5.6}$=7.9 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.5 (t), 22.1 (t), 27.4 (t), 29.2 (q, C9), 40.0 (d, C4), 106.6 (s, C4a), 108.9 (d), 118.0 (d), 119.5 (d), 121.3 (d), 126.3 (s, C4b), 137.0, 137.6 (s, C8a, C9a), 177.6 (s, C10).

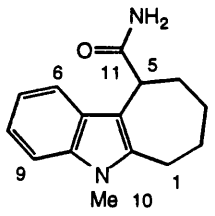
MS (EI, 70 eV): m/z = 228 (M^+, 52), 184 (M^+-$CONH_2$, 100), 156 (69), 93 (59), 49 (61).

Ir (KBr): ν = 3346 (s, NH), 2939 (m), 1692 (s, C=O), 740 (m).

CHN $C_{14}H_{16}N_2O$ calc. C 73.66 H 7.07 N 12.27
found C 73.13 H 6.63 N 12.90

5-Methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxamide (45c)

Following the method described in VIII.2.4, 5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole-10-carboxylic acid (5.7 g, 23 mmol) is reacted with triethylamine (2.4 g, 27 mmol) and ethyl chloroformate (2.5 g, 27 mmol) in dichloromethane. A yellow amorphous solid (5.0 g, 21 mmol, 90 %) with mp. 60 °C is obtained.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.60 - 1.66 (m; 1H, H2, H3 or H4),
1.73 - 1.90 (m; 2H, H2, H3 or H4),
1.91 - 2.09 (m; 2H, H2, H3, H4),
2.70 - 2.75 (m; 1H, H4),
2.83 (ddd, $^3J_{1.2}$=2.5 Hz, $^3J_{1.2}$=11.5 Hz, $^2J_{1.1}$=16.0 Hz; 1H, H1),
3.03 (ddd, $^3J_{1.2}$=2.0Hz, $^3J_{1.2}$=6.9 Hz, $^2J_{1.1}$=16.1 Hz; 1H, H1),
3.73 (s; 3H, H10),
4.10 (t, $^3J_{5.4}$=4.2 Hz; 1H, H5),
5.70 (s, br; 1H, NH),
5.71 (s, br; 1H, NH),
7.15 (ddd, ^{4}J=1.0Hz, ^{3}J=6.9Hz, ^{3}J=7.9Hz; 1H, H7 or H8),
7.23 (ddd, ^{4}J=1.1Hz, ^{3}J=7.0Hz, ^{3}J=8.1Hz; 1H, H7 or H8),
7.31 (d, $^3J_{9.8}$=8.1 Hz; 1H, H9),
7.50 (d, $^3J_{6.7}$=7.8 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.1, 26.6, 26.9 (t, C2, C3, C4), 29.7 (q, C10), 30.1 (t, C1), 41.6 (d, C5), 109.2 (d, C9), 110.6 (s, C5a), 117.4 (d, C6), 119.7 (d, C7), 121.3 (d, C8), 127.6 (s, C5b), 136.2 (s, C9a), 139.8 (s, C9b), 176.6 (s, C12).

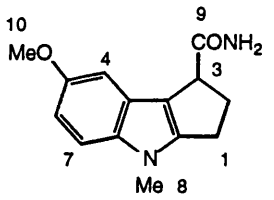
MS (EI, 70 eV): m/z = 242 (M^+, 69), 198 (M^+-$CONH_2$, 100), 170 (67), 107 (65), 42 (35).

Ir (KBr): ν = 3456 (s, NH), 2927 (m), 1677 (s, C=O), 734 (m).

CHN $C_{15}H_{18}N_2O$ calc. C 74.35 H 7.49 N 11.56
found C 72.97 H 7.59 N 10.97

7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole-1-carboxamide (46 a)

Following the method described in VIII.2.4, a mixture of 7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole-1- and 3-carboxylic acid (9.0, 37 mmol) is reacted with triethylamine (4.0 g, 40 mmol) and ethyl chloroformate (4.0 g, 40 mmol) in dichloromethane. A colourless solid (4.2 g, 16 mmol, 44 %) with mp. 205-206 °C is obtained.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.61 - 2.65 (m; 1H, H2),
2.85 - 2.89 (m; 1H, H1 or H2),
2.91 - 2.98 (m; 2H, H1 or H2),
3.63 (s; 3H, H8),
3.83 (s; 3H, H10),
3.88 (d, $^3J_{3,2}$=7.4 Hz, 1H, H3),
5.38 (s, br; 1H, NH),
5.72 (s, br; 1H, NH),
6.83 (dd,$^4J_{6,4}$=2.6 Hz,$^3J_{6,7}$=8.8 Hz; 1H, H6),
6.92 (d,$^4J_{4,6}$=2.5 Hz; 1H, H4),
7.14 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.8 (t, C2), 31.0 (q, C8), 35.7 (t, C1), 45.6 (d, C3), 56.0 (q, C10), 101.5 (d), 110.6 (d), 111.3 (d), 120.0 (s, C3a), 124.0 (s, C3b), 137.3 (s, C7a), 143.3 (s, C8a), 154.1 (s), 176.3 (s, C11).

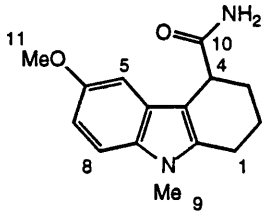
MS (EI, 70 eV): m/z = 244 (M^+, 73), 200 (M^+-$CONH_2$, 100), 109 (92), 68 (93).

Ir (KBr): ν = 3405 (s,br, NH), 2938 (m), 1651 (s, C=O), 1489 (m), 1226 (m, C-O).

CHN $C_{14}H_{16}N_2O_2$ calc. C 68.83 H 6.60 N 11.46
found C 68.50 H 6.39 N 11.18

6-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (46 b)

Following the method described in VIII.2.4, 6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid (3.3 g, 13 mmol) is reacted with triethylamine (1.3 g, 13 mmol) and methyl chloroformate (1.2 g, 13 mmol) in dichloromethane. A pale yellow solid (2.5 g, 9.6 mmol, 74 %) with mp. 157-158 °C (recr. from MeOH) is obtained.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.88 - 1.95 (m; 3H, H2 and H3),
2.27 - 2.31 (m; 1H, H2 or H3),
2.62 (ddd, $^3J_{1.2}$=6.2 Hz, $^3J_{1.2}$=8.1 Hz; 1H, H1),
2.72 (ddd, $^3J_{1.2}$=4.2Hz, $^3J_{1.2}$=5.0Hz, ^2J=16.4 Hz;1H,H1),
3.56 (s; 3H, H9),
3.65 (m; 1H, H4),
3.77 (s; 3H, H11),
5.80 (s, br; 1H, NH),
6.30 (s, br; 1H, NH),
6.78 (dd, $^4J_{7.5}$=2.3 Hz, $^3J_{7.8}$=8.7 Hz; 1H, H7),
6.88 (d, $^4J_{5.7}$=2.3 Hz; 1H, H5),
7.12 (d, $^3J_{8.7}$=8.7 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.3 (t), 22.0 (t), 27.3 (t), 29.0 (q, C9), 39.9 (d, C4), 55.7 (q, C11), 100.0 (d), 106.0 (s, C4a), 109.3 (d), 110.6 (d), 126.5 (s, C4b), 132.1 (s, C8a), 137.9 (s, C9a), 153.9 (s), 177.7 (s, C10).

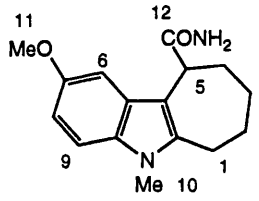
MS (EI, 70 eV): m/z = 258 (M^+, 32), 214 (M^+-$CONH_2$, 100), 114 (97), 68 (93).

Ir (KBr): ν = 3393 (s, NH), 2932 (s), 1682 (s, C=O), 1481 (s), 1224 (m, C-O).

CHN $C_{15}H_{18}N_2O_2$ calc. C 69.74 H 7.02 N 10.84
found C 68.82 H 6.96 N 10.83

2-Methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxamide (46c)

Following the method described in VIII.2.4, 2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxylic acid (3.0 g, 11 mmol) is reacted with triethylamine (1.3 g, 12 mmol) and ethyl chloroformate (1.3 g, 12 mmol) in dichloromethane. A beige coloured solid (1.9 g, 6.9 mmol, 63 %) with mp. 185-190 °C is obtained.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.54 - 1.57 (m; 1H, H2, H3 or H4),
1.68 - 1.82 (m; 2H, H2, H3 or H4),
1.97 - 2.00 (m; 2H, H2, H3, H4),
2.66 - 2.69 (m; 1H, H4),
2.70 - 2.78 (m; 1H, H1),
3.03 (dd, $^3J_{1.2}$=1.6Hz, $^3J_{1.2}$=5.7 Hz; 1H, H1),
3.65 (s; 3H, H10),
3.82 (s; 3H, H11),
4.00 (t, $^3J_{5.4}$=3.6 Hz; 1H, H5),
5.47 (s, br; 1H, NH),
5.69 (s, br; 1H, NH),
6.82 (dd,$^4J_{8.6}$=2.4 Hz,$^3J_{8.9}$=8.8 Hz; 1H, H8),
6.88 (d,$^4J_{6.8}$=2.1 Hz; 1H, H6),
7.13 (d, $^3J_{9.8}$=8.9 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.1, 26.6, 26.8 (t, C2, C3, C4), 29.7 (q, C10), 30.1 (t, C1), 41.6 (d, C5), 55.9 (q, C11), 99.3 (d), 109.9 (d), 110.2 (s, C5a), 111.2 (d), 127.8 (s, C5b), 131.4 (s, C9a), 140.3 (s, C9b), 154.3 (s), 176.5 (s, C12).

MS (EI, 70 eV): m/z = 272 (M^+, 44), 228 (M^+-$CONH_2$, 100), 137 (97), 84 (93).

Ir (KBr): ν = 3460 (s, NH), 2932 (m), 1671 (s, C=O), 1470 (m), 1228 (m, C-O), 734 (m).

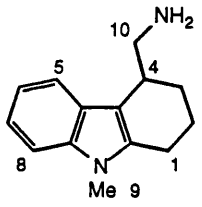
CHN	$C_{16}H_{20}N_2O_2$	calc.	C 70.56	H 7.40	N 10.29
		found	C 70.21	H 7.36	N 10.08

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (47a)

4-Methyl-1,2,3,4-tetrahydrocyclopent[b]indole-1-carboxamide (2.4 g, 11 mmol) is reduced with lithium aluminium hydride (3.0 g) as described in VIII.2.5, procedure A. The product (1.7 g, 8.5 mmol, 77 %) is a yellow oil which is directly used for the subsequent acylation.

4-Aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (47b)

9-Methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (2.0 g, 9 mmol) is reduced with borane (10 ml, 1M) as described in VIII.2.5, procedure B. The product (1.3 g, 6.2 mmol, 69 %) is a yellow oil which is directly used for the subsequent acylation.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.54 (s, br; 2H, NH_2),
1.82 - 1.90 (m; 3H, H2 and H3),
1.97 - 2.02 (m; 1H, H2 or H3),
2.62 - 2.73 (m; 2H, H1),
2.96 (dd, ^2J=14.4 Hz, $^3J_{10.4}$=7.7 Hz; 1H, H10),
3.06 (m; 1H, H4),
3.14 (dd, ^2J=12.3 Hz, $^3J_{10.4}$=3.9 Hz; 1H, H10),
3.60 (s; 3H, H9),
7.06 (dd, ^3J=7.3 Hz, ^3J=7.5 Hz; 1H, H6 or H7),
7.15 (dd, ^3J=7.2 Hz, ^3J=7.9 Hz; 1H, H6 or H7),
7.26 (d, $^3J_{8.7}$=8.1 Hz; 1H, H8),
7.57 (d, $^3J_{5.6}$=7.9 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.9 (t), 22.1 (t), 26.1 (t), 28.9 (q, C9), 35.9 (d, C4), 46.1 (t, C10), 108.6 (d), 110.1 (s, C4a), 118.3 (d), 118.7 (d), 120.4 (d), 126.7 (s), 136.6 (s),136.7 (s).

MS (EI, 70 eV): m/z = 214 (M^+, 10), 184 (M^+-CH_2NH_2, 100), 167 (26).

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (47c)

5-Methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxamide (2.4 g, 10 mmol) is reduced with lithium aluminium hydride (3.0 g) as described in VIII.2.5, procedure A. The product (1.3 g, 5.7 mmol, 57 %) is a yellow oil which is directly used for the subsequent acylation.

1-Aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (48a)

7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole-1-carboxamide (2.0 g, 8.2 mmol) is reduced with lithium aluminium hydride (2.5 g) as described in VIII.2.5, procedure A. The product (1.1 g, 4.8 mmol, 58 %) is a yellow oil which is directly used for the subsequent acylation.

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (48b)

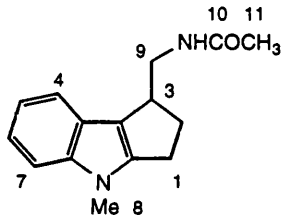
6-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (1.0 g, 3.9 mmol) is reduced with borane-THF-complex (8 ml, 1M) as described in VIII.2.5, procedure B. The product (0.6 g, 2.5 mmol, 63 %) is a yellow oil which is directly used for the subsequent acylation.

10-Aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole (48c)

2-Methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole-10-carboxamide (1.9 g, 7.0 mmol) is reduced with lithium aluminium hydride (2.5 g) as described in VIII.2.5, procedure A. The product (1.3 g, 5.0 mmol, 72 %) is a yellow oil which is directly used for the subsequent acylation.

N-Acetyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (49a)

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.15 g, 0.75 mmol) is treated with acetic anhydride (0.08 g, 0.75 mmol) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 91 % yield (0.17 g, 0.68 mmol). Mp. 148-149 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.97 (s; 3H, H11),
2.21 - 2.25 (m; 1H, H2),
2.67 - 2.71 (m; 1H, H2),
2.78 - 2.85 (m; 1H, H1),
2.88 - 2.92 (m; 1H, H1),
3.48 - 3.67 (m; 3H, H3, H9),
3.69 (s; 3H, H8),
5.63 (s, br; 1H, NH),
7.11 (ddd, ^{4}J=1.1Hz, ^{3}J=7.0Hz, ^{3}J=8.0Hz; 1H, H6 or H7),
7.17 (ddd, ^{4}J=1.2Hz, ^{3}J=7.0Hz, ^{3}J=8.2Hz; 1H, H6 or H7),
7.28 (d, $^3J_{7,6}$=8.1 Hz; 1H, H7),
7.45 (d, $^3J_{4,5}$=7.4 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.5 (q, C11), 24.0 (t, C2), 30.8 (q, C8), 32.6 (t, C1), 38.8 (d, C3), 43.9 (t, C9), 109.6 (d), 117.4 (s, C3a), 118.0 (d), 119.3 (d), 120.2 (d), 123.9 (s, C3b), 141.4 (s, C7a), 147.1 (s, C8a), 170.2 (s, C10).

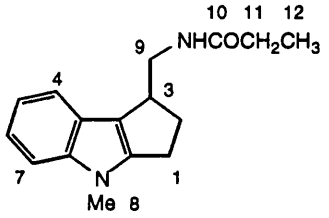
MS (EI, 70 eV): m/z = 242 (M^+, 31), 183 (M^+-NH_2COCH_3, 100), 170 (M^+-$CH_2NHCOCH_3$, 100), 154 (42), 128 (35).

Ir (KBr): ν = 3306 (s, NH), 2955 (m), 1638 (s, C=O), 1558 (m), 1296 (m), 732 (s).

CHN $C_{15}H_{18}N_2O$ calc. C 74.35 H 7.49 N 11.56
found C 73.62 H 7.58 N 11.23

N-Propanoyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (49b)

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.15 g, 0.75 mmol) is treated with propanoic anhydride (0.09 g, 0.75 mmol) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product crystallised at -20 °C. Yield: 0.14 g (0.55 mmol, 73 %), mp. 105-107 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.14 (t, $^3J_{12.11}$=7.6 Hz; 3H, H12),
2.17 (q, $^3J_{11.12}$=7.5 Hz; 2H, H11),
2.22 - 2.25 (m; 1H, H2),
2.67 - 2.72 (m; 1H, H2),
2.77 - 2.87 (m; 1H, H1),
2.89 - 2.94 (m; 1H, H1),
3.48 - 3.66 (m; 3H, H3, H9),
3.67 (s; 3H, H8),
5.63 (s, br; 1H, NH),
7.10 (ddd,^{4}J=1.0Hz,^{3}J=7.0Hz,^{3}J=8.1Hz;1H,H6 or H7),
7.18 (ddd,^{4}J=1.1Hz,^{3}J=7.1Hz,^{3}J=8.2Hz;1H,H6 or H7),
7.27 (d, $^3J_{7.6}$=8.2 Hz; 1H, H7),
7.44 (d, $^3J_{4.5}$=7.6 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.6 (q, C12), 23.9 (t, C2), 29.8 (q, C8), 30.8 (t, C11), 32.7 (t, C1), 38.9 (d, C3), 43.8 (t, C9), 109.6 (d), 117.5 (s, C3a), 118.0 (d), 119.2 (d), 120.2 (d), 123.9 (s, C3b), 141.4 (s, C7a), 147.1 (s, C8a), 173.9 (s, C10).

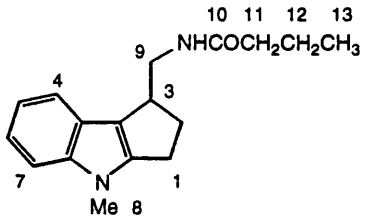
MS (EI, 70 eV): m/z = 256 (M^+, 29), 183 (M^+-$NH_2COC_2H_5$, 84), 170 (M^+-$CH_2NHCOC_2H_5$, 100), 154 (40), 128 (20).

Ir (KBr): ν = 3309 (s, NH), 2943 (m), 1645 (s, C=O), 1544 (m), 734 (s).

CHN $C_{16}H_{20}N_2O$ calc. C 74.96 H 7.86 N 10.93
found C 74.83 H 7.55 N 10.80

N-Butanoyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (49c)

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.15 g, 0.75 mmol) is treated with butanoic anhydride (0.1 g, 0.75 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with ether. Yield: 0.17 g (0.63 mmol, 84 %), mp. 118-119 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{13.12}$=7.3 Hz; 3H, H13),
1.63 (se; 2H, H12),
2.10 (t, $^3J_{11.12}$=7.5 Hz; 2H, H11),
2.20 - 2.22 (m; 1H, H2),
2.60 - 2.70 (m; 1H, H2),
2.75 - 2.81 (m; 1H, H1),
2.82 - 2.88 (m; 1H, H1),
3.52 - 3.57 (m; 3H, H3, H9),
3.66 (s; 3H, H8),
5.55 (s, br; 1H, NH),
7.07 (ddd,^{4}J=1.1Hz,^{3}J=7.0Hz,^{3}J=7.8Hz;1H,H6 or H7),
7.15 (ddd,^{4}J=1.1Hz,^{3}J=7.1Hz,^{3}J=8.3Hz;1H,H6 or H7),
7.25 (d, $^3J_{7.6}$=8.1 Hz; 1H, H7),
7.43 (d, $^3J_{4.5}$=7.6 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.8 (q, C13), 19.2 (t, C12), 24.1 (t, C2), 30.9 (q, C8), 32.8 (t, C1), 38.9 (t, C11), 39.1 (d, C3), 43.7 (t, C9), 109.7 (d), 117.6 (s, C3a), 118.1 (d), 119.4 (d), 120.3 (d), 124.0 (s, C3b), 141.5 (s, C7a), 147.2 (s, C8a), 173.2 (s, C10).

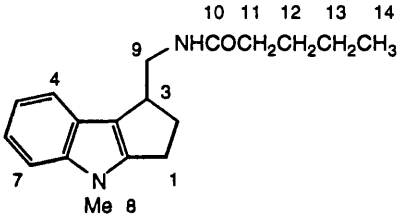
MS (EI, 70 eV): m/z = 270 (M^+, 45), 183 (M^+-$NH_2COC_3H_7$, 92), 170 (M^+-$CH_2NHCOC_3H_7$, 100), 154 (49), 128 (37).

Ir (KBr): ν = 3304 (s, NH), 2958 (m), 1638 (s, C=O), 1558 (m), 733 (s).

CHN $C_{17}H_{22}N_2O$ calc. C 75.52 H 8.20 N 10.36
found C 75.13 H 8.04 N 10.29

N-Pentanoyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (49d)

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.15 g, 0.75 mmol) is treated with valeryl chloride (0.1 g, 0.75 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with ether. Yield: 0.19 g (0.67 mmol, 89 %), mp. 109-110 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{14.13}$=7.4 Hz; 3H, H14),
1.30 - 1.40 (m; 2H, H13),
1.56 - 1.62 (m; 2H, H12),
2.16 (t, $^3J_{11.12}$=7.5 Hz; 2H, H11),
2.20 - 2.25 (m; 1H, H2),
2.67 - 2.73 (m; 1H, H2),
2.79 - 2.86 (m; 1H, H1),
2.88 - 2.95 (m; 1H, H1),
3.54 - 3.64 (m; 3H, H3, H9),
3.69 (s; 3H, H8),
5.58 (s, br; 1H, NH),
7.09 (ddd,^{4}J=1.2Hz, ^{3}J=7.4Hz,^{3}J=7.4Hz;1H,H6 or H7),
7.18 (ddd,^{4}J=1.2Hz,^{3}J=7.1Hz,^{3}J=8.1Hz;1H,H6 or H7),
7.28 (d, $^3J_{7.6}$=8.4 Hz; 1H, H7),
7.46 (d, $^3J_{4.5}$=7.6 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C14), 22.3 (t, C13), 24.0 (t, C2), 27.8 (t, C12), 30.8 (q, C8), 32.6 (t, C1), 36.6 (t, C11), 38.9 (d, C3), 43.6 (t, C9), 109.6 (d), 117.4 (s, C3a), 118.0 (d), 119.2 (d), 120.2 (d), 123.8 (s, C3b), 141.4 (s, C7a), 147.1 (s, C8a), 173.3 (s, C10).

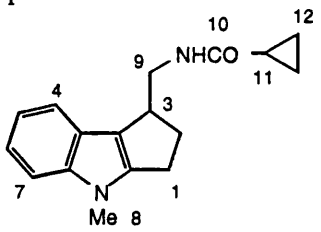
MS (EI, 70 eV): m/z = 284 (M^+, 22), 183 (M^+-$NH_2COC_4H_9$, 97), 170 (M^+-$CH_2NHCOC_4H_9$, 100), 154 (37), 128 (30).

Ir (KBr): ν = 3305 (s, NH), 2967 (m), 1640 (s, C=O), 1541 (m), 736 (s).

CHN $C_{18}H_{24}N_2O$ calc. C 76.02 H 8.51 N 9.85
found C 75.73 H 8.43 N 9.71

N-Cyclopropanoyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole (49e)

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole (0.15 g, 0.75 mmol) is treated with cyclopropanecarbonyl chloride (0.09 g, 0.75 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and crystallised after trituration with ether. Yield: 0.12 g (0.45 mmol, 60 %), mp. 160.5-161.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.73 - 0.80 (m; 2H, H12),
0.93 - 1.05 (m; 2H, H12),
1.31 - 1.36 (m; 1H, H11),
2.22 - 2.29 (m; 1H, H2),
2.67 - 2.75 (m; 1H, H2),
2.80 - 2.87 (m; 1H, H1),
2.91 - 2.99 (m; 1H, H1),
3.51 - 3.60 (m; 3H, H3, H9),
3.70 (s; 3H, H8),
5.90 (s, br; 1H, NH),
7.13 (ddd, ^4J=1.0Hz, ^3J=7.6Hz, ^3J=8.1Hz; 1H, H6 or H7),
7.20 (ddd, ^4J=1.1Hz, ^3J=7.1Hz, ^3J=8.1Hz; 1H, H6 or H7),
7.29 (d, $^3J_{7,6}$=8.1 Hz; 1H, H7),
7.52 (d, $^3J_{4,5}$=7.8 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 6.91 (t, C12), 14.1 (d, C11), 23.9 (t, C2), 30.7 (q, C8), 32.6 (t, C1), 39.0 (d, C3), 44.1 (t, C9), 109.5 (d), 117.6 (s, C3a), 118.1 (d), 119.2 (d), 120.1 (d), 123.9 (s, C3b), 141.4 (s, C7a), 147.0 (s, C8a), 173.6 (s, C10).

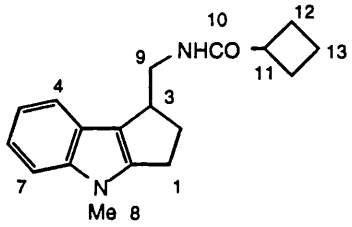
MS (EI, 70 eV): m/z = 268 (M^+, 16), 183 (M^+-$NH_2COC_3H_5$, 94), 170 (M^+-$CH_2NHCOC_3H_5$, 100), 154 (27), 128 (19).

Ir (KBr): ν = 3300 (s, NH), 2943 (m), 1638 (s, C=O), 1539 (m), 740 (m).

CHN $C_{17}H_{20}N_2O$ calc. C 76.08 H 7.51 N 10.44
found C 75.87 H 7.42 N 10.23

N-Cyclobutanoyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole (49 f)

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.15 g, 0.75 mmol) is treated with cyclobutanecarbonyl chloride (0.1 g, 0.75 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with ether. Yield: 0.16 g (0.57 mmol, 76 %), mp. 100.5-101.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.80 - 1.93 (m; 2H, H12, H13),
2.04 - 2.12 (m; 1H, H12 or H13),
2.15 - 2.29 (m; 4H, H2, H12, H13),
2.62 - 2.67 (m; 1H, H2),
2.78 - 2.85 (m; 1H, H1),
2.86 - 2.94 (m; 2H, H1, H11),
3.52 - 3.57 (m; 3H, H3, H9),
3.65 (s; 3H, H8),
5.45 (s, br; 1H, NH),
7.06 (ddd, ^4J=1.1Hz, ^3J=7.0Hz, ^3J=7.8Hz; 1H, H6 or H7),
7.13 (ddd, ^4J=1.3Hz, ^3J=7.1Hz, ^3J=8.1Hz; 1H, H6 or H7),
7.24 (d, $^3J_{7,6}$=8.1 Hz; 1H, H7),
7.39 (d, $^3J_{4,5}$=7.3 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 18.2 (t, C12 or C13), 24.1 (t, C2), 25.4 (t, C12 or C13), 30.9 (q, C8), 32.8 (t, C1), 39.1 (d, C3), 40.1 (d, C11), 43.9 (t, C9), 109.7 (d), 117.7 (s, C3a), 118.1 (d), 119.4 (d), 120.3 (d), 124.0 (s, C3b), 141.5 (s, C7a), 147.2 (s, C8a), 175.1 (s, C10).

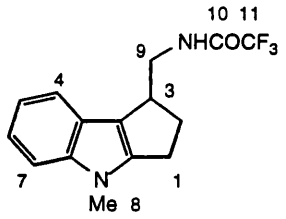
MS (EI, 70 eV): m/z = 282 (M^+, 13), 183 (M^+-$NH_2COC_4H_7$, 100), 170 (M^+-$CH_2NHCOC_4H_7$, 100), 154 (21), 128 (18).

Ir (KBr): ν = 3298 (s, NH), 2931 (m), 1634 (s, C=O), 1539 (m), 741 (m).

CHN $C_{18}H_{22}N_2O$ calc. C 76.56 H 7.85 N 9.92
found C 76.69 H 7.97 N 9.86

N-Trifluoroacetyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (49 f)

1-Aminomethyl-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.15 g, 0.75 mmol) is treated with ethyl trifluoroacetate (2 ml) according to procedure C VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with ether. Yield: 0.16 g (0.54 mmol, 72 %), mp. 160-161 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.25 - 2.32 (m; 1H, H2),
2.68 - 2.77 (m; 1H, H2),
2.78 - 2.81 (m; 1H, H1),
2.88 - 2.92 (m; 1H, H1),
2.99 (dd, $^3J_{9,3}$=8.2 Hz, $^2J_{9,9}$=12.9 Hz; 1H, H9),
3.27 (dd, $^3J_{9,3}$=3.4 Hz, $^2J_{9,9}$=13.6 Hz; 1H, H9),
3.59 - 3.62 (m; 1H, H3),
3.61 (s; 3H, H8),
6.80 (s, br; 1H, NH),
6.99 - 7.06 (m; 2H, H6, H7),
7.17 (d, $^3J_{7,6}$=8.2 Hz; 1H, H7),
7.37 (d, $^3J_{4,5}$=7.6 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.8 (t, C2), 30.8 (q, C8), 32.5 (t, C1), 37.3 (d, C3), 44.0 (t, C9), 109.7 (d), 114.7 (s, C3a), 117.8 (d), 118.0 (s, C11), 119.5 (d), 120.5 (d), 123.4 (s, C3b), 141.6 (s, C7a), 147.6 (s, C8a), 162.2 (s, $J_{C,F}$=35 Hz, C10).

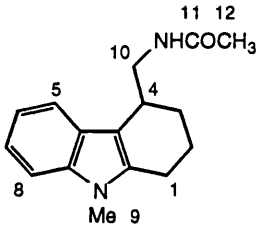
MS (EI, 70 eV): m/z = 296 (M^+, 2), 200 (M^+-$COCF_3$, 55), 183 (M^+-NH_2COCF_3, 20), 170 (M^+-$CH_2NHCOCF_3$, 100), 154 (59), 128 (51).

Ir (KBr): ν = 3306 (s, NH), 2925 (m), 1666 (s, C=O), 1527 (m), 1205 (s), 1175 (s), 1146 (s).

CHN $C_{15}H_{15}N_2OF_3$ calc. C 60.81 H 5.10 N 9.45
found C 60.53 H 4.92 N 9.49

N-Acetyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (50a)

4-Aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (0.3 g, 1.4 mmol) is treated with acetic anhydride (0.15 g, 1.4 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and recrystallised from benzene. Yield: 0.27 g (1.1 mmol, 76 %), mp. 173-173.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.75 - 1.96 (m; 4H, H2 and H3),
1.92 (s; 3H, H12),
2.64 - 2.74 (m; 2H, H1),
3.24 (m; 1H, H4),
3.55 - 3.67 (m; 2H, H10),
3.60 (s; 3H, H9),
5.59 (s, br; 1H, NH),
7.06 (ddd, ^4J=1.0 Hz, ^3J=7.0 Hz, ^3J=7.9 Hz; 1H, H6 or H7),
7.15 (ddd, ^4J=1.0 Hz, ^3J=7.0 Hz, ^3J=8.1 Hz; 1H, H6 or H7),
7.25 (d, $^3J_{8,7}$=8.1 Hz; 1H, H8),
7.56 (d, $^3J_{5,6}$=7.7 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.7 (t), 22.0 (t), 23.5 (q, C12), 26.6 (t), 29.0 (q, C9), 32.6 (d, C4), 43.5 (t, C10), 108.7 (d), 109.3 (s, C4a), 118.3 (d), 119.0 (d), 120.7 (d), 126.6 (s, C4b), 136.8, 137.0 (s, C8a, C9a), 170.2 (s, C11).

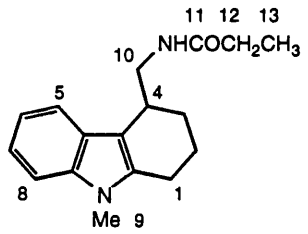
MS (EI, 70 eV): m/z = 256 (M^+, 27), 197 (M^+-NH_2COCH_3, 100), 184 (M^+-$CH_2NHCOCH_3$, 100), 168 (55), 142 (37).

Ir (KBr): ν = 3292 (s, NH), 2925 (s), 1645 (s, C=O), 1468 (s), 740 (s).

CHN $C_{16}H_{20}N_2O$ calc. C 74.96 H 7.86 N 10.93
found C 74.74 H 7.71 N 10.97

N-Propanoyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (50b)

4-Aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (0.3 g, 1.4 mmol) is treated with propanoic anhydride (0.18 g, 1.4 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and recrystallised from benzene/pet. ether 60-80. Yield: 0.33 g (1.2 mmol, 83 %), mp. 109-111 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.11 (t, $^3J_{13,12}$=7.5 Hz; 3H, H13),
1.78 - 2.00 (m; 4H, H2 and H3),
2.14 (q, $^3J_{12,13}$=7.7 Hz; 2H, H12),
2.65 - 2.71 (m; 2H, H1),
3.23 (m; 1H, H4),
3.52 - 3.70 (m; 2H, H10),
3.61 (s; 3H, H9),
5.55 (s, br; 1H, NH),
7.06 (ddd,^{4}J=1.0 Hz,^{3}J=6.9 Hz,^{3}J=8.0 Hz; 1H, H6 or H7),
7.15 (ddd,^{4}J=1.1 Hz,^{3}J=7.1 Hz,^{3}J=8.1 Hz; 1H, H6 or H7),
7.26 (d, $^3J_{8,7}$=8.1 Hz; 1H, H8),
7.58 (d, $^3J_{5,6}$=7.8 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.9 (q, C13), 20.0 (t), 22.1 (t), 26.6 (t), 29.1 (q, C9), 29.8 (t, C12), 32.6 (d, C4), 43.3 (t, C10), 108.7 (d), 109.4 (s, C4a), 118.4 (d), 119.0 (d), 120.7 (d), 126.6 (s, C4b), 136.8, 136.9 (s, C8a, C9a), 173.9 (s, C11).

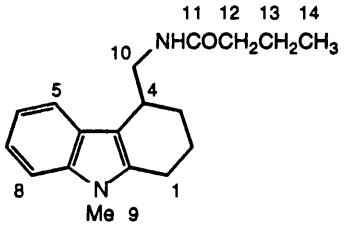
MS (EI, 70 eV): m/z = 270 (M^+, 32), 197 (M^+-$NH_2COC_2H_5$, 98), 184 (M^+-$CH_2NHCOC_2H_5$, 100), 168 (28), 142 (22).

Ir (KBr): ν = 3299 (s, NH), 2925 (m), 1635 (s, C=O), 1465 (s), 734 (s).

CHN $C_{17}H_{22}N_2O$ calc. C 75.52 H 8.20 N 10.36
found C 75.30 H 8.00 N 10.46

N-Butanoyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (50c)

4-Aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (0.20 g, 1.0 mmol) is treated with butanoic anhydride (0.16 g, 1.0 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2) and recrystallised from benzene. Yield: 0.23 g (0.9 mmol, 91 %), mp. 113-115 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.92 (t, $^3J_{14.13}$=7.4 Hz; 3H, H14),
1.61 - 1.68 (m; 2H, H13),
1.78 - 1.90 (m; 3H, H2 and H3),
1.97 - 2.02 (m; 1H, H2 or H3),
2.11 (t, $^3J_{12.13}$=7.5 Hz; 2H, H12),
2.64 - 2.70 (m; 2H, H1),
3.23 (m; 1H, H4),
3.48 - 3.55 (m; 1H, H10),
3.60 (s; 3H, H9),
3.68 - 3.74 (m; 1H, H10),
5.77 (s, br; 1H, NH),
7.07 (ddd, ^4J=1.0 Hz, ^3J=6.9 Hz, ^3J=8.0 Hz; 1H, H6 or H7),
7.16 (ddd, ^4J=1.2 Hz, ^3J=7.0 Hz, ^3J=8.1 Hz; 1H, H6 or H7),
7.26 (d, $^3J_{8.7}$=8.1 Hz; 1H, H8),
7.61 (d, $^3J_{5.6}$=7.7 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C14), 19.0 (t, C13), 19.5 (t), 21.9 (t), 26.4 (t), 28.9 (q, C9), 32.6 (d, C4), 38.7 (t, C12), 43.1 (t, C10), 108.6 (d), 109.3 (s, C4a), 118.3 (d), 118.9 (d), 120.5 (d), 126.5 (s, C4b), 136.7, 136.9 (s, C8a, C9a), 173.1 (s, C11).

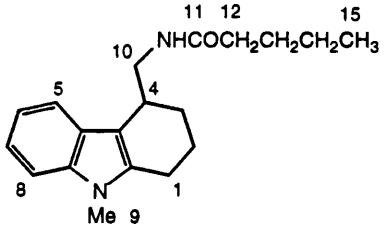
MS (EI, 70 eV): m/z = 284 (M^+, 34), 197 (M^+-$NH_2COC_3H_7$, 100), 184 (M^+-$CH_2NHCOC_3H_7$, 100), 168 (39), 142 (33).

Ir (KBr): ν = 3284 (s, NH), 2929 (s), 1630 (s, C=O), 1546 (s), 1456 (m), 738 (m).

CHN $C_{18}H_{24}N_2O$ calc. C 76.01 H 8.51 N 9.85
found C 75.88 H 8.48 N 9.74

N-Pentanoyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (50d)

4-Aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (0.3 g, 1.4 mmol) is treated with valeryl chloride (0.17 g, 1.4 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with ether. Yield: 0.52 g (1.3 mmol, 91 %), mp. 146-148 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{15,14}$=7.3 Hz; 3H, H15),
1.32 (m; 2H, H14),
1.58 (m; 2H, H13),
1.78 - 1.85 (m; 2H, H2),
1.85 - 1.91 (m; 1H, H3),
1.94 - 2.02 (m; 1H, H3),
2.13 (t, $^3J_{12,13}$=6.7 Hz; 2H, H12),
2.64 - 2.72 (m; 2H, H1),
3.23 (m; 1H, H4),
3.47 - 3.54 (m; 1H, H10),
3.59 (s; 3H, H9),
3.62 - 3.73 (m; 1H, H10),
5.82 (s, br; 1H, NH),
7.06 (dd, ^3J=7.1 Hz, ^3J=7.8 Hz; 1H, H6 or H7),
7.15 (dd, ^3J=7.0 Hz, ^3J=8.0 Hz; 1H, H6 or H7),
7.25 (d, $^3J_{8,7}$=8.1 Hz; 1H, H8),
7.61 (d, $^3J_{5,6}$=7.6 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C15), 19.5 (t), 21.9 (t), 22.3 (C14), 26.4 (t), 27.7 (t, C13), 28.9 (q, C9), 32.5 (d, C4), 36.5 (t, C12), 43.1 (t, C10), 108.6 (d), 109.3 (s, C4a), 118.3 (d), 118.8 (d), 120.5 (d), 126.5 (s, C4b), 136.7, 136.8 (s, C8a, C9a), 173.3 (s, C11).

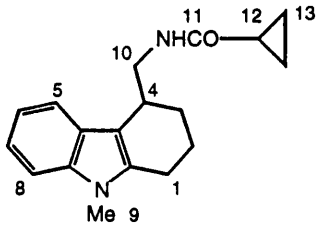
MS (EI, 70 eV): m/z = 298 (M^+, 22), 197 (M^+-$NH_2COC_4H_9$, 100), 184 (M^+-$CH_2NHCOC_4H_9$, 100), 168 (51), 142 (43).

Ir (KBr): ν = 3279 (s, NH), 2925 (s), 1631 (s, C=O), 1548 (s), 740 (s).

CHN $C_{19}H_{26}N_2O$ calc. C 76.47 H 8.78 N 9.39
found C 75.70 H 8.31 N 9.37

N-Cyclopropanoyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydro-carbazole (50e)

4-Aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (0.30 g, 1.4 mmol) is treated with cyclopropanecarbonyl chloride (0.15 g, 1.4 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with ether. Yield: 0.35 g (1.2 mmol, 88 %), mp. 182-182.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.98 - 1.05 (m; 2H, H13),
1.27 - 1.35 (m; 2H, H13),
1.81 - 1.87 (m; 4H, H2 and H3),
1.87 - 2.00 (m; 1H, H12),
2.62 - 2.72 (m; 2H, H1),
3.23 - 3.26 (m; 1H, H4),
3.46 - 3.49 (ddd, ^2J=13.6 Hz, ^3J=5.8 Hz, $^3J_{10.4}$=6.2 Hz; 1H, H10),
3.60 (s; 3H, H9),
3.71 - 3.77 (ddd, ^2J=13.5 Hz, ^3J=5.9 Hz, $^3J_{10.4}$=5.0 Hz; 1H, H10),
5.20 (t, br, ^3J= 5.8 Hz; 1H, NH),
7.09 (ddd, ^4J=1.5 Hz, ^3J=7.5 Hz, ^3J=7.5 Hz; 1H, H6 or H7),
7.17 (ddd, ^4J=1.0 Hz, ^3J=7.1 Hz, ^3J=7.5 Hz; 1H, H6 or H7),
7.25 (d, $^3J_{8.7}$=7.0 Hz; 1H, H8),
7.66 (d, $^3J_{5.6}$=7.7 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 6.84 (t, C13), 14.6 (d, C12), 19.3 (t), 21.9 (t), 26.2 (t), 28.8 (q, C9), 32.5 (d, C4), 43.4 (t, C10), 108.5 (d), 109.3 (s, C4a), 118.3 (d), 118.8 (d), 120.4 (d), 126.5 (s, C4b), 136.7, 136.8 (s, C8a, C9a), 173.8 (s, C11).

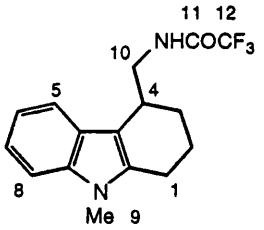
MS (EI, 70 eV): m/z = 282 (M^+, 19), 197 (M^+-$NH_2COC_3H_5$, 98), 184 (M^+-$CH_2NHCOC_3H_5$, 100), 168 (22), 142 (35).

Ir (KBr): ν = 3246 (s, NH), 2912 (m), 1631 (s, C=O), 1551 (s), 740 (s).

CHN $C_{18}H_{22}N_2O$ calc. C 76.56 H 7.85 N 9.92
found C 76.39 H 7.73 N 9.89

N-Trifluoroacetyl-4-methylamino-9-methyl-1,2,3,4-tetrahydrocarbazole (50g)

4-Aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (0.20 g, 1.0 mmol) is treated with ethyl trifluoroacetate (1 ml) according to procedure C VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH). Yield: 0.20 g (0.63 mmol, 63 %), mp. 134-135 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.86 - 2.05 (m; 4H, H2 and H3),
2.72 - 2.79 (m; 2H, H1),
3.38 (m; 1H, H4),
3.66 (s; 3H, H9),
3.83 - 3.89 (m; 2H, H10),
6.94 (s, br; 1H, NH),
7.16 (ddd, ^4J=1.1 Hz, ^3J=7.3 Hz, ^3J=7.0 Hz; 1H, H6 or H7),
7.25 (ddd, ^4J=1.0 Hz, ^3J=7.0 Hz, ^3J=7.1 Hz; 1H, H6 or H7),
7.35 (d, $^3J_{8,7}$=8.0 Hz; 1H, H8),
7.65 (d, $^3J_{5,6}$=7.8 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.1 (t), 21.8 (t), 26.0 (t), 28.9 (q, C9), 31.9 (d, C4), 43.6 (t, C10), 108.2 (s, C4a), 108.8 (d), 117.3 (s, $J_{C,F}$=288 Hz, C12), 117.8 (d), 119.1 (d), 120.7 (d), 126.2 (s, C4b), 136.8, 137.0 (s, C8a, C9a), 157.4 (s, $J_{C,F}$=37 Hz, C11).

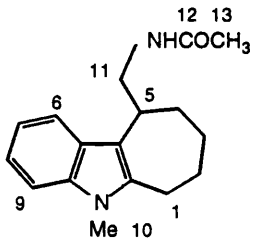
MS (EI, 70 eV): m/z = 310 (M^+, 1), 214 (M^+-$COCF_3$, 65), 197 (M^+-NH_2COCF_3, 23), 184 (M^+-$CH_2NHCOCF_3$, 100), 154 (53), 128 (32).

Ir (KBr): ν = 3319 (s, NH), 2932 (m), 1692 (s, C=O), 1198 (s), 1157 (s), 740 (m).

CHN $C_{16}H_{17}F_3N_2O$ calc. C 61.93 H 5.52 N 9.03
found C 61.08 H 5.28 N 8.94

N-Acetyl-10-aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (51a)

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.9 mmol) is treated with acetic anhydride (0.1 g, 0.9 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and solidified after trituration with ether. Yield 0.20 g (0.74 mmol, 82 %), mp. 151.5-153 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.68 - 1.72 (m; 1H, H2, H3 or H4),
1.88 - 1.97 (m; 1H, H2, H3 or H4),
1.98 (s; 3H, H13),
2.03 - 2.31 (m; 4H, H2, H3, H4),
2.82 (ddd, $^3J_{1.2}$=3.0 Hz, $^3J_{1.2}$=12.2 Hz, $^2J_{1.1}$=16.6 Hz; 1H, H1),
3.06 (ddd, $^3J_{1.2}$=2.5 Hz, $^3J_{1.2}$=5.6 Hz, $^2J_{1.1}$=15.8 Hz; 1H, H1),
3.33 (ddd, $^3J_{11.NH}$=4.0 Hz, $^3J_{11.5}$=9.0 Hz, $^2J_{11.11}$=12.8 Hz; 1H, H11),
3.60 - 3.64 (m; 1H, H5),
3.82 (s; 3H, H10),
3.83 (dd, $^3J_{11.5}$=6.5 Hz, $^2J_{11.11}$=13.2Hz; 1H, H11),
5.67 (s, br; 1H, NH),
7.11 (ddd,^{4}J=1.0Hz,^{3}J=7.4Hz,^{3}J=7.4Hz; 1H, H7 or H8),
7.19 (ddd,^{4}J=1.1Hz,^{3}J=7.5Hz,^{3}J=7.7Hz; 1H, H7 or H8),
7.35 (d, $^3J_{9.8}$=8.1 Hz; 1H, H9),
7.55 (d, $^3J_{6.7}$=7.7 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.2 (q, C13), 25.6, 25.8, 27.3 (t, C2, C3, C4), 29.4 (q, C10), 30.4 (t, C1), 34.1 (d, C5), 43.0 (t, C11), 108.9 (d, C9), 113.1 (s, C5a), 117.2 (d, C6), 119.0 (d, C7), 120.5 (d, C8), 128.1 (s, C5b), 135.7 (s, C9a), 138.7 (s, C10a), 170.0 (s, C12).

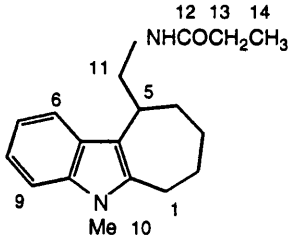
MS (EI, 70 eV): m/z = 270 (M^+, 32), 211 (M^+-NH_2COCH_3, 57), 198 (M^+-$CH_2NHCOCH_3$, 76), 107 (71), 84 (76).

Ir (KBr): ν = 3246 (s, NH), 2925 (m), 1637 (s, C=O), 1548 (s), 731 (m).

CHN $C_{17}H_{22}N_2O$ calc. C 75.52 H 8.20 N 10.36
found C 75.39 H 8.21 N 10.24

N-Propanoyl-10-aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (51b)

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.9 mmol) is treated with propanoic anhydride (0.09 g, 0.9 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH and solidified after trituration with ether. Yield 0.25 g (0.88 mmol, 98 %), mp. 178-179 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.00 (t, $^3J_{14.13}$=7.5 Hz; 3H, H14),
1.51 - 1.55 (m; 1H, H2, H3 or H4),
1.71 - 1.84 (m; 1H, H2, H3 or H4),
2.02 (q, $^3J_{13.14}$=7.7 Hz; 2H, H13),
1.87 - 2.13 (m; 4H, H2, H3, H4),
2.77 (ddd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=12.1 Hz, $^3J_{1.1}$=15.0 Hz; 1H, H1),
3.01 (ddd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=5.3 Hz, $^2J_{1.1}$=15.3 Hz; 1H, H1),
3.30 (ddd, $^3J_{11.NH}$=4.0 Hz, $^3J_{11.5}$=9.3 Hz, $^2J_{11.11}$=11.8 Hz; 1H, H11),
3.41 - 3.48 (m; 1H, H5),
3.65 (s; 3H, H10),
3.68 (dd, $^3J_{11.5}$=6.4 Hz, $^2J_{11.11}$=12.9Hz; 1H, H11),
5.48 (s, br; 1H, NH),
7.06 (ddd, ^{4}J=1.0Hz, ^{3}J=6.9Hz, ^{3}J=7.9Hz; 1H, H7 or H8),
7.14 (ddd, ^{4}J=1.2Hz, ^{3}J=7.0Hz, ^{3}J=8.0Hz; 1H, H7 or H8),
7.23 (d, $^3J_{9.8}$=8.4 Hz; 1H, H9),
7.49 (d, $^3J_{6.7}$=7.6 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.6 (q, C14), 25.7, 25.8, 27.3 (t, C2, C3, C4), 29.5 (q, C10), 29.7 (t, C13), 30.5 (t, C1), 34.2 (d, C5), 42.9 (t, C11), 108.9 (d, C9), 113.2 (s, C5a), 117.3 (d, C6), 119.0 (d, C7), 120.7 (d, C8), 128.1 (s, C5b), 135.8 (s, C9a), 138.7 (s, C10a), 173.6 (s, C12).

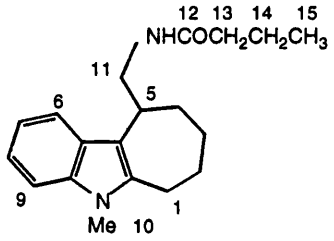
MS (EI, 70 eV): m/z = 284 (M^+, 29), 211 (M^+-$NH_2COC_2H_5$, 51), 198 (M^+-$CH_2NHCOC_2H_5$, 70), 107 (74), 84 (78).

Ir (KBr): ν = 3245 (s, NH), 2923 (m), 1636 (s, C=O), 1552 (m), 735 (m).

CHN $C_{18}H_{24}N_2O$ calc. C 76.01 H 8.51 N 9.85
found C 75.94 H 8.42 N 9.76

N-Butanoyl-10-aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (51c)

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.9 mmol) is treated with butanoic anhydride (0.10 g, 0.9 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2) and solidified after trituration with ether. Yield 0.22 g (0.74 mmol, 82 %), mp. 131-132 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.84 (t, $^3J_{15.14}$=7.5 Hz; 3H, H15),
1.51 - 1.57 (m; 3H, H2, H3 or H4 and H14),
1.71 - 2.13 (m; 7H, H2, H3, H4, H13),
2.73 - 2.81 (m; 1H, H1),
3.00 (ddd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=5.8 Hz, $^2J_{1.1}$=15.8 Hz; 1H, H1),
3.31 (ddd, $^3J_{11.NH}$=4.2 Hz, $^3J_{11.5}$=9.0 Hz, $^2J_{11.11}$=12.7 Hz; 1H, H11),
3.42 - 3.46 (m; 1H, H5),
3.65 (s; 3H, H10),
3.69 (dd, $^3J_{11.5}$=6.2 Hz, $^2J_{11.11}$=12.6Hz; 1H, H11),
5.49 (s, br; 1H, NH),
7.06 (dd, ^{3}J=7.6 Hz,^{3}J=7.2 Hz; 1H, H7 or H8),
7.13 (ddd,^{4}J=1.1Hz,^{3}J=7.6Hz,^{3}J=9.0Hz; 1H, H7 or H8),
7.23 (d, $^3J_{9.8}$=8.2 Hz; 1H, H9),
7.49 (d, $^3J_{6.7}$=7.9 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6 (q, C15), 18.9 (t, C14), 25.7, 25.8, 27.3 (t, C2, C3, C4), 29.5 (q, C10), 30.4 (t, C1), 34.3 (d, C5), 38.7 (t, C13), 42.8 (t, C11), 108.9 (d, C9), 113.2 (s, C5a), 117.3 (d, C6), 119.0 (d, C7), 120.6 (d, C8), 128.1 (s, C5b), 135.8 (s, C9a), 138.8 (s, C10a), 172.9 (s, C12).

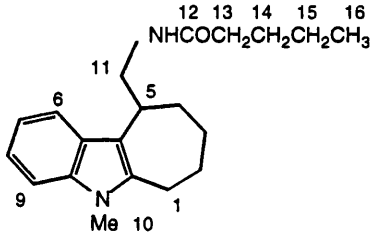
MS (EI, 70 eV): m/z = 298 (M^+, 33), 211 (M^+-$NH_2COC_3H_7$, 60), 198 (M^+-$CH_2NHCOC_3H_7$, 69), 159 (41), 84 (70).

Ir (KBr): ν = 3244 (s, NH), 2919 (m), 1637 (s, C=O), 1559 (m), 732 (s).

CHN $C_{19}H_{26}N_2O$ calc. C 76.47 H 8.78 N 9.39
found C 76.42 H 8.80 N 9.31

N-Pentanoyl-10-aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (51d)

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.9 mmol) is treated with valeryl chloride (0.10 g, 0.9 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2) and solidified after trituration with ether. Yield 0.24 g (0.8 mmol, 89 %), mp. 130-132 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.83 (t, $^3J_{16.15}$=7.3 Hz; 3H, H16),
1.19 - 1.25 (m; 2H, H15),
1.41 - 1.47 (m; 2H, H14),
1.49 - 1.54 (m; 1H, H2, H3 or H4),
1.71 - 2.13 (m; 7H, H2, H3, H4, H13),
2.77 (ddd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=12.1 Hz, $^3J_{1.1}$=15.0 Hz; 1H, H1),
3.00 (ddd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=5.8 Hz, $^2J_{1.1}$=16.0 Hz; 1H, H1),
3.30 (ddd, $^3J_{11.NH}$=4.3 Hz, $^3J_{11.5}$=9.3 Hz, $^2J_{11.11}$=12.6 Hz; H11),
3.41 - 3.46 (m; 1H, H5),
3.66 (s; 3H, H10),
3.69 (dd, $^3J_{11.5}$=6.5 Hz, $^2J_{11.11}$=12.8Hz; 1H, H11),
5.43 (s, br; 1H, NH),
7.06 (dd, ^{3}J=7.9 Hz,^{3}J=7.0 Hz; 1H, H7 or H8),
7.14 (ddd,^{4}J=1.1Hz,^{3}J=7.1Hz,^{3}J=7.9Hz; 1H, H7 or H8),
7.23 (d, $^3J_{9.8}$=8.3 Hz; 1H, H9),
7.49 (d, $^3J_{6.7}$=7.6 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C16), 22.3 (t, C15), 25.7, 25.8, 27.4, 27.6 (t, C2, C3, C4, C14), 29.5 (q, C10), 30.5 (t, C1), 34.3 (d, C5), 36.5 (t, C13), 42.9 (t, C11), 109.0 (d, C9), 113.2 (s, C5a), 117.4 (d, C6), 119.1 (d, C7), 120.6 (d, C8), 128.2 (s, C5b), 135.8 (s, C9a), 138.8 (s, C10a), 173.0 (s, C12).

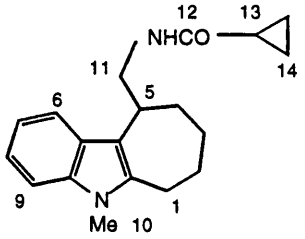
MS (EI, 70 eV): m/z = 312 (M^+, 17), 211 (M^+-$NH_2COC_4H_9$, 89), 198 (M^+-$CH_2NHCOC_4H_9$, 100), 170 (36), 41 (29).

Ir (KBr): ν = 3248 (s, NH), 2924 (m), 1634 (s, C=O), 1547 (s).

CHN $C_{20}H_{28}N_2O$ calc. C 76.88 H 9.03 N 8.96
found C 76.51 H 9.07 N 8.95

N-Cyclopropanoyl-10-aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept-[b]indole (51e)

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.9 mmol) is treated with cyclopropanecarbonyl chloride (0.10 g, 0.9 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and solidified after trituration with ether. Yield 0.21 g (0.68 mmol, 75 %), mp. 130-132 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.58 - 0.67 (m; 2H, H14),
0.84 - 0.97 (m; 2H, H14),
1.07 - 1.12 (m; 1H, H13),
1.52 - 1.56 (m; 1H, H2, H3 or H4),
1.72 - 2.14 (m; 5H, H2, H3, H4),
2.77 (ddd, $^3J_{1.2}$=2.6 Hz, $^3J_{1.2}$=6.5 Hz, $^2J_{1.1}$=12.1 Hz; 1H, H1),
3.01 (ddd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=5.8 Hz, $^2J_{1.1}$=12.0 Hz; 1H, H1),
3.31 (ddd, $^3J_{11.NH}$=4.5 Hz, $^3J_{11.5}$=8.7 Hz, $^2J_{11.11}$=15.5 Hz; 1H, H11),
3.44 - 3.48 (m; 1H, H5),
3.66 (s; 3H, H10),
3.67 - 3.74 (m; 1H, H11),
5.63 (s, br; 1H, NH),
7.06 (ddd,^{4}J=1.0Hz,^{3}J=7.0Hz,^{3}J=7.8Hz; 1H, H7 or H8),
7.13 (dd, ^{3}J=7.0 Hz, ^{3}J=8.0 Hz; 1H, H7 or H8),
7.23 (d, $^3J_{9.8}$=8.1 Hz; 1H, H9),
7.52 (d, $^3J_{6.7}$=7.7 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 6.86 (t, C14), 14.8 (d, C13), 25.7, 25.8, 27.4 (t, C2, C3, C4), 29.5 (q, C10), 30.5 (t, C1), 34.4 (d, C5), 43.3 (t, C11), 108.9 (d, C9), 113.3 (s, C5a), 117.5 (d, C6), 119.1 (d, C7), 120.6 (d, C8), 128.2 (s, C5b), 135.9 (s, C9a), 138.8 (s, C10a), 173.5 (s, C12).

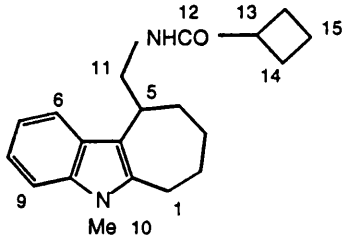
MS (EI, 70 eV): m/z = 296 (M^+, 23), 211 (M^+-$NH_2COC_3H_5$, 56), 198 (M^+-$CH_2NHCOC_3H_5$, 100), 170 (36), 41 (92).

Ir (KBr): ν = 3248 (s, NH), 2913 (m), 1630 (s, C=O), 1556 (s), 739 (s).

CHN $C_{19}H_{24}N_2O$ calc. C 76.99 H 8.16 N 9.45
found C 76.73 H 8.08 N 9.40

N-Cyclobutanoyl-10-aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept-[b]indole (51f)

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.9 mmol) is treated with cyclobutanecarbonyl chloride (0.10 g, 0.9 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2). Yield 0.19 g (0.61 mmol, 68 %), mp. 177-179 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.51 - 1.57 (m; 1H, H2, H3 or H4),
1.69 - 2.22 (m; 12H, H2, H3, H4, H14, H15),
2.73 - 2.81 (m; 2H, H1, H13),
3.01 (ddd, $^3J_{1.2}$=2.0 Hz, $^3J_{1.2}$=5.5 Hz, $^2J_{1.1}$=10.2 Hz; 1H, H1),
3.29 (ddd, $^3J_{11.NH}$=4.0 Hz, $^3J_{11.5}$=8.7 Hz, $^2J_{11.11}$=11.5 Hz; 1H, H11),
3.40 - 3.45 (m; 1H, H5),
3.65 (s; 3H, H10),
3.63 - 3.71 (m; 1H, H11),
5.35 (s, br; 1H, NH),
7.06 (ddd,^{4}J=1.0Hz,^{3}J=6.9Hz,^{3}J=7.8Hz; 1H, H7 or H8),
7.13 (ddd,^{4}J=1.1Hz,^{3}J=7.1Hz,^{3}J=8.1Hz; 1H, H7 or H8),
7.22 (d, $^3J_{9.8}$=8.2 Hz; 1H, H9),
7.47 (d, $^3J_{6.7}$=7.7 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 17.9 (t, C14 or C15), 25.1, 25.2, 25.7, 25.8, 27.3 (t, C2, C3, C4, C14, C15), 29.5 (q, C10), 30.5 (t, C1), 34.3 (d, C5), 39.9 (d, C13), 42.9 (t, C11), 108.9 (d, C9), 113.2 (s, C5a), 117.4 (d, C6), 119.0 (d, C7), 120.6 (d, C8), 128.2 (s, C5b), 135.8 (s, C9a), 138.7 (s, C10a), 174.8 (s, C12).

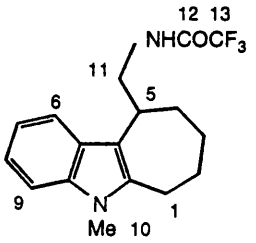
MS (EI, 70 eV): m/z = 310 (M^+, 28), 211 (M^+-$NH_2COC_4H_7$, 51), 198 (M^+-$CH_2NHCOC_4H_7$, 100), 170 (33), 41 (84).

Ir (KBr): ν = 3245 (s, NH), 2919 (m), 1634 (s, C=O), 1557 (s), 742 (s).

CHN $C_{20}H_{26}N_2O$ calc. C 77.38 H 8.44 N 9.03
found C 77.25 H 8.48 N 8.97

N-Trifluoroacetyl-10-aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept-[b]indole (51g)

10-Aminomethyl-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.10 g, 0.44 mmol) is treated with ethyl trifluoroacetate (2 ml) according to procedure C VIII.2.6. The product is purified by SPC (CH_2Cl_2) to yield 0.11 g (0.34 mmol, 77 %) tan crystalls, mp. 157-159 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.41 - 1.50 (m; 1H, H2, H3 or H4),
1.75 - 1.79 (m; 2H, H2, H3 or H4),
1.97 - 2.08 (m; 3H, H2, H3, H4),
2.73 (dd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=11.2 Hz; 1H, H1),
2.94 - 3.07 (m; 3H, H1, H11),
3.53 - 3.55 (m; 1H, H5),
3.65 (s; 3H, H10),
5.67 (s, br; 1H, NH),
6.98 - 7.00 (m; 2H, H7, H8),
7.15 (d, $^3J_{9.8}$=9.0 Hz; 1H, H9),
7.40 (s, br; 1H, NH),
7.51 (d, $^3J_{6.7}$=8.9 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 25.5, 25.7, 27.2 (t, C2, C3, C4), 29.6 (q, C10), 29.8 (t, C1), 32.5 (d, C5), 42.7 (t, C11), 109.2 (d, C9), 110.1 (s, C5a), 117.3 (d, C6), 117.9 (s, C13), 119.5 (d, C7), 120.8 (d, C8), 127.8 (s, C5b), 135.9 (s, C9a), 140.0 (s, C10a), 161.8 (s, C12).

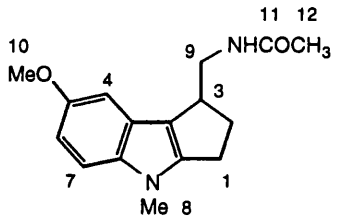
MS (EI, 70 eV): m/z = 324 (M^+, 0.7), 228 (M^+-$COCF_3$, 87), 211 (M^+-NH_2COCF_3, 9), 198 (M^+-$CH_2NHCOCF_3$, 100), 170 (90), 128 (50).

Ir (KBr): ν = 3323 (s, NH), 2930 (m), 1690 (s, C=O), 1187 (s), 1159 (s), 740 (m).

CHN $C_{17}H_{19}N_2OF_3$ calc. C 62.95 H 5.91 N 8.63
found C 62.49 H 5.88 N 8.57

N-Acetyl-1-aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (52a)

1-Aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.10 g, 0.4 mmol) is treated with acetic anhydride (0.05 g, 0.40 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and crystallised after trituration with ether. Yield: 0.10 g (0.37 mmol, 92 %), mp. 134-136 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.92 (s; 3H, H12),
2.20 - 2.25 (m; 1H, H2),
2.65 - 2.83 (m; 3H, H1, H2),
3.23 - 3.29 (m; 1H, H9),
3.44 - 3.46 (m; 1H, H3),
3.66 (s; 3H, H8),
3.62 - 3.72 (m; 1H, H9),
3.83 (s; 3H, H10),
5.50 (s, br; 1H, NH),
6.81 (dd, $^4J_{6.4}$=2.3 Hz, $^3J_{6.7}$=8.9 Hz; 1H, H6),
6.90 (d, $^4J_{4.6}$=2.4 Hz; 1H, H4),
7.12 (d, $^3J_{7.6}$=8.1 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.4 (q, C12), 23.5 (t, C2), 31.0 (q, C8), 33.7 (t, C1), 38.2 (d, C3), 42.9 (t, C9), 56.0 (q, C10), 101.3 (d), 110.2 (d), 110.5 (d), 118.6 (s), 124.2 (s), 137.3 (s), 145.9 (s), 154.0 (s, C5), 170.5 (s, C11).

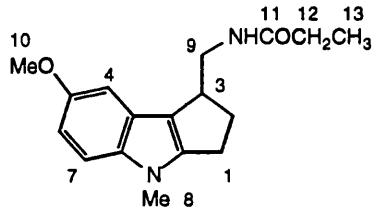
MS (EI, 70 eV): m/z = 272 (M^+, 31), 213 (M^+-NH_2COCH_3, 74), 200 (M^+-$CH_2NHCOCH_3$, 100), 157 (48), 43 (67).

Ir (KBr): ν = 3310 (s, NH), 2950 (m), 1643 (s, C=O), 1230 (m, C-O).

CHN $C_{16}H_{20}N_2O_2$ calc. C 70.56 H 7.40 N 10.29
found C 69.98 H 7.21 N 10.04

N-Propanoyl-1-aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (52b)

1-Aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.10 g, 0.4 mmol) is treated with propanoic acid anhydride (0.07 g, 0.40 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and crystallised after trituration with ether. Yield: 0.1 g (0.35 mmol, 87 %), mp. 118-120 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.08 (t, $^3J_{13.12}$=7.6 Hz; 3H, H13),
2.13 (q, $^3J_{12.13}$=7.6 Hz; 2H, H12)
2.20 - 2.25 (m; 1H, H2),
2.64 - 2.81 (m; 3H, H1, H2),
3.21 - 3.27 (m; 1H, H9),
3.44 - 3.45 (m; 1H, H3),
3.66 (s; 3H, H8),
3.68 - 3.73 (m; 1H, H9),
3.82 (s; 3H, H10),
5.57 (s, br; 1H, NH),
6.80 (dd,$^4J_{6.4}$=2.4 Hz,$^3J_{6.7}$=8.9 Hz; 1H, H6),
6.90 (d,$^4J_{4.6}$=2.4 Hz; 1H, H4),
7.11 (d, $^3J_{7.6}$=8.9 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.6 (q, C13), 23.5 (t, C2), 30.5 (t, C12), 30.8 (q, C8), 33.6 (t, C1), 38.3 (d, C3), 43.1 (t, C9), 56.0 (q, C10), 101.2 (d), 110.1 (d), 110.5 (d), 118.6 (s), 124.2 (s), 137.3 (s), 145.9 (s), 154.1 (s, C5), 171.6 (s, C11).

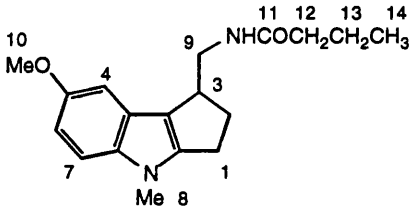
MS (EI, 70 eV): m/z = 286 (M^+, 46), 213 (M^+-$NH_2COC_2H_5$, 91), 200 (M^+-$CH_2NHCOC_2H_5$, 100), 157 (40), 43 (80).

Ir (KBr): ν = 3311 (s, NH), 2940 (m), 1644 (s, C=O), 1227 (m, C-O).

CHN $C_{17}H_{22}N_2O_2$ calc. C 71.30 H 7.74 N 9.78
found C 71.05 H 7.55 N 9.59

N-Butanoyl-1-aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent-[b]indole (52c)

1-Aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.10 g, 0.4 mmol) is treated with butanoic anhydride (0.07 g, 0.40 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with ether. Yield: 0.09 g (0.30 mmol, 75 %), mp. 122-123 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{14.13}$=7.3 Hz; 3H, H14),
1.57 - 1.64 (m; 2H, H13),
2.08 (t, $^3J_{12.13}$=7.3 Hz; 2H, H12)
2.20 - 2.25 (m; 1H, H2),
2.66 - 2.82 (m; 3H, H1, H2),
3.26 (ddd, $^3J_{9.3}$=4.6 Hz, $^3J_{9.3}$=6.2 Hz, $^2J_{9.9}$=13.5 Hz; 1H, H9),
3.45 - 3.47 (m; 1H, H3),
3.67 (s; 3H, H8),
3.73 (ddd, $^3J_{9.3}$=3.9 Hz, $^3J_{9.3}$=6.0 Hz, $^2J_{9.9}$=15.2 Hz; 1H, H9),
3.83 (s; 3H, H10),
5.41 (s, br; 1H, NH),
6.80 (dd,$^4J_{6.4}$=2.5 Hz,$^3J_{6.7}$=8.8 Hz; 1H, H6),
6.90 (d,$^4J_{4.6}$=2.5 Hz; 1H, H4),
7.12 (d, $^3J_{7.6}$=8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.8 (q, C14), 19.1 (t, C13), 23.5 (t, C2), 30.5 (q, C8), 33.7 (t, C1), 38.3 (d, C3), 38.7 (t, C12), 42.7 (t, C9), 56.0 (q, C10), 101.2 (d), 110.2 (d), 110.5 (d), 118.6 (s), 124.2 (s), 138.3 (s), 145.9 (s), 154.1 (s, C5), 171.8 (s, C11).

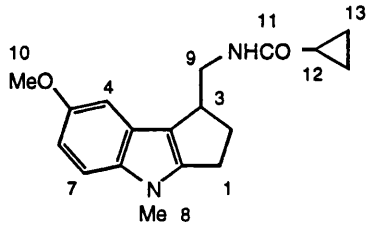
MS (EI, 70 eV): m/z = 300 (M^+, 46), 213 (M^+-$NH_2COC_3H_7$, 88), 200 (M^+-$CH_2NHCOC_3H_7$, 100), 157 (47), 43 (53).

Ir (KBr): ν = 3309 (s, NH), 2964 (m), 1646 (s, C=O), 1226 (m, C-O).

CHN $C_{18}H_{24}N_2O_2$ calc. C 71.97 H 8.05 N 9.33
found C 71.76 H 7.88 N 9.15

N-Cyclopropanoyl-1-aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole (52e)

1-Aminomethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (0.10 g, 0.4 mmol) is treated with cyclopropanecarbonyl chloride (0.04 g, 0.40 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and crystallised after trituration with ether. Yield: 0.08 g (0.27 mmol, 67 %), mp. 139-140 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.67 - 0.74 (m; 2H, H13),
0.87 - 0.99 (m; 2H, H13),
1.21 - 1.28 (m; 1H, H12),
2.22 - 2.27 (m; 1H, H2),
2.65 - 2.87 (m; 3H, H1, H2),
3.23 - 3.29 (m; 1H, H9),
3.43 - 3.47 (m; 1H, H3),
3.67 (s; 3H, H8),
3.67 - 3.75 (m; 1H, H9),
3.83 (s; 3H, H10),
5.72 (s, br; 1H, NH),
6.80 (dd, $^4J_{6.4}$=2.3 Hz, $^3J_{6.7}$=9.0 Hz; 1H, H6),
6.91 (d, $^4J_{4.6}$=2.4 Hz; 1H, H4),
7.13 (d, $^3J_{7.6}$=8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 7.18 (t, C13), 14.7 (d, C12), 23.4 (t, C2), 31.0 (q, C8), 33.7 (t, C1), 38.3 (d, C3), 43.1 (t, C9), 56.0 (q, C10), 101.2 (d), 110.2 (d), 110.4 (d), 118.4 (s), 124.2 (s), 137.2 (s), 146.2 (s), 153.9 (s, C5), 174.0 (s, C11).

MS (EI, 70 eV): m/z = 298 (M^+, 12), 226 (83), 215 (25), 159 (45), 43 (100).

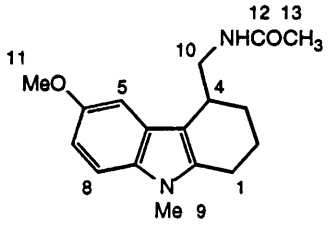
Ir (KBr): ν = 3315 (s, NH), 2924 (m), 1637 (s, C=O), 1232 (m, C-O).

CHN $C_{18}H_{22}N_2O_2$ calc. C 72.45 H 7.43 N 9.39
found C 72.03 H 7.10 N 9.14

N-Acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (53a)

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (0.30 g, 1.2 mmol) is treated with acetyl chloride (0.10 g, 1.2 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and solidified after trituration with ether. Yield: 0.25 g (0.88 mmol, 73 %), mp. 162-163 °C.

The racemic mixture is resolved on a Chiracel OD analytical HPLC column (Daicel Chemical Industries, Ltd.) using a mixture of 2-propanol (20 %) and n-hexane (80 %) as eluent.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.74 - 1.94 (m; 4H, H2 and H3),
1.92 (s; 3H, H13),
2.57 - 2.64 (m; 2H, H1),
3.15 (m; 1H, H4),
3.31 - 3.44 (m; 1H, H10),
3.52 (s; 3H, H9),
3.54 - 3.66 (m; 1H, H10),
3.81 (s; 3H, H11),
6.02 (s, br; 1H, NH),
6.76 (dd, $^4J_{7,5}$=2.5 Hz, $^3J_{7,8}$=8.7 Hz; 1H, H7),
7.06 (d, $^4J_{5,7}$=2.5 Hz; 1H, H5),
7.09 (d, $^3J_{8,7}$=8.7 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.3 (t), 21.9 (t), 23.2 (q, C13), 26.2 (t), 28.9 (q, C9), 32.3 (d, C4), 43.0 (t, C10), 55.8 (q, C11), 100.5 (d), 108.9 (s, C4a), 109.1 (d), 110.0 (d), 126.7 (s, C4b), 131.9 (s, C8a), 137.3 (s, C9a), 153.6 (s, C6), 170.2 (s, C12).

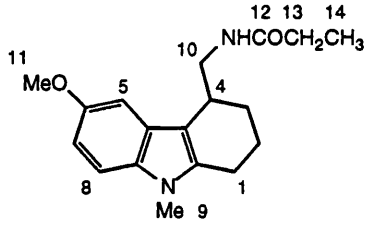
MS (EI, 70 eV): m/z = 286 (M^+, 56), 227 (M^+-NH_2COCH_3, 98), 214 (M^+-$CH_2NHCOCH_3$, 100), 123 (54), 102 (43).

Ir (KBr): ν = 3305 (m, NH), 2929 (m), 1637 (s, C=O), 1550 (s), 1216 (m, C-O).

CHN $C_{17}H_{22}N_2O_2$ calc. C 71.30 H 7.74 N 9.78
found C 70.38 H 7.35 N 9.73

N-Propanoyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (53b)

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (0.30 g, 1.2 mmol) is treated with propanoyl chloride (0.11 g, 1.2 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) to result a yellow oil. Yield: 0.20 g (0.67 mmol, 56 %)



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.10 (t, $^3J_{14,13}$=7.6 Hz; 3H, H14),
1.75 - 1.80 (m; 2H, H2 or H3),
1.81 - 1.87 (m; 1H, H2 or H3),
1.93 - 1.97 (m; 1H, H2 and H3),
2.15 (q, $^3J_{13,14}$=7.6 Hz; 2H, H13),
2.59 - 2.65 (m; 2H, H1),
3.16 (m; 1H, H4),
3.45 (ddd, ^{3}J=5.9 Hz, ^{3}J=6.2 Hz, ^{2}J=13.4 Hz; 1H, H10),
3.54 (s; 3H, H9),
3.66 (ddd, ^{3}J=5.2 Hz, ^{3}J=5.6 Hz, ^{2}J=13.4 Hz; 1H, H10),
3.82 (s; 3H, H11),
5.84 (s, br; 1H, NH),
6.78 (dd,$^4J_{7,5}$=2.2 Hz,$^3J_{7,8}$=8.7 Hz; 1H, H7),
7.07 (d,$^4J_{5,7}$=2.3 Hz; 1H, H5),
7.11 (d, $^3J_{8,7}$=8.8 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.8 (q, C14), 19.3 (t), 22.0 (t), 26.3 (t), 28.9 (q, C9), 29.7 (t, C13), 32.4 (d, C4), 42.9 (t, C10), 55.9 (q, C11), 100.8 (d), 109.0 (s, C4a), 109.2 (d), 110.1 (d), 126.8 (s, C4b), 132.1 (s, C8a), 137.3 (s, C9a), 153.6 (s, C6), 173.8 (s, C12).

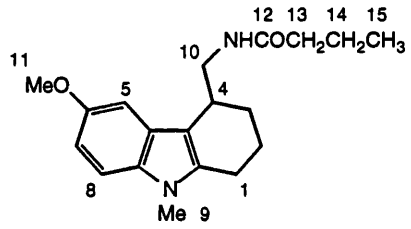
MS (EI, 70 eV): m/z = 300 (M^+, 40), 227 (M^+-$NH_2COC_2H_5$, 97), 228 (M^+-$CH_2NHCOC_2H_5$, 100), 123 (45), 102 (40).

Ir (film): ν = 3310 (m, NH), 2940 (m), 1645 (s, C=O), 1555 (s), 1220 (m, C-O).

CHN $C_{18}H_{24}N_2O_2$ calc. C 71.97 H 8.05 N 9.33
found C 71.83 H 7.95 N 9.29

N-Butanoyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (53c)

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (0.40 g, 1.6 mmol) is treated with butanoyl chloride (0.17 g, 1.6 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH). Yield: 0.42 g (1.3 mmol, 83 %), mp. 128-129 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{15,14}$=7.4 Hz; 3H, H15),
1.60 - 1.68 (m; 2H, H14),
1.76 - 1.86 (m; 3H, H2 and H3),
1.93 - 1.95 (m; 1H, H2 or H3),
2.12 (t, $^3J_{13,14}$=7.5 Hz; 2H, H13),
2.58 - 2.64 (m; 2H, H1),
3.17 (m; 1H, H4),
3.41 (ddd, ^3J=5.4 Hz, ^3J=6.2 Hz, ^2J=13.5 Hz; 1H, H10),
3.51 (s; 3H, H9),
3.71 (ddd, ^3J=4.9 Hz, ^3J=5.6 Hz, ^2J=13.5 Hz; 1H, H10),
3.82 (s; 3H, H11),
6.12 (t, br, ^3J=5.6 Hz; 1H, NH),
6.78 (dd,$^4J_{7,5}$=2.3 Hz,$^3J_{7,8}$=8.8 Hz; 1H, H7),
7.10 (d, $^3J_{8,7}$=8.7 Hz; 1H, H8).
7.11 (d,$^4J_{5,7}$=2.5 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.5 (q, C15), 19.0 (t, C14), 19.2 (t), 21.9 (t), 26.1 (t), 28.8 (q, C9), 32.3 (d, C4), 38.5 (t, C13), 42.8 (t, C10), 55.8 (q, C11), 100.7 (d), 108.9 (s, C4a), 109.0 (d), 109.9 (d), 126.7 (s, C4b), 132.0 (s, C8a), 137.2 (s, C9a), 153.5 (s, C6), 173.2 (s, C12).

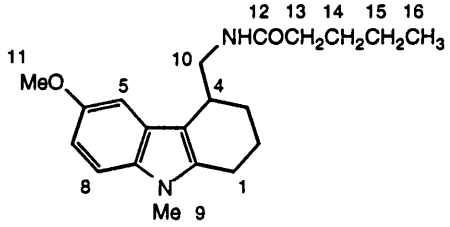
MS (EI, 70 eV): m/z = 314 (M^+, 23), 227 (M^+-$NH_2COC_3H_7$, 100), 228 (M^+-$CH_2NHCOC_3H_7$, 100), 123 (52), 102 (44).

Ir (KBr): ν = 3306 (m, NH), 2932 (m), 1635 (s, C=O), 1541 (m), 1221 (m, C-O).

CHN $C_{19}H_{26}N_2O_2$ calc. C 72.58 H 8.34 N 8.91
found C 72.15 H 8.26 N 8.94

N-Pentanoyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (53d)

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (0.50 g, 2.0 mmol) is treated with valeryl chloride (0.24 g, 2.0 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH). Yield: 0.51 g (1.6 mmol, 78 %), mp. 113-115 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.86 (t, $^3J_{16.15}$=7.3 Hz; 3H, H16),
1.26 - 1.33 (m; 2H, H15),
1.53 - 1.60 (m; 2H, H14),
1.75 - 1.86 (m; 3H, H2 and H3),
1.95 - 1.96 (m; 1H, H2 or H3),
2.12 (t, $^3J_{13.14}$=7.5 Hz; 2H, H13),
2.61 - 2.66 (m; 2H, H1),
3.18 (m; 1H, H4),
3.46 (ddd, ^{3}J=5.9 Hz, ^{3}J=6.1 Hz, ^{2}J=13.5 Hz; 1H, H10),
3.55 (s; 3H, H9),
3.68 (ddd, ^{3}J=5.1 Hz, ^{3}J=5.7 Hz, ^{2}J=13.5 Hz; 1H, H10),
3.83 (s; 3H, H11),
5.73 (t, br; 1H, NH),
6.79 (dd,$^4J_{7.5}$=2.4 Hz,$^3J_{7.8}$=8.7 Hz; 1H, H7),
7.07 (d,$^4J_{5.7}$=2.2 Hz; 1H, H5),
7.12 (d, $^3J_{8.7}$=8.7 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C16), 19.5 (t), 22.1 (t), 22.3 (t, C15), 26.4 (t), 27.8 (t, C14), 29.0 (q, C9), 32.6 (d, C4), 36.6 (t, C13), 42.9 (t, C10), 56.0 (q, C11), 100.8 (d), 108.9 (s, C4a), 109.2 (d), 110.2 (d), 126.8 (s, C4b), 132.1 (s, C8a), 137.5 (s, C9a), 153.7 (s, C6), 173.3 (s, C12).

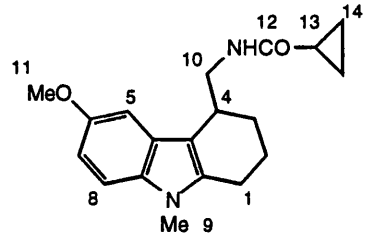
MS (EI, 70 eV): m/z = 328 (M^+, 36), 227 (M^+-$NH_2COC_4H_9$, 96), 228 (M^+-$CH_2NHCOC_4H_9$, 100), 123 (42), 102 (25).

Ir (KBr): ν = 3305 (m, NH), 2932 (m), 1635 (s, C=O), 1541 (s), 1221 (s, C-O).

CHN $C_{20}H_{28}N_2O_2$ calc. C 73.13 H 8.59 N 8.53
found C 72.87 H 8.37 N 8.43

N-Cyclopropanoyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydro-carbazole (53e)

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (0.40 g, 1.6 mmol) is treated with cyclopropanoyl chloride (0.17 g, 1.6 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) to yield 0.29 g (0.93 mmol, 58 %) with mp. 173-174 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.96 - 1.03 (m; 2H, H14),
1.24 - 1.33 (m; 2H, H14),
1.81 - 1.85 (m; 3H, H2 or H3),
1.87 - 1.92 (m; 1H, H2 or H3),
1.96 - 2.01 (m; 1H, H13),
2.64 - 2.74 (m; 2H, H1),
3.22 (m; 1H, H4),
3.56 - 3.69 (m; 2H, H10),
3.60 (s; 3H, H9),
3.86 (s; 3H, H11),
5.98 (t, br, ^3J=5.3 Hz; 1H, NH),
6.83 (dd, $^4J_{7,5}$=2.4 Hz, $^3J_{7,8}$=8.8 Hz; 1H, H7),
7.11 (d, $^4J_{5,7}$=2.3 Hz; 1H, H5),
7.17 (d, $^3J_{8,7}$=8.9 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 7.0 (t, C14), 14.8 (d, C13), 19.4 (t), 22.1 (t), 26.5 (t), 29.1 (q, C9), 32.5 (d, C4), 43.4 (t, C10), 56.0 (q, C11), 100.8 (d), 109.1 (s, C4a), 109.3 (d), 110.2 (d), 126.9 (s, C4b), 132.1 (s, C8a), 137.5 (s, C9a), 153.7 (s, C6), 173.6 (s, C12).

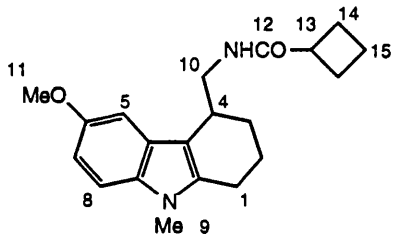
MS (EI, 70 eV): m/z = 312 (M^+, 21), 227 (M^+-$NH_2COC_3H_5$, 97), 228 (M^+-$CH_2NHCOC_3H_5$, 100), 123 (38), 102 (29).

Ir (KBr): ν = 3265 (s, NH), 2945 (m), 1635 (s, C=O), 1558 (s), 1218 (m, C-O).

CHN $C_{19}H_{24}N_2O_2$ calc. C 73.04 H 7.74 N 8.97
found C 72.89 H 7.70 N 8.83

N-Cyclobutanoyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (53f)

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (0.30 g, 1.2 mmol) is treated with cyclobutanoyl chloride (0.10 g, 1.2 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2). Yield: 0.32 g (0.98 mmol, 82 %), mp. 160-161 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.75 - 1.97 (m; 6H, H2, H3, H15),
2.02 - 2.11 (m; 2H, H14),
2.19 - 2.36 (m; 2H, H14),
2.61 - 2.67 (m; 2H, H1),
2.93 (qi, J=0.9 Hz, ^{3}J=8.6 Hz; 1H, H13),
3.21 (m; 1H, H4),
3.51 (m; 1H, H10),
3.56 (s; 3H, H9),
3.65 (m; 1H, H10),
3.83 (s; 3H, H11),
5.55 (s, br; 1H, NH),
6.79 (dd, $^4J_{7,5}$=2.4 Hz, $^3J_{7,8}$=8.8 Hz; 1H, H7),
7.04 (d, $^4J_{5,7}$=2.5 Hz; 1H, H5),
7.13 (d, $^3J_{8,7}$=8.8 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 18.1 (t, C14 or C15), 19.4 (t), 22.1 (t), 25.2 (t, C14 or C15), 26.4 (t), 29.1 (q, C9), 32.5 (d, C4), 40.0 (d, C13), 43.0 (t, C10), 56.0 (q, C11), 100.8 (d), 109.0 (s, C4a), 109.3 (d), 110.2 (d), 126.8 (s, C4b), 132.1 (s, C8a), 137.5 (s, C9a), 153.7 (s, C6), 175.1 (s, C12).

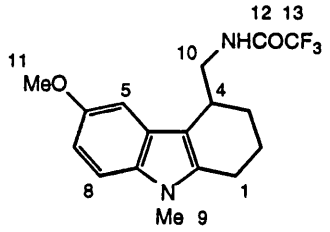
MS (EI, 70 eV): m/z = 326 (M^+, 38), 227 (M^+-$NH_2COC_4H_7$, 93), 228 (M^+-$CH_2NHCOC_4H_7$, 100), 123 (26), 102 (20).

Ir (KBr): ν = 3301 (m, NH), 2922 (m), 1632 (s, C=O), 1551 (s), 1228 (m, C-O).

CHN $C_{20}H_{26}N_2O_2$ calc. C 73.58 H 8.03 N 8.58
found C 73.79 H 7.64 N 8.49

N-Trifluoroacetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (53g)

4-Aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (0.30 g, 1.2 mmol) is treated with ethyl trifluoroacetate (1 ml) according to procedure C VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH). Yield: 0.2 g (0.76 mmol, 63 %), mp. 163-164 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.77 - 1.95 (m; 4H, H2, H3),
2.64 - 2.71 (m; 2H, H1),
3.26 (m; 1H, H4),
3.58 (s; 3H, H9),
3.59 (m; 1H, H10),
3.74 (m; 1H, H10),
3.84 (s; 3H, H11),
6.82 (dd, $^4J_{7,5}$=2.5 Hz, $^3J_{7,8}$=8.8 Hz; 1H, H7),
7.01 (d, $^4J_{5,7}$=2.5 Hz; 1H, H5),
7.16 (d, $^3J_{8,7}$=8.8 Hz; 1H, H8),
7.55 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.3 (t), 22.0 (t), 26.4 (t), 29.2 (q, C9), 32.0 (d, C4), 43.7 (t, C10), 56.0 (q, C11), 100.2 (d), 107.8 (s, C4a), 109.6 (d), 110.6 (d), 118.2 (s, $J_{C,F}$=280 Hz, C13), 126.5 (s, C4b), 132.2 (s, C8a), 137.7 (s, C9a), 154.0 (s, C6), 175.1 (s, $J_{C,F}$=40 Hz, C12).

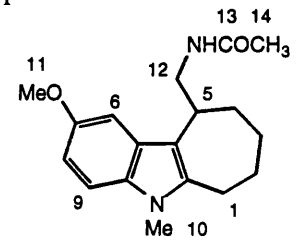
MS (EI, 70 eV): m/z = 340 (M^+, 0.5), 243 (M^+-$COCF_3$, 77), 227 (M^+-NH_2COCF_3, 18), 214 (M^+-$CH_2NHCOCF_3$, 100), 123 (29), 102 (14).

Ir (KBr): ν = 3305 (m, NH), 2921 (m), 1692 (s, C=O), 1553 (s), 1228 (m, C-O), 1198 (m).

CHN $C_{17}H_{19}N_2O_2F_3$ calc. C 59.99 H 5.63 N 8.22
found C 59.72 H 5.50 N 8.17

N-Acetyl-10-aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept-[b]indole (54a)

10-Aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.77 mmol) is treated with acetic anhydride (0.09 g, 0.77 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and solidified after trituration with ether. Yield: 0.16 g (0.53 mmol, 69 %), mp. 132-134 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.49 - 1.53 (m; 1H, H2, H3 or H4),
1.72 - 2.12 (m; 5H, H2, H3, H4),
1.82 (s; 3H, H14),
2.69 - 2.77 (m; 1H, H1),
2.95 (ddd, $^3J_{1.2}$=2.4 Hz, $^3J_{1.2}$=5.7 Hz, $^2J_{1.1}$=12.6 Hz; 1H, H1),
3.25 (ddd, $^3J_{12.NH}$=4.0 Hz, $^3J_{12.5}$=9.4 Hz, $^2J_{12.12}$=12.4 Hz; 1H, H12),
3.35 - 3.40 (m; 1H, H5),
3.62 (s; 3H, H10),
3.65 - 3.72 (m; 1H, H12),
3.83 (s; 3H, H11),
5.45 (s, br; 1H, NH),
6.78 (dd,$^4J_{8.6}$=2.4 Hz,$^3J_{8.9}$=8.8 Hz; 1H, H8),
6.95 (d,$^4J_{6.8}$=2.3 Hz; 1H, H6),
7.11 (d, $^3J_{9.8}$=8.7 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.5 (q, C14), 25.8, 26.1, 27.4 (t, C2, C3, C4), 29.7 (q, C10), 30.6 (t, C1), 34.4 (d, C5), 43.2 (t, C12), 56.0 (q, C11), 99.4 (d), 109.8 (d), 110.7 (d), 112.9 (s, C5a), 128.5 (s, C5b), 131.2 (s, C9a), 139.5 (s, C10a), 154.1 (s, C7), 170.1 (s, C13).

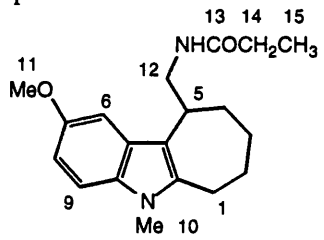
MS (EI, 70 eV): m/z = 300 (M^+, 43), 241 (M^+-NH_2COCH_3, 97), 228 (M^+-$CH_2NHCOCH_3$, 100), 137 (80), 122 (73), 43 (83).

Ir (KBr): ν = 3332 (s, NH), 2920 (s), 1639 (s, C=O), 1531 (s), 1233 (m, C-O).

CHN $C_{18}H_{24}N_2O_2$ calc. C 71.97 H 8.05 N 9.33
found C 71.84 H 8.01 N 9.21

N-Propanoyl-10-aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole (54b)

10-Aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.77 mmol) is treated with propanoic anhydride (0.09 g, 0.77 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) and solidified after trituration with ether. Yield: 0.22 g (0.70 mmol, 91 %), mp. 125-127 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.00 (t, $^3J_{15,14}$=7.7 Hz; 3H, H15),
1.49 - 1.52 (m; 1H, H2, H3 or H4),
1.72 - 2.15 (m; 7H, H2, H3, H4, H14),
2.73 - 2.77 (m; 1H, H1),
2.94 - 2.99(m; 1H, H1),
3.26 - 3.30 (m; 1H, H12),
3.35 - 3.40 (m; 1H, H5),
3.62 (s; 3H, H10),
3.64 - 3.73(m; 1H, H12),
3.82 (s; 3H, H11),
5.40 (s, br; 1H, NH),
6.78 (dd,$^4J_{8,6}$=2.3 Hz,$^3J_{8,9}$=8.7 Hz; 1H, H8),
6.94 (d,$^4J_{6,8}$=2.0 Hz; 1H, H6),
7.11 (d, $^3J_{9,8}$=8.8 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.7 (q, C15), 25.8, 26.0, 27.4 (t, C2, C3, C4), 29.6 (q, C10), 29.8 (t, C14), 30.6 (t, C1), 34.3 (d, C5), 42.9 (t, C12), 55.9 (q, C11), 99.4 (d), 109.7 (d), 110.6 (d), 112.9 (s, C5a), 128.4 (s, C5b), 131.1 (s, C9a), 139.5 (s, C10a), 154.0 (s, C7), 173.6 (s, C13).

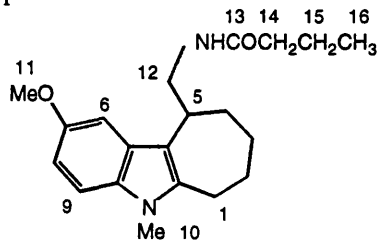
MS (EI, 70 eV): m/z = 314 (M^+, 40), 241 (M^+-$NH_2COC_2H_5$, 92), 228 (M^+-$CH_2NHCOC_2H_5$, 100), 137 (85), 122 (62), 43 (93).

Ir (KBr): ν = 3338 (s, NH), 2917 (s), 1640 (s, C=O), 1524 (s), 1229 (s, C-O).

CHN $C_{19}H_{26}N_2O_2$ calc. C 72.58 H 8.34 N 8.91
found C 72.32 H 8.27 N 8.65

N-Butanoyl-10-aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole (54c)

10-Aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.77 mmol) is treated with butanoic anhydride (0.10 g, 0.77 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH) to give 0.21 g (0.64 mmol, 83 %) of an amorphous solid. Mp. 58-60 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.82 (t, $^3J_{16.15}$=7.4 Hz; 3H, H16),
1.48 - 1.56 (m; 3H, H2, H3 or H4 and H15),
1.63 - 2.11 (m; 5H, H2, H3 or H4),
2.00 (t, $^3J_{14.15}$=6.9 Hz; 2H, H14),
2.69 - 2.77 (m; 1H, H1),
2.93 - 2.98 (m; 1H, H1),
3.28 (ddd, $^3J_{12.NH}$=4.0 Hz, $^3J_{12.5}$=9.3 Hz, $^2J_{12.12}$=12.1 Hz; H12),
3.34 - 3.38 (m; 1H, H5),
3.61 (s; 3H, H10),
3.33 (ddd, $^3J_{12.NH}$=6.0 Hz, $^3J_{12.5}$=7.4 Hz, $^2J_{12.12}$=12.7 Hz; H12),
3.82 (s; 3H, H11),
5.47 (s, br; 1H, NH),
6.78 (dd,$^4J_{8.6}$=2.4 Hz,$^3J_{8.9}$=8.8 Hz; 1H, H8),
6.95 (d,$^4J_{6.8}$=2.2 Hz; 1H, H6),
7.10 (d, $^3J_{9.8}$=8.1 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C16), 19.0 (t, C15), 25.7, 25.9, 27.4 (t, C2, C3, C4), 29.6 (q, C10), 30.5 (t, C1), 34.4 (d, C5), 38.7 (t, C14), 42.8 (t, C12), 56.0 (q, C11), 99.5 (d), 109.7 (d), 110.5 (d), 112.9 (s, C5a), 128.3 (s, C5b), 131.2 (s, C9a), 139.5 (s, C10a), 154.0 (s, C6), 172.9 (s, C13).

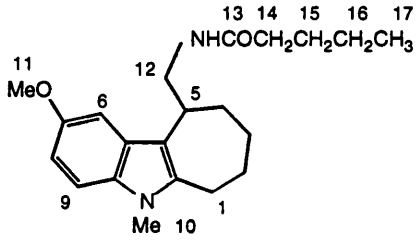
MS (EI, 70 eV): m/z = 328 (M^+, 45), 241 (M^+-$NH_2COC_3H_7$, 97), 228 (M^+-$CH_2NHCOC_3H_7$, 100), 137 (96), 122 (88), 43 (100).

Ir (KBr): ν = 3340 (s, NH), 2923 (s), 1641 (s, C=O), 1530 (s), 1234 (s, C-O).

CHN $C_{20}H_{28}N_2O_2$ calc. C 73.13 H 8.59 N 8.53
found C 72.38 H 8.22 N 8.43

N-Pentanoyl-10-aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole (54d)

10-Aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.77 mmol) is treated with valeryl chloride (0.09 g, 0.77 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2) to yield 0.20 g (0.58 mmol, 76 %) of an amorphous solid. Mp. 78-82 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.81 (t, $^3J_{17,16}$=7.3 Hz; 3H, H17),
1.17 - 1.23 (m; 2H, H16),
1.40 - 1.54 (m; 3H, H2, H3 or H4 and H15),
1.69 - 2.11 (m; 5H, H2, H3 or H4),
2.00 (t, $^3J_{14,15}$=7.9 Hz; 2H, H14),
2.69 - 2.77 (m; 1H, H1),
2.94 (ddd, $^3J_{1,2}$=2.5 Hz, $^3J_{1,2}$=5.6 Hz, $^2J_{1,1}$=13.3 Hz; 1H, H1),
3.26 - 3.35 (m; 1H, H12),
3.37 - 3.38 (m; 1H, H5),
3.61 (s; 3H, H10),
3.63 - 3.70 (m; 1H, H12),
3.82 (s; 3H, H11),
5.47 (s, br; 1H, NH),
6.78 (dd,$^4J_{8,6}$=2.5 Hz,$^3J_{8,9}$=9.0 Hz; 1H, H8),
6.94 (d,$^4J_{6,8}$=2.5 Hz; 1H, H6),
7.10 (d, $^3J_{9,8}$=8.9 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C17), 22.3 (t, C16), 25.7, 25.9, 27.4, 27.6 (t, C2, C3, C4, C15), 29.6 (q, C10), 30.5 (t, C1), 34.3 (d, C5), 36.6 (t, C14), 42.8 (t, C12), 55.9 (q, C11), 99.5 (d), 109.7 (d), 110.5 (d), 112.8 (s, C5a), 128.3 (s, C5b), 131.2 (s, C9a), 139.5 (s, C10a), 154.0 (s, C7), 173.1 (s, C13).

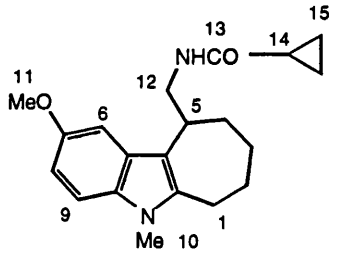
MS (EI, 70 eV): m/z = 342 (M^+, 34), 241 (M^+-$NH_2COC_4H_9$, 92), 228 (M^+-$CH_2NHCOC_4H_9$, 100), 137 (85), 122 (71), 43 (40).

Ir (KBr): ν = 3337 (s, NH), 2929 (s), 1636 (s, C=O), 1230 (m, C-O).

CHN $C_{21}H_{30}N_2O_2$ calc. C 73.64 H 8.83 N 8.18
found C 73.53 H 8.86 N 8.00

N-Cyclopropanoyl-10-aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indole (54e)

10-Aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.77 mmol) is treated with cyclopropanecarbonyl chloride (0.09 g, 0.77 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2 with 1 % MeOH). Yield: 0.23 g (0.71 mmol, 92 %), mp. 160-161 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.58 - 0.68 (m; 2H, H15),
0.83 - 0.88 (m; 1H, H15),
0.92 - 0.98 (m; 1H, H15),
1.11 - 1.14 (m; 1H, H14),
1.50 - 1.53 (m; 1H, H2, H3 or H4),
1.73 - 2.14 (m; 5H, H2, H3, H4),
2.71 - 2.78 (m; 1H, H1),
2.97 (ddd, $^3J_{1.2}$=3.8 Hz, $^3J_{1.2}$=5.4 Hz, $^2J_{1.1}$=12.1 Hz; 1H, H1),
3.28 (ddd, $^3J_{12.NH}$=3.7 Hz, $^3J_{12.5}$=9.1 Hz, $^2J_{12.12}$=12.8 Hz; H12),
3.36 - 3.41 (m; 1H, H5),
3.62 (s; 3H, H10),
3.33 (m;1H,H12),
3.83 (s; 3H, H11),
5.71 (s, br; 1H, NH),
6.78 (dd,$^4J_{8.6}$=2.3 Hz,$^3J_{8.9}$=8.8 Hz; 1H, H8),
6.98 (d,$^4J_{6.8}$=2.1 Hz; 1H, H6),
7.11 (d, $^3J_{9.8}$=8.7 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 6.7 (t, C15), 14.7 (t, C14), 25.7, 26.0, 27.3 (t, C2, C3, C4), 29.6 (q, C10), 30.6 (t, C1), 34.5 (d, C5), 43.2 (t, C12), 55.9 (q, C11), 99.5 (d), 109.7 (d), 110.6 (d), 113.0 (s, C5a), 128.4 (s, C5b), 131.1 (s, C9a), 139.4 (s, C10a), 154.0 (s, C7), 173.3 (s, C13).

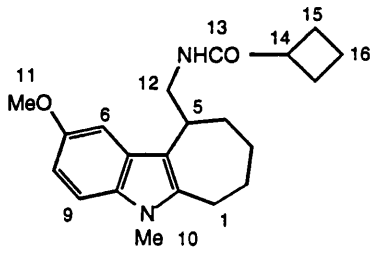
MS (EI, 70 eV): m/z = 326 (M^+, 35), 241 (M^+-$NH_2COC_3H_5$, 62), 228 (M^+-$CH_2NHCOC_3H_5$, 100), 69 (36), 41 (55).

Ir (KBr): ν = 3327 (s, NH), 2924 (s), 1636 (s, C=O), 1542 (s), 1236 (s, C-O).

CHN	$C_{20}H_{26}N_2O_2$	calc.	C 73.59 H 8.03 N 8.58
		found	C 72.26 H 7.70 N 8.09

N-Cyclobutanoyl-10-aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (54f)

10-Aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (0.20 g, 0.77 mmol) is treated with cyclobutanecarbonyl chloride (0.09 g, 0.77 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2). Yield: 0.18 g (0.53 mmol, 69 %), mp. 119-121 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.48 - 1.52 (m; 1H, H2, H3 or H4),
1.70 - 2.14 (m; 11H, H2, H3, H4, H15, H16),
2.70 - 2.80 (m; 2H, H1, H13),
2.97 (ddd, $^3J_{1.2}$=2.3 Hz, $^3J_{1.2}$=5.7 Hz, $^2J_{1.1}$=13.2 Hz; 1H, H1),
3.28 (ddd, $^3J_{12.NH}$=4.0 Hz, $^3J_{12.5}$=9.6 Hz, $^2J_{12.12}$=12.3 Hz; 1H, H12),
3.34 - 3.38 (m; 1H, H5),
3.62 (s; 3H, H10),
3.33 (ddd, $^3J_{12.NH}$=5.8 Hz, $^3J_{12.5}$=7.5 Hz, $^2J_{12.12}$=12.4 Hz; 1H, H12),
3.82 (s; 3H, H11),
5.33 (s, br; 1H, NH),
6.78 (dd,$^4J_{8.6}$=2.4 Hz,$^3J_{8.9}$=8.8 Hz; 1H, H8),
6.93 (d,$^4J_{6.8}$=2.4 Hz; 1H, H6),
7.10 (d, $^3J_{9.8}$=8.7 Hz; 1H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 18.0 (t, C16), 25.3, 25.9, 26.1, 27.5 (t, C2, C3, C4, C15), 29.7 (q, C10), 30.7 (t, C1), 34.5 (d, C5), 40.1 (t, C14), 42.9 (t, C12), 56.1 (q, C11), 99.6 (d), 109.8 (d), 110.6 (d), 113.0 (s, C5a), 128.5 (s, C5b), 131.2 (s, C9a), 139.6 (s, C10a), 154.1 (s, C7), 174.9 (s, C13).

MS (EI, 70 eV): m/z = 340 (M^+, 32), 241 (M^+-$NH_2COC_4H_7$, 70), 228 (M^+-$CH_2NHCOC_4H_7$, 100), 69 (44), 41 (78).

Ir (KBr): ν = 3331 (s, NH), 2920 (s), 1638 (s, C=O), 1537 (s), 1232 (s, C-O).

CHN $C_{20}H_{26}N_2O_2$ calc. C 74.08 H 8.29 N 8.23
found C 73.56 H 8.13 N 8.02

N-Acetyl-N-methyl-4-aminophenol (56)

4-Methylaminophenol sulphate (metol, 200 g, 0.585 mol) are dissolved at 90 °C in water (800 ml). After the slow addition of sodium carbonate (62 g, 0.585 mol) acetic acid (90 ml) and acetic anhydride (150 ml) is added. After cooling to room temp. the white product is filtered under suction and washed with water.

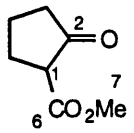
Yield: 185 g (1.12 mol, 96 %); mp > 180 °C (subl.)

^{1}H-nmr (200 MHz, $CDCl_3$): δ = 2.87 (s; 3H, $COCH_3$),
3.25 (s; 3H, NCH_3),
6.90 (d, ^{3}J=8 Hz; 2H, H_{ar}),
7.10 (d, ^{3}J=8 Hz; 2H, H_{ar}).

Ir (KBr): ν = 3100-2800 (m, OH), 1621 (s, C=O), 1458 (s), 1271 (s), 840 (s).

Methyl 2-oxocyclopentanecarboxylate (58)

A mechanically stirred suspension of sodium (23 g, 1 mol) in xylene (250 ml) is heated to 80 °C. Dimethyl adipate (174 g, 1 mol) is added dropwise at 100 - 115 °C. Dry xylene (in total 400 ml) is added from time to time to keep the reaction mixture fluid enough for stirring. After 5 h the mixture is cooled in an ice-bath and poured into 1 l of 10 % acetic acid at 0 °C. The organic layer is separated, washed with water (200 ml) and with cold 10 % sodium bicarbonate solution (2x100 ml) After drying over magnesium sulphate the xylene is removed *in vacuo* and the product is distilled at 110 °C/10 mmHg. Yield: 78 g (0.78 mol, 55 %, lit. 75%[150])

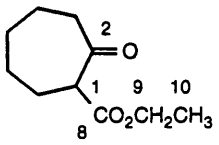


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.75 - 1.81 (m; 1H),
2.00 - 2.07 (m; 1H),
2.15 - 2.25 (m; 4H),
3.03 - 3.09 (m; 1H, H1),
3.63 (s; 3H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.6 (t), 27.0 (t), 37.7 (t), 52.1 (d, C1), 54.3 (q, C7), 169.5 (s, C6), 212.0 (s, C2).

Methyl 2-oxocycloheptanecarboxylate (62)

A mixture of cycloheptanone (11.2 g, 0.1 mol), potassium *tert*-butanolate (11.2 g, 0.1 mol) and diethyl carbonate (20.0 g, 0.17 mol) in benzene (30 ml) is heated under reflux for 7 h. The orange solution is poured into water and the organic layer is separated. The aqueous layer is extracted with benzene (2x20 ml) and the combined organic layers are washed with brine. After drying over magnesium sulphate the solvent is evaporated and the product is distilled at 130 °C/10 mmHg. Yield: 8.3 g (45 mmol, 45 %, lit. 40 %[152])



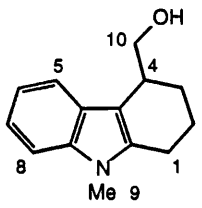
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.22 (t, $^3J_{10,9}$=7.0 Hz; 3H, H10),
1.30 - 1.45 (m; 2H),
1.51 - 1.59 (m; 2H),
1.77 - 1.90 (m; 4H),
2.02 - 2.07 (m; 1H),
2.34 - 2.38 (m; 1H),
3.49 (dd, $^3J_{1,7}$=3.9 Hz, $^3J_{1,7}$=10.4 Hz; 1H, H1),
4.13 (q, $^3J_{9,10}$=7.0 Hz; 2H, H9).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.1 (q, C10), 24.4, 27.6, 28.0, 29.6 (t, C4, C5,C6, C7), 43.1 (t, C3), 59.0 (d, C1), 61.0 (t, C9), 170.5 (s, C8), 209.0 (s, C2).

4-Hydroxymethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (63)

Method A: A solution of ethyl 9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid (6.9 g, 27 mmol) in THF (100 ml) is added dropwise to a stirred suspension of lithium aluminium hydride (2.1 g, 55 mmol) in THF (125 ml). The mixture is refluxed for 2 h. Then excess hydride is decomposed by careful addition of water (2 ml) and 20 % sodium hydroxide solution (2 ml). The precipitate is filtered under suction and the filtrate is washed with dil. hydrochloric acid (20 ml) and brine (20 ml). After drying over magnesium sulphate the solvent is evaporated to yield the alcohol as a colourless oil (3.6 g, 17 mmol, 62 %).

Method B: 9-Methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (2.0 g, 9 mmol) is reduced with lithium aluminium hydride as described in VIII.2.5, procedure A. After work-up 0.50 g (2.3 mmol, 26 %) of the amine **47b** and 1.30 g (6.0 mmol, 67 %) of the alcohol **63** are obtained as oils.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.82 - 1.87 (m; 3H, H2 and H3),
1.90 - 2.01 (m; 1H, H2 or H3),
2.05 (s, br; 1H, OH),
2.60 - 2.63 (m; 1H, H1),
2.70 (dd, ^2J=16.3 Hz, $^3J_{10.4}$=4.5 Hz; 1H, H1),
3.20 - 3.25 (m; 1H, H4),
3.62 (s; 3H, H9),
3.52 (dd, ^2J=14.4 Hz, $^3J_{10.4}$=7.7 Hz; 1H, H10),
3.83 (dd, ^2J=12.3 Hz, $^3J_{10.4}$=3.9 Hz; 1H, H10),
7.06 (dd, ^3J=7.3 Hz, ^3J=7.5 Hz; 1H, H6 or H7),
7.15 (dd, ^3J=7.2 Hz, ^3J=7.9 Hz; 1H, H6 or H7),
7.26 (d, $^3J_{8.7}$=8.1 Hz; 1H, H8),
7.57 (d, $^3J_{5.6}$=7.9 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.7 (t), 22.7 (t), 26.1 (t), 30.0 (q, C9), 31.5 (d, C4), 43.7 (t, C10), 108.6 (d), 109.8 (s, C4a), 118.7 (d), 119.9 (d), 121.7 (d), 127.0 (s), 137.7 (s), 138.0 (s).

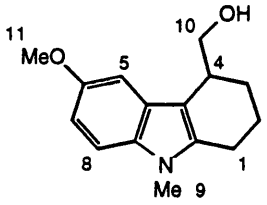
Ir (KBr): ν = 3340 cm^{-1} (s, br, OH), 1472 (m), 1305 (m), 745 (s).

MS (NH_3 EI, 70 eV): m/z = 216 (M^++1, 100), 204 (15), 184 (10).

4-Hydroxymethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (64)

Method A: A solution of ethyl 6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid (9.0 g, 31 mmol) in ether (100 ml) is added dropwise to a stirred suspension of lithium aluminium hydride (2.27 g, 60 mmol) in ether (100 ml). The mixture is refluxed for 2 h. Then excess hydride is decomposed by careful addition of water (2 ml) and 20 % sodium hydroxide solution (2 ml). The precipitate is filtered under suction and the filtrate is washed with dil. hydrochloric acid (20 ml) and brine (20 ml). After drying over magnesium sulphate the solvent is evaporated to yield the alcohol as a yellow oil (5.5 g, 22.3 mmol, 72 %).

Method B: 6-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (2.3 g, 9 mmol) is reduced with lithium aluminium hydride as described in VIII.2.5, procedure A. After work-up 0.3 g (1.3 mmol, 14 %) of the amine **47b** and 1.8 g (7.3 mmol, 81 %) of the alcohol **63** are obtained as oils.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.60 (s, br; 1H, OH),
1.84 - 2.04 (m; 4H, H2, H3),
2.66 - 2.71 (m; 2H, H1),
3.18 - 3.26 (m; 1H, H4),
3.58 (s; 3H, H9),
3.59 (m; 1H, H10),
3.84 (s; 3H, H11),
3.86 (m; 1H, H10),
6.81 (dd, $^4J_{7,5}$=2.5 Hz, $^3J_{7,8}$=8.8 Hz; 1H, H7),
7.01 (d, $^4J_{5,7}$=2.4 Hz; 1H, H5),
7.16 (d, $^3J_{8,7}$=8.7 Hz; 1H, H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.7 (t), 22.2 (t), 25.6 (t), 29.2 (q, C9), 35.2 (d, C4), 56.1 (q, C11), 65.8 (t, C10), 100.8 (d), 107.9 (s, C4a), 109.4 (d), 110.2 (d), 127.0 (s, C4b), 132.2 (s, C8a), 138.0 (s, C9a), 153.8 (s, C6).

MS (NH_3 EI, 70 eV): m/z = 246 (M^++1, 100), 234 (28).

Ir (KBr): ν = 3500 (m, br, OH), 2925 (m), 1481 (s), 1218 (m, C-O), 1147 (s).

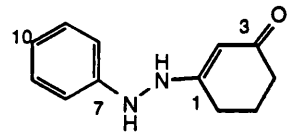
4-Cyano-1,2,3,4-tetrahydro-9-*p*-tolylsulphonyl-carbazole (74)

An ice cold solution of tosylmethyl isocyanide (3.0 g, 15 mmol) in HMPT is added to potassium tert.-butoxide (4.4 g, 35 mmol). Methanol (0.1 ml) is added and the mixture is stirred at 0 °C under nitrogen. After 5 min 2,3-dihydro-9-*p*-tolylsulphonyl-carbazol-4(1H)-one (1.7 g, 5 mmol) and the reaction mixture is stirred at 45 °C for 65 h. Then water is added, the solution is acidified with 2N hydrochloric acid to pH~6 and the product is extractedwith ethyl acetate. After washing with brine and

drying over magnesium sulphate the solvent is evaporated to result a colourless solid (1.4 g), which ir, ^{1}H nmr and mass spectrum is identical to 2,3-dihydrocarbazol-4(1H)one (**79**).

1,3-Cyclohexandione-monophenylhydrazone (78)

A solution of phenylhydrazine (5.4 g, 50 mmol) in 10 % aq. acetic acid (150 ml) is treated with a solution of 1,3-cyclohexandione (5.6 g, 50 mmol) in 10 % aq. acetic acid (50 ml). Stirring for 10 min at 50 °C results in a colourless solid, which is filtered and washed with water to yield 9.3 g (46 mmol, 92 %). An analytical sample is recrystallised from ethanol. Mp. 185-186 °C (lit. 178-179 °C[250]).



^{1}H-nmr (400 MHz, d_6-DMSO): δ = 1.40 (m; 2H, H5),
1.67 (t, ^{3}J=6.5 Hz; 2H, H4 or H6),
1.89 (t, ^{3}J=6.0 Hz; 2H, H4 or H6),
4.68 (s; 1H, H2),
6.17 - 6.21 (m; 3H, H_{ar}),
6.58 - 6.62 (m; 2H, H_{ar}),
6.92 (s, br; 1H, NH),
8.07 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, d_6-DMSO): δ = 21.6 (t), 25.8 (t), 36.5 (t), 95.8 (d, C2), 111.9 (d), 118.8 (d), 128.6 (d), 147.6 (s), 165.6 (s), 196.0 (s, C3).

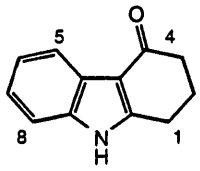
MS (EI, 70 eV): m/z = 202 (M^+, 100), 173 (M^+-CO, 15), 105 (31), 92 (60), 77 (82).

Ir (KBr): ν = 3466 (m, br, OH), 3246 (s, NH), 1575 (s), 1538 (s), 1491 (s).

CHN $C_{12}H_{14}N_2O$ calc. C 71.26 H 6.98 N 13.85
found C 71.43 H 7.05 N 13.73

2,3-Dihydrocarbazol-4(1H)one (79)

1,3-Cyclohexane-mono-phenylhydrazone (9.0 g, 45 mmol) is dissolved in 120 ml of 40 % sulphuric acid. After the purple reaction mixture has been heated for 90 min on a steam bath it is slowly poured into stirred ice water (600 ml). A brown solid precipitates which is filtered washed with water (4.7 g, 26 mmol, 57 %). An analytical sample is recrystallised from ethanol. Mp. 214-215 °C (lit. 223 °C[166])



^{1}H-nmr (400 MHz, d_6-DMSO): δ = 1.59 - 1.62 (m; 2H, H2),
1.91 (t, $^3J_{3,2}$=5.6 Hz; 2H, H3),
2.45 (t, $^3J_{1,2}$=6.1 Hz; 2H, H1),
6.63 - 6.66 (m; 2H, H6, H7),
6.89 (d,^{3}J=6.9 Hz; 1H, H_{ar}),
7.44 (d,^{3}J=7.7 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, d_6-DMSO): δ = 22.8 (t), 23.5 (t), 37.9 (t, C3), 111.6 (d), 111.8 (s), 120.2 (d), 121.6 (d), 122.5 (d), 124.5 (s), 135.9 (s), 152.4 (s), 193.0 (s, C4).

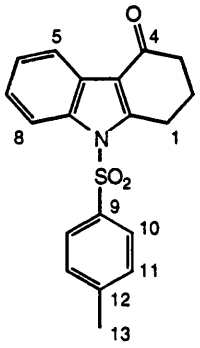
MS (EI, 70 eV): m/z = 185 (M^+, 95), 157 (M^+-CO, 100), 129 (M^+-C_2H_4,-CO, 70).

Ir (KBr): ν = 3200 (m, NH), 2918 (m), 1466 (s), 1381 (s).

CHN $C_{12}H_{11}NO$ calc. C 77.81 H 5.99 N 7.56
found C 77.72 H 5.93 N 7.70

2,3-Dihydro-9-*p*-tolylsulphonyl-carbazol-4(1H)-one (80)

A mechanically stirred mixture of 2,3-tetrahydrocarbazol-4(1H)-one (13.6 g, 73 mmol), anhydrous potassium carbonate (46 g, 0.37 mol), toluene-*p*-sulphonyl chloride (13.9 g, 73 mmol) and ethyl methyl ketone (250 ml) is heated under reflux for 4 h. The hot mixture is filtered and the filter cake is washed with ethyl acetate (150 ml). Evaporation of the solvent yields a brown oil from which, after titruation with ether (40 ml), a colourless solid precipitates (9.3 g, 28 mmol, 38 %). Mp. 149-150 °C from methanol (lit. 152-154 °C[167]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.19 (m; 2H, H2),
2.34 (s; 3H, H13),
2.54 (t, $^3J_{3,2}$=6.7 Hz; 2H, H3),
3.30 (t, $^3J_{1,2}$=6.1 Hz; 2H, H1),
7.24 (d, $^3J_{11,10}$=8.0 Hz; 2H, H11),
7.29 - 7.35 (m; 2H, H6, H7),
7.74 (d, $^3J_{10,11}$=8.5 Hz; 2H, H10),
8.13 (d, ^3J=8.7 Hz; 1H, H5 or H8),
8.21 (d, ^3J=8.2 Hz; 1H, H5 or H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 21.6 (q, C13), 23.1, 24.4, 37.8 (t, C1, C2, C3), 113.8 (d), 117.8 (s), 121.8 (d), 124.9 (d), 125.3 (d), 125.7 (s), 126.5, 130.2 (d, C10, C11), 135.4 (s), 135.8 (s), 145.8 (s), 150.9 (s), 195.1 (s, C4).

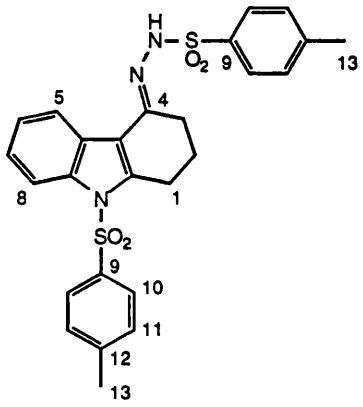
MS (EI, 70 eV): m/z = 340 (M^++1, 95), 185 (M^+-$SO_2C_7H_7$, 30), 154 (47), 91 (64), 55 (100).

Ir (KBr): ν = 2921 (m), 1655 (s, CO), 1184 (s), 1165 (s).

CHN	$C_{19}H_{17}NO_3S$	calc.	C 67.23	H 5.05	N 4.13
		found	C 66.38	H 4.66	N 4.01

p-Tolylsulphonylhydrazone of 2,3-dihydro-9-p-tolylsulphonylcarbazol-4(1H)-one (81)

A solution of 2,3-dihydro-9-*p*-tolylsulphonylcarbazol-4(1H)-one (1.70 g, 5.0 mmol), *p*-tolylsulphonylhydrazine (1.10 g, 6.0 mmol) in tetrahydrofuran (20 ml) is refluxed with *p*-toluenesulphonic acid (0.01 g) for 3 h. After evaporation of the solvent, the crude product is dissolved in ethyl acetate and the solution is washed with 5 % sodium bicarbonate solution and brine. The solvent is evaporated to result 1.50 g (3.0 mmol, 60 %) of a colourless solid.

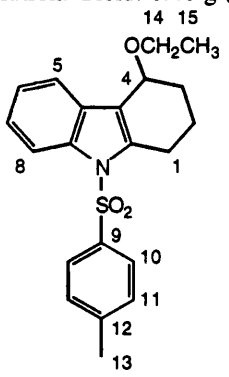


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.17 (s; 3H, H13),
2.20 (s; 3H, H13),
2.35 - 2.40 (m; 2H, H2),
2.91 - 2.96 (m; 2H, H3),
3.53 - 3.57 (m; 2H, H1),
7.00 - 7.12 (m; 6H, H_{ar}),
7.63 - 7.76 (m; 4H, H_{ar}),
7.88 (d, ^{3}J=7.9 Hz; 1H, H5 or H8),
7.93 (d, ^{3}J=8.3 Hz; 1H, H5 or H8),
9.65 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 21.1 (q, C13), 21.5, 23.4, 24.2 (t, C1, C2, C3), 113.3 (d), 115.8 (s), 122.4 (d), 123.6 (d), 124.3 (d), 125.9 (s), 125.8, 127.6, 128.9, 129.6 (d, C10, C11), 135.1 (s), 135.7 (s), 141.6 (s), 143.0 (s), 144.9 (s), 151.7 (s).

4-Ethoxy-9-*p*-tolylsulphonyl-1,2,3,4-tetrahydrocarbazole (82)

A solution of the *p*-tolylsulphonylhydrazone of 2,3-dihydro-9-*p*-tolylsulphonyl-carbazol-4(1H)-one (1.0 g, 2 mmol) in ethanol (20 ml) is refluxed under nitrogen with potassium cyanide (1.6 g) for 24 h. The cold mixture is poured into water to precipitate a grey solid, which is filtered and washed with water and 2N sodium hydroxide solution. Yield: 0.40 g (1.1 mmol, 54 %), mp. 124-127 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.44 (t, $^3J_{15,14}$=7.0 Hz; 3H, H15),
1.97 - 2.04 (m; 2H, H2 and H3),
2.16 - 2.22 (m; 2H, H2 or H3),
2.53 (s; 3H, H13),
3.12 - 3.14 (m; 1H, H1),
3.25 (ddd, ^2J=17.8 Hz, $^3J_{1,2}$=5.1 Hz, $^3J_{1,2}$=5.2 Hz; 1H, H1),
3.80 (t, $^3J_{14,15}$=7.0 Hz; 2H, H14),
4.81 (t, $^3J_{4,3}$=3.1 Hz; 1H, H4),
7.34 - 7.49 (m; 4H, H6, H7, H10 or H11),
7.52 (d, ^3J=7.3 Hz; 1H, H5 or H8),
7.87 (d, ^3J=8.4 Hz; 2H, H10 or H11),
8.32 (d, ^3J=7.7 Hz; 1H, H5 or H8).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 15.8 (q, C13 or C15), 19.1 (t), 21.5 (q, C13 or C15), 24.7 (t), 27.4 (t), 64.0 (t, C14), 70.4 (d, C4), 114.1 (d), 118.3 (s), 119.0 (d), 123.3 (d), 124.0 (d), 124.7 (s), 126.5 (d, C10 or C11), 129.9 (d, C10 or C11), 136.2 (s), 137.6 (s), 144.7 (s), 151.6 (s).

MS (EI, 70 eV): m/z = 369 (M^+, 10), 324 (M^+-OEt, 85), 168 (M^+-OEt-$SO_2C_7H_7$, 100).

Ir (KBr): ν = 2931 (m), 1368 (s, SO), 1171 (s,SO), 1087 (s).

CHN $C_{21}H_{23}NO_3S$ calc. C 68.26 H 6.28 N 3.79
found C 66.92 H 5.61 N 3.51

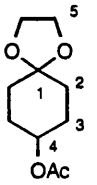
Ethyl 1,2,3,4-tetrahydro-9-*p*-tolylsulphonyl-carbazole-4-spiro-2'oxiran-3'carboxylate (83)

A stirred solution of 2,3-dihydro-9-*p*-tolylsulphonyl-carbazol-4(1H)-one (1.0 g, 3 mmol) and ethyl chloroacetate (0.6 g, 3 mmol) in benzene (10 ml) under nitrogen is cooled in an ice-bath and a solution of potassium tert-butoxide (1.4 g, 14 mmol) in 5 ml of tert-butanol is added over 10 min. The reaction mixture is stirred for a further 30 min and finally refluxed for 60 min before being evaporated to dryness *in vacuo*. A solution of the residue is washed with 2N hydrochloric acid, sodium bicarbonate solution and brine. Evaporation of the dried solution gives 0.50 g of a product, which ir, ^{1}H nmr and mass spectra are identical to 2,3-dihydrocarbazol-4(1H)-one (**79**).

4,4-Ethylenedioxycyclohexanone (89)

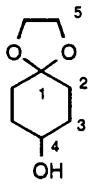
- Procedure A[173]

4-Acetoxy-cyclohexanone (53.0 g, 0.34 mol), ethanediol (60 ml) and *p*-toluenesulphonic acid (1 g) are refluxed in dry benzene (400 ml) under a Dean-Stark trap. After 8 h the solvent is removed by evaporation *in vacuo* and the residue is taken up in chloroform (200 ml), washed with water (2x50 ml) and dried over magnesium sulphate. The chloroform is removed under reduced pressure, yielding 4,4-ethylenedioxycyclohexyl acetate (52.5 g, 0.26 mol, 77 %) as a pale yellow oil.



^{1}H-nmr (200 MHz, $CDCl_3$): δ = 1.45 - 1.65 (m; 4H, H2),
1.70 - 1.85 (m; 4H, H3),
1.85 (s; 3H, $COCH_3$),
3.90 (s; 4H, H5),
4.89-4.91 (m; 1H, H4).

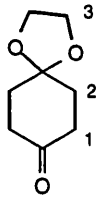
A solution of the crude 4,4-ethylenedioxycyclohexyl acetate (52.5 g, 0.26 mol) in methanol (300 ml) and 20 % sodium hydroxide solution (30 ml) is refluxed for 5 h. Water is added and the methanol is removed by distillation. The product is then extracted with dichloromethane (3x100 ml) and the extracts are dried over magnesium sulphate to yield, after distillation of the solvent, 32 g (0.20 mol, 78 %) of 4,4-ethylenedioxycyclohexanol as a yellow oil.



^{1}H nmr (400 MHz, $CDCl_3$): δ = 1.47 - 1.62 (m; 4H, H2),
1.71 - 1.83 (m; 4H, H3),
2.16 (s, br; 1H, OH),
3.68 - 3.73 (m; 1H, H4),
3.90 (s; 4H, H5).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 31.5 (t), 31.8 (t), 64.1 (t, C5), 67.9 (d, C4), 108.2 (s, C1).

Chromium trioxide (24.0 g) is added with stirring to dichloromethane (600 ml) containing pyridine (38.0 g). The suspension is cooled to 0 °C and the crude 4,4-ethylenedioxycyclohexanol (6.75 g, 43 mmol) is added in one portion. The mixture is stirred a further 20 min at 0 °C. Then the liquid is decanted from the tarry residue, which is washed with ether (4x50 ml). The combined organic layer is washed with brine (4x50 ml) and is dried over magnesium sulphate. After removing the solvent by evaporation in vacuo a colourless solid (4.4 g, 28 mmol, 66 %) with mp. 69 - 70 °C (lit. 71 - 73 °C[173]) is obtained.



^{1}H nmr (400 MHz, $CDCl_3$): δ = 1.93 (t, J=7.1 Hz; 4H, CH_2),
2.42 (t, J=7.2 Hz; 4H, CH_2),
3.95 (s; 4H, H3).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 33.7 (t), 38.0 (t), 64.5 (t, C3), 106.9 (s), 210.2 (s, CO).

Ir (KBr): ν = 2968 cm^{-1} (m), 1720 (s; CO), 1243 (s), 725 (s).

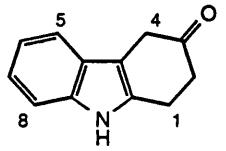
- Procedure B[196]

Cyclohexan-1,4-dione (29.3 g, 0.26 mol), ethanediol (20 g, 0.32 mol) and *p*-toluenesulphonic acid (0.1 g) are refluxed in dry benzene (500 ml) under a Dean-Stark trap. After 8 h the cold reaction mixture is washed with water (3x50 ml) to remove unreacted diketone. Then the benzene solution is stirred vigorously with 20 % sodium bisulfite solution (3x200 ml). The combined aqueous layer is

saturated with potassium carbonate and the product is extracted with dichloromethane (3x50 ml) to give 4.7 g (31 mmol, 12 %) of 4,4-ethylenedioxycyclohexanone as a colourless solid.

1,2-Dihydrocarbazol-3(4H)-one (90)

A solution of 3,3-ethylenedioxy-1,2,3,4-tetrahydrocarbazole (**169**, 2.0 g, 8.7 mmol) in acetone (100 ml) and water (5 ml) is refluxed with *p*-toluenesulphonic acid (0.2 g) for 4 h. Water (50 ml) is added, acetone is removed by distillation and the product is extracted with ethyl acetate (2x50 ml). After washing with brine (50 ml) the combined organic layer is dried over magnesium sulphate and the solvent is removed by distillation to yield a pale brown solid (0.5 g, 2.7 mmol, 31 %) with mp. 142 - 145 °C (lit. 148 - 150 °C[194]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.78 (t, ^{3}J=6.8 Hz; 2H, H1 or H2),
3.13 (t, ^{3}J=7.0 Hz; 2H, H1 or H2),
3.60 (s; 2H, H4),
7.11 (ddd,^{4}J=1.2Hz,^{3}J=7.0Hz,^{3}J=7.9Hz;1H,H6 or H7),
7.13 (ddd,^{4}J=1.2Hz,^{3}J=7.2Hz,^{3}J=8.0Hz;1H,H6 or H7),
7.30 (d, $^3J_{7,6}$=7.6 Hz; 1H, H7),
7.39 (d, $^3J_{4,5}$=7.6 Hz; 1H, H4).
7.90 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 22.7, 36.6, 38.7 (t, C1, C2, C4), 107.4 (s, C4a), 110.8 (d), 117.8 (d), 119.8 (d), 122.1 (d), 127.1 (s), 131.7 (s), 136.6 (s), 209.8 (s, C3).

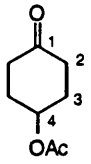
Ms (EI, 70 eV): m/z (%) = 185 (90, M^+), 156 (100, M^+-CO).

Ir (KBr): ν = 3296 (s, NH), 2857 (m), 1696 (s, C=O), 746 (s).

4-Acetoxy-cylcohexanone (99)

To a cooled solution of the monoacetate **110** (11.0 g, 70 mmol) in glacial acetic acid (30 ml) a solution of chromium(IV)oxide (6.8 g, 68 mmol) in acetic acid (15 ml glacial acetic acid, 4 ml water) is added dropwise, mantaining the temperature below 35 °C. After stirring for further 18 h, 30 ml of water are added and the ketone is extracted with 4x200 ml of ether. The ethereal extracts are washed with water (5x50 ml) and dil. potassium carbonate (150 ml). The solvent is evaporated and the product

is purified by Kugelrohr distillation (bp. 70 °C/1 Torr) to give 8.1 g (52 mmol, 74 %) 4-acetoxy-cyclohexanone.



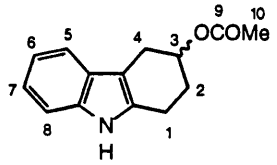
^{1}H-nmr (400 MHz, $CDCl_3$): δ =1.76-1.84 (m; 4H, H3),
1.84 (s; 3H, $COCH_3$),
2.08-2.13 (m; 2H, H2),
2.24-2.30 (m; 2H, H2),
4.89-4.91 (m; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.65 (q, $CO\underline{C}H_3$), 29.81 (t, C3), 36.66 (t, C2), 68.05 (d, C4), 169.60 (s, $\underline{C}OCH_3$), 208.90 (s, C1).

Ir (CH_2Cl_2): ν = 2952 cm^{-1} (m), 1722 (s; CO), 1421 (s; CO), 1288-1234 (s), 914-889 (s), 780-674 (s).

3-Acetoxy-1,2,3,4-tetrahydrocarbazole (100a)

Treating 4-acetoxycyclohexanone (3.12 g, 20 mmol) and *p*-phenylhydrazine (2.20 g, 20 mmol) according to the procedure VIII.2.7 gives 3-acetoxy-1,2,3,4-tetrahydro-carbazole (3.9 g, 17 mmol, 85 %) with mp. 96-97 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ =2.07 (s; 3H, H10),
2.05 - 2.12 (m; 2H, H2),
2.74 (m; 2H, H1),
2.84 (dd, ^2J=15.6 Hz, $^3J_{4,3}$=6.6 Hz; 1H, H4),
3.11 (dd, ^2J=15.6 Hz, $^3J_{4,3}$=4.8 Hz; 1H, H4),
5.32 (m; 1H, H3),
7.10-7.21 (m; 3H, H_{ar}),
7.46 (d, ^3J=7.3 Hz; 1H, H_{ar}),
8.1 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.8 (q, C10), 20.9 (t, C2), 26.6, 27.3 (t, C1, C4), 69.9 (d, C3), 105.9 (s), 110.3 (d), 117.2 (d), 118.7 (d), 120.7 (d), 127.0 (s), 132.3 (s), 135.9 (s), 168.3 (s, C9).

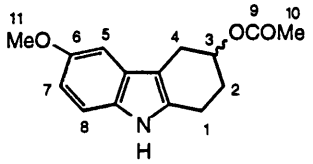
Ms (EI, 70 eV): m/z (%) = 229 (20, M^+), 168 (100, M^+-OAc), 143 (23), 80 (77), 43 (97).

Ir (KBr): ν = 3453 (m), 1722 (s, CO), 1461 (s), 1364 (s), 1231 (s), 1204 (s), 1044 (s), 910 (s), 627 (s).

CHN $C_{14}H_{15}NO_2$ calc. C 73.34 H 6.60 N 6.11
found C 73.17 H 6.45 N 5.89

3-Acetoxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (100b)

Treating 4-acetoxycyclohexanone (3.12 g, 20 mmol) and *p*-methoxyphenyl-hydrazine (2.74 g, 20 mmol) according to procedure VIII.2.7 gives 3-acetoxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (4.0 g, 15 mmol, 77 %) with mp. 104 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ =2.05 (s; 3H, H10),
2.05 - 2.12 (m; 2H, H2),
2.77 - 2.83 (m; 3H, 2H, H4),
3.06 (dd, ^2J=15.4 Hz, $^3J_{4,3}$=5.1 Hz; 1H, H4),
3.83 (s; 3H, H11),
5.29 (m; 1H, H3),
6.78 (dd, $^3J_{7,8}$=8.8 Hz, $^4J_{7,5}$=2.5 Hz; 1H, H7),
6.87 (d,$^4J_{5,7}$=2.4 Hz; 1H, H5),
7.15 (d,$^4J_{8,7}$=8.7 Hz; 1H, H8),
7.68 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.5 (q, C10), 21.5 (t, C2), 27.1, 27.7 (t, C1, C4), 55.9 (q, C11), 70.1 (d, C3), 100.1 (d), 106.8 (s, C4a), 111.0 (d), 111.2 (d), 127.9 (s, C4b), 131.2 (s), 133.4 (s), 153.9 (s, C6), 170.9 (s, C9).

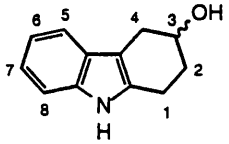
Ms (EI, 70 eV): m/z (%) = 259 (8, M^+), 200 (100, M^+-OAc), 169 (15, M^+-OAc, -OMe), 80 (40).

Ir (KBr): ν = 3385 (s, NH), 1732 (s; CO), 1241 (s), 1214 (s), 1031 (s).

CHN	$C_{15}H_{17}NO_3$	calc.	C 69.48 H 6.61 N 5.40
		found	C 69.23 H 6.48 N 5.16

3-Hydroxy-1,2,3,4-tetrahydrocarbazole (101a)

3-Acetoxy-1,2,3,4-tetrahydrocarbazole (3.7 g, 16 mmol) is saponified according to procedure VIII.2.8 to yield 1.6 g (8.5 mmol, 53 %) of a yellow solid (mp. 144 °C).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.75 (s, br; 1H, OH),
1.97 - 2.13 (m; 2H, H2),
2.84 (dd, ^2J=15.2 Hz, $^3J_{4,3}$=6.8 Hz; 1H, H4),
2.75 - 2.91 (m; 2H, H1),
3.08 (dd, ^2J=15.2 Hz, $^3J_{4,3}$=7.0 Hz; 1H, H4),
4.23 - 4.29 (m; 1H, H3),
7.04 - 7.14 (m; 2H, H6, H7),
7.26 (d, ^3J=7.6 Hz; 1H, H5 or H8),
7.44 (d, ^3J=7.6 Hz; 1H, H5 or H8),
7.76 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.5 (t, C2), 30.5, 31.0 (t, C1, C4), 67.6 (d, C3), 107.2 (s, C4a), 110.5 (d), 117.7 (d), 119.3 (d), 121.3 (d), 127.7 (s), 132.7 (s), 136.2 (s).

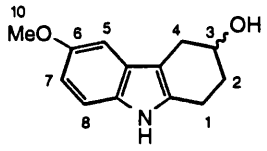
Ms (EI, 70 eV): m/z (%) = 187 (12, M^+), 169 (100, M^+-H_2O), 143 (29), 80 (74), 43 (100).

Ir (KBr): ν = 3300 (s, br, OH), 1474 (s), 1324 (s), 915 (s), 630 (s).

CHN	$C_{12}H_{13}NO$	calc.	C 76.98 H 7.00 N 7.48
		found	C 76.61 H 7.00 N 7.51

3-Hydroxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (101b)

3-Acetoxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (4.1 g, 16 mmol) is saponified according to procedure VIII.2.8 to yield 2.0 g (9.3 mmol, 58 %) of the alcohol with mp. 102 - 104 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.88 - 2.32 (m; 2H, H2),
2.62 - 2.79 (m; 2H, H1),
2.63 (dd, $^2J_{4.4}$=15.2 Hz, $^3J_{4.3}$=6.7 Hz; 1H, H4),
3.00 (dd, $^2J_{4.4}$=14.9 Hz, $^3J_{4.3}$=4.5 Hz; 1H, H4),
3.85 (s; 3H, H10),
4.22 (m; 1H, H3),
6.78 (dd, $^3J_{7.8}$=8.6 Hz, $^4J_{7.5}$=2.3 Hz; 1H, H7),
7.08 (d,$^4J_{5.7}$=2.5 Hz; 1H, H5),
7.11 (d,$^4J_{8.7}$=8.7 Hz; 1H, H8),
7.90 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.4 (t, C2), 30.3, 30.9 (t, C1, C4), 55.9 (q, C10), 67.5 (d, C3), 100.1 (d), 106.7 (s, C4a), 110.6 (d), 111.2 (d), 127.9 (s, C4b), 131.3 (s), 133.8 (s), 153.6 (s, C6).

Ms (EI, 70 eV): m/z (%) = 217 (5, M^+), 199 (100, M^+-H_2O), 168 (29, M^+-H_2O, -OMe), 78 (63), 40 (36).

Ir (KBr): ν = 3519-3025 (m, br; OH), 3345 (s; NH), 1481 (s), 1451 (s, ROR'), 1428 (s), 1211 (s), 1041 (s).

CHN $C_{13}H_{15}NO_2$ calc. C 71.87 H 6.96 N 6.44
found C 70.84 H 6.98 N 5.76

The attempted tosylation of 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrocarbazole resulted a product, which nmr data are similar to the starting material (significant differences are underlined). The mass and ir spectrum were identical to the alcohol **101b**.

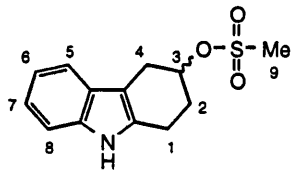
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.22 - 2.34 (m; 2H, H2),
2.73-2.93 (m; 2H, H1),
3.05 (dd, ^2J=15.6 Hz, $^3J_{4.3}$=6.8 Hz; 1H, H4),
3.31 (dd, ^2J=15.7 Hz, $^3J_{4.3}$=4.8 Hz; 1H, H4),
3.90 (s; 3H, H10),
4.52 (m; 1H, H3),
6.85 (dd, $^3J_{7.8}$=8.7 Hz, $^4J_{7.5}$=2.5 Hz; 1H, H7),
6.95 (d,$^4J_{5.7}$=2.5 Hz; 1H, H5),
7.14 (d,$^4J_{8.7}$=8.7 Hz; 1H, H8),

8.05 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 21.1 (t, C2), 21.9, 32.2 (t, C1, C4), 55.9 (q, C10), 56.68 (d, C3), 100.0 (d), 106.8 (s, C4a), 110.9 (d), 111.3 (d), 127.5 (s, C4b), 131.1 (s), 133.0 (s), 153.7 (s, C6).

3-Methylsulphonyloxy-1,2,3,4-tetrahydrocarbazole (102a)

3-Hydroxy-1,2,3,4-tetrahydrocarbazole (1.5 g, 8 mmol) in pyridine (20 ml) is reacted with methanesulphonyl chloride (1.1 g, 9.6 mmol) according to VIII.2.9 to yield 1.8 g (85 %) of a pale yellow oil..



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.18 - 2.30 (m; 2H, H2),
2.81 - 3.10 (m; 3H, 2H1+H4),
3.00 (s; 3H, H9),
3.18 - 3.23 (m; 1H, H4),
5.23 (m; 1H, H3),
7.09 - 7.15 (dd; 2H, H6, H7),
7.26 (d, J=8.7 Hz; 1H, H5 or H8),
7.41 (d, ^{3}J=7.5 Hz; 1H, H5 or H8),
7.99 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.9 (t, C2), 28.0, 30.9 (t, C1, C4), 38.6 (q, C9), 78.0 (d, C3), 105.4 (s, C4a), 110.6 (d), 117.5 (d), 119.3 (d), 121.4 (d), 127.0 (s), 132.1 (s), 136.1 (s).

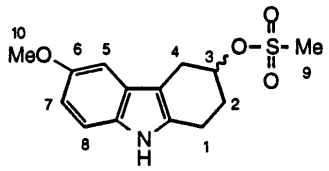
Ms (EI, 70 eV): m/z (%) = 265 (13, M^+), 186 (100, M^+-SO_2CH_3), 168 (25).

Ir (film): ν = 3393 (m; NH), 1334 (s, $ROSO_2$), 1171 (s, $ROSO_2$), 934 (s), 904 (s), 744 (s).

3-Methanesulphonyloxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (102b)

3-Hydroxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (2.0 g, 8 mmol) in pyridine (20 ml) is reacted with methanesulphonyl chloride (1.1 g, 9.6 mmol) according to procedure VIII.2.9. After spinning plate chromatography 1.3 g (49 %) of an oil (R_f=0.7) are obtained. The oil solidifies in the cold

(mp=90-5°C) and is identified as the mesylate. Another fraction (R_f=0.4) containes the isomerised starting material **101b**. The nmr spectrum of which has already been described.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.19 - 2.30 (m; 2H, H2),
2.79 - 2.95 (m; 2H, H1),
2.97 - 3.0 (m; 1H, H4),
3.01 (s; 3H, H9),
3.15 (dd, ^2J=15.1 Hz, $^3J_{4,3}$=4.8 Hz; 1H, H4),
3.82 (s; 3H, H10),
5.26 (m; 1H, H3),
6.76 (dd, $^3J_{7,8}$=8.7 Hz, $^4J_{7,5}$=2.4 Hz; 1H, H7),
6.86 (d,$^4J_{5,7}$=2.3 Hz; 1H, H5),
7.13 (d,$^4J_{8,7}$=8.7 Hz; 1H, H8),
7.88 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.0 (t, C2), 28.2, 28.8 (t, C1, C4), 38.6 (q, C9), 55.8 (q, C10), 78.1 (d, C3), 99.8 (d), 105.4 (s, C4a), 111.1 (d), 111.3 (d), 127.5 (s), 131.2 (s), 133.0 (s), 153.9 (s, C6).

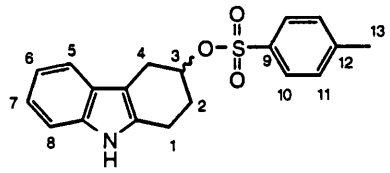
Ms (EI, 70 eV): m/z (%) = 295 (10, M^+), 216 (100, M^+-SO_2CH_3), 189 (42, M^+-SO_2CH_3,-OMe).

Ir (film): ν = 3392 (m; NH), 1475 (s), 1341 (s, $ROSO_2$), 1171 (s, $ROSO_2$).

CHN $C_{14}H_{17}NO_4S$ calc. C 56.93 H 5.80 N 4.74
found C 55.87 H 5.53 N 4.66

3-Toluenesulphonyloxy-1,2,3,4-tetrahydrocarbazole (103a)

3-Hydroxy-1,2,3,4-tetrahydrocarbazole (1.5 g, 8 mmol) in pyridine (20 ml) is reacted with *para*-toluenesulphonyl chloride (1.8 g, 9.6 mmol) according to procedure VIII.2.9 to give 1.8 g (5.3 mmol, 66 %) of a white solid (mp. 148 °C).



^{1}H-nmr (200 MHz, $CDCl_3$): δ = 2.0 - 2.3 (m; 2H, H2),
2.45 (s; 3H, H13),
2.60 - 2.85 (m; 3H, 2H1+H4),
3.90 (dd, $^2J_{4.4}$=14.0 Hz, $^3J_{4.3}$=6.0 Hz; 1H, H4),
5.00 (m; 1H, H3),
7.05 - 7.25 (dd; 2H, H6, H7),
7.20 - 7.30 (m; 2H, H5, H8),
7.30 (d,^{3}J=8 Hz; 2H, H10, H11),
7.80 (d,^{3}J=8 Hz; 2H, H10, H11),
9.80 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.2 (t, C2), 21.7 (q, C13), 27.7, 28.6 (t, C1, C4), 78.6 (d, C3), 106.0 (s, C4a), 110.5 (d), 117.6 (d), 119.4 (d), 121.6 (d), 127.1 (s), 127.6, 129.8 (d, C10, C11), 132.1 (s), 134.3 (s, C12), 136.2 (s), 144.6 (s, C9).

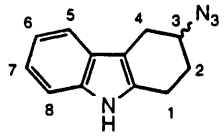
Ms (EI, 70 eV): m/z (%) = 341 (9, M^+), 186 (100, M^+-$SO_2C_7H_7$), 168 (21).

Ir (KBr): ν = 3412 (m; NH), 1591 (s), 1481 (s), 1465 (m), 1341 (s, $ROSO_2$), 1171 (s, $ROSO_2$), 931 (s, $ROSO_2$).

CHN $C_{19}H_{19}NO_3S$ calc. C 66.84 H 5.61 N 4.10
found C 66.36 H 5.95 N 3.78

3-Azido-1,2,3,4-tetrahydrocarbazole (104a)

3-Toluenesulphonyloxy-1,2,3,4-tetrahydrocarbazole (1.2 g, 3.5 mmol) and sodium azide (0.4 g, 6.2 mmol) are treated according to procedure VIII.2.10 to give 0.6 g (5.0 mmol, 82 %) of the azide as a brown oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.99 - 2.07 (m; 1H, H2),
2.14 - 2.20 (m; 1H, H2),
2.75 - 2.96 (m; 3H, 2H1+H4),
3.11 (dd, $^2J_{4.4}$=15.2 Hz, $^3J_{4.3}$=5.1 Hz; 1H, H4),
3.90 - 3.97 (m; 1H, H3),
7.11 (dd, ^{3}J=6.4 Hz, ^{3}J=7.8 Hz; 1H, H5 or H8),
7.15 (dd, ^{3}J=6.6 Hz, ^{3}J=7.0 Hz; 1H, H5 or H8),
7.24 (d, ^{3}J=7.4 Hz; 1H, H6 or H7),
7.45 (d, ^{3}J=7.6 Hz; 1H, H6 or H7),
7.75 (s, br; 1H, NH).

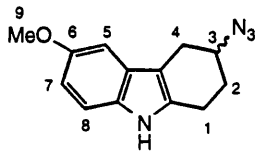
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.9 (t, C2), 26.8, 28.0 (t, C1, C4), 57.1 (d, C3), 106.2 (s, C4a), 110.4 (d), 117.4 (d), 119.0 (d), 121.0 (d), 127.0 (s), 132.4 (s), 135.9 (s).

Ir (film): ν = 3400 (m; NH), 2020 (m, N_3), 1463 (m), 785 (m).

CHN $C_{12}H_{12}N_4$ calc. C 67.91 H 5.70 N 26.39
found C 69.23 H 6.04 N 25.58

3-Azido-6-methoxy-1,2,3,4-tetrahydrocarbazole (104b)

3-Methanesulphonyloxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (1.0 g, 3.5 mmol) and 0.4 g (6.2 mmol) of sodium azide are treated according to procedure VIII.2.10 to give 0.7 g (2.9 mmol, 83 %) of an anorphous solid with mp. > 90 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.71 - 1.77 (m; 1H, H2),
1.98 - 2.05 (m; 1H, H2),
2.41 (dd, $^2J_{4.4}$=14.9 Hz, $^3J_{4.3}$=8.2 Hz; 1H, H4),
2.66 - 2.74 (m; 2H, H1),
3.11 (dd, $^2J_{4.4}$=14.9 Hz, $^3J_{4.3}$=5.1 Hz; 1H, H4),
3.23 - 3.26 (m; 1H, H3),

3.84 (s; 3H, H9),
6.76 (dd, $^3J_{7,8}$=8.7 Hz, $^4J_{7,5}$=2.4 Hz; 1H, H7),
6.89 (d, $^4J_{5,7}$=2.5 Hz; 1H, H5),
7.10 (d, $^4J_{8,7}$=8.7 Hz; 1H, H8),
7.93 (s, br; 1H, NH).

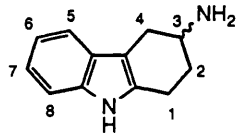
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 21.5 (t, C2), 31.0, 32.4 (t, C1, C4), 55.8 (q, C9), 65.8 (d, C3), 100.1 (d), 105.8 (s, C4a), 110.6 (d), 111.1 (d), 127.9 (s), 131.2 (s), 133.9 (s), 153.7 (s, C6).

Ir (KBr): ν = 3400 (m; NH), 2091 (m, N_3), 1481 (s, OMe), 1211 (s), 1027 (m).

3-Amino-1,2,3,4-tetrahydrocarbazole (105a)

3-Azido-1,2,3,4-tetrahydrocarbazole (0.53 g, 2.5 mmol) is catalytically hydrogenated according to procedure A VIII.2.11 to give 0.31 g (1.7 mmol, 67 %) of a yellow oil, which solidifies in the cold (mp=173 - 175 °C).

A higher yield of 0.39 g (2.1 mmol, 84 %) is obtained when the reaction is carried out with lithium aluminium hydride (procedure B VIII.2.11) as reducing agent.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.53 (s, br; 2H, NH_2),
1.76 - 1.81 (m; 1H, H2),
2.02 - 2.07 (m; 1H, H2),
2.42 - 2.48 (m; 1H, H4),
2.80 - 2.83 (m; 2H, H1),
2.99 - 3.04 (m, ^2J=15.1 Hz; 1H, H4),
3.25 - 3.28 (m; 1H, H3),
7.04 - 7.23 (m; 2H, H5 and H8),
7.26 (d, J=8.0 Hz; 1H, H6 or H7),
7.43 (d, J=7.6 Hz; 1H, H6 or H7),
7.74 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 21.6 (t, C2), 31.2, 32.7 (t, C1, C4), 47.8 (d, C3), 106.3 (s, C4a), 110.4 (d), 117.7 (d), 119.2 (d), 121.2 (d), 127.1 (s), 132.4 (s), 135.9 (s).

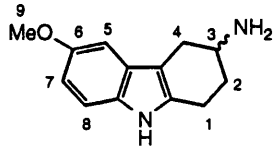
Ms (EI, 70 eV): m/z (%) = 186 (12, M^+), 169 (100, M^+-NH_3), 142 (42), 65 (54).

Ir (KBr): ν = 3399 (m; NH), 3600-3100 (m, br; NH_2), 2905 (m), 1461 (m), 1324 (m), 1141 (m), 744 (s).

CHN $C_{12}H_{14}N_2$ calc. C 77.37 H 7.58 N 15.04
found C 76.74 H 7.63 N 14.85

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (105b)

3-Azido-6-methoxy-1,2,3,4-tetrahydrocarbazole (0.60 g, 2.5 mmol) is reduced with lithium aluminium hydride (1.2 g) according to procedure B VIII.2.11 to yield 0.29 g (1.4 mmol, 54 %) of a yellow oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.69 (s, br; 2H, NH_2),
1.86 - 2.10 (m; 2H, H2),
2.35 - 2.45 (m; 1H, H4),
2.62 - 2.66 (m; 2H, H1),
2.73 - 2.74 (m; 2H, H1),
2.89 - 2.92 (m, ^{2}J=14.3 Hz; 1H, H4),
3.17 - 3.18 (m; 1H, H3),
3.77 (s; 3H, H9),
6.70 (m; 1H, H7),
6.84 (m; 1H, H5),
7.05 (m; 1H, H8),
7.93 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 21.1 (t, C2), 30.3, 30.6 (t, C1, C4), 47.5 (d, C3), 55.5 (q, C9), 99.8 (d), 107.0 (s, C4a), 110.1 (d), 111.0 (d), 127.5 (s), 131.1 (s), 133.8 (s), 153.3 (s, C6).

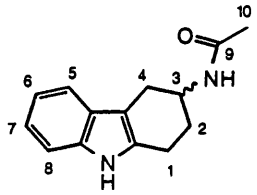
Ir (film): ν = 3400 (m; NH), 3600-3100 (m, br; NH_2), 2905 (m), 1480 (s), 1450 (s, OMe), 1325 (s), 1210 (s), 1140 (m), 824 (m), 744 (s).

Ms (EI, 70 eV): m/z (%) = 216 (35, M^+), 199 (15, M^+-NH_3), 173 (100), 158 (50).

CHN	$C_{13}H_{16}N_2O$	calc.	C 72.19	H 7.46	N 12.96
		found	C 71.93	H 7.08	N 12.61

N-Acetyl-3-amino-1,2,3,4-tetrahydrocarbazole (106a)

3-Amino-1,2,3,4-tetrahydrocarbazole (0.20 g, 1 mmol) is treated with acetic anhydride (0.10 g, 1 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2, 1 % MeOH). Yield: 0.16 g (0.7 mmol, 70 %), mp 120 - 125 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.98 - 2.12 (m; 2H, H2),
2.12 (s, 3H, H10),
2.56 (dd, ^2J=15.1 Hz, $^3J_{4,3}$=6.2 Hz; 1H, H4),
2.72 - 2.78 (m; 2H, H1),
3.01 (dd, ^2J=15.4 Hz, $^3J_{4,3}$=5.1 Hz; 1H, H4),
4.36 (m; 1H, H3),
5.90 (d, br, ^3J=5.5 Hz; 1H, NH),
7.01 - 7.10 (m; 2H, H5 and H8),
7.24 (d, ^3J=7.6 Hz; 1H, H6 or H7),
7.37 (d, ^3J=7.7 Hz; 1H, H6 or H7),
8.31 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.3 (t, C2), 23.3 (q, C10), 27.5, 27.9 (t, C1, C4), 45.0 (d, C3), 106.9 (s, C4a), 110.5 (d), 117.4 (d), 119.1 (d), 121.1 (d), 127.4 (s), 132.9 (s), 136.1 (s), 169.9 (s, C9).

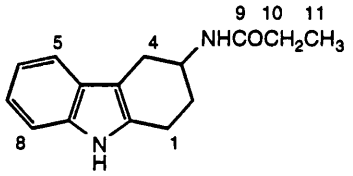
Ms (EI, 70 eV): m/z (%) = 228 (5, M^+), 169 (100, M^+-$NHCOCH_3$), 143 (40), 58 (45), 43 (60, $COCH_3$).

Ir (KBr): ν = 3406 (m, br; NH), 3300 (m, br; NH), 1625 (s, CO), 1555 (m), 737 (s).

CHN	$C_{14}H_{16}N_2O$	calc.	C 73.65	H 7.06	N 12.27
		found	C 73.27	H 6.97	N 12.03

N-Propanoyl-3-amino-1,2,3,4-tetrahydrocarbazole (106b)

3-Amino-1,2,3,4-tetrahydrocarbazole (0.20 g, 1 mmol) is treated with propanoic anhydride (0.15 g, 1 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2, 1 % MeOH) and crystallised after trituration with benzene. Yield: 0.19 g (0.78 mmol, 78 %), mp. 190 - 193 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.13 (t, $^3J_{11,10}$=7.6 Hz ; 3H, H11),
1.88 - 1.93 (m; 1H, H2),
1.93 - 2.03 (m; 1H, H2),
2.15 (q, $^3J_{10,11}$=7.6 Hz ; 2H, H10),
2.51 - 2.57 (m; 1H, H4),
2.70 - 2.76 (m; 2H, H1),
3.02 (dd, ^2J=15.2 Hz, $^3J_{4,3}$=5.0 Hz; 1H, H4),
4.37 (m; 1H, H3),
5.93 (s, br; 1H, NHCO),
7.04 (dd, ^3J=6.5 Hz, ^3J=7.0 Hz; 1H, H6 or H7),
7.07 (dd, ^3J=6.7 Hz, ^3J=7.1 Hz; 1H, H6 or H7),
7.25 (d, ^3J=7.9 Hz; 1H, H5 or H8),
7.38 (d, ^3J=7.6 Hz; 1H, H5 or H8),
8.68 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.9 (q, C11), 20.4 (t, C2), 27.5, 28.0 (t, C1 and C4), 29.6 (t, C10), 45.0 (d, C3), 106.7 (s, C4a), 110.6 (d), 117.4 (d), 118.8 (d), 121.0 (d), 127.3 (s), 133.0 (s), 136.1 (s), 173.5 (s, C9).

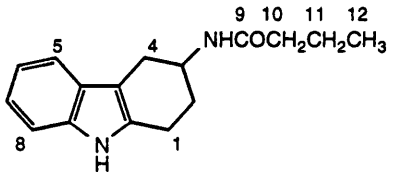
Ms (EI, 70 eV): m/z (%) = 242 (12, M^+), 169 (100, M^+-$NHCOC_2H_5$), 143 (32), 58 (40).

Ir (KBr): ν = 3379 (s; NH), 3279 (s; NH), 1635 (s, CO), 1548 (s), 740 (s).

CHN $C_{15}H_{18}N_2O$ calc. C 74.35 H 7.49 N 11.56
found C 74.49 H 7.52 N 11.20

N-Butanoyl-3-amino-1,2,3,4-tetrahydrocarbazole (106c)

3-Amino-1,2,3,4-tetrahydrocarbazole (0.20 g, 1 mmol) is treated with butyric acid anhydride (0.15 g, 1 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2) and crystallised after trituration with benzene. Yield: 0.21 g (0.82 mmol, 82 %), mp. 227 - 228 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.96 (t, $^3J_{12.11}$=7.3 Hz ; 3H, H12),
1.63 - 1.67 (m; 2H, H11),
1.90 - 2.00 (m; 2H, H2),
2.11 (t, $^3J_{10.11}$=6.7 Hz ; 2H, H10),
2.54 (dd,^{2}J=15.2 Hz,$^3J_{4.3}$=6.2 Hz; 1H, H4),
2.70 - 2.75 (m; 2H, H1),
2.96 (dd,^{2}J=14.9 Hz,$^3J_{4.3}$=5.0 Hz; 1H, H4),
4.37 (m; 1H, H3),
5.96 (s, br; 1H, NHCO),
7.00 (dd, ^{3}J=6.8 Hz, ^{3}J=7.5 Hz; 1H, H6 or H7),
7.07 (dd, ^{3}J=6.8 Hz, ^{3}J=7.8 Hz; 1H, H6 or H7),
7.23 (d, ^{3}J=7.2 Hz; 1H, H5 or H8),
7.35 (d, ^{3}J=7.6 Hz; 1H, H5 or H8),
8.45 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6 (q, C12), 19.2 (t, C11), 20.3 (t, C2), 27.4, 27.9 (t, C1 and C4), 38.5 (t, C10), 45.1 (d, C3), 106.7 (s, C4a), 110.5 (d), 117.4 (d), 119.0 (d), 121.0 (d), 127.3 (s), 132.9 (s), 136.1 (s), 173.3 (s, C9).

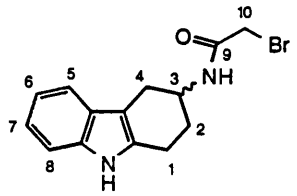
MS (NH_3 EI, 70 eV): m/z = 257 (M^++1, 100), 169 (M^+-$NH_2COC_3H_7$, 30).

Ir (KBr): ν = 3248 (s, NH), 2924 (m), 1634 (s, C=O), 1547 (s).

CHN $C_{16}H_{20}N_2O$ calc. C 74.97 H 7.87 N 10.92
found C 74.70 H 8.14 N 10.37

N-Bromoacetyl-3-amino-1,2,3,4-tetrahydrocarbazole (106d)

3-Amino-1,2,3,4-tetrahydrocarbazole (0.20 g, 1 mmol) is treated with bromoacetyl chloride (0.1 g, 1 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2). Yield: 0.24 g (0.78 mmol, 78 %), mp. 205-206 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.06-2.14 (m; 2H, H2),
2.66 (dd, ^2J=15.2 Hz, $^3J_{4,3}$=6.9 Hz; 1H, H4),
2.80 - 2.90 (m; 2H, H1),
3.11 (dd, ^2J=15.4 Hz, $^3J_{4,3}$=5.0 Hz; 1H, H4),
4.04 (s; 2H, H10),
4.42 (m; 1H, H3),
6.68 (d, br, ^3J=7.6 Hz; 1H, NH),
7.05 - 7.15 (m; 2H, H5 and H8),
7.28 (d, J=8.0 Hz; 1H, H6 or H7),
7.42 (d, J=7.6 Hz; 1H, H6 or H7),
7.89 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.5 (t, C2), 27.4, 27.9 (t, C1, C4), 42.6 (t, C10), 45.8 (d, C3), 107.0 (s, C4a), 110.5 (d), 117.7 (d), 119.4 (d), 121.4 (d), 127.4 (s), 132.5 (s), 136.1 (s), 165.5 (s, C9).

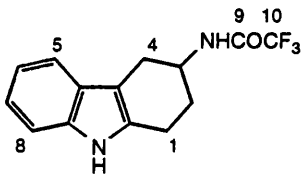
Ms (EI, 70 eV): m/z (%) = 183 (15, M^+-$COCH_2Br$), 169 (100, M^+-$NHCOCH_2Br$), 143 (40).

Ir (KBr): ν = 3379 (s; NH), 3272 (s; NH), 1641 (s), 1555 (m), 1448 (m), 744 (m).

CHN $C_{14}H_{15}N_2OBr$ calc. C 54.74 H 4.92 N 9.12
found C 54.60 H 4.85 N 9.91

N-Trifluroacetyl-3-amino-1,2,3,4-tetrahydrocarbazole (106e)

3-Amino-1,2,3,4-tetrahydrocarbazole (0.20 g, 1 mmol) is treated with ethyl trifluoroacetate (1 ml) according to procedure C VIII.2.6. The product is purified by SPC (CH_2Cl_2, 1 % MeOH). Yield: 0.25 g (0.88 mmol, 88 %), mp. 205-208 °C.



^{1}H-nmr (400 MHz, d_6-DMSO, $CDCl_3$): δ = 1.77 - 1.94 (m; 2H, H2),
2.47 - 2.58 (m; 1H, H4),
2.63 - 2.71 (m; 2H, H1),
2.80 - 2.90 (m; 1H, H4),
4.07 (m; 1H, H3),
6.75 - 6.88 (m; 2H, H6 or H7),
7.06 (d, ^{3}J=7.7 Hz; 1H, H5 or H8),
7.14 (d, ^{3}J=8.0 Hz; 1H, H5 or H8),
8.31 (s, br; 1H, NHCO),
9.43 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, d_6-DMSO, $CDCl_3$): δ = 20.8 (t, C2), 26.3, 27.5 (t, C1 and C4), 46.3 (d, C3), 105.9 (s, C4a), 110.2 (d), 116.8 (d), 116.9 (s, $J_{C,F}$=288 Hz, C10), 118.2 (d), 120.3 (d), 126.7 (s), 132.5 (s), 135.8 (s), 156.1 (s, C9).

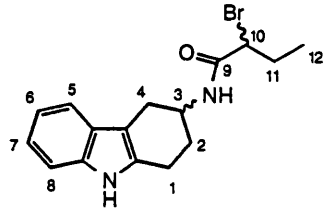
Ms (EI, 70 eV): m/z (%) = 282 (25, M^+), 169 (100, M^+-$NHCOCF_3$), 143 (23).

Ir (KBr): ν = 3386 (s; NH), 3286 (s; NH), 1692 (s), 1551 (s), 744 (s).

CHN $C_{14}H_{13}N_2OF_3$ calc. C 59.77 H 4.56 N 9.51
found C 59.57 H 4.33 N 9.21

N-2-Bromobutanoyl-3-amino-1,2,3,4-tetrahydrocarbazole (106f)

3-Amino-1,2,3,4-tetrahydrocarbazole (0.20 g, 1 mmol) is treated with (±)2-bromo-butanoyl bromide (0.2 g, 1 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2). Yield: 0.3 g (0.9 mmol, 90 %), mp. 183 - 184 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.02 (t, J=7.2 Hz; 3H, H12),
1.06 - 1.24 (m; 2H, H11),
1.95 - 2.19 (m; 2H, H2),
2.60 - 2.68 (m; 1H, H1),
2.78 - 2.86 (m; 2H, H1, H4),
3.11 (dd, ^{2}J=15.5 Hz, ^{3}J=3.7 Hz; 1H, H4),
3.21-3.32 (m; 1H, H10),
4.24 (m; 1H, H3),
6.45 (d, br; 1H, NH),
7.06-7.23 (m; 2H, H5 and H8),
7.28 (d, J=7.9 Hz; 1H, H6 or H7),
7.42 (d, J=7.6 Hz; 1H, H6 or H7),
7.85 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 11.7 (q, C12), 20.5 (t, C2), 27.4, 27.7 (t, C1, C4), 29.3 (t, C11), 45.9 (d, C3), 53.5 (d, C10), 107.0 (s, C4a), 110.6 (d), 117.7 (d), 119.4 (d), 121.6 (d), 127.1 (s), 132.4 (s), 135.9 (s), 167.3 (C9).

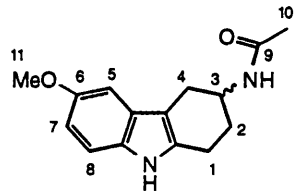
Ms (EI, 70 eV): m/z (%) = 334, 336 (20, 18, M^+), 169 (100, M^+-NHCOCHBrEt), 143 (50).

Ir (KBr): ν = 3412 (s; NH), 3271 (s; NH), 1642 (s), 1556 (m), 1448 (m), 744 (m).

CHN $C_{16}H_{19}N_2OBr$ calc. C 57.32 H 5.71 N 8.36
found C 57.02 H 5.58 N 8.21

N-Acetyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (107a)

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (0.22 g, 1 mmol) is treated with acetic anhydride (0.1 g, 1 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2, 2 % MeOH). Yield: 0.24 g (0.93 mmol, 93 %), mp. 91 - 95 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.83 - 1.98 (m; 2H, H2),
1.91 (s, 3H, H10),
2.51 (dd, ^2J=15.0 Hz, $^3J_{4.3}$=6.3 Hz; 1H, H4),
2.68 - 2.74 (m; 2H, H1),
2.97 (dd, ^2J=15.2 Hz, $^3J_{4.3}$=5.0 Hz; 1H, H4),
3.78 (s; 3H, H11),
4.36 (m; 1H, H3),
5.96 (d, br; 1H, NH),
6.72 (dd, $^3J_{7.8}$=8.7 Hz, $^4J_{7.5}$=2.4 Hz; 1H, H7),
6.82 (d,$^4J_{5.7}$=2.3 Hz; 1H, H5),
7.10 (d,$^4J_{8.7}$=8.7 Hz; 1H, H8),
7.24 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.4 (t, C2), 23.4 (q, C10), 27.6, 27.9 (t, C1, C4), 45.1 (d, C3), 55.8 (q, C11), 99.9 (d), 106.8 (s, C4a), 110.8 (d), 111.3 (d), 127.9 (s), 131.2 (s), 133.3 (s), 153.7 (s, C6), 170.0 (s, C9).

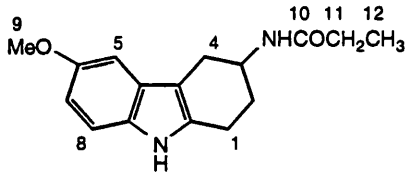
Ms (EI, 70 eV): m/z (%) = 258 (3, M^+), 199 (100, M^+-NHAc), 173 (12), 158 (28).

Ir (KBr): ν = 3300 (m, br; NH), 3100 (m, br; NH), 1652 (s, CO), 1625 (s), 1485 (m), 1455 (m), 1431 (m), 1031 (m).

CHN	$C_{15}H_{18}N_2O_2$	calc.	C 69.74	H 7.02	N 10.84
		found	C 69.48	H 6.88	N 10.69

N-Propanoyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (107b)

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (0.22 g, 1 mmol) is treated with propionic anhydride (0.15 g, 1 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2, 1 % MeOH) to yield 0.16 g (0.59 mmol, 59 %) of a pale brown oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.13 (t, $^3J_{12.11}$=7.5 Hz ; 3H, H12),
1.98 - 2.06 (m; 2H, H2),
2.16 (q, $^3J_{11.12}$=7.7 Hz ; 2H, H11),
2.55 (dd, ^2J=15.2 Hz,$^3J_{4.3}$=6.0 Hz; 1H, H4),
2.75 - 2.80 (m; 2H, H1),
3.04 (dd,^2J=15.4 Hz,$^3J_{4.3}$=5.4 Hz; 1H, H4),
3.82 (s; 3H, H9),
4.42 (m; 1H, H3),
5.62 (s, br; 1H, NHCO),
6.76 (dd, $^4J_{7.5}$=1.4 Hz, $^3J_{7.8}$=8.7 Hz; 1H, H7),
6.87 (d, $^4J_{5.7}$=1.3 Hz; 1H, H5),
7.16 (d, $^3J_{8.7}$=8.7 Hz; 1H, H8),
7.85 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.9 (q, C12), 20.5 (t, C2), 27.7, 27.9 (t, C1, C4), 29.9 (t, C11), 44.9 (d, C3), 55.9 (q, C10), 100.0 (d), 107.1 (s, C4a), 111.0 (d), 111.2 (d), 127.9 (s), 131.2 (s), 133.7 (s), 153.9 (s), 173.5 (s, C9).

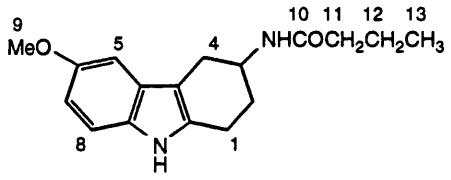
Ms (EI, 70 eV): m/z (%) = 272 (6, M^+), 199 (100, M^+-$NHCOC_2H_5$), 173 (17), 158 (20).

Ir (KBr): ν = 3312 (s; NH), 3130 (s; NH), 1651 (s, CO), 1625 (s), 1429 (m), 1034 (m).

CHN	$C_{16}H_{20}N_2O_2$	calc.	C 70.56	H 7.40	N 10.29
		found	C 69.98	H 7.22	N 10.08

N-Butanoyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (107c)

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (0.22 g, 1 mmol) is treated with butanoic anhydride (0.20 g, 1 mmol) according to procedure A VIII.2.6. The product is purified by SPC (CH_2Cl_2). Yield: 0.27 g (0.93 mmol, 93 %), mp. 140 - 144 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{13,12}$=7.4 Hz ; 3H, H13),
1.57 - 1.65 (m; 2H, H12),
1.91 - 2.06 (m; 2H, H2),
2.09 (t, $^3J_{11,12}$=7.1 Hz ; 2H, H11),
2.52 (dd, ^2J=15.4 Hz,$^3J_{4,3}$=6.6 Hz; 1H, H4),
2.69 - 2.75 (m; 2H, H1),
2.99 (dd,^2J=15.4 Hz,$^3J_{4,3}$=5.0 Hz; 1H, H4),
3.79 (s; 3H, H9),
4.37 (m; 1H, H3),
5.85 (d, br, ^3J=8.2 Hz; 1H, NHCO),
6.73 (dd, $^4J_{7,5}$=2.5 Hz, $^3J_{7,8}$=8.7 Hz; 1H, H7),
6.83 (d, $^4J_{5,7}$=2.2 Hz; 1H, H5),
7.11 (d, $^3J_{8,7}$=8.7 Hz; 1H, H8),
8.26 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6 (q, C13), 19.2 (t, C12), 20.4 (t, C2), 27.6, 27.9 (t, C1, C4), 38.6 (t, C11), 44.9 (d, C3), 55.8 (q, C10), 99.9 (d), 106.8 (s, C4a), 110.7 (d), 111.2 (d), 127.8 (s), 131.1 (s), 133.8 (s), 153.7 (s), 172.8 (s, C9).

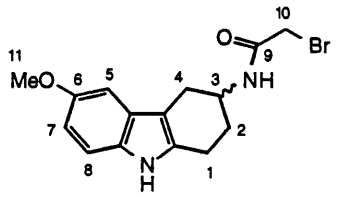
Ms (EI, 70 eV): m/z (%) = 286 (7, M^+), 199 (100, M^+-NHC_3H_7), 173 (35), 158 (50).

Ir (KBr): ν = 3292 (s, br; NH), 1641 (s, CO), 1468 (m), 1278 (m).

CHN $C_{17}H_{22}N_2O_2$ calc. C 71.30 H 7.74 N 9.78
found C 71.16 H 7.36 N 9.35

N-Bromoacetyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (107d)

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (0.22 g, 1 mmol) is treated with bromoacetyl chloride (0.15 g, 1 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2, 2 % MeOH) to yield 0.28 g (0.83 mmol, 83 %) of a pale yellow oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.95 - 2.11 (m; 2H, H2),
2.58 (dd, ^2J=15.4 Hz, $^3J_{4,3}$=6.8 Hz; 1H, H4),
2.68 - 2.81 (m; 2H, H1),
3.04 (dd, ^2J=15.2 Hz, $^3J_{4,3}$=5.2 Hz; 1H, H4),
3.78 (s; 3H, H11),
3.81 (s; 2H, H10),
4.35 (m; 1H, H3),
6.53 (d, br, ^3J=7.3 Hz; 1H, NH),
6.74 (dd, $^3J_{7,8}$=8.7 Hz, $^4J_{7,5}$=2.4 Hz; 1H, H7),
6.83 (d,$^4J_{5,7}$=2.5 Hz; 1H, H5),
7.13 (d,$^4J_{8,7}$=8.7 Hz; 1H, H8),
7.20 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.6 (t, C2), 27.6, 27.9 (t, C1, C4), 29.4 (t, C10), 46.1 (d, C3), 55.9 (q, C11), 100.1 (d), 106.9 (s, C4a), 111.2 (d), 111.3 (d), 127.9 (s), 131.2 (s), 133.5 (s), 154.05 (s, C6), 165.2 (s, C9).

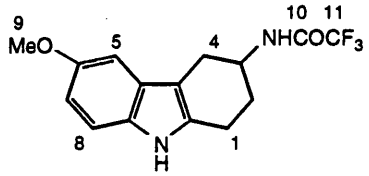
Ms (EI, 70 eV): m/z (%) = 336, 338 (3, M^+), 199 (100, M^+-$NHCOCH_2Br$), 173 (15), 158 (20).

Ir (KBr): ν = 3300 (m, br; NH), 3100 (m, br; NH), 1651 (s, CO), 1623 (s), 1486 (s), 1031 (m).

CHN $C_{15}H_{17}N_2O_2Br$ calc. C 53.42 H 5.08 N 8.31
found C 52.37 H 4.69 N 8.20

N-Trifluoroacetyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (107e)

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (0.22 g, 1 mmol) is treated with ethyl trifluoroacetate (1.5 ml) according to procedure C VIII.2.6. The product is purified by SPC (CH_2Cl_2, 3 % MeOH) to yield 0.1 g (0.32 mmol, 32 %) of a yellow oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.10 - 2.15 (m; 2H, H2),
2.70 (dd, ^2J=15.4 Hz, $^3J_{4.3}$=6.3 Hz; 1H, H4),
2.78 - 2.88 (m; 2H, H1),
3.15 (dd, ^2J=15.4 Hz, $^3J_{4.3}$=5.1 Hz; 1H, H4),
3.86 (s; 3H, H9),
4.49 (m; 1H, H3),
6.49 (s, br; 1H, NHCO),
6.83 (dd, $^4J_{7.5}$=2.5 Hz, $^3J_{7.8}$=8.7 Hz; 1H, H7),
6.90 (d, $^4J_{5.7}$=2.3 Hz; 1H, H5),
7.20 (d, $^3J_{8.7}$=8.7 Hz; 1H, H8),
7.80 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.2 (t, C2), 27.3, 27.4 (t, C1, C4), 46.2 (d, C3), 55.9 (q, C9), 100.0 (d), 106.2 (s, C4a), 111.3 (d), 111.4 (d), 117.2 (s, $J_{C,F}$=286 Hz, C10), 127.7 (s), 131.1 (s), 133.1 (s), 154.1 (s), 173.8 (s, C9).

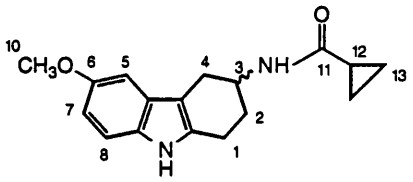
Ms (EI, 70 eV): m/z (%) = 312 (40, M^+), 199 (100, M^+-$NHCOCF_3$), 173 (80), 158 (40).

Ir (KBr): ν = 3300 (m, br; NH), 3100 (m, br; NH), 1691 (s, CO), 1620 (s), 1482 (s), 1025 (m).

CHN $C_{15}H_{15}N_2O_2F_3$ calc. C 57.69 H 4.84 N 8.97
found C 57.47 H 4.72 N 8.88

N-Cyclopropanoyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (107g)

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (0.22 g, 1 mmol) is treated with cyclopropanecarbonyl chloride (0.15 g, 1 mmol) according to procedure B VIII.2.6. The product is purified by SPC (CH_2Cl_2, 1 % MeOH) to yield 0.18 g (0.63 mmol, 63 %) of a pale brown oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ =0.70 - 0.79 (m; 2H, H13),
0.93 - 1.03 (m; 2H, H13),
1.23 (m; 1H, H12),
1.99 - 2.07 (m; 2H, H1),
2.58 (dd, ^2J=15.4 Hz, $^3J_{4,3}$=6.0 Hz; 1H, H4),
2.71 - 2.81 (m; 2H, H2),
3.04 (dd, ^2J=15.4 Hz, $^3J_{4,3}$=5.1 Hz; 1H, H4),
3.82 (s; 3H, H10),
4.44 (m; 1H, H3),
5.81 (d,^3J=7.6 Hz; 1H, NH),
6.76 (dd, $^3J_{7,8}$=8.7 Hz, $^4J_{7,5}$=2.5 Hz; 1H, H7),
6.87 (d,$^4J_{5,7}$=2.5 Hz; 1H, H5),
7.15 (d,$^4J_{8,7}$=8.6 Hz; 1H, H8),
7.82 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 7.2 (t, C13), 14.9 (t, C12), 20.5 (t, C2), 27.9, 28.1 (t, C1, C4), 45.2 (d, C3), 56.0 (q, C10), 100.1 (d), 107.2 (s, C4a), 111.1 (d), 111.2 (d), 128.0 (s), 131.2 (s), 133.8 (s), 154.0 (s, C6), 173.2 (s, C9).

Ms (EI, 70 eV): m/z (%) = 284 (50, M^+), 199 (50, M^+-NHCO-cyclopropyl).

Ir (KBr): ν = 3279 (m, br; NH), 1742 (s), 1692 (m), 1635 (s), 1555 (m), 1478 (m), 1388 (s), 1151 (m).

CHN $C_{17}H_{20}N_2O_2$ calc. C 71.80 H 7.09 N 9.85
found C 71.67 H 6.94 N 9.86

1,4-Diacetoxycyclohexane (109)

A mixture of 1,4-cyclohexanediol (40.0 g, 0.34 mol) and acetic anhydride (150 ml) is refluxed for 1 h. The solvent is evaporated to give pale yellow 1,4-diacetoxycyclohexane (mp. 105 °C) in quantitative yield[177].

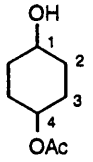
^{1}H nmr (400 MHz, $CDCl_3$): δ =1.44-1.48 (m; 4H, CH_2),
1.87-1.93 (m; 4H, CH_2),
1.97 (s; 6H, $COCH_3$),
4.70 (m; 2H, CH).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 21.24 (q, $CO\underline{C}H_3$), 28.00 (t), 70.86 (d), 170.46 (s, CO).

Ir (KBr): ν = 2945 cm^{-1} (m), 1721 (s; CO), 1240 (s, br), 1044 (s).

1-Acetoxy-4-hydroxycyclohexane (110)

At 45 °C, a solution of potassium hydroxide (6.5 g, 0.12 mol) in 30 ml of 50 % ethanol is added dropwise within 5 min to a solution of 1,4-diacetoxycyclohexane (29.4 g, 0.15 mol) in 200 ml of 50 % ethanol. The mixture is stirred at 50 °C for further 30 min, the solvent is evaporated and the solution is cooled to 0°C. The precipitated diacetate is removed by filtration and the filtrate is distilled to give 12.0 g (76 mmol, 63 %) of 1-acetoxy-4-hydroxycyclohexane (bp. 136 °C/15 torr).



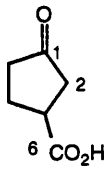
^{1}H nmr (400 MHz, $CDCl_3$): δ =1.17-1.37 (m; 4H, CH_2),
1.72-1.94 (m; 4H, CH_2),
1.95 (s; 3H, $COCH_3$),
2.50 (s, br; 1H, OH),
3.56-3.61 (m; 1H, H1),
4.61-4.65 (m; 1H, H4).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 21.26 (q, $CO\underline{C}H_3$), 28.56 (t, C3), 32.09 (t, C2), 68.70 (d, C1),
71.77 (d, C4), 170.17 (s, CO).

Ir ($CHCl_3$): ν = 3573-3092 cm^{-1} (m, br; OH), 1718 (s; CO), 1238 (s), 1200 (s),
804 (s).

Cyclopentanone-3-carboxylic acid (111)

A solution of dimethyl cyclopentanone-2,3-dicarboxylate and dimethyl cyclopentanone-2,4-dicarboxylate (10 g, 0.05 mol) in 2N sulphuric acid (100 ml) is refluxed for 2 h. After neutralisation with sodium carbonate the alcohol is removed by evaporation *in vacuo*. The aqueous solution is acidified with 1.7 M citric acid and the product is extracted with ethyl acetate (5x20 ml) to yield after evaporation of the solvent 4.3 g (34 mmol, 67 %) of a brown oil.

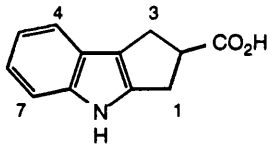


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.02 - 2.50 (m; 6H),
3.09 - 3.15 (m; 1H, H3),
8.70 (s, br; 1H, COOH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.2 (t, C4), 37.2 (t, C2 or C5), 40.4 (d, C3), 40.8 (t, C2 or C5), 179.0 (s, C6), 217.4 (s, C1).

1,2,3,4-Tetrahydrocyclopent[b]indole-2-carboxylic acid (112)

Phenylhydrazine hydrochloride (7.25 g, 0.05 mol) and cyclopentanone-3-carboxylic acid (6.4 g, 0.05 mol) are refluxed in methanol (50 ml) for 10 min. The alcohol is removed by evaporation *in vacuo* and the residue is dissolved in acetic acid (20 ml). After refluxing for 4 h the cold solution is poured into water (200 ml) to yield a brown precipitate (3.0 g, 15 mmol, 30 %). An analytical sample was recrystallized from aq. methanol. Mp. 217 °C (lit. 215 °C[176]).



^{1}H-nmr (400 MHz, d_6-DMSO): δ = 2.43 (dd, ^{3}J=5.8 Hz, ^{2}J=14.3 Hz; 1H, H1 or H3),
2.57 (m, ^{3}J=8.1 Hz, ^{3}J=9.2 Hz, ^{2}J=14.1 Hz; 3H, H1 or H3),
3.23 (m, ^{3}J=5.9 Hz,^{3}J=6.1 Hz; 1H, H2),
6.43 (ddd, ^{3}J=7.2 Hz, ^{3}J=7.4 Hz, ^{4}J=1.1 Hz; 1H, H5 or H6),
6.48 (ddd, ^{3}J=8.1 Hz, ^{3}J=7.0 Hz, ^{4}J= 1.3Hz; 1H, H5 or H6),
6.77 (d, ^{3}J=7.6 Hz; 1H, H4 or H7),
6.81 (d, ^{3}J=7.3 Hz; 1H, H4 or H7),
10.35 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, d_6-DMSO): δ = 28.4, 28.9 (t, C1, C3), 46.7 (d, C2), 111.7 (d), 115.5 (s, C3a), 117.8 (d), 118.6 (d), 119.8 (d), 123.9 (s), 140.9 (s), 142.0 (s), 176.5 (s, COOH).

Ms (FAB, 70 eV): m/z (%) = 201 (90, M^+), 156 (20, M^+-CO_2).

Ir (KBr): ν = 3400 (m, br, OH), 2930 (s), 1705 (s, C=O), 1216 (s), 735 (s).

CHN $C_{12}H_{11}NO_2$ calc. C 71.62 H 5.51 N 6.96
found C 71.10 H 5.54 N 6.76

2-Amine-1,2,3,4-tetrahydrocyclopent[b]indole (113)

- Attempted Schmidt reaction

Under cooling with ice conc. sulphuric acid (0.8 ml) is added to a suspension of 1,2,3,4-tetrahydrocyclopent[b]indole-2-carboxylic acid (0.5 g, 2.7 mmol) and sodium azide (0.4 g, 6 mmol) in chloroform (20 ml). Initially the mixture is stirred for 12 h at 25 °C and then at 50 °C for 4 h. The mixture is treated with ice-water (20 g) and insoluble starting material is removed by filtration. The filtrate is made alkaline by addition of 2N sodium hydroxide solution and is then extracted with dichloromethane. No product is isolated from the organic layer.

- Attempted preparation of 2-azide-1,2,3,4-tetrahydrocyclopent[b]indole

At 0 °C triethylamine (0.4 g, 4 mmol) is added to a stirred suspension of 1,2,3,4-cyclopent[b]indole-2-carboxylic acid (0.5 g, 2.7 mmol) in acetone (30 ml). After 20 min methyl chloroformate (0.4 g, 4.5 mmol) is added dropwise and stirring is continued for 2 h at 0 °C. Then a solution of sodium azide (0.3 g, 5 mmol) in water (1 ml) is added. After 1 h the reaction mixture is poured into ice-water (200 ml) and dichloromethane (100 ml). Insoluble starting material is recovered by filtration. No product is isolated from the organic layer.

- Attempted preparation of 2-carboxamide-1,2,3,4-tetrahydrocyclopent[b]indole

Under nitrogen 1,2,3,4-cyclopent[b]indole-2-carboxylic acid (0.5 g, 2.7 mmol) is heated with urea (5 g) at 180 °C for 1 h. The reaction mixture is poured into water to yield a solid, which is insoluble in acetone, DMSO and ethylacetate.

- Reaction of 1,2,3,4-tetrahydrocyclopent[b]indole with thionyl chloride

A suspension of 1,2,3,4-cyclopent[b]indole-2-carboxylic acid (0.5 g, 2.7 mmol) and thionyl chloride (5 ml) in chloroform (20 ml) is refluxed until cessation of gas evolution (15 min). Then the reaction mixture is cooled to room temperature and ammonium hydroxide solution is added. After 2 h insoluble material is removed by filtration and the layers are separated. Neither starting material nor product could be isolated from aqueous and organic layer.

Butane-1,2,4-tricarboxylic acid (115)

1,2,3,6-Tetrahydrobenzaldehyde (100 ml, 94 g, 0.85 mol) is added dropwise to a mechanically stirred solution of 71 % nitric acid (300 g), water (130 ml), ammonium vanadate (2.2 g) and copper powder (5.5 g). Initial heating might be necessary to start the exothermic reaction. Once the reaction has commenced the temperature is maintained below 55 °C by cooling with an ice-bath. After the addition is completed the mixture is stirred for another hour at 25 °C. Then the volatile components are removed *in vacuo* at 80 °C and the cold residue is triturated with the same volume of dichloromethane to yield 150 g (0.79 mol, 93 %) of a pale brown solid, mp. 115 - 117 °C (lit. 118.5 - 120 °C[179]).

Trimethyl butane-1,2,4-tricarboxyate (116)

A solution of butane-1,2,4-tricarboxylic acid (100 g, 0.53 mol), methanol (200 g), conc. sulphuric acid (10 ml) and 1,2-dichloroethane (1 l) is refluxed for 6 h. After cooling to 25 °C the lower layer is separated and the solvent is removed by evaporation *in vacuo*. The residue is diluted with benzene (200 ml) and the solution is washed with water (100 ml), sat. sodium bicarbonate solution (100 ml) and brine (50 ml). The product is purified by distillation of a Vigreux column to yield a viscous colourless oil (110 g, 0.47 mol, 89 %) with bp. 100 - 110 °C/0.1 mmHg.

- Attempted condensation of ethyl chloropropionate with diethyl succinate

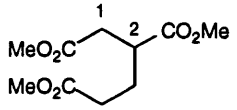
A solution of diethyl succinate (8.7 g, 50 mmol) in THF (40 ml) is added to a suspension of sodium hydride (1.2 g, 50 mmol) in THF (50 ml). After stirring the orange mixture at 25 °C for 1 h,

ethyl chloropropionate (6.1 g, 50 mmol) is added dropwise and stirring is continued for 12 h at 25 °C. Then water is carefully added and the starting materials are recovered by extractive work-up.

Under the same reaction conditions diethyl succinate (8.7 g, 50 mmol) and ethyl chloropropionate (6.1 g, 50 mmol) are reacted in the presence of 2.4 g (0.1 mol) of sodium hydride. The starting materials and ethyl acrylate, the latter identified by the olefinic signals in the ^{1}H nmr spectrum, are recovered.

- Attempted Michael reaction between diethyl succinate or succinic acid anhydride and ethyl acrylate

A suspension of diethyl succinate (8.7 g, 50 mmol) or succinic acid anhydride (5.0 g , 50 mmol), sodium methanolate (0.3 g, 5 mmol) and ethyl acrylate (4.3 g, 50 mmol) in THF (50 ml) is refluxed for 3 d. After extractive work-up the starting materials are recovered quantitatively.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.80 - 1.87 (m; 2H),
2.27 - 2.32 (m; 2H),
2.38 (dd, J=5.3 Hz, J=16.6 Hz; 1H, H1),
2.67 (dd, J=8.9 Hz, J=16.6 Hz; 1H, H1),
2.78 - 2.80 (m; 1H, H2),
3.60 (s; 6H, 2 Me),
3.62 (s; 3H, Me).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.5 (t), 31.2 (t), 35.6 (t), 40.2 (d, C2), 51.5, 51.6, 51.8 (q, OMe), 171.8, 172.8, 174.4 (s, CO).

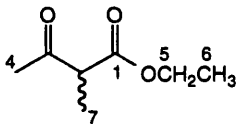
Dimethyl cyclopentanone-2,3-dicarboxylate and dimethyl cyclopentanone-2,4-dicarboxylate (117)

At 80 °C a solution of trimethyl butane-1,2,4-tricarboxylate (**116**, 110 g, 0.47 mol) in toluene (80 ml) and methanol (1 ml) is added dropwise to a mechanically stirred suspension of sodium hydride (0.55 mol) in toluene (350 ml). After the addition is completed the mixture is stirred for further 60 min at 80 °C before it is cooled to 25 °C and water (200 ml) is carefully added. The aqueous layer is acidified with 1.7 M citric acid and the product is extracted with ethyl acetate to yield after Kugelrohr distillation (bp. 200 °C/1 mmHg) a colourless oil (39 g, 0.20 mol, 42 %).

^{1}H-nmr (200 MHz, $CDCl_3$): δ = 2.36 - 2.54 (m; 4H),
3.56 - 3.64 (m; 2H),
3.66 (s; 3H, major isomer, $COOCH_3$),
3.70 (s; 3H, major isomer, $COOCH_3$),
3.74 (s; 3H, minor isomer, $COOCH_3$),
3.78 (s; 3H, minor isomer, $COOCH_3$).

Ethyl 2-methyl-3-oxo-butyrate (128)

Pyrrolidine (170.4 g, 2.4 mol) is added dropwise to a solution of ethyl acetoacetate (250 g, 1.92 mol) in benzene (100 ml). After cessation of the exothermic reaction, benzene and excess ethyl acetoacetate are removed by distillation *in vacuo*. Then dimethyl sulphate (240 g, 1.9 mol) is added dropwise to the residue at 80 °C. After 10 min. water (250 ml) is added and the mixture is refluxed for 20 min. The product is extracted with ether (3x200 ml) and the extracts are washed with 2N hydrochloric acid (2x50 ml) and brine. After distillation a viscous oil (bp. 60-65 °C/5 mmHg) is obtained. Yield: 163 g (1.15 mol, 60 %).



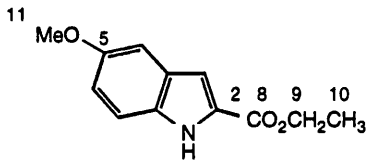
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{6,5}$ = 7.1 Hz; 3H, H6),
1.29 (d, $^3J_{7,2}$ = 8.0 Hz; 3H, H7),
2.20 (s; 3H, H4),
3.44 (q, $^3J_{2,7}$ = 8.1 Hz; 1H, H2),
4.14 (q, $^3J_{5,6}$ = 6.9 Hz; 2H, H5).
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 12.6 (q, C6), 14.0 (q, C7), 28.3 (q, C4), 52.3 (d, C2), 61.3 (t, C5), 170.5 (s), 204.9 (s).

Ethyl 5-methoxy-indole-2-carboxylate (130)

A solution of sodium nitrite (30.5 g, 0.43 mol) in water (100 ml) is added dropwise at 0 °C to a solution of *p*-anisidine (48 g, 0.39 mol) in 15 % aq. hydrochloric acid (200 ml). Sodium acetate (44 g, 0.32 mol) is added and the mixture is kept at 0 °C.

Ethyl 2-methyl-3-oxo-butyrate (63 g, 0.44 mol) in ethanol (400 ml) is treated at 0 °C with a solution of potassium hydroxide (24 g, 0.44 mol) in water (40 ml) followed at once by ice (600 g). Then the mixture of the diazonium salt is added immediatly and the pH is adjusted to 5.5. After

stirring the mixture for 4 h at 0 °C the product is extracted with benzene (3x150 ml). The organic layer is washed with water (2x100 ml) and is dried over magnesium sulphate. Evaporation of the solvent *in vacuo* results a red oil, which is heated for 4 h at 80 °C/0.1 mmHg. Then the oil is poured into 70 °C warm ethanol, through which a stream of hydrogen chloride is passed. The mixture is refluxed for 20 min and then left at 25 °C for 16 h to yield a red solid (47.5 g, 0.25 mol, 56 %), which is filtered and washed with cold ethanol. Mp. 152 - 154 °C (lit. 154 - 157 °C[188]).



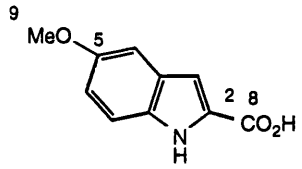
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.42 (t, $^3J_{10.9}$ = 7.2 Hz; 3H, H10),
3.86 (s; 3H, H11),
4.41 (q, $^3J_{9.10}$ = 7.1 Hz; 2H, H9),
7.01 (dd, $^4J_{6.4}$ = 2.5 Hz, $^3J_{6.7}$ = 9.1 Hz; 1H, H6),
7.08 (d, J = 2.3 Hz; 1H, H3 or H4),
7.15 (d, J = 2.1 Hz; 1H, H3 or H4),
7.32 (d, $^3J_{7.6}$ = 8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.5 (q, C10), 55.8 (q, C11), 61.0 (t, C9), 102.4 (d), 108.3 (d), 112.6 (d), 116.9 (d, C3), 127.8 (s), 127.9 (s), 154.6 (s, C5), 161.9 (s, C8).

Ir (KBr): ν = 3451 (m), 1725 (s, CO), 1460 (s), 1360 (s), 1227 (s), 634 (s).

5-Methoxy-indole-2-carboxylic acid (131)

A solution of ethyl 5-methoxy-indole-2-carboxylic acid (**130**, 40.0 g, 0.18 mol) in methanol (200 ml) and water (20 ml) is refluxed with sodium hydroxide (10.0 g, 0.18 mol) for 30 min. Methanol is removed by evaporation *in vacuo* and the alkaline solution is washed with dichloromethane (50 ml). After addition of ice-cold 2N hydrochloric acid a precipitate is obtained, which is filtered and dried. Yield: 33.4 g (0.17 mol, 97 %), mp. 192 - 194 °C (lit. 196 °C[251]).



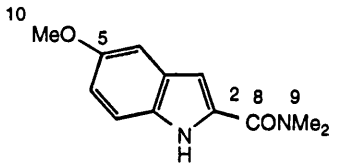
^{1}H-nmr (400 MHz, d_6-DMSO): δ = 3.92 (s; 3H, H9),
6.95 (dd, $^4J_{6.4}$ = 2.2 Hz, $^3J_{6.7}$ = 8.7 Hz; 1H, H6),
7.02 (d, J = 2.1 Hz; 1H, H3 or H4),
7.11 (d, J = 2.0 Hz; 1H, H3 or H4),
7.27 (d, $^3J_{7.6}$ = 8.6 Hz; 1H, H7).

^{13}C-nmr (100 MHz, d_6-DMSO): δ = 55.6 (q, C9), 102.2 (d), 108.2 (d), 112.5 (d), 114.2 (d, C3),
127.8 (s), 127.9 (s), 154.6 (s, C5), 180.7 (s, C9).

Ir (KBr): ν = 3415 (m, br, OH), 2934 (m), 1695 (s, C=O), 1220 (m, C-O).

N,N-Dimethyl-5-methoxy-indole-2-carboxamide (132)

At 40 °C thionyl chloride (33.3 g, 0.28 mol) is added dropwise to a suspension of 5-methoxy-indole-2-carboxylic acid (**131**, 41.9 g, 0.22 mol) in benzene (500 ml). Then the mixture is heated at 45 °C for 90 min and excess thionyl chloride is removed by evaporation *in vacuo*. The cold solution is added to a solution of dimethylamine (20 g) in benzene (80 ml). A solid precipitates, which is filtered and recrystallised from ethanol to yield 25.6 g (0.12 mol, 55 %) of pale yellow crystals, mp. 205 - 206 °C.



^{1}H-nmr (400 MHz, d_6-DMSO, $CDCl_3$): δ = 3.20 (s, br; 3H, H9),
3.40 (s, br; 3H, H9),
3.87 (s; 3H, H10),
6.78 (d, J = 2.2 Hz; 1H, H3 or H4),
6.94 (dd, $^4J_{6.4}$ = 1.9 Hz, $^3J_{6.7}$ = 9.0 Hz; 1H, H6),
7.08 (d, J = 1.8 Hz; 1H, H3 or H4),
7.41 (d, $^3J_{7.6}$ = 9.0 Hz; 1H, H7).

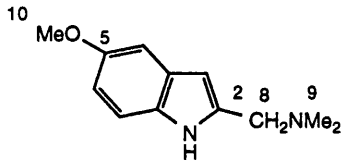
^{13}C-nmr (100 MHz, d_6-DMSO, $CDCl_3$): δ = 38.4, 38.5 (q, C9), 54.9 (q, C10), 103.7 (s), 104.3 (d), 112.4 (d), 114.4 (d, C3), 127.0 (d), 129.7 (s), 130.5 (s), 153.5 (s, C5), 162.6 (s, C8).

Ir (KBr): ν = 3450 (s), 2932 (s), 1682 (s, C=O), 1481 (s), 1224 (m, C-O).

2-(N,N-Dimethylaminomethyl)-5-methoxy-indole (133)

A solution of N,N-dimethyl-5-methoxy-indole-2-carboxamide (**132**, 25.6 g, 0.12 mol) in THF (400 ml) is added dropwise to a mechanically stirred suspension of lithium aluminium hydride (10.6 g, 0.28 mol) in THF (250 ml). After the addition is completed the reaction mixture is refluxed for 2 h. Excess lithium aluminium hydride is decomposed by careful addition of water (10 ml). The reaction mixture is filtered under suction and the filter cake is washed with ethyl acetate.

After washing the filtrate with water (50 ml) the product is extracted with dil. hydrochloric acid (2x50 ml). The aqueous layer is washed with ethyl acetate (50 ml). 2N Sodium hydroxide solution is then added to the aqueous layer to liberate the dimethylamine and the product is extracted with ethyl acetate (2x50 ml). After drying over magnesium sulfate and evaporation of the solvent the amine is obtained as brown oil (9.1 g, 44 mmol, 37 %).



^{1}H-nmr (200 MHz, $CDCl_3$): δ = 2.30 (s; 6H, $N(CH_3)_2$),
3.55 (s; 2H, $-CH_2-$),
3.80 (s; 3H, OCH_3),
6.85 (d, $^3J_{6,7}$ = 9 Hz; 1H, H6),
6.95 (s; 1H, H3 or H4),
7.10 (s; 1H, H3 or H4),
7.20 (d, $^3J_{7,6}$ = 9 Hz; 1H, H7),
8.25 (s, br; 1H, NH).

Ir (KBr): ν = 3359 cm^{-1} (br,m; NH), 1480 (s; -OMe), 1210 (m).

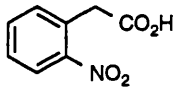
Alkylation of 2-(N,N-dimethylaminomethyl)-5-methoxy-indole (133)

To a solution of 2-(N,N-dimethylaminomethyl)-5-methoxy-indole (1.0 g, 4.9 mmol) in ethyl acetate (50 ml) is added a solution of methyl iodide (0.8 g, 5.4 mmol) in ethyl acetate (5 ml). After

10 min at 25 °C the precipitated solid is filtered and washed with ethyl acetate. An attempt to recrystallise the amorphous brown solid (1.0 g) from ethanol resulted in decomposition.

2-Nitro-phenylacetic acid (138)

2-Nitrotoluene (27.4 g, 0.2 mol) is added dropwise to a mechanically stirred suspension obtained by mixing diethyl oxalate (32.2 g, 0.22 mol) with sodium hydride (5.52 g, 0.23 mol) in THF (200 ml). The mixture is refluxed for 10 h and then treated with water (200 ml). At 25 °C the resulting solution is treated alternately with 30 % hydrogen peroxide solution (50 ml) and 10N sodium hydroxide solution (50 ml). The reaction mixture is washed with ethyl acetate (50 ml) to remove unreacted 2-nitrotoluene and is then acidified with ice-cold 15 % hydrochloric acid. A solid precipitates, which is filtered and recrystallised from methanol to yield 22.6 g (0.13 mol, 63 %) of beige coloured crystals, mp. 140 - 141 °C (lit. 141 °C[252]).



^{1}H-nmr (400 MHz, d_6-DMSO, $CDCl_3$): δ = 3.64 (s; 2H, CH_2),
7.04 - 7.05 (m; 1H, CH),
7.11 - 7.16 (m; 1H, CH),
7.25 - 7.29 (m; 1H, CH),
7.70 - 7.73 (m; 1H, CH).

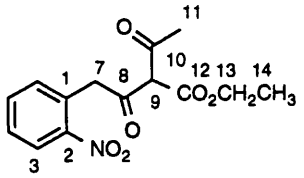
^{13}C-nmr (100 MHz, d_6-DMSO, $CDCl_3$): δ = 38.8 (t), 124.1 (d), 127.5 (d), 129.5 (s), 132.6 (d), 132.7 (d), 147.9 (s, CNO_2), 170.8 (s, CO).

Ethyl 1-(2-nitrophenyl)-2,4-dioxopentan-3-carboxylate (142)

At 50 °C thionyl chloride (7.9 g, 66 mmol) is added dropwise to a stirred suspension of 2-nitrophenylacetic acid (**138**, 11.9 g, 66 mmol) in toluene (90 ml). After cessation of gas evolution a stream of dry nitrogen is bubbled through the reaction mixture for 15 min.

A solution of ethyl acetoacetate (8.6 g, 60 mmol) in THF (50 ml) is added dropwise to a stirred cold (0 - 5 °C) suspension of sodium hydride (1.4 g, 60 mmol) in THF (50 ml). The resulting solution is added to the cold solution of the acid chloride, and the mixture is stired for 16 h at 25 °C. Water (200 ml) is added, the organic layer is separated and the aqueous layer is extracted with ethyl acetate (3x75 ml). The combined organic layer is washed with water (2x50 ml) and dried over magnesium sulphate. The solvent is then removed by evaporation *in vacuo* to yield a red oil, from

which a solid crystallises after trituration with ice-cold ether. Yield: 3.3 g (11 mmol, 19 %), mp. 77 - 79 °C (lit. 76 - 77 °C[253]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{14.13}$ = 7.1 Hz; 3H, H14),
2.39 (s; 3H, H11),
4.29 (q, $^3J_{13.14}$ = 7.1 Hz; 2H, H13),
4.51 (s; 2H, H9),
7.31 (d, ^3J = 7.6 Hz; 1H, H3 or H6),
7.45 (dd, ^3J = 7.4 Hz, ^3J = 8.1 Hz; 1H, H4 or H5),
7.58 (dd, ^3J = 7.5 Hz, ^3J = 7.4 Hz; 1H, H4 or H5),
8.10 (d, ^3J = 8.3 Hz; 1H, H3 or H6).

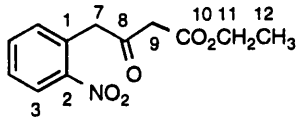
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.3 (q, C14), 25.1 (q, C11), 44.5 (t, C7), 60.9 (t, C13), 108.1 (s, C9), 124.1 (d), 125.2 (d), 128.4 (d), 130.6 (s), 133.5 (d), 133.6 (d), 148.8 (s, C2), 188.8, 193.8, 198.0 (s).

Ms (FAB, 70 eV): m/z (%) = 294 (100, M^++1).

Ir (KBr): ν = 2960 (s), 1710 (m), 1640 (s, CO), 1625 (s, CO).

Ethyl 4-(2-nitrophenyl)-3-oxobutyrate (143)

A suspension of Ethyl 1-(2-nitrophenyl)-2,4-dioxopentan-3-carboxylate (**142**, 3.1 g, 0.11 mol) in methanol (25 ml) and ammonium hydroxide solution (5 ml) is stirred at 25 °C for 1 h. The solvent is removed by evaporation *in vacuo* to yield a mixture of the crude product with acetamide, which is of sufficient purity for the reductive cyclisation with sodium dithionite.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{12.11}$ = 7.0 Hz; 3H, H12),
1.95 (s; 3H, CH_3CONH_2)
3.67 (s; 2H, H7 or H9),
4.25 (q, $^3J_{11.12}$ = 7.0 Hz; 2H, H11),
4.32 (s; 2H, H7 or H9),
6.30 (s, br; 1H, CH_3CONH_2),
6.68 (s, br; 1H, CH_3CONH_2),
7.30 (d, ^3J = 7.7 Hz; 1H, H3 or H6),
7.48 (dd, ^3J = 7.5 Hz, ^3J = 8.2 Hz; 1H, H4 or H5),
7.54 (dd, ^3J = 7.4 Hz, ^3J = 7.5 Hz; 1H, H4 or H5),
8.06 (d, ^3J = 8.3 Hz; 1H, H3 or H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.8 (q, C12), 21.7 (q, CH_3CONH_2), 47.2, 48.3 (t, C7, C9), 60.9 (t, C11), 124.0 (d), 127.9 (d), 129.1 (s), 133.1 (s), 133.2 (d), 147.9 (s, C2), 166.3, 173.6, 198.2 (s, CO, CH_3CONH_2).

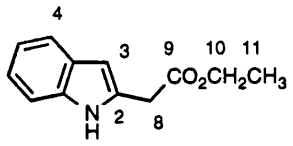
Ethyl indole-2-acetate (144)

- Procedure A

To a solution of crude ethyl 4-(2-nitrophenyl)-3-oxobutyrate (**143**, 1.7 g, 6 mmol) in methanol (90 ml) are added 0.5 g 10 % palladium-on-charcoal and ammonium formate (10 g). After stirring at 25 °C for 16 h and 50 °C for 4 h, no reaction is observed by TLC. The reaction mixture is filtered through a bed of Celite and the solvent is removed by evaporation *in vacuo* to recover the mixture of starting materials.

- Procedure B

A suspension of crude ethyl 4-(2-nitrophenyl)-3-oxobutyrate (**143**, 1.7 g, 6 mmol) in methanol (80 ml) and water (20 ml) is refluxed with sodium dithionite (5 g) for 20 min. Methanol is removed by evaporation in vacuo and the product is extracted with ethyl acetate (3x20 ml) to yield a yellow oil (0.8 g, 4 mmol, 66 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{11.10}$ = 7.1 Hz; 3H, H11),
3.82 (s; 2H, H8),
4.22 (q, $^3J_{10.11}$ = 7.1 Hz; 2H, H10),
6.36 (s; 1H, H3),
7.10 (dd, ^3J = 7.1 Hz, ^3J = 7.8 Hz; 1H, H5 or H6),
7.17 (dd, ^3J = 7.9 Hz, ^3J = 7.1 Hz; 1H, H5 or H6),
7.33 (d, ^3J = 8.1 Hz; 1H, H4 or H7),
7.56 (d, ^3J = 7.9 Hz; 1H, H4 or H7),
8.72 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.1 (q, C11), 33.9 (t, C8), 61.4 (t, C10), 101.7 (d), 110.8 (d), 119.7 (d), 120.0 (d), 121.6 (d), 128.1 (s), 130.5 (s), 136.3 (s), 170.6 (s, C9).

Ms (FAB, 70 eV): m/z (%) = 204 (100, M^++1).

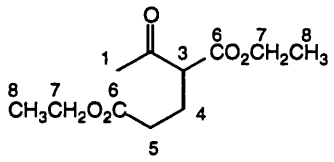
Ir (film): ν = 3370 (s, NH), 2970 (m), 17200 (m), 1595 (s, CO), 1205 (s).

Attempted synthesis of ethyl 3-(N,N-dimethylaminomethyl)-indole-2-acetate (145)

A solution of ethyl indole-2-acetate (**144**, 2.5 g, 12 mmol) in 1,4-dioxane (40 ml) is added dropwise to a cooled mixture of 37 % formalin (2.5 g), 33 % ethanolic dimethylamine (4.5 g), acetic acid (30 ml) and 1,4-dioxane (30 ml). After stirring the mixture for 16 h at 25 °C it is poured into water and extracted with ethyl acetate to yield 2.0 g of a neutral product. The aqueous layer is treated with 20 % sodium hydroxide solution. No product is obtained by extraction of the alkaline aqueous layer.

Diethyl 2-acetyl-glutarate (149)

At 100 °C ethyl acrylate (100 g, 1 mol) is added dropwise to a mixture of ethyl acetoacetate (130 g, 1 mol), ethanol (3 ml) and potassium hydroxide (1 g)[190]. After the addition is completed, the cold mixture is diluted with ether (400 ml) and washed with dil. acetic acid (2x50 ml). Then the organic layer is dried over magnesium sulphate and the mixture is distilled at 140 - 145 °C/2 mmHg to yield 82 g (0.36 mol, 36 %) of a colourless liquid.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.72 (m; 6H, H8),
2.03 - 2.11 (m; 2H, H4),
2.18 (s; 3H, H1),
2.24 - 2.31 (m; 2H, H5),
3.46 - 3.51 (m; 1H, H3),
4.02 - 4.17 (m; 4H, H7).

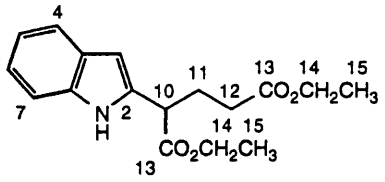
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.9, 14.1 (q, C8), 22.8 (t, C4), 29.0 (q, C1), 31.3 (t, C5), 58.2 (d, C3), 60.4, 61.4 (t, C7), 169.1, 172.4 (s, C6), 202.4 (s, C2).

Diethyl 2-bromoacetyl-glutarate (150)

Diethyl 2-acetylglutarate (23 g. 0.1 mol) is reacted with bromine (16 g, 0.1 mol) in ether (100 ml) according to procedure VIII.2.1 to yield 23.8 g (77 mmol, 77 %) of the brominated crude product.

Diethyl 2-(2-indole)-glutarate (151)

Diethyl 2-bromoacetyl-glutarate (6.1 g, 0.02 mol) is reacted with aniline (3.8 g, 0.04 mol) and zinc chloride (10 g) according to procedure VIII.2.2. The crude product is purified by absorptive filtration on silica gel (eluent: dichloromethane) to yield an orange oil (3.0 g, 10 mmol, 49 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.14 - 1.23 (m; 6H, H15),
2.16 - 2.40 (m; 4H, H11, H12),
3.83 - 3.92 (m; 1H, H10),
4.08 - 4.20 (m; 4H, H14),
6.36 (s; 1H, H3),
7.00 - 7.20 (m; 2H, H5, H6),
7.32 (d, ^{3}J=8.0 Hz; 1H, H4 or H7),
7.66 (d, ^{3}J=7.4 Hz; 1H, H4 or H7),
8.66 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6, 13.7 (q, C15), 27.8, 31.3 (t, C11, C12), 41.2 (d, C10), 60.1, 61.5 (t, C14), 100.4 (d), 110.4 (d), 120.0 (d), 120.3 (d), 122.0 (d), 128.2 (s), 131.2 (s), 135.8 (s), 171.5, 172.0 (s, C13).

Ms (FAB, 70 eV): m/z (%) = 303 (100, M^+).

4-(2-Indole)-butyric acid (152)

Diethyl 2-(2-indole)-glutarate (**151**, 2.9 g, 0.01 mol) in methanol (150 ml) is refluxed with potassium hydroxide (10 g) in water (20 ml) for 6 h. Then the methanol is removed by evaporation *in vacuo*, water (100 ml) is added and the cold solution is washed with ethyl acetate (2x20 ml). After

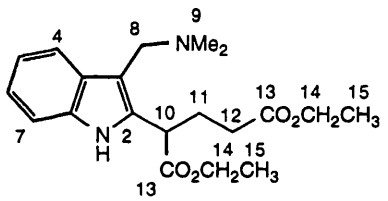
acidifying with cold 15 % hydrochloric acid, the product is extracted with ethyl acetate (2x50 ml) to yield a brown oil (0.9 g, 4.4 mmol, 44 %).

Attempted esterification of 4-(2-indole)-butyric acid (152)

A solution of 4-(2-indole)-butyric acid (0.4 g, 2 mmol), methanol (30 ml) and conc. sulphuric acid (20 µl) is refluxed for 5 h. Then the cold mixture is poured into water to yield a non-extractable black product.

Diethyl 2-(2-(3-dimethylaminomethyl)indole)glutarate (154)

A solution of diethyl 2-(2-indole)glutarate (**151**, 6.2 g, 0.02 mol) in 1,4-dioxane (20 ml) is added dropwise to a cold solution of 37 % formalin (1.7 ml), 33 % ethanolic dimethylamine (4.5 ml), acetic acid (20 ml) and 1,4-dioxane (20 ml). After stirring the mixture for 2 h at 25 °C it is poured into water and washed with dichloromethane to recover 2.3 g of starting material. The aqueous layer is treated with 20 % sodium hydroxide solution to obtain after extraction with dichloromethane a pale yellow oil (1.2 g, 3.4 mmol, 17 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.16 - 1.22 (m; 6H, H15),
2.22 (s; 6H, H9),
2.18 - 2.37 (m; 4H, H11, H12),
3.67 (s; 2H, H8),
4.03 - 4.13 (m; 4H, H14),
4.13 - 4.21 (m; 1H, H10),
7.06 (ddd, ^3J = 6.9 Hz, ^3J = 8.0 Hz, ^4J = 1.0 Hz; 1H, H5 or H6),
7.11 (ddd, ^3J = 7.7 Hz, ^3J = 7.0 Hz, ^4J = 1.3 Hz; 1H, H5 or H6),
7.27 (d, ^3J = 7.9 Hz; 1H, H4 or H7),
7.65 (d, ^3J = 7.6 Hz; 1H, H4 or H7),
8.99 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.8, 13.9 (q, C15), 27.9, 31.2 (t, C11, C12), 41.4 (d, C10), 45.1 (q, C9), 53.1 (t, C8), 60.2, 61.0 (t, C14), 110.6 (d), 110.9 (s, C3), 118.9 (d), 119.2 (d), 121.6 (d), 128.2 (s), 132.0 (s), 135.5 (s), 172.5, 173.0 (s, C13).

Ms (FAB, 70 eV): m/z (%) = 361 (100, M^++1).

Attempted preparation of diethyl 2-(2-(3-cyanomethyl)-indole)glutarate (155)

- Procedure A

A solution of diethyl 2-(2-(3-dimethylaminomethyl)indole)glutarate (**154**, 1.0 g, 2.8 mmol) in methanol (40 ml), DMF (5 ml) and water (5 ml) is stirred with methyl iodide (4.0 g, 28 mmol) and potassium cyanide (1.8 g, 28 mmol) at 50 °C for 5 d. The reaction mixture is poured into water (200 ml) and is washed with dichloromethane (20 ml). After acidification with 2N hydrochloric acid a yellow oil (0.5 g) is obtained by extraction with dichloromethane (2x20 ml). The product mixture could not be separated by column chromatography.

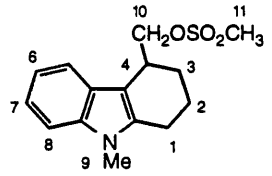
- Procedure B

A suspension of diethyl 2-(2-(3-dimethylaminomethyl)indole)glutarate (1.0 g, 2.8 mmol) in ethanol (10 ml) and water (5 ml) is refluxed for 5 d with sodium cyanide (2 g, 40 mmol) . The reaction mixture is poured into water (200 ml) and is acidified with 2N hydrochloric acid to give a yellow oil (0.6 g) after extraction with dichloromethane (2x20 ml).

A solution of the product (0.2 g) in methanol (10 ml) containing 2 drops of conc. sulphuric acid is refluxed for 5 h. After 30 min a brown solid is formed, which is insoluble in acetone, DMSO and water.

4-Mesyloxymethyl-N-methyl-1,2,3,4-tetrahydrocarbazole (158)

At - 10 °C a solution of 4-hydroxymethyl-N-methyl-1,2,3,4-tetrahydrocarbazole (3.6 g, 16.7 mmol) in pyridine (40 ml) is reacted with methanesulfonyl chloride (2.3 g, 1.6 ml, 20.5 mmol) according to procedure VIII.2.9. After spinning plate chromatography a yellow solid (3.5 g, 72 %) with mp. 187 - 191 °C is obtained. Attempted recrystallisation from ethanol gives an oil as a decomposition product.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.00 - 2.19 (m; 4H, H2 and H3),
2.67 - 2.72 (dd; 2H, H1),
2.97 (s; 3H, H11
3.62 (s; 3H, H9),
4.00 (m; 1H, H4),
4.15 - 4.23 (m; 2H, H10),
7.08 (dd, ^{3}J=7.3 Hz, ^{3}J=7.5 Hz; 1H, H6 or H7),
7.17 (dd, ^{3}J=7.1 Hz, ^{3}J=7.7 Hz; 1H, H6 or H7),
7.22 (d, $^3J_{8,7}$=8.0 Hz; 1H, H8),
7.58 (d, $^3J_{5,6}$=7.9 Hz; 1H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.5 (t), 21.4 (t), 26.1 (t), 29.1 (q, C9), 38.9 (q, C11), 32.6 (d, C4), 52.4 (t, C10), 108.7 (d), 109.9 (s, C4a), 119.1 (d), 119.9 (d), 121.8 (d), 126.2 (s), 137.7 (s), 138.0 (s).

Ms (FAB, 70 eV): m/z (%) = 294 (100, M^++1), 214 (32, M^+-SO_2Me).

Ir (KBr): ν = 2932 (m), 1625 (CO), 1471 (s, OR), 1418 (m), 1194 (s), 1034 (s), 767 (s).

4-Mesyloxymethyl-6-methoxy-N-methyl-1,2,3,4-tetrahydrocarbazole (159)

- Procedure A

At - 10 °C a solution of 4-hydroxymethyl-6-methoxy-N-methyl-1,2,3,4-tetrahydro-carbazole (3.9 g, 16 mmol) in pyridine (40 ml) is reacted with methanesulfonyl chloride (2.3 g, 1.6 ml, 20.5 mmol) according to procedure VIII.2.9.

- Procedure B

A solution of 4-hydroxymethyl-6-methoxy-N-methyl-1,2,3,4-tetrahydrocarbazole (0.3 g, 1.4 mmol) in THF (20 ml) is added to a suspension of sodium hydride (0.03 g, 1.4 mmol) in THF (20 ml). After 30 min at 0 °C methanesulphonyl chloride (0.4 g, 1.4 mmol) is added and the heterogenous mixture is stirred at 25 °C for 2 d. Then water is added (50 ml) and the product is extracted with dichloromethane (3x30 ml) to yield a brown oil. After SPC with dichloromethane a yellow solid is obtained.

In both procedures an inseparable mixture of compounds is obtained, which shows a new dd at δ=4.16 ppm but no s at δ=2.97 ppm.

N-Acetyl-9-amine-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (161)

A solution of 4-methanesulphonyloxymethyl-1,2,3,4-tetrahydrocarbazole (1.0 g, 3.4 mmol) is reacted with sodium azide (0.4 g, 6.8 mmol) according to procedure VIII.2.10. The crude azide (0.3 g, 37 %), which is a yellow oil, is reduced with lithium aluminium hydride (0.5 g) in THF (25 ml) according to procedure VIII.2.11 to yield 0.10 g (35 %) of the amine as a yellow oil. Following procedure A, VIII.2.6, acetylation of the amine with acetic anhydride (20 µl) gives 47 mg of a 1:2 mixture of N-acetyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (**50a**) and N-acetyl-9-amine-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (**161**).

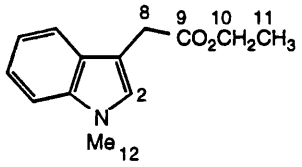
^{1}H-nmr (200 MHz, $CDCl_3$): δ = 1.75 - 1.92 (m),
1.90 (s; $COCH_3$, major product),
1.96 (s; $COCH_3$, minor product),
2.00 - 2.14 (m), 2.64 - 2.74 (m), 2.84 - 2.98 (m),
3.00 - 3.10 (m),
3.64 (s; NCH_3, minor product),
3.70 (s; NCH_3, major product),
3.55 - 3.67 (m; overlayed),
4.38 (m),
5.64 (d, br; NH, major product),
5.82 (t, br; NH, minor product),
7.04 - 7.28 (m; H_{ar}),
7.32 (d, ^3J = 8.0 Hz; H_{ar}),
7.52 (d, ^3J = 7.5 Hz; H_{ar}, major product),
7.64 (d, ^3J = 7.5 Hz; H_{ar}, minor product).

γ-Bromo-acetoacetate (163)

A solution of ethyl acetate (130 g, 1 mol) in ether (150 ml) is treated with bromine (51 ml, 1 mol) according to procedure VIII.2.1 to yield 186 g (0.89 mol, 89 %) of crude γ-bromo-acetoacetate as a pale yellow oil[157].

Ethyl N-methyl-indole-3-acetate (164)

N-Methyl-aniline (28.7 g, 0.26 mol) is reacted with γ-bromo-acetoacetate (28.0 g, 0.13 mol) and zinc chloride (15 g) according to procedure VIII.2.2 to yield a yellow oil (15.6 g, 72 mmol, 55 %) which is of sufficient purity for use in the subsequent Claisen condensation.



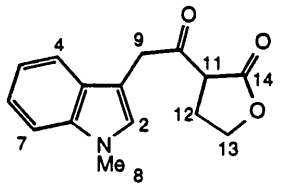
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.42 (t, $^3J_{11.10}$ = 7.3 Hz; 3H, H11),
3.78 (s; 3H, H12),
3.80 (s; 2H, H8),
4.40 (q, $^3J_{10.11}$ = 7.1 Hz; 2H, H10),
7.07 (s; 1H, H2),
7.16 (dd, ^{3}J=7.0 Hz, ^{3}J=7.9 Hz; 1H, H5 or H6),
7.27 (dd, ^{3}J=7.0 Hz, ^{3}J=8.1 Hz; 1H, H5 or H6),
7.32 (d, $^3J_{7.6}$=8.2 Hz; 1H, H7),
7.63 (d, $^3J_{4.5}$=7.3 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.5 (q, C11), 31.0 (t, C8), 32.7 (q, C12), 61.0 (t, C10), 106.8 (s, C3), 108.9 (d), 118.4 (d), 118.8 (d), 121.3 (d), 128.5 (s), 129.5 (d), 136.8 (s), 172.5 (s, C9).

Ir (film): ν = 3455 (m), 1722 (s, CO), 1448 (s), 1224 (s), 635 (s).

1-Oxo-1-(3-(2-oxo-oxacyclopentane))-2-(3-(N-methylindolyl))ethane (165)

A suspension of ethyl N-methyl-indole-3-acetate (1.2 g, 5.5 mmol), γ-butyrolactone (2.0 g, 2.9 mmol) and freshly prepared sodium methanolate (3.0 g, 55 mmol) in 1,4-dioxane (25 ml) is refluxed for 2 d. The cold reaction mixture is treated with water (200 ml) and is acidified with 2N hydrochloric acid. After extraction with dichloromethane the product is purified by SPC (eluent: dichloromethane) to yield a yellow oil (1.2 g, 5.1 mmol, 92 %). With sodium hydride (55 mol) instead of sodium methanolate as above no product is obtained.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.06 - 2.10 (m; 1H, H12),
2.64 - 2.69 (m; 1H, H12),
3.76 (s; 3H, H8),
3.85 (t, $^3J_{11.12}$=9.0 Hz; 1H, H11),
4.14 - 4.18 (m, $^2J_{13.13}$=16.3 Hz; 2H, H13, H9),
4.26 - 4.33 (m, $^2J_{13.13}$=16.6 Hz; 2H, H13, H9),
7.09 (s; 1H, H2),
7.19 (dd, ^{3}J=6.9 Hz, ^{3}J=8.0 Hz; 1H, H5 or H6),
7.30 (dd, ^{3}J=7.0 Hz, ^{3}J=7.5 Hz; 1H, H5 or H6),
7.35 (d, $^3J_{7.6}$=7.3 Hz; 1H, H7),
7.64 (d, $^3J_{4.5}$=8.4 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.7 (t, C12), 32.5 (q, C8), 38.6 (t, C9), 49.8 (d, C11), 67.0 (t, C13), 105.4 (s, C3), 109.2 (d), 118.5 (d), 119.1 (d), 121.6 (d), 127.4 (s), 128.3 (d), 136.6 (s), 172.9 (s, C14), 200.6 (s, C10).

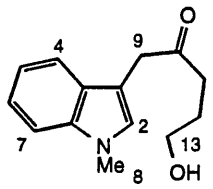
Ms (FAB, 70 eV): m/z (%) = 258 (100, M^++1).

Ir (film): ν = 3460 (m), 1775 (s, CO), 1720(s, CO), 1453 (s), 1220 (s), 638 (s).

5-(N-Methyl-3-indolyl)-4-oxopentanol (166)

A solution of the lactone **165** (0.4 g, 1.6 mmol) in 2N sodium hydroxide solution (20 ml) and 1,4-dioxane (40 ml) is refluxed for 16 h. Ether (100 ml) is added and the organic layer is washed with

brine and dried over magnesium sulphate. The solvent is then removed by evaporation *in vacuo* to yield a yellow oil (0.25 g, 1.1 mmol, 68 %), which is purified by SPC (eluents: dichloromethane to 3% MeOH in dichloromethane).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.77 (qi, ^3J=6.7 Hz; 2H, H12),
2.30 (s, br; 1H, OH),
2.60 (t, $^3J_{11,12}$=6.9 Hz; 2H, H11),
3.53 (t, $^3J_{13,12}$=6.2 Hz; 2H, H13),
3.73 (s; 3H, H8),
3.81 (s; 2H, H9),
6.98 (s; 1H, H2),
7.13 (ddd,^3J=8.0Hz,^3J=6.8Hz,^4J=1.5Hz; 1H, H5 or H6),
7.24 (ddd,^3J=8.4Hz,^3J=8.2Hz,^4J=1.5Hz; 1H, H5 or H6),
7.30 (d, $^3J_{7,6}$=8.2 Hz; 1H, H7),
7.54 (d, $^3J_{4,5}$=7.9 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.4 (t, C12), 32.5 (q, C8), 37.9, 39.8 (t, C9, C11), 61.8 (t, C13), 106.8 (s, C3), 109.2 (d), 118.6 (d), 119.1 (d), 121.7 (d), 127.5 (s), 127.8 (d), 136.8 (s), 209.9 (s, C10).

Ms (FAB, 70 eV): m/z (%) = 232 (100, M^++1), 214 (32, M^++1-H_2O).

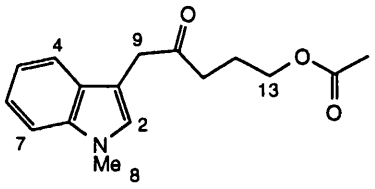
Ir (film): ν = 3350 (s, br, OH), 1731 (s, CO), 1212 (m), 641 (m).

Attempted cyclisation of 5-(N-methyl-3-indolyl)-4-oxopentanol (166)

A mixture of the alcohol **166** (0.6 g, 2.6 mmol) and borontrifluoride-etherate (10 ml) in ether (20 ml) is refluxed for 1 h under nitrogen to yield a black insoluble solid.

5-(N-Methyl-3-indolyl)-4-oxopentyl acetate (167)

A solution of the alcohol **166** (0.25 g, 1 mmol) in glacial acetic acid (20 ml) is stirred at 25 °C for 4 h. Water (100 ml) is added and the product is extracted with dichloromethane (2x20 ml). After washing with brine and drying over magnesium sulphate the solvent is removed by evacuation *in vacuo* to yield a yellow oil (0.14 g, 0.51 mmol, 51 %).



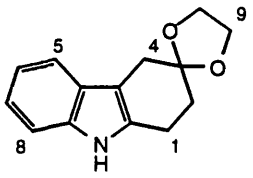
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.88 (qi, ^3J = 7.0 Hz; 2H, H12),
1.95 (s; 3H, H15),
2.55 (t, $^3J_{11.12}$ = 7.3 Hz; 2H, H11),
3.73 (s; 3H, H8),
3.78 (s; 2H, H9),
3.98 (t, $^3J_{13.12}$ = 6.4 Hz; 2H, H13),
6.97 (s; 1H, H2),
7.13 (dd, ^3J = 7.3 Hz, ^4J = 1.1 Hz; 1H, H5 or H6),
7.25 (ddd,^3J=7.5Hz,^3J=7.6Hz,^4J=1.1Hz; 1H, H5 or H6),
7.29 (d, $^3J_{7.6}$ = 8.2 Hz; 1H, H7),
7.52 (d, $^3J_{4.5}$ = 7.9 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.7 (q, 15), 22.6 (t, C12), 32.5 (q, C8), 37.2, 39.7 (t, C9, C11), 63.4 (t, C13), 106.7 (s, C3), 109.2 (d), 118.5 (d), 119.1 (d), 121.7 (d), 127.5 (s), 127.7 (d), 136.8 (s), 170.8 (s, C14), 209.9 (s, C10).

Ir (film): ν = 3309 (m), 1734 (s, CO), 1694 (s, CO), 1210 (m).

3,3-Ethylenedioxy-1,2,3,4-tetrahydrocarbazole (169)

A mixture of 4,4-ethylenedioxycyclohexanone (4.1 g, 26 mmol) and phenylhydrazine (2.8 g, 26 mmol) in water (50 ml) is heated on a steam-bath for 20 min. The cold reaction mixture is extracted with ethyl acetate (5x20 ml). After drying over magnesium sulphate the solvent is removed by evaporation *in vacuo* to yield the crude hydrazone, which is dissolved in benzene (50 ml). Then dry zinc chloride (10 g) is added and the mixture is refluxed for 4 h under a Dean-Stark trap. The reaction mixture is partitioned between ethyl acetate (50 ml) and 2N hydrochloric acid (50 ml) and extracted with ethyl acetate (2x50 ml). The combined organic layer is washed with brine (3x50 ml) to yield, after drying over magnesium sulphate and distillation of the solvent, a brown solid (2.4 g, 10.4 mmol, 40 %) with mp. 143 - 146 °C (lit. 145.5 - 147 °C[173]).



^{1}H nmr (400 MHz, $CDCl_3$): δ = 2.05 - 2.20 (m; 2H, H2),
2.87 - 3.00 (m; 2H, H1),
3.00 (s; 2H, H4),
4.03 - 4.09 (m; 4H, H9),
7.07 - 7.18 (m; 2H, H6, H7),
7.20 - 7.23 (m; 1H, H5 or H8),
7.40 - 7.45 (m; 1H, H5 or H8),
7.78 (s, br; 1H, NH).

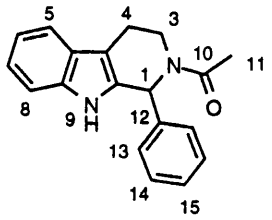
^{13}C nmr (100 MHz, $CDCl_3$): δ = 21.4 (t, C2), 31.7, 31.9 (t, C1 and C4), 64.6 (t, C9), 108.0, 109.1 (s, C4a, C3), 110.5 (d), 117.5 (d), 119.1 (d), 122.0 (d), 127.6 (s), 132.3 (s), 136.5 (s).

Ms (EI, 70 eV): m/z (%) = 229 (20, M^+), 143 (100).

Ir (KBr): ν = 3270 (s, NH), 1451 (s, C-O).

N-Acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (170a)

3-Phenyl-3,4,5,6-tetrahydro-β-carboline (1.2 g, 4 mmol) and acetic anhydride are reacted in dichloromethane and triethylamine according to procedure A, VIII.2.6 to yield 1.0 g (3.4 mmol, 86 %) of the amide, which is recrystallised from 100 ml ethanol/methanol (1:1). Mp. 284 - 286 °C, R_f = 0.32 (cyclohexane/ethyl acetate(1:1)) The colourless product is insoluble in ether, ethanol, water, chloroform and tetrachloromethane, but soluble in dimethyl sulfoxide.



^{1}H nmr (400 MHz, d_6-DMSO): δ = 2.15 (s; 3H, H11),
2.79 (dd, $^2J_{4,4'}$=15.2 Hz, $^3J_{4,3}$=4.2 Hz; 1H, H4),
2.88 (dt, $^2J_{4',4}$=10.8 Hz, $^3J_{4',3}$=4.9 Hz, $^3J_{4',3'}$=4.6 Hz; 1H, H4'),
3.23 (dt, $^2J_{3,3'}$=10.0 Hz, $^3J_{3,4?}$=3.8 Hz; 1H, H3),
3.96 (dd, $^2J_{3',3}$=14.0 Hz, $^3J_{3',4'}$=4.6 Hz; 1H, H3'),
6.86 (s; 1H, H1),
7.01 (dd, $^3J_{6,5}$=7.2 Hz, $^3J_{6,7}$=7.2 Hz; 1H, H6),
7.09 (dd, $^3J_{7,8}$=7.5 Hz, $^3J_{7,6}$=7.3 Hz; 1H, H7),
7.22 (d, $^3J_{8,7}$=7.9 Hz; 1H, H8),
7.24 - 7.40 (m; 5H, H13, H14, H15),
7.47 (d, $^3J_{5,6}$=7.8 Hz; 1H, H5),
11.01 (s, br; 1H, H9).

^{13}C nmr (100 MHz, d_6-DMSO): δ = 21.4 (q, C11), 39.9 (t, C4), 50.8 (t, C3), 56.1 (d, C1), 108.3 (s, C4a), 111.1 (d, C8), 117.8, 118.5 (d, C5, C6), 121.2 (d, C7), 126.1 (s, C4b), 127.6 (d, C15), 127.9, 128.3 (d, C13, C14), 131.8 (s, C9a), 136.1 (s, C8a), 140.4 (s, C12), 168.7 (s, C10).

Ms (EI, 70 eV): m/z (%) = 291 (21, M^++1), 290 (100, M^+), 247 (44, M^+-$COCH_3$), 232 (30, M^+-$NHCOCH_3$), 219 (28, M^+-CH_2NCOCH_3), 213 (20, M^+-C_6H_5), 171 (34, M^+-C_6H_6-$COCH_3$), 144 (34, M^+-$C_6H_5CH_2COCH_3$), 115 (11, M^+-C_6H_5CH-$NCOCH_3$-C_2H_4), 77 (7, $C_6H_5^+$), 43 (19, $COCH_3^+$).

Ir (KBr): ν = 3200 (s, NH), 2840 (m), 1620 (s, CO), 1480 (s), 1260 (s), 720 (s), 640 (s).

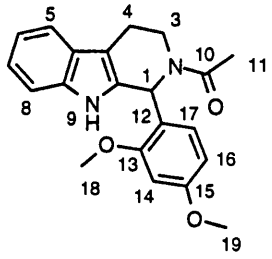
CHN	$C_{19}H_{18}N_2O$	calc.	C 78.54 H 6.25 N 9.65
		found	C 78.58 H 6.32 N 9.70

The purity of the compound was determined by HPLC.

column:	250x4.6 mm "Sphensorb ODS 2, 5 µm"
mobile phase:	A = water
	D = acetonitril; gradient: 20% D to 80% D in 30 min
flow rate:	1.0 cm^3/min
detector:	UV 254 nm
purity:	98.33 %
retention time:	23.07 min

N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carbazole (170b)

A solution of tryptamine (3.2 g, 0.02 mol) in ethanol (20 ml) is treated with 2,4-dimethoxybenzaldehyde (4.15 g, 0.025 mol). After stirring for 2 min the mixture is cooled to 0 °C and conc. hydrochloric acid (2.6 ml) is added dropwise. After heating at 60 °C for 1 h the cooled mixture is washed with ether (20 ml) and poured into 100 ml of a 4N sodium hydroxide solution. The yellow solution is extracted with ether (2x40 ml) and dried over magnesium sulphate. Then the ethereal solution of the crude 3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carbazole is treated with acetic anhydride and triethylamine as described in procedure A, VIII.2.6 to yield a solid, which decomposes in ethanol. Recrystallisation from ethyl acetate gave 1.2 g (9.8 mmol, 49 %) of a colourless product, which is soluble in ethanol, chloroform, acetone and hot ethyl acetate. The amide is slightly soluble in isopropanol and insoluble in water and methanol. Mp. 208 °C (decomp.), R_f = 0.05 (cyclohexane/ethyl acetate(1:1)).



Ms (EI, 70 eV): m/z (%) = 351 (23, M^++1), 350 (100, M^+), 319 (24, M^+-OCH_3), 307 (72, M^+-$COCH_3$), 276 (17, M^+-OCH_3- $COCH_3$), 248 (23, M^+-2x(OCH_3)-$COCH_3$), 43 (100, $COCH_3^+$).

Ir (KBr): ν = 3260 (s, NH), 2940 (m), 1640 (s, CO), 1560 (s), 1440 (s), 1420 (s), 1260 (s), 1210 (s), 740 (m), 690 (m).

CHN $C_{21}H_{22}N_2O_3$ calc. C 71.98 H 6.33 N 7.99
found C 70.58 H 6.41 N 7.43

Major isomer of 170b:

^{1}H nmr (400 MHz, $CDCl_3$): δ = 2.19 (s; 3H, H11),
2.78 (dd, $^2J_{4.4'}$=15.5 Hz, $^3J_{4.3}$=3.1 Hz; 1H, H4),
2.85 - 2.92 (m; 1H, H4'),
3.10 (dt, $^2J_{3.3'}$=12.1 Hz, $^3J_{3.4?}$=4.2 Hz, $^3J_{3.4?}$=4.4 Hz; 1H, H3),
3.76 (s; 3H, H18 or H19),
3.95 (s; 3H, H18 or H19),
4.96 (dd, $^2J_{3'.3}$=12.9 Hz, $^3J_{3'.4'}$=4.5 Hz; 1H, H3'),
6.28 (s; 1H, H1),
6.36 (dd, $^3J_{16.17}$=8.4 Hz, $^4J_{16.14}$=2.3 Hz; 1H, H16),
6.54 (d, $^4J_{14.16}$=2.3 Hz; 1H, H14),
6.87 (d, $^3J_{17.16}$=8.6 Hz; 1H, H17),
7.06 - 7.15 (m; 2H, H6, H7),
7.24 (d, $^3J_{8.7}$=8.3 Hz; 1H, H8),
7.51 (d, $^3J_{5.6}$=7.4 Hz; 1H, H5),
8.42 (s, br; 1H, H9).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 21.0 (q, C11), 22.2 (t, C4), 37.5 (t, C3), 51.7 (s, C1), 55.4, 55.7 (q, C18, C19), 99.1, 104.8 (d, C14, C16), 110.0 (s, C4a), 111.0 (d, C8), 118.3, 119.5 (d, C5, C6), 120.7 (s, C12), 121.0 (d, C7), 126.6 (s, C4b), 128.9 (d, C17), 132.4 (s, C9a), 136.2 (s, C8a), 157.3, 160.8 (s, C13, C15), 170.7 (s, C10).

Minor isomer of 170b:

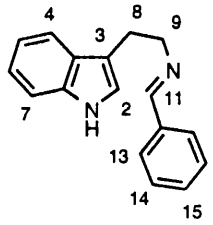
^{1}H nmr (400 MHz, $CDCl_3$): δ = 2.20 (s; 3H, H11),
2.85 - 2.92 (m; 2H, H4, H4'),
3.58 - 3.67 (m; 1H, H3),
3.75 (s; 3H, H19),
3.86 (s; 3H, H18),
4.03 (dd, $^2J_{3'.3}$=14.1 Hz, $^3J_{3'.4'}$=3.1 Hz; 1H, H3'),
6.34 (dd, $^3J_{16.17}$=7.9 Hz, $^4J_{16.14}$=2.5 Hz; 1H, H16),
6.50 (d, $^4J_{14.16}$=2.5 Hz; 1H, H14),
6.86 (d, $^3J_{17.16}$=8.4 Hz; 1H, H17),

7.02 (s; 1H, H1),
7.06 - 7.15 (m; 2H, H6, H7),
7.27 (d, $^3J_{8,7}$=7.7 Hz; 1H, H8),
7.47 (d, $^3J_{5,6}$=7.6 Hz; 1H, H5),
8.51 (s, br; 1H, H9).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 21.7 (q, C11), 22.1 (t, C4), 42.4 (t, C3), 47.6 (d, C1), 55.4, 56.0 (q, C18, C19), 99.4 (d, C14), 104.5 (d, C16), 108.2 (s, C4a), 111.0 (d, C8), 117.9, 119.3 (d, C5, C6), 121.2 (s, C12), 121.7 (d, C7), 126.6 (s, C4b), 128.7 (d, C17), 133.6 (s, C9a), 136.0 (s, C8a), 158.1, 160.5 (s, C13, C15), 170.7 (s, C10).

N-Benzylidene-tryptamine (173)

A solution of tryptamine (3.2 g, 0.02 mol) in ethanol (20 ml) is treated with freshly distilled benzaldehyde (2.35 g, 0.025 mol). After stirring for 2 min a white solid precipitates, which is recrystallised from ethanol. Yield 4.9 g (0.02 mol, 99 %), mp. 121 °C (lit. 118 - 120 °C[203])



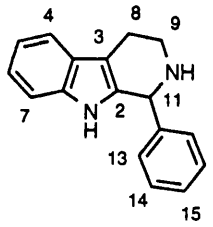
^{1}H nmr (400 MHz, $CDCl_3$): δ = 3.15 (t, $^3J_{8,9}$=7.3 Hz; 2H, H8),
3.92 (dt, $^3J_{9,8}$=7.3 Hz, $^4J_{9,11}$=1.2 Hz; 2H, H9),
6.88 (d, $^3J_{2,1}$=2.2 Hz; 1H, H2),
7.10 (ddd, $^3J_{5,4}$=7.7 Hz, $^3J_{5,6}$=7.0 Hz, $^4J_{5,7}$=1.4 Hz; 1H, H5),
7.16 (ddd, $^3J_{6,5}$=7.0 Hz, $^3J_{6,7}$=8.0 Hz, $^4J_{6,4}$=1.3 Hz; 1H, H6),
7.25 (d, $^3J_{7,6}$=8.0 Hz; 1H, H7),
7.33 - 7.40 (m; 3H, H14, H15),
7.64 (dd, $^3J_{4,5}$=7.6 Hz, $^4J_{4,6}$=0.5 Hz; 1H, H4),
7.67 - 7.70 (m; 2H, H13),
8.12 (s; 1H, H11),
8.21 (s, br; 1H, H1).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 26.8 (t, C8), 62.0 (t, C9), 111.1 (d, C7), 113.7 (s, C3), 118.9, 119.1, 121.3, 122.2 (t, C2, C4, C5, C6), 127.4 (s, C3a), 128.0, 128.6 (d, C13, C14), 130.5 (d, C15), 136.1, 136.2 (s, C7a, C12), 161.6 (s, C11).

Ir (KBr): ν = 3140 cm^{-1} (s; NH), 3060 (m), 1640 (s; C=N), 740 (s), 690 (s).

3-Phenyl-3,4,5,6-tetrahydro-β-carboline (174a)

An ice-cold solution of N-benzylidene-tryptamine (4.9 g, 0.02 mol) in ethanol is treated dropwise with conc. hydrochloric acid (2.6 ml). After heating at 60 °C for 1 h the cooled mixture is washed with ether (20 ml) and poured into 100 ml of a 4N sodium hydroxide solution. The yellow solution is extracted with ether (2x40 ml). Then the ether layer is dried over magnesium sulphate and the solvent is removed by distillation to yield, after trituration with ether, yellow crystals (2.7 g, 11 mmol, 54 %) with mp. 165 °C (lit. 168 °C[203]).

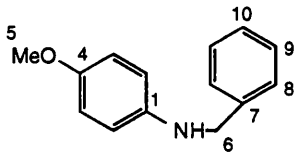


Ir (KBr): ν = 3393, 3285 cm^{-1} (m, br; NH), 3165 (m; NH), 3052 (m), 740 (s), 697 (s).

Ms (EI, 70 eV): m/z (%) = 249 (19, M^++1), 248 (88, M^+), 220 (25, M^+-CH_2N), 219 (97, M^+-CH_2NH), 218 (100), 171 (80, M^+-C_6H_5), 144 (17, M^+-C_6H_5CHN), 115 (17, M^+-$C_2H_4C_6H_5CHN$).

N-Benzyl-4-anisidine (176)

At 50 °C, sodium borohydride (6.5 g, 0.17 mol) is added to a stirred solution of N-benzylidene-4-methoxy-aniline (17.9 g, 0.08 mol) in methanol. The mixture is heated on a steam bath for 1 h and is then poured into 500 ml of ice-water to precipitate a pale brown solid (15.8 g, 0.15 mol, 87 %; mp. 45 - 49 °C (lit. 46.5 - 47 °C[211]), which is soluble in dil. hydrochloric acid. The amine is of sufficient purity for the following Bischler reaction.

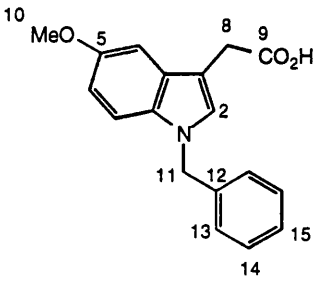


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.77 (s; 3H, H5),
4.31 (s; 2H, H6),
4.88 (s, br; 1H, NH),
6.64 (d, ^{3}J=6.6 Hz; 2H, H2 or H3),
6.81 (d, ^{3}J=6.7 Hz; 2H, H2 or H3),
7.30 - 7.41 (m; 5H, H8, H9, H10).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 49.1 (t, C6), 55.7 (q, C5), 114.0 (d, C2 or C3), 114.8 (d, C2 or C3), 127.1 (d), 127.5 (d), 128.5 (d), 139.6 (s, C7), 142.4 (s), 152.1 (s, C4).

N-Benzyl-5-methoxy-indole-3-acetic acid (180)

N-Benzyl-4-anisidine (14.1 g, 0.07 mol) is reacted with γ-bromo-acetoacetate (6.9 g, 0.035 mol) and zinc chloride (10 g) according to procedure VIII.2.2 to obtain a black oil. The crude indole-3-acetate is dissolved in methanol (100ml) and is saponified according to procedure VIII.2.3 to yield 4.9 g (16 mmol, 46 %) of a pale brown solid, mp. 125 - 127 °C (lit. 128 - 129 °C[157]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.90 (s; 2H, H8),
3.86 (s; 3H, H10),
5.25 (s; 2H, H11),
6.86 (dd, $^4J_{6,4}$=2.0 Hz, $^3J_{6,7}$=9.1 Hz; 1H, H6),
7.00 (d, $^4J_{4,6}$=2.2 Hz; 1H, H4),
7.05 (s; 1H, H2),
7.11 - 7.15 (m; 2H, H13),
7.16 (d, $^3J_{7,6}$=8.5 Hz; 1H, H7),
7.20 - 7.33 (m; 3H, H14, H15).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 31.2 (t, C8), 50.1 (t, C11), 55.6 (q, C10), 100.3 (d), 106,6 (s, C3), 110.8 (d), 112.8 (d), 126.9 (d, C13 or C14), 127.5 (d), 127.9 (s), 128.1 (d, C15), 128.9 (d, C13 or C14), 131.8 (s), 137.1 (s, C12), 154.3 (s, C5), 182.4 (s, C9).

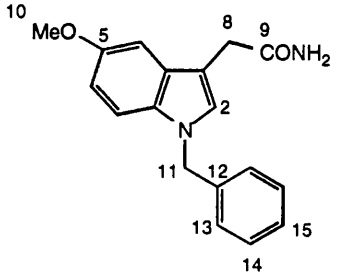
MS (EI, 70 eV): m/z = 297 (M^+, 8), 250 (M^+-COOH, 95), 159 (M^+-COOH-$CH_2C_6H_5$, 100).

Ir (KBr): ν = 3415 (m, br, OH), 2936 (m), 1697 (s, C=O), 1216 (m, C-O).

CHN $C_{18}H_{19}NO_3$ calc. C 72.70 H 6.44 N 4.71
found C 71.75 H 6.57 N 4.66

3-Acetamide-N-benzyl-5-methoxy-indole (181)

A solution of N-benzyl-5-methoxy-indole-3-acetic acid (4.9 g, 16.5 mmol) in dichloromethane (30 ml) is treated with triethylamine (1.7 g, 16.5 mmol), methyl chloroformate (1.6 g, 16.5 mmol) and ammonia according to procedure VIII.2.4 to yield a brown solid, which is purified by SPC (5 % MeOH in dichloromethane) to give 2.2 g (7.4 mmol, 45 %) of the amide with mp. 146 - 148 °C (lit. 156 - 157 °C[157]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.71 (s; 2H, H8),
3.85 (s; 3H, H10),
5.27 (s; 2H, H11),
5.63 (s, br; 1H, NH),
5.71 (s, br; 1H, NH),
6.88 (dd, $^4J_{6,4}$=2.1 Hz, $^3J_{6,7}$=9.0 Hz; 1H, H6),
7.01 (d, $^4J_{4,6}$=2.2 Hz; 1H, H4),
7.07 (s; 1H, H2),
7.11 - 7.13 (m; 2H, H13),
7.18 (d, $^3J_{7,6}$=8.7 Hz; 1H, H7),
7.22 - 7.34 (m; 3H, H14, H15).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 33.0 (t, C8), 50.2 (t, C11), 55.8 (q, C10), 100.3 (d), 107.9 (s, C4a), 110.9 (d), 112.8 (d), 126.8 (d, C13 or C14), 127.8 (d), 127.9 (s), 128.0 (d, C15), 128.8 (d, C13 or C14), 132.0 (s), 137.1 (s, C12), 154.4 (s, C5), 174.2 (s, C9).

MS (EI, 70 eV): m/z = 294 (M^+, 65), 250 (M^+-$CONH_2$, 100), 159 (M^+-COOH-$CH_2C_6H_5$, 100).

Ir (KBr): ν = 3373 (s,br, NH), 2941 (m), 1641 (s, C=O), 1488 (m), 1381 (m), 1214 (m, C-O).

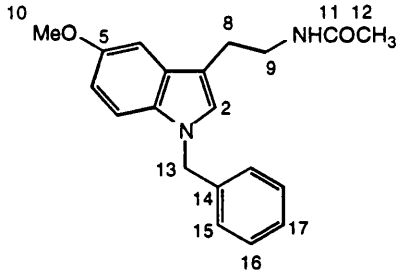
CHN $C_{18}H_{18}N_2O_2$ calc. C 73.45 H 6.16 N 9.51
found C 73.01 H 6.39 N 9.16

N-Benzyl-5-methoxy-tryptamine (182)

3-Acetamide-N-benzyl-5-methoxy-indole (2.2 g, 7.5 mmol) is reduced with lithium aluminium hydride (0.9 g) in THF (150 ml) according to procedure A, VIII.2.5 to give 1.4 g (5.0 mmol, 67 %) of a yellow oil, which is of sufficient purity for the subsequent acylation.

N-Benzyl-melatonin (183a)

A solution of N-benzyl-5-methoxy-tryptamine (0.60 g, 2.1 mmol) in dichloromethane (20 ml) and triethylamine (5 ml) is reacted with acetic anhydride (0.20 g) according to procedure A, VIII.2.6 to give, after SPC with dichloromethane containing 1 % of methanol, a colourless solid (0.3 g, 0.9 mmol, 44 %) with mp. 105 - 106 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.89 (s; 3H, H12),
2.92 (t, $^3J_{8.9}$=7.0 Hz; 2H, H8),
3.54 (dt, $^3J_{9.8}$=6.8 Hz, $^3J_{9.NH}$=6.2 Hz; 2H, H9),
3.83 (s; 3H, H10),
5.19 (s; 2H, H13),
5.85 (s,br; 1H, NH),
6.83 (dd, $^4J_{6.4}$=2.2 Hz, $^3J_{6.7}$=9.0 Hz; 1H, H6),
6.91 (s; 1H, H2),
7.05 (d, $^3J_{15.16}$=5.9 Hz; 2H, H15),
7.08 (d, $^4J_{4.6}$=0.9 Hz; 1H, H4),
7.13 (d, $^3J_{7.6}$=8.8 Hz; 1H, H7),
7.22 - 7.29 (m; 3H, H16, H17).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.2 (q, C12), 25.1 (t, C8), 39.7 (t, C9), 49.9 (t, C13), 55.7 (q, C10), 100.5 (d), 110.5 (d), 111.5 (s, C4a), 112.0 (d), 126.6 (d, C15 or C16), 127.5 (d), 128.2 (s), 128.4 (d, C17), 128.6 (d, C15 or C16), 131.8 (s), 137.5 (s, C14), 153.8 (s, C5), 170.0 (s, C11).

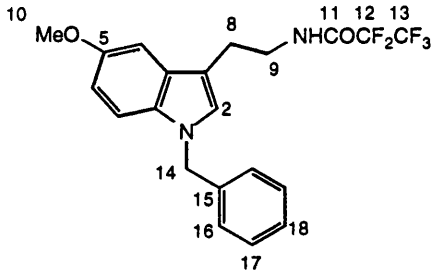
MS (EI, 70 eV): m/z = 322 (M^+, 10), 263 (M^+-NH_2COCH_3, 90), 172 (M^+-NH_2COCH_3-$CH_2C_6H_5$, 100), 159 (M^+-$CH_2NHCOCH_3$-$CH_2C_6H_5$, 100).

Ir (KBr): ν = 3299 (s, NH), 2912 (m), 1645 (s, C=O), 1485 (s), 1228 (s), 1041 (s).

CHN $C_{20}H_{22}N_2O_2$ calc. C 74.50 H 6.88 N 8.69
found C 74.33 H 6.83 N 8.50

N'-Benzyl-5-methoxy-N-pentafluoropropanoyl-tryptamine (183b)

A solution of N-benzyl-5-methoxy-tryptamine (0.6 g, 2.1 mmol) in methanol (20 ml) is reacted with ethyl pentafluoropropionate (0.4 g) according to procedure C, VIII.2.6 to give, after SPC with dichloromethane, a colourless oil (0.7 g, 1.6 mmol, 78 %) which crystallised after trituration with ether. Mp. 105.5 - 106 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.05 (t, $^3J_{8,9}$=6.7 Hz; 2H, H8),
3.72 (dt, $^3J_{9,8}$=6.5 Hz, $^3J_{9,NH}$=6.4 Hz; 2H, H9),
3.89 (s; 3H, H10),
5.26 (s; 2H, H14),
6.80 (s,br; 1H, NH)
6.91 (dd, $^4J_{6,4}$=2.2 Hz, $^3J_{6,7}$=8.8 Hz; 1H, H6),
6.96 (s; 1H, H2),
7.08 (d, $^4J_{4,6}$=0.9 Hz; 1H, H4),
7.14 (d, $^3J_{15,16}$=7.3 Hz; 2H, H16),
7.21 (d, $^3J_{7,6}$=8.9 Hz; 1H, H7),
7.26 - 7.38 (m; 3H, H17, H18).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 24.6 (t, C8), 40.1 (t, C9), 50.0 (t, C14), 55.8 (q, C10), 100.4 (d), 110.2 (s, C4a), 110.8 (d), 112.3 (d), 114.8 (d, $J_{C,F}$=266 Hz (t), C12), 126.7 (d, C16 or C17), 127.1 (d, (m) C13), 127.6 (d), 127.9 (s), 128.6 (d, C18), 128.7 (d, C16 or C17), 132.1 (s), 137.3 (s, C14), 154.0 (s, C5), 157.5 (s, C11).

MS (FAB, 70 eV): m/z = 426 (M^+, 100), 172 (M^+-$NH_2COC_2F_5$-$CH_2C_6H_5$, 20).

Ir (KBr): ν = 3286 (s, NH), 2910 (m), 1692 (s, C=O), 1485 (s), 1231 (s), 1157 (s).

CHN $C_{21}H_{19}N_2O_2F_5$ calc. C 59.15 H 4.49 N 6.57
found C 58.42 H 4.35 N 6.59

Attempted debenzylation of N'-benzyl-5-methoxy-N-pentafluoro-propanoyl-tryptamine (183b)

- Procedure A

A solution of N'-benzyl-5-methoxy-N-pentafluoropropanoyl-tryptamine (0.3 g, 0.7 mmol) in methanol or methanol containing 1 % acetic acid is shaken with 10 % palladium-on-carbon (0.2 g)

under hydrogen (60 psi) for 2 d at 25 °C. Filtration through celite and evaporation of the solvent gives the starting material.

- Procedure B

A suspension of N'-benzyl-5-methoxy-N-pentafluoropropanoyl-tryptamine (0.3 g, 0.7 mmol) and aluminium trichloride (0.5 g) in benzene (20 ml) is stirred for 1 h at 25 °C. Filtration of the inorganic salts and washing of the benzene solution with brine (20 ml) gives, after evaporation of the solvent, the starting material.

- Procedure C

A solution of N'-benzyl-5-methoxy-N-pentafluoropropanoyl-tryptamine (0.3 g, 0.7 mmol) in THF (5 ml) is added to a solution of sodium (0.5 g) in liquid ammonia (20 ml) at - 40 °C. The mixture is stirred at - 40 °C for 6 h, then the ammonia is evaporated and water is carefully added. After extraction with ethyl acetate, evaporation of the solvent yields the starting material.

N-Benzylidene-4-methoxy-aniline (185)

A mixture of benzaldehyde (10.6 g, 0.1 mol) and *p*-anisidine (12.3 g, 0.1 mol) is heated on a steam bath for 30 min. After cooling to 25 °C, the mixture is treated with ether (150 ml) and the organic layer is washed with dil. acetic acid (20 ml) and brine (20 ml). Then the solution is dried over magnesium sulphate and the solvent is removed by distillation to yield 17.6 g (83 mmol, 83 %) of a brown solid, which is recrystallised from methanol. Mp. 69 - 69.5 °C (lit. 70 - 71 °C[210]).

Ir (KBr): ν = 1618 (s, C=N), 1498 (s), 1244 (s), 1027 (s).

Ethyl 4-bromo-2-methyl-3-oxo-butyrate (186a)

At 0 °C, a solution of ethyl 2-methyl-3-oxo-butyrate (28.0 g, 0.2 mol) in ether (100 ml) is treated with bromine (32.0 g, 0.2 mol) according to procedure VIII.2.1 to give 38.9 g (180 mmol, 89 %) of a pale yellow liquid.

Ethyl 4-bromo-2,2-dimethyl-3-oxo-butyrate (186b)

At 0 °C, a solution of ethyl 2,2-dimethyl-3-oxo-butyrate (15.8 g, 0.1 mol) in ether (100 ml) is treated with bromine (15.9 g, 0.1 mol) according to procedure VIII.2.1 to give 19.1 g (81 mmol, 81 %) of a pale yellow liquid.

Ethyl 1-bromoacetyl-cyclopentane-1-carboxylate (186c)

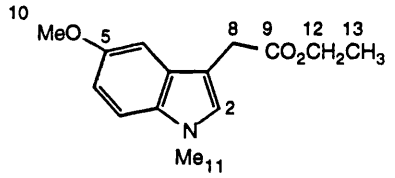
At 0 °C, a solution of ethyl 1-acetyl-cyclopentane-1-carboxylate (21.2 g, 0.11 mol) in ether (100 ml) is treated with bromine (18.4 g, 0.11 mol) according to procedure VIII.2.1 to give 29.0 g (0.11 mol, 98 %) of a colourless liquid.

Ethyl 1-bromoacetyl-cyclopropane-1-carboxylate (186d)

At 0 °C a solution of ethyl 1-acetyl-cyclopropane-1-carboxylate (5.2 g, 33 mmol) in ether (30 ml) is treated with bromine (5.3 g, 33 mmol) according to procedure VIII.2.1 to give 8.0 g (33 mmol, 98 %) of a brown liquid.

2-(3-(N-Methyl-5-methoxyindolyl))acetic acid (187a)

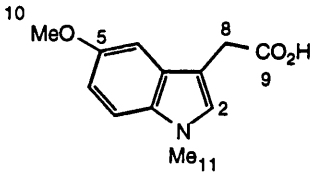
N-Methyl-*p*-anisidine (27.0 g, 0.2 mol) is reacted with ethyl γ-bromo-acetoacetate (20.6 g, 0.1 mol) and zinc chloride (15 g) according to procedure VIII.2.2 to give 22.0 g (44 mmol, 44 %) of crude ethyl 2-(3-(N-methyl-5-methoxy-indolyl))acetate as a brown oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{13.12}$=7.2 Hz; 3H, H13),
3.72 (s; 2H, H8),
3.73 (s; 3H, H11),
3.87 (s; 3H, H10),
4.17 (q, $^3J_{12.13}$=7.2 Hz; 2H, H12),
6.88 (dd, $^4J_{6.4}$=2.5 Hz, $^3J_{6.7}$=9.0 Hz; 1H, H6),
7.02 (s; 1H, H2),
7.06 (d, $^4J_{4.6}$=2.3 Hz; 1H, H4),
7.18 (d, $^3J_{7.6}$=8.7 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.2 (q, C13), 31.4 (t, C8), 32.8 (q, C11), 55.9 (q, C10), 60.7 (t, C12), 100.7 (d), 106.3 (s, C3), 110.0 (d), 112.0 (d), 128.1 (s), 128.2 (d), 132.3 (s), 153.9 (s, C5), 172.1 (s, C9).

A solution of the crude ester (5.5 g, 22 mmol) in methanol (50 ml) is saponified with 10 % sodium hydroxide solution according to procedure VIII.2.3 to give 2.5 g (11.4 mmol, 52 %) of a brown solid, mp. 139 - 140 °C (lit. 139 - 140 °C[157]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.71 (s; 3H, H11),
3.74 (s; 2H, H8),
3.83 (s; 3H, H10),
6.88 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=9.0 Hz; 1H, H6),
7.00 (s; 1H, H2),
7.00 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.17 (d, $^3J_{7,6}$=8.7 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 30.9 (t, C8), 32.9 (q, C11), 55.9 (q, C10), 100.6 (d), 105.5 (s, C4a), 110.2 (d), 112.3 (d), 127.8 (s), 128.5 (d), 132.3 (s), 154.1 (s, C5), 172.3 (s, C9).

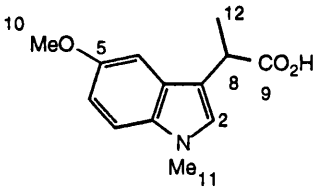
MS (EI, 70 eV): m/z = 219 (M^+, 32), 174 (M^+-COOH, 100).

Ir (KBr): ν = 3419 (m, br, OH), 2925 (m), 1692 (s, C=O), 1221 (m, C-O).

CHN $C_{12}H_{13}NO_3$ calc. C 65.74 H 5.98 N 6.39
found C 64.89 H 6.05 N 6.24

2-(3-(N-Methyl-5-methoxyindolyl))propanoic acid (187b)

N-Methyl-*p*-anisidine (15.5 g, 0.11 mol) is reacted with ethyl 4-bromo-2-methyl-3-oxo-butyrate (12.1 g, 0.055 mol) and zinc chloride (16 g) according to procedure VIII.2.2 to give a brown oil. A solution of the crude ester in methanol (50 ml) is saponified with 10 % sodium hydroxide solution according to procedure VIII.2.3 to give 5.2 g (44 mmol, 40 %) of a yellow solid, mp. 118 - 120 °C (lit. 123 - 124 °C[154]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.62 (d, $^3J_{12,8}$=7.1 Hz; 3H, H12),
3.70 (s; 3H, H11),
3.86 (s; 3H, H10),
4.00 (q, $^3J_{8,12}$=7.1 Hz; 1H, H8),
6.91 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=8.7 Hz; 1H, H6),
6.99 (s; 1H, H2),
7.14 (d, $^4J_{4,6}$=2.4 Hz; 1H, H4),
7.18 (d, $^3J_{7,6}$=8.7 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 17.4 (q, C12), 32.8 (q, C11), 36.8 (d, C8), 55.8 (q, C10), 101.0 (d), 110.1 (d), 112.1 (d), 112.5 (s, C3), 126.9 (d), 127.0 (s), 132.3 (s), 153.8 (s, C5), 181.4 (s, C9).

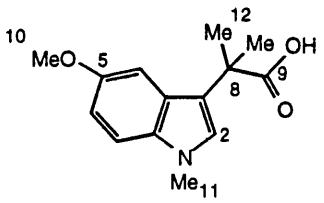
MS (EI, 70 eV): m/z = 233 (M^+, 20), 188 (M^+-COOH, 100).

Ir (KBr): ν = 3408 (m, br, OH), 2919 (m), 1695 (s, C=O), 1223 (m, C-O).

CHN $C_{13}H_{15}NO_3$ calc. C 66.93 H 6.48 N 6.01
found C 66.72 H 6.62 N 5.90

2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))-propanoic acid (187c)

N-Methyl-*p*-anisidine (21.9 g, 0.16 mol) is reacted with ethyl 4-bromo-2,2-dimethyl-3-oxo-butyrate (19.2 g, 0.08 mol) and zinc chloride (25 g) according to procedure VIII.2.2 to give a brown oil (10 g). A solution of the crude ester in methanol (50 ml) is saponified with 10 % sodium hydroxide solution according to procedure VIII.2.3 to give 5.9 g (24 mmol, 30 %) of a pale brown solid, mp. 78 - 81 °C (lit. 80.5 - 82 °C[154]).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.67 (s; 6H, H12),
3.71 (s; 3H, H11),
3.76 (s; 3H, H10),
6.86 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
6.92 (s; 1H, H2),
7.11 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.16 (d, $^3J_{7,6}$=8.9 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 25.8 (q, C12), 32.9 (q, C11), 41.8 (s, C8), 55.8 (q, C10), 102.3 (d, C2), 110.2 (d), 111.8 (d), 117.6 (s, C3), 126.1 (s), 126.1 (d), 132.9 (s), 153.6 (s, C5), 180.3 (s, C9).

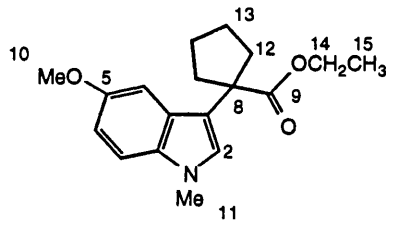
MS (EI, 70 eV): m/z = 247 (M^+, 5), 202 (M^+-COOH, 100).

Ir (KBr): ν = 3423 (m, br, OH), 2923 (m), 1698 (s, C=O), 1220 (m, C-O).

CHN $C_{14}H_{17}NO_3$ calc. C 67.99 H 6.93 N 5.67
found C 67.72 H 6.90 N 5.60

1-(3-(N-Methyl-5-methoxyindolyl))cyclopentane-1-carboxylic acid (187d)

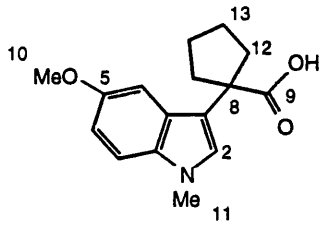
N-Methyl-*p*-anisidine (13.7 g, 0.1 mol) is reacted with ethyl 1-bromoacetyl-cyclopentane-1-carboxylate (13.1 g, 0.05 mol) and zinc chloride (15 g) according to procedure VIII.2.2 to give 14.5 g (48 mmol, 96 %) of crude ethyl 2-(3-(N-methyl-5-methoxyindolyl))acetate as a brown oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.16 (t, $^3J_{15,14}$=7.1 Hz; 3H, H15),
1.73 - 1.77 (m; 2H, H12 or H13),
2.04 - 2.10 (m; 1H, H12 or H13),
2.64 - 2.67 (m; 1H, H12 or H13),
3.68 (s; 3H, H11),
3.85 (s; 3H, H10),
4.09 (t, $^3J_{6,7}$=7.1 Hz, 2H, H14),
6.87 (dd, $^4J_{6,4}$=2.4 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
6.91 (s; 1H, H2),
7.14 (d, $^3J_{7,6}$=8.7 Hz; 1H, H7),
7.20 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.1 (q, C15), 23.8 (t, C13), 32.8 (q, C11), 35.9 (t, C12), 53.5 (s, C8), 55.8 (q, C10), 60.6 (t, C14), 102.6 (d, C2), 109.8 (d), 111.6 (d), 116.7 (s, C3), 126.4 (s), 126.8 (d), 132.7 (s), 153.4 (s, C5), 176.3 (s, C9).

A solution of the crude ester (14.5 g, 48 mmol) in methanol (100 ml) is saponified with 10 % sodium hydroxide solution according to procedure VIII.2.3 to give 7.1 g (26 mmol, 54 %) of a pale brown amorphous solid, mp. 60 - 70 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.75 (m; 2H, H12 or H13),
2.06 - 2.09 (m; 1H, H12 or H13),
2.63 - 2.67 (m; 1H, H12 or H13),
3.70 (s; 3H, H11),
3.80 (s; 3H, H10),
6.86 - 6.89 (m; 1H, H6),
6.93 (s; 1H, H2),
7.15 - 7.17 (m; 2H, H4, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.9 (t, C13), 32.9 (q, C11), 35.8 (t, C12), 53.3 (s, C8), 55.8 (q, C10), 102.7 (d, C2), 110.0 (d), 111.8 (d), 116.0 (s, C3a), 126.7 (s, C7a), 126.7 (d), 132.8 (s), 153.5 (s, C5), 182.4 (s, C9).

MS (EI, 70 eV): m/z = 273 (M^+, 17), 228 (M^+-COOH, 100).

Ir (KBr): ν = 3430 (m, br, OH), 2929 (m), 1715 (s, C=O), 1218 (m, C-O).

CHN $C_{16}H_{19}NO_3$ calc. C 70.31 H 7.01 N 5.13
found C 69.91 H 6.94 N 5.00

1-(3-(N-Methyl-5-methoxyindolyl))cyclopropane-1-carboxylic acid (187e)

N-Methyl-*p*-anisidine (9.3 g, 68 mmol) is reacted with ethyl 1-bromoacetyl-cyclopropane-1-carboxylate (8.2 g, 34 mmol) and zinc chloride (10 g) according to procedure VIII.2.2 to give a black solid insoluble in acetone, ethyl acetate and methanol.

2-(3-(N-Methyl-5-methoxyindolyl))acetamide (188a)

- Attempt A:

Following the method described in VIII.2.4, 2-(3-(N-methyl-5-methoxyindolyl))acetic acid (2.4 g, 11 mmol) is reacted with triethylamine (1.1 g, 11 mmol) and methyl chloroformate (1.0 g, 11 mmol) in dichloromethane. The starting material was recovered.

- Attempt B:

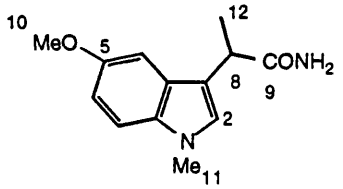
A solution of 2-(3-(N-methyl-5-methoxyindolyl))acetic acid (2.2 g, 11 mmol) in THF (20 ml) is added dropwise to a suspension of sodium hydride (0.3 g, 11 mmol) in THF (20 ml). After 20 min at 25 °C methyl chloroformate (1.0 g, 11 mmol) is added at 0 °C. The further method follows procedure VIII.2.4 to give the starting material.

- Attempt C:

Under argon a mixture of 2-(3-(N-methyl-5-methoxyindolyl))acetic acid (2.2 g, 11 mmol) and urea (8.0 g) is heated to 150 °C for 30 min. The hot viscous reaction mixture is poured into water to yield a black solid, insoluble in acetone or methanol.

2-(3-(N-Methyl-5-methoxyindolyl))propanamide (188b)

Following the method described in VIII.2.4, 2-(3-(N-methyl-5-methoxy-indolyl))propanoic acid (5.1 g, 22 mmol) is reacted with triethylamine (2.2 g, 22 mmol) and methyl chloroformate (2.1 g, 22 mmol) in dichloromethane to obtain 3.5 g (15 mmol, 68 %) of an amorphous solid, mp. 80 - 89 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.63 (d, $^3J_{12,8}$=7.3 Hz; 3H, H12),
3.74 (s; 3H, H11),
3.82 (q, $^3J_{8,12}$=7.0 Hz; 1H, H8),
3.84 (s; 3H, H10),
5.62 - 5.68 (s,br; 2H, NH_2),
6.91 (dd, $^4J_{6,4}$=2.4 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
6.98 (s; 1H, H2),
7.02 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.20 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 17.7 (q, C12), 32.9 (q, C11), 38.1 (d, C8), 55.9 (q, C10), 100.7 (d), 110.3 (d), 112.4 (d), 113.9 (s, C3), 126.9 (s), 127.0 (d), 132.5 (s), 154.0 (s, C5), 177.8 (s, C9).

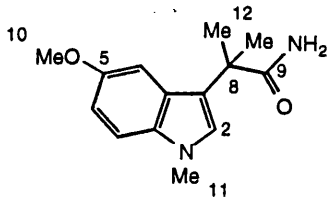
MS (EI, 70 eV): m/z = 232 (M^+, 63), 188 (M^+-$CONH_2$, 100), 97 (72).

Ir (KBr): ν = 3410 (s,br, NH), 2939 (m), 1650 (s, C=O), 1492 (m), 1228 (m, C-O).

CHN $C_{13}H_{16}N_2O_2$ calc. C 67.22 H 6.94 N 12.06
found C 67.08 H 6.65 N 11.98

2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))-propanamide (188c)

Following the method described in VIII.2.4, 2-methyl-2-(3-(N-methyl-5-methoxy-indolyl))propanoic acid (2.0 g, 8 mmol) is reacted with triethylamine (0.80 g, 8 mmol) and methyl chloroformate (0.8 g, 80 mmol) in dichloromethane to obtain 1.3 g (5.3 mmol, 66 %) of an amorphous solid, mp. 43 - 51 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.66 (s; 6H, H12),
3.75 (s; 3H, H11),
3.82 (s; 3H, H10),
5.55 (t, br; 1H, NH),
5.63 (t, br; 1H, NH),
6.91 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
6.97 (s; 1H, H2),
7.01 (d, $^4J_{4,6}$=2.4 Hz; 1H, H4),
7.21 (d, $^3J_{7,6}$=8.9 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.6 (q, C12), 32.9 (q, C11), 42.1 (s, C8), 55.9 (q, C10), 102.2 (C2), 110.2 (d), 112.2 (d), 118.8 (s, C3), 125.9 (s, C7a), 126.4 (d), 133.0 (s), 153.7 (s, C5), 180.3 (s, C9).

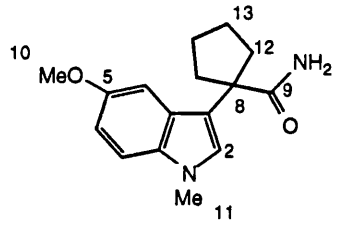
MS (EI, 70 eV): m/z = 246 (M^+, 40), 176 (M^+-$CONH_2$, 100), 97 (52).

Ir (KBr): ν = 3408 (s,br, NH), 2946 (m), 1649 (s, C=O), 1490 (m), 1225 (m, C-O).

CHN	$C_{14}H_{18}N_2O_2$	calc.	C 68.27 H 7.37 N 11.38
		found	C 68.01 H 7.29 N 11.28

1-(3-(N-Methyl-5-methoxyindolyl))-cyclopentane-1-carboxamide (188d)

Following the method described in VIII.2.4, 1-(3-(N-methyl-5-methoxyindolyl))-cyclopentane-1-carboxylic acid (7.0 g, 26 mmol) is reacted with triethylamine (2.6 g, 26 mmol) and methyl chloroformate (2.4 g, 26 mmol) in dichloromethane to obtain 4.7 g (17 mmol, 66 %) of an amorphous solid, mp. 63 - 74 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.63 - 1.68 (m; 1H, H12 or H13),
1.81 - 1.85 (m; 1H, H12 or H13),
2.11 - 2.17 (m; 1H, H12 or H13),
2.42 - 2.49 (m; 1H, H12 or H13),
3.73 (s; 3H, H11),
3.80 (s; 3H, H10),
5.27 (s, br; 1H, NH),
5.47 (s, br; 1H, NH),
6.86 (dd, $^4J_{6.4}$=2.4 Hz, $^3J_{6.7}$=8.8 Hz; 1H, H6),
6.93 (s; 1H, H2),
6.97 (d, $^4J_{4.6}$=2.3 Hz; 1H, H4),
7.17 (d, $^3J_{7.6}$=8.9 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 24.7 (t, C13), 32.9 (q, C11), 36.9 (t, C12), 53.0 (s, C8), 55.9 (q, C10), 102.1 (d, C2), 110.2 (d), 112.4 (d), 117.3 (s, C3), 126.4 (s), 126.7 (d), 133.1 (s), 153.8 (s, C5), 180.0 (s, C9).

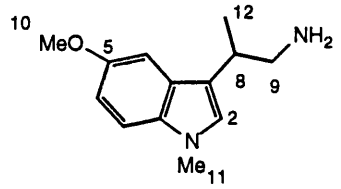
MS (EI, 70 eV): m/z = 272 (M^+, 40), 202 (M^+-$CONH_2$, 100), 65 (38).

Ir (KBr): ν = 3404 (s,br, NH), 2948 (m), 1658 (s, C=O), 1498 (m), 1216 (m, C-O).

CHN	$C_{16}H_{20}N_2O_2$	calc.	C 70.56 H 7.40 N 10.29
		found	C 70.40 H 7.28 N 10.23

2-(3-(N-Methyl-5-methoxyindolyl))propanamine (189a)

2-(3-(N-Methyl-5-methoxyindolyl))propanamide (2.5 g, 11 mmol) is reduced with lithium aluminium hydride (3.0 g) as described in VIII.2.5, procedure A. The product (1.0 g, 4.6 mmol, 42 %) is a yellow oil which is directly used for the subsequent acylation.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.32 (d, $^3J_{12,8}$=6.9 Hz; 3H, H12),
2.81 - 2.95 (m; 2H, H9),
3.01 - 3.04 (m; 1H, H8),
3.69 (s; 3H, H11),
3.84 (s; 3H, H10),
6.81 (s; 1H, H2),
6.86 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=8.7 Hz; 1H, H6),
7.05 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.16 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 18.7 (q, C12), 32.7 (q, C11), 34.3 (d, C8), 48.5 (t, C9), 55.9 (q, C10), 101.2 (d), 109.9 (d), 111.5 (d), 112.3 (s, C3), 126.1 (d), 126.9 (s), 132.5 (s), 153.4 (s, C5).

2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (189b)

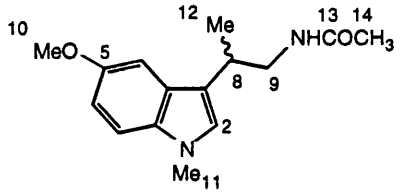
2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))-propanamide (1.3 g, 5.3 mmol) is reduced with lithium aluminium hydride (1.5 g) as described in VIII.2.5, procedure A. The product (1.2 g, 5.1 mmol, 98 %) is a yellow oil which is directly used for the subsequent acylation.

1-(3-(N-Methyl-5-methoxyindolyl))-1-aminomethyl-cyclopentane (189c)

1-(3-(N-Methyl-5-methoxyindolyl))-cyclopentane-1-carboxamide (4.5 g, 17 mmol) is reduced with lithium aluminium hydride (2.0 g) as described in VIII.2.5, procedure A. The product (2.9 g, 11 mmol, 67 %) is a yellow oil which is directly used for the subsequent acylation.

N-Acetyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (190a)

2-(3-(N-Methyl-5-methoxyindolyl))propanamine (0.40 g, 1.8 mmol) is treated with acetic anhydride (0.2 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1.5 % MeOH) the product is obtained in 54 % yield (1.0 mmol, 0.25 g). Mp. 45 - 47 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.31 (d, $^3J_{12,8}$=7.0 Hz; 3H, H12),
1.86 (s; 3H, H14),
3.18 - 3.22 (m; 1H, H8),
3.41 - 3.48 (m; 2H, H9),
3.62 (s; 3H, H11),
3.80 (s; 3H, H10),
6.39 (t, br; 1H, NH),
6.78 (s; 1H, H2),
6.83 (dd, $^4J_{6,4}$=2.2 Hz, $^3J_{6,7}$=9.0 Hz; 1H, H6),
7.09 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.10 (d, $^3J_{7,6}$=8.7 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 18.4 (q, C12), 22.6 (q, C14), 30.5 (d, C8), 32.3 (q, C11), 45.5 (t, C9), 55.4 (q, C10), 100.7 (d), 109.7 (d), 111.3 (d), 116.4 (s, C3), 125.5 (d), 127.0 (s), 132.1 (s), 153.2 (s, C5), 170.3 (s, C13).

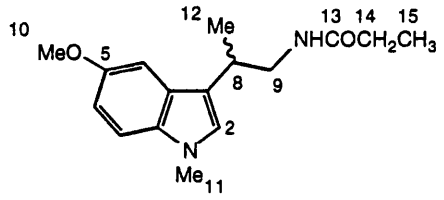
MS (EI, 70 eV): m/z = 260 (M^+, 31), 201 (M^+-NH_2COCH_3, 100).

Ir (KBr): ν = 3305 (s, NH), 2943 (m), 1639 (s, C=O), 1498 (m), 1218 (m, C-O).

CHN $C_{15}H_{20}N_2O_2$ calc. C 69.20 H 7.74 N 10.76
found C 69.09 H 7.58 N 10.35

N-Propanoyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (190b)

2-(3-(N-Methyl-5-methoxyindolyl))propanamine (0.40 g, 1.8 mmol) is treated with propanoic anhydride (0.25 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained as a yellow oil in 60 % yield (1.1 mmol, 0.30 g).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.05 (t, $^3J_{15,14}$=7.6 Hz; 3H, H15),
1.31 (d, $^3J_{12,8}$=7.0 Hz; 3H, H12),
2.07 (q, $^3J_{14,15}$=7.0 Hz; 2H, H14),
3.20 - 3.30 (m; 1H, H8),
3.52 - 3.65 (m; 2H, H9),
3.67 (s; 3H, H11),
3.81 (s; 3H, H10),
5.23 (t, br; 1H, NH),
6.80 (s; 1H, H2),
6.85 (dd, $^4J_{6,4}$=2.4 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
7.06 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.14 (d, $^3J_{7,6}$=9.0 Hz; 1H, H7).

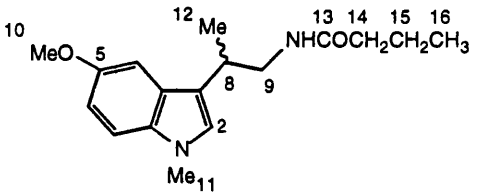
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.7 (q, C15), 18.7 (q, C12), 29.5 (t, C14), 30.8 (d, C8), 32.6 (q, C11), 45.5 (t, C9), 55.8 (q, C10), 100.9 (d), 109.9 (d), 111.7 (d), 116.7 (s, C3), 125.8 (d), 127.2 (s), 132.4 (s), 153.5 (s, C5), 173.6 (s, C13).

MS (EI, 70 eV): m/z = 274 (M^+, 15), 201 (M^+-$NH_2COC_2H_5$, 100).

Ir (film): ν = 3289 (s, NH), 2940 (m), 1651 (s, C=O), 1494 (m), 1210 (m, C-O).

N-Butanoyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (190c)

2-(3-(N-Methyl-5-methoxyindolyl))propanamine (0.40 g, 1.8 mmol) is treated with butanoic anhydride (0.3 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 0.5 % MeOH) the product is obtained as a yellow oil in 70 % yield (1.3 mmol, 0.36 g).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{16,15}$=8.4 Hz; 3H, H16),
1.31 (d, $^3J_{12,8}$=7.0 Hz; 3H, H12),
1.52 - 1.61 (m; 2H, H15),
2.03 (t, $^3J_{14,15}$=7.0 Hz; 2H, H14),
3.17 - 3.22 (m; 1H, H8),
3.42 - 3.53 (m; 2H, H9),
3.67 (s; 3H, H11),
3.82 (s; 3H, H10),
5.78 (t, br; 1H, NH),
6.80 (s; 1H, H2),
6.85 (dd, $^4J_{6,4}$=2.4 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
7.07 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.14 (d, $^3J_{7,6}$=8.9 Hz; 1H, H7).

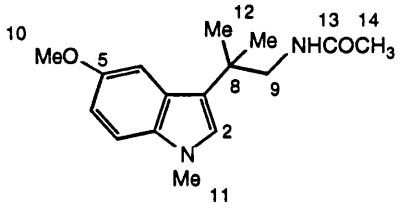
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6 (q, C16), 18.4 (q, C12), 20.6 (t, C15), 29.5 (t, C14), 30.5 (d, C8), 32.3 (q, C11), 45.5 (t, C9), 55.4 (q, C10), 100.7 (d), 109.7 (d), 111.3 (d), 116.4 (s, C3), 125.5 (d), 127.0 (s), 132.1 (s), 153.2 (s, C5), 172.6 (s, C13).

MS (EI, 70 eV): m/z = 288 (M^+, 4), 201 (M^+-$NH_2COC_3H_7$, 100).

Ir (film): ν = 3283 (s, NH), 2943 (m), 1655 (s, C=O), 1493 (m), 1210 (s, C-O).

N-Acetyl-2-methyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (191a)

2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (0.20 g, 0.9 mmol) is treated with acetic anhydride (0.1 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 83 % yield (0.74 mmol, 0.20 g), mp. 32 - 35 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.39 (s; 6H, H12),
1.84 (s; 3H, H14),
3.61 (d, $^3J_{9,NH}$=5.9 Hz; 2H, H9),
3.71 (s; 3H, H11),
3.84 (s; 3H, H10),
5.18 (t, br; 1H, NH),
6.80 (s; 1H, H2),
6.89 (dd, $^4J_{6,4}$=2.3 Hz, $^3J_{6,7}$=8.8 Hz; 1H, H6),
7.17 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.19 (d, $^3J_{7,6}$=8.9 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.4 (q, C14), 26.5 (q, C12), 32.9 (q, C11), 35.7 (s, C8), 48.9 (t, C9), 56.0 (q, C10), 103.2 (C2), 110.2 (d), 111.4 (d), 119.2 (s, C3), 125.9 (s), 127.0 (d), 133.3 (s), 153.3 (s, C5), 170.1 (s, C13).

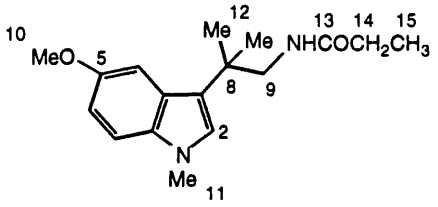
MS (EI, 70 eV): m/z = 274 (M^+, 46), 215 (M^+-NH_2COCH_3, 100).

Ir (KBr): ν = 3297 (s, NH), 2941 (m), 1640 (s, C=O), 1497 (m), 1218 (s, C-O).

CHN	$C_{16}H_{22}N_2O_2$	calc.	C 70.04	H 8.08	N 10.21
		found	C 69.89	H 7.98	N 10.24

N-Propanoyl-2-methyl-2-(3-(N-methyl-5-methoxyindolyl))-propanamine (191b)

2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (0.20 g, 0.9 mmol) is treated with propionic anhydride (0.15 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 55 % yield (0.50 mmol, 0.14 g) as a yellow oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.04 (t, $^3J_{15.14}$=7.6 Hz; 3H, H15),
1.39 (s; 6H, H12),
2.05 (q, $^3J_{14.15}$=7.6 Hz; 2H, H14),
3.60 (d, $^3J_{9.NH}$=5.9 Hz; 2H, H9),
3.71 (s; 3H, H11),
3.84 (s; 3H, H10),
5.18 (t, br; 1H, NH),
6.80 (s; 1H, H2),
6.89 (dd, $^4J_{6.4}$=2.3 Hz, $^3J_{6.7}$=8.7 Hz; 1H, H6),
7.17 (d, $^4J_{4.6}$=2.3 Hz; 1H, H4),
7.19 (d, $^3J_{7.6}$=8.8 Hz; 1H, H7).

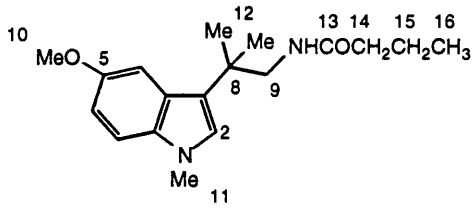
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 10.0 (q, C15), 26.6 (q, C12), 29.9 (t, C14), 32.9 (q, C11), 35.9 (s, C8), 48.7 (t, C9), 56.1 (q, C10), 103.3 (C2), 110.3 (d), 111.5 (d), 119.4 (s, C3), 126.0 (s), 127.1 (d), 133.4 (s), 153.4 (s, C5), 173.8 (s, C13).

MS (EI, 70 eV): m/z = 288 (M^+, 25), 215 (M^+-$NH_2COC_2H_5$, 100).

Ir (film): ν = 3308 (s, NH), 2935 (m), 1631 (s, C=O), 1494 (s), 1212 (s, C-O).

N-Butanoyl-2-methyl-2-(3-(N-methyl-5-methoxyindolyl))-propanamine (191c)

2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (0.20 g, 0.9 mmol) is treated with butanoic anhydride (0.15 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 40 % yield (0.36 mmol, 0.11 g) as a yellow oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{16,15}$=7.4 Hz; 3H, H16),
1.39 (s; 6H, H12),
1.52 - 1.61 (m; 2H, H15),
2.00 (t, $^3J_{14,15}$=7.1 Hz; 2H, H14),
3.61 (d, $^3J_{9,NH}$=6.0 Hz; 2H, H9),
3.71 (s; 3H, H11),
3.84 (s; 3H, H10),
5.28 (t, br; 1H, NH),
6.79 (s; 1H, H2),
6.89 (dd, $^4J_{6,4}$=2.1 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
7.16 (d, $^4J_{4,6}$=2.0 Hz; 1H, H4),
7.17 (d, $^3J_{7,6}$=9.0 Hz; 1H, H7).

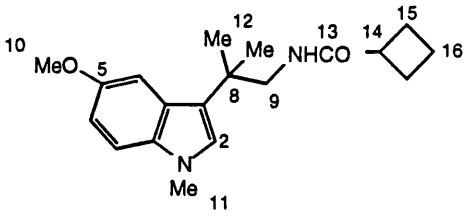
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C16), 19.2 (t, C15), 26.5 (q, C12), 32.3 (q, C11), 35.7 (t, C14), 38.8 (s, C8), 48.6 (t, C9), 56.1 (q, C10), 103.7 (C2), 110.2 (d), 111.4 (d), 119.3 (s, C3), 125.9 (s), 127.0 (d), 133.2 (s), 153.3 (s, C5), 173.0 (s, C13).

MS (EI, 70 eV): m/z = 302 (M^+, 30), 215 (M^+-$NH_2COC_3H_7$, 100).

Ir (film): ν = 3305 (m, NH), 2925 (m), 1630 (s, C=O), 1494 (m), 1220 (m, C-O).

N-Cyclobutanecarbonyl-2-methyl-2-(3-(N-methyl-5-methoxyindolyl))-propanamine (191e)

2-Methyl-2-(3-(N-methyl-5-methoxyindolyl))propanamine (0.20 g, 0.9 mmol) is treated with cyclobutanecarbonyl chloride (0.25 g) according to procedure B VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 62 % yield (0.56 mmol, 0.17 g), mp. 135 - 137 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.38 (s; 6H, H12),
1.78 - 1.89 (m; 2H, H16),
1.96 - 2.05 (m; 2H, H15),
2.11 - 2.19 (m; 2H, H15),
2.80 (qi, $^3J_{14.15}$=7.4 Hz; 1H, H14),
3.68 (d, $^3J_{9.NH}$=4.0 Hz; 2H, H9),
3.70 (s; 3H, H11),
3.84 (s; 3H, H10),
5.09 (s, br; 1H, NH),
6.79 (s; 1H, H2),
6.89 (dd, $^4J_{6.4}$=2.3 Hz, $^3J_{6.7}$=8.9 Hz; 1H, H6),
7.17 (d, $^4J_{4.6}$=2.5 Hz; 1H, H4),
7.19 (d, $^3J_{7.6}$=9.2 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 18.1 (t, C16), 25.3 (t, C15), 26.5 (q, C12), 32.9 (q, C11), 35.8 (s, C8), 39.8 (d, C14), 48.5 (t, C9), 56.2 (q, C10), 103.2 (d, C2), 110.2 (d), 111.3 (d), 119.4 (s, C3), 125.9 (s), 126.8 (d), 133.3 (s), 153.2 (s, C5), 174.9 (s, C13).

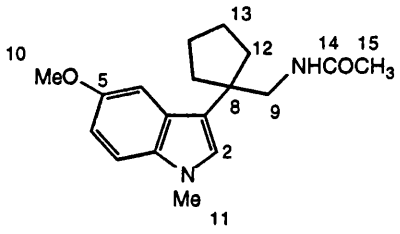
MS (EI, 70 eV): m/z = 304 (M^+, 10), 215 (M^+-$NH_2COC_4H_7$, 100).

Ir (KBr): ν = 3295 (s, NH), 2941 (m), 1635 (s, C=O), 1490 (m), 1210 (m, C-O).

CHN	$C_{19}H_{26}N_2O_2$	calc.	C 74.98	H 5.30	N 9.21
		found	C 74.89	H 5.34	N 9.24

1-(3-(N-Methyl-5-methoxyindolyl))-1-(N-acetyl-aminomethyl)-cyclopentane (192a)

1-(3-(N-Methyl-5-methoxyindolyl))-1-aminomethyl-cyclopentane (0.50 g, 2 mmol) is treated with acetic anhydride (0.10 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 53 % yield (1.1 mmol, 0.32 g), mp. 97 - 98 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.67 - 1.73 (m; 1H, H12 or H13),
1.76 - 1.79 (m; 1H, H12 or H13),
1.80 (s; 3H, H15),
1.91 - 2.01 (m; 2H, H12 or H13),
3.53 (d, $^3J_{9,NH}$ = 5.7 Hz; 2H, H9),
3.68 (s; 3H, H11),
3.81 (s; 3H, H10),
5.39 (t, br; 1H, NH),
6.82 (s; 1H, H2),
6.86 (dd, $^4J_{6,4}$ = 2.3 Hz, $^3J_{6,7}$ = 8.8 Hz; 1H, H6),
7.10 (d, $^4J_{4,6}$ = 2.4 Hz; 1H, H4),
7.15 (d, $^3J_{7,6}$ = 9.0 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.0 (q, C15), 23.8 (t, C13), 32.6 (q, C11), 35.7 (t, C12), 46.7 (t, C9), 46.8 (s, C8), 55.7 (q, C10), 102.6 (d, C2), 110.0 (d), 111.3 (d), 118.8 (s, C3), 126.2 (s), 126.8 (d), 133.1 (s), 153.1 (s, C5), 169.9 (s, C14).

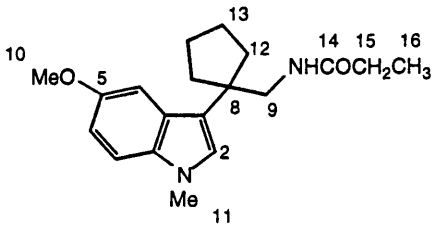
MS (EI, 70 eV): m/z = 300 (M^+, 10), 241 (M^+-NH_2COCH_3, 100).

Ir (KBr): ν = 3290 (s, NH), 2940 (m), 1634 (s, C=O), 1483 (s), 1211 (m, C-O).

CHN $C_{18}H_{24}N_2O_2$ calc. C 71.97 H 8.05 N 9.32
found C 71.88 H 8.04 N 9.27

1-(3-(N-Methyl-5-methoxyindolyl))-1-(N-propanoyl-aminomethyl)-cyclopentane (192b)

1-(3-(N-Methyl-5-methoxyindolyl))-1-aminomethyl-cyclopentane (0.50 g, 2 mmol) is treated with propanoic anhydride (0.2 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 72 % yield (1.4 mmol, 0.45 g), mp. 118 - 119 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.03 (t, $^3J_{16.15}$ = 7.5 Hz; 3H, H16),
1.67 - 1.77 (m; 1H, H12 or H13),
1.79 - 1.81 (m; 1H, H12 or H13),
1.82 - 1.98 (m; 2H, H12 or H13),
2.04 (q, $^3J_{15.16}$ = 7.6 Hz; 2H, H15),
3.54 (d, $^3J_{9.NH}$ = 5.9 Hz; 2H, H9),
3.70 (s; 3H, H11),
3.82 (s; 3H, H10),
5.29 (t, br; 1H, NH),
6.82 (s; 1H, H2),
6.87 (dd, $^4J_{6.4}$ = 2.3 Hz, $^3J_{6.7}$ = 8.8 Hz; 1H, H6),
7.11 (d, $^4J_{4.6}$ = 2.4 Hz; 1H, H4),
7.17 (d, $^3J_{7.6}$ = 8.9 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.8 (q, C16), 23.8 (t, C13), 29.6 (t, C15), 32.7 (q, C11), 35.8 (t, C12), 46.5 (t, C9), 47.0 (s, C8), 55.8 (q, C10), 102.7 (d, C2), 110.0 (d), 111.4 (d), 119.0 (s, C3), 126.3 (s), 126.7 (d), 133.1 (s), 153.2 (s, C5), 173.6 (s, C14).

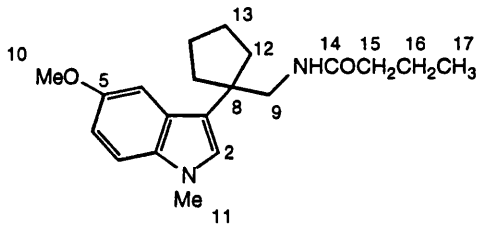
MS (EI, 70 eV): m/z = 314 (M^+, 10), 241 (M^+-$NH_2COC_2H_5$, 100).

Ir (KBr): ν = 3292 (s, NH), 2935 (m), 1646 (s, C=O), 1480 (m), 1215 (m, C-O).

CHN	$C_{19}H_{26}N_2O_2$	calc.	C 72.58	H 8.34	N 8.91
		found	C 72.29	H 8.31	N 8.80

1-(3-(N-Methyl-5-methoxyindolyl))-1-(N-butanoyl-aminomethyl)-cyclopentane (192c)

1-(3-(N-Methyl-5-methoxyindolyl))-1-aminomethyl-cyclopentane (0.50 g, 2 mmol) is treated with butanoic anhydride (0.35 g) according to procedure A VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 68 % yield (1.4 mmol, 0.45 g), mp. 108 - 108.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{17.16}$ = 7.4 Hz; 3H, H17),
1.54 (m, ^3J = 7.5 Hz; 2H, H16),
1.67 - 1.73 (m; 1H, H12 or H13),
1.75 - 1.82 (m; 1H, H12 or H13),
1.93 - 2.00 (m; 4H, H12 or H13, H15),
3.55 (d, $^3J_{9.NH}$ = 5.9 Hz; 2H, H9),
3.70 (s; 3H, H11),
3.82 (s; 3H, H10),
5.26 (t, br, $^3J_{NH.9}$ = 5.2 Hz; 1H, NH),
6.81 (s; 1H, H2),
6.88 (dd, $^4J_{6.4}$ = 2.3 Hz, $^3J_{6.7}$ = 8.9 Hz; 1H, H6),
7.10 (d, $^4J_{4.6}$ = 2.4 Hz; 1H, H4),
7.17 (d, $^3J_{7.6}$ = 9.0 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6 (q, C17), 19.0 (t, C16), 23.9 (t, C13), 32.7 (q, C11), 35.9 (t, C12), 38.6 (t, C15), 46.5 (t, C9), 47.0 (s, C8), 55.8 (q, C10), 102.8 (d, C2), 110.0 (d), 111.4 (d), 119.1 (s, C3), 126.3 (s), 126.8 (d), 133.2 (s), 153.2 (s, C5), 172.8 (s, C14).

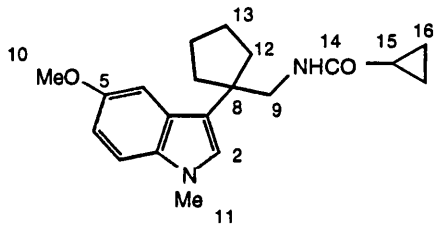
MS (EI, 70 eV): m/z = 328 (M^+, 24), 241 (M^+-$NH_2COC_3H_7$, 100).

Ir (KBr): ν = 3351 (s, NH), 2930 (m), 1648 (s, C=O), 1483 (m), 1215 (s, C-O).

CHN $C_{20}H_{28}N_2O_2$ calc. C 73.13 H 8.59 N 8.53
found C 72.91 H 8.47 N 8.48

1-(3-(N-Methyl-5-methoxyindolyl))-1-(N-cyclopropanoyl-aminomethyl)-cyclopentane (192d)

1-(3-(N-Methyl-5-methoxyindolyl))-1-aminomethyl-cyclopentane (0.50 g, 2 mmol) is treated with cyclopropanoyl chloride (0.20 g) according to procedure B VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 84 % yield (1.7 mmol, 0.55 g), mp. 134 - 135 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.59 - 0.62 (m; 1H, H16),
0.87 - 0.91 (m; 2H, H16),
1.13 - 1.17 (m; 1H, H16),
1.69 - 1.74 (m; 1H, H12 or H13),
1.75 - 1.82 (m; 1H, H12 or H13),
1.94 - 2.00 (m; 3H, 2 H12 or H13, H15),
3.56 (d, $^3J_{9,NH}$ = 5.9 Hz; 2H, H9),
3.70 (s; 3H, H11),
3.82 (s; 3H, H10),
5.58 (t, br, $^3J_{NH,9}$ = 5.6 Hz; 1H, NH),
6.86 (s; 1H, H2),
6.87 (dd, $^4J_{6,4}$ = 2.0 Hz; 1H, H6),
7.13 (d, $^4J_{4,6}$ = 2.0 Hz; 1H, H4),
7.17 (d, $^3J_{7,6}$ = 8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 6.7 (t, C16), 14.5 (d, C15), 23.8 (t, C13), 32.6 (q, C11), 35.7 (t, C12), 46.9 (t, C9), 47.0 (s, C8), 55.7 (q, C10), 102.7 (d, C2), 110.0 (d), 111.3 (d), 119.0 (s, C3), 126.3 (s), 126.8 (d), 133.1 (s), 153.1 (s, C5), 173.4 (s, C14).

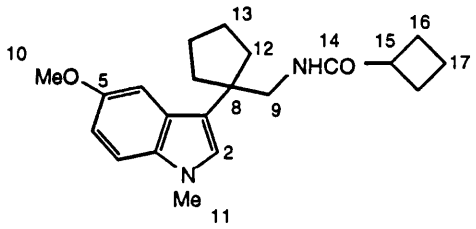
MS (EI, 70 eV): m/z = 326 (M^+, 9), 241 (M^+-$NH_2COC_3H_5$, 100).

Ir (KBr): ν = 3347 (s, NH), 2952 (m), 1652 (s, C=O), 1480 (m), 1217 (s, C-O).

CHN	$C_{20}H_{26}N_2O_2$	calc.	C 73.58	H 8.03	N 8.58
		found	C 73.06	H 8.13	N 8.49

1-(3-(N-Methyl-5-methoxyindolyl))-1-(N-cyclobutanoyl-aminomethyl)-cyclopentane (192e)

1-(3-(N-Methyl-5-methoxyindolyl))-1-aminomethyl-cyclopentane (0.50 g, 2 mmol) is treated with cyclobutanecarbonyl chloride (0.25 g) according to procedure B VIII.2.6. After purification by SPC (CH_2Cl_2 with 1 % MeOH) the product is obtained in 66 % yield (1.3 mmol, 0.45 g), mp. 121 - 123 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.67 - 1.73 (m; 1H, H12 or H13),
1.75 - 1.92 (m; 3H, H12 or H13, 2 H17),
1.94 - 2.03 (m; 4H, 2 H12 or H13, 2 H16),
2.10 - 2.18 (m; 2H, H16),
2.80 (qi, $^3J_{15.16}$ = 8.5 Hz; 1H, H15),
3.52 (d, $^3J_{9.NH}$ = 5.9 Hz; 2H, H9),
3.70 (s; 3H, H11),
3.82 (s; 3H, H10),
5.18 (t, br, $^3J_{NH.9}$ = 5.4 Hz; 1H, NH),
6.80 (s; 1H, H2),
6.87 (dd, $^4J_{6.4}$ = 2.3 Hz, $^3J_{6.7}$ = 8.7 Hz; 1H, H6),
7.10 (d, $^4J_{4.6}$ = 2.3 Hz; 1H, H4),
7.16 (d, $^3J_{7.6}$ = 8.7 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 17.9 (t, C17), 23.8 (t, C13), 25.1 (t, C16), 32.6 (q, C11), 35.8 (t, C12), 39.8 (d, C15), 46.4 (t, C9), 47.1 (s, C8), 55.8 (q, C10), 102.8 (d, C2), 110.0 (d), 111.3 (d), 119.1 (s, C3), 126.3 (s), 126.7 (d), 133.1 (s), 153.2 (s, C5), 174.7 (s, C14).

MS (EI, 70 eV): m/z = 340 (M^+, 6), 241 (M^+-$NH_2COC_4H_7$, 100).

Ir (KBr): ν = 3329 (s, NH), 2950 (m), 1651 (s, C=O), 1482 (m), 1217 (s, C-O).

CHN	$C_{21}H_{28}N_2O_2$	calc.	C 74.08	H 8.29	N 8.23
		found	C 73.90	H 8.27	N 8.07

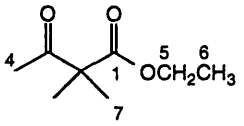
Ethyl 2,2-dimethyl-3-oxo-butanoate (193)

- Procedure A[215]

At 5 °C ethyl 2-methyl-3-oxo-butanoate (35.2 g, 0.25 mol) is added dropwise to a suspension of sodium hydride (6.0 g, 0.25 mol) in benzene (80 ml) and DMF (80 ml). After 20 min at 25 °C, dimethyl sulphate (31.5 g, 0.25 mol) is added. Then the mixture is refluxed for 3 h, water (80 ml) is added and the layers are separated. The aqueous layer is extracted with dichloromethane (2x50 ml) and the combined organic layer is dried over magnesium sulphate. The product is distilled at 67 - 69 °C/10 mmHg to yield 31.2 g (0.2 mol, 79 %) of a colourless oil.

- Procedure B

At 5 °C ethyl acetoacetate (32.5 g, 0.25 mol) is added dropwise to a suspension of sodium hydride (14.4 g, 0.6 mol) in benzene (160 ml) and DMF (160 ml). After 20 min at 25 °C, dimethyl sulphate (75.7 g, 0.6 mol) is added. Then the mixture is refluxed for 3 h and purified according to procedure A to give 23.8 g (0.15 mol, 60 %).

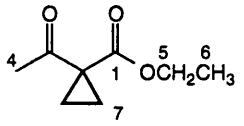


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.19 (t, $^{3}J_{6,5}$=7.1 Hz; 3H, H6),
1.29 (s; 6H, H7),
2.09 (s; 3H, H4),
4.12 (q, $^{3}J_{5,6}$=6.8 Hz; 2H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.9 (q, C6), 21.7 (q, C7), 25.6 (q, C4), 55.6 (s, C2), 61.2 (t, C5), 173.5 (s), 205.9 (s).

Ethyl 1-acetyl-cyclopropane-1-carboxylate (194)[216]

A solution of sodium (5.0 g, 0.22 mol) in ethanol (60 ml) is treated with ethyl acetoacetate (26 g, 0.2 mol) and 1,2-dibromoethane (20 g, 0.11 mol). The mixture is refluxed for 8 h, then the solvent is removed by distillation *in vacuo*, the residue is treated with water (200 ml) and the product is extracted with ether (3x50 ml). After drying over magnesium sulphate and evaporation of the solvent the product is purified by distillation, bp. 88 - 102 °C/8 mmHg. Yield: 7.8 g (55 mmol, 25 %).

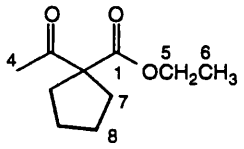


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.20 (t, $^3J_{6,5}$=7.3 Hz; 3H, H6),
1.71 - 2.52 (m; 4H, H7),
1.92 (s; 3H, H4),
4.12 (q, $^3J_{5,6}$=7.2 Hz; 2H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.0 (q, C6), 19.0, 19.4 (t, C7), 28.1 (q, C4), 51.4 (s, C2), 61.1 (t, C5), 171.8 (s), 202.6 (s).

Ethyl 1-acetyl-cyclopentane-1-carboxylate (195)[216]

A solution of sodium (9.2 g, 0.4 mol) in ethanol (130 ml) is treated with ethyl acetoacetate (52 g, 0.4 mol) and 1,4-dibromobutane (44 g, 0.2 mol). The mixture is refluxed for 8 h, then the solvent is removed by distillation *in vacuo*, the residue is treated with water (200 ml) and the product is extracted with ether (3x50 ml). After drying over magnesium sulphate and evaporation of the solvent the product is purified by distillation, bp. 106 - 112 °C/8 mmHg. Yield: 24.8 g (0.14 mol, 34 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.14 (t, $^3J_{6,5}$=7.1 Hz; 3H, H6),
1.47 - 1.57 (m; 4H, H7 or H8),
1.96 - 2.05 (m; 4H, H7 or H8),
2.03 (s; 3H, H4),
4.07 (q, $^3J_{5,6}$=7.1 Hz; 2H, H5).

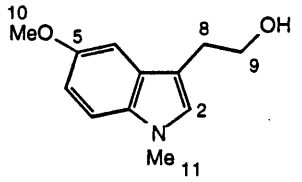
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.8 (q, C6), 25.5 (t, C8), 26.2 (q, C4), 32.8 (t, C7), 55.6 (s, C2), 61.1 (t, C5), 173.2 (s), 203.7 (s).

5-Methoxy-N-methyltryptophol (196)

A solution of 2-(3-(N-methyl-5-methoxyindolyl))acetic acid (1.7 g, 7.3 mmol) in anhydrous THF (100 ml) is added dropwise to a suspension of lithium aluminium hydride (1.0 g) in anhydrous THF (20 ml). After the addition is completed the reaction mixture is refluxed for 2 h. Excess lithium

aluminium hydride is decomposed by careful addition of water (2 ml). The reaction mixture is filtered under suction and the filter cake is washed with ethyl acetate.

After washing the filtrate with water (20 ml) the product is extracted with ethyl acetate (3x20 ml). The organic layer is washed with brine (20 ml) and dried over magnesium sulphate. Evaporation of the solvent yields the alcohol (1.2 g, 5.8 mmol, 80 %) as colourless oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.23 (t, $^3J_{8,9}$=7.3 Hz ; 2H, H8),
3.72 (s; 3H, H11),
3.79 (t, $^3J_{9,8}$=7.4 Hz; 2H, H9),
3.91 (s; 3H, H10),
6.92 (s; 1H, H2),
6.95 (dd, $^4J_{6,4}$=2.2 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
7.06 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.22 (d, $^3J_{7,6}$=8.7 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 28.9 (t, C8), 32.7 (q, C11), 44.6 (t, C9), 55.9 (q, C10), 100.3 (d), 110.1 (d), 110.2 (s, C3), 111.8 (d), 127.6 (d), 127.7 (s), 132.2 (s), 153.8 (s, C5).

Ms (EI, 70 eV): m/z (%) = 205 (2, M^+), 187 (100, M^+-H_2O), 156 (22, M^+-H_2O, -OMe).

Ir (film): ν = 3511-3025 (m, br; OH), 1452 (m), 1210 (s), 1041 (m).

2-(3-(N-Methyl-5-methoxyindolyl))-methylsulphonyloxy-ethane (197)

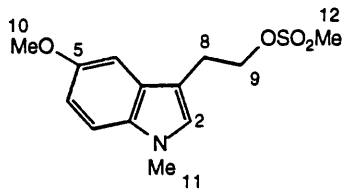
- Attempted reaction in pyridine

5-Methoxy-N-methyltryptophol (0.5 g, 2.4 mmol) in pyridine (10 ml) is reacted with methanesulphonyl chloride (0.25 g, 2.5 mmol) according to procedure VIII.2.9 to recover the starting material.

- Reaction with sodium hydride

A solution of 5-methoxy-N-methyltryptophol (2.5 g, 12 mmol) in THF (20 ml) is added to a suspension of sodium hydride (0.3 g, 13 mmol) in THF (20 ml). After 30 min at 25 °C methanesulphonyl chloride (1.4 g, 13 mmol) is added and the mixture is stirred at 25 °C for 4 h to

obtain after work-up according to procedure VIII.2.9 the product (2.5 g, 9.4 mmol, 78 %) as a brown oil.

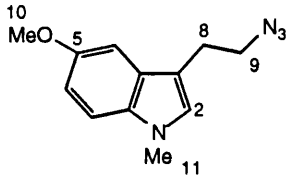


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.96 (t, $^3J_{8,9}$=6.6 Hz ; 2H, H8),
3.61 (s; 3H, H12),
3.69 (s; 3H, H11),
3.84 (s; 3H, H10),
3.85 (m; 2H, H9),
6.87 (dd, $^4J_{6,4}$=2.8 Hz, $^3J_{6,7}$=8.9 Hz; 1H, H6),
6.88 (s; 1H, H2),
7.03 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.17 (d, $^3J_{7,6}$=8.7 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 28.5 (t, C8), 32.7 (q, C11), 52.7 (q, C12), 55.9 (q, C10), 62.7 (t, C9), 100.7 (d), 110.0 (d), 110.8 (s, C3), 111.8 (d), 127.6 (d), 128.1 (s), 132.5 (s), 153.7 (s, C5).

2-(3-(N-Methyl-5-methoxyindolyl))-azidoethane (198)

The crude 2-(3-(N-methyl-5-methoxyindolyl))-methylsulphonyloxyethane (2.5 g, 9.4 mmol) and sodium azide (1 g) are reacted according to procedure VIII.2.10 to give 1.3 g (5.6 mmol, 60 %) of the azide as a brown oil.

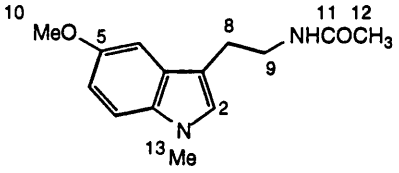


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.97 (t, $^3J_{8,9}$=6.6 Hz ; 2H, H8),
3.71 (s; 3H, H11),
3.85 (s; 3H, H10),
3.86 (m; 2H, H9),
6.88 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=8.7 Hz; 1H, H6),
6.90 (s; 1H, H2),
7.03 (d, $^4J_{4,6}$=2.5 Hz; 1H, H4),
7.18 (d, $^3J_{7,6}$=9.0 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 28.6 (t, C8), 32.7 (q, C11), 55.9 (q, C10), 62.7 (t, C9), 100.7 (d), 110.0 (s, C3), 110.0 (d), 111.9 (d), 127.8 (d), 128.1 (s), 132.5 (s), 153.7 (s, C5).

N-Methylmelatonin (199)

Crude 2-(3-(N-methyl-5-methoxyindolyl))-azidoethane (1.4 g, 6 mmol) is reduced with lithium aluminium hydride (1 g) according to procedure B VIII.2.11 to give 0.15 g (0.72 mmol, 12 %) of a yellow oil. The crude amine is acetylated with 0.1 g of acetic anhydride according to procedure A, VIII.2.6. N-Methylmelatonin (0.14 g, 0.56 mmol, overall yield 9 %) is purified by SPC (CH_2Cl_2 with 1 % MeOH) as a pale yellow oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.89 (s; 3H, H12),
2.88 (t, $^3J_{8,9}$=6.7 Hz; 2H, H8),
3.52 (dt, $^3J_{9,8}$=6.8 Hz, $^3J_{9,NH}$=5.9 Hz; 2H, H9),
3.67 (s; 3H, H13),
3.82 (s; 3H, H10),
6.07 (s,br; 1H, NH),
6.81 (s; 1H, H2),
6.86 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=8.8 Hz; 1H, H6),
7.02 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.14 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7).

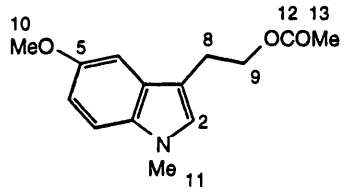
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.0 (q, C12), 25.0 (t, C8), 32.5 (q, C13), 39.8 (t, C9), 55.7 (q, C10), 100.4 (d), 109.9 (d), 110.7 (s, C3), 111.7 (d), 127.1 (d), 127.8 (s), 132.2 (s), 153.5 (s, C5), 170.0 (s, C11).

MS (FAB, 70 eV): m/z = 247 (M^++1, 100).

Ir (film): ν = 3264 (s, NH), 2930 (m), 1633 (s, C=O), 1480 (m), 1210 (m, C-O).

O-Acetyl-5-methoxy-N-methyltryptophol (200)

Crude 5-methoxy-N-methyltryptophol (0.5 g, 2.4 mmol) in 20 ml of dichloromethane is acetylated with 0.3 g of acetic anhydride. After stirring for 16 h at 25 °C the mixture is treated with water (20 ml) and the product is extracted with dichloromethane (2x20 ml). The combined organic layer is then washed with brine and dried over magnesium sulphate. Evaporation of the solvent followed by SPC (CH_2Cl_2 with 1 % MeOH) gives the product (0.34 g, 1.4mmol, 57 %) as a yellow oil.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.13 (s; 3H, H13),
3.11 (t, $^3J_{8,9}$=7.3 Hz ; 2H, H8),
3.72 (s; 3H, H11),
3.93 (s; 3H, H10),
4.39 (t, $^3J_{9,8}$=7.3 Hz; 2H, H9),
6.90 (s; 1H, H2),
6.96 (dd, $^4J_{6,4}$=2.5 Hz, $^3J_{6,7}$=8.8 Hz; 1H, H6),
7.15 (d, $^4J_{4,6}$=2.3 Hz; 1H, H4),
7.22 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 20.9 (q, C13), 24.5 (t, C8), 32.5 (q, C11), 55.7 (q, C10), 64.6 (t, C9), 100.4 (d), 109.6 (s, C3), 109.9 (d), 111.7 (d), 127.3 (d), 127.9 (s), 132.1 (s), 153.6 (s, C5), 170.9 (s, C12).

MS (FAB, 70 eV): m/z = 247 (M^+, 100).

Ir (film): ν = 2930 (m), 1730 (s; CO), 1240 (s), 1026 (s).

N-Acetylnortryptamine (201)

- Acetylation with acetic anhydride/sodium acetate

At 0 °C crude nortryptamine (0.5 g, 3.4 mmol) is added to a solution of sodium acetate trihydrate (1.0 g) in acetic anhydride (15 ml). After 4 h the mixture is poured into 20 ml of cold water and extracted with methylene chloride (3x15 ml). The organic layer is washed with water, dried over magnesium sulphate and the solvent is removed by evaporation *in vacuo* to yield a brown oily solid, which cannot be purified by SPC.

- Acetylation with acetic anhydride/triethylamine in methylene chloride

A solution of crude nortryptamine (0.50 g, 3.4 mmol) in dry dichloromethane (5 ml) and triethylamine (1 ml) is treated with acetic anhydride (0.2 g) according to procedure A, VIII.2.6. The crude mixture is an oil consisting of at least 6 different products according to TLC (chloroform/methanol 9:1), which could not be separated.

- Acetylation of the crude product from the Devarda's-alloy-reduction of indole-3-carbaldehyde oxime

The ether extracts of the crude indole-3-methaneamine obtained from the reduction of the oxime (0.9 g, 6 mmol) with Devarda's alloy are concentrated at 15 °C *in vacuo* to a volume of 100 ml. This solution is stirred with triethylamine (1.4 ml, 10 mmol) and acetic anhydride (0.8 ml, 9 mmol) at 0 °C. After 5 min a solid precipitated, which is removed by filtration after 2 h. The pale yellow solid, which is washed with water and ether, is insoluble in chloroform but soluble in benzene, from which it was recrystallised, mp. 70 - 92 °C. The product is contaminated with at least three other compounds as indicated by TLC (cyclohexane/ethyl acetate 1:1; R_f=0, 0.8, 0.9).

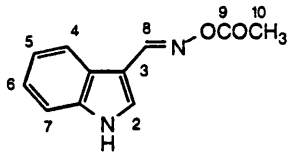
Ir (KBr): ν = 3232 cm^{-1} (s), 1625 (s, CO), 1204 (s), 740 (s).

- Reduction of the oxime in the presence of acetic acid anhydride

A solution of indole-3-carbaldehyde oxime (1.6 g, 10 mmol) in acetic anhydride (50 ml) is treated with platinum oxide (80 mg). The brown reaction mixture is stirred under hydrogen (1 atm) at 20 °C for 1 week. After 3 days another 20 mg of catalyst are added. The catalyst is removed by filtration and the solvent is evaporated to yield a brown solid, which on column chromatography gives (eluent: benzene/ethyl acetate 1:1) two solid compounds.

O-Acetyl-indole-3-carbaldehyde oxime (**213a**)

Yellow crystals, 0.70 g (3.5 mmol, 35 %), recrystallised from benzene (mp. 158 - 159 °C, R_f=0.8).



^{1}H nmr (400 MHz, d_6-DMSO: δ = 2.21 (s; 3H, H10),
6.93 - 6.98 (m; 3H, H2, H5, H6),
7.17 (d, ^{3}J=7.8 Hz; 1H, H4 or H7),
7.88 (d, ^{3}J=7.6 Hz; 1H, H4 or H7),
8.31 (s; 1H, H8).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 23.7 (C10), 114.1, 118.9, 121.4, 123.1, 124.7, 126.3, 127.4, 134.1, 136.1, 169.4 (C9).

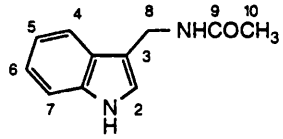
Ir (KBr): ν = 2224 cm^{-1} (m), 1725 (s, CO), 1548 (m), 1445 (m), 1374 (m), 1211 (s), 757 (m).

Ms (EI, 70 eV): m/z (%) = 203 (95, M^++1), 144 (100, M^+-OCOMe).

CHN $C_{11}H_{10}N_2O_2$ calc. C 65.33 H 4.98 N 13.86
found C 65.19 H 4.90 N 13.72

N-Acetyl-3-aminomethyl-indole (**201**)

Yellow oil, 0.75 g (4.0 mmol, 40 %), crystallised from benzene to give colourless crystals (mp. 130 - 131 °C (lit. 133 - 134 °C[219]), R_f=0.2).



^{1}H nmr (400 MHz, $CDCl_3$): δ = 1.96 (s; 3H, H10),
4.59 (d, J=5.1 Hz; 2H, H8),
5.7 (s, br; 1H, NH),
7.13 (m; 1H, H5 or H6),
7.21 (dd, ^{3}J=8.0 Hz, ^{3}J=7.1 Hz; 1H, H5 or H6),
7.37 (d, ^{3}J=8.1 Hz; 1H, H4 or H7),
7.61 (d, ^{3}J=7.7 Hz; 1H, H4 or H7),
8.31 (s, br; 1H, NH).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 23.3 (C10), 35.2 (C8), 111.4, 112.5, 118.8, 119.9, 122.5, 123.3, 126.4, 136.3, 169.9 (C9).

Ir (KBr): ν = 3306 cm^{-1} (s, NH_{indole}), 1608 (s, CO), 1538 (s), 1431 (m), 1354 (m), 1081 (m), 1011 (m), 737 (s).

Ms (EI, 70 eV): m/z (%) = 189 (95, M^++1), 130 (100, M^+-NH_2COMe).

CHN $C_{11}H_{12}N_2O$ calc. C 70.19 H 6.43 N 14.89

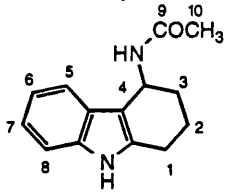
found C 69.85 H 6.36 N 14.67

- Attempted reduction of O-acetyl-indole-3-carbaldehyde oxime (**213a**)

At 20 °C a mixture of O-acetyl-2-methylindole-3-carbaldehyde oxime (0.15 g) and platinum oxide (80 mg) in acetic anhydride (20 ml) is stirred under hydrogen (1 atm) for 1 week. The catalyst is removed by filtration and the solvent is evaporated to give a yellow oil, the ^{1}H nmr spectrum of which is identical to that of the starting material.

N-Acetyl-4-amino-1,2,3,4-tetrahydrocarbazole (202)

A solution of the oxime of 4-oxo-1,2,3,4-tetrahydrocarbazole (0.45 g, 2.25 mmol) in acetic anhydride (50 ml) is treated with platinum oxide (80 mg). The suspension is stirred at 20 °C under hydrogen (1 atm). After 2 d a further 20 mg of platinum oxide is added. After 1 week the mixture is filtered and the solvent is removed by evaporation *in vacuo* to yield 0.66 g of a yellow oil, which is chromatographed over silica with benzene/ethyl acetate 1:1 as eluent to give 0.46 g (2.0 mmol, 90 %) of N-acetyl-4-amino-1,2,3,4-tetrahydrocarbazole (R_f=0.1, mp. = 151 - 153 °C (lit. 160 °C[218])).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.87 - 2.05 (m; 4H, H2, H3),

1.97 (s; 3H, H10),

2.62-2.77 (m; 2H, H1),

5.33 (t, ^{3}J=4.2 Hz; 1H, H4),

5.93 (d, ^{3}J=7.3 Hz; 1H, NH),

7.06 (dd, ^{3}J=7.3 Hz, ^{3}J=7.5 Hz; 1H, H6 or H7),

7.13 (dd, ^{3}J=7.8 Hz, ^{3}J=7.1 Hz; 1H, H6 or H7),

7.27 (d, ^{3}J=7.9 Hz; 1H, H5 or H8),

7.47 (d, ^{3}J=7.6 Hz; 1H, H5 or H8),

8.65 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 19.4, 22.9, 30.2 (t, C1, C2, C3), 23.3, (q, C10), 42.6 (d, C4), 109.0 (s), 110.7 (d), 117.9 (d), 119.4 (d), 121.3 (d), 126.2 (s), 135.7 (s), 136.6 (s), 169.51 (C9).

Ir (KBr): ν = 3386 cm^{-1} (s; NH), 3232 (s, br; NH), 1615 (s; CO), 1551 (m, br), 1461 (m), 744 (s).

Ms (EI, 70 eV): m/z (%) = 228 (5, M^+), 169 (100, M^+-H_2NCOMe), 43 (30, $COMe^+$).

CHN $C_{16}H_{22}N_2O_2$ calc. C 73.65 H 7.06 N 12.27
found C 72.89 H 7.01 N 12.24

3-Aminomethyl-indole (205)

Reduction of indole-3-carbaldehyde oxime (**207a**)

To a solution of indole-3-carbaldehyde oxime (1.0 g, 25 mmol) in methanol (40 ml) and 520 ml of 1 N aq. sodium hydroxide solution are added 4 g of Devarda's alloy (50 % Cu, 45 % Al, 5 % Zn). While cooling with ice the mixture is stirred for 5 h until gas evolution ceased. The suspension is carefully extracted with ether (6x100 ml) and the solvent is removed by evaporation *in vacuo* to yield a yellow viscous oil, which is directly used for the subsequent acylation.

^{1}H nmr (200 MHz, d_6-DMSO): δ = 3.1 - 3.6 (s, br; 2H, NH_2),
3.93 (s; 2H, CH_2),
6.97 - 7.05 (dd; 1H, H5),
7.11 (dd, $^3J_{6,5}$=7.0 Hz, $^3J_{6,7}$=7.9 Hz; 1H, H6),
7.25 (s; 1H, H2),
7.39 (d, $^3J_{7,6}$=7.8 Hz; 1H, H7),
7.63 (d, $^3J_{4,5}$=7.7 Hz; 1H, H4),
10.9 - 11.0 (s, br; 1H, NH).

^{13}C nmr (100 MHz, d_6-DMSO): δ = 37.2 (t), 111.6 (d), 117.2 (s), 118.4 (d), 118.8 (d), 121.2 (d), 122.6 (d), 126.6 (s), 136.6 (s).

Ir (CH_2Cl_2): ν = 3600 cm^{-1} (m, br), 3459 (s, NH), 1634 (m), 1087 (m), 1011 (m).

Upon treatment of an ethereal solution of the amine with hydrogen chloride a brown oil separates from the solution.

An attempt to prepare the hydrooxalate was made. The crude amine is obtained by reduction of 1 g of the oxime **207a** in methanol (10 ml) and this is treated with a solution of oxalic acid (2.0 g) in

ether. After stirring for 10 min the solvent is evaporated and the residue is recrystallised from 70% aq. ethanol to yield a brown solid (mp. 180 °C).

CHN	$C_{11}H_{12}N_2O_4$	calc.	C 55.93 H 5.12 N 11.85
		found	C 61.79 H 5.30 N 9.09

Reduction of 3-cyanoindole (208)

- Reduction with lithium aluminium hydride

A solution of 3-cyanoindole (5.6 g, 0.04 mol) in THF (50 ml) is reacted with lithium aluminium hydride (2.0 g) according to procedure A, VIII.2.5 to yield the starting material.

- Hydrogenation with palladium-on-charcoal in the presence of ammonia

3-Cyanoindole (5.6 g, 0.04 mol) is dissolved in a mixture of 99% ethanol (50 ml) and 35% aqueous ammonia solution (20 ml). 10 % Palladium-on-charcoal (0.2 g) is added and the mixture is shaken under hydrogen (60 p.s.i.) for 48 h at 20 °C. No reaction is observed.

- Hydrogenation with palladium-on-charcoal in the presence of hydrochloric acid

Conc. hydrochloric acid (33 ml) is added to the ethanolic solution of the nitrile recovered from the previous experiment. After the mixture has been hydrogenated for 24 h at 50 °C, the catalyst is removed by filtration through celite and the solvent is evaporated. The brown solid (mp. > 225 °C) is dissolved in water. Then the aqueous solution is washed with 2x40 ml of ether and neutralised with 10 % aq. sodium hydroxide solution. The precipitate is insoluble in methylene chloride, ether or ethyl acetate.

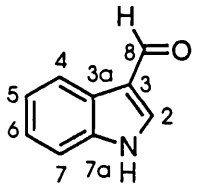
- Hydrogenation with Raney-nickel W-2 in the presence of ammonia

A solution of 3-cyanoindole (5.2 g, 37 mmol) in a mixture of 99% ethanol (250 ml) and 35% aqueous ammonia solution (5.2 ml) is hydrogenated in the presence of Raney-nickel W-2 (about 2.0 g). The initial hydrogen pressure is 60 p.s.i.. After 24 h at 20 °C the catalyst is removed by filtration and the solution is concentrated *in vacuo* to yield the crude 3-methaneamine-indole as a brown oil.

Indole-3-carbaldehyde (206a)

While cooling with ice, 26.4 ml (43.4 g, 0.28 mol) of phosphoryl chloride are added to a solution of indole (29.9 g, 0.26 mol) in 90 ml dimethylformamide at such a rate as to maintain the temperature below 10 °C. The mixture is stirred at 35 °C for 1.5 h to give a viscous yellow material which is carefully dissolved in 300 ml cold water. The resulting red solution is made alkaline by

adding a 20 % aq. sodium hydroxide solution and the aldehyde precipitates in pale yellow crystals, which are washed with water. Recrystallisation from methanol yields 35.2 g (0.27 mol, 95 %) of indole-3-carbaldehyde (mp. 200 -201 °C).



^{1}H nmr (400 MHz, d_6-DMSO): δ = 6.25 - 6.34 (m; 2H, H5, H6),
6.57 (dd, ^3J=8.2 Hz, ^4J=1.0 Hz; 1H, H_{ar}),
7.16 (dd, ^3J=7.9 Hz, ^4J=1.1 Hz; 1H, H_{ar}),
7.33 (d, ^4J=1.2 Hz; 1H, H2),
8.98 (d, ^4J=1.2 Hz; 1H, H8),
12.7 (s, br; 1H, NH).

^{13}C nmr (100 MHz, d_6-DMSO): δ = 112.60 (d), 118.30 (d), 120.98 (d), 122.34 (d), 123.66 (d), 124.23 (s), 137.20 (s), 138.69 (s), 185.28 (s, C8).

Ir (KBr): ν = 3000 (s, NH_{indole}), 1650 (m, CO), 1450 (s), 1380 (s), 1250 (m), 1120 (m).

Ms (EI, 70 eV): m/z (%) = 145 (90, M^++1), 144 (100, M^+), 116 (15, M^+-CH_2O), 89 (50), 63 (40).

CHN C_9H_7NO calc. C 74.47 H 4.86 N 9.65
found C 74.13 H 4.67 N 9.60

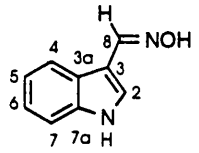
2-Methylindole-3-carbaldehyde (206b)

While cooling with ice, phosphoryl chloride (43.4 g, 0.28 mol) is added to a solution of 2-methylindole (34.1 g, 0.26 mol) in DMF (90 ml) at such a rate as to maintain the temperature below 10 °C. The mixture is stirred at 35 °C for 1.5 h to give a viscous yellow material which is carefully dissolved in 300 ml cold water. The resulting red solution is made alkaline by adding a 20 % aq. sodium hydroxide solution. The aldehyde precipitates as pale yellow crystals, which are washed with water. Recrystallisation from methanol yields 38.1 g (0.26 mol, 92 %) of 2-methylindole-3-carbaldehyde (mp. 200 -201 °C). Sublimation at T>160 °C.

Ir (KBr): ν = 3453 cm^{-1} (m, NH_{indole}), 1618 (s, CO), 1578 (s), 1461 (s), 1381 (s), 1241 (s), 744 (s), 627 (s).

Indole-3-carbaldehyde oxime (207a)

To a solution of indole-3-carbaldehyde (10.2 g, 0.07 mol) in 100 ml 95 % ethanol a solution of hydroxylamine hydrochloride (7.7 g, 0.11 mol) and 7.0 g of potassium carbonate in 20 ml water is added in one portion. A solid precipitates immediately. After 30 min at 70 °C, water (100 ml) is added and the ethanol is removed by evaporation *in vacuo*. The resulting yellow solid is filtered and washed with water to yield, after recrystallisation from methanol, 10.4 g (65 mmol, 93 %) of the oxime (mp. 203 - 204 °C) which is insoluble in chloroform and soluble in dimethylsulphoxide.



^{1}H nmr (60 MHz, d_6-DMSO): δ = 6.2 - 6.4 (m; 2H, H5, H6),
6.5 - 6.6 (m; 1H, H_{ar}),
6.7 - 6.9 (m; 2H, H_{ar}),
7.4 (d, ^4J=2 Hz; 1H, H2),
10.0, 10.2 (s, br; 2H, NH, OH).

Ir (KBr): ν = 3000 (s, NH_{indole}), 1670 (m, C=N), 1450 (s), 1430 (s), 1340 (s), 1240 (s), 1100 (s), 930 (s), 750 (s).

Ms (EI, 70 eV): m/z (%) = 160 (95, M^+), 142 (42, M^+-H_2O), 117 (100, indole$^+$), 104 (22), 89 (50), 63 (37).

CHN	$C_9H_8N_2O$	calc.	C 67.49	H 5.04	N 17.48
		found	C 66.94	H 4.81	N 17.18

2-Methylindole-3-carbaldehyde oxime (207 b)

A solution of hydroxylamine hydrochloride (7.7 g, 0.11 mol) and 7.0 g of potassium carbonate in 20 ml water is added in one portion to a solution of 2-methylindole-3-carbaldehyde (**206b**, 11.2 g, 0.07 mol) in 95 % ethanol (100 ml). A solid precipitates immediately. The mixture is heated at 70 °C for 30 min and water (100 ml) is then added and the ethanol is removed by evaporation *in vacuo*. The resulting yellow solid is removed by filtration and washed with water. After recrystallisation from methanol 11.2 g (0.1 mol, 92 %) of the oxime (mp. 140 °C) are obtained.

Ir (KBr): ν = 3265 cm^{-1} (s, NH_{indole}), 1625 (m, C=N), 900 (s), 727 (s).

3-Cyanoindole (208)

In small portions hydroxylamine hydrochloride (5.3 g, 0.08 mol) is added to a solution of indole-3-carboxaldehyde (10.0 g, 0.07 mol) in refluxing DMF (20 ml). After the addition is complete the solution is heated for a further 10 min. The mixture is allowed to cool to 20 °C and poured into 400 ml of water. A pink solid precipitates, which is recrystallised from about 300 ml of 50% aq. ethanol in the presence of decolourising charcoal to give 9.0 g (63 mmol, 90 %) of pale pink 3-cyanoindole (mp. 181 - 183 °C, lit. 187 - 188 °C[225]).

Ir (KBr): ν = 3226 cm^{-1} (s, br), 2224 (s, CN), 1521 (m), 1428 (m), 754 (s).

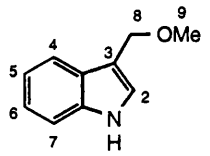
Ms (EI, 70 eV): m/z (%) = 142 (100, M^+), 115 (30, M^+-HCN).

CHN $C_9H_6N_2$ calc. C 76.05 H 4.26 N 19.70

found C 75.69 H 4.25 N 19.47

3-Methoxymethylindole (209a)

A solution of sodium methanolate in methanol is prepared by dissolving sodium (0.8 g, 35 mmol) in methanol (100 ml). Indole (11.7 g, 0.1 mol) and paraformaldehyde (6.0 g, 0.2 mol) are then added. The mixture is refluxed for 10 h and is then poured into 450 ml of cold water. The resulting emulsion is stirred for 2 h to give a yellow precipitate, which is filtered and washed with water. The melting point of the crude product is 86 °C (lit. 94 - 95.5 °C[227]). Yield: 12.2 g (76 mmol, 76 %)



^{1}H nmr (200 MHz, $CDCl_3$): δ = 3.40 (s; 3H, Me),
4.67 (s; 2H, CH_2),
7.10 (s; 1H, H2),
7.15 - 7.28 (m; 2H, H5, H6),
7.33, 7.65 (d, J=8 Hz; 2H, H4, H7),
8.20 (s, br; 1H, NH).

Ir (KBr): ν = 3412 - 3145 cm^{-1} (m, br), 3266 (s, NH), 1435 (m), 1088 (s), 1067 (s), 944 (s), 730 (s).

Ms (EI, 70 eV): m/z (%) = 161 (35, M^+), 130 (100, M^+-OMe), 77 (10).

3-Ethoxymethylindole (209b)

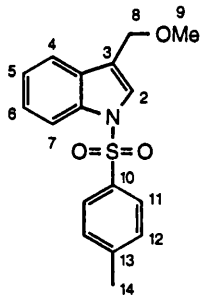
3-Methoxymethylindole (1.6 g, 10 mmol) is dissolved in 40 ml of ethanol. 0.5 g (9 mmol) of sodium methanolate is added and the mixture is refluxed for 5 h. The solvent is evaporated, the residue is treated with water (20 ml) and the product is extracted with dichloromethane (2x20 ml). The organic layer is dried over magnesium sulphate and the solvent is removed by evaporation *in vacuo* to give a yellow solid (1.4 g, 8.1 mmol, 81 % yield, mp. 83 °C).

^{1}H nmr (200 MHz, $CDCl_3$): δ = 1.47 (t, J=8 Hz; 3H, $CH_2C\underline{H}_3$),
3.83 (q, J=8Hz; 2 H, $C\underline{H}_2CH_3$),
4.91 (s; 2H, CH_2),
7.00 (d, J=1.5 Hz; 1H, H2),
7.20-7.45 (m; 2H, H5, H6),
7.55, 8.00 (d, J=8 Hz; 2H, H4, H7),
8.90 (s, br; 1H, NH).

N-Tosyl-3-methoxymethylindole (209c)

A solution of 3-methoxymethylindole (1.4 g, 9 mmol) in THF (20 ml) is added to a suspension of sodium hydride (0.6 g of a 80% dispersion, 20 mmol) in THF (20 ml). The mixture is stirred at 20 °C for 1 h, then a solution of *para*-toluenesulphonyl chloride (3.4 g, 18 mmol) in THF (10 ml) is

added. After 2 d the mixture is poured into water (gas evolution indicates that only one equivalent of sodium hydride reacted with the indole). The product is extracted with dichloromethane, and the organic layer is washed with dil. sodium hydroxide solution. Evaporation of the solvent gives the crude product, which is purified by SPC (eluent: methylene chloride, R_f=0.7). Mp. 118 °C.



^{1}H nmr (400 MHz, $CDCl_3$): δ = 2.31 (s; 3H, H14),
3.38 (s; 3H, H9),
4.57 (s; 2H, H8),
7.18-7.27 (m; 3H, H5 or H6, H12),
7.30 (t; 1H, H5 or H6),
7.52 (s; 1H, H2),
7.58, 7.98 (d; 2H, H4, H7),
7.76 (d; 2H, H11).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 21.8 (q, C14), 57.8 (q, C9), 66.3 (t, C8), 113.4 (d), 119.8 (s, C3), 120.1 (d), 123.3 (d), 124.4 (d), 125.0 (d), 127.0, 130.0 (d, C11, C12), 130.2 (s), 135.1 (s), 135.7 (s, C10), 145 (s, C13).

Ir (KBr): ν = 3626-3252 cm^{-1} (m, br), 1444 (s), 1361 (s, SO_2), 1174 (s), 1117 (s, SO_2), 1091 (s), 1067 (s), 744 (s), 670 (s).

Ms (EI, 70 eV): m/z (%) = 315 (45, M^+), 284 (40, M^+-OMe), 155 (60, *p*-toluenesulphonyl), 91 (100).

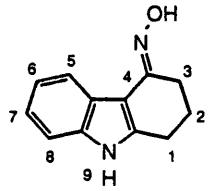
CHN $C_{17}H_{17}NO_3S$ calc. C 64.74 H 5.43 N 4.44
found C 64.62 H 5.29 N 4.38

3-Azidomethylindole (210)

A suspension of 3-methoxymethylindole (1.5 g, 10 mmol), sodium methanolate (0.1 g) and sodium azide (2.0 g, 30 mmol) in THF (30 ml) or ethanol (30 ml) is refluxed for 2 d. The solvent is removed by evaporation *in vacuo*, the residue is treated with water (100 ml) and 3-methoxymethylindole is recovered by extraction with ether.

4-Oxo-1,2,3,4-tetrahydrocarbazole oxime (211)

A solution of 4-oxo-1,2,3,4-tetrahydrocarbazole (1.85 g, 10 mmol) in pyridine (60 ml) is treated with hydroxylamine hydrochloride (1.4 g, 20 mmol). The mixture is refluxed for 3 h and is then poured into ice water (300 ml). A brown oil separates, which is extracted with ether (3x100 ml). The ethereal extracts are washed with 2N hydrochloric acid (3x100 ml) and water (3x100 ml). Evaporation of the solvent yields the crude oxime (mp = 195 - 197°C), which is recrystallised from ethanol. Mp. = 208 - 210 °C, yield: 1.23 g (6.7 mmol, 67 %).



^{1}H-nmr (400 MHz, d6-DMSO): δ = 1.42 (t, ^{3}J=7.0 Hz; 2H, H2),
2.18 (t, ^{3}J=6.1 Hz; 2H, H1),
2.30 (t, ^{3}J=6.2 Hz; 2H, H3),
6.50 - 6.60 (m; 2H, H6, H7),
6.81 (d, ^{3}J=7.9 Hz; 1H, H5 or H8),
7.38 (d, ^{3}J=7.6 Hz; 1H, H5 or H8),
9.77, 10.73 (s, br; 1H, NH and OH).

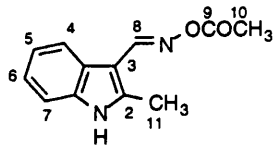
^{13}C-nmr (100 MHz, d6-DMSO): δ = 22.0, 22.5, 22.6 (t, C1, C2, C3), 106.5 (s), 111.0 (d), 119.8 (d), 121.1 (d), 121.3 (d), 124.1 (s), 136.0 (s), 141.5 (s), 152.6 (s).

Ir (KBr): ν = 3405 cm^{-1} (s, NH), 1621 (m), 1481 (s), 1418 (s), 920 (s), 887 (s), 747 (s).

Ms (EI, 70 eV): m/z (%) = 200 (100, M^+), 184 (25), 155 (65).

O-Acetyl-2-methylindole-3-carbaldehyde oxime (213b)

At 0 °C acetyl chloride (3 ml) is slowly added to a solution of 2-methylindole-3-carbaldehyde oxime (0.9 g, 5.1 mmol) in dichloromethane (40 ml) and triethylamine (10 ml). The suspension is stirred under nitrogen at 20 °C for 2 d. The reaction mixture is then treated with water (50 ml) and the organic layer is separated. After washing with 2N hydrochloric acid (2x50 ml) and water (50 ml) the organic layer is dried over calcium chloride. Evaporation of the solvent gives a brown oil, which is purified by column chromatography (eluent: ethyl acetate/hexane 3:2, R_f=0.5). A colourless solid (mp. 161 - 162 °C, 0.9 g, 4.2 mmol, 82 %) is obtained.



^{1}H nmr (400 MHz, $CDCl_3$): δ = 2.30, 2.39 (s; 3H, H10, H11),
7.08 - 7.17 (m; 2H, H5, H6),
7.26 (d, ^{3}J=8.1 Hz; 1H, H4 or H7),
8.03 (d, ^{3}J=7.6 Hz; 1H, H4 or H7),
8.52 (s; 1H, H8),
8.85 (s, br; 1H, NH).

^{13}C nmr (100 MHz, $CDCl_3$): δ = 11.9 (q, C11), 20.0 (q, C10), 104.0, 110.7, 121.4, 121.5, 122.7, 125.4, 135.5, 141.3, 150.9, 170.3 (C9).

Ir (KBr): ν = 3266 cm^{-1} (m, NH_{indole}), 1718 (s, CO), 1238 (s), 944 (m), 754 (m).

Ms (EI, 70 eV): m/z (%) = 216 (15, M^+), 174 (20, M^+-COMe), 156 (100, M^+-HOCOMe), 130 (25, M^+-CHNOCOMe), 43 (45, $COMe^+$).

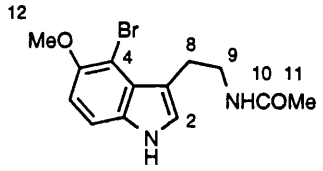
CHN $C_{12}H_{12}N_2O_2$ calc. C 66.66 H 5.59 N 12.95
found C 65.69 H 5.48 N 12.78

Attempted reduction of O-acetyl-2-methylindole-3-carbaldehyde oxime (213b)

At 20 °C a solution of O-acetyl-2-methylindole-3-carbaldehyde oxime (0.2 g) in methanol (40 ml) is treated with about 5 g of Raney-nickel W2 catalyst. This suspension is hydrogenated at 60 psi for 3 d. The catalyst is removed by filtration and the solvent is evaporated to yield a yellow oil, which contains several products by TLC. The ^{1}H nmr spectrum shows no singlet that could be assigned to an acetyl group.

N-Acetyl-4-bromo-5-methoxytryptamine (214)

A solution of 4-bromo-5-methoxytryptamine (**232**, 0.40 g, 1.5 mmol), acetyl chloride (0.10 g, 1.5 mmol) and triethylamine (5 ml) in dichloromethane (25 ml) is stirred at 20 °C for 1 h. The reaction mixture is treated with 2N hydrochloric acid (20 ml) and the product is extracted with dichloromethane (2x30 ml). After washing with water (30 ml) and sodium bicarbonate solution (30 ml) the solution is dried over calcium chloride and the solvent is removed by evaporation *in vacuo*. The yellow oil is purified by column chromatography eluting with 3% methanol in dichloromethane (R_f=0.1). The product (0.12 g, 0.4 mmol, 26 %) is pure by TLC and melts between 117 and 148 °C.



^{1}H nmr (400 MHz, $CDCl_3$): d = 1.91 (s; 3H, H11),
2.92 (t, $^3J_{8,9}$=6.6 Hz; 2H, H8),
3.57 (dt, $^3J_{9,8}$=6.5 Hz, $^3J_{9,NH}$=6.2 Hz; 2H, H9),
3.84 (s; 3H, H12),
5.54 (t, br; 1H, NH),
6.85 (d, $^3J_{6,7}$=8.7 Hz; 1H, H6),
7.01 (s, br; 1H, H2),
7.25 (d, $^3J_{7,6}$=9.1 Hz; 1H, H7),
8.02 (s, br; 1H, NH).

^{13}C nmr (100 MHz, $CDCl_3$): d = 23.5 (q, C11), 25.3 (t, C8), 39.7 (t, C9), 56.0 (q, C12), 100.4 (s), 112.0 (d), 112.5 (d), 115.8 (s), 122.8 (d), 123.1 (s), 131.6 (s), 154.1 (s, C5), 170.1 (s, CO).

Ir (KBr): n = 3357 cm^{-1} (s, br; NH), 1625 (s; CO), 1555 (m), 1473 (s; -OMe), 1410 (s), 794 (s).

Ms (EI, 70 eV): m/z (%) = 310, 312 (5, M^+), 251, 253 (40, M^+-NH_2COCH_3), 238, 240 (50, M^+-$CH_2NHCOCH_3$), 143 (100), 130 (100).

CHN $C_{13}H_{15}N_2O_2Br$ calc. C 50.18 H 4.86 N 9.00
found C 49.92 H 4.75 N 8.92

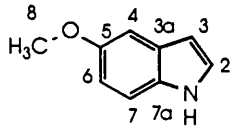
5-Methoxyindole (215)

- Procedure A

A solution of 5-methoxy-N-(tert-butoxycarbonyl)indole (0.25 g, 1 mmol) in a mixture of ethanol (10 ml) and 20 % aq. sodium hydroxide solution (1 ml) is refluxed for 3 h. The resulting heterogeneous brown mixture is diluted with 30 ml water and extracted with ether. The ethereal extract is washed with brine and dried over magnesium sulphate. Evaporation of the solvent yields 0.13 g (0.9 mmol, 88 %) of 5-methoxyindole (mp. 55-56 °C).

- Procedure B

A solution of the crude b-dimethylamino-5-methoxy-2-nitro-styrene (about 5 g) in benzene (50 ml) is shaken with palladium-on-charcoal (0.2 g) under hydrogen (60 psi) for 90 min. The initial hydrogen uptake is rapid. The catalyst is removed by filtration and the filtrate is washed with 4 % aq. hydrochloric acid (4x400 ml), dil. aq. $NaHCO_3$ (2x200 ml) and dried over magnesium sulphate. Evaporation of the solvent gives a brown solid (ca. 60 % yield), which is purified by spinning plate chromatography (petroleum spirit - dichloromethane 3:1). Yield: 1.8 g (12 mmol, 54 %)



^{1}H nmr (400 MHz, $CDCl_3$): d = 3.95 (d, ^5J=1.0 Hz; 3H, H8),
6.59 - 6.60 (m; 1H, H3),
7.01 (ddd, ^3J=9.0 Hz, ^4J=2.2 Hz, ^4J=1.8 Hz; 1H, H_{ar}),
7.14 (dd, ^4J=2.9 Hz, ^4J=2.8 Hz; 1H, H_{ar}),
7.24 - 7.27 (m; 2H, H_{ar}),
8.12 (s, br; 1H, NH).

^{13}C nmr (100 MHz, $CDCl_3$): d = 55.7 (q, C8), 101.9 (d), 102.1 (d), 111.8 (d), 112.0 (d), 125.0 (d), 128.1 (s, C3a), 130.8 (s, C7a), 153.9 (s, C5).

Ir (KBr): n = 3472 (s, NH), 1478 (s), 1448 (s), 1151 (s), 1124 (s), 1027 (s), 907 (s).

Ms (EI, 70 eV): m/z (%) = 147 (100, M^+), 132 (75, M^+-CH_3), 104 (55), 77 (15).

CHN	C_9H_9NO	calc.	C 73.44	H 6.16	N 9.52
		found	C 73.20	H 6.05	N 9.47

3-Cyanomethyl-5-methoxyindole (216)

- Procedure A

Potassium cyanide (30.6 g, 0.47 mol) and methyl iodide (15.3g, 6.7 ml, 0.24 mol) are added to a solution of 5-methoxygramine (9.5 g, 47 mmol) in methanol (500 ml), N,N-dimethylformamide (16.5 ml) and water (16.5 ml) . The mixture is stirred at 40 °C for 2 h, more methyl iodide (7 ml) being periodically added. After stirring for 6 h at 40 °C the mixture is poured into 400 ml of ice-water and the product is extracted with dichloromethane (3x150 ml). The organic phase is washed with water (4x150 ml) to remove the DMF. Evaporation of the solvent gives a brown oil, which is purified by spinning plate chromatography (eluent: petroleum spirit/ethyl acetate 3:1) to give 4.9 g (13 mmol, 56 %) of the nitrile as a yellow oil. Mp. » 26 °C.

- Procedure B

Methyl iodide (1.7 ml, 60 mmol) is added to a solution of 5-methoxygramine (3.3 g, 16 mmol) in ethanol (10 ml) at 0 °C. A solid precipitates and after 30 min a solution of potassium cyanide (3.0 g, 46 mmol) in water (3 ml) is added. The mixture is refluxed for 4 h and is then poured into 400 ml of ice-water. The product is extracted with ether (3x150 ml) and the organic phase is washed with dil. hydrochloric acid (2x100 ml) and brine (100 ml). Evaporation of the solvent gives a brown oil, which was purified by spinning plate chromatography (eluent: petroleum spirit/ethyl acetate 3:1) to yield 1.3 g (7.0 mmol, 44 %) of the nitrile as a yellow oil.

^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.77 (s; 2H, $C\underline{H}_2CN$),
3.85 (s; 3H, OCH_3),
6.89 (dd, $^4J_{6,4}$=2.3 Hz, $^3J_{6,7}$=8.7 Hz; 1H, H6),
6.98 (d, $^4J_{4,6}$=2.2 Hz; 1H, H4),
7.14 (s, br; 1H, H2),
7.25 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7),
8.51 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.4 ($\underline{C}H_2CN$), 55.8 ($O\underline{C}H_3$), 99.6 (d), 104.1 (s, C3), 112.3 (d), 113.1 (d), 118.2 (CN), 123.4 (d), 126.3 (s, C3a), 131.2 (s, C7a), 154.4 (C5).

Ir (KBr): ν = 3465 cm^{-1} (s; NH), 2237 (m; CN), 1700 (s), 1478 (s; -OMe), 1170 (s), 1050 (s), 825 (s).

Ms (EI, 70 eV): m/z (%) = 186 (100, M^+), 171 (100, M^+-CH_3), 160 (15, M^+-CN), 143 (50), 116 (17), 89 (15).

3-Cyanomethyl-4-bromo-5-methoxyindole (217)

A solution of 2.6 g (15 mmol) N-bromosuccinimide in dichloromethane (200 ml) is added within 1 h to a suspension of 3-cyanomethyl-5-methoxyindole (**216**, 2.7 g, 15 mmol) and 30 g BDH silica (previously dried at 110 °C for 12 h) in dichloromethane (300 ml) . Stirring is continued for 30 min, the mixture is filtered and the purple residue is washed with dichloromethane (500 ml). Evaporation of the solvent gives 1.5 g (5.9 mmol, 39 %) of a yellow oil, which solidifies in the cold, mp. 136 - 137 °C.

^{1}H-nmr (400 MHz, $CDCl_3$): d = 3.90 (s; 3H, OCH_3),
4.22 (s; 2H, $C\underline{H}_2CN$),
6.92 (d, $^3J_{6,7}$=8.8 Hz; 1H, H6),
7.26 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7),
7.30 (s, br; 1H, H2),
8.41 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): d = 16.3 ($\underline{C}H_2CN$), 58.0 ($O\underline{C}H_3$), 102.4 (s), 105.9 (s), 110.3 (s), 110.6 (d), 111.0 (d), 118.6 (CN), 125.5 (d), 132.8 (s, C7a), 150.5 (s, C5).

Ir (KBr): n = 3305 cm^{-1} (s, br; NH), 2251 (m; CN), 1561 (s), 1478 (s; -OMe), 1408 (s), 1284 (s), 1181 (s), 1047 (s).

Ms (EI, 70 eV): m/z (%) = 264, 266 (100, M^+), 249, 251 (95, M^+-CH_3), 221, 223 (50, M^+-H-HCN-CH_3), 170 (25, M^+-Br-CH_3), 142 (30, M^+-HBr-HCN-CH_3).

3-Methyl-4-nitrophenol (219)

A solution of *m*-cresol (140 g, 1.29 mol) in glacial acetic acid (240 g) is cooled to - 8 °C and added to a mechanically stirred mixture of nitric acid (d = 1.42, 250 g) and glacial acetic acid (400 g). The brown viscous reaction mixture is stirred at 5 °C for 90 min and then poured onto 1.5 kg of crushed ice. The brown precipitate is collected by filtration and steam distilled. About 2 l of distillate are collected to yield 5-methyl-2-nitro-phenol (48 g, 24 %) as a yellow solid (mp. 53 °C). From the cooled residue a black solid precipitates, which is sublimed at 0.1 torr and 100 °C to yield pale yellow 3-methyl-4-nitrophenol (102 g, 0.67 mol, 52 %, mp. 128 °C).

5-methyl-2-nitrophenol (**220**)

^{1}H nmr (200 MHz, $CDCl_3$): d =2.37 (s; 3H, CH_3),
6.76 (dd, $^3J_{4.3}$=9.0 Hz, $^4J_{4.6}$=0.8 Hz; 1H, H4),
6.91 (d, $^4J_{6.4}$=0.8 Hz; 1H, H6),
7.94 (d, $^3J_{3.4}$=8.8 Hz; 1H, H3),
10.59 (s; 1H, OH).

^{13}C nmr (100 MHz, $CDCl_3$): d = 21.80 (CH_3), 119.52 (C6), 121.50 (C4), 124.77 (C3), 131.9 (C2), 149.75 (C5), 154.99 (C1).

Ir (KBr): n = 3192 cm^{-1} (m, br), 1621 (s), 1581 (s), 1525 (s), 1471 (s), 1451 (s), 1321 (s), 1264 (s), 1184 (s), 663 (s).

3-methyl-4-nitrophenol (**219**)

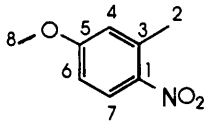
^{1}H nmr (200 MHz, $CDCl_3$): d =2.60 (s; 3H, CH_3),
6.0-6.4 (s, br; 1H, OH),
6.75 (m, ^{3}J=8.3 Hz; 2H, H2, H6),
8.04 (d, $^3J_{5.6}$=9.7 Hz; 1H, H5).

^{13}C nmr (100 MHz, $CDCl_3$): d = 21.6 (q, CH_3), 113.6 (d, C6), 118.9 (d, C2), 127.9 (d, C5), 137.6 (s, C3), 141.5 (s, C4), 159.9 (s, C1).

Ir (KBr): n = 3299 cm^{-1} (s, br), 1605 (s), 1585 (s), 1505 (m), 1475 (m), 1455 (m), 1314 (s), 1258 (s), 1204 (s).

3-Methyl-4-nitroanisol (221)

Dimethyl sulphate (80.0 g, 0.63 mol, 60 ml) is added dropwise to a refluxing mixture of 3-methyl-4-nitrophenol (76.6 g, 0.5 mol) and 110.0 g (0.8 mol) of potassium carbonate in 300 ml toluene. After 22 h the cold heterogeneous mixture is treated with 100 ml 3% aq. NaOH. The toluene is removed by steam distillation. On cooling the product precipitates. The crude 3-methyl-4-nitroanisole is removed by filtration and washed with 200 ml water. An analytical sample is recrystallised from 20 ml petroleum spirit to yield colourless crystals, mp. 50 °C. The yield of the dried crude product, which is directly used in the following reduction step, is 78.2 g (0.47 mol, 94 %).



^{1}H nmr (400 MHz, $CDCl_3$): d = 2.59 (d; 3H, H2),
3.84 (s; 3H, H8),
6.74 (d, $^4J_{4,6}$=2.7 Hz; 1H, H4),
6.75 (dd, $^3J_{6,7}$=9.0 Hz, $^4J_{6,4}$=2.8 Hz; 1H, H6),
8.04 (d, $^3J_{7,6}$=8.9 Hz; 1H, H7).

^{13}C nmr (100 MHz, $CDCl_3$): d = 21.7 (q, C2), 55.7 (q, C8), 111.8 (d, C6), 117.3 (d, C4), 127.5 (d, C7), 137.0 (s, C3), 142.0 (s, C1), 163.0 (s, C5).

Ir (KBr): n = 1608 cm^{-1} (m), 1491 (s), 1328 (s), 1251 (s).

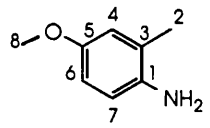
Ms (EI, 70 eV): m/z (%) = 167 (38, M^+), 150 (85), 91 (64), 78 (100), 77 (95), 65 (65).

CHN	$C_8H_9NO_3$	calc.	C 57.48	H 5.43	N 8.38
		found	C 57.23	H 5.80	N 8.21

4-Methoxy-2-methylaniline (222)

- Hydrogenation with palladium-on-charcoal

A suspension of 3-methyl-4-nitroanisole (37.5 g, 0.22 mol) in 40 ml conc. hydrochloric acid, 200 ml water and 1.7 g of 5% palladium on charcoal is shaken in a hydrogen atmosphere at 80 psi for 2 h at 50 °C. The cold mixture is filtered through celite and the resulting green solution is evaporated to dryness to yield the hydrochloric salt of 4-methoxy-2-methylaniline. A solution of the salt in water (200 ml) is washed with ether to remove impurities. Cooling with ice, 20% aq. sodium hydroxide solution is added until the brown solution gave a basic reaction. The product is extracted with ether and the dried ethereal layer is distilled under reduced pressure to yield 23.5 g (0.19 mol, 88 %) of 4-methoxy-2-methylaniline (bp. 86 °C / 1 torr).



^{1}H nmr (400 MHz, $CDCl_3$): d = 2.12 (s; 3H, H2),
3.51 (s, br; 2H, NH_2),
3.71 (s; 3H, H8),
6.60 (s; 1H, H4),
6.55 - 6.75 (m; 2H, H6, H7).

^{13}C nmr (100 MHz, $CDCl_3$): d = 17.6 (q, C2), 55.5 (q, C8), 111.9 (d, C6), 115.8, 116.2 (d, C4, C7), 123.8 (s, C3), 138.1 (s, C1), 152.5 (s, C5).

Ir (CH_2Cl_2): n =2931 cm^{-1} (s), 2831 (s), 1604 (s), 1498 (s), 1157 (s), 1044 (s).

Ms (EI, 70 eV): m/z (%) = 137 (85, M^+), 122 (100, M^+-CH_3), 94 (73), 77 (62), 66 (59).

- Reduction with Raney-nickel

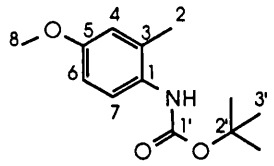
12 g of Raney-nickel alloy are heated with 400 ml of 2N NaOH-solution at 50 °C for 30 min. The water is decanted and the solid is washed several times with distilled water and ethanol. The catalyst is transferred together with 3-methyl-4-nitroanisole (20.7 g, 0.12 mol) and 200 ml of ethanol into a Parr-apparatus. Then the suspension is shaken in a hydrogen atmosphere at 60 psi for 24 h at 50 °C. The cold mixture is filtered through celite and the resulting green solution is evaporated to dryness to yield the crude 4-methoxy-2-methylaniline. The crude material is dissolved in ether, washed with water and extracted with dil. hydrochloric acid. The acidic solution of the salt is washed with ether to remove impurities. After cooling with ice, 20% aq. sodium hydroxide solution is added until the brown solution gives a basic reaction. The product is extracted with ether and the dried ethereal layer is distilled under reduced pressure to yield 14 g (0.10 mol, 85 %) of 4-methoxy-2-methylaniline (bp. 86 °C / 1 torr).

- Reduction with tin(II) chloride

60.0 g (0.36 mol) of 3-methyl-4-nitroanisole are heated on a steam bath with tin(II) chloride (270 g, 1.42 mol) in 350 ml conc. hydrochloric acid. After 4 h the brown heterogeneous mixture is made alkaline by adding sodium hydroxide pellets. The mixture is steam distilled and the product is extracted from the distillate with ether to yield 5.0 g (36 mmol, 10 %) of the crude amine.

4-Methoxy-2-methyl-N-(tert-butoxycarbonyl)aniline (223)

A solution of 4-methoxy-2-methylaniline (4.0 g, 0.03 mol) in 40 ml THF containing 7.2 g (0.033 mol) of di-tert-butyl dicarbonate is refluxed for 2 h. The solvent is removed by evaporation *in vacuo* and the oily residue is diluted with 25 ml of ethyl acetate. This solution is washed with an aqueous citric acid solution (1M) and brine. The dried organic layer is evaporated to yield a brown solid which is recrystallised from petroleum spirit in the presence of decolourising charcoal to give 6.9 g (29 mmol, 97 %) of colourless 4-methoxy-2-methyl-N-(tert-butoxycarbonyl)-aniline (mp. 88 - 89 °C).



^{1}H nmr (400 MHz, $CDCl_3$): d = 1.49 (s; 9H, H3'),
2.21 (s; 3H, H2),
3.75 (s; 3H, H8),
6.10 (s; 1H, H_{ar}),
6.65 - 6.75 (m; 2H, H_{ar}),
7.40 -7.50 (s, br; 1H, NH).

^{13}C nmr (100 MHz, $CDCl_3$): d = 18.0 (q, C2), 28.3 (q, C3'), 55.4 (q, C8), 80.1 (s, C2'), 111.4 (d, C6), 115.8 (d), 124.0 (s), 124.0 (s), 124.1 (s), 129.1 (d), 156.4 (s, C1').

Ir (KBr): n = 3325 cm^{-1} (s), 2965 (s), 1695 (s, CO) 1515 (s, CO), 1248 (s), 1168 (s).

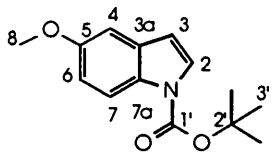
Ms (EI, 70 eV): m/z (%) = 237 (24, M^+), 181 (100, M^+-$C(CH_3)_3$), 163 (15, M^+-$OC(CH_3)_3$), 137 (32, M^+-$COOC(CH_3)_3$), 122 (50, M^+-$NHCOOC(CH_3)_3$), 57 (80, $C(CH_3)_3^+$).

CHN $C_{13}H_{19}NO_3$ calc. C 65.80 H 8.07 N 5.90
found C 66.06 H 8.11 N 5.47

5-Methoxy-N-tert-butoxycarbonylindole (226)

A solution of 4-methoxy-2-methyl-N-(tert-butoxycarbonyl)aniline (**223**, 0.8 g, 3.4 mmol) in 15 ml dry THF is cooled to - 40 °C and 5.8 ml of a 1.3 M solution of sec-butyl lithium in cyclohexane (7.4 mmol) is added at such a rate as to maintain the internal temperature below - 20 °C. During the addition of the second equivalent of the base, the colour of the mixture turns yellow. After 5 min at - 40 °C, dimethylformamide (0.53 ml, 6.8 mmol) is added. The colourless mixture is poured into water (30 ml) and the product is extracted with ether. The combined ethereal extracts are concentrated *in vacuo* and the residue of the intermediate alcohol is dissolved in 5 ml THF and treated with 0.2 ml of 12 N hydrochloric acid. This solution is stirred for 20 min at 20 °C (after 8 min the dehydration is over according to TLC [cyclohexane/ethyl acetate (10:1) R_f = 0.5 (alcohol), R_f = 0.9 (indole)]. Ether (30 ml) is added and the organic layer is washed with water (15 ml) and sat. sodium bicarbonate solution (15 ml). After drying over magnesium sulphate the solvent is removed by evaporation *in vacuo* to give a pale yellow solid, which was purified by spinning plate chromatography (silica gel,

cyclohexane/ethyl acetate (20:1)) to yield 0.8 g (3 mmol, 95 %) of pale yellow 5-methoxy-N-(tert-butoxycarbonyl)-indole (mp. 75 °C).



^{1}H nmr (400 MHz, $CDCl_3$): d = 1.66 (s; 9H, H3'),
3.80 (d, ^{5}J=0.7 Hz; 3H, H8),
6.48 (d, ^{3}J=4 Hz; 1H, H3),
6.94 (d, ^{3}J=9 Hz; 1H, H2),
7.00 (s; 1H, H4),
7.53 (d, ^{3}J=4 Hz; 1H, H_{ar}), 8.08 (d, ^{3}J=9 Hz; 1H, H_{ar}).

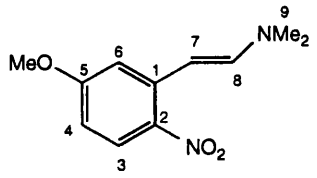
^{13}C nmr (100 MHz, $CDCl_3$): d = 27.8 (q, C3'), 55.1 (q, C8), 83.0 (s, C2'), 103.0 (d), 106.9 (s), 112.7 (d), 115.5 (d), 126.1, 129.6, 131.1 (s), 149.32 (s, C1'), 155.56 (s, C5).

Ir (KBr): n = 1722 (s), 1471 (s), 1444 (s), 1378 (s), 1268 (s), 1121 (s).

CHN	$C_{14}H_{17}NO_3$	calc.	C 68.00	H 6.93	N 5.66
		found	C 68.58	H 7.21	N 5.27

1-(N,N-Dimethylamino)-2-(2-nitro-5-methoxyphenyl)ethene (227)

A solution of 5-methoxy-2-nitrotoluene (10.5 g, 60 mmol) in dry DMF (100 ml) is treated with 1.2 eq. of N,N-dimethylformamide dimethylketal. The red mixture, which is placed in a flask fitted with a one-foot Vigreux-column attached with a variable still head, was refluxed at T≤71 °C for 22 h under nitrogen. Then the solvent is evaporated *in vacuo*. The residue 9.8 g (44 mmol, 74 %) solidifies at room temperature and is directly used for the reductive cyclisation.



^{1}H nmr (400 MHz, $CDCl_3$): d = 2.87 (s; 6H, H9),
3.81 (s; 3H, OMe),
6.03 (d, $^3J_{trans}$=13.3 Hz; 1H, H7),
6.46 (dd, $^4J_{4.6}$=2.7 Hz, $^3J_{4.3}$=9.3 Hz; 1H, H4),
6.78 (d, $^4J_{6.4}$=2.6 Hz; 1H, H6),
6.89 (d, $^3J_{trans}$=13.3 Hz; 1H, H8),
7.92 (d, $^3J_{3.4}$=9.2 Hz; 1H, H3).

^{13}C nmr (100 MHz, $CDCl_3$): d = 40.7 (q, C9), 55.5 (q, OMe), 92.2, 107.4, 109.15, 128.2, 128.2, 138.9, 144.9, 162.6.

Ir (CH_2Cl_2): n = 3039 (m), 1294-1240 (s), 910-890(s), 784-677 (s).

N,N-Dimethylformamide dimethylketal (229)

A mixture of N,N-dimethylformamide (73.2 g, 1 mol) and dimethyl sulphate (1 mol, 95 ml) is heated for 3 h at 70 °C to give a yellow mixture. Sodium (23 g, 1 mol) is dissolved in methanol (325 ml) and the yellow mixture is then added at 0 °C. A solid precipitates and the mixture is stirred mechanically under nitrogen for 16 h. The methanol is distilled over a one-foot Vigreux-column (bp. 64-68 °C). The boiling point of the product is 102 - 105 °C for the ketal of formamide (70 g), which is contaminated with 10 % N,N-dimethylformamide.

^{1}H nmr (200 MHz, $CDCl_3$): d = 3.12 (s; 6H, OMe),
3.18 (s; 6H, NMe),
3.80 (s; 1H).

3-Dimethylaminomethyl-5-methoxyindole (230)

At 0 °C a solution of 5-methoxyindole (**215**, 8.3 g, 56 mmol) in 1,4-dioxane (60 ml) is added dropwise to a mixture of acetic acid (60 ml), 1,4-dioxane (60 ml), formaldehyde (5.3 ml of a 37% solution in water, 66 mmol) and dimethylamine (11.8 ml of a 33% solution in methylated spirit). The mixture is stirred at 0 °C for another 2 h and is then allowed to warm to room temperature overnight. Sodium hydroxide solution (20 %) is added until a brown oil separates, which is extracted with ether (3x150 ml). The combined organic layers are washed with brine (100 ml) and extracted with

dil. hydrochloric acid (2M, 3x100 ml). The acidic extracts are then washed with ether (100 ml) and treated with diluted sodium hydroxide solution. The separated oil is extracted with ether (3x100 ml) and the ethereal layer is washed with brine and dried over calcium chloride. The solvent is evaporated to yield a colourless oil (9.5 g, 46 mmol, 83 %), which solidifies in the cold. An analytical sample is recrystallised from benzene/hexane 1:1. Mp. 122-23 °C.

^{1}H-nmr (400 MHz, $CDCl_3$): d = 2.31 (s; 6H, $N(CH_3)_2$),
3.61 (s; 2H, $-CH_2-$),
3.81 (s; 3H, OCH_3),
6.85 (dd, $^4J_{6,4}$=2.3 Hz, $^3J_{6,7}$=8.7 Hz; 1H, H6),
7.09 (d, $^4J_{4,6}$=2.2 Hz; 1H, H4),
7.14 (d, J=2.5 Hz; 1H, H2),
7.23 (d, $^3J_{7,6}$=8.8 Hz; 1H, H7),
8.23 (s, br; 1H, NH).

^{13}C-nmr (100 MHz, $CDCl_3$): d = 45.3 ($N(\underline{C}H_3)_2$), 54.5, 55.9 ($-\underline{C}H_2-$ and $O\underline{C}H_3$), 101.0 (d), 111.7 (d), 112.1 (d), 113.0 (C3), 124.4 (d), 128.3 (C3a), 131.3 (C7a), 154.0 (C5).

Ir (KBr): n = 3359 cm^{-1} (br, m; NH), 1480 (s; -OMe).

Ms (EI, 70 eV): m/z (%) = 204 (25, M^+), 160 (100, M^+-$N(CH_3)_2$), 116 (15), 89 (15).

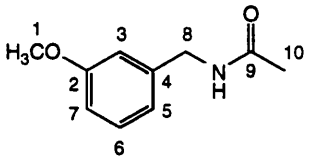
4-Bromo-5-methoxytryptamine (232)

A solution of 3-cyanomethyl-4-bromo-5-methoxyindole (**217**, 0.65 g, 2.5 mmol) in dry ether (50 ml) is added to a suspension of lithium aluminium hydride (1.0 g, 26 mmol) in ether (50 ml). The mixture is stirred for 16 h at 20 °C. Excess lithium aluminium hydride is decomposed by addition of water (5 ml). The solid is filtered under suction and washed with ether (200 ml). The ethereal layer is then extracted with 2N hydrochloric acid (2x50 ml) and the acidic layer is washed with ether (50 ml). Sodium hydroxide solution is added and the mixture is extracted with ether (2x50 ml). Drying and evaporation of the combined ether layers yields 0.60 g (2.3 mmol, 90 %) of solid 4-bromo-5-methoxytryptamine (decomp. 85 °C).

Ir (KBr): n = 3405 cm^{-1} (s, br; NH), 1461 (s; -OMe), 1425 (s), 1248 (m), 794 (s).

N-Acetyl-1-aminomethyl-3-methoxybenzene (233a)

3-Methoxybenzylamine (1.4 g, 10 mmol) is reacted with acetic anhydride (1 ml) in triethylamine (5 ml) and dichloromethane (20 ml) according to procedure A, VIII.2.6 to give 1.4 g (7.8 mmol, 78 %) of a colourless solid after SPC with dichloromethane. Mp. 58 - 59 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.00 (s; 3H, H10),
3.78 (s; 3H, H1),
4.36 (m; 2H, H8),
6.10 (s, br; 1H, NH),
6.79 - 6.85 (m; 3H, H_{ar}),
7.20 - 7.27 (m; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.1 (q, C10), 43.6 (t, C8), 55.2 (q, C1), 112.8, 113.4, 119.9, 129.6 (d, C3, C5, C6, C7), 139.8 (s, C5), 159.8 (s, C2), 170.1 (s, C9).

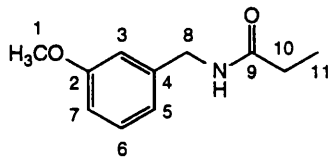
MS (EI, 70 eV): m/z = 179 (M^+, 2), 120 (M^+-NH_2COCH_3, 100), 107 (M^+-$CH_3NHCOCH_3$, 15).

Ir (KBr): ν = 3245 (s, NH), 3081 (m), 1651 (s, C=O), 1561 (s), 1245 (s, C-O), 755 (s).

CHN $C_{10}H_{13}NO_2$ calc. C 67.01 H 7.31 N 7.82
found C 66.83 H 7.17 N 7.70

N-Propanoyl-1-aminomethyl-3-methoxybenzene (233b)

3-Methoxybenzylamine (1.40 g, 10 mmol) is reacted with propanoic anhydride (1 ml) in triethylamine (5 ml) and dichloromethane (20 ml) according to procedure A, VIII.2.6 to give 1.30 g (6.8 mmol, 68 %) of a colourless solid after SPC (dichloromethane with 1 % methanol). Mp. 57 - 58 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.08 (t, $^3J_{11.10}$=7.6 Hz; 3H, H11),
2.15 (q, $^3J_{10.11}$=7.5 Hz; 2H, H10),
3.70 (s; 3H, H1),
4.27 (m; 2H, H8),
6.60 (s, br; 1H, NH),
6.72 - 6.78 (m; 3H, H_{ar}),
7.14 - 7.18 (m; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.7 (q, C11), 23.1 (t, C10), 43.6 (t, C8), 55.1 (q, C1), 112.8, 113.3, 119.9, 129.5 (d, C3, C5, C6, C7), 140.1 (s, C5), 159.6 (s, C2), 174.0 (s, C9).

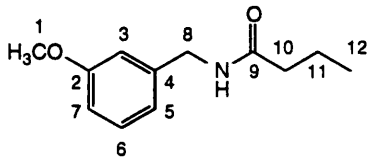
MS (EI, 70 eV): m/z = 193 (M^+, 4), 120 (M^+-$NH_2COC_2H_5$, 100), 107 (M^+-$CH_3NHCOC_2H_5$, 8).

Ir (KBr): ν = 3238 (s, NH), 3076 (m), 1650 (s, C=O), 1555 (s), 1249 (s, C-O), 750 (s).

CHN $C_{11}H_{15}NO_2$ calc. C 68.37 H 7.82 N 7.25
found C 68.20 H 7.77 N 7.19

N-Butanoyl-1-aminomethyl-3-methoxybenzene (233c)

3-Methoxybenzylamine (1.40 g, 10 mmol) is reacted with butanoic anhydride (1 ml) in triethylamine (5 ml) and dichloromethane (20 ml) according to procedure A, VIII.2.6 to give 1.5 g (7.3 mmol, 73 %) of a pale yellow solid after SPC with dichloromethane. Mp. 36 - 37 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{12.11}$=7.3 Hz; 3H, H12),
1.57 - 1.63 (m; 2H, H11),
2.11 (t, $^3J_{10.11}$=7.1 Hz; 2H, H10),
3.71 (s; 3H, H1),
4.30 (m; 2H, H8),

6.60 (s, br; 1H, NH),
6.73 - 6.79 (m; 3H, H_{ar}),
7.15 - 7.18 (m; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.5 (q, C12), 19.0 (t, C11), 38.2 (t, C10), 43.0 (t, C8), 54.9 (q, C1), 112.4, 113.0, 119.6, 129.3 (d, C3, C5, C6, C7), 140.0 (s, C5), 159.5 (s, C2), 173.0 (s, C9).

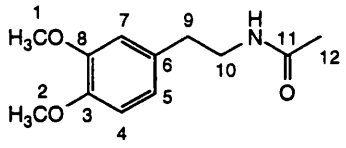
MS (EI, 70 eV): m/z = 207 (M^+, 0.4), 120 (M^+-$NH_2COC_3H_7$, 100), 107 (M^+-$CH_3NHCOC_3H_7$, 3).

Ir (KBr): ν = 3247 (s, NH), 3082 (m), 1653 (s, C=O), 1554 (m), 1240 (s, C-O), 759 (m).

CHN $C_{12}H_{17}NO_2$ calc. C 69.53 H 8.27 N 6.76
found C 68.74 H 8.30 N 6.69

N-Acetyl-2-(3,4-dimethoxyphenyl)ethanamine (234a)

2-(3,4-Dimethoxyphenyl)ethanamine (1.80 g, 10 mmol) is reacted with acetic anhydride (1 ml) in triethylamine (5 ml) and dichloromethane (20 ml) according to procedure A, VIII.2.6 to give 1.80 g (8.2 mmol, 82 %) of a colourless solid after SPC with dichloromethane. Mp. 95 - 96 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.90 (s; 3H, H12),
2.72 (t, $^3J_{9,10}$=7.0 Hz; 2H, H9),
3.44 (dt, $^3J_{10,9}$=7.0 Hz, $^3J_{10,NH}$=6.1 Hz; 2H, H10),
3.82 (s; 3H, H1 or H2),
3.82 (s; 3H, H1 or H2),
5.65 (s, br; 1H, NH),
6.67 (s; 1H, H7),
6.69 (d, ^3J=7.8 Hz; 1H, H4 or H5),
6.76 (d, ^3J=7.9 Hz; 1H, H4 or H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.2 (q, C12), 35.1, 40.7 (t, C9, C10), 55.7, 55.8 (q, C1, C2), 111.2, 111.7, 120.5 (d, C4, C5, C7), 131.2 (s, C6), 147.5, 148.9 (s, C3, C8), 170.0 (s, C11).

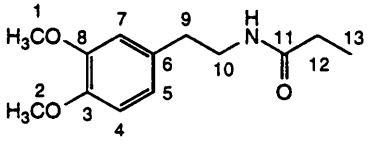
MS (EI, 70 eV): m/z = 223 (M^+, 2), 164 (M^+-NH_2COCH_3, 100), 151 (M^+-$CH_3NHCOCH_3$, 48).

Ir (KBr): ν = 3245 (s, NH), 3080 (m), 1655 (s, C=O), 1550 (s), 1242 (s,br, C-O), 750 (m).

CHN $C_{12}H_{17}NO_3$ calc. C 69.55 H 7.68 N 6.28
found C 68.94 H 7.60 N 6.10

N-Propanoyl-2-(3,4-dimethoxyphenyl)ethanamine (234b)

2-(3,4-Dimethoxyphenyl)ethanamine (1.8 g, 10 mmol) is reacted with propanoic anhydride (1 ml) in triethylamine (5 ml) and dichloromethane (20 ml) according to procedure A, VIII.2.6 to give after SPC with dichloromethane 1.50 g (6.2 mmol, 62 %) of a colourless oil, which solidifies in the cold. Mp. 43 - 44 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.06 (t, $^3J_{13.12}$=7.5 Hz; 3H, H13),
2.10 (q, $^3J_{12.13}$=7.6 Hz; 2H, H12),
2.69 (t, $^3J_{9.10}$=7.0 Hz; 2H, H9),
3.41 (dt, $^3J_{10.9}$=7.0 Hz, $^3J_{10.NH}$=6.1 Hz; 2H, H10),
3.78 (s; 3H, H1 or H2),
3.79 (s; 3H, H1 or H2),
5.73 (s, br; 1H, NH),
6.65 - 6.67 (m; 2H, H_{ar}),
6.73 (d, ^3J=8.6 Hz; 1H, H4 or H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.8 (q, C13), 29.5 (t, C12), 35.1, 40.5 (t, C9, C10), 55.6, 55.7 (q, C1, C2), 111.1, 111.7, 120.4 (d, C4, C5, C7), 131.3 (s, C6), 147.4, 148.8 (s, C3, C8), 173.7 (s, C11).

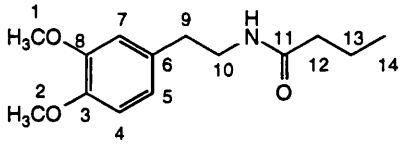
MS (EI, 70 eV): m/z = 237 (M^+, 4), 164 (M^+-$NH_2COC_2H_5$, 100), 151 (M^+-$CH_3NHCOC_2H_5$, 44).

Ir (KBr): ν = 3243 (s, NH), 3082 (m), 1654 (s, C=O), 1553 (m), 1240 (s,br, C-O), 750 (m).

CHN $C_{13}H_{19}NO_3$ calc. C 65.80 H 8.07 N 5.90
found C 65.63 H 7.69 N 5.71

N-Butanoyl-2-(3,4-dimethoxyphenyl)ethanamine (234c)

2-(3,4-Dimethoxyphenyl)ethanamine (1.80 g, 10 mmol) is reacted with butanoic anhydride (1 ml) in triethylamine (5 ml) and dichloromethane (20 ml) according to procedure A, VIII.2.6 to give after SPC with dichloromethane 1.70 g (6.8 mmol, 68 %) of a colourless oil, which solidifies slowly. Mp. 48.5 - 49.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{14.13}$=7.3 Hz; 3H, H14),
1.58 - 1.69 (m; 2H, H13),
2.08 (t, $^3J_{12.13}$=7.3 Hz; 2H, H12),
2.74 (t, $^3J_{9.10}$=7.0 Hz; 2H, H9),
3.47 (dt, $^3J_{10.9}$=6.7 Hz, $^3J_{10.NH}$=6.4 Hz; 2H, H10),
3.84 (s; 6H, H1, H2),
5.43 (s, br; 1H, NH),
6.69 (s; 1H, H7),
6.70 (d, ^3J=7.3 Hz; 1H, H4 or H5),
6.78 (d, ^3J=7.6 Hz; 1H, H4 or H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C14), 19.1 (t, C13), 35.3 (t, C9 or C10), 38.7 (t, C12), 40.6 (t, C9 or C10), 55.8, 55.9 (q, C1, C2), 111.2, 111.8, 120.6 (d, C4, C5, C7), 131.4 (s, C6), 147.6, 149.0 (s, C3, C8), 173.0 (s, C11).

MS (EI, 70 eV): m/z = 251 (M^+, 0.5), 164 (M^+-$NH_2COC_3H_7$, 100), 151 (M^+-$CH_3NHCOC_3H_7$, 25).

Ir (KBr): ν = 3240 (s, NH), 3087 (m), 1652 (s, C=O), 1549 (m), 1239 (s,br, C-O), 746 (s).

CHN $C_{14}H_{21}NO_3$ calc. C 66.90 H 8.42 N 5.57
found C 66.72 H 8.30 N 5.43

2-Methoxyphenylacetic acid (236a)

A 25 °C dimethyl sulphate (17.0 g, 130 mmol) is added dropwise to a solution of 4-hydroxyphenylacetic acid (10.2 g, 67 mmol) in 10 % sodium hydroxide (100 ml). After refluxing the mixture for 30 min, it is cooled to 20 °C, washed with dichloromethane and acidified with dil.

hydrochloric acid to give a colourless solid (8.9 g, 0.10 mol, 80 %) with mp. 121 - 122 °C (lit. 122 - 125 °C[254]).

^{1}H-nmr (200 MHz, $CDCl_3$): δ = 3.72 (s; 2H, CH_2),
3.84 (s; 3H, OMe),
6.88 - 7.02(m; 2H, H_{ar}),
7.20 - 7.40 (m; 2H, H_{ar}).

- Attempted synthesis of 2-methoxyphenylacetamide (**238**)

A solution of 2-methoxyphenylacetic acid (9.3 g, 56 mmol) in 1,4-dioxane (40 ml) is treated with thionyl chloride (10 g, 84 mmol). The mixture is stirred at 40 °C until cessation of gas evolution and is then poured into a cold ammonium hydroxide solution (200 ml). No product is obtained by extraction of the alkaline solution with dichloromethane. After acidification with dil. hydrochloric acid a white solid precipitates, which is identical to the starting material.

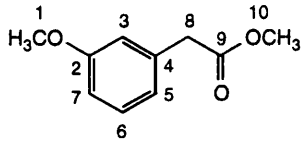
4-Methoxyphenylacetic acid (236c)

A 25 °C dimethyl sulphate (17 g, 130 mmol) is added dropwise to a solution of 4-hydroxyphenylacetic acid (10.2 g, 67 mmol) in 10 % sodium hydroxide (100 ml). After refluxing the mixture for 30 min, it is cooled to 20 °C, washed with dichloromethane and acidified with dil. hydrochloric acid. Extraction with dichloromethane (2x20 ml) gives a colourless solid (8.0 g, 0.09 mol, 72 %) with mp. 85.5 - 86.5 °C (lit. 86 - 88.5 °C[254]).

^{1}H-nmr (200 MHz, $CDCl_3$): δ = 3.60 (s; 2H, CH_2),
3.80 (s; 3H, OMe),
6.89 (d, ^{3}J=9.0 Hz; 2H, H_{ar}),
7.22 (d, ^{3}J=9.0 Hz; 2H, H_{ar}).

Methyl 2-(3-methoxyphenyl)acetate (237b)

A solution of 3-methoxyphenylacetic acid (5.0 g, 30 mmol) in dichloromethane (50 ml) is reacted with triethylamine (3.0 g, 30 mmol) and methyl chloroformate (2.8 g, 30 mmol) according to procedure VIII.2.4 to give after treatment with ammonia a colourless solid (4.8 g, 27 mmol, 89 %) with mp. 30 - 32 °C.

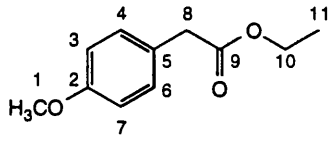


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 3.59 (s; 2H, H8),
3.67 (s; 3H, H10),
3.77 (s; 3H, H1),
6.83 (s; 1H, H3),
6.79 - 6.86 (m; 2H, H_{ar}),
7.22 (dd, ^3J=7.9 Hz, ^3J=7.6 Hz; 1H, H6).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 41.0 (t, C8), 51.9 (q, C10), 55.0 (q, C1), 112.4, 114.7, 121.4, 129.4 (d, C3, C5, C6, C7), 135.2 (s, C5), 159.5 (s, C2), 171.7 (s, C9).

Ethyl 2-(4-methoxyphenyl)acetate (237c)

A solution of 4-methoxyphenylacetic acid (5.0 g, 30 mmol) in dichloromethane (50 ml) is reacted with triethylamine (3.0 g, 30 mmol) and ethyl chloroformate (3.1 g, 30 mmol) according to procedure VIII.2.4 to give after treatment with ammonia a colourless oil (4.5 g, 25 mmol, 83 %).

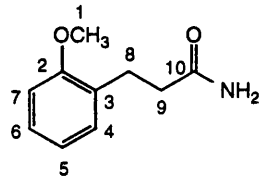


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{11.10}$=7.1 Hz; 3H, H11),
3.56 (s; 2H, H8),
3.78 (s; 3H, H1),
4.15 (q, $^3J_{10.11}$=7.1 Hz; 2H, H10),
6.87 (d, ^3J=8.8 Hz; 2H, H_{ar}),
7.21 (d, ^3J=8.7 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.0 (q, C11), 40.3 (t, C8), 55.0 (q, C1), 60.6 (t, C10), 113.8, 130.1 (d, C3, C4, C6, C7), 126.1 (s, C5), 158.5 (s, C2), 171.8 (s, C9).

3-(2-Methoxyphenyl)propanamide (240a)

A solution of 3-(2-methoxyphenyl)propionic acid (5.0 g, 28 mmol) in dichloromethane (50 ml) is reacted with triethylamine (2.8 g, 28 mmol) and methyl chloroformate (2.6 g, 28 mmol) according to procedure VIII.2.4 to give after treatment with ammonia a colourless solid (3.2 g, 18 mmol, 65 %) with mp. 112 - 112.5 °C.

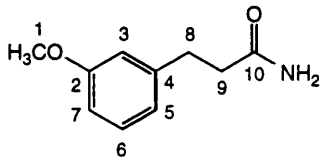


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.49 (t, $^3J_{8,9}$=8.0 Hz; 2H, H8),
2.92 (t, $^3J_{9,8}$=8.1 Hz; 2H, H9),
3.80 (s; 3H, H1),
5.52 (s, br; 1H, NH),
5.75 (s, br; 1H, NH),
6.81 - 6.88 (m; 2H, H_{ar}),
7.12 - 7.20 (m; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.5, 36.0 (t, C8, C9), 55.3 (q, C1), 110.3, 120.6, 127.7, 130.0 (d, C4, C5, C6, C7), 128.9 (s, C3), 157.3 (s, C2), 175.3 (s, C10).

3-(3-Methoxyphenyl)propanamide (240b)

A solution of 3-(3-methoxyphenyl)propionic acid (5.4 g, 30 mmol) in dichloromethane (50 ml) is reacted with triethylamine (3.0 g, 30 mmol) and methyl chloroformate (2.8 g, 30 mmol) according to procedure VIII.2.4 to give after treatment with ammonia a colourless solid (3.9 g, 22 mmol, 72 %) with mp. 51 - 52 °C.



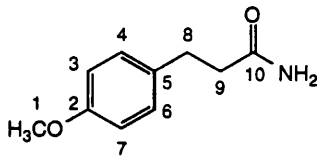
^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.49 (t, $^3J_{8,9}$=8.1 Hz; 2H, H8),
2.90 (t, $^3J_{9,8}$=8.1 Hz; 2H, H9),
3.75 (s; 3H, H1),
5.58 (s, br; 1H, NH),

5.96 (s, br; 1H, NH),
6.73 (s; 1H,H3),
6.71 - 6.78 (m; 2H, H_{ar}),
7.18 (ddd, ^3J=7.3Hz, ^3J=7.5Hz, ^4J=1.2Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 31.3, 37.3 (t, C8, C9), 55.1 (q, C1), 111.4, 114.0, 120.5, 129.5 (d, C3, C5, C6, C7), 142.3 (s, C5), 159.6 (s, C2), 174.8 (s, C10).

3-(4-Methoxyphenyl)propanamide (240c)

A solution of 3-(4-methoxyphenyl)propionic acid (5.4 g, 30 mmol) in dichloromethane (50 ml) is reacted with triethylamine (3.0 g, 30 mmol) and methyl chloroformate (2.8 g, 30 mmol) according to procedure VIII.2.4 to give after treatment with ammonia a colourless solid (3.6 g, 20 mmol, 67 %).

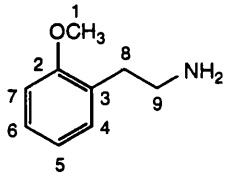


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 2.45 (t, $^3J_{8,9}$=8.0 Hz; 2H, H8),
2.87 (t, $^3J_{9,8}$=8.1 Hz; 2H, H9),
3.75 (s; 3H, H1),
5.55 (s, br; 1H, NH),
5.93 (s, br; 1H, NH),
6.79 (d, ^3J=8.7 Hz; 2H, H_{ar}),
7.09 (d, ^3J=8.8 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 30.5, 37.8 (t, C8, C9), 55.2 (q, C1), 113.9, 129.2 (d, C3, C4, C6, C7), 132.6 (s, C5), 158.0 (s, C2), 174.9 (s, C10).

2-(2-Methoxyphenyl)ethanamine (241a)

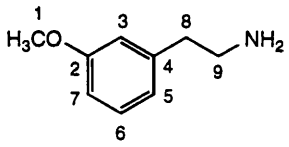
A solution of sodium hypobromide is prepared by treating a solution of sodium hydroxide (5.0 g) in water (45 ml) with bromine (1.3 ml). This solution is then added to 3-(2-methoxyphenyl)propionamide (**240a**, 3.7 g, 20 mmol) at 0 °C. The mixture is stirred at 60 °C for 30 min and is then poured into dil. hydrochloric acid. After washing with dichloromethane sodium hydroxide solution is added to give a yellow oil (1.0 g, 7.0 mmol, 35 %) after extraction with dichloromethane.



^{1}H-nmr (200 MHz, $CDCl_3$): δ = 1.15 (s, br; 2H, NH),
2.72 (t, $^3J_{8,9}$=6.8 Hz; 2H, H8),
2.88 (t, $^3J_{9,8}$=6.8 Hz; 2H, H9),
3.76 (s; 3H, H1),
6.80 - 6.90 (m; 2H, H_{ar}),
7.10 - 7.22 (m; 2H, H_{ar}).

2-(3-Methoxyphenyl)ethanamine (241b)

A solution of sodium hypobromide is prepared by treating a solution of sodium hydroxide (5.0 g) in water (45 ml) with bromine (1.3 ml). This solution is then added to 3-(3-methoxyphenyl)propionamide (**240b**, 3.7 g, 20 mmol) at 0 °C. The heterogeneous mixture is stirred at 60 °C for 30 min and is then poured into dil. hydrochloric acid. After washing with dichloromethane sodium hydroxide solution is added to give a yellow oil (1.6 g, 11.2 mmol, 56 %) after extraction with dichloromethane.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.21 (s, br; 2H, NH),
2.71 (t, $^3J_{8,9}$=6.8 Hz; 2H, H8),
2.93 (t, $^3J_{9,8}$=6.8 Hz; 2H, H9),
3.76 (s; 3H, H1),
6.73 - 6.78 (m; 3H, H_{ar}),
7.19 (dd, ^3J=8.2 Hz, ^3J=7.5 Hz; 1H, H_{ar}).

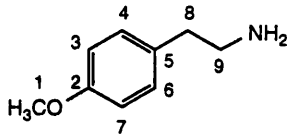
^{13}C-nmr (100 MHz, $CDCl_3$): δ = 39.9 (t, C8), 43.3 (t, C9), 54.9 (q, C1), 111.2, 114.4, 121.0, 129.2 (d, C3, C5, C6, C7), 141.3 (s, C5), 159.5 (s, C2).

MS (EI, 70 eV): m/z = 151 (M^+, 26), 134 (M^+-NH_3, 10), 122 (M^+-CH_2NH, 23), 78 (33), 30 (100).

Ir (film): ν = 3300 (s, NH), 2967 (s), 1240 (m, C-O).

2-(4-Methoxyphenyl)ethanamine (241c)

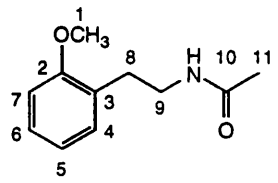
A solution of sodium hypobromide is prepared by treating a solution of sodium hydroxide (4.6 g) in water (40 ml) with bromine (1.2 ml). This solution is then added to 3-(4-methoxyphenyl)propionamide (**240c**, 3.4 g, 19 mmol) at 0 °C. The heterogeneous mixture is stirred at 60 °C for 30 min and is then poured into dil. hydrochloric acid. After washing with dichloromethane sodium hydroxide solution is added to give a yellow oil (1.9 g, 12.7 mmol, 67 %) after extraction with dichloromethane.



^{1}H-nmr (200 MHz, $CDCl_3$): δ = 1.10 (s, br; 2H, NH),
2.56 (t, $^3J_{8,9}$=7.0 Hz; 2H, H8),
2.82 (t, $^3J_{9,8}$=7.0 Hz; 2H, H9),
3.66 (s; 3H, H1),
6.75 (d, ^3J=8.0 Hz; 2H, H_{ar}),
7.04 (d, ^3J=8.2 Hz; 1H, H_{ar}).

N-Acetyl-2-(2-methoxyphenyl)ethanamine (242a)

2-(2-Methoxyphenyl)ethanamine (**241a**, 0.15 g, 1 mmol) is treated with acetic anhydride (0.5 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.17 g, 0.9 mmol, 88 %) with mp. 84 - 85 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.93 (s; 3H, H11),
2.84 (t, $^3J_{8,9}$=6.6 Hz; 2H, H8),
3.48 (dt, $^3J_{9,8}$=6.7 Hz, $^3J_{9,NH}$=6.6 Hz; 2H, H9),
3.85 (s; 3H, H1),
5.72 (s, br; 1H, NH),
6.87 - 6.94 (m; 2H, H_{ar}),

7.14 (d, ^3J=7.5 Hz; 1H, H_{ar}),

7.24 (dd,^3J=8.0 Hz,^3J=7.8 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.3 (q, C11), 30.1 (t, C8), 39.8 (t, C9), 55.2 (q, C1), 110.3, 120.5, 127.8, 130.6 (d, C4, C5, C6, C7), 127.3 (s, C3), 157.4 (s, C2), 170.0 (s, C11).

MS (EI, 70 eV): m/z = 193 (M^+, 2), 134 (M^+-NH_2COCH_3, 100), 121 (M^+-$CH_3NHCOCH_3$, 51), 91 (100).

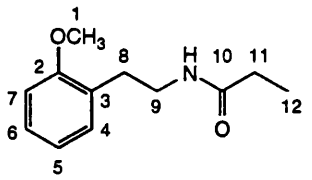
Ir (KBr): ν = 3266 (s, NH), 3080 (m), 1650 (s, C=O), 1561 (s), 1245 (s, C-O), 755 (s).

CHN $C_{11}H_{15}NO_2$ calc. C 68.37 H 7.82 N 7.25

found C 68.02 H 7.69 N 7.18

N-Propanoyl-2-(2-methoxyphenyl)ethanamine (242b)

2-(2-Methoxyphenyl)ethanamine (**241a**, 0.15 g, 1 mmol) is treated with propanoic anhydride (0.5 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.19 g, 0.9 mmol, 92 %) with mp. 53 - 54 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.09 (t, $^3J_{12.11}$=7.7 Hz; 3H, H12),

2.12 (q, $^3J_{11.12}$=7.6 Hz; 2H, H11),

2.81 (t, $^3J_{8.9}$=6.7 Hz; 2H, H8),

3.46 (dt, $^3J_{9.8}$=6.5 Hz, $^3J_{9.NH}$=5.6 Hz; 2H, H9),

3.82 (s; 3H, H1),

5.68 (s, br; 1H, NH),

6.84 - 6.90 (m; 2H, H_{ar}),

7.10 (dd, ^3J=7.5 Hz, ^4J=1.6 Hz; 1H, H_{ar}),

7.20 (ddd,^3J=8.1 Hz,^3J=8.0 Hz ,^4J=1.7 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.8 (q, C12), 29.8 (t, C11), 30.1 (t, C8), 39.8 (t, C9), 55.2 (q, C1), 110.3, 120.7, 127.8, 130.6 (d, C4, C5, C6, C7), 127.4 (s, C3), 157.4 (s, C2), 173.0 (s, C11).

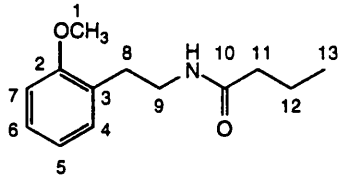
MS (EI, 70 eV): m/z = 207 (M^+, 5), 134 (M^+-$NH_2COC_2H_5$, 100), 121 (M^+-$CH_3NHCOC_2H_5$, 47), 91 (100).

Ir (KBr): ν = 3268 (s, NH), 3073 (m), 1641 (s, C=O), 1540 (m), 1247 (s, C-O), 759 (s).

CHN $C_{12}H_{17}NO_2$ calc. C 69.54 H 8.27 N 6.75
found C 69.21 H 7.89 N 6.67

N-Butanoyl-2-(2-methoxyphenyl)ethanamine (242c)

2-(2-Methoxyphenyl)ethanamine (**241a**, 0.15 g, 1 mmol) is treated with butanoic anhydride (0.5 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless oil (0.15 g, 0.7 mmol, 68 %) after SPC with dichloromethane/1% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{13,12}$=7.4 Hz; 3H, H13),
1.61 (se; 2H, H12),
2.09 (t, $^3J_{11,12}$=7.9 Hz; 2H, H11),
2.83 (t, $^3J_{8,9}$=6.8 Hz; 2H, H8),
3.48 (dt, $^3J_{9,8}$=6.7 Hz, $^3J_{9,NH}$=5.7 Hz; 2H, H9),
3.83 (s; 3H, H1),
5.83 (s, br; 1H, NH),
6.86 (d, ^3J=8.3 Hz; 1H, H_{ar}),
6.90 (ddd, ^3J=8.2 Hz, ^3J=8.4 Hz, ^4J=1.0 Hz; 1H, H_{ar}),
7.12 (dd, ^3J=7.2 Hz, ^4J=1.3 Hz; 1H, H_{ar}),
7.22 (ddd, ^3J=8.2 Hz, ^3J=8.0 Hz, ^4J=1.7 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C13), 19.0 (t, C12), 30.1 (t, C8), 38.6 (t, C11), 39.6 (t, C9), 55.2 (q, C1), 110.2, 120.6, 127.7, 130.5 (d, C4, C5, C6, C7), 127.3 (s, C3), 157.3 (s, C2), 172.9 (s, C11).

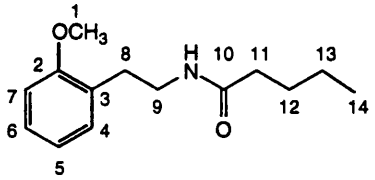
MS (EI, 70 eV): m/z = 221 (M^+, 7), 134 (M^+-$NH_2COC_3H_7$, 100), 121 (M^+-$CH_3NHCOC_3H_7$, 44), 91 (100).

Ir (KBr): ν = 3268 (s, NH), 3064 (m), 1650 (s, C=O), 1558 (m), 1241 (s, C-O), 750 (m).

CHN $C_{13}H_{19}NO_2$ calc. C 70.55 H 8.65 N 6.33
found C 70.09 H 8.33 N 6.30

N-Pentanoyl-2-(2-methoxyphenyl)ethanamine (242d)

2-(2-Methoxyphenyl)ethanamine (**241a**, 0.15 g, 1 mmol) is treated with valeroyl chloride (0.5 ml) in triethylamine and dichloromethane according to procedure B, VIII.2.6 to give a colourless oil (0.15 g, 0.6 mmol, 64 %) after SPC with dichloromethane/1% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{14,13}$=7.4 Hz; 3H, H14),
1.28 (m; 2H, H12 or H13),
1.55 (m; 2H, H12 or H13),
2.10 (t, $^3J_{11,12}$=7.7 Hz; 2H, H11),
2.83 (t, $^3J_{8,9}$=6.8 Hz; 2H, H8),
3.46 (dt, $^3J_{9,8}$=6.6 Hz, $^3J_{9,NH}$=5.8 Hz; 2H, H9),
3.81 (s; 3H, H1),
5.90 (s, br; 1H, NH),
6.84 - 6.90 (m; 2H, H_{ar}),
7.11 (dd, ^3J=7.3 Hz; 1H, H_{ar}),
7.19 (ddd, ^3J=7.8; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C14), 22.2, 27.7 (t, C12, C13), 30.0 (t, C8), 36.4 (t, C11), 39.6 (t, C9), 55.1 (q, C1), 110.2, 120.5, 127.7, 130.4 (d, C4, C5, C6, C7), 127.3 (s, C3), 157.3 (s, C2), 173.0 (s, C11).

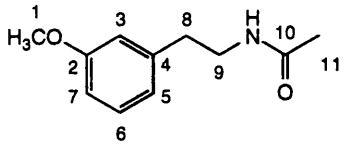
MS (EI, 70 eV): m/z = 235 (M^+, 17), 134 (M^+-$NH_2COC_4H_9$, 100), 121 (M^+-$CH_3NHCOC_4H_9$, 38), 91 (100).

Ir (KBr): ν = 3268 (s, NH), 3064 (m), 1650 (s, C=O), 1558 (m), 1241 (s, C-O), 750 (m).

CHN $C_{14}H_{21}NO_2$ calc. C 71.45 H 9.00 N 5.95
found C 71.06 H 8.93 N 5.84

N-Acetyl-2-(3-methoxyphenyl)ethanamine (243a)

2-(3-Methoxyphenyl)ethanamine (**241b**, 0.45 g, 2.6 mmol) is treated with acetic anhydride (1 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a pale yellow oil (0.35 g, 1.8 mmol, 70 %) after SPC with dichloromethane/5% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.90 (s; 3H, H11),
2.75 (t, $^3J_{8,9}$=7.0 Hz; 2H, H8),
3.47 (q, $^3J_{9,8}$=7.0 Hz, $^3J_{9,NH}$=5.9 Hz; 2H, H9),
3.76 (s; 3H, H1),
5.73 (s, br; 1H, NH),
6.70 - 6.80 (m; 3H, H_{ar}),
7.19 (dd, ^3J=7.9 Hz, ^3J=7.7 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.3 (q, C11), 35.6 (t, C8), 40.5 (t, C9), 55.1 (q, C1), 111.7, 114.4, 121.0, 129.6 (d, C3, C5, C6, C7), 140.5 (s, C5), 159.7 (s, C2), 170.1 (s, C10).

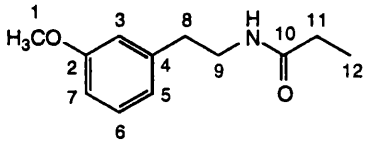
MS (EI, 70 eV): m/z = 193 (M^+, 25), 134 (M^+-NH_2COCH_3, 100), 121 (M^+-$CH_3NHCOCH_3$, 67), 57 (100).

Ir (film): ν = 3292 (s, NH), 2935 (s), 1644 (s, C=O), 1440 (s), 1224 (m, C-O).

CHN $C_{11}H_{15}NO_2$ calc. C 68.37 H 7.82 N 7.25
found C 67.98 H 7.49 N 7.27

N-Propanoyl-2-(3-methoxyphenyl)ethanamine (243b)

2-(3-Methoxyphenyl)ethanamine (**241b**, 0.45 g, 2.6 mmol) is treated with propanoic anhydride (1 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a yellow oil (0.37 g, 1.8 mmol, 69 %) after SPC with dichloromethane/2% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.11 (t, $^3J_{12,11}$=7.7 Hz; 3H, H12),
2.17 (q, $^3J_{11,12}$=7.5 Hz; 2H, H11),
2.77 (t, $^3J_{8,9}$=7.0 Hz; 2H, H8),
3.48 (q, $^3J_{9,8}$=7.0 Hz, $^3J_{9,NH}$=6.0 Hz; 2H, H9),
3.77 (s; 3H, H1),
5.78 (s, br; 1H, NH),

6.72 - 6.77 (m; 3H, H_{ar}),

7.20 (dd, ^3J=7.8 Hz, ^3J=7.7 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.8 (q, C12), 29.6 (t, C11), 35.6 (t, C8), 40.4 (t, C9), 55.0 (q, C1), 111.7, 114.3, 120.9, 129.5 (d, C3, C5, C6, C7), 140.5 (s, C5), 159.6 (s, C2), 173.8 (s, C10).

MS (EI, 70 eV): m/z = 207 (M^+, 30), 134 (M^+-$NH_2COC_2H_5$, 100), 121 (M^+-$CH_3NHCOC_2H_5$, 50), 57 (98).

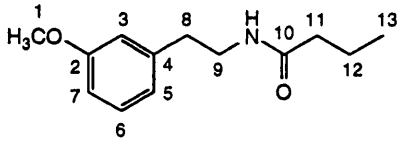
Ir (film): ν = 3290 (s, NH), 2940 (s), 1645 (s, C=O), 1443 (s), 1226 (m, C-O).

CHN $C_{12}H_{17}NO_2$ calc. C 69.53 H 8.27 N 6.76

found C 68.47 H 8.03 N 5.66

N-Butanoyl-2-(3-methoxyphenyl)ethanamine (243c)

2-(3-Methoxyphenyl)ethanamine (**241b**, 0.45 g, 2.6 mmol) is treated with butanoic anhydride (1 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a yellow oil (0.45 g, 2.0 mmol, 78 %) after SPC with dichloromethane/2% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{13,12}$=7.4 Hz; 3H, H13),

1.60 (m; 2H, H12),

2.07 (t, $^3J_{11,12}$=7.4 Hz; 2H, H11),

2.76 (t, $^3J_{8,9}$=6.9 Hz; 2H, H8),

3.48 (q, $^3J_{9,8}$=6.9 Hz, $^3J_{9,NH}$=6.0 Hz; 2H, H9),

3.76 (s; 3H, H1),

5.58 (s, br; 1H, NH),

6.70 - 6.76 (m; 3H, H_{ar}),

7.19 (dd, ^3J=8.0 Hz, ^3J=7.8 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C13), 19.1 (t, C12), 35.7 (t, C8), 38.6 (t, C11), 40.3 (t, C9), 55.1 (q, C1), 111.8, 114.3, 121.0, 129.5 (d, C3, C5, C6, C7), 140.5 (s, C5), 159.7 (s, C2), 172.9 (s, C10).

MS (EI, 70 eV): m/z = 221 (M^+, 42), 134 (M^+-$NH_2COC_3H_7$, 100), 121 (M^+-$CH_3NHCOC_3H_7$, 43), 57 (91).

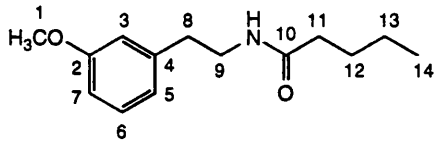
Ir (film): ν = 3299 (s, NH), 2963 (s), 1638 (s, C=O), 1440 (s), 1223 (m, C-O).

CHN $C_{13}H_{19}NO_2$ calc. C 70.55 H 8.65 N 6.33

found C 69.67 H 8.49 N 6.30

N-Pentanoyl-2-(3-methoxyphenyl)ethanamine (243d)

2-(3-Methoxyphenyl)ethanamine (**241b**, 0.45 g, 2.6 mmol) is treated with valeroyl chloride (0.7 ml) in triethylamine and dichloromethane according to procedure B, VIII.2.6 to give a yellow oil (0.52 g, 2.2 mmol, 85 %) after SPC with dichloromethane/ 1% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.82 (t, $^3J_{14,13}$=7.3 Hz; 3H, H14),
1.25 (se; 2H, H13),
1.50 (qi; 2H, H12),
2.08 (t, $^3J_{11,12}$=7.8 Hz; 2H, H11),
2.73 (t, $^3J_{8,9}$=7.0 Hz; 2H, H8),
3.42 (q, $^3J_{9,8}$=7.1 Hz, $^3J_{9,NH}$=5.9 Hz; 2H, H9),
3.72 (s; 3H, H1),
6.05 (s, br; 1H, NH),
6.68 - 6.72 (m; 3H, H_{ar}),
7.15 (dd, ^3J=7.9 Hz, ^3J=7.6 Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6 (q, C14), 22.2 (t, C13), 27.7 (t, C12), 35.6 (t, C8), 36.2 (t, C11), 40.3 (t, C9), 54.9 (q, C1), 111.5, 114.2, 120.8, 129.3 (d, C3, C5, C6, C7), 140.4 (s, C5), 159.5 (s, C2), 173.1 (s, C10).

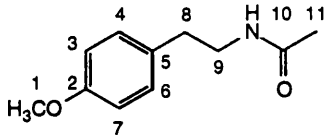
MS (EI, 70 eV): m/z = 235 (M^+, 54), 134 (M^+-$NH_2COC_4H_9$, 100), 121 (M^+-$CH_3NHCOC_4H_9$, 64), 57 (100).

Ir (film): ν = 3283 (s, NH), 2967 (s), 1645 (s, C=O), 1441 (s), 1228 (m, C-O).

CHN $C_{14}H_{21}NO_2$ calc. C 71.45 H 9.00 N 5.95
found C 70.73 H 8.82 N 5.88

N-Acetyl-2-(4-methoxyphenyl)ethanamine (244a)

2-(4-Methoxyphenyl)ethanamine (**241c**, 0.5 g, 3 mmol) is treated with acetic anhydride (0.3 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.5 g, 2.6 mmol, 86 %) after SPC with dichloromethane/5% methanol. Mp. 83.5 - 84.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.96 (s; 3H, H11),
2.78 (t, $^3J_{8,9}$=7.3 Hz; 2H, H8),
3.48 (dt, $^3J_{9,8}$=7.1 Hz, $^3J_{9,NH}$=5.9 Hz; 2H, H9),
3.81 (s; 3H, H1),
5.97 (s, br; 1H, NH),
6.87 (d, ^3J=8.7 Hz; 2H, H_{ar}),
7.13 (d, ^3J=8.6 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.1 (q, C11), 34.6 (t, C8), 40.8 (t, C9), 55.1 (q, C1), 113.9, 129.5 (d, C3, C4, C6, C7), 130.7 (s, C5), 158.1 (s, C2), 170.1 (s, C10).

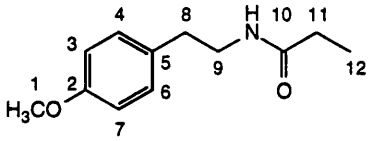
MS (EI, 70 eV): m/z = 193 (M^+, 0.2), 134 (M^+-NH_2COCH_3, 100), 121 (M^+-$CH_3NHCOCH_3$, 100), 78 (52).

Ir (KBr): ν = 3287 (s, NH), 3087 (m), 1638 (s, C=O), 1515 (s), 1251 (s, C-O).

CHN $C_{11}H_{15}NO_2$ calc. C 68.37 H 7.82 N 7.25
found C 68.01 H 7.46 N 7.13

N-Propanoyl-2-(4-methoxyphenyl)ethanamine (244b)

2-(4-Methoxyphenyl)ethanamine (**241c**, 0.5 g, 3 mmol) is treated with propanoic anhydride (0.4 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.4 g, 1.9 mmol, 64 %) after SPC with dichloromethane/2% methanol. Mp. 79 - 80 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.11 (t, $^3J_{12,11}$=7.7 Hz; 3H, H12),
2.17 (q, $^3J_{11,12}$=7.5 Hz; 2H, H11),
2.74 (t, $^3J_{8,9}$=7.0 Hz; 2H, H8),
3.44 (q, $^3J_{9,8}$=7.1 Hz, $^3J_{9,NH}$=5.9 Hz; 2H, H9),
3.76 (s; 3H, H1),
5.60 (s, br; 1H, NH),
6.82 (d, ^3J=8.7 Hz; 2H, H_{ar}),
7.07 (d, ^3J=8.7 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.8 (q, C12), 29.6 (t, C11), 34.7 (t, C8), 40.6 (t, C9), 55.1 (q, C1), 113.9, 129.6 (d, C3, C4, C6, C7), 130.8 (s, C5), 158.1 (s, C2), 173.7 (s, C10).

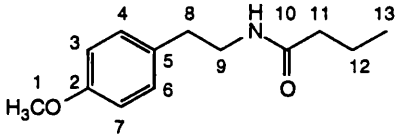
MS (EI, 70 eV): m/z = 207 (M^+, 5), 134 (M^+-$NH_2COC_2H_5$, 100), 121 (M^+-$CH_3NHCOC_2H_5$, 100), 78 (63).

Ir (KBr): ν = 3295 (s, NH), 3066 (m), 1639 (s, C=O), 1513 (m),1250 (s, C-O).

CHN $C_{12}H_{17}NO_2$ calc. C 69.54 H 8.27 N 6.75
found C 69.34 H 7.99 N 6.77

N-Butanoyl-2-(4-methoxyphenyl)ethanamine (244c)

2-(4-Methoxyphenyl)ethanamine (**241c**, 0.5 g, 3 mmol) is treated with butanoic anhydride (0.5 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.55 g, 2.5 mmol, 83 %) after SPC with dichloromethane/ 1% methanol. Mp. 89.5 - 90.5 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{13.12}$=7.4 Hz; 3H, H13),
1.59 (se; 2H, H12),
2.07 (t, $^3J_{11.12}$=7.8 Hz; 2H, H11),
2.72 (t, $^3J_{8.9}$=7.0 Hz; 2H, H8),
3.44 (q, $^3J_{9.8}$=7.0 Hz, $^3J_{9.NH}$=5.9 Hz; 2H, H9),
3.76 (s; 3H, H1),
5.60 (s, br; 1H, NH),
6.81 (d, ^{3}J=8.7 Hz; 2H, H_{ar}),
7.07 (d, ^{3}J=8.6 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C13), 19.1 (t, C12), 34.7 (t, C8), 38.6 (t, C11), 40.6 (t, C9), 55.2 (q, C1), 113.9, 129.6 (d, C3, C4, C6, C7), 130.8 (s, C5), 158.1 (s, C2), 172.9 (s, C10).

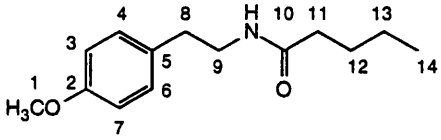
MS (EI, 70 eV): m/z = 221 (M^+, 3), 134 (M^+-$NH_2COC_3H_7$, 100), 121 (M^+-$CH_3NHCOC_3H_7$, 100), 78 (51).

Ir (KBr): ν = 3285 (s, NH), 3066 (m), 1640 (s, C=O), 1518 (m),1255 (s, C-O).

CHN $C_{13}H_{19}NO_2$ calc. C 70.55 H 8.65 N 6.33
found C 70.36 H 8.58 N 6.29

N-Pentanoyl-2-(4-methoxyphenyl)ethanamine (244d)

2-(4-Methoxyphenyl)ethanamine (**241c**, 0.5 g, 3 mmol) is treated with valeroyl chloride (0.4 ml) in triethylamine and dichloromethane according to procedure B, VIII.2.6 to give a colourless solid (0.50 g, 2.1 mmol, 71 %) after SPC with dichloromethane. Mp. 77 - 78 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{14,13}$=7.4 Hz; 3H, H14),
1.26 (se; 2H, H13),
1.53 (qi; 2H, H12),
2.08 (t, $^3J_{11,12}$=7.6 Hz; 2H, H11),
2.71 (t, $^3J_{8,9}$=7.0 Hz; 2H, H8),
3.42 (q, $^3J_{9,8}$=6.9 Hz, $^3J_{9,NH}$=6.1 Hz; 2H, H9),
3.74 (s; 3H, H1),
5.74 (s, br; 1H, NH),
6.79 (d, ^3J=8.7 Hz; 2H, H_{ar}),
7.06 (d, ^3J=8.7 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.8 (q, C14), 22.3 (t, C13), 27.8 (t, C12), 34.7 (t, C8), 36.5 (t, C11), 40.7 (t, C9), 55.2 (q, C1), 113.9, 129.6 (d, C3, C4, C6, C7), 130.9 (s, C5), 158.1 (s, C2), 173.2 (s, C10).

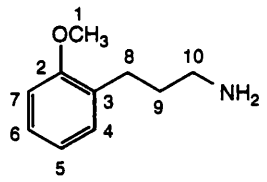
MS (EI, 70 eV): m/z = 235 (M^+, 3), 134 (M^+-$NH_2COC_4H_9$, 100), 121 (M^+-$CH_3NHCOC_4H_9$, 100), 78 (44).

Ir (KBr): ν = 3290 (s, NH), 3042 (m), 1636 (s, C=O), 1499 (m),1253 (s, C-O).

CHN $C_{14}H_{21}NO_2$ calc. C 71.45 H 9.00 N 5.95
found C 71.09 H 8.78 N 5.67

3-(2-Methoxyphenyl)propanamine (245a)

3-(2-Methoxyphenyl)propanamide (**240a**, 3.2 g, 18 mmol) is treated with lithium aluminium hydride (2.0 g) in THF (50 ml) according to procedure A, VIII.2.5 to give a colourless oil (1.8 g, 11 mmol, 60 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.36 (s, br; 2H, NH),
1.71 (m; 2H, H9),
2.63 (t, ^3J=7.5 Hz; 2H, H8 or H10),
2.68 (t, ^3J=7.0 Hz; 2H, H8 or H10),
3.80 (s; 3H, H1),
6.81 - 6.88 (m; 2H, H_{ar}),
7.10 - 7.17 (m; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 27.2, 33.9, 41.8 (t, C8, C9, C10), 55.1 (q, C1), 110.1, 120.3, 126.9, 129.7 (d, C4, C5, C6, C7), 130.3 (s, C3), 157.3 (s, C2).

3-(3-Methoxyphenyl)propanamine (245b)

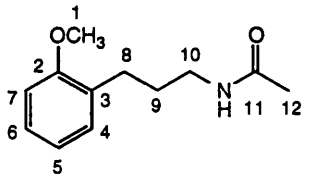
3-(3-Methoxyphenyl)propanamide (**240b**, 2.3 g, 13 mmol) is treated with lithium aluminium hydride (2.0 g) in THF (50 ml) according to procedure A, VIII.2.5 to give a colourless oil (0.60 g, 3.6 mmol, 28 %).

3-(4-Methoxyphenyl)propanamine (245c)

3-(4-Methoxyphenyl)propanamide (**240c**, 3.6 g, 20 mmol) is treated with lithium aluminium hydride (2.0 g) in THF (50 ml) according to procedure A, VIII.2.5 to give a yellow oil (2.0 g, 12 mmol, 61 %).

N-Acetyl-3-(2-methoxyphenyl)propanamine (246a)

3-(2-Methoxyphenyl)propanamine (**245a**, 0.4 g, 2.4 mmol) is treated with acetic anhydride (0.3 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless oil (0.27 g, 1.0 mmol, 43 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.77 (m; 2H, H9),
1.93 (s; 3H, H12),
2.63 (t, $^3J_{8,9}$=7.3 Hz; 2H, H8),
3.21 (dt, $^3J_{10,9}$=7.0 Hz, $^3J_{10,NH}$=6.0 Hz; 2H, H10),
3.78 (s; 3H, H1),
6.33 (s, br; 1H, NH),
6.81 (d, ^3J=8.2 Hz; 1H, H_{ar}),
6.86 (dd, ^3J=7.5 Hz, ^3J=7.4 Hz; 1H, H_{ar}),
7.09 (d, ^3J=7.4 Hz; 1H, H_{ar}),
7.13 (ddd,^3J=7.7Hz,^3J=7.9Hz,^4J=1.6Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.0 (q, C12), 27.2, 29.3, 39.0, (t, C8, C9, C10), 55.0 (q, C1), 110.0, 120.3, 127.1, 129.6 (d, C4, C5, C6, C7), 129.5 (s, C3), 157.1 (s, C2), 170.0 (s, C11).

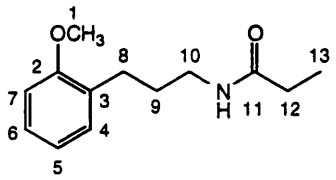
MS (EI, 70 eV): m/z = 207 (M^+, 2), 148 (M^+-NH_2COCH_3, 100), 135 (M^+-$CH_3NHCOCH_3$, 48).

Ir (KBr): ν = 3264 (s, NH), 3073 (m), 1646 (s, C=O), 1560 (m),1243 (s, C-O).

CHN $C_{12}H_{17}NO_2$ calc. C 69.53 H 8.28 N 6.76
found C 69.15 H 8.12 N 6.59

N-Propanoyl-3-(2-methoxyphenyl)propanamine (246b)

3-(2-Methoxyphenyl)propanamine (**245a**, 0.4 g, 2.4 mmol) is treated with propanoic anhydride (0.3 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless oil (0.47 g, 1.7 mmol, 71 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.10 (t, $^3J_{13.12}$=7.6 Hz; 3H, H13),
1.75 (m; 2H, H9),
2.14 (t, $^3J_{12.13}$=7.6 Hz; 2H, H12),
2.61 (t, $^3J_{8.9}$=7.3 Hz; 2H, H8),
3.20 (dt, $^3J_{10.9}$=6.9 Hz, $^3J_{10.NH}$=5.9 Hz; 2H, H10),
3.76 (s; 3H, H1),
6.31 (s, br; 1H, NH),
6.79 (d, ^3J=7.2 Hz; 1H, H_{ar}),
6.83 (ddd,^3J=7.5Hz,^3J=7.5Hz,^4J=1.0Hz; 1H, H_{ar}),
7.08 (d, ^3J=7.3 Hz; 1H, H_{ar}),
7.13 (ddd,^3J=7.7Hz,^3J=7.9Hz,^4J=1.7Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.7 (q, C13), 27.1, 27.2, 29.4, 38.7, (t, C8, C9, C10, C12), 54.9 (q, C1), 109.9, 120.2, 126.9, 129.6 (d, C4, C5, C6, C7), 129.5 (s, C3), 157.0 (s, C2), 173.7 (s, C11).

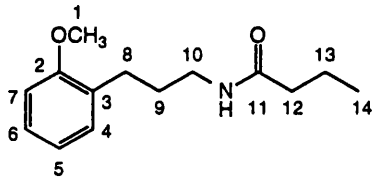
MS (EI, 70 eV): m/z = 221 (M^+, 0.5), 148 (M^+-$NH_2COC_2H_5$, 100), 135 (M^+-$CH_3NHCOC_2H_5$, 32).

Ir (KBr): ν = 3292 (s, NH), 3070 (s), 1652 (s, C=O), 1552 (m),1244 (m, C-O).

CHN $C_{13}H_{19}NO_2$ calc. C 70.55 H 8.65 N 6.33
found C 70.03 H 8.59 N 6.25

N-Butanoyl-3-(2-methoxyphenyl)propanamine (246c)

3-(2-Methoxyphenyl)propanamine (**245a**, 0.4 g, 2.4 mmol) is treated with butanoic anhydride (0.4 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a yellow oil (0.50 g, 2.1 mmol, 89 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{14,13}$=7.3 Hz; 3H, H14),
1.57 (m; 2H, H13),
1.75 (m; 2H, H9),
2.10 (t, $^3J_{12,13}$=7.3 Hz; 2H, H12),
2.62 (t, $^3J_{8,9}$=7.6 Hz; 2H, H8),
3.22 (dt, $^3J_{10,9}$=6.7 Hz, $^3J_{10,NH}$=6.2 Hz; 2H, H10),
3.79 (s; 3H, H1),
5.75 (s, br; 1H, NH),
6.81 - 6.88 (m; 2H, H_{ar}),
7.07 - 7.18 (m; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C14), 19.1 (t, C13), 27.2, 29.7, 38.7, 38.8 (t, C8, C9, C10, C12), 55.2 (q, C1), 110.2, 120.5, 127.2, 129.8 (d, C4, C5, C6, C7), 129.7 (s, C3), 157.2 (s, C2), 172.8 (s, C11).

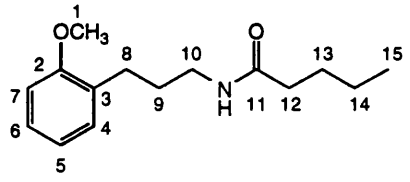
MS (EI, 70 eV): m/z = 235 (M^+, 2), 148 (M^+-$NH_2COC_3H_7$, 100), 135 (M^+-$CH_3NHCOC_3H_7$, 62).

Ir (KBr): ν = 3312 (s, NH), 3045 (m), 1650 (s, C=O), 1550 (m), 1240 (m, C-O).

CHN $C_{14}H_{21}NO_2$ calc. C 71.45 H 9.00 N 5.95
found C 71.47 H 8.79 N 5.75

N-Pentanoyl-3-(2-methoxyphenyl)propanamine (246d)

3-(2-Methoxyphenyl)propanamine (**245a**, 0.4 g, 2.4 mmol) is treated with valeroyl chloride (0.4 ml) in triethylamine and dichloromethane according to procedure B, VIII.2.6 to give a pale yellow oil (0.45 g, 1.8 mmol, 75 %).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.87 (t, $^3J_{15,14}$=5.5 Hz; 3H, H15),
1.26 (m; 2H, H14),
1.55 (m; 2H, H13),
1.74 (m; 2H, H9),
2.10 (t, $^3J_{12,13}$=7.9 Hz; 2H, H12),
2.60 (t, $^3J_{8,9}$=7.3 Hz; 2H, H8),
3.19 (dt, $^3J_{10,9}$=6.6 Hz, $^3J_{10,NH}$=6.2 Hz; 2H, H10),
3.77 (s; 3H, H1),
5.90 (s, br; 1H, NH),
6.79 - 6.85 (m; 2H, H_{ar}),
7.06 - 7.15 (m; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C15), 20.6 (t, C14), 22.2 (t, C13), 27.2, 29.6, 36.4, 38.8 (t, C8, C9, C10, C12), 55.1 (q, C1), 110.1, 120.4, 127.1, 129.7 (d, C4, C5, C6, C7), 129.5 (s, C3), 157.1 (s, C2), 173.0 (s, C11).

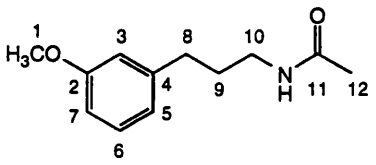
MS (EI, 70 eV): m/z = 249 (M^+, 0.3), 148 (M^+-$NH_2COC_4H_9$, 100), 135 (M^+-$CH_3NHCOC_4H_9$, 30).

Ir (KBr): ν = 3311 (s, NH), 3046 (m), 1648 (s, C=O), 1553 (m), 1241 (m, C-O).

CHN $C_{15}H_{23}NO_2$ calc. C 72.25 H 9.30 N 5.62
found C 72.00 H 9.11 N 5.65

N-Acetyl-3-(3-methoxyphenyl)propanamine (247a)

3-(3-Methoxyphenyl)propanamine (**245b**, 0.20 g, 1.2 mmol) is treated with acetic anhydride (0.2 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless oil (0.20 g, 1.0 mmol, 81 %) after SPC with dichloromethane/1% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.78 (m; 2H, H9),
1.90 (s; 3H, H12),
2.58 (t, $^3J_{8,9}$=7.8 Hz; 2H, H8),
3.22 (dt, $^3J_{10,9}$=7.1 Hz, $^3J_{10,NH}$=6.7 Hz; 2H, H10),
3.74 (s; 3H, H1),
5.90 (s, br; 1H, NH),
6.69 - 6.75 (m; 3H, H_{ar}),
7.15 (ddd,^{3}J=7.5Hz,^{3}J=7.6Hz,^{4}J=1.7Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.1 (q, C12), 30.9, 33.2, 39.1 (t, C8, C9, C10), 55.0 (q, C1), 111.1, 114.0, 120.6, 129.3 (d, C3, C5, C6, C7), 143.0 (s, C5), 159.5 (s, C2), 170.1 (s, C11).

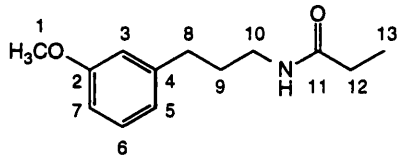
MS (EI, 70 eV): m/z = 207 (M^+, 5), 148 (M^+-NH_2COCH_3, 100), 135 (M^+-$CH_3NHCOCH_3$, 54).

Ir (KBr): ν = 3260 (s, NH), 3072 (m), 1642 (s, C=O), 1542 (m),1240 (s, C-O).

CHN $C_{12}H_{17}NO_2$ calc. C 69.53 H 8.28 N 6.76
found C 69.35 H 8.04 N 6.49

N-Propanoyl-3-(3-methoxyphenyl)propanamine (247b)

3-(3-Methoxyphenyl)propanamine (**245b**, 0.20 g, 1.2 mmol) is treated with propanoic anhydride (0.2 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless oil (0.25 g, 1.1 mmol, 94 %) after SPC with dichloromethane/1% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.10 (t, $^3J_{13.12}$=7.4 Hz; 3H, H13),
1.81 (m; 2H, H9),
2.13 (q, $^3J_{12.13}$=7.7 Hz; 2H, H12),
2.60 (t, $^3J_{8.9}$=7.9 Hz; 2H, H8),
3.26 (dt, $^3J_{10.9}$=7.0 Hz, $^3J_{10.NH}$=6.2 Hz; 2H, H10),
3.76 (s; 3H, H1),
5.54 (s, br; 1H, NH),
6.68 - 6.78 (m; 3H, H_{ar}),
7.17 (ddd,^{3}J=7.9Hz,^{3}J=6.8Hz,^{4}J=1.4Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.9 (q, C13), 29.7 (t, C12), 31.0, 33.3, 39.1 (t, C8, C9, C10), 55.2 (q, C1), 111.3, 114.0, 120.8, 129.4 (d, C3, C5, C6, C7), 143.1 (s, C5), 159.6 (s, C2), 173.7 (s, C11).

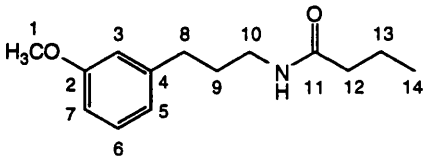
MS (EI, 70 eV): m/z = 221 (M^+, 5), 148 (M^+-$NH_2COC_2H_5$, 100), 135 (M^+-$CH_3NHCOC_2H_5$, 40).

Ir (KBr): ν = 3294 (s, NH), 3056 (m), 1651 (s, C=O), 1550 (m), 1242 (m, C-O).

CHN $C_{13}H_{19}NO_2$ calc. C 70.55 H 8.65 N 6.33
found C 70.33 H 8.25 N 6.37

N-Butanoyl-3-(3-methoxyphenyl)propanamine (247c)

3-(3-Methoxyphenyl)propanamine (**245b**, 0.20 g, 1.2 mmol) is treated with butanoic anhydride (0.2 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless oil (0.20 g, 0.9 mmol, 71 %) after SPC with dichloromethane/1% methanol.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{14.13}$=5.1 Hz; 3H, H14),
1.60 (m; 2H, H13),
1.78 (m; 2H, H9),
2.08 (t, $^3J_{12.13}$=7.3 Hz; 2H, H12),
2.57 (t, $^3J_{8.9}$=7.4 Hz; 2H, H8),
3.23 (dt, $^3J_{10.9}$=7.0 Hz, $^3J_{10.NH}$=6.2 Hz; 2H, H10),
3.74 (s; 3H, H1),
5.80 (s, br; 1H, NH),
6.68 - 6.76 (m; 3H, H_{ar}),
7.17 (ddd, ^3J=7.5Hz, ^3J=6.3Hz, ^4J=1.9Hz; 1H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.6 (q, C14), 19.1 (t, C13), 31.0, 33.2, 38.5, 39.0 (t, C8, C9, C10, C12), 55.0 (q, C1), 111.0, 114.0, 120.6, 129.3 (d, C3, C5, C6, C7), 143.0 (s, C5), 159.5 (s, C2), 173.1 (s, C11).

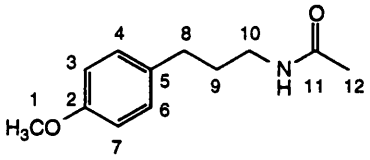
MS (EI, 70 eV): m/z = 235 (M^+, 6), 148 (M^+-$NH_2COC_3H_7$, 100), 135 (M^+-$CH_3NHCOC_3H_7$, 30).

Ir (KBr): ν = 3310 (s, NH), 3042 (m), 1647 (s, C=O), 1548 (m), 1244 (m, C-O).

CHN $C_{14}H_{21}NO_2$ calc. C 71.45 H 9.00 N 5.95
found C 71.01 H 8.79 N 5.85

N-Acetyl-3-(4-methoxyphenyl)propanamine (248a)

3-(4-Methoxyphenyl)propanamine (**245c**, 0.70 g, 4.2 mmol) is treated with acetic anhydride (0.4 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.37 g, 1.8 mmol, 43 %) with mp. 48 - 49 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.76 (m; 2H, H9),
1.91 (s; 3H, H12),
2.55 (t, $^3J_{8.9}$=7.9 Hz; 2H, H8),
3.22 (dt, $^3J_{10.9}$=7.1 Hz, $^3J_{10.NH}$=5.9 Hz; 2H, H10),
3.74 (s; 3H, H1),
5.80 (s, br; 1H, NH),
6.79 (d, ^3J=8.7 Hz; 2H, H_{ar}),
7.05 (d, ^3J=8.6 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.2 (q, C12), 31.3, 32.3, 39.2 (t, C8, C9, C10), 55.2 (q, C1), 113.7, 129.1 (d, C3, C4, C6, C7), 133.4 (s, C5), 157.7 (s, C2), 170.1 (s, C11).

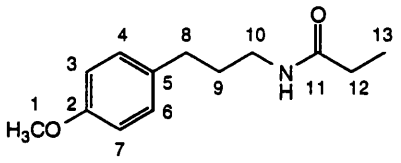
MS (EI, 70 eV): m/z = 207 (M^+, 10), 148 (M^+-NH_2COCH_3, 100), 135 (M^+-$CH_3NHCOCH_3$, 43).

Ir (KBr): ν = 3308 (s, NH), 3067 (m), 1640 (s, C=O), 1540 (s), 1238 (s, C-O).

CHN $C_{12}H_{17}NO_2$ calc. C 69.53 H 8.28 N 6.76
found C 68.83 H 8.14 N 6.57

N-Propanoyl-3-(4-methoxyphenyl)propanamine (248b)

3-(4-Methoxyphenyl)propanamine (**245c**, 0.70 g, 4.2 mmol) is treated with propanoic anhydride (0.55 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.48 g, 2.2 mmol, 52 %) with mp. 56 - 57 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.10 (t, $^3J_{13.12}$=7.6 Hz; 3H, H13),
1.78 (m; 2H, H9),
2.13 (q, $^3J_{12.13}$=7.6 Hz; 2H, H12),
2.57 (t, $^3J_{8.9}$=7.6 Hz; 2H, H8),
3.25 (dt, $^3J_{10.9}$=6.9 Hz, $^3J_{10.NH}$=6.2 Hz; 2H, H10),
3.76 (s; 3H, H1),
5.42 (s, br; 1H, NH),
6.79 (d, ^3J=8.5 Hz; 2H, H_{ar}),
7.06 (d, ^3J=8.4 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 9.8 (q, C13), 29.7, 31.4, 32.3, 39.1 (t, C8, C9, C10, C12), 55.2 (q, C1), 113.8, 129.2 (d, C3, C4, C6, C7), 133.4 (s, C5), 157.8 (s, C2), 173.4 (s, C11).

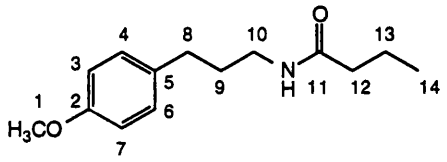
MS (EI, 70 eV): m/z = 221 (M^+, 12), 148 (M^+-$NH_2COC_2H_5$, 100), 135 (M^+-$CH_3NHCOC_2H_5$, 55).

Ir (KBr): ν = 3290 (s, NH), 3035 (m), 1653 (s, C=O), 1551 (m), 1240 (m, C-O).

CHN $C_{13}H_{19}NO_2$ calc. C 70.55 H 8.65 N 6.33
found C 70.36 H 8.40 N 6.19

N-Butanoyl-3-(4-methoxyphenyl)propanamine (248c)

3-(4-Methoxyphenyl)propanamine (**245c**, 0.70 g, 4.2 mmol) is treated with butanoic anhydride (0.7 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a colourless solid (0.65 g, 2.8 mmol, 66 %) with mp. 53 - 54 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{14.13}$=7.4 Hz; 3H, H14),
1.60 (m; 2H, H13),
1.76 (m; 2H, H9),
2.08 (t, $^3J_{12.13}$=7.1 Hz; 2H, H12),
2.56 (t, $^3J_{8.9}$=7.7 Hz; 2H, H8),
3.23 (dt, $^3J_{10.9}$=7.0 Hz, $^3J_{10.NH}$=6.1 Hz; 2H, H10),
3.75 (s; 3H, H1),
5.70 (s, br; 1H, NH),
6.79 (d, ^3J=8.5 Hz; 2H, H_{ar}),
7.06 (d, ^3J=8.4 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C14), 19.1 (t, C13), 31.4, 32.3, 38.6, 39.0 (t, C8, C9, C10, C12), 55.1 (q, C1), 113.7, 129.1 (d, C3, C4, C6, C7), 133.4 (s, C5), 157.7 (s, C2), 172.9 (s, C11).

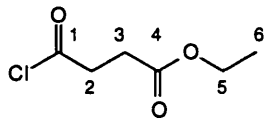
MS (EI, 70 eV): m/z = 235 (M^+, 9), 148 (M^+-$NH_2COC_3H_7$, 100), 135 (M^+-$CH_3NHCOC_3H_7$, 34).

Ir (KBr): ν = 3310 (s, NH), 3026 (m), 1648 (s, C=O), 1556 (m), 1232 (m, C-O).

CHN $C_{14}H_{21}NO_2$ calc. C 71.45 H 9.00 N 5.95
found C 71.32 H 8.80 N 5.91

Ethyl 4-chloro-4-oxo-butanoate (250)

A mixture of succinic anhydride (50 g, 0.5 mol) and ethanol (35 ml) is refluxed for 1 h[246]. Excess ethanol is removed by evaporation *in vacuo* and thionyl chloride (60 ml) is added dropwise at 50 °C. After cessation of gas evolution the product is purified by distillation to obtain a viscous oil (54 g, 0.33 mol, 66 %), bp. 100 - 105 °C/1 mmHg.

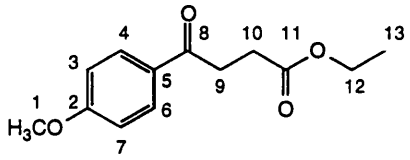


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.20 (t, $^3J_{6,5}$=7.2 Hz; 3H, H6),
2.61 (t, ^3J=6.5 Hz; 2H, H3 or H2),
3.15 (t, ^3J=6.6 Hz; 2H, H3 or H2),
4.11 (q, $^3J_{5,6}$=7.3 Hz; 2H, H5).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.9 (q, C6), 29.2, 41.6 (t, C2, C3), 61.0 (t, C5), 170.7, 172.8 (s, C1, C4).

Ethyl 4-oxo-4-(4-methoxyphenyl)butanoate (251)

A solution of *p*-bromoanisole (56 g, 0.3 mol) in anhydrous benzene (50 ml) and ether (150 ml) is added dropwise to magnesium (7.7 g, 0.315 mol) in ether (20 ml). The mixture is stirred at 25 °C for 30 min, cooled to 0 °C and dry cadmium chloride (33 g, 0.18 mol) is added at once. Then the reaction mixture is refluxed for 30 min, the ether is removed by distillation and anhydrous benzene (200 ml) is added. A solution of ethyl 4-chloro-4-oxo-butyrate (**250**, 57.6 g, 0.35 mol) is added within 5 min to the hot reaction mixture. After refluxing for 1 h, dil. hydrochloric acid is added and the product is extracted with ether. Distillation yields a viscous oil (19.5 g, 84 mmol, 28 %), bp. 160 - 174 °C/1mmHg.

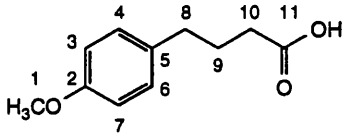


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{13,12}$=7.2 Hz; 3H, H13),
2.70 (t, $^3J_{9,10}$=6.6 Hz; 2H, H9),
3.23 (t, $^3J_{10,9}$=6.7 Hz; 2H, H10),
3.83 (s; 3H, H1),
4.12 (q, $^3J_{12,13}$=7.2 Hz; 2H, H12),
6.90 (d, ^3J=9.0 Hz; 2H, H_{ar}),
7.93 (d, ^3J=9.0 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 14.2 (q, C13), 28.4, 33.0 (t, C9, C10), 55.5 (q, C1), 60.7 (t, C12), 113.7, 130.0 (d, C3, C4, C6, C7), 129.7 (s, C5), 163.6 (s, C2), 173.1 (s, C11), 196.7 (s, C8).

4-(4-Methoxyphenyl)butanoic acid (252)

A mixture of ethyl 4-oxo-4-(4-methoxyphenyl)butanoate (**251**, 19.5 g, 83 mmol), 99 % hydrazine hydrate (15 ml) and potassium hydroxide (28 g) in diethylene glycol (140 ml) is refluxed for 6 h. After cooling to 25 °C, the reaction mixture is acidified by adding hydrochloric acid. The product is extracted with ether and the combined ethereal extracts are dried over magnesium sulphate. Evaporation of the solvent yields 7.5 g (38 mmol, 46 %) of a colourless solid, which is of sufficient purity for the subsequent conversion into the amide **253**.

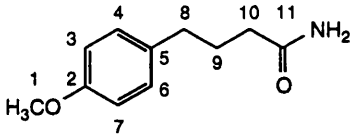


^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.91 (qi; 2H, H9),
2.34 (t, $^3J_{10,9}$=7.3 Hz; 2H, H10),
2.60 (t, $^3J_{8,9}$=7.3 Hz; 2H, H8),
3.77 (s; 3H, H1),
6.81 (d, ^3J=8.6 Hz; 2H, H_{ar}),
7.08 (d, ^3J=8.6 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 26.5 (t, C9), 33.3, 34.1 (t, C8, C10), 55.3 (q, C1), 113.9, 129.4 (d, C3, C4, C6, C7), 133.3 (s, C5), 157.9 (s, C2), 179.7 (s, C11).

4-(4-Methoxyphenyl)butanamide (253)

4-(4-Methoxyphenyl)butanoic acid (**252**, 7.5 g, 38 mmol) is treated with triethylamine (3.9 g) and ethyl chloroformate (4.2 g) in dichloromethane (50 ml) according to procedure VIII.2.4 to give 6.1 g (32 mmol, 83 %) of a colourless solid (mp. 125 - 127 °C).



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.90 (qi; 2H, H9),
2.17 (t, $^3J_{10,9}$=7.8 Hz; 2H, H10),
2.58 (t, $^3J_{8,9}$=7.3 Hz; 2H, H8),
3.75 (s; 3H, H1),
5.55 (s, br; 1H, NH),
6.00 (s, br; 1H, NH),
6.79 (d, ^{3}J=8.6 Hz; 2H, H_{ar}),
7.06 (d, ^{3}J=8.6 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 27.0 (t, C9), 34.1, 34.9 (t, C8, C10), 55.2 (q, C1), 113.7, 129.2 (d, C3, C4, C6, C7), 133.4 (s, C5), 157.8 (s, C2), 175.6 (s, C11).

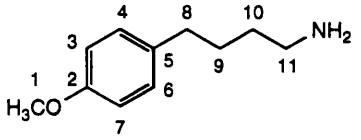
MS (EI, 70 eV): m/z = 193 (M^+, 55), 134 (M^+-CH_3CONH_2, 100), 121 (M^+-$C_2H_4CONH_2$, 100), 91 (70).

Ir (KBr): ν = 3390 (s,br, NH), 2938 (m), 1650 (s, C=O), 1460 (m), 1223 (m, C-O).

CHN $C_{11}H_{15}NO_2$ calc. C 68.37 H 7.82 N 7.25
found C 67.72 H 7.46 N 7.22

4-(4-Methoxyphenyl)butanamine (254)

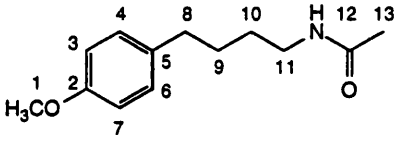
4-(4-Methoxyphenyl)butanamide (**253**, 4.0 g, 21 mmol) is reduced with lithium aluminium hydride (1.0 g) in THF (150 ml) according to procedure A, VIII.2.5 to yield 2.5 g (14 mmol, 66 %) of a yellow oil.



^{1}H-nmr (200 MHz, $CDCl_3$): δ = 1.30 (s, br; 2H, NH_2),
1.42 (qi; 2H, H9 or H10),
1.56 (qi; 2H, H9 or H10),
2.52 (t, $^3J_{11,10}$=7.8 Hz; 2H, H11),
2.65 (t, $^3J_{8,9}$=7.4 Hz; 2H, H8),
3.75 (s; 3H, H1),
6.80 (d, ^{3}J=8.6 Hz; 2H, H_{ar}),
7.08 (d, ^{3}J=8.6 Hz; 2H, H_{ar}).

N-Acetyl-4-(4-methoxyphenyl)butanamine (255a)

4-(4-Methoxyphenyl)butanamine (**254**, 0.20 g, 1.1 mmol) is treated with acetic anhydride (0.2 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a pale yellow oil (0.2 g, 0.9 mmol, 81 %), which solidifies after SPC (dichloromethane/1 % methanol) and trituration with ether, mp. 39 - 40 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.48 (qi; 2H, H9 or H10),
1.57 (m; 2H, H9 or H10),
1.91 (s; 3H, H13),
2.53 (t, $^3J_{8,9}$=6.7 Hz; 2H, H8),
3.20 (dt, $^3J_{11,10}$=6.7 Hz, $^3J_{11,NH}$=6.4 Hz; 2H, H11),
3.75 (s; 3H, H1),
5.72 (s, br; 1H, NH),
6.78 (d, ^3J=8.5 Hz; 2H, H_{ar}),
7.04 (d, ^3J=8.5 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 23.2 (q, C13), 28.8, 29.0, 34.5, 39.4 (t, C8, C9, C10, C11), 55.2 (q, C1), 113.7, 129.2 (d, C3, C4, C6, C7), 134.1 (s, C5), 157.7 (s, C2), 170.1 (s, C12).

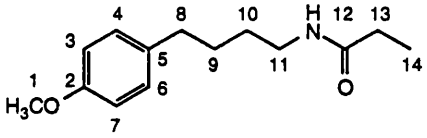
MS (EI, 70 eV): m/z = 221 (M^+, 8), 162 (M^+-NH_2COCH_3, 28), 121 (M^+-$C_3H_6NHCOCH_3$, 100), 57 (43).

Ir (KBr): ν = 3294 (s, NH), 2936 (s), 1651 (s, C=O), 1513 (s), 1245 (s, C-O).

CHN $C_{13}H_{19}NO_2$ calc. C 70.56 H 8.66 N 6.33
found C 69.76 H 8.14 N 6.11

N-Propanoyl-4-(4-methoxyphenyl)butanamine (255b)

4-(4-Methoxyphenyl)butanamine (**254**, 0.20 g, 1.1 mmol) is treated with propanoic anhydride (0.2 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a pale yellow oil (0.24 g, 1.0 mmol, 91 %), which solidifies after SPC (dichloromethane/1 % methanol) and trituration with ether, mp. 31 - 33 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.11 (t, $^3J_{14,15}$=7.6 Hz; 3H, H14),
1.46 - 1.51 (m; 2H, H9 or H10),
1.54 - 1.60 (m; 2H, H9 or H10),
2.14 (q, $^3J_{13,14}$=7.6 Hz; 2H, H13),
2.54 (t, $^3J_{8,9}$=7.2 Hz; 2H, H8),
3.18 - 3.24 (m; 2H, H11),
3.75 (s; 3H, H1),
5.65 (s, br; 1H, NH),
6.78 (d, ^3J=8.7 Hz; 2H, H_{ar}),
7.04 (d, ^3J=8.4 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 10.0 (q, C14), 28.9, 29.2, 29.8, 34.6, 39.4 (t, C8, C9, C10, C11, C13), 55.3 (q, C1), 113.8, 129.3 (d, C3, C4, C6, C7), 134.2 (s, C5), 157.8 (s, C2), 173.8 (s, C12).

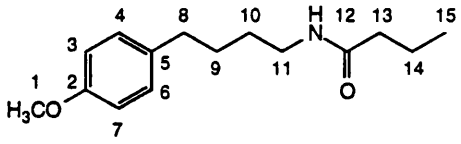
MS (EI, 70 eV): m/z = 235 (M^+, 12), 162 (M^+-$NH_2COC_2H_5$, 28), 121 (M^+-$C_3H_6NHCOC_2H_5$, 100), 57 (61).

Ir (KBr): ν = 3294 (s, NH), 2939 (s), 1649 (s, C=O), 1510 (s), 1243 (s, C-O).

CHN $C_{14}H_{21}NO_2$ calc. C 71.45 H 9.00 N 5.95
found C 70.66 H 8.80 N 5.78

N-Butanoyl-4-(4-methoxyphenyl)butanamine (255c)

4-(4-Methoxyphenyl)butanamine (**254**, 0.20 g, 1.1 mmol) is treated with butanoic anhydride (0.3 ml) in triethylamine and dichloromethane according to procedure A, VIII.2.6 to give a pale yellow solid (0.2 g, 0.8 mmol, 72 %) after SPC (dichloromethane/1 % methanol), mp. 60 - 61 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.92 (t, $^3J_{15,14}$=7.4 Hz; 3H, H15),
1.51 (qi; 2H, H9 or H10),
1.60 (m; 2H, H9 or H10),
1.64 (m; 2H, H14),
2.11 (t, $^3J_{13,14}$=7.3 Hz; 2H, H13),
2.55 (t, $^3J_{8,9}$=7.3 Hz; 2H, H8),
3.24 (dt, $^3J_{11,10}$=7.0 Hz, $^3J_{11,NH}$=5.9 Hz; 2H, H11),
3.77 (s; 3H, H1),
5.78 (s, br; 1H, NH),
6.80 (d, ^3J=8.6 Hz; 2H, H_{ar}),
7.06 (d, ^3J=8.7 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C15), 19.1 (t, C14), 28.8, 29.0, 34.4, 39.1 (t, C8, C9, C10, C11), 38.6 (t, C13), 55.1 (q, C1), 113.6, 129.1 (d, C3, C4, C6, C7), 134.1 (s, C5), 157.6 (s, C2), 173.0 (s, C12).

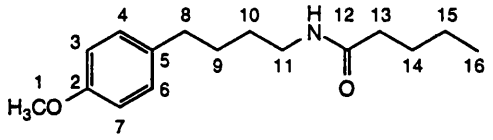
MS (EI, 70 eV): m/z = 249 (M^+, 15), 162 (M^+-$NH_2COC_3H_7$, 23), 121 (M^+-$C_3H_6NHCOC_3H_7$, 100), 57 (69).

Ir (KBr): ν = 3292 (s, NH), 2944 (s), 1647 (s, C=O), 1515 (s), 1240 (s, C-O).

CHN $C_{15}H_{23}NO_2$ calc. C 72.25 H 9.30 N 5.62
found C 71.93 H 9.06 N 5.34

N-Pentanoyl-4-(4-methoxyphenyl)butanamine (255d)

4-(4-Methoxyphenyl)butanamine (**254**, 0.2 g, 1.1 mmol) is treated with valeroyl chloride (0.3 ml) in triethylamine and dichloromethane according to procedure B, VIII.2.6 to give a pale yellow solid (0.25 g, 85 %) after SPC (dichloromethane), mp. 58 - 59 °C.



^{1}H-nmr (400 MHz, $CDCl_3$): δ = 0.86 (t, $^3J_{16.15}$=7.4 Hz; 3H, H16),
1.25 - 1.31 (m; 2H, H9 or H10),
1.43 - 1.50 (m; 2H, H14 or H15),
1.51 - 1.58 (m; 4H, H9, H10, H14 or H15),
2.10 (t, $^3J_{13.14}$=7.4 Hz; 2H, H13),
2.52 (t, $^3J_{8.9}$=7.2 Hz; 2H, H8),
3.20 (dt, $^3J_{11.10}$=6.8 Hz, $^3J_{11.NH}$=5.9 Hz; 2H, H11),
3.72 (s; 3H, H1),
6.00 (s, br; 1H, NH),
6.77 (d, ^3J=8.7 Hz; 2H, H_{ar}),
7.02 (d, ^3J=8.7 Hz; 2H, H_{ar}).

^{13}C-nmr (100 MHz, $CDCl_3$): δ = 13.7 (q, C16), 22.3, 27.8, 28.8, 29.0, 34.4, 36.4, 39.1 (t, C8, C9, C10, C11, C13, C14, C15), 55.1 (q, C1), 113.6, 129.1 (d, C3, C4, C6, C7), 134.1 (s, C5), 157.6 (s, C2), 173.1 (s, C12).

MS (EI, 70 eV): m/z = 263 (M^+, 23), 162 (M^+-$NH_2COC_4H_9$, 17), 121 (M^+-$C_3H_6NHCOC_4H_9$, 100), 57 (68).

Ir (KBr): ν = 3282 (s, NH), 2952 (s), 1649 (s, C=O), 1514 (s), 1242 (s, C-O).

CHN $C_{16}H_{25}NO_2$ calc. C 72.96 H 9.57 N 5.32
found C 72.68 H 9.45 N 5.27

References

(1) *The Independent*; 10th September, 1993.

(2) *The Guardian*; 5th October, 1993.

(3) Lerner, A. B.; Case, J. D.; Lee, T. H.; Mori, W. *J. Am. Chem. Soc.* **1958**, *80*, 2587.

(4) Wurtman, R. J.; Axelrod, J.; Phillips, L. S. *Science* **1963**, *142*, 1071.

(5) Wurtman, R. J.; Axelrod, J. *Sci. Am.* **1965**, *213*, 50.

(6) Quay, W. B. *Gen. Comp. Endocrinol.* **1963**, *3*, 473.

(7) Hoffman, R. A.; Reiter, R. J. *Science* **1965**, *148*, 1609.

(8) Yu, H.-S.; Reiter, R. J. *Melatonin: Biosynthesis, Physiological Effects and Clinical Application*; CRC Press: Boca Raton, FL, 1993.

(9) *Proceedings of the 6th Colloquium of the European Pineal Society*; Copenhagen, 1993.

(10) Karsch, F. J.; Bittman, E. L.; Foster, D. L.; Goodman, R. L.; Legan, S. J.; Robinson, J.E. *Rec. Prog. Horm. Res.* **1984**, *40*, 185.

(11) Lincoln, G. *Nature* **1983**, *302*, 755.

(12) Mason, R.; Brooks, A. *Neuroscience Lett.* **1988**, *95*, 296.

(13) Saarela, S.; Reiter, R. J. *Life Sciences* **1994**, *54*, 295.

(14) Dubocovich, M. L. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 902.

(15) Duncan, M. J.; Goldman, B. D. *J. Exp. Zool.* **1984**, *230*, 89.

(16) Arendt, J. *Clin. Endocrinol.* **1988**, *29*, 205.

(17) Wetterberg, L.; Beck-Friis, J.; Kiellman, B. F. In *Biological Rhythms, mood disorders, light therapy and the pineal gland*; M. Shafii and S. L. Shafii, Ed.; American Psychiatric Press: Washington, 1990; p 69.

(18) Wehr, T. A. *J. Clin. Endocrinol. Metab.* **1991**, *73*, 1276.

(19) Petrie, K.; Conaglen, J. V.; Thompson, L.; Chamberlain, K. *Br. Med. J.* **1989**, *298*, 705.

(20) Tamarkin, L.; Baird, C. J.; Almeida, O. F. X. *Science* **1985**, *227*, 714.

(21) Demaine, C.; Semm, P. *Neurosci. Lett.* **1985**, *62*, 119.

(22) Ebadi, M. In *The Pineal Gland*; R. J. Reiter, Ed.; Raven Press: New York, 1984; p 1.

(23) Ralph, C. L. In *The Pineal Gland*; R. J. Reiter, Ed.; Raven Press: New York, 1984; p 193.

(24) Mason, R.; Harrington, M. E.; Rusak, B. *Neuroscience Letters* **1987**, *80*, 173.

(25) Cardinali, D. P.; Vacas, M. I. *Cell. Mol. Neurobiology* **1987**, *7*, 323.

(26) Ebadi, M.; Govitrapong, P. *J. Neural Transm. (Suppl.)* **1986**, *21*, 125.

(27) Axelrod, J. In *The Pineal Gland and its Endocrine Role*; J. Axelrod, F. Fraschini and G. P. Velo, Ed.; Plenum Press: New York, 1983; p 1.

(28) Simonneaux, V.; Ebadi, M.; Bylund, D. B. *Adv. Pin. Res.* **1991**, *5*, 51.

(29) Klein, D. C.; Sugden, D.; Weller, J. L. *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 559.

(30) Alphs, L.; Heller, A.; Lovenberg, W. *Neurochem.* **1980**, *34*, 83.

(31) Reuss, S.; Schröder, H. *Adv. Pin. Res.* **1991**, *5*, 55.

(32) Ebadi, M.; Govitrapong, P. *Pin. Res. Rev.* **1986**, *4*, 1.

(33) Simonneaux, V.; Murrin, L. C.; Ebadi, M. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 214.

(34) Zatz, M.; Brownstein, M. J. *Brain Res.* **1979**, *160*, 381.

(35) Kaku, K.; Tsuchiya, M.; Tahizawa, Y.; Okuya, S.; Inoue, Y.; Kaneko, T.; Yanaihara, N. *Endocrinology* **1986**, *117*, 2371.

(36) Reuss, S.; Schröder, E. *Neurosci. Lett.* **1987**, *74*, 158.

(37) Withyachumnamkul, B.; Nonaka, K. O.; Santana, C.; Attia, A. M.; Reiter, R. J. *J. Interferon Res.* **1990**, *10*, 403.

(38) Vacas, M. I.; Sarmiento, M. I. K.; Pereyra, E. N.; Etchegoyen, G. S.; Cardinali, D. P. *Mol. Cell. Endocrinol.* **1987**, *50*, 23.
(39) Birau, N. *Melatonin, endokrinologische und humangenetische Untersuchung*; Minerva-Publikation: München, 1982.
(40) Moore, R. Y. *Prog, Reprod. Biol.* **1978**, *4*, 1.
(41) Bispink, G.; Zimmermann, R.; Weise, H. C.; Leidenberger, F. *J. Pineal Res.* **1990**, *8*, 97.
(42) Hedlund, L.; Lischko, M. M. *Science* **1977**, *195*, 686.
(43) Klein, D. C. *Nature New Biology* **1972**, *237*, 117.
(44) Germ, W. A.; Ralph, C. L. *Science* **1979**, *204*, 183.
(45) Bubenik, G. A.; Brown, G. M.; Grota, L. G. *Brain Res.* **1976**, *118*, 417.
(46) Raihklin, N. T.; Kvetnoy, I. M.; Tolkachev, V. N. *Nature* **1975**, *255*, 344.
(47) Huether, G. *Experientia* **1993**, *49*, 665.
(48) Kopin, I. J.; Pare, C. M. B.; Axelrod, J. *J. Biochem. Biophys. Acta* **1960**, *40*, 377.
(49) Hirata, F.; Hayaishi, O.; Takuyama, T.; Senoh, S. *J. Biol. Chem.* **1974**, *249*, 1311.
(50) Kennaway, D. J.; Blake, P.; Webb, H. A. *Brain Res.* **1989**, *495*, 349.
(51) Cardinali, D. P. *Endocrinol. Rev.* **1981**, *2*, 327.
(52) Datta, P. C.; King, M. G. *Neurosci. Biobehav. Rev.* **1980**, *4*, 451.
(53) Tamarkin, L.; Westrom, W. K.; Hamill, A. I.; Goldman, B. D. *Endocrinology* **1976**, *99*, 1534.
(54) Reiter, R. J. *Endocr. Rev.* **1980**, *1*, 109.
(55) Reiter, R. J. ; in Neural Hormones and Reproduction, D.E. Scott, G.P. Kozlowski A. Weindl, ed., Karger: Basel, 1978, pp 344.
(56) Herbert, J. ; in Biological Clocks in Seasonal Reproductive Cycles, B.K. Follett, D.E. Follett, ed., Wiley: New York, 1980, pp 261.
(57) Guardiola-Lemaitre, B. *Adv. Pineal. Res.* **1991**, *5*, 351.
(58) Rao, M. L.; Gross, G.; Strebel, B.; Halaris, A.; Huber, G.; Braunig, P.; Marler, M. *Biological Psychiatry* **1994**, *35*, 151.
(59) Poeggeler, B.; Reiter, R. J.; Tan, D.-X.; Chen, L.-D.; Manchester, L. C. *J. Pineal Res.* **1993**, *14*, 151.
(60) Reiter, R. J. *Bioessays* **1992**, *14*, 169.
(61) Blickenstaff, R. T.; Brandstadter, S. M.; Reddy, S.; Witt, R. *J. Pharm. Sci.* **1994**, *83*, 216.
(62) Lesniewska, B.; Nowak, M.; Nussdorfer, G. G.; Malendowicz, L. K. *Life Sci.* **1990**, *47*, 241.
(63) Cavallo, A. *J. Pineal Res.* **1993**, *15*, 115.
(64) Klein, D. C.; Martin, J. E. *Sexual Endocrinological Hormone Relations and the Physiopathology of Pregnancy - Hormone Investigation*, R. De Manbenge, Inc.: New York, 1978, p 175.
(65) Pavel, S. *Neural Transm. (Suppl.)* **1978**, *13*, 135.
(66) Sandyk, R. *Int. J. Neurosci.* **1992**, *66*, 237.
(67) Reiter, R. J.; Poeggeler, B.; Tan, D.; Chen., L. D.; Manchester, L. C.; Guerrero, J. M. *Neuroendocrinology Letters* **1993**, *15*, 103.
(68) Sandyk, R. *Int. J. Neuroscience* **1992**, *66*, 209.
(69) Blask, D. E.; Hill, S. M. *J. Neural Transm. (Suppl.)* **1986**, *21*, 433.
(70) Bartsch, C.; Bartsch, H.; Lippert, T. H. *Cancer Journal* **1992**, *5*, 194.
(71) Kennaway, D. J.; Gilmore, T. A.; Seamark, R. F. *Endocrinology* **1982**, *110*, 1766.
(72) Milne, J. A.; Loudon, A. S. I.; Sibbald, A. M.; Curlewis, J. D.; McNeilly, A. S. *J. Endocrinol.* **1990**, *125*, 241.
(73) Gaffori, O.; Ree, J. M. V. *Neuropharmacol.* **1985**, *24*, 237.

(74) Holmes, S. W.; Sugden, D. *Br. J. Pharmacol.* **1982**, *76*, 95.
(75) Sugden, D. *J. Pharmacol. Exp. Ther.* **1983**, *227*, 587.
(76) Halberg, F. ; Masson & Cie.: Paris, 1967.
(77) Lewy, A. J.; Sack, R. L.; Miller, L. S.; Hoban, T. M. *Science* **1987**, *235*, 352.
(78) Arendt, J.; Aldhouse, M.; Markus, V. *Br. Med. J.* **1986**, *292*, 1170.
(79) Dawson, D.; Encel, N. *J. Pineal Res.* **1993**, *15*, 1.
(80) Rosenthal, N. E.; Sack, D. A.; Jacobsen, F. M.; James, S. P.; Parry, B. L.; Arendt, J.; Tamarkin, L.; Wehr, T. A. *J. Neural Transm. (Suppl.)* **1986**, *21*, 257.
(81) Dubocovich, M. L.; Mogilnicka, E.; Areso, P. M. *Eur. J. Pharmacol.* **1990**, *182*, 313.
(82) Holmes, S. W.; Sugden, D. *Br. J. Pharmacol.* **1982**, *76*, 95.
(83) Pierpaoli, W.; Maestroni, G. *patent: PCT Int.Appl. WO 88 07,367* **1989**,
(84) Marangos, P.; Patel, J.; Hirata, F.; Sonhein, D.; Parl, S. M.; Skolnick, P.; Goodwin, F. K. *Life Sci.* **1981**, *29*, 259.
(85) Cohen, M. *patent: PCT Int.Appl. WO 88 07,370* **1989**,
(86) Cohen, M. *patent: US 4,945,103* **1990**,
(87) Morgan, P. J.; Barrett, P.; Howell, H. E.; Helliwell, R. *Neurochem. Int.* **1994**, *24*, 101.
(88) Sugden, D. *Neuochem. Int.* **1994**, *24*, 147.
(89) Vanecek, J.; Pavlik, A.; Illnerova, H. *Brain Res* **1987**, *435*, 359.
(90) Vakkuri, O.; Leppaluoto, J.; Vuolteenaho, O. *Acta Endocr.* **1984**, *106*, 152.
(91) Niles, L. P.; Wong, Y.-W.; MIshra, R. K.; Brown, G. M. *Eur. J. Pharmacology* **1979**, *55*, 219.
(92) Cardinali, D. P.; Vacas, M. I.; Boyer, E. E. *Endocrinology* **1979**, *105*, 437.
(93) Martinoli, M. G.; Williams, L. M.; Kah, O.; Titchener, L. T.; Pelletier, G. *Molec. cell. Neurosci.* **1991**, *2*, 78.
(94) Dubocovich, M. L. *Adv. Pineal Res.* **1991**, *5*, 167.
(95) Lee, P. P.; Pang, S. F. *Life Sci.* **1992**, *50*, 117.
(96) Pang, C. S.; Pang, S. F. *J. Pineal Res.* **1992**, *12*, 167.
(97) Song, Y.; Ayre, E. A.; Pang, S. F. *J. Endocr.* **1992**, *135*, 353.
(98) Liu, Z. M.; Pang, S. F. *Biol. Signals* **1992**, *1*, 245.
(99) Viswanathan, M.; Laitinen, J. T.; Saavedra, J. M. *Proc. Natl. Acad. Sci., USA* **1990**, *87*, 6200.
(100) Rollag, M. D. *Pineal Res. Rev.* **1988**, *6*, 67.
(101) Ebisawa, T.; Karne, S.; Lerner, M. R.; Reppert, S. M. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 6133.
(102) Ruffin, N.; Reed, B.; Finnin, B. *Life Sci.* **1969**, *8*, 1167.
(103) Ayre, E. A.; Yuan, H.; Pang, S. F. *J. Endocr.* **1992**, *133*, 5.
(104) vanVuuren, R. J. J.; Pitout, M. J.; Vanaswegen, C. H.; Theron, J. J. *Clin. Biochem.* **1992**, *25*, 125.
(105) Ng, T. B.; Lo, L. L. *J. Pineal Res.* **1988**, *5*, 229.
(106) Laudon, M.; Zisapel, N. *FEBS Lett.* **1991**, *288*, 105.
(107) Anis, Y.; Zisapel, N. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 1147.
(108) Dubocovich, M. L.; Takahashi, J. S. *Proc. Natl. Acad. USA* **1987**, *84*, 3916.
(109) Sugden, D.; Chong, N. W. S. *Brain Res.* **1991**, *539*, 151.
(110) Dubocovich, M. L.; Shankar, G.; Mickel, M. *Eur. J. Pharmacology* **1989**, *162*, 289.
(111) Paterson, A.; Chong, N. W. S.; Brinklow, B. R.; Loudon, A. S. I.; Sugden, D. *Comp. Biochem. Physiol.* **1992**, *102A*, 55.
(112) Duncan, M. J.; Takahashi, J. S.; Dubocovich, M. L. *Endocrinology* **1988**, *125*, 1825.

(113) Dubocovich, M. L.; Molinari, E.; Hoganesch, J. N.; North, P. C.; Hagan, R. M. Poster presented at *IUPHAR Congress*; Montreal, Canada, 1994.
(114) Heward, C. B.; Hadley, M. E. *Life Sci.* **1975**, *17*, 1167.
(115) Messenger, E. A.; Warner, A. E. *Br. J. Pharmacol.* **1977**, *61*, 607.
(116) Kennaway, D. J.; Hugel, H. M.; Clarke, S.; Tjandra, A.; Johnson, D. W.; Royles, P.; Webb, H. A.; Carbone, F. *Aust. J. Biol. Sci.* **1988**, *41*, 393.
(117) Flaugh, M. E.; Crowell, T. A.; Clemens, T. A.; Sawyer, B. D. *J. Med. Chem.* **1979**, *22*, 63.
(118) Frohn, M. A.; Seaborn, C. J.; Johnson, D. W.; Phillipou, G.; Seamark, R. F.; Matthews, C. D. *Life Sci.* **1980**, *27*, 2043.
(119) Caignard, D. H. Poster presented at *6th Colloquium of the European Pineal Society*; Copenhagen, 1993.
(120) Garratt, P. J.; Jones, R.; Rowe, S. J.; Sugden, D. *BioMed Chem. Lett.* **1994**, *4*, 1555.
(121) Sugden, D. *Br. J. Pharmacol.* **1991**, *104*, 922.
(122) Clemens, F. A.; Flaugh, M. E. *J. Neural Transm. (Suppl.)* **1986**, *21*, 451.
(123) Chong, N. W. S. PhD Thesis, University of London, 1993.
(124) Duranti, E.; Stankov, B.; Spadoni, G.; Duranti, A.; Lucini, V.; Capsoni, S.; Biella, G.; Fraschini, F. *Life Sci.* **1992**, *51*, 479.
(125) Spadoni, G.; Stankov, B.; Duranti, A.; Biella, G.; Lucini, V.; Salvatori, A.; Fraschini, F. *J. Med. Chem.* **1993**, *36*, 4069.
(126) Campaigne, E.; Hornfeld, E.; Mais, D. E. *J. Het. Chem.* **1978**, *15*, 1351.
(127) Depreux, P.; Andrieux, J.; Adam, G.; Caignard, D. H.; Guardiola-Lemaitre, B.; Lesieur, D. *Patent EP 0.527.687 A* **1993**,
(128) Yous, S.; Andrieux, J.; Howell, H. E.; Morgan, P. J.; Renard, P.; Pfeiffer, B.; Lesieur, D.; Guardiola-Lemaitre, B. *J. Med. Chem.* **1992**, *35*, 1484.
(129) Copinga, S.; Tepper, P. G.; Grol, V. J.; Horn, A. S.; Dubocovich, M. L. *J. Med. Chem.* **1993**, *36*, 2891.
(130) Jansen, J. M.; Karlén, A.; Grol, C. J.; Hacksell, U. *Drug Design Disc.* **1993**, *10*, 115.
(131) Sugden, D. *Eur. J. Pharmacol.* **1994**, *254*, 271.
(132) Dubocovich, M. L. *Eur. J. Pharmacol.* **1984**, *105*, 193.
(133) Howell, H. E.; Morgan, P. J. *Adv. Pineal Res.* **1990**, *5*, 205.
(134) Sugden, D. *Eur. J. Phar.* **1992**, *213*, 405.
(135) Zisapel, N.; Laudon, M. A. *ur. J. Pharmacol.* **1987**, *136*, 259.
(136) Morgan, P. J.; Williams, L. M.; Davidson, G. R.; Lawson, W.; Howell, H. E. *J. Neuroendocr.* **1989**, *1*, 1.
(137) Dubocovich, M. L. Poster presented at *6th Colloquium of the European Pineal Society*; Copenhagen, 1993.
(138) Lewis, D. F. V.; Arendt, J.; English, J. *J Pharmacol Exp Ther* **1989**, *252*, 370.
(139) Horn, A. S. *J. Pharm. Pharmacol.* **1974**, *26*, 735.
(140) King, F. D.; Brown, A. M.; Gaster, L. M.; Kaumann, A. J.; Medhurst, A. D.; Parker, S. G.; Parsons, A. A.; Patch, T. L.; Raval, P. *J. Med. Chem.* **1993**, *36*, 1918.
(141) Böshagen, H.; Rosentreter, U.; Lieb, F.; Oediger, H.; Seuter, F.; Perzborn, E.; Fiedler, V. B. *Patent DE 3.631.824* **1988**,
(142) Alexander, E. J.; Mooradian, A. *Patent US 3.979.391* **1976**,
(143) Berger, L.; Corraz, A. J. *Patent US 4.009.181* **1977**,
(144) Gillard, J. W.; Guindon, Y.; Morton, H. E.; Girard, Y.; Yoakim, C. *Patent EP 304.156* **1989**,

(145) McManus, J. M. *Patent Ger.Offen. 2.042.280, UK 1.260.768* **1971**,
(146) Julia, M.; Lenzi, J. *Bull. Soc. Chim. Fr.* **1962**, 2262.
(147) Julia, M.; Bagot, J. *Bull. Soc. Chim. Fr.* **1964**, 1924.
(148) Julia, M.; Igolen, J. *Bull. Soc. Chim. Fr.* **1962**, 1056.
(149) Utaka, M.; Koyama, J.; Takeda, A. *J. Am. Chem. Soc.* **1976**, *98*, 984.
(150) Pinkney, P. S. *Org. Synth., Coll. Vol. II* 116.
(151) Prelog, V.; Hinden, W. *Helv. Chim. Acta* **1944**, *27*, 1854.
(152) Christol, H.; Mousseron, M.; Plenat, F. *Bull. Soc. Chim. Fr.* **1959**, 543.
(153) Julia, M.; Manoury, P.; Igolen, J. *C.R.* **1960**, *251*, 394.
(154) Julia, M.; Lenzi, J. *Bull. Soc. Chim. Fr.* **1962**, 1051.
(155) Julia, M.; Lenzi, J. *Bull. Soc. Chim. Fr.* **1971**, 4084.
(156) Sundberg, R. J. In *The Chemistry of Indoles*; R. J. Sundberg, Ed.; Academic Press: New York, 1970; pp 164.
(157) Julia, M.; Igolen, J.; Igolen, H. *Bull. Soc. Chim. Fr.* **1962**, 1060.
(158) Guthrie, J. L.; Robjohn, N. *Org. Synth., Coll. Vol. IV* **1963**, 513.
(159) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.
(160) Morales-Rios, M. S.; Espiñeira, J.; Joseph-Nathan, P. *Magn. Res. Chem.* **1987**, *25*, 377.
(161) Bischler, A. *Ber.* **1892**, *25*, 2860.
(162) Crowther, A. F.; Mann, F. G.; Purdie, D. *J. Chem. Soc.* **1943**, 58.
(163) Brown, F.; Mann, F. G. *J. Chem. Soc.* **1947**, 1041.
(164) Weygand, F.; Richter, E. *Chem. Ber.* **1955**, *88*, 499.
(165) Bowman, R. E.; Evans, D. D.; Guyett, J.; Nagy, H.; Weale, J.; Weyell, D. J.; White, A. C. *J. Chem. Soc., Perkin Trans. I* **1972**, 1926.
(166) Clemo, G. R.; Felton, D. G. I. *J. Chem. Soc.* **1951**, 700.
(167) Evans, D. D. *Aust. J. Chem.* **1973**, *26*, 2555.
(168) Oldenziel, O. H.; van Leussen, D. ; van Leussen, A. M. *J. Organomet. Chem.* **1977**, *42*, 3114.
(169) Orere, D. M.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1977**, 280.
(170) Wood, P. L.; McQuade, P. S. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1984**, *8*, 773.
(171) L. Berger, A.J. Corraz, *Patent US 4.009.181, CA 115 P49398,* **1989**.
(172) Friedman, E.; Meller, E.; Hallock, M. *J. Neurochem.* **1981**, *36*, 931.
(173) Britten, A.; Lockwood, G. *J. Chem. Soc., Perkin Trans. I* **1974**, 1824.
(174) Coombes, G. E. A.; Harvey, D. J.; Reid, S. T. *J. Chem. Soc. (C)* **1970**, 325.
(175) Bird, C. W.; Wee, A. G. H. *J. Heterocyclic Chem.* **1985**, *22*, 191.
(176) Lacoume, B.; Milcent, G.; Olivier, A. *Terahedron* **1972**, *28*, 667.
(177) Aldersley, J. B.; Burkhardt, G. N.; Gillam, A. E.; Hindley, N. C. *J. Chem. Soc.* **1940**, 10.
(178) Jones, E. H. R.; Sondheimer, F. *J. Chem. Soc.* **1949**, 615.
(179) White, W. L.; Anzeveno, P. B.; Johnson, F. *J. Organomet. Chem.* **1982**, *47*, 2379.
(180) Kay, F. W.; Perkin, W. H. *J. Chem. Soc.* **1906**, *89*, 1640.
(181) Weinstock, J. *J. Organomet. Chem.* **1961**, *26*, 3511.
(182) Snyder, H. R.; Pilgrim, F. J. *J. Am. Chem. Soc.* **1948**, *70*, 3770.
(183) Kozikowski, A. P.; Ma, D.; Romeo, E.; Auta, J.; Papadopoulos, V.; Puia, G.; Costa, E.; Guidotti, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1060.
(184) Schindler, W. *Helv. Chim. Acta* **1957**, *40*, 2156.
(185) Schindler, W. *Helv. Chim. Acta* **1958**, *41*, 1441.
(186) Mahboobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034.

(187) Modi, S. P.; McComb, T.; Zayed, A.-H.; Oglesby, R. C.; Archer, S. *Terahedron* **1990**, *46*, 5555.
(188) Heath-Brown, B.; Philpott, P. G. *J. Chem. Soc.* **1965**, 7185.
(189) Capuano, L.; Ahlhelm, A.; Hartmann, H. *Chem. Ber.* **1986**, *119*, 2069.
(190) Henecka, H. *Chem. Ber.* **1948**, *81*, 197.
(191) Jackson, A. H.; Naidoo, B.; Smith, P. *Terahedron* **1968**, *24*, 6119.
(192) Burger, A.; Ullyot, G. E. *J. Organomet. Chem.* **1947**, *12*, 342.
(193) Martin, T.; Moody, C. J. *J. Chem. Soc., Perkin Trans. I* **1988**, 235.
(194) Harley-Mason, J.; Pavri, E. H. *J. Chem. Soc.* **1963**, 2504.
(195) Teuber, H.-J.; Cornelius, D.; Woelcke, U. *Liebigs Ann. Chem.* **1966**, *696*, 116.
(196) Courtot, P. *Ann. Chim.* **1963**, *8*, 197.
(197) Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404.
(198) DeBoer, T. J.; Backer, H. J. *Org. Synth., Coll. Vol. IV* **1963**, 225.
(199) Abramovitch, R. A.; Spencer, I. D. *Adv. Heterocyclic Chem.* **1964**, *3*, 79.
(200) Sundberg, R. J. In *The Chemistry of Indoles*; R. J. Sundberg, Ed.; Academic Press: New York, 1970; p 236.
(201) Wieland, T.; Neeb, E. *Liebigs Ann. Chem.* **1956**, *600*, 161.
(202) Hoshino, T.; Kotake, Y. *Liebigs Ann. Chem.* **1935**, *516*, 76.
(203) Jackson, A. H.; Smith, A. E. *Terahedron* **1968**, *24*, 403.
(204) Wakahara, A.; Fujiwara, T.; Tomita, K. *Chem. Lett.* **1972**, 1139.
(205) Quarles, W.; Templeton, D.; Zalkin, A. *Acta Cryst., Sec. B* **1974**, *30*, 99.
(206) Mostrad, A.; Rømming, C. *Acta Chem. Scand., Ser. B* **1974**, *28*, 564.
(207) Hulinská, H.; Taufmann, P.; Frycová, H.; Protiva, M. *Coll. Czech. Chem. Commun.* **1988**, *53*, 373.
(208) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976.
(209) Heinzelman, R. V.; Anthony, W. C.; Lyttle, D. A.; Szmuszkovicz, J. *J. Organomet. Chem.* **1960**, *25*, 1548.
(210) Law, H. D. *J. Chem. Soc.* **1912**, *101*, 154.
(211) Billman, J. H.; Diesing, A. C. *J. Organomet. Chem.* **1957**, *22*, 1068.
(212) Vigneaud, V. d.; Behrens, O. K. *J. Biol. Chem.* **1937**, *117*, 27.
(213) Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *7*, 263.
(214) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738.
(215) Marshall, F. J.; Cannon, W. N. *J. Organomet. Chem.* **1956**, *21*, 245.
(216) Goldsworthy, L. J. *J. Chem. Soc.* **1934**, 377.
(217) Troxler, F. In *Indoles Part II*; W. J. Houlihan, Ed.; Wiley-Interscience: New York, 1972; p 179.
(218) Vogel, T.; Huth, H.-U.; Fritz, H. *Liebigs Ann. Chem.* **1982**, 739.
(219) Gower, B. G.; Leete, E. *J. Am. Chem. Soc.* **1963**, *85*, 3683.
(220) Putochin, N. *Ber.* **1926**, *59*, 1987.
(221) Suh, J. T.; Puma, B. M. *J. Organomet. Chem.* **1965**, *30*, 2253.
(222) Woolridge, E. M.; Rokita, S. E. *Tetrahedron Lett.* **1989**, *30*, 6117.
(223) Schallenberg, J.; Meyer, E. *Z. Naturforsch.* **1983**, *38b*, 108.
(224) Troxler, F.; Peyer, J.; Hofmann, A. *Helv. Chim. Acta* **1955**, *38*, 1452.
(225) Liebscher, J.; Hartmann, H. *Z. Chem.* **1975**, *15*, 302.
(226) Somei, M.; Kobayashi, K.; Shimizu, K.; Kawasaki, T. *Heterocycles* **1992**, *33*, 77.
(227) Runti, C. S. *Gaz. Chim. Ital.* **1951**, *81*, 613.

(228) Teuber, H.-J.; Cornelius, D. *Liebigs Ann. Chem.* **1964**, *671*, 127.
(229) Gannon, W. F.; Benigni, J. D.; Suzuki, J.; Daly, J. W. *Tetrahedron Lett.* **1967**, 1531.
(230) Kruse, L. I.; Meyer, M. D. *J. Organomet. Chem.* **1984**, *49*, 4761.
(231) Julia, M.; Lallemand, J.-Y. *Bull. Soc. Chim. Fr.* **1973**, 2046.
(232) Blaikie, K. G.; Perkin, W. H. *J. Chem. Soc.* **1924**, *125*, 296.
(233) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871.
(234) Kline, T. *J. Heterocycl. Chem.* **1985**, *22*, 505.
(235) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.
(236) Bredereck, H.; Effenberger, F.; Simchen, G. *Amgew. Chem.* **1961**, *73*, 493.
(237) Lloyd, D. H.; Nichols, D. E. *J. Organomet. Chem.* **1986**, *51*, 4294.
(238) Lloyd, D. H.; Nichols, D. E. *Tetrahedron Lett.* **1983**, *24*, 4561.
(239) Reppert, S. M.; Weaver, D. R.; Rivkees, S. A.; Stopa, E. G. *Science* **1988**, *242*, 78.
(240) Speeter, M. E.; Anthony, W. C. *J. Am. Chem. Soc.* **1954**, *76*, 6208.
(241) Pfail, E.; Hardegger, U. *Angew. Chemie* **1967**, *79*, 188.
(242) Majima, R.; Hoshino, T. *Ber. dt. Chem. Ges.* **1925**, *58*, 2042.
(243) Suvorov, N. N.; Fedotova, M. V.; Orlova, L. M.; Ogareva, O. B. *J. Gen. Chem. USSR* **1962**, *32*, 2325.
(244) Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.
(245) Dauben, W. G.; Tanabe, M. *J. Am. Chem. Soc.* **1949**, *71*, 2877.
(246) SmithIII, A. B.; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071.
(247) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
(248) Rollag, M. D.; Adelman, M. R. *Pigment Cell Res.* **1993**, *6*, 1.
(249) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1980.
(250) Neukomm, G.; Hesse, M. *Helv. Chim. Acta* **1977**, *60*, 2431.
(251) Kraft, T.; Asma, W. J.; Haeck, H. H.; Moed, H. *Rec. Trav. Chim.* **1961**, *80*, 313.
(252) Dippy, J. F. J.; Lewis, R. H. *J. Chem. Soc.* **1937**, 1426.
(253) Arndt, F.; Eistert, S.; Partale, W. *Ber.* **1928**, *61*, 1107.
(254) Aldrich Catalogue

Appendix A Selected NMR Spectra

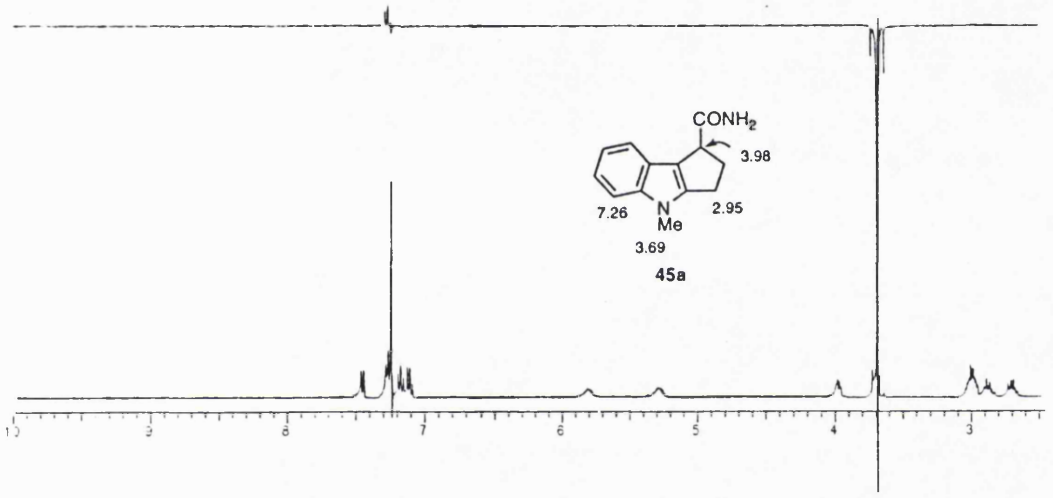


Figure 12: NOE experiment for 4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole-1-carboxamide (**45a**)

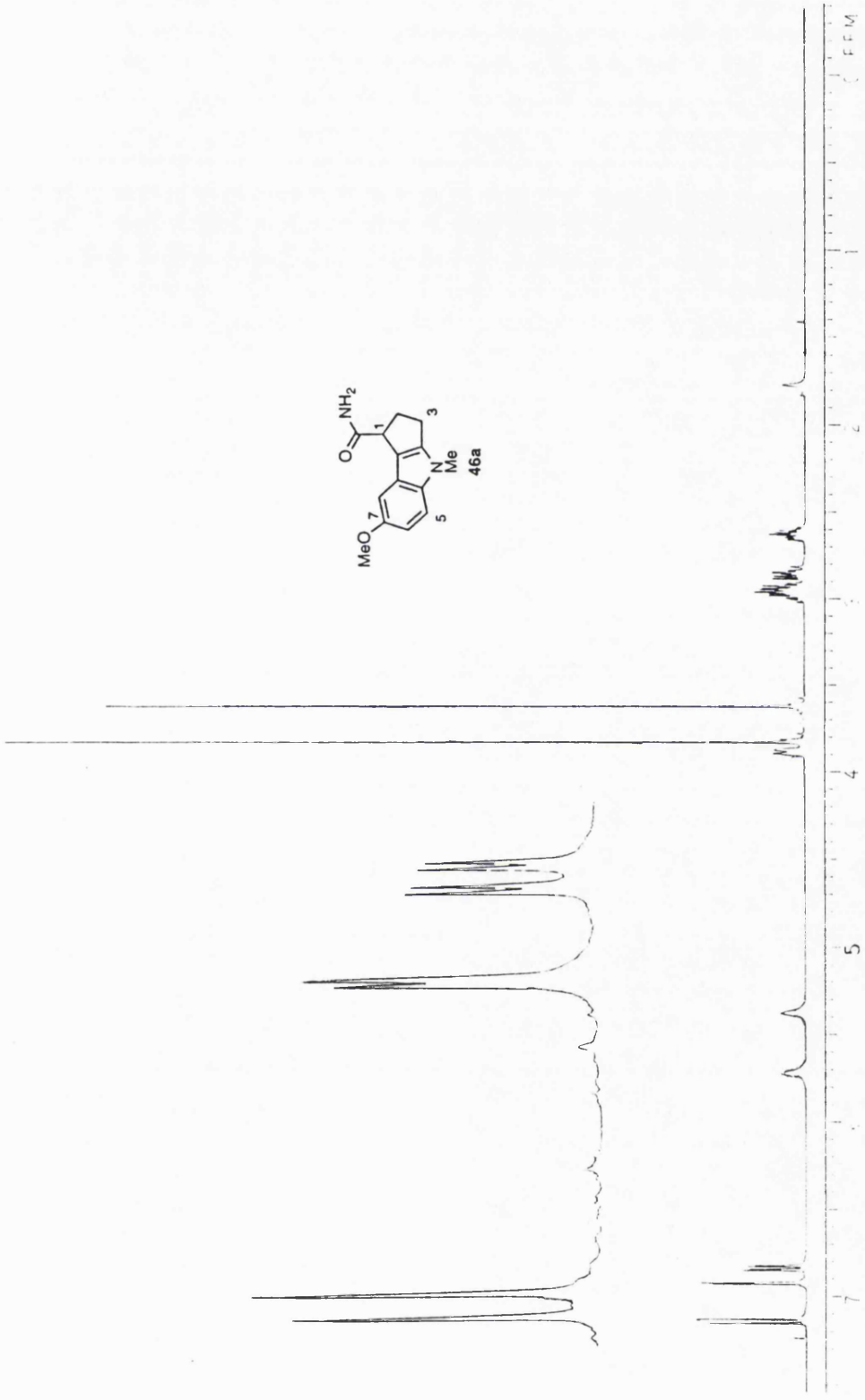


Figure 13: ^{1}H nmr spectrum of 7-methoxy-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole-1-carboxamide (**46a**)

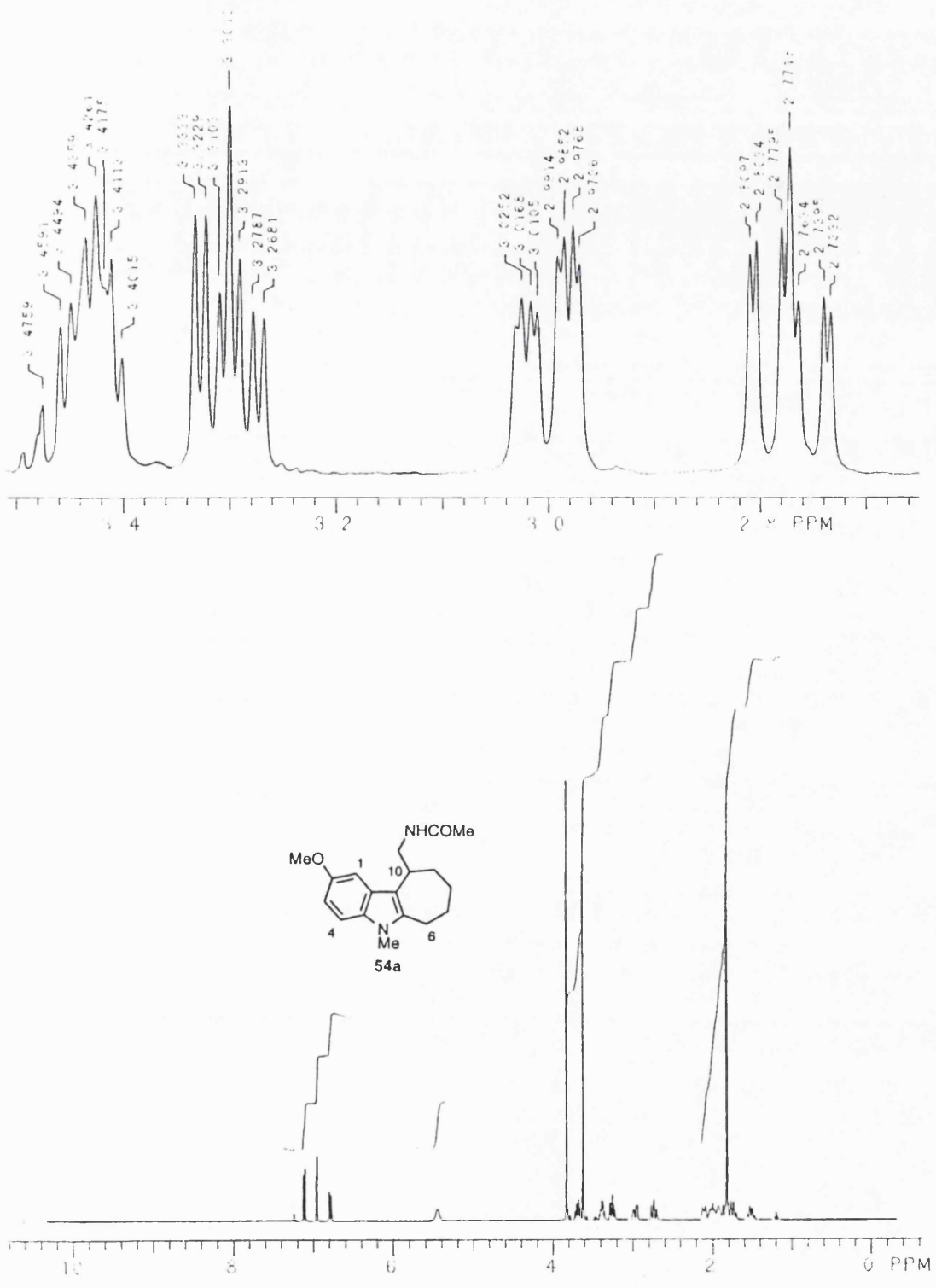


Figure 14: ^{1}H nmr spectrum of N-acetyl-10-aminomethyl-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (**54a**)

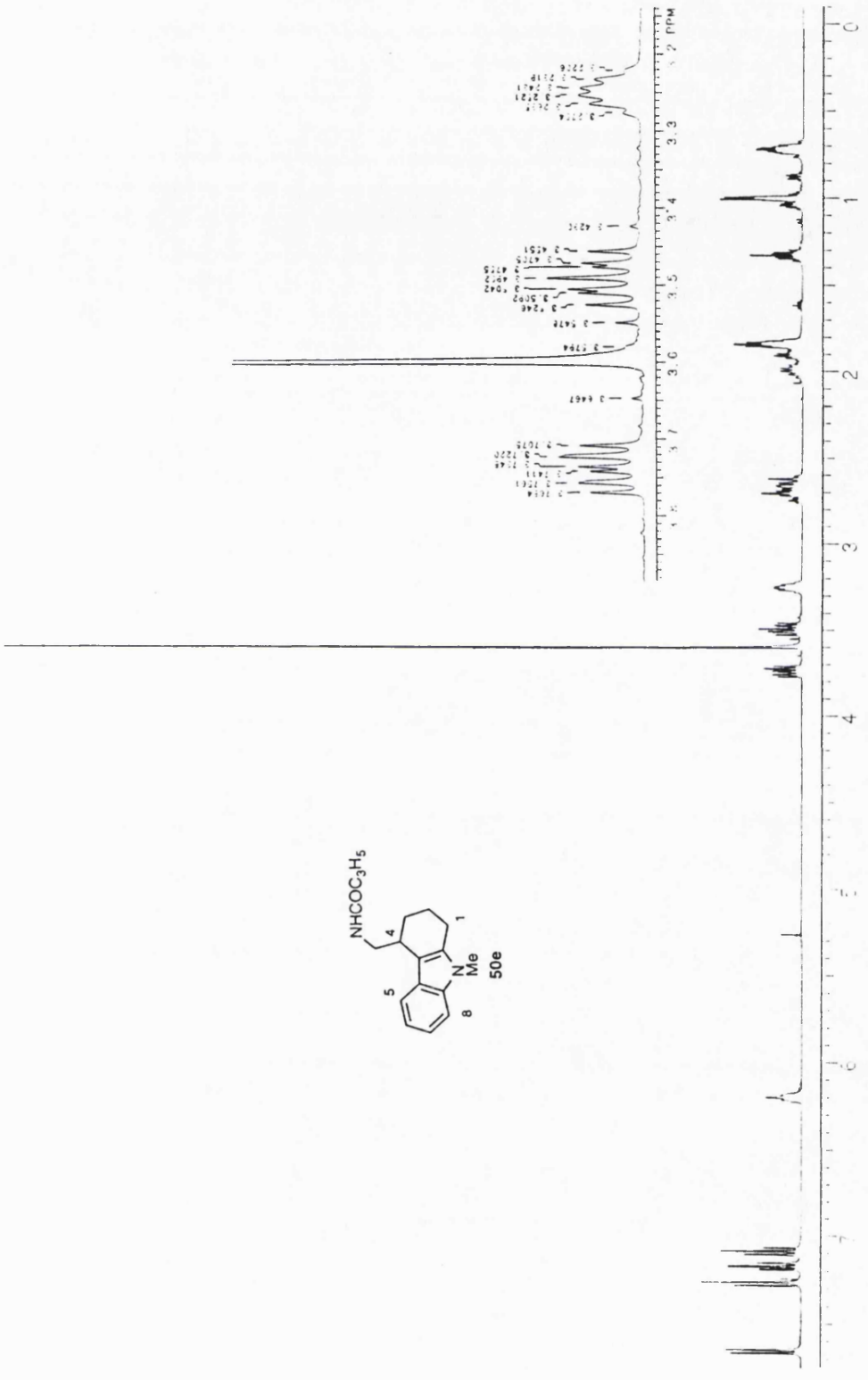


Figure 15: ^{1}H nmr spectrum of N-butanoyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (**50e**)

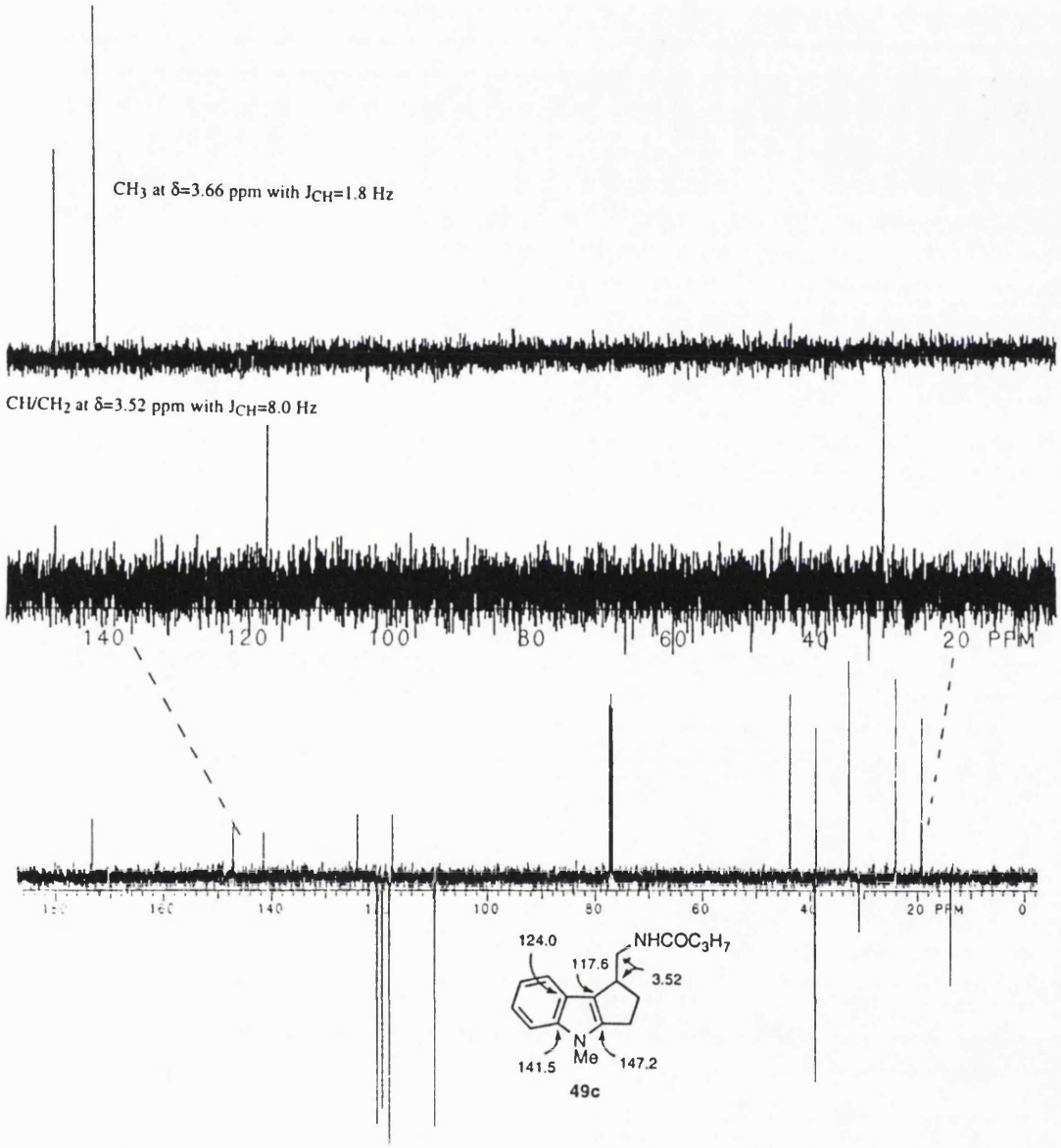


Figure 16: INEPT experiment for N-butanoyl-1-aminomethyl-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole (**49c**)

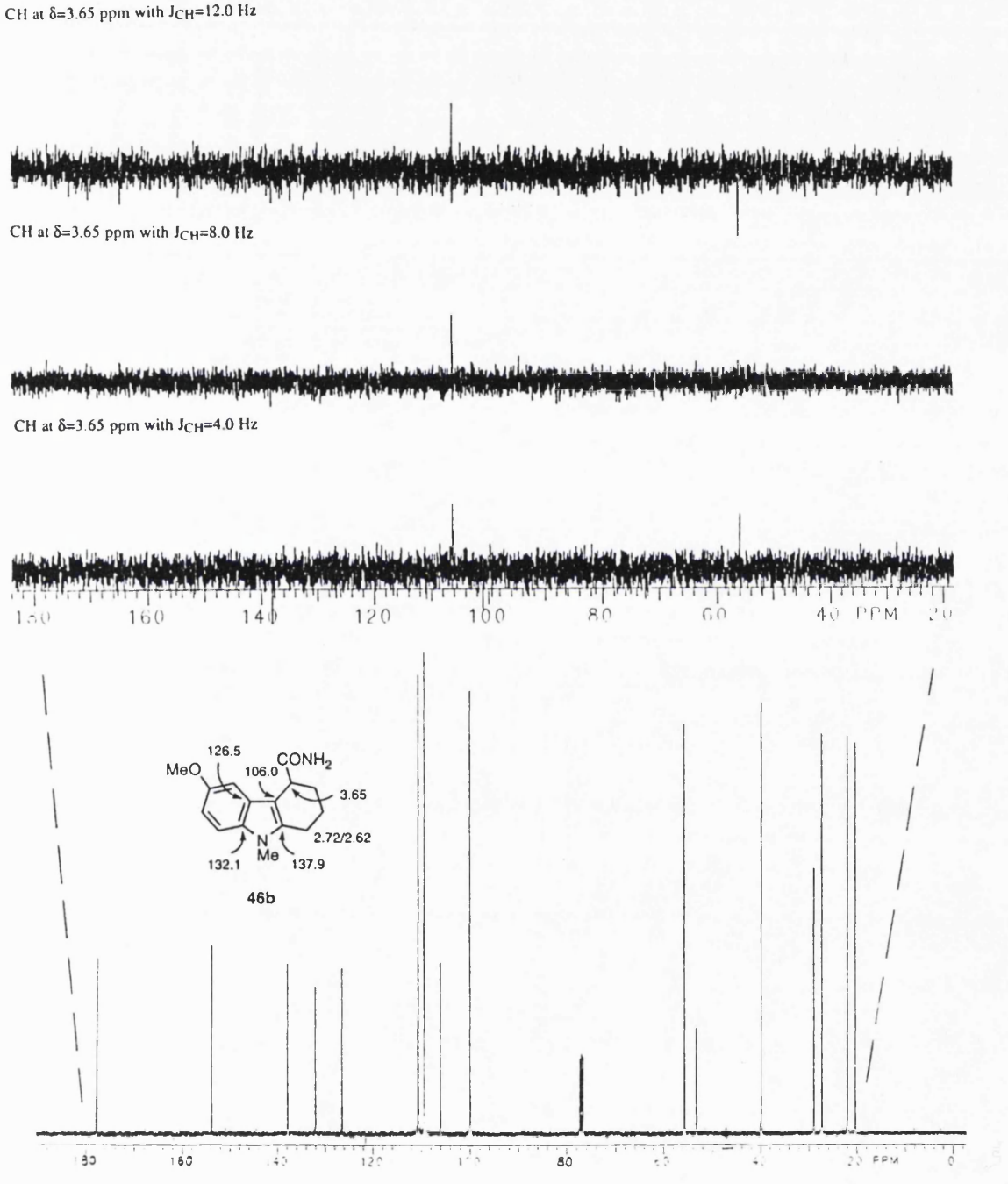


Figure 17: INEPT experiment for 4-carboxamido-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**46b**)

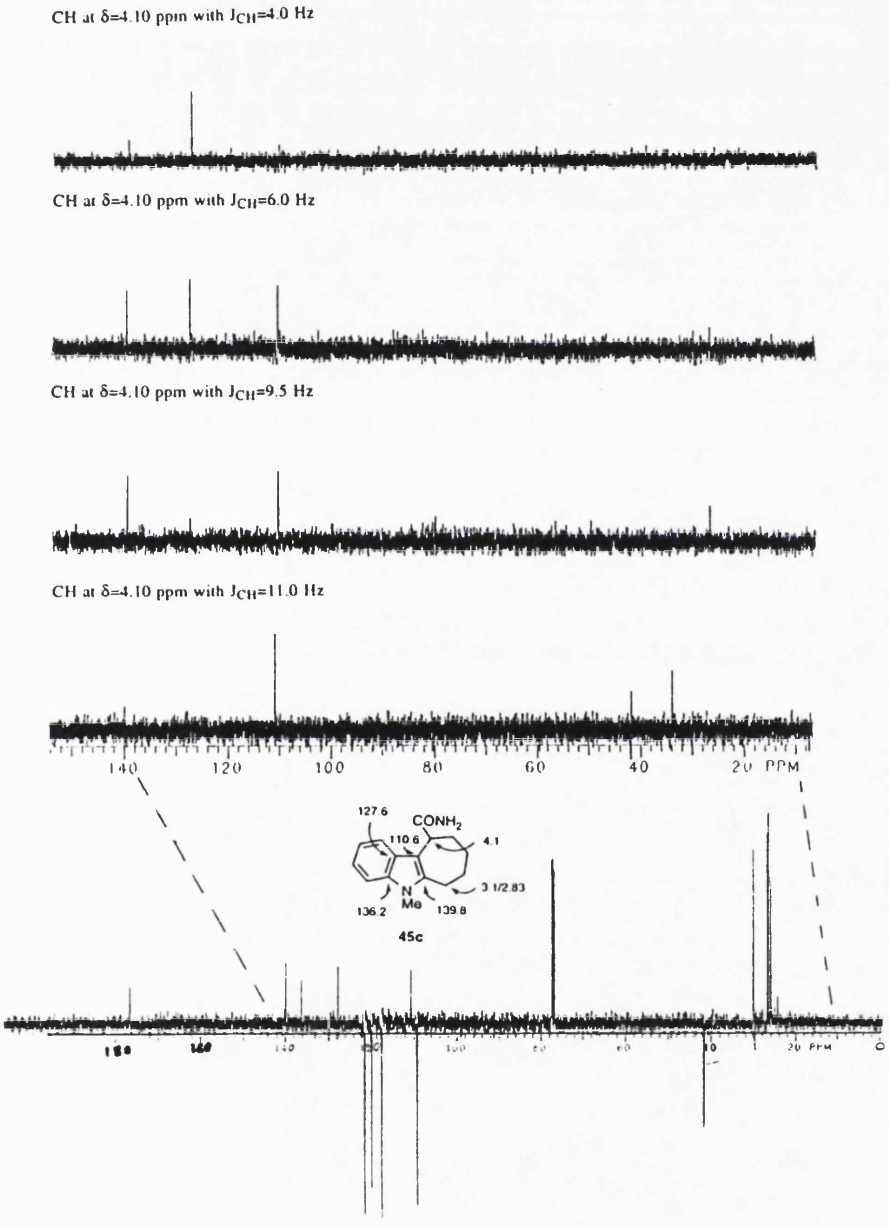


Figure 18: INEPT experiment for 10-carboxamido-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (**45c**)

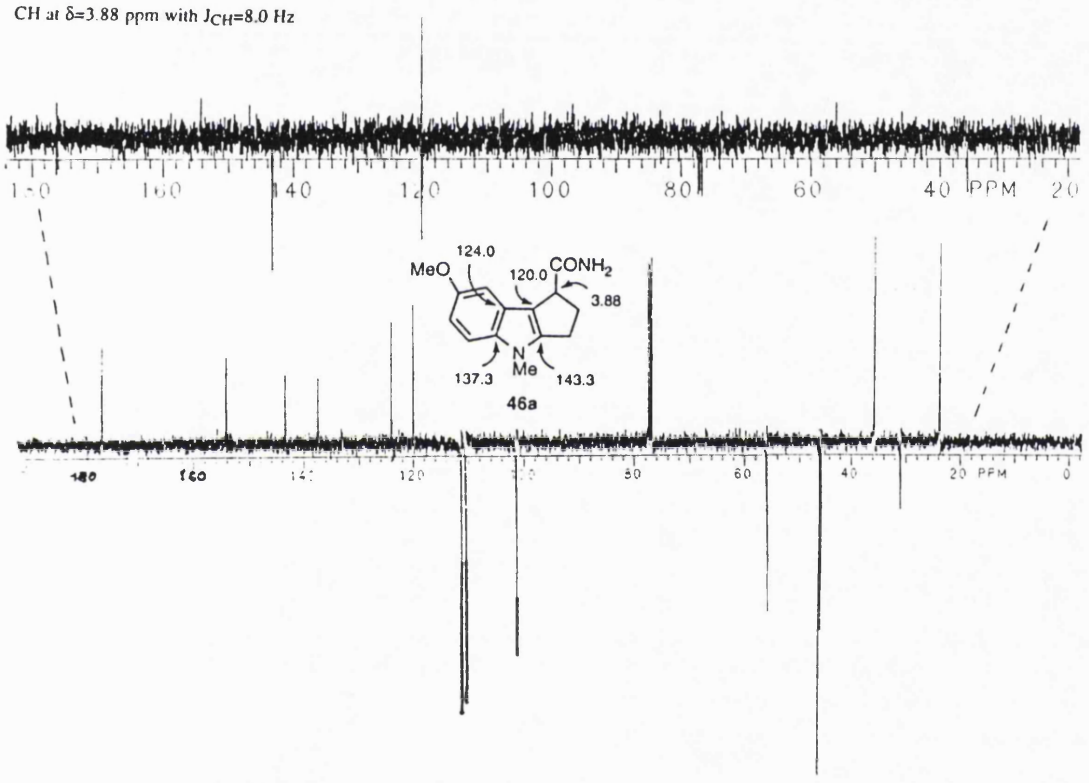


Figure 19: INEPT experiment for 1-carboxamido-7-methoxy-4-methyl-1,2,3,4-tetrahydro-cyclopent[b]indole (**46a**)

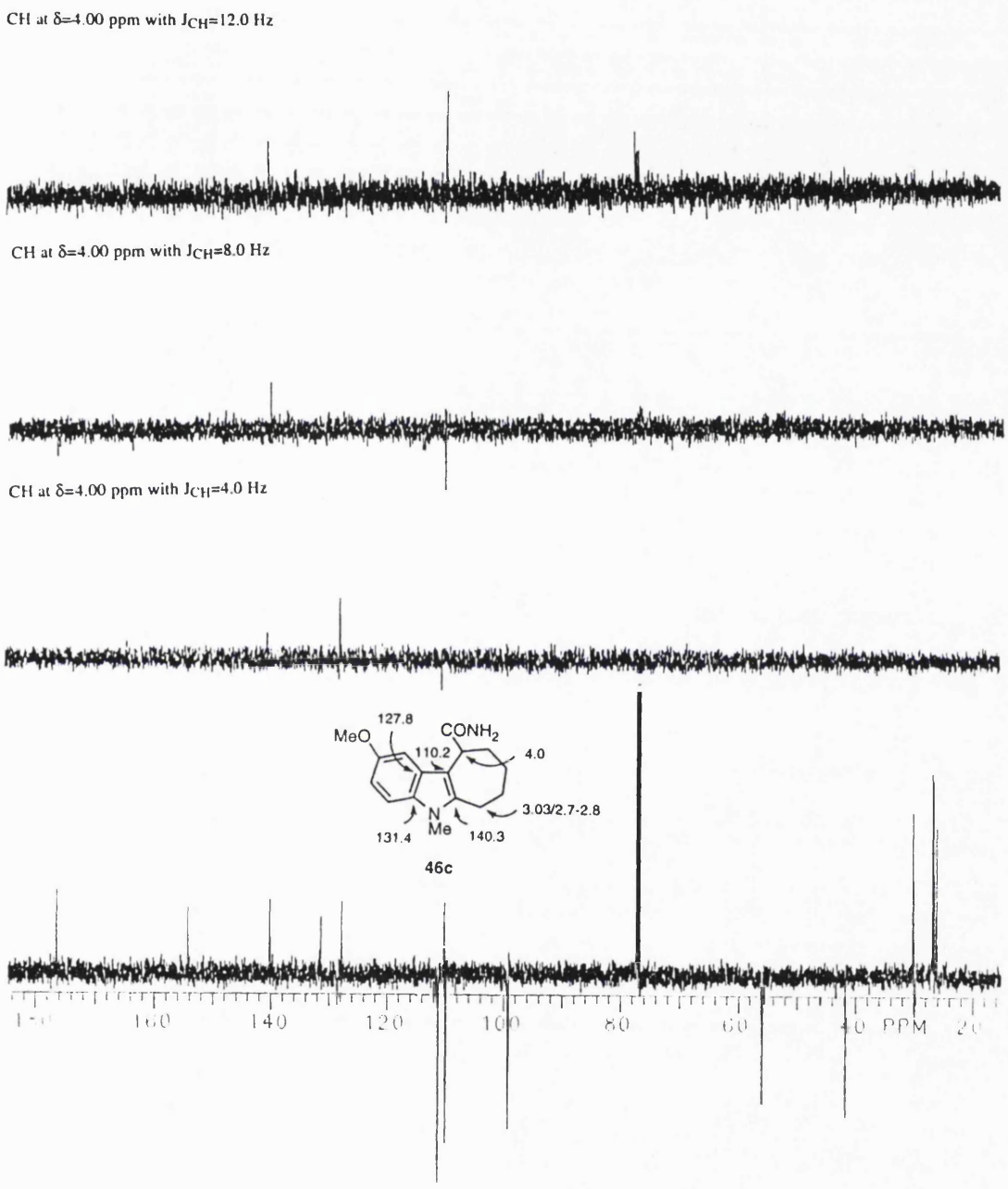


Figure 20: INEPT experiment for 10-carboxamido-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[b]indole (**46c**)

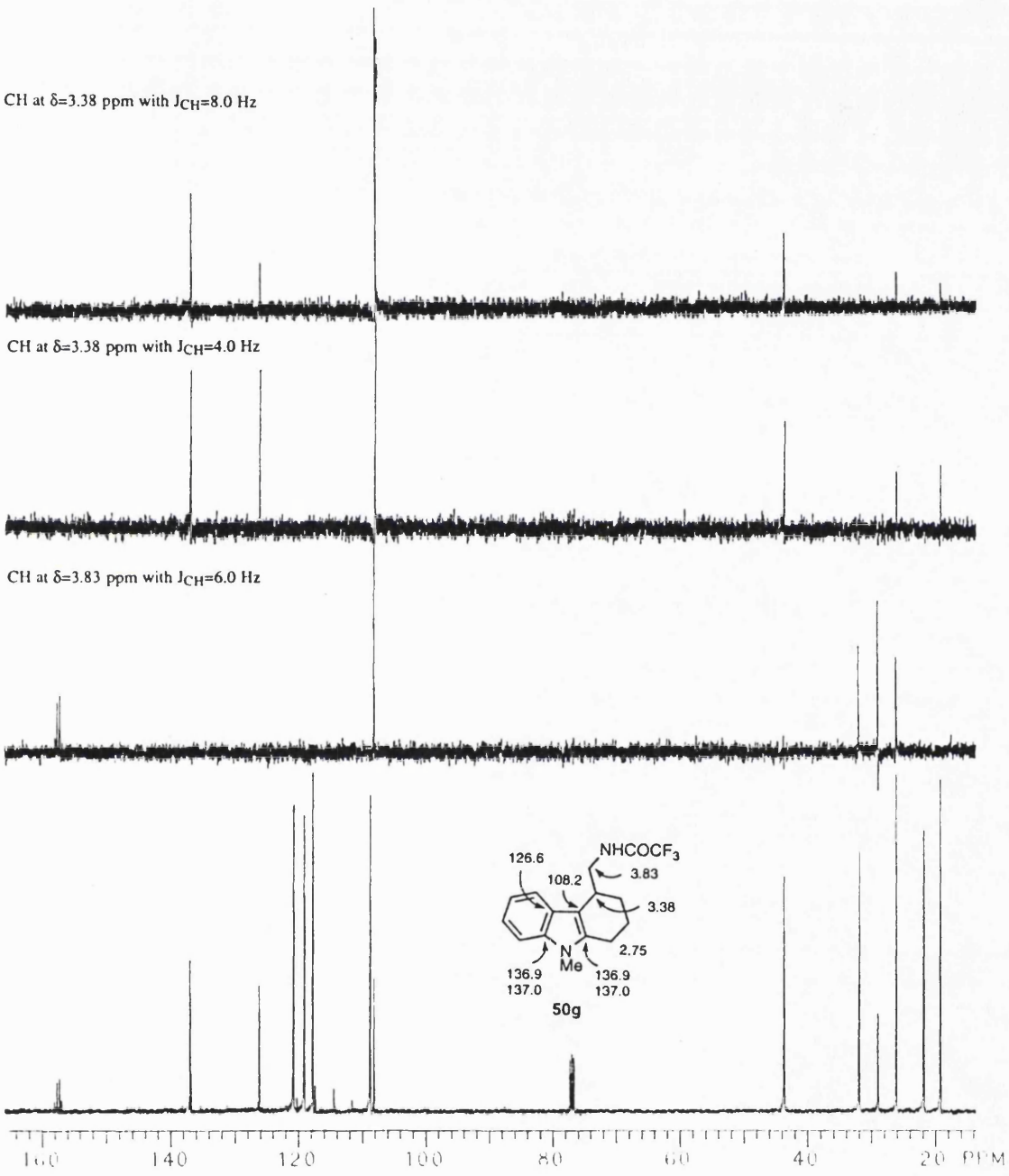


Figure 21: INEPT experiment for N-trifluoroacetyl-4-aminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (**50g**)

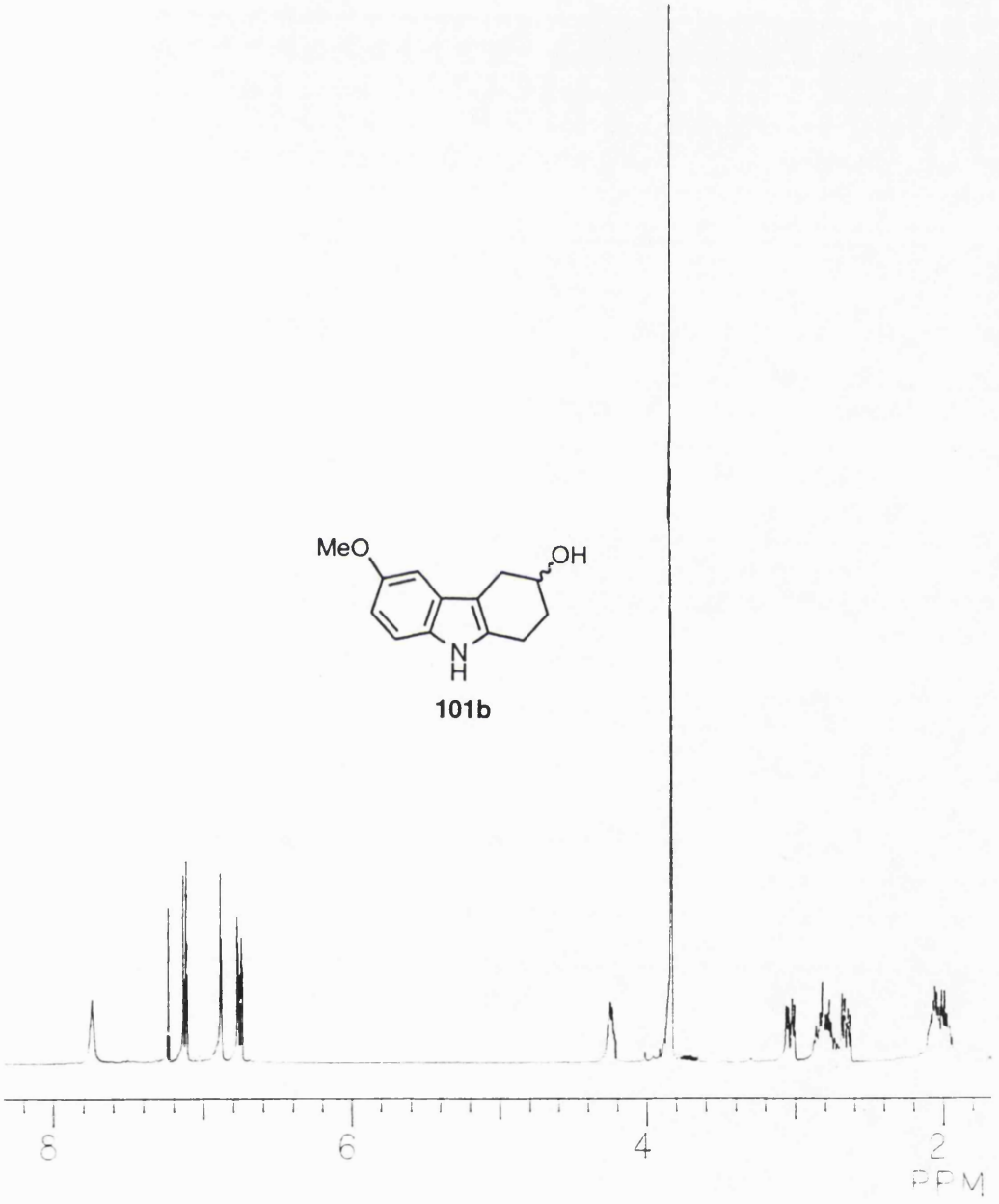


Figure 22: ^{1}H nmr spectrum of 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrocarbazole (**101b**)

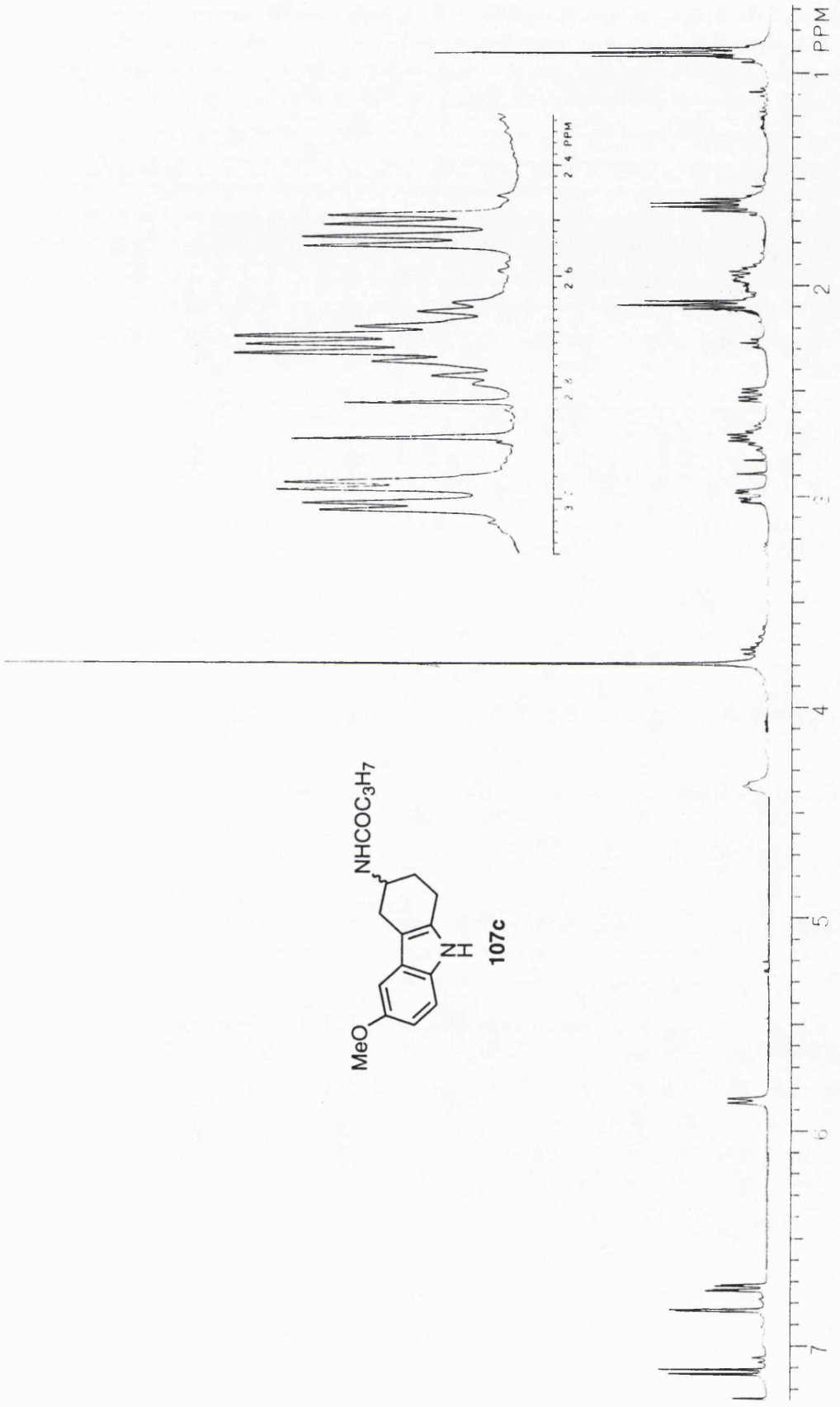


Figure 23: ^{1}H nmr spectrum of N-butanoyl-3-amine-6-methoxy-1,2,3,4-tetrahydrocarbazole (**107c**)

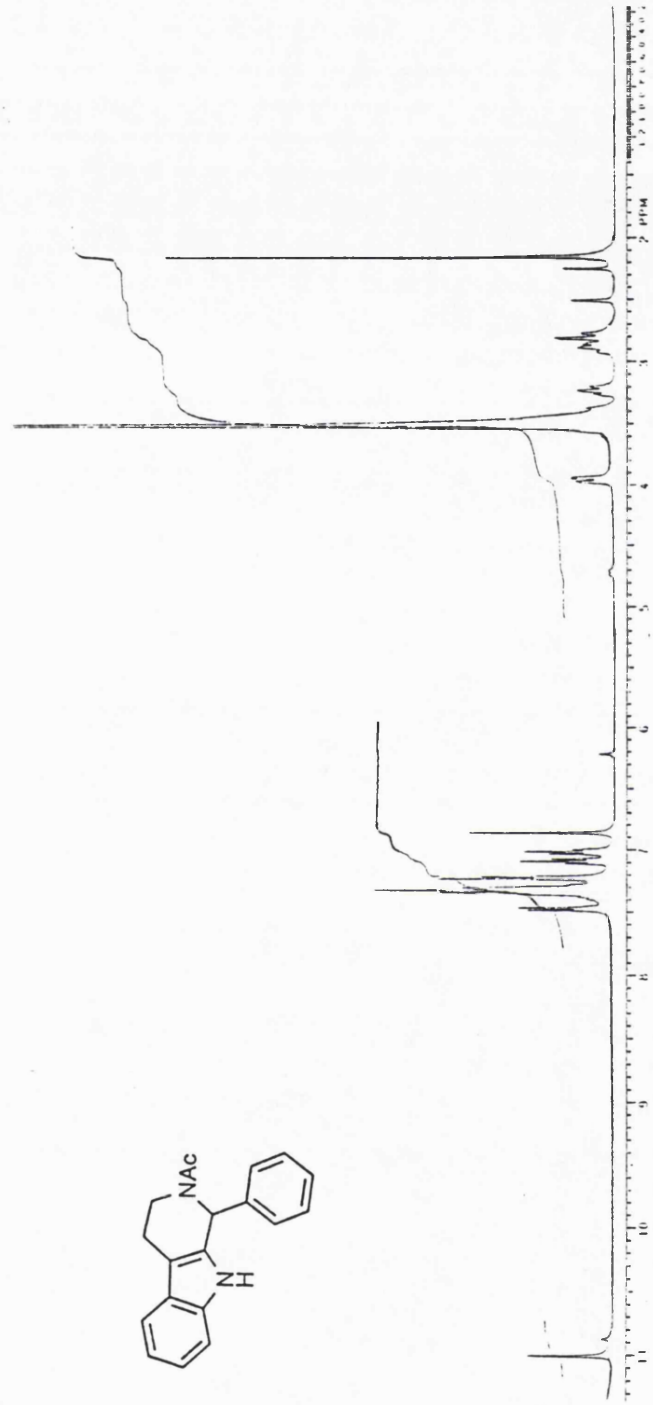


Figure 24: ^{1}H nmr spectrum of N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**)

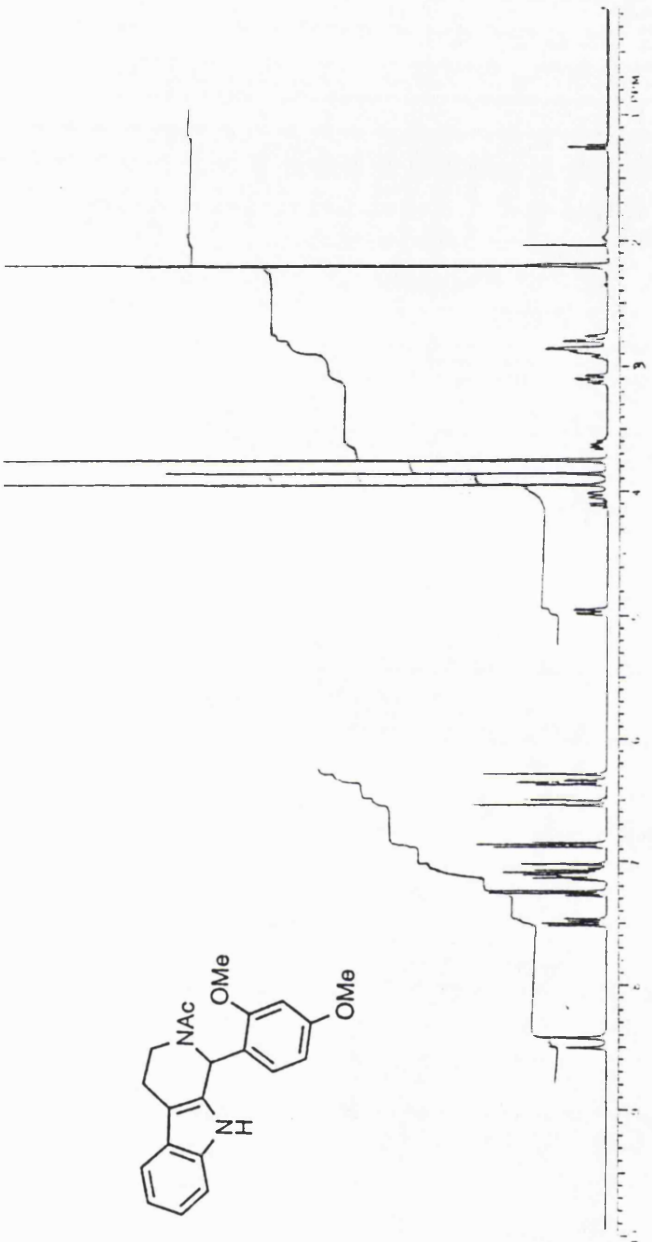


Figure 25: ^{1}H nmr spectrum of N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**)

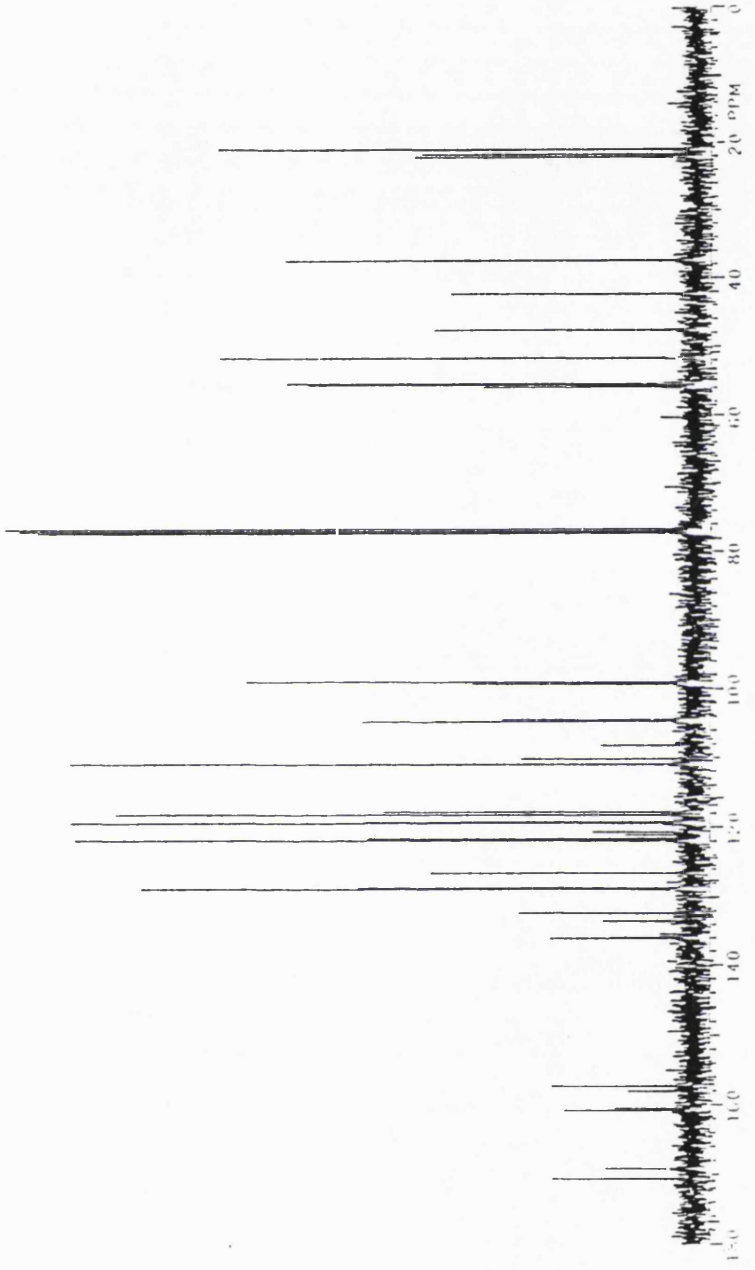


Figure 26: ^{13}C nmr spectrum of N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**)

Appendix B X-ray Crystal Structures

N-Trifluoroacetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (53g)

formula	$C_{17}H_{19}N_2O_2F_3$
fw, g/mol	340.32
space group	Pnaa
a, Å	10.021 (1)
b, Å	14.221 (3)
c, Å	22.992 (4)
α, °	90.0
β, °	90.0
γ, °	90.0
V, Å^3	3277
Z	8
F(000)	1424
$d_{calc.}$, g/cm^3	1.38
cryst. size, mm	0.80 x 0.32 x 0.31
μ(Mo-K_α), cm	1.08
data collection instrument	Nicolet R3mN
radiation	Mo-K_α λ=0.71073 Å
orientation reflections: no.; range (2Θ)	30; 13° ≤ 2Θ ≤22°
temp., °C	20
no. of unique data	2787
total with I ≥ 3σ(I)	1469
no. of parameters	217
R=Σ[|F_0|-|F_c|]/Σ|F_0|	0.0589
R'=Σ[|F_0-F_c|x√w]/Σ[F_0x√w]	0.0586
weighting scheme	w=1/(σ^2(F)+0.000332xF^2)
largest shift/esd. fin. cycle	0.001
largest peak, e/A^3	0.22

Table 9: Crystallographic data for N-trifluoroacetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbzole (**53g**)

F(1)-C(13)	1.314 (7)	F(2)-C(13)	1.309 (6)
F(3)-C(13)	1.306 (7)	O(1)-C(6)	1.379 (6)
O(1)-C(10)	1.364 (7)	O(2)-C(12)	1.211 (6)
N(1)-C(8a)	1.384 (6)	N(1)-C(8b)	1.387 (6)
N(1)-C(9)	1.449 (6)	N(2)-C(11)	1.464 (5)
N(2)-C(12)	1.320 (6)	C(1)-C(2)	1.532 (7)
C(1)-C(8b)	1.471 (6)	C(2)-C(3)	1.519 (7)
C(3)-C(4)	1.536 (6)	C(4)-C(4a)	1.505 (6)
C(4)-C(11)	1.539 (6)	C(4a)-C(4b)	1.424 (6)
C(4a)-C(8b)	1.369 (6)	C(4b)-C(5)	1.391 (6)
C(4b)-C(8a)	1.413 (6)	C(5)-C(6)	1.363 (7)
C(6)-C(7)	1.405 (7)	C(7)-C(8)	1.375 (7)
C(8)-C(8a)	1.378 (7)	C(12)-C(13)	1.525 (7)

Table 10: Bond length (Å) for N-trifluoroacetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**53g**)

C(6)-O(1)-C(10)	119.9 (4)	C(8a)-N(1)-C(8b)	109.1 (3)
C(8a)-N(1)-C(9)	125.3 (4)	C(8b)-N(1)-C(9)	125.5 (4)
C(11)-N(2)-C(12)	120.5 (4)	C(2)-C(1)-C(8b)	108.8 (4)
C(1)-C(2)-C(3)	113.3 (4)	C(2)-C(3)-C(4)	112.8 (4)
C(3)-C(4)-C(4a)	110.1 (3)	C(3)-C(4)-C(11)	112.9 (4)
C(4a)-C(4)-C11	109.8 (3)	C(4)-C(4a)-C(4b)	128.5 (4)
C(4)-C(4a)-C(8b)	123.5 (4)	C(4b)-C(4a)-C(8b)	108.0 (4)
C(4a)-C(4b)-C(5)	134.6 (4)	C(4a)-C(4b)-C(8a)	106.8 (4)
C(5)-C(4b)-C(8a)	118.6 (4)	C(4b)-C(5)-C(6)	120.0 (4)
O(1)-C(6)-C(5)	116.2 (4)	O(1)-C(6)-C(7)	123.1 (4)
C(5)-C(6)-C(7)	120.8 (4)	C(6)-C(7)-C(8)	120.4 (5)
C(7)-C(8)-C(8a)	118.7 (4)	N(1)-C(8a)-C(4b)	107.4 (4)
N(1)-C(8a)-C(8)	131.1 (4)	C(4b)-C(8a)-C(8)	121.5 (4)
N(1)-C(8b)-C(1)	125.1 (4)	N(1)-C(8b)-C(4a)	108.8 (4)
C(1)-C(8b)-C(4a)	126.1 (4)	N(2)-C(11)-C(4)	112.0 (3)
O(2)-C(12)-N(2)	126.5 (4)	O(2)-C(12)-C(13)	118.1 (4)
N(2)-C(12)-C(13)	115.3 (4)	F(1)-C(13)-F(2)	105.6 (5)
F(1)-C(13)-F(3)	108.2 (5)	F(2)-C(13)-F(3)	107.0 (4)
F(1)-C(13)-C(12)	110.4 (4)	F(2)-C(13)-C(12)	111.0 (5)
F(3)-C(13)-C(12)	114.3 (4)		

Table 11: Bond angles (°) for N-trifluoroacetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**53g**)

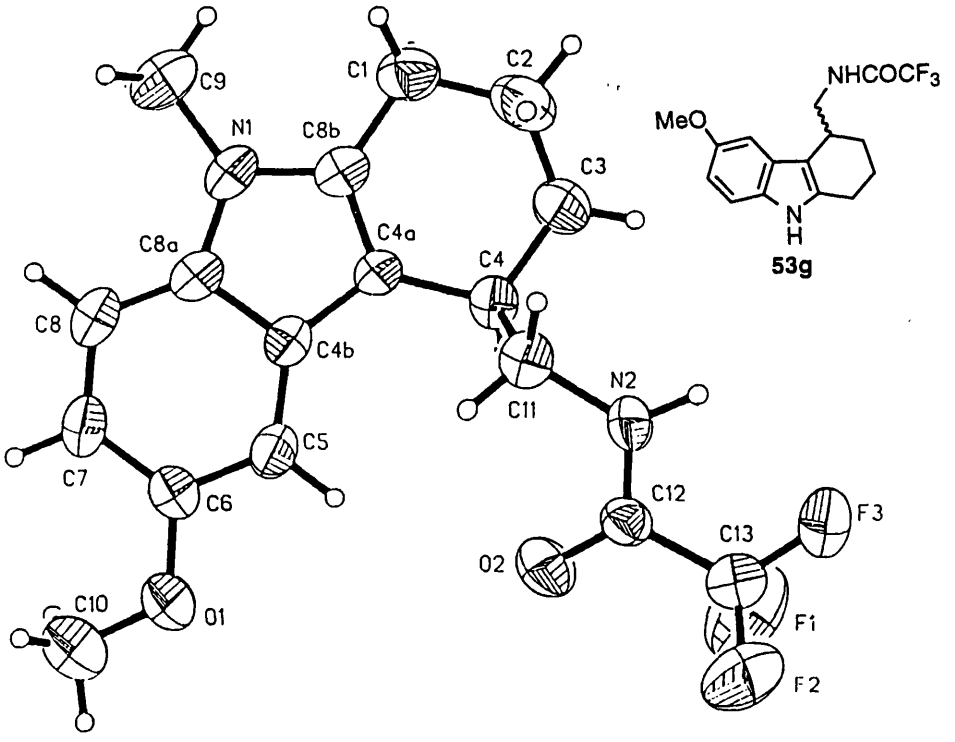


Figure 5: X-ray crystal structure of N-trifluoroacetyl-4-aminomethyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (**53g**), 50 % probability thermal ellipsoids

N-Acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (170a)

formula	$C_{19}H_{18}ON_2$
fw, g/mol	290.36
space group	$Pc2_1b$
a, Å	8.055 (3)
b, Å	11.184 (3)
c, Å	17.081 (6)
α, °	90.0
β, °	90.0
γ, °	90.0
V, $Å^3$	1538.96
Z	4
F(000)	616
$d_{calc.}$, g/cm^3	1.25
cryst. size, mm	0.8 x 0.8 x 0.4
μ(Mo-K_α), cm	0.73
data collection instrument	Nicolet R3mN
radiation	Mo-K_α λ=0.71073 Å
orientation reflections: no.; range (2Θ)	28; 8° ≤ 2Θ ≤27°
temp., °C	19
no. of unique data	1442
total with $I \geq 3\sigma(I)$	1200
no. of parameters	198
$R=\Sigma[\|F_0\|-\|F_c\|]/\Sigma\|F_0\|$	0.0496
$R'=\Sigma[\|F_0-F_c\|x\sqrt{w}]/\Sigma[F_0x\sqrt{w}]$	0.0590
weighting scheme	$w=1/(\sigma^2(F)+0.009609xF^2)$
largest shift/esd. fin. cycle	0.001
largest peak, e/A^3	0.165

Table 12: Crystallographic data for N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**)

O(1)-C(16)	1.230 (6)	N(2)-C(1)	1.468 (7)
N(2)-C(3)	1.474 (5)	N(2)-C(16)	1.325 (7)
N(9)-C(8a)	1.363 (5)	N(9)-C(9a)	1.360 (6)
C(1)-C(9a)	1.482 (7)	C(1)-C(10)	1.522 (6)
C(3)-C(4)	1.503 (6)	C(4)-C(4a)	1.480 (7)
C(4a)-C(4b)	1.429 (7)	C(4a)-C(9a)	1.370 (6)
C(4b)-C(5)	1.397 (7)	C(4b)-C(8a)	1.397 (7)
C(5)-C(6)	1.369 (9)	C(6)-C(7)	1.396 (10)
C(7)-C(8)	1.362 (9)	C(8)-C(8a)	1.387 (8)
C(10)-C(11)	1.374 (8)	C(10)-C(15)	1.380 (8)
C(11)-C(12)	1.379 (7)	C(12)-C(13)	1.351 (9)
C(13)-C(14)	1.364 (11)	C(14)-C(15)	1.372 (7)
C(16)-C(17)	1.484 (9)		

Table 13: Bond length (Å) for N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**)

C(1)-N(2)-C(3)	113.8 (4)	C(1)-N(2)-C(16)	120.0 (4)
C(3)-N(2)-C(16)	126.0 (5)	C(8a)-N(9)-C(9a)	108.7 (3)
N(2)-C(1)-C(9a)	107.0 (3)	N(2)-C(1)-C(10)	111.1 (4)
C(9a)-C(1)-C(10)	114.9 (4)	N(2)-C(3)-C(4)	111.0 (3)
C(3)-C(4)-C(4a)	109.8 (3)	C(4)-C(4a)-C(4b)	132.2 (4)
C(4)-C(4a)-C(9a)	121.6 (4)	C(4b)-C(4a)-C(9a)	106.2 (4)
C(4a)-C(4b)-C(5)	134.1 (5)	C(4a)-C(4b)-C(8a)	106.7 (4)
C(5)-C(4b)-C(8a)	119.2 (5)	C(4b)-C(5)-C(6)	118.1 (5)
C(5)-C(6)-C(7)	122.1 (6)	C(6)-C(7)-C(8)	120.4 (6)
C(7)-C(8)-C(8a)	118.2 (5)	N(9)-C(8a)-C(4b)	108.3 (4)
N(9)-C(8a)-C(8)	129.7 (4)	C(4b)-C(8a)-C(8)	121.9 (4)
N(9)-C(9a)-C(1)	124.0 (4)	N(9)-C(9a)-C(4a)	110.1 (4)
C(1)-C(9a)-C(4a)	125.9 (5)	C(1)-C(10)-C(11)	122.3 (4)
C(1)-C(10)-C(15)	119.1 (5)	C(11)-C(10)-C(15)	118.5 (4)
C(10)-C(11)-C(12)	120.7 (5)	C(11)-C(12)-C(13)	120.2 (6)
C(12)-C(13)-C(14)	119.7 (5)	C(13)-C(14)-C(15)	120.9 (6)
C(10)-C(15)-C(14)	119.9 (6)	O(1)-C(16)-N(2)	121.2 (6)
O(1)-C(16)-C(17)	120.2 (6)	N(2)-C(16)-C(17)	118.6 (5)

Table 14: Bond angles (°) for N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**)

C3-C4-C4a-C9a	- 14.5	N2-C3-C4-C4a	45.5
C1-N2-C3-C4	- 67.0	C9a-C1-N2-C3	- 47.8
C4a-C9a-C1-N2	15.3	C4-C4a-C9a-C1	- 0.5
C16-N2-C3-C4	107.7		

indole ring plane - acetyl group	50.2
indole ring plane - phenyl ring plane	101.5
phenyl ring plane - acetyl group	103.1

Table 15: torsion angles (°) and angle between planes (°) for N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**)

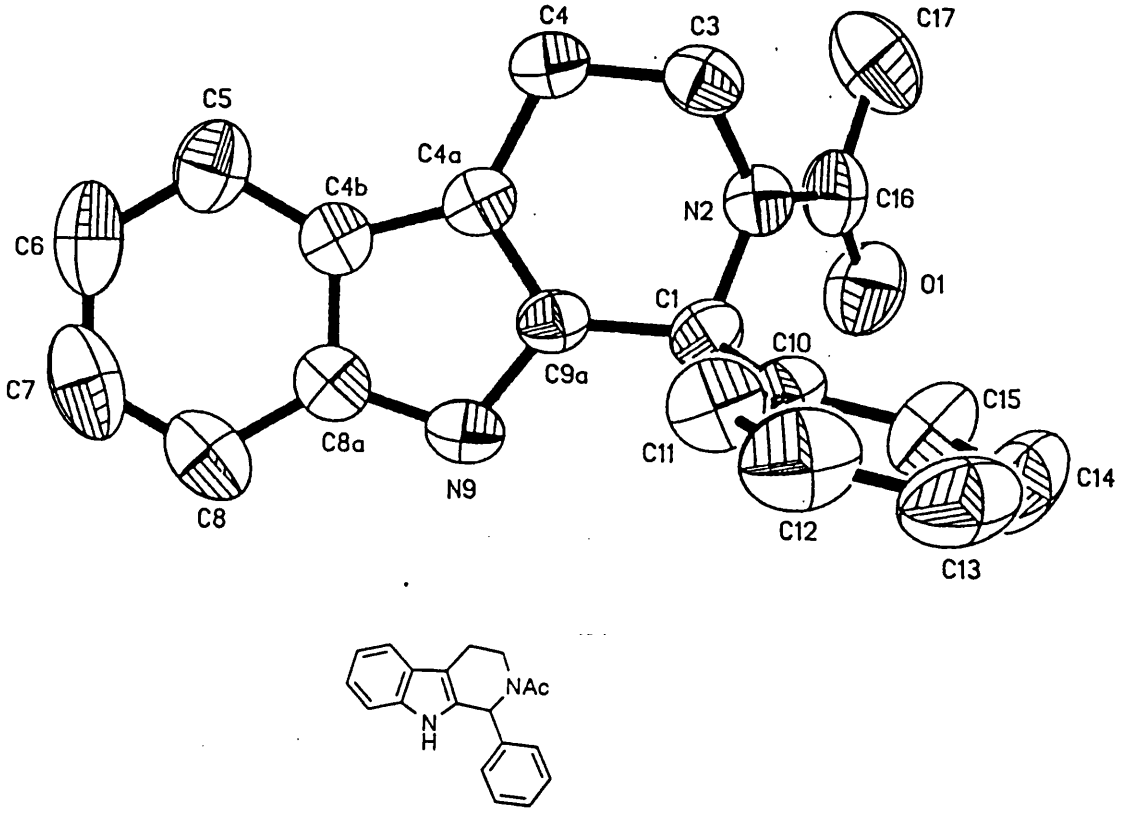


Figure 27: X-ray crystal structure of N-acetyl-3-phenyl-3,4,5,6-tetrahydro-β-carboline (**170a**), 50 % probability thermal ellipsoids

N-Acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (170b)

formula	$C_{21}H_{22}O_3N_2$
fw, g/mol	350.42
space group	$P2_1/c$
a, Å	9.469 (3)
b, Å	7.665 (3)
c, Å	25.56 (1)
α, °	90.0
β, °	93.32 (3)
γ, °	90.0
V, $Å^3$	1851.75
Z	4
F(000)	744
$d_{calc.}$, g/cm^3	1.26
cryst. size, mm	0.4 x 0.25 x 0.25
μ(Mo-K_α), cm	0.8
data collection instrument	Nicolet R3mN
radiation	Mo-K_α λ=0.71073 Å
orientation reflections: no.; range (2Θ)	29; 7° ≤ 2Θ ≤16°
temp., °C	19
no. of unique data	3060
total with $I \geq 3\sigma(I)$	1563
no. of parameters	235
$R=\Sigma[\|F_0\|-\|F_c\|]/\Sigma\|F_0\|$	0.0913
$R'=\Sigma[\|F_0-F_c\|x\sqrt{w}]/\Sigma[F_0x\sqrt{w}]$	0.0821
weighting scheme	$w=1/(\sigma^2(F)+0.000168xF^2)$
largest shift/esd. fin. cycle	0.001
largest peak, e/A^3	0.305

Table 16: Crystallographic data for N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**)

O(1)-C(16)	1.243 (9)	O(2)-C(15)	1.373 (8)
O(2)-C(18)	1.434 (7)	O(3)-C(13)	1.382 (8)
O(3)-C(19)	1.427 (9)	N(2)-C(1)	1.508 (8)
N(2)-C(3)	1.476 (8)	N(2)-C(16)	1.365 (9)
N(9)-C(8a)	1.398 (8)	N(9)-C(9a)	1.394 (9)
C(1)-C(9a)	1.514 (9)	C(1)-C(10)	1.530 (9)
C(3)-C(4)	1.525 (10)	C(4)-C(4a)	1.506 (10)
C(4a)-C(4b)	1.431 (9)	C(4a)-C(9a)	1.375 (9)
C(4b)-C(5)	1.399 (9)	C(4b)-C(8a)	1.432 (10)
C(5)-C(6)	1.384 (12)	C(6)-C(7)	1.402 (13)
C(7)-C(8)	1.385 (12)	C(8)-C(8a)	1.399 (11)
C(10)-C(11)	1.377 (9)	C(10)-C(15)	1.415 (8)
C(11)-C(12)	1.401 (10)	C(12)-C(13)	1.373 (10)
C(13)-C(14)	1.404 (9)	C(14)-C(15)	1.395 (9)
C(16)-C(17)	1.515 (9)		

Table 17: Bond length (Å) for N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**)

C(15)-O(2)-C(18)	118.6 (5)	C(13)-O(3)-C(19)	117.6 (5)
C(1)-N(2)-C(3)	113.5 (5)	C(1)-N(2)-C(16)	124.5 (5)
C(3)-N(2)-C(16)	120.7 (5)	C(8a)-N(9)-C(9a)	108.0 (5)
N(2)-C(1)-C(9a)	105.2 (5)	N(2)-C(1)-C(10)	110.3 (5)
C(9a)-C(1)-C(10)	114.8 (5)	N(2)-C(3)-C(4)	111.5 (6)
C(3)-C(4)-C(4a)	111.4 (6)	C(4)-C(4a)-C(4b)	131.5 (6)
C(4)-C(4a)-C(9a)	121.3 (6)	C(4b)-C(4a)-C(9a)	107.0 (6)
C(4a)-C(4b)-C(5)	135.1 (7)	C(4a)-C(4b)-C(8a)	107.2 (6)
C(5)-C(4b)-C(8a)	117.6 (6)	C(4b)-C(5)-C(6)	120.1 (7)
C(5)-C(6)-C(7)	121.0 (7)	C(6)-C(7)-C(8)	121.3 (8)
C(7)-C(8)-C(8a)	117.4 (7)	N(9)-C(8a)-C(4b)	107.3 (6)
N(9)-C(8a)-C(8)	130.0 (6)	C(4b)-C(8a)-C(8)	122.6 (6)
N(9)-C(9a)-C(1)	123.3 (5)	N(9)-C(9a)-C(4a)	110.3 (6)
C(1)-C(9a)-C(4a)	126.0 (6)	C(1)-C(10)-C(11)	122.1 (5)
C(1)-C(10)-C(15)	119.8 (5)	C(11)-C(10)-C(15)	118.1 (6)
C(10)-C(11)-C(12)	122.2 (6)	C(11)-C(12)-C(13)	118.7 (6)
O(3)-C(13)-C(12)	125.1 (6)	O(3)-C(13)-C(14)	113.5 (6)
C(12)-C(13)-C(14)	121.4 (6)	C(13)-C(14)-C(15)	118.8 (6)
O(2)-C(15)-C(10)	115.8 (6)	O(2)-C(15)-C(14)	123.5 (5)
C(10)-C(15)-C(14)	120.7 (6)	O(1)-C(16)-N(2)	120.2 (6)
O(1)-C(16)-C(17)	119.9 (6)	N(2)-C(16)-C(17)	119.9 (6)

Table 18: Bond angles (°) for N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**)

C3-C4-C4a-C9a	- 6.0	N2-C3-C4-C4a	38.6
C1-N2-C3-C4	- 66.6	C9a-C1-N2-C3	- 53.0
C4a-C9a-C1-N2	19.0	C4-C4a-C9a-C1	- 3.3
C16-N2-C3-C4	100.8		

indole ring plane - acetyl group	110.3
indole ring plane - phenyl ring plane	96.5
phenyl ring plane - acetyl group	107.8

Table 19: Torsion angles (°) and angle between planes (°) for N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**)

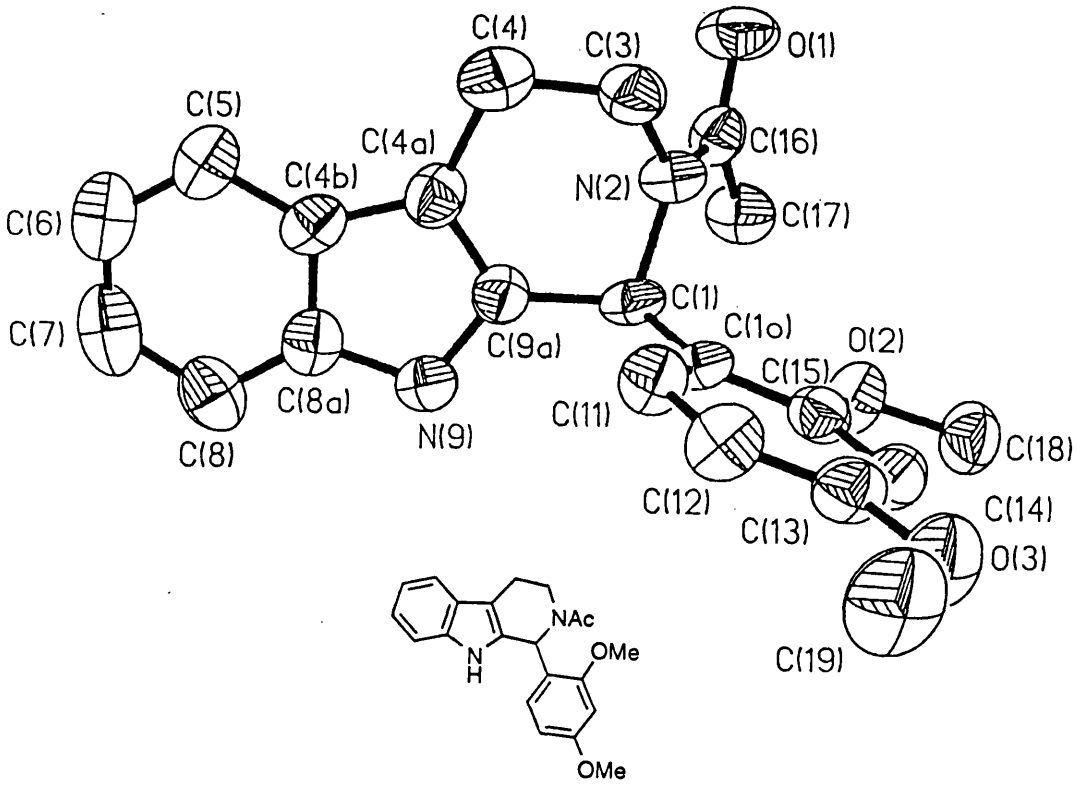


Figure 28: X-ray crystal structure of N-acetyl-3-(2,4-dimethoxyphenyl)-3,4,5,6-tetrahydro-β-carboline (**170b**), 50 % probability thermal ellipsoids

3-Acetoxyiminomethyl-2-methyl-indole (213a)

formula	$C_{12}H_{12}O_2N_2$
fw, g/mol	216.22
space group	$P2_1/n$
a, Å	8.699 (2)
b, Å	7.927 (2)
c, Å	15.963 (5)
α, °	90.0
β, °	95.09 (2)
γ, °	90.0
V, Å^3	1096
Z	4
F(000)	456
$d_{calc.}$, g/cm^3	1.31
cryst. size, mm	0.35 x 0.35 x 0.30
μ(Mo-K_α), cm	0.85
data collection instrument	Nicolet R3mN
radiation	Mo-K_α λ=0.71073 Å
orientation reflections: no.; range (2Θ)	29; 11° ≤ 2Θ ≤25°
temp., K	293
no. of unique data	2475
total with $I \geq 3\sigma(I)$	1417
no. of parameters	145
$R=\Sigma[\|F_0\|-\|F_c\|]/\Sigma\|F_0\|$	0.0666
$R'=\Sigma[\|F_0-F_c\|x\sqrt{w}]/\Sigma[F_0x\sqrt{w}]$	0.0688
weighting scheme	$w=1/(\sigma^2(F)+0.00042xF^2)$
largest shift/esd. fin. cycle	0.002
largest peak, e/A^3	0.33

Table 20: Crystallographic data for 3-acetoxyiminomethyl-2-methyl-indole (**213a**)

O(1)-N(2)	1.457 (3)	O(1)-C(11)	1.345 (4)
O(2)-C(11)	1.202 (5)	N(1)-C(6)	1.386 (5)
N(1)-C(7)	1.366 (4)	N(2)-C(10)	1.286 (5)
C(1)-C(2)	1.401 (5)	C(1)-C(6)	1.407 (5)
C(1)-C(9)	1.450 (5)	C(2)-C(3)	1.387 (5)
C(3)-C(4)	1.399 (5)	C(4)-C(5)	1.379 (6)
C(5)-C(6)	1.389 (5)	C(7)-C(8)	1.492 (5)
C(7)-C(9)	1.387 (5)	C(9)-C(10)	1.439 (5)
C(11)-C(12)	1.488 (5)		

Table 21: Bond length (Å) for 3-acetoxyiminomethyl-2-methyl-indole (**213a**)

N(2)-O(1)-C(11)	114.8 (2)	C(6)-N(1)-C(7)	110.2 (3)
O(1)-N(2)-C(10)	106.5 (3)	C(2)-C(1)-C(6)	118.9 (3)
C(2)-C(1)-C(9)	134.1 (3)	C(6)-C(1)-C(9)	106.9 (3)
C(1)-C(2)-C(3)	118.9 (3)	C(2)-C(3)-C(4)	120.9 (4)
C(3)-C(4)-C(5)	121.3 (3)	C(4)-C(5)-C(6)	117.6 (3)
N(1)-C(6)-C(1)	107.2 (3)	N(1)-C(6)-C(5)	130.4 (3)
C(1)-C(6)-C(5)	122.4 (3)	N(1)-C(7)-C(8)	120.8 (3)
N(1)-C(7)-C(9)	108.9 (3)	C(8)-C(7)-C(9)	130.3 (3)
C(1)-C(9)-C(7)	106.7 (3)	C(1)-C(9)-C(10)	129.4 (3)
C(7)-C(9)-C(10)	123.5 (3)	N(2)-C(10)-C(9)	122.8 (3)
O(1)-C(11)-O(2)	123.7 (3)	O(1)-C(11)-C(12)	109.6 (3)
O(2)-C(11)-C(12)	126.6 (3)		

Table 22: Bond angles (°) for 3-acetoxyiminomethyl-2-methyl-indole (**213a**)

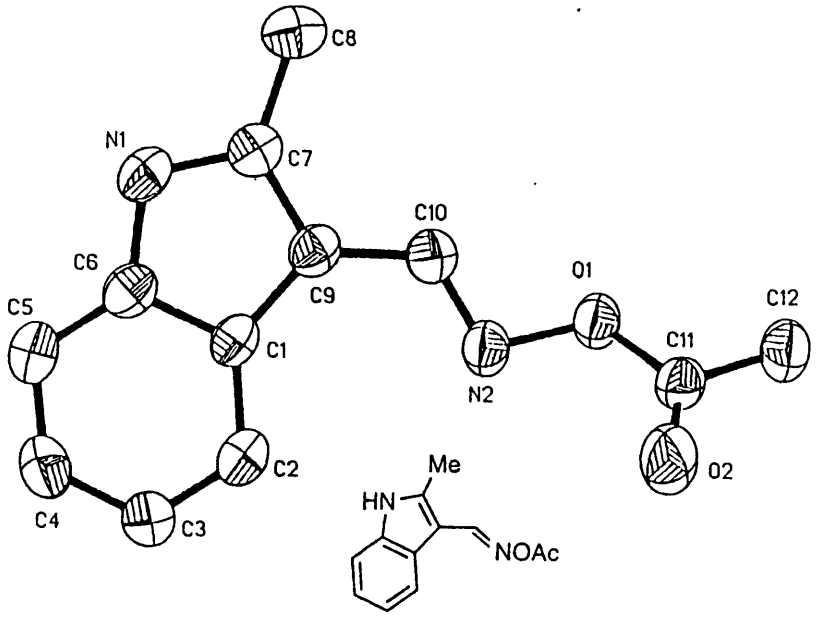
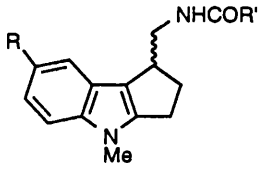
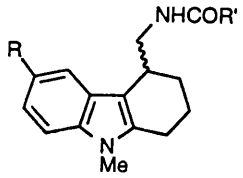


Figure 29: X-ray crystal structure of 3-acetoxyiminomethyl-2-methyl-indole (**213a**), 50 % probability thermal ellipsoids

Appendix C Biological Results

Structure	No	R	R'	K_i/nM	Act.
	**49a**	H	CH_3	516±33	NT
	49b	H	C_2H_5	272±33	NT
	49c	H	n-C_3H_7	239±24	NT
	49d	H	n-C_4H_9	11200±1000	NT
	49e	H	c-C_3H_5	5100±500	NT
	49f	H	c-C_4H_7	5700±600	NT
	49g	H	CF_3	>10000	NT
	52a	OMe	CH_3	161±20	NT
	52b	OMe	C_2H_5	16±2.2	NT
	52c	OMe	n-C_3H_7	23±3.6	NT
	52e	OMe	c-C_3H_5	459±46	NT

Structure	No	R	R'	K_i/nM	Act.
	**50a**	H	CH_3	227±39	Ant
	50b	H	C_2H_5	204±34	Ant
	50c	H	n-C_3H_7	215±33	Ant
	50d	H	n-C_4H_9	>10000	NT
	50e	H	c-C_3H_5	4460±710	NT
	50g	H	CF_3	>10000	NT
	53a	OMe	CH_3	0.97±0.20	Ag
	53b	OMe	C_2H_5	1.44±0.18	NT
	53c	OMe	n-C_3H_7	0.378±0.056	Ag
	53d	OMe	n-C_4H_9	82±11	NT
	53e	OMe	c-C_3H_5	30±3.7	NT
	53f	OMe	c-C_4H_7	271±9	Ag
	53g	OMe	CF_3	1.98±0.38	NT

Tables 1 and 2: Binding affinity and biological activity of N-acyl-1-aminomethyl-1,2,3,4-tetrahydro-cyclopent[b]indoles **49** and **52** and N-acyl-4-aminomethyl-1,2,3,4-tetrahydrocarbazoles **50** and **53**

NT = not tested, Ant = antagonist, Ag = agonist

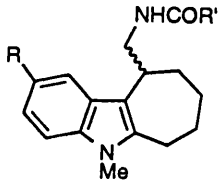
Structure	No	R	R'	K_i/nM	Act.
	**51a**	H	CH_3	424±36	NT
	51b	H	C_2H_5	129±12	NT
	51c	H	n-C_3H_7	84±9	NT
	51d	H	n-C_4H_9	8300±700	NT
	51e	H	c-C_3H_5	1220±180	NT
	51f	H	c-C_4H_7	1690±340	NT
	51g	H	CF_3	15800±700	NT
	54a	OMe	CH_3	24±3.5	NT
	54b	OMe	C_2H_5	7±0.8	NT
	54c	OMe	n-C_3H_7	10.3±1.6	NT
	54d	OMe	n-C_4H_9	471±92	NT
	54e	OMe	c-C_3H_5	44.7±6.9	NT
	54f	OMe	c-C_4H_7	144.8±23.9	NT

Table 3: Binding affinity and biological activity of N-acyl-10-aminomethyl-5,6,7,8,9,10-hexahydro-cyclohept[b]indoles **51** and **54**

NT = not tested

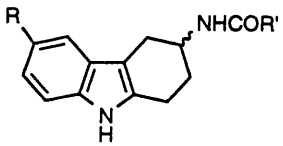
Structure	No	R	R'	K_i/nM	Act.
	**106a**	H	CH_3	5350±810	NT
	106b	H	C_2H_5	436±105	pAg
	106c	H	n-C_3H_7	1060±160	NE
	106d	H	CH_2Br	740±150	pAg
	106e	H	CF_3	4630±1080	NT
	106f	H	$CHBrC_2H_5$	>10000	NT
	107a	OMe	CH_3	219±50	Ag
	107b	OMe	C_2H_5	41±6	NT
	107c	OMe	n-C_3H_7	560±110	Ag
	107d	OMe	CH_2Br	8.3±1.3	(Ag)
	107e	OMe	CF_3	102±22	NT
	107g	OMe	c-C_3H_5	570±112	NT

Table 4: Binding affinity and biological activity of N-acyl-3-amine-1,2,3,4-tetrahydrocarbazoles **106** and **107** NT = not tested, pAg = partial agonist

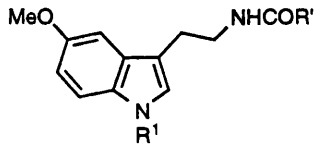
Structure	No	R^1	R'	K_i/nM	Act.
	**1a**	H	H	5900	NT
	1	H	CH_3	0.58	Ag
	1b	H	C_2H_5	0.11	Ag
	1c	H	n-C_3H_7	0.045	Ag
	1d	H	n-C_4H_9	12.6	Ag
	1e	H	n-C_5H_{11}	5500	Ag
	1f	H	CH_2OCH_3	>1000	Ag
	1g	H	$CH(CH_3)_2$	6.1	Ag
	1	H	CH_3	0.58	Ag
	199	CH_3	CH_3	25±4	NT
	183a	Bn	CH_3	897±199	NT
	183b	Bn	C_2F_5	>10000	NT

Table 5: Binding affinity and biological activity of melatonin analogues

NT = not tested, Ag = agonist

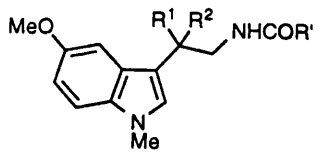
Structure	No	R^1	R^2	R'	K_i/nM	Act.
	**199**	H	H	CH_3	25±4	
	190a	CH_3	H	CH_3	15.4±2.2	
	190b	CH_3	H	C_2H_5	8.0±1.1	
	190c	CH_3	H	n-C_3H_7	3.0±0.4	NT
	191a	CH_3	CH_3	CH_3	5.8±0.7	NT
	191b	CH_3	CH_3	C_2H_5	2.3±0.4	NT
	191c	CH_3	CH_3	n-C_3H_7	1.2±0.26	NT
	191e	CH_3	CH_3	c-C_4H_7	70.2±12.9	NT
	192a	-$(CH_2)_4$-		CH_3	182±37	NT
	192b	-$(CH_2)_4$-		C_2H_5	168±33	NT
	192c	-$(CH_2)_4$-		n-C_3H_7	288±51	NT
	192d	-$(CH_2)_4$-		c-C_3H_5	616±85	NT
	192e	-$(CH_2)_4$-		c-C_4H_7	1810±220	NT

Table 6: Binding affinity and biological activity of β-branched melatonin analogues

NT = not tested

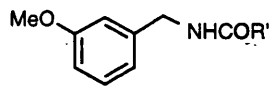
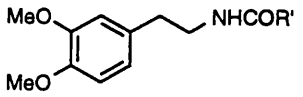
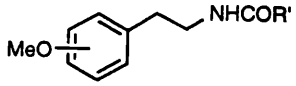
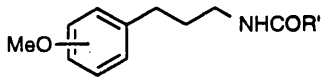
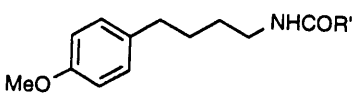
Structure	No	R	R'	K_i/nM	Act.
	**233a**		CH_3	NE at 10000	NT
	233b		C_2H_5	>10000	NT
	233c		n-C_3H_7	>10000	NT
	**234a**		CH_3	870±130	NT
	234b		C_2H_5	130±20.5	NT
	234c		n-C_3H_7	59.1±9.2	NT
	**242a**	2-OMe	CH_3	573±68	NT
	242b	2-OMe	C_2H_5	135±21	NT
	242c	2-OMe	n-C_3H_7	69±12	NT
	242d	2-OMe	n-C_4H_9	16000±1600	NT
	243a	3-OMe	CH_3	958±108	NT
	243b	3-OMe	C_2H_5	62±7	NT
	243c	3-OMe	n-C_3H_7	39.9±6.4	NT
	243d	3-OMe	n-C_4H_9	741±63	NT
	244a	4-OMe	CH_3	133±75.4 µM	NT
	244b	4-OMe	C_2H_5	19.2±5.1 µM	NT
	244c	4-OMe	n-C_3H_7	17.9±5.2 µM	NT
	244d	4-OMe	n-C_4H_9	70.8±41 µM	NT
	**246a**	2-OMe	CH_3	1430±310	NT
	246b	2-OMe	C_2H_5	374±80	NT
	246c	2-OMe	n-C_3H_7	442±122	NT
	246d	2-OMe	n-C_4H_9	>10000	NT
	247a	3-OMe	CH_3	63.4±4.0	NT
	247b	3-OMe	C_2H_5	5.6±1.7	NT
	247c	3-OMe	n-C_3H_7	5.5±1.8	NT
	248a	4-OMe	CH_3	>10000	NT
	248b	4-OMe	C_2H_5	2900±800	NT
	248c	4-OMe	n-C_3H_7	860±210	NT
	**255a**		CH_3	7300±1300	NT
	255b		C_2H_5	1400±300	NT
	255c		n-C_3H_7	822±192	NT
	255d		n-C_4H_9	7000±1100	NT

Table 8: Binding affinity and biological activity of N-acyl-ω-aminoalkyl-anisidines

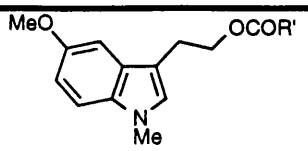
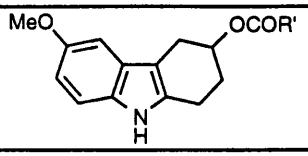
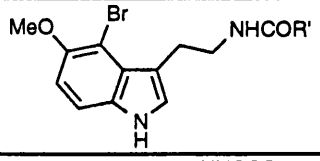
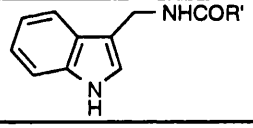
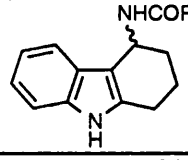
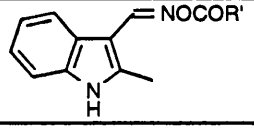
Structure	No	R'	K_i/nM	Activity
	**200**	CH_3	>10000	NT
	**100b**	CH_3	>10000	NT
	**214**	CH_3	1.1±0.1	NT
	**201**	CH_3	>10000	NT
	**202**	CH_3	>10000	NT
	**213b**	CH_3	>10000	NT

Table 23: Binding affinity and biological activity of various melatonin analogues