

Fig. 2. Projection of the molecule in a plane normal to **a**. H atoms are omitted.

A packing diagram is shown in Fig. 2. Layers of molecules are displaced with respect to one another to relieve short intermolecular contacts. The structure consists of individual molecules packed in the crystal *via* van der Waals forces. There are no unusually short

intermolecular contacts, so that packing forces are unlikely to influence the geometry of the molecule to an appreciable extent.

The authors thank Dr Siddhartha Ray, IACS, Jadavpur, Calcutta for advice on Computation and some stimulating discussions and Dr A. J. Bhattacharya of the Department of Chemistry, University of Burdwan, for supplying the sample used in this investigation. Financial assistance from the University of Burdwan is gratefully acknowledged.

#### References

- BANERJEE, P. K. & BHATTACHARYA, A. J. (1977). *Indian J. Chem.* **15B**, 953–955.  
 GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* **A27**, 368–376.  
 HAZELL, A. C. & HAZELL, R. G. (1977). *Acta Cryst.* **B33**, 360–365.  
 HAZELL, A. C., JONES, D. W. & SOWDEN, J. M. (1977). *Acta Cryst.* **B33**, 1516–1522.  
*International Tables for X-ray Crystallography* (1974). Vol. IV, pp. 72–73. Birmingham: Kynoch Press.  
 SETH, S. & CHAKRABORTY, S. (1981). *Acta Cryst.* **B37**, 1144–1146.  
 SETH, S. & CHAKRABORTY, S. (1982). *Acta Cryst.* **B38**, 1380–1383.  
 VICKERY, B. L., BRIGHT, D. & MALLINSON, P. R. (1971). *XRAY ARC. IBM 1130 Program System for Crystallography modified for a Burroughs Computer.*

*Acta Cryst.* (1983). **C39**, 627–630

### Nucleic Acid Binding Drugs. VIII. Structures of 1-[2-(Diethylamino)ethylamino]anthracene-9,10-dione, $C_{20}H_{22}N_2O_2$ (I), and 1,5-Bis[2-(diethylamino)ethylamino]anthracene-9,10-dione, $C_{26}H_{36}N_4O_2$ (II), Models for Antitumour Drugs

BY P. ALMOND, S. D. CUTBUSH, S. A. ISLAM, R. KURODA\* AND S. NEIDLE

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

B. M. GANDECHA

*School of Pharmacy, Leicester Polytechnic, PO Box 143, Leicester LE1 9BH, England*

AND J. R. BROWN

*Department of Pharmaceutical Chemistry, Sunderland Polytechnic, Green Terrace, Sunderland SR1 3SD, England*

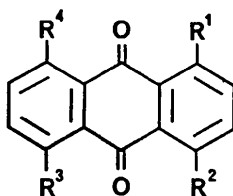
(Received 21 October 1982; accepted 19 January 1983)

**Abstract.** (I)  $M_r = 322.41$ ,  $P2_1/n$ ,  $a = 7.118$  (1),  $b = 26.873$  (2),  $c = 8.886$  (1) Å,  $\beta = 97.74$  (1)°,  $V = 1684.3$  (6) Å<sup>3</sup>,  $Z = 4$ ,  $D_m = 1.27$ ,  $D_x = 1.271$  Mg m<sup>-3</sup>,  $\lambda$  (Cu  $K\alpha$ ) = 1.54178 Å,  $\mu = 6.67$  cm<sup>-1</sup>,  $F(000) = 688$ ,  $T = 298$  K,  $R_w = 0.049$  for 981 unique significant reflections. (II)  $M_r = 436.61$ ,  $P2_1/c$ ,  $a = 15.360$  (2),  $b = 5.245$  (1),  $c = 15.483$  (1) Å,  $\beta = 94.23$  (1)°,  $V = 1244.0$  (5) Å<sup>3</sup>,  $Z = 2$ ,  $D_m = 1.17$ ,  $D_x = 1.165$  Mg m<sup>-3</sup>,

\* To whom correspondence should be addressed.

$\lambda(\text{Cu } K\alpha) = 1.54178 \text{ \AA}$ ,  $\mu = 5.98 \text{ cm}^{-1}$ ,  $F(000) = 472$ ,  $T = 298 \text{ K}$ ,  $R_w = 0.090$  for 457 unique significant reflections. The chromophore is highly planar in both compounds.

**Introduction.** The antitumour activity of the drug Adriamycin is thought to be mediated *via* intercalation of its aromatic ring system between DNA base pairs (Neidle, 1978, 1979; Pigram, Fuller & Hamilton, 1972). Its broad spectrum of activity has resulted in extensive clinical use; however, its high toxicity has produced many problems. Accordingly, a number of investigations have searched for less-toxic analogues (Brown, 1978; Doyle, 1980). Tricyclic anthraquinone derivatives are one of the promising families of analogues, with mitoxantrone (IV) being in current clinical trial as an antitumour agent (von Hoff, Myers, Kuhn, Sandbach, Poelinko, Clark & Coltman, 1981). The molecular structures of the title compounds (I, II) were determined as part of a study to establish structure-activity relationships using biophysical and structural information (Islam, Neidle, Gandecha & Brown, 1982).



- I:  $R^1 = L, R^2 = R^3 = R^4 = \text{H}$   
 II:  $R^1 = R^3 = L, R^2 = R^4 = \text{H}$       $L = \text{HNCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$   
 III:  $R^1 = R^4 = L, R^2 = R^3 = \text{H}$   
 IV:  $R^1 = R^2 = \text{NHCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OH}, R^3 = R^4 = \text{OH}$

**Experimental.** Thin oblong plate-type crystals obtained from ethanol solution for both compounds, density measured by flotation, X-ray photographs taken to determine crystal class, accurate cell dimensions determined by least squares analysis of 25  $\theta$  values; Enraf-Nonius CAD-4 diffractometer, graphite-monochromated Cu  $K\alpha$  radiation,  $\theta$ - $2\theta$  scan mode up to  $\theta = 50^\circ$  ( $0 \leq h \leq 7, 0 \leq k \leq 26, -8 \leq l \leq 8$ ) for I and up to  $\theta = 60^\circ$  ( $-17 \leq h \leq 17, 0 \leq k \leq 5, 0 \leq l \leq 17$ ) for II, crystals approximately  $0.06 \times 0.55 \times 0.08 \text{ mm}$  for I and  $0.03 \times 0.10 \times 0.32 \text{ mm}$  for II; three standard reflections were monitored at intervals of 3600 s in each case, no crystal decay was observed during the data collection; systematic absences: I:  $h0l, h + l = 2n; 0k0, k = 2n$ ; II:  $h0l, l = 2n; 0k0, k = 2n$ . 1550 reflections were recorded for I, 981 with  $I \geq 2\sigma(I)$  used for the refinement. Crystals of II exhibited strong cleavage, hence they are very thin resulting in poor diffraction data quality. 1266 independent reflections were recorded, only 619 had  $I \geq 1\sigma(I)$  and 457 had

$I \geq 3\sigma(I)$ . The reflections satisfying the latter condition were employed for the refinement. An empirical absorption correction was applied in each case, using a computer program written by N. Walker of Queen Mary College London.

The structure of I was solved by direct methods (*MULTAN80*: Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and refined on  $F$  with full-matrix least-squares techniques; H-atom positions located from difference Fourier synthesis and kept fixed during the refinement; final difference map did not show any peaks  $> 0.12 \text{ e \AA}^{-3}$ .  $R_w = 0.049$ ,  $w = 1/[\sigma(I)^2 + (0.03I)^2]^{1/2}$ ; there was a zero shift/error in the final least-squares cycle.

The application of similar structure-determination procedures for II was unsuccessful. The number of molecules in the unit cell and the space-group assignment indicated that the molecule resides on a centre of inversion.  $E$  maps of the top two sets with highest combined figures of merit revealed part of a fused aromatic ring system. The peaks at about  $1.4 \text{ \AA}$  from an inversion centre which join to form a benzene ring were used for partial-structure phase determination; however, the rest of the structure did not develop.

At this stage, a reciprocal-search method was employed using the computer program *PATTOR* [an implementation of the Tollin (1966) algorithm on a PDP11/34A computer by A. Aggarwal of King's College] to find the orientation of the molecule. The input geometry was that of anthraquinone itself. The best two orientations had the chromophore plane almost parallel to the crystallographic  $bc$  plane with the long axis of the chromophore tilted only  $\sim 10^\circ$  from the  $b$  axis. Since the  $b$  axis is short ( $5.246 \text{ \AA}$ ), these orientations were discarded. The third-best orientation, however, showed reasonable crystal packing, hence this was adopted. The chromophore was translated along the crystal axes so that the molecular and crystallographic inversion centres met.  $R = 0.0468$  after the scale factor refinement and a subsequent Fourier map revealed two carbon and one nitrogen atoms of the side chain. A series of least-squares refinements (on  $F$ ) and Fourier and difference Fourier maps gradually revealed the other non-hydrogen atoms of the side chain. Owing to the poor quality of the crystal and the flexibility of the long side chain, the atoms, particularly those in the side chain, were not well located. The terminal carbon atoms, C(14) and C(16), were both disordered between two sites with approximately equal site-occupancy factors. H atoms were not located. A final difference map did not show any peaks  $> 0.18 \text{ e \AA}^{-3}$ .  $R_w = 0.09$  with unit weights. The shift/error maxima associated with disordered atoms in the side chain and that associated with ordered atoms of the chromophore are  $0.68$  and  $0.21$  respectively.

Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974).

All calculations were performed on a PDP 11/34A computer using the *SDP* program system.\*

**Discussion.** The final atomic parameters are listed in Table 1 and the molecular structures of I and II are shown in Fig. 1 with the numbering scheme employed. Bond lengths and angles of I and II are compared in Table 2. The chromophore is highly planar in both compounds: the dihedral angle between the two terminal aromatic rings is 2.7 and 2.4° for I and II, respectively. The conformation of the side chain is

\* Tables of structure factors, hydrogen-atom coordinates (for I only), anisotropic thermal parameters, and deviations of atoms in the side chain from the least-squares plane of the chromophore for compounds I, II, and III have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38337 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester, CH1 2HU, England.

Table 1. Final unit-cell coordinates for the non-hydrogen atoms and their average thermal parameters

Estimated standard deviations are in parentheses.  $B_{eq} = \frac{1}{3} \sum_i \sum_j B_{ij} a_i^* a_j^* a_i a_j$ .

	x	y	z	$B_{eq}(\text{Å}^2)$
Compound I				
O(9)	0.2783 (5)	0.4576 (1)	0.2613 (3)	5.18 (8)
O(10)	0.3318 (5)	0.6069 (1)	-0.1324 (3)	6.29 (9)
N(1)	0.1588 (6)	0.3964 (1)	0.0364 (4)	4.7 (1)
N(2)	0.2119 (5)	0.3106 (1)	0.2337 (4)	4.8 (1)
C(1)	0.1784 (6)	0.4356 (1)	-0.0565 (5)	3.8 (1)
C(2)	0.1378 (7)	0.4304 (2)	-0.2161 (5)	4.4 (1)
C(3)	0.1525 (7)	0.4700 (2)	-0.3113 (5)	4.9 (1)
C(4)	0.2068 (7)	0.5162 (2)	-0.2533 (5)	4.7 (1)
C(4a)	0.2510 (6)	0.5225 (1)	-0.0980 (5)	3.7 (1)
C(5)	0.4047 (7)	0.6286 (2)	0.1791 (6)	5.1 (1)
C(6)	0.4384 (7)	0.6366 (2)	0.3331 (6)	6.1 (1)
C(7)	0.4250 (7)	0.5980 (2)	0.4334 (5)	5.7 (1)
C(8)	0.3740 (7)	0.5510 (2)	0.3787 (5)	4.6 (1)
C(8a)	0.3383 (6)	0.5422 (1)	0.2233 (5)	3.8 (1)
C(9)	0.2843 (6)	0.4913 (2)	0.1671 (5)	3.8 (1)
C(9a)	0.2397 (6)	0.4828 (1)	0.0036 (4)	3.5 (1)
C(10)	0.3140 (7)	0.5732 (1)	-0.0426 (5)	4.4 (1)
C(10a)	0.3531 (6)	0.5815 (1)	0.1220 (5)	3.9 (1)
C(11)	0.1017 (7)	0.3467 (2)	-0.0182 (5)	4.6 (1)
C(12)	0.0530 (7)	0.3159 (2)	0.1113 (5)	5.1 (1)
C(13)	0.3507 (8)	0.2730 (2)	0.1917 (6)	6.2 (1)
C(14)	0.5453 (8)	0.2815 (2)	0.2700 (6)	6.7 (2)
C(15)	0.1450 (8)	0.2971 (2)	0.3761 (6)	6.2 (1)
C(16)	0.0520 (8)	0.3401 (2)	0.4478 (5)	7.5 (2)
Compound II				
O(9)	0.6729 (6)	0.966 (2)	0.4755 (7)	7.8 (3)
N(1)	0.6440 (8)	0.589 (3)	0.3654 (9)	7.4 (4)
N(2)	0.8212 (9)	0.589 (3)	0.036 (13)	12.9 (6)
C(1)	0.559 (1)	0.616 (3)	0.378 (1)	6.9 (4)
C(2)	0.496 (1)	0.456 (3)	0.334 (1)	7.5 (5)
C(3)	0.407 (1)	0.480 (3)	0.355 (1)	6.9 (5)
C(4)	0.3754 (9)	0.668 (3)	0.416 (1)	7.0 (4)
C(4a)	0.4393 (9)	0.826 (3)	0.4529 (9)	5.8 (4)
C(9)	0.5943 (9)	0.983 (3)	0.4867 (9)	5.3 (4)
C(9a)	0.5274 (8)	0.810 (3)	0.4380 (9)	4.6 (4)
C(11)	0.671 (1)	0.383 (3)	0.307 (1)	9.3 (5)
C(12)	0.773 (1)	0.359 (4)	0.339 (2)	12.0 (7)
C(13)	0.820 (2)	0.607 (6)	0.203 (2)	18 (1)
C(141)	0.857 (2)	0.765 (10)	0.137 (3)	14 (2)
C(142)	0.872 (3)	0.473 (9)	0.158 (3)	13 (2)
C(15)	0.909 (1)	0.627 (6)	0.348 (2)	17 (1)
C(161)	0.913 (3)	0.779 (9)	0.436 (3)	14 (2)
C(162)	0.878 (0)	0.606 (9)	0.440 (3)	12 (1)

similar in the two compounds: the N(1)–C(11) bond is coplanar with the aromatic plane and this part of the geometry of the molecule is governed by a strong intramolecular hydrogen bond between O(9) and N(1) [I: O(9)···H(N1) = 1.862 (3), N(1)–H(N1) = 1.020 (3), O(9)···N(1) = 2.638 (3) Å,  $\angle$ O(9)···H(N1)–N(1) = 130.2 (3)°; II: O(9)···N(1) = 2.63 (2) Å]. C(12) and N(2) deviate slightly from the aromatic plane and the two terminal ethyl groups occupy opposite sides of the plane. Torsion angles of the side chain are similar in the two molecules except for the *N*-ethyl termini, which have a marked degree of freedom (Table 3). In 1,8-bis[2-(diethylamino)ethylamino]anthracene-9,10-dione (III) (Islam, Neidle, Gandecha & Brown, 1982), which is an isomer of II, the side chains at the 1 and 8 positions interact sterically, resulting in the conformation of the

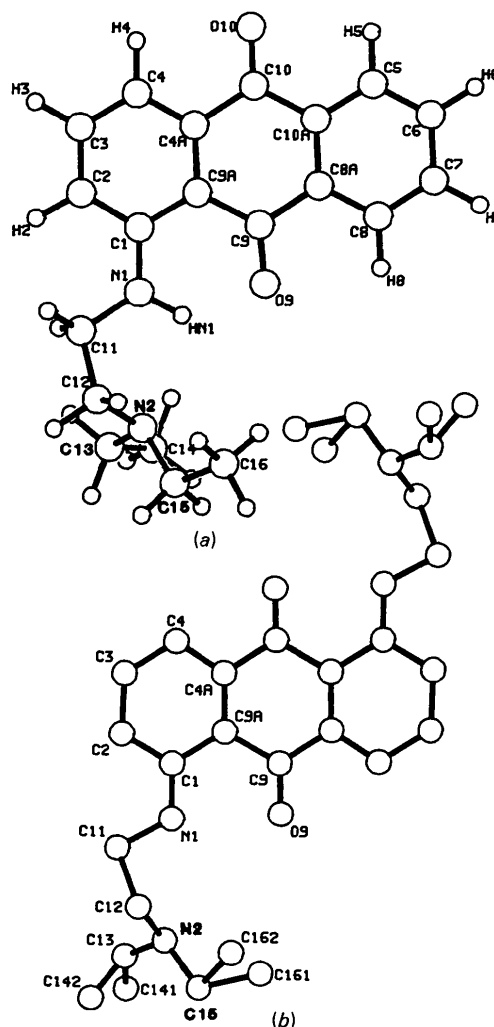


Fig. 1. A computer-drawn view of (a) molecule I, 1-[2-(diethylamino)ethylamino]anthracene-9,10-dione, and (b) molecule II, 1,5-bis[2-(diethylamino)ethylamino]anthracene-9,10-dione, looking on to the aromatic plane of the molecule.

Table 2. Bond lengths (Å) and angles (°) for the non-hydrogen atoms

Estimated standard deviations are in parentheses. II has a crystallographic centre of inversion, hence only half of the molecule is independent.

I		II		I		II	
C(1)–C(2)	1.407 (4)	1.42 (2)	C(9a)–C(1)	1.422 (4)	1.48 (3)		
C(5)–C(6)	1.375 (5)		C(10a)–C(5)	1.393 (4)			
C(2)–C(3)	1.377 (4)	1.44 (3)	C(9)–O(9)	1.238 (3)	1.23 (2)		
C(6)–C(7)	1.378 (5)		C(10)–O(10)	1.224 (3)			
C(3)–C(4)	1.381 (4)	1.47 (2)	C(1)–N(1)	1.356 (4)	1.34 (2)		
C(7)–C(8)	1.384 (4)		N(1)–C(11)	1.460 (4)			
C(4)–C(4a)	1.384 (4)	1.38 (2)	C(11)–C(12)	1.496 (4)	1.62 (2)		
C(8)–C(8a)	1.390 (4)		C(12)–N(2)	1.467 (4)			
C(4a)–C(9a)	1.406 (4)	1.39 (3)	N(2)–C(13)	1.494 (4)	1.57 (5)		
C(8a)–C(10a)	1.401 (4)		N(2)–C(15)	1.457 (4)			
C(4a)–C(10)	1.497 (4)	1.49 (2)	C(13)–C(14)	1.482 (5)	1.46 (5), 1.31 (8)*		
C(8a)–C(9)	1.489 (4)		C(15)–C(16)	1.512 (5)			
C(9a)–C(9)	1.462 (4)	1.53 (3)			1.58 (9), 1.56 (6)*		
C(10a)–C(10)	1.469 (4)						
C(9a)–C(1)–C(2)	118.4 (3)	118 (2)	C(9a)–C(9)–O(9)	122.3 (3)	121 (1)		
C(10a)–C(5)–C(6)	120.4 (3)		C(10a)–C(10)–O(10)	121.0 (3)			
C(1)–C(2)–C(3)	121.5 (3)	118 (2)	C(8a)–C(9)–O(9)	118.4 (3)	121 (1)		
C(5)–C(6)–C(7)	120.6 (3)		C(4a)–C(10)–O(10)	120.7 (3)			
C(2)–C(3)–C(4)	120.2 (3)	124 (1)	C(9a)–C(9)–C(8a)	119.2 (3)	117 (2)		
C(6)–C(7)–C(8)	119.8 (3)		C(2)–C(1)–N(1)	120.6 (3)			
C(3)–C(4)–C(4a)	119.8 (3)	115 (2)	C(9a)–C(1)–N(1)	121.0 (3)	122 (1)		
C(7)–C(8)–C(8a)	120.6 (3)		N(1)–C(1)–C(12)	109.5 (3)			
C(4)–C(4a)–C(9a)	121.5 (3)	124 (2)	C(11)–C(12)–N(2)	112.9 (3)	108 (1)		
C(8)–C(8a)–C(10a)	119.4 (3)		C(12)–N(2)–C(13)	110.5 (3)			
C(4)–C(4a)–C(10)	117.2 (3)	114 (2)	C(12)–N(2)–C(15)	111.0 (3)	115 (2)		
C(9a)–C(4a)–C(10)	121.3 (3)		C(13)–N(2)–C(15)	110.7 (3)			
C(1)–C(9a)–C(4a)	118.5 (3)	121 (1)	N(2)–C(13)–C(14)	112.7 (4)	139 (3), 121 (4)*		
C(5)–C(10a)–C(8a)	119.3 (3)		N(2)–C(15)–C(16)	112.9 (3)			
C(1)–C(9a)–C(9)	121.8 (3)	118 (1)			95 (3)*		
C(5)–C(10a)–C(10)	120.4 (3)						
C(4a)–C(9a)–C(9)	119.7 (3)	121 (1)					
C(8a)–C(10a)–C(10)	120.3 (3)						

\* Atoms C(14) and C(16) are disordered in compound II.

Table 3. Comparison of side-chain torsion angles (°)

	I		II		III†	
					side chain at	
					1	8
C(1)–N(1)–C(11)–C(12)	–167.6 (4)	–160 (1)			–174.6 (8)	–176.7 (9)
N(1)–C(11)–C(12)–N(2)	–59.6 (3)	–75 (1)			–66.0 (6)	–41.5 (6)
C(11)–C(12)–N(2)–C(13)	–77.7 (3)	–63 (1)			157.3 (9)	–69.0 (9)
C(11)–C(12)–N(2)–C(15)	159.0 (4)	165 (1)			–85.0 (8)	165 (1)
C(12)–N(2)–C(13)–C(14)	154.0 (4)	–175 (3), –80 (3)*			–48 (1)	160 (1)
C(12)–N(2)–C(15)–C(16)	–73.8 (3)	–83 (2), –48 (2)*			168 (1)	–65 (1)

\* Atoms C(14) and C(16) are disordered in compound II.

† Islam *et al.* (1982).

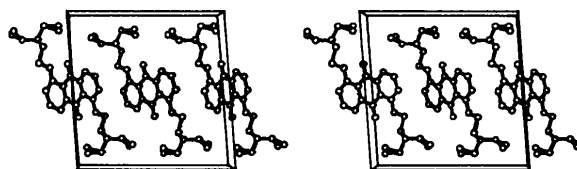


Fig. 2. Stereoview of the packing in the unit cell of molecule II. (Origin at lower left, *a* vertical, *c* horizontal.)

side chain at the 8 position being similar to that of I, while the side chain at the 1 position adopts a quite different conformation.

The packing diagram of II (Fig. 2) shows a herring-bone pattern and explains the cleavage observed parallel to the crystal *bc* plane.

We are grateful to the Cancer Research Campaign for support (grant SP/1384 and Career Development Award to SN).

#### References

- BROWN, J. R. (1978). *Prog. Med. Chem.* **15**, 125–164.
- DOYLE, T. W. (1980). In *Anthracyclines, Current Status and New Developments*, edited by S. T. CROOKE & S. D. REICH, pp. 27–41. New York: Academic Press.
- HOFF, D. D. VON, MYERS, J. W., KUHN, J., SANDBACH, J. E., POELINKO, R., CLARK, G. & COLTMAN, C. A. (1981). *Cancer Res.* **41**, 3118–3121.
- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press.
- ISLAM, S., NEIDLE, S., GANDECHA, B. M. & BROWN, J. R. (1982). *Biochem. Pharmacol.* Submitted.
- MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J. P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.
- NEIDLE, S. (1978). In *Topics in Antibiotic Chemistry*, edited by P. G. SAMMES, Vol. 3, pp. 240–278. Chichester: Ellis Horwood.
- NEIDLE, S. (1979). *Prog. Med. Chem.* **16**, 151–221.
- PIGRAM, W. J., FULLER, W. & HAMILTON, L. D. (1972). *Nature (London)*, **235**, 17–19.
- TOLLIN, P. (1966). *Acta Cryst.* **21**, 613–614.