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The Structure of the Metabolite 7-Hydroxychlorpromazine

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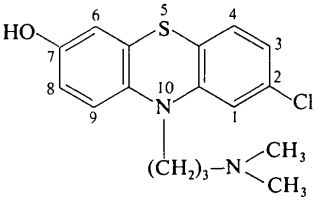
$ClSON_2C_{17}H_{19}$, 7-hydroxy-2-chloro-10-(3′-dimethylamino-*n*-propyl)phenothiazine,



is monoclinic, $P2_1/c$ with $a = 5{\cdot}914\,(2)$, $b = 18{\cdot}860\,(2)$, $c = 15{\cdot}492\,(2)$ Å, $\beta = 105{\cdot}2\,(8)°$. $D_m = 1{\cdot}340$, $D_c = 1{\cdot}334$ g cm^{-3} for $Z = 4$. In the tricyclic group, C–S–C is 98·4 (1)°, C–S bonds are 1·768 (3) and 1·770 (3), C–O is 1·367 (3) and C–Cl is 1·749 (3) Å. The dihedral angle between the planes of the benzene rings is 138·7°.

Introduction

Dr A. A. Manian of the National Institute of Mental Health generously supplied the powdered material. Colourless, transparent plate-like crystals were grown by repeated slow recrystallizations from a solution of 7-OH–CPZ in isopropyl alcohol. Systematic absences noted on Weissenberg photographs were $h0l$, $l \neq 2n$ and $0k0$, $k \neq 2n$. 2930 intensities, including 100 systematically extinct and 639 which, not significantly different from background, rated as 'unobserveds', were measured within a sphere $\theta_{max} = 25°$ by a Philips PW 1100 automatic diffractometer, with graphite-monochromated Mo $K\alpha$ radiation at a temperature of 20 °C. The ω-scan mode was used, with a scan rate of 0·03 s^{-1} and a scan width of 1·0°. Background counts of 33·3 s on each side were taken. The usual correction factors were applied, but absorption was neglected as μR for the crystal (0·5 × 0·4 × 0·2 mm) was < 0·1.

The structure was solved by a combination of Fourier techniques and direct methods with $E \geq 1{\cdot}2$, with the X-RAY system (1972) and *SHELX* (Sheldrick, 1975). The analytical scattering factors of Cromer & Mann (1968) were used for Cl, S, O, N and C; the values given by Stewart, Davidson & Simpson (1965) were used for H. Two cycles of full-matrix least-

Table 1. *Final atomic fractional coordinates* (×10⁴) *and thermal parameters* (×10⁴) *with estimated standard deviations*

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl	7634(1)	1251(1)	5355(1)	643(5)	1027(7)	536(4)	103(4)	10(4)	156(4)
S	-1354(1)	1533(0)	2161(0)	394(3)	655(4)	472(4)	- 74(3)	138(3)	-103(3)
O	- 872(3)	1466(1)	-1128(1)	498(9)	645(11)	374(9)	- 86(9)	31(8)	- 70(8)
N(1)	2966(4)	2367(1)	2388(1)	505(12)	402(11)	414(11)	-104(9)	11(9)	- 72(9)
N(2)	5590(3)	4469(1)	3302(1)	438(11)	339(10)	483(12)	- 42(8)	71(9)	- 22(9)
C(1)	5150(5)	1302(2)	4448(2)	568(16)	603(17)	414(14)	106(13)	122(12)	- 5(12)
C(2)	3268(6)	869(2)	4425(2)	710(19)	645(18)	503(16)	- 5(15)	221(15)	65(14)
C(3)	1322(5)	923(2)	3700(2)	609(17)	636(18)	517(16)	-136(14)	208(14)	- 14(14)
C(4)	1232(4)	1415(1)	3033(2)	468(14)	493(15)	418(13)	- 29(11)	151(11)	- 98(11)
C(5)	3156(4)	1859(1)	3063(2)	478(13)	387(13)	374(12)	5(10)	112(10)	- 75(10)
C(6)	5167(5)	1785(2)	3775(2)	452(14)	496(15)	444(14)	3(12)	107(11)	- 65(11)
C(7)	- 38(4)	1734(1)	1288(2)	369(12)	372(12)	430(13)	5(10)	81(10)	- 58(10)
C(8)	-1032(4)	1491(1)	418(2)	337(12)	396(13)	443(13)	- 25(10)	40(10)	- 71(10)
C(9)	- 10(4)	1671(1)	- 257(2)	407(12)	405(13)	390(13)	46(10)	24(10)	- 17(10)
C(10)	2019(4)	2078(1)	- 62(2)	487(14)	499(15)	427(14)	- 54(11)	119(11)	28(11)
C(11)	3031(4)	2300(1)	806(2)	432(13)	454(14)	486(14)	- 88(11)	84(11)	- 5(11)
C(12)	2000(4)	2140(1)	1489(2)	423(13)	339(12)	422(13)	- 27(10)	49(10)	- 51(10)
C(13)	4479(5)	2994(1)	2557(2)	514(15)	388(14)	469(15)	- 70(11)	- 26(12)	- 51(11)
C(14)	3185(6)	3659(2)	2141(2)	674(20)	487(17)	571(18)	5(14)	-127(15)	- 76(14)
C(15)	4679(6)	4322(2)	2348(2)	724(19)	434(15)	519(16)	21(14)	39(14)	94(13)
C(16)	3722(7)	4560(2)	3752(3)	687(21)	671(22)	806(23)	- 1(17)	290(18)	- 87(18)
C(17)	7020(7)	5117(2)	3438(3)	653(21)	449(18)	1071(29)	-134(15)	86(20)	- 19(18)

squares refinement of coordinates and individual isotropic B's of all non-H atoms, followed by two cycles with anisotropic β's, reduced R to 0·07, where $R = \Sigma ||F_o| - |F_c||/\Sigma |F_o|$. The function minimized was $R_1 = \Sigma w(hkl)[|F_o(hkl) - F_c(hkl)|]^2$, with equal weights given to all terms in the initial stages; later $w(hkl) = \sin\theta/A \times C/F_o$, with $A = 0{\cdot}333$ and $C = 35{\cdot}0$. All H atoms were clearly located on a difference Fourier synthesis; and were assigned isotropic B's of the atoms to which they were bonded, four cycles of refinement of coordinates of all atoms and U_{ij} of all non-H atoms converged to a final R of 0·038 for 2830 reflexions. The average shift/e.s.d. = 0·25. Tables 1 and 2 give positional and thermal-motion parameters; bond lengths and angles are listed in Table 3; Fig. 1 shows the atomic numbering and molecular configuration, drawn by *ORTEP* (Johnson, 1970).*

Discussion

7-OH–CPZ is an important member of the unconjugated phenolic metabolites of chlorpromazine. The chemistry of the metabolic transformations of CPZ has been extensively studied (Bolt, Forrest & Serra, 1966; Bolt & Forrest, 1967; Brookes, Holmes, Forrest, Bacon, Duffield & Solomon, 1971). The principal pathways of CPZ detoxication in man appear to be sulphoxidation, hydroxylation of the ring and demethylation of the aliphatic side-chain, followed by conjugation, mainly with glucuronic acid (Forrest, Bolt & Aber, 1968). Evidence from studies carried out by Manian, Efron & Goldberg (1965) suggested that hydroxy metabolites of CPZ are of importance in mediating the various physiological responses observed with CPZ therapy. It was shown (Manian, Efron & Harris, 1971) that 7-OH–CPZ possessed activity similar, if not superior, to its parent compound, and that after dosage with CPZ the metabolite was actually present in the central nervous systems of certain animals. The present study was undertaken to investigate the suggestion of Green (1975) that the unusual pharmacology of 7-OH–CPZ might, as in morphine, be ascribed to the dienone character of the C(7)–C(12) ring, resulting in a significant inclination of the C(12)–N(1) bond to the plane of the ring, unusual sp^3 character at C(12) and atypical bond lengths.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32099 (4 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Final hydrogen atomic fractional coordinates* (×10³) *and isotropic temperature factors* (×10³) *with estimated standard deviations*

	x	y	z	U
H(2)	330(5)	52(2)	492(2)	59
H(3)	5(5)	64(2)	366(2)	57
H(6)	643(5)	208(1)	381(2)	47
H(8)	-242(4)	119(1)	30(1)	41
H(9)	-217(4)	114(1)	-125(2)	51
H(10)	269(4)	218(1)	- 56(2)	46
H(11)	450(4)	257(1)	91(2)	47
H(131)	491(4)	305(1)	322(2)	48
H(132)	594(5)	293(1)	236(2)	48
H(141)	185(5)	368(2)	236(2)	59
H(142)	279(5)	360(2)	151(2)	59
H(151)	367(5)	476(2)	206(2)	61
H(152)	625(5)	431(2)	214(2)	61
H(161)	265(6)	497(2)	348(2)	72
H(162)	442(6)	468(2)	439(2)	72
H(163)	277(6)	412(2)	366(2)	72
H(171)	819(6)	502(2)	308(2)	71
H(172)	610(6)	554(2)	314(2)	71
H(173)	766(6)	517(2)	412(2)	71

Table 3. *Bond lengths* (Å) *and bond angles with estimated standard deviations*

The e.s.d.'s in the heavy-atom bond lengths (× 10³), the C–H bond lengths (× 10²) and the bond angles (×10) are given in parentheses.

C(1) - C(2)	1.374(4)	C(2) - H(2)	1.01(3)
C(2) - C(3)	1.386(4)	C(3) - H(3)	.91(3)
C(3) - C(4)	1.378(4)	C(6) - H(6)	.92(3)
C(4) - C(5)	1.403(4)	C(8) - H(8)	.97(2)
C(5) - C(6)	1.401(4)	O - H(9)	.96(2)
C(6) - C(1)	1.386(4)	C(10) - H(10)	.97(3)
C(1) - Cl	1.749(3)	C(11) - H(11)	.98(2)
C(7) - C(8)	1.399(3)		
C(8) - C(9)	1.380(4)	C(13) - H(131)	.99(3)
C(9) - C(10)	1.390(4)	C(13) - H(132)	1.00(3)
C(10) - C(11)	1.385(4)	C(14) - H(141)	.94(3)
C(11) - C(12)	1.386(4)	C(14) - H(142)	.95(3)
C(12) - C(7)	1.392(3)	C(15) - H(151)	1.05(3)
C(9) - O	1.367(3)	C(15) - H(152)	1.06(3)
C(7) - S	1.768(3)		
C(4) - S	1.770(3)	C(16) - H(161)	1.02(3)
C(12) - N(1)	1.427(3)	C(16) - H(162)	1.00(4)
C(5) - N(1)	1.400(3)	C(16) - H(163)	.99(3)
N(1) - C(13)	1.465(3)		
C(13) - C(14)	1.522(4)		
C(14) - C(15)	1.517(4)	C(17) - H(171)	1.01(4)
C(15) - N(2)	1.461(4)	C(17) - H(172)	1.01(3)
N(2) - C(16)	1.462(5)	C(17) - H(173)	1.03(3)
N(2) - C(17)	1.469(4)		

C(6) - C(1) - C(2)	122.5(2)	C(1) - C(2) - H(2)	121.1(15)
C(1) - C(2) - C(3)	118.1(3)	C(3) - C(2) - H(2)	120.8(15)
C(2) - C(3) - C(4)	121.3(3)	C(2) - C(3) - H(3)	120.3(17)
C(3) - C(4) - C(5)	120.3(2)	C(4) - C(3) - H(3)	118.4(17)
C(4) - C(5) - C(6)	118.7(2)	C(1) - C(6) - H(6)	120.9(15)
C(5) - C(6) - C(1)	119.0(2)	C(5) - C(6) - H(6)	119.9(15)
C(6) - C(1) - C(2)	119.4(2)	C(7) - C(8) - H(8)	119.9(14)
C(6) - C(1) - Cl	118.0(2)	C(9) - C(8) - H(8)	120.6(14)
		C(8) - C(9) - H(9)	116.2(15)
		C(9) - C(10) - H(10)	116.6(13)
C(12) - C(7) - C(8)	121.0(2)	C(11) - C(10) - H(10)	122.9(13)
C(7) - C(8) - C(9)	119.5(2)	C(10) - C(11) - H(11)	117.2(15)
C(8) - C(9) - C(10)	119.7(2)	C(12) - C(11) - H(11)	122.2(15)
C(9) - C(10) - C(11)	120.5(3)		
C(10) - C(11) - C(12)	120.7(2)	N(1) - C(13) - H(131)	104.9(15)
C(11) - C(12) - C(7)	118.6(2)	N(1) - C(13) - H(132)	112.5(15)
O - C(9) - C(8)	124.6(2)	C(14) - C(13) - H(131)	107.8(15)
O - C(9) - C(10)	116.6(2)	C(14) - C(13) - H(132)	110.6(15)
		H(131) - C(13) - H(132)	108.7(21)
		C(13) - C(14) - H(141)	105.3(18)
C(4) - S - C(7)	98.4(1)	C(13) - C(14) - H(142)	107.3(17)
S - C(7) - C(12)	118.4(2)	C(15) - C(14) - H(141)	112.4(18)
C(7) - C(12) - N(1)	119.0(2)	C(15) - C(14) - H(142)	106.7(18)
C(12) - N(1) - C(5)	117.2(2)	H(141) - C(14) - H(142)	112.2(24)
N(1) - C(5) - C(4)	118.5(2)	C(14) - C(15) - N(2)	109.1(15)
C(5) - C(4) - S	118.7(2)	C(14) - C(15) - H(151)	115.5(15)
		N(2) - C(15) - H(151)	107.1(16)
		N(2) - C(15) - H(152)	101.3(14)
C(3) - C(4) - S	120.9(2)	H(151) - C(15) - H(152)	109.1(23)
C(8) - C(7) - S	120.6(2)		
C(6) - C(5) - N(1)	122.7(2)	C(15) - C(16) - H(161)	110.7(21)
C(11) - C(12) - N(1)	122.4(2)	N(2) - C(16) - H(162)	109.5(21)
C(5) - N(1) - C(13)	119.6(2)	N(2) - C(16) - H(163)	107.8(21)
C(12) - N(1) - C(13)	119.1(2)	H(161) - C(16) - H(162)	106.9(26)
		H(162) - C(16) - H(163)	113.9(27)
		H(163) - C(16) - H(161)	108.0(26)
N(1) - C(13) - C(14)	112.0(2)	C(16) - C(17) - H(171)	103.1(18)
C(13) - C(14) - C(15)	112.9(2)	N(2) - C(17) - H(172)	111.8(18)
C(14) - C(15) - N(2)	114.2(3)	N(2) - C(17) - H(173)	105.1(19)
C(15) - N(2) - C(16)	112.3(2)	H(171) - C(17) - H(172)	105.2(28)
C(15) - N(2) - C(17)	110.4(3)	H(172) - C(17) - H(173)	113.7(26)
C(16) - N(2) - C(17)	108.3(3)	H(173) - C(17) - H(171)	117.5(26)

No unusual bond lengths or angles were found; the C(7)–C(12) ring showed no marked deviations from average values; all bonds are in close agreement with mean values calculated for other phenothiazine derivatives (McDowell, 1976). Table 4 shows that the benzene rings may be regarded as planar, while S and N(1) lie outside the planes. Figs. 2 and 3 illustrate views of the cell contents. The molecules are tightly held in sheets perpendicular to **b** by a strong intermolecular hydrogen bond between N(2) and O at $1 + x, \frac{1}{2} - y, \frac{1}{2} + z$ [O–H(9)···N(2), 2·701 (3); N(2)···H(9), 1·76 (2) Å; N(2)–H(9)–O, 167 (2)°].

There is evidence in support of the theory that the clinical effects of the neuroleptic drugs may be due to their ability to block dopamine receptors in the brain (Hawkins & Pauling, 1973; Horn, Post & Kennard, 1975). The conformational similarities between the molecular structures of chlorpromazine and dopamine

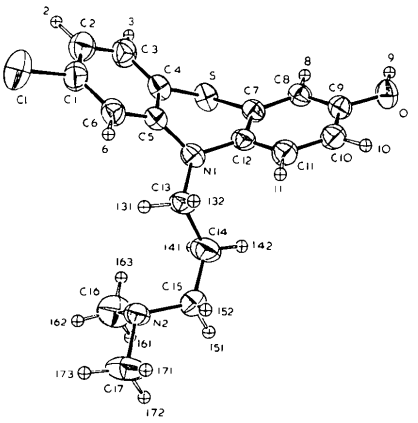


Fig. 1. Thermal-vibration ellipsoids and atomic numbering. ⊕ denotes H atoms.

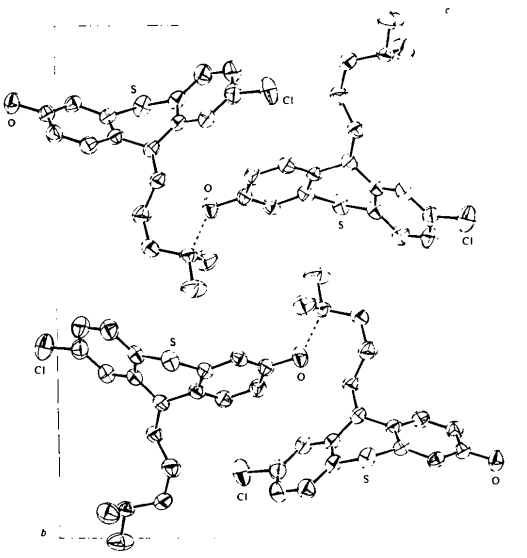


Fig. 2. The structure viewed down **a**.

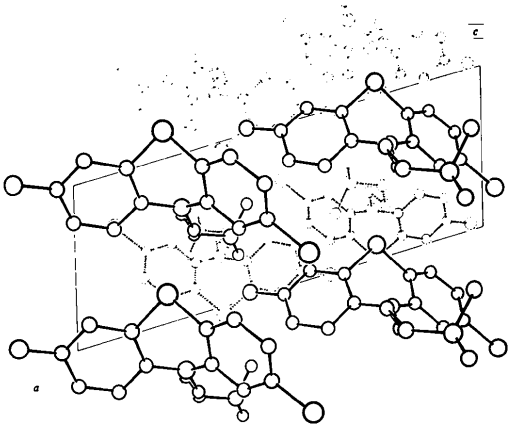


Fig. 3. The structure viewed down **b**.

Table 4. *Mean-plane parameters and deviations of atoms from the plane*

(I) C(1)–C(6)

$$-3{\cdot}0999x + 12{\cdot}9587y + 9{\cdot}6505z = 4{\cdot}3742$$

Deviations of atoms defining the plane		Distances of atoms not defining the plane	
C(1)	0·0086 Å	S	0·1173 Å
C(2)	0·0097	N(1)	0·0779
C(3)	−0·0165	Cl	0·0476
C(4)	0·0048	C(13)	0·5845
C(5)	0·0132	H(2)	0·0171
C(6)	−0·0198	H(3)	−0·0261
		H(6)	0·0027

(II) C(7)–C(12)

$$-3{\cdot}0705x + 15{\cdot}7302y - 0{\cdot}6806z = 2{\cdot}6450$$

C(7)	0·0062	S	0·0354
C(8)	−0·0105	N(1)	0·0042
C(9)	0·0036	O	0·0054
C(10)	0·0078	C(13)	0·5150
C(11)	−0·0122	H(8)	−0·0450
C(12)	0·0051	H(9)	−0·0977
		H(10)	0·0026
		H(11)	−0·0500

Table 5. *Experimental torsion angles of the alkyl side-chains of chlorpromazine and 7-hydroxychlorpromazine*

		CPZ	7-OH–CPZ
τ_1	C(4)–C(5)–N(1)–C(13)	165°	157°
τ_2	C(7)–C(12)–N(1)–C(13)	−162	−156
τ_3	C(5)–N(1)–C(13)–C(14)	−69	−141
τ_4	C(12)–N(1)–C(13)–C(14)	139	62
τ_5	N(1)–C(13)–C(14)–C(15)	164	177
τ_6	C(13)–C(14)–C(15)–N(2)	−69	−58
τ_7	C(14)–C(15)–N(2)–C(16)	−76	−59
τ_8	C(14)–C(15)–N(2)–C(17)	162	180

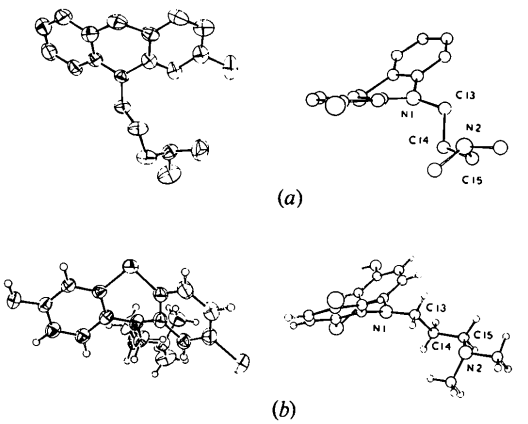


Fig. 4. Comparison of the conformation of the alkyl side-chain relative to the tricyclic group in (*a*) chlorpromazine and (*b*) 7-hydroxychlorpromazine.

have been demonstrated (Horn & Snyder, 1971). Kaufman & Kerman (1974) suggested not only that the activity of 7-OH–CPZ may be due to the involvement of the *a* ring (with Cl substituent) but that the *c* ring (with OH group) also probably plays an important role in the interference of the dopamine pathway.

The most striking feature of the metabolite molecule, as compared with the drug molecule chlorpromazine (McDowell, 1969), is the difference in the conformation of the alkyl side-chain relative to the tricyclic group, which is illustrated in Fig. 4. The torsion angles of the alkyl side-chains calculated from the atomic coordinates of the two molecules are given in Table 5. It will be noted that τ_1 and τ_2 are closely similar as expected, whereas τ_3 and τ_4 differ substantially in the two molecules. This may partly be attributed to the crystal packing forces, particularly the formation of the H bond. Theoretical calculations on the conformation of the side-chain with respect to the tricyclic group have been carried out for chlorpromazine by Kaufman & Kerman (1974), using CNDO/2 and INDO methods. The crystallographic structure with dihedral angle 139·4° has a conformation with energy very close to the theoretical total energy minimum; however, there are a few other possible conformations of the side-chain which have small differences in energy, indicating that the alkyl chain has a certain flexibility. The possibility of conformations existing in solution different from that of the solid state cannot therefore be excluded, and it is hoped that the NMR studies on both CPZ and 7-OH–CPZ, which are currently in progress in this laboratory, may assist in elucidating this problem.

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References

BOLT, A. G. & FORREST, I. S. (1967). *J. Pharm. Sci.* **56**, 1533–1534.

BOLT, A. G., FORREST, I. S. & SERRA, M. T. (1966). *J. Pharm. Sci.* **55**, 1205–1208.

BROOKES, L. G., HOLMES, M. A., FORREST, I. S., BACON, V. A., DUFFIELD, A. M. & SOLOMON, M. D. (1971). *Agressologie*, **12**, 333–342.

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321–324.

FORREST, I. S., BOLT, A. G. & ABER, R. C. (1968). *Agressologie*, **9**, 259–265.

GREEN, D. E. (1975). Private communication.

HAWKINS, D. & PAULING, L. (1973). *Orthomolecular Psychiatry*. San Francisco: Freeman.

HORN, A. S., POST, M. L. & KENNARD, O. (1975). *J. Pharm. Pharmacol.* **27**, 553–563.

HORN, A. S. & SNYDER, S. H. (1971). *Proc. Natl. Acad. Sci. US*, **68**, 2325–2328.

JOHNSON, C. K. (1970). *ORTEP*. Oak Ridge National Laboratory Report ORNL-3794.

KAUFMAN, J. J. & KERMAN, E. (1974). *The Phenothiazines and Structurally Related Drugs*, edited by I. S. FORREST, C. J. CARR & E. USDIN, pp. 55–75. New York: Raven Press.

MCDOWELL, J. J. H. (1969). *Acta Cryst.* B**25**, 2175–2181.

MCDOWELL, J. J. H. (1976). *Acta Cryst.* B**32**, 5–10.

MANIAN, A. A., EFRON, D. H. & GOLDBERG, M. E. (1965). *Life Sci.* **4**, 2425–2438.

MANIAN, A. A., EFRON, D. H. & HARRIS, S. R. (1971). *Life Sci.* **10**, 679–684.

SHELDRICK, G. M. (1975). *SHELX. A Program for Crystal Structure Determination*. Univ. of Cambridge, England.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

X-RAY system (1972). Tech. Rep. TR-192 of the Computer Science Center, Univ. of Maryland, College Park, Maryland, revised 1974.