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Nucleic Acid Binding Drugs. VI.* The Structure of 3,9-Diamino-7-ethoxyacridine (Rivanol) as the Lactate Monohydrate Salt

BY S. NEIDLE AND A. AGGARWAL

Cancer Research Campaign Biomolecular Structure Research Group, Department of Biophysics, University of London King's College, 26–29 Drury Lane, London WC2B 5RL, England

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Abstract

$C_{15}H_{16}N_3O^+.C_3H_5O_3^-.H_2O$, $M_r = 361{\cdot}4$, triclinic, $P\bar{1}$, with $a = 7{\cdot}912$ (2), $b = 10{\cdot}016$ (1), $c = 12{\cdot}246$ (3) Å, $\alpha = 107{\cdot}75$ (1), $\beta = 103{\cdot}08$ (2), $\gamma = 94{\cdot}47$ (2)°, $U = 888{\cdot}9$ Å^3, $Z = 2$, $D_m = 1{\cdot}35$ (2), $D_c = 1{\cdot}350$ Mg m^{-3}, $F(000) = 380$, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 0{\cdot}836$ mm^{-1}. 3542 reflections were measured, of which 2149 had significant intensity. The structure refined to an R of 0·063 after having been solved by reciprocal-space search methods. The molecular geometry reflects the 3,9-diamino substitution of the planar acridine ring, in terms of bond distances. The crystal structure is extensively hydrogen-bonded with interactions involving anions, acridine substituents and water molecules.

Introduction

The interactions of acridines with nucleic acids (Neidle, 1979) are generally acknowledged to be, at least in part, responsible for their biological activities. The intercalation hypothesis (Lerman, 1961) suggests that the planar aromatic ring system of the acridines becomes inserted (intercalated) between adjacent base pairs of a double-stranded nucleic acid. Furthermore, additional stabilization may be mediated through electrostatic/hydrogen bonds between the nucleic acid phosphate groups and suitably placed hydrogen-bond donor groups attached to the acridine skeleton. This has been demonstrated in the case of 3,6-diaminoacridine (proflavine) by crystallographic analyses of its ribodinucleoside phosphate complexes (Neidle *et al.*, 1977; Berman *et al.*, 1979; Reddy, Seshadri, Sakore & Sobell, 1979).

This paper reports the first stage in a systematic examination of the DNA-binding properties of acridines with amino substitution at other than the 3,6 positions. Many such amino-acridines have been prepared (Albert, 1966); however, their DNA-binding and related biological properties (particularly mutagenesis) have not been extensively studied.

The title compound, which has a 3,7-diamino substitution pattern, has found extensive use as an antibacterial agent (Albert, 1966). It is clinically administered, and normally available as the relatively soluble lactate salt.

Experimental

Rivanol (Aldrich) was recrystallized from ethanol as prismatic needles. X-ray photographs indicated triclinic symmetry, which was confirmed by a diffractometric analysis. Accurate cell dimensions were obtained from measurements of 25 θ values on an Enraf–Nonius CAD-4 diffractometer. Space group $P\bar{1}$ was confirmed by the structure analysis. Data were collected on the diffractometer with ω–2θ scans and graphite-monochromated Cu $K\alpha$ radiation ($1{\cdot}5 < \theta < 70{\cdot}0°$). 3542 reflections were measured, 2149 of which had significant intensity [$I > 2{\cdot}5\sigma(I)$]. There was no crystal decomposition during data collection.

Applications of various direct-methods procedures in attempts to solve the crystal structure were unsuccessful in both space groups $P1$ and $P\bar{1}$. In the centrosymmetric case, the phase sets examined produced images of the acridine ring system. However, none of these produced the rest of the structure in subsequent Fourier syntheses, and clearly had the acridine group incorrectly positioned in the unit cell.

The structure was eventually solved by reciprocal-space search techniques (Tollin & Cochran, 1964). Since it was initially unclear which of the two possible space groups was correct, $P1$ was assumed, thus necessitating the location of two planar acridine groups in the asymmetric unit. An $I(\theta,\varphi)$ search produced a single strong maximum, indicating that the two acridine rings had at least partially identical orientational parameters, and unequivocally gave the orientation of the disc within which the planar groups must lie. A subsequent one-dimensional rotation-function search

* Part V: Neidle & Taylor (1979).

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utilizing the $I(\theta,\varphi)$ results fully determined the orientation of the molecular plane. This was independently confirmed by a three-dimensional rotation-function search. Since in space group $P1$ the cell origin is arbitrarily fixed, the arbitrary coordinates of one correctly oriented acridine ring were utilized for a structure-factor calculation. Resulting Fourier and difference Fourier syntheses revealed the position of the second acridine skeleton, together with substituent atoms on both molecules. Water and anion atoms were not located. A check on the symmetry relationship between individual 'equivalent' atoms of the two molecules showed that they were actually related by a centre of symmetry. Accordingly, the space group was changed to $P\bar{1}$; a subsequent Fourier map then revealed the complete structure, which was refined by full-matrix least-squares methods. H-atom positions were found in a ΔF map, and all except those for the water molecule were included in the refinement. A problem concerning the inability to locate all the H atoms in the lactate ion was encountered; accordingly, the positions of some were calculated using standard geometry, and were not refined.

Refinement converged to $R = 0{\cdot}063$ and $R_w = 0{\cdot}077$, with weights $w = 1/[\sigma^2(F) + 0{\cdot}03(F)^2]$. Tables 1 and 2 list atomic parameters.* All calculations were performed on a PDP11/34A computer, using the Nonius *SDP* package, and other programs written in our laboratory.

Table 1. *Non-hydrogen-atom positional parameters* ($\times 10^4$), *and equivalent isotropic thermal parameters*

$B_{eq} = \frac{1}{3}(B_{11} + B_{22} + B_{33})$.

	x	y	z	B_{eq} (Å^2)
O(7)	1103 (3)	9464 (2)	6679 (2)	3·86 (9)
O(1*L*)	4567 (4)	7832 (2)	473 (2)	5·3 (1)
O(2*L*)	3510 (4)	6593 (3)	1446 (2)	6·5 (1)
O(3*L*)	2455 (4)	6386 (3)	−1580 (2)	6·2 (1)
O(*W*)	6452 (4)	8068 (2)	3250 (2)	5·1 (1)
N(9)	2539 (4)	4367 (3)	6085 (2)	3·45 (9)
N(10)	2743 (4)	5346 (2)	3074 (2)	3·45 (9)
N(15)	4205 (4)	828 (3)	1199 (2)	4·6 (1)
C(1)	3383 (4)	2301 (3)	4114 (3)	3·1 (1)
C(2)	3763 (4)	1384 (3)	3163 (3)	3·4 (1)
C(3)	3781 (4)	1757 (3)	2138 (3)	3·0 (1)
C(4)	3429 (4)	3084 (3)	2121 (3)	3·4 (1)
C(5)	2033 (4)	7659 (3)	3899 (3)	3·6 (1)
C(6)	1624 (4)	8650 (3)	4800 (3)	3·7 (1)
C(7)	1502 (4)	8363 (3)	5828 (3)	3·2 (1)
C(8)	1763 (4)	7073 (3)	5942 (3)	2·9 (1)
C(9)	2565 (4)	4659 (3)	5107 (2)	2·7 (1)
C(11)	3049 (4)	4035 (3)	3112 (3)	2·9 (1)
C(12)	2968 (4)	3664 (3)	4121 (3)	2·7 (1)
C(13)	2209 (4)	6029 (3)	5029 (2)	2·5 (1)
C(14)	2326 (4)	6329 (3)	4001 (3)	2·9 (1)
C(72)	597 (5)	10641 (4)	8554 (3)	4·7 (2)
C(71)	1003 (4)	9276 (3)	7785 (3)	3·6 (1)
C(1*L*)	3547 (5)	6855 (4)	520 (3)	4·4 (1)
C(2*L*)	2161 (8)	5984 (4)	−614 (3)	8·2 (2)
C(3*L*)	1905 (9)	4505 (5)	−891 (4)	9·3 (3)

Table 2. *Hydrogen-atom positional parameters* ($\times 10^3$), *isotropic thermal parameters, and* X—H *bond distance r* (Å)

	x	y	z	B (Å^2)	r
H(1)	339 (3)	200 (3)	478 (2)	1·9 (6)	0·96 (2)
H(2)	402 (4)	44 (3)	318 (2)	3·0 (7)	0·99 (2)
H(4)	342 (4)	340 (3)	141 (3)	4·6 (3)	1·02 (2)
H(5)	217 (4)	785 (3)	319 (2)	3·7 (7)	0·97 (2)
H(6)	154 (4)	956 (3)	475 (3)	5·0 (9)	0·93 (2)
H(711)	7 (4)	837 (3)	759 (3)	4·5 (8)	1·05 (2)
H(712)	218 (4)	902 (3)	817 (2)	3·7 (8)	1·03 (2)
H(721)	−50 (5)	1075 (4)	804 (3)	7·3 (11)	0·99 (3)
H(722)	155 (5)	1146 (4)	881 (3)	6·9 (11)	0·99 (3)
H(723)	59 (5)	1049 (4)	936 (3)	6·7 (10)	1·05 (3)
H(8)	178 (3)	687 (3)	664 (2)	3·0 (7)	0·94 (2)
H(91)	284 (4)	363 (3)	621 (3)	4·5 (8)	0·84 (2)
H(92)	256 (4)	506 (3)	679 (3)	5·4 (9)	0·92 (3)
H(10)	269 (4)	564 (3)	236 (3)	6·0 (10)	0·99 (3)
H(151)	402 (4)	114 (3)	53 (3)	4·8 (8)	0·95 (2)
H(152)	423 (4)	−12 (4)	114 (3)	6·3 (10)	0·93 (3)
H(*W*1)*	709	887	307	9·0	1·02
H(*W*2)*	541	770	250	9·0	1·03
H(O3*L*)	351 (9)	717 (7)	−95 (6)	19·8 (25)	1·07 (5)
H(2*L*)*	102	623	−45	6·0	1·00
H(31*L*)*	154	426	−24	6·0	1·00
H(32*L*)*	97	406	−165	6·0	1·00
H(33*L*)*	303	414	−98	6·0	1·00

* Not refined.

Results and discussion

Molecular structure

The molecular structure of rivanol is shown in Fig. 1, and Tables 3 and 4 detail the molecular geometry.

A large number of structure analyses of acridine derivatives have now been reported. Many of medicinal interest possess a modified amino group at the 9

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36861 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

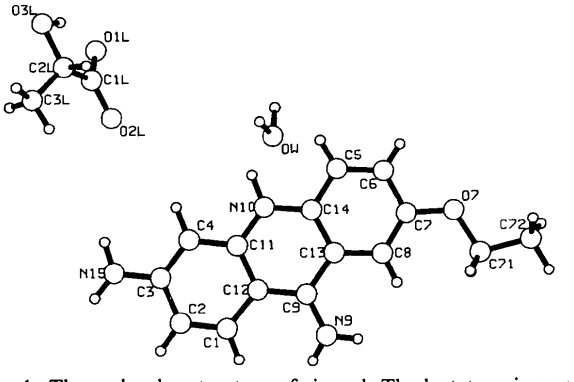

Fig. 1. The molecular structure of rivanol. The lactate anion and the water molecule in the asymmetric unit are also shown.

Table 3. *Bond distances* (Å) *in rivanol*

(*a*) In the 3,9-diamino-7-ethoxyacridine moiety

C(1)–C(2)	1·357 (3)	O(7)–C(71)	1·442 (3)
–C(12)	1·427 (3)	C(8)–C(13)	1·412 (3)
C(2)–C(3)	1·416 (3)	C(9)–N(9)	1·321 (2)
C(3)–C(4)	1·385 (3)	–C(12)	1·429 (3)
–N(15)	1·368 (3)	–C(13)	1·449 (3)
C(4)–C(11)	1·405 (3)	N(10)–C(11)	1·366 (2)
C(5)–C(6)	1·361 (3)	–C(14)	1·380 (2)
–C(14)	1·407 (3)	C(11)–C(12)	1·407 (3)
C(6)–C(7)	1·396 (3)	C(13)–C(14)	1·400 (3)
C(7)–O(7)	1·380 (2)	C(71)–C(72)	1·510 (3)
–C(8)	1·367 (3)		

(*b*) In the lactate ion

C(1*L*)–O(1*L*)	1·243 (3)	C(2*L*)–O(3*L*)	1·420 (3)
–O(2*L*)	1·245 (3)	–C(3*L*)	1·402 (4)
–C(2*L*)	1·522 (4)		

Table 4. *Bond angles* (°) *in rivanol*

(*a*) In the 3,9-diamino-7-ethoxyacridine moiety

C(2)–C(1)–C(12)	121·7 (2)	N(9)–C(9)–C(12)	121·7 (2)
C(1)–C(2)–C(3)	120·9 (3)	N(9)–C(9)–C(13)	119·7 (2)
C(2)–C(3)–C(4)	119·2 (2)	C(13)–C(9)–C(13)	118·6 (2)
C(2)–C(3)–N(15)	119·9 (2)	C(11)–N(10)–C(14)	121·7 (2)
C(4)–C(3)–N(15)	120·8 (2)	C(4)–C(11)–N(10)	118·2 (2)
C(3)–C(4)–C(11)	119·7 (2)	C(4)–C(11)–C(12)	121·8 (2)
C(6)–C(5)–C(14)	119·7 (2)	N(10)–C(11)–C(12)	120·0 (2)
C(5)–C(6)–C(7)	120·6 (2)	C(1)–C(12)–C(9)	123·3 (2)
C(6)–C(7)–O(7)	114·8 (2)	C(1)–C(12)–C(11)	116·6 (2)
C(6)–C(7)–C(8)	120·7 (2)	C(9)–C(12)–C(11)	120·0 (2)
O(7)–C(7)–C(8)	124·5 (2)	C(8)–C(13)–C(9)	123·0 (2)
C(7)–O(7)–C(71)	118·6 (2)	C(8)–C(13)–C(14)	118·8 (2)
C(7)–C(8)–C(13)	120·0 (2)	C(9)–C(13)–C(14)	118·2 (2)
		C(5)–C(14)–N(10)	118·4 (2)
		C(5)–C(14)–C(13)	120·2 (2)
		N(10)–C(14)–C(13)	121·4 (2)
		O(7)–C(71)–C(72)	107·4 (2)

(*b*) In the lactate ion

O(1*L*)–C(1*L*)–O(2*L*)	124·5 (3)	C(1*L*)–C(2*L*)–O(3*L*)	109·5 (2)
O(1*L*)–C(1*L*)–C(2*L*)	117·8 (2)	C(1*L*)–C(2*L*)–C(3*L*)	117·3 (3)
N(2*L*)–C(1*L*)–C(2*L*)	117·5 (2)	O(3*L*)–C(2*L*)–C(3*L*)	111·8 (3)

position, *viz* the antitumour agent *m*-AMSA [4′-(9-acridinylamino)-3′-methoxymethanesulphonanilide] (Karle, Cysyk & Karle, 1980), and the antimalarial compound quinacrine (6-chloro-9-{[4-(diethylamino)-1-methylbutyl]amino}-2-methoxyacridine) (Courseille, Busetta & Hospital, 1973). Amino substitution is also common at the 3 and 6 positions; 3,6-diaminoacridine (proflavine) has been analysed crystallographically as the free base (Achari & Neidle, 1976), as the N(10)-protonated salt (Jones & Neidle, 1975), and as the N(10),N(15)-diprotonated salt (Obendorf, Carrell & Glusker, 1974). To date, no acridine structures with 3,9-diamino substitution have been reported.

The analysis has shown clearly that rivanol is protonated at the central N(10) atom, rather than on the terminal amino groups. Bond lengths in rivanol show numerous significant differences from the analogous ones in proflavine hemisulphate (Jones & Neidle, 1975). Thus, bond C(9)–C(12) is 1·429 (3) and C(9)–C(13) is 1·449 (3) Å, whereas in proflavine hemisulphate these bonds are 1·386 (11) and 1·389 (11) Å respectively. Bond lengths around C(9) similar to those for rivanol have been found in other N(9)-substituted acridines such as *m*-AMSA [1·433 (6) and 1·440 (6) Å] (Karle *et al.*, 1980) and 9-amino-acridine [1·434 (3) and 1·439 (2) Å] (Talacki, Carrell & Glusker, 1974). The asymmetry introduced by the ethoxy substituent at C(7) and the amino substituent at C(3) has introduced small, though significant, structural differences between the two benzenoid rings of the acridine nucleus. Bonds C(2)–C(3) and C(6)–C(7) differ by 0·020 (7) Å, and C(3)–C(4) and C(5)–C(6) by 0·024 (3) Å. The overall pattern of acridine asymmetry is less than that observed in 6,9-dichloro-2-methoxyacridine (Neidle, 1982). The acridine ring system in rivanol is almost exactly planar (Table 5), whereas in 6,9-dichloro-2-methoxyacridine deviations from planarity are more marked.

Table 5. *Deviations* (Å) *of atoms from various least-squares planes*

Distances marked with an asterisk were excluded from the plane's calculation. E.s.d.s are in parentheses.

(*a*) The acridine group

	Plane (1)	Plane (2)	Plane (3)
C(1)	−0·034 (3)	−0·019 (3)	
C(2)	−0·025 (3)	−0·015 (3)	
C(3)	0·016 (3)	0·012 (3)	
C(4)	0·027 (3)	0·014 (3)	
C(5)	−0·022 (4)		−0·005 (4)
C(6)	−0·018 (4)		−0·007 (4)
C(7)	−0·002 (3)		−0·007 (3)
C(8)	0·032 (3)		0·018 (3)
C(9)	0·000 (3)	0·012 (3)	−0·017 (3)
N(10)	−0·008 (3)	−0·024 (3)	0·005 (3)
H(10)	0·063 (35)*		
N(9)	−0·043 (3)*		
H(91)	−0·139 (32)*		
H(92)	−0·266 (34)*		
N(15)	−0·004 (3)*		
H(151)	0·144 (33)*		
H(152)	0·152 (36)*		
O(7)	−0·019 (2)*		
C(11)	0·007 (3)	0·000 (3)	
C(12)	0·012 (3)	0·019 (3)	
C(13)	0·014 (3)		0·006 (3)
C(14)	−0·001 (3)		0·006 (3)

Angle between planes (2) and (3): 1·2 (2)°.

(*b*) The lactate ion

	Plane (4)	Plane (5)
C(1*L*)	0·022 (4)	0·000
C(2*L*)	−0·006 (6)	0·000
O(1*L*)	−0·008 (3)	0·770 (3)*
O(2*L*)	−0·008 (3)	−0·830 (3)*
O(3*L*)	0·093 (3)*	1·044 (3)*
C(3*L*)	0·887 (7)*	0·000

The anionic species in this structure initially posed a problem. Rivanol is normally prepared (Albert, 1966) as the lactate salt, and therefore the anion here was presumed to be this. The connectivity of C and O atoms supports such an assignment. However, in spite of numerous attempts, it was not possible to locate an H atom on C(2*L*), or the third methyl H on C(3*L*). This, together with the abnormally short C(2*L*)–C(3*L*) distance of 1·402 (4) Å, suggested that this bond is not an sp^3–sp^3 single one, but is close to a double bond. It is nonetheless difficult to reconcile this hypothesis with the lack of coplanarity of the various substituent atoms around C(2*L*) and C(3*L*). Accordingly, a proton NMR spectrum of the compound was obtained, which unequivocally showed that C(2*L*) does have an H atom attached to it, and C(3*L*) has three H atoms. The anion is thus a lactate, and the abnormally short bond distance for C(2*L*)–C(3*L*) is possibly a result of the very high U_{11} values for these two atoms (0·204 and 0·215 Å^2 respectively).

Fig. 3. A view of the crystal structure along **c**, with 15° rotations around **a** and **b**.

Crystal structure

The structure is extensively hydrogen-bonded (Figs. 2 and 3). All the relevant groups on the acridine ring utilize their maximum hydrogen-bonding potential. N(9) and N(15) are each involved in two hydrogen bonds (Table 6), and the protonated cationic N(10) interacts with O(2*L*) of the lactate anion. More surprisingly, there is a hydrogen bond between the water molecule and the ether O(7), which although relatively long for such an O···O interaction does have an acceptable angle about the proton.

The role of the anion is of prime importance in determining the arrangement in this crystal structure. It is involved in five intermolecular hydrogen bonds, with the hydroxyl O(3*L*) acting as both donor and acceptor. [In the former case this is in an intramolecular hydrogen bond with the carboxylic acid O(1*L*).] Overall, the anion and the water molecule serve to sandwich together the flat sheets of planar acridine molecules, with networks of hydrogen-bonded molecules extending in three dimensions.

Table 6. *Hydrogen-bonded contacts*

D–H···*A*	*D*···*A*	∠*D*–H···*A*	Symmetry operation
N(9)–H(91)···O(*W*)	2·910 Å	172°	$1-x, 1-y, 1-z$
N(9)–H(92)···O(3*L*)	2·975	172	$x, y, 1+z$
N(10)–H(10)···O(2*L*)	2·803	155	*x*,*y*,*z*
N(15)–H(151)···O(1*L*)	2·916	159	$x, y-1, z$
N(15)–H(152)···O(1*L*)	3·051	143	$1-x, 1-y, -z$
O(3*L*)–H(O3*L*)···O(1*L*)	2·591	144	*x*,*y*,*z*
O(*W*)–H(*W*1)···O(7)	2·985	159	$1-x, 2-y, 1-z$
O(*W*)–H(*W*2)···O(2*L*)	2·762	139	*x*,*y*,*z*

The average e.s.d. for distances is 0·004 Å, and for angles 2°.

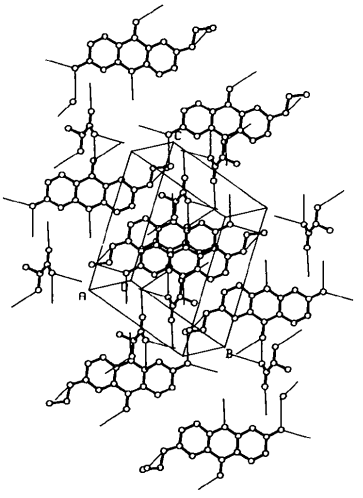

Fig. 2. A view of the crystal structure along **a**, with 15° rotations around **b** and **c**.

Pairs of centrosymmetrically related acridine molecules are ~3·4 Å apart. The stacking (as judged by molecular overlap) is small, and is very similar in mutual orientation to that found in 9-aminoacridine (Talacki *et al.*, 1974).

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The Structures of (Dimethylaminopropyl)phenothiazine Drugs and Their Metabolites. I. Levomepromazine Sulphoxide at 120 K

BY E. HOUGH AND M. HJORTH

Department of Chemistry, Institute of Mathematical and Physical Sciences, University of Tromsø, N-9000, Tromsø, Norway

AND S. G. DAHL

Department of Pharmacology, Institute of Medical Biology, University of Tromsø, N-9000, Tromsø, Norway

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Abstract

Levomepromazine sulphoxide [10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine 5-oxide], $C_{19}H_{24}N_2O_2S$, crystallizes in the orthorhombic space group $P2_12_12_1$, $Z = 4$, with unit-cell dimensions: $a = 7{\cdot}636$ (2), $b = 12{\cdot}783$ (7), $c = 18{\cdot}317$ (7) Å and $V = 1787{\cdot}94$ Å^3 at 120 K; $a = 7{\cdot}689$ (2), $b = 12{\cdot}908$ (4), $c = 18{\cdot}599$ (5) Å, $V = 1845{\cdot}94$ Å^3, $D_m = 1{\cdot}223$, $D_c = 1{\cdot}239$ g cm^{-3} at 293 K. The structure was determined by the multiple tangent-formula method, and refined by full-matrix least squares to a final R of 0·037, using 2529 reflections. The sulphoxide O atom lies in the boat-axial conformation, and the N(10) side chain has the same conformation as that in chlorpromazine and several other psychoactive phenothiazine derivatives.

Phenothiazine drugs and their metabolites

The phenothiazine derivatives form a class of drugs which are used as neuroleptics, sedatives, analgesics and anti-emetics. Receptor-binding studies have demonstrated that they show high binding affinity to dopaminergic, anticholinergic, anti-adrenergic and anti-histaminic neurotransmitter receptors (Peroutka & Snyder, 1980; Bylund, 1981). The crystal structures of several phenothiazines have been reported in the literature, as reviewed by Horn, Post & Kennard (1975) and Tollenaere, Moereels & Koch (1977). The present studies are being carried out in parallel with pharmacodynamic and pharmacokinetic investigations, and will include metabolites of chlorpromazine (CPZ) and levomepromazine (LM), the latter also known as methotrimeprazine in the United States.

The chemical structures of LM, CPZ and their major metabolites in man are shown in Fig. 1. In addition to the metabolic pathways indicated in Fig. 1, levomepromazine is metabolized in man by *O*-demethylation of the R^1 substituent (Johnsen & Dahl, 1982), and both LM and CPZ may undergo several steps of biotransformation, yielding a large number of different metabolites. As reviewed previously (Dahl, 1981), the

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