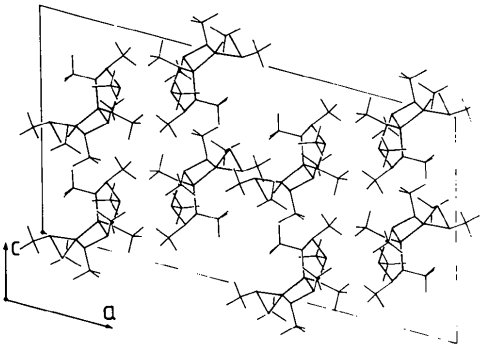


Fig. 2. Projektion der Kristallstruktur nach [010].

Die vorliegende Arbeit entstand in Zusammenarbeit mit Frau Prof. Dr M. Baudler und Fräulein Dipl.-Chem. U. Schings, die uns die Kristalle überlassen und Anregungen bei der Diskussion der Ergebnisse gegeben haben. Bei der Durchführung der Messung hat uns Herr Dipl.-Chem. Th. Heinlein unterstützt. Diese Arbeit wurde durch eine Sachmittelspende des Fonds der Chemischen Industrie gefördert. Den Genannten sei für ihre Hilfe gedankt.

Literatur

BAUDLER, M. & PONTZEN, TH. (1982). *Z. Anorg. Allg. Chem.* **491**, 27–33.

BAUDLER, M., PONTZEN, TH., SCHINGS, U., TEBBE, K.-F. & FEHÉR, M. (1983). *Angew. Chem.* **95**, 803–804; *Angew. Chem. Int. Ed. Engl.* **22**, 775–776.

BUSING, W. R., MARTIN, K. O., LEVY, H. A., BROWN, G. M., JOHNSON, C. K. & THIESSEN, W. E. (1977). *ORFFE*4. Oak Ridge National Laboratory, Tennessee, V. St. A.

CALABRESE, J. C., OAKLEY, R. T. & WEST, R. (1979). *Can. J. Chem.* **57**, 1909–1914.

CORDES, A. W., SCHUBERT, P. F. & OAKLEY, R. T. (1979). *Can. J. Chem.* **57**, 174–179.

FEHÉR, M., FRÖHLICH, R. & TEBBE, K.-F. (1981). *Z. Anorg. Allg. Chem.* **158**, 241–253.

FEHÉR, M., HEINLEIN, TH. & TEBBE, K.-F. (1983). *Abstr.* 8. *Eur. Crystallogr. Meet. Liège* 2a. 24-P, S.92.

FRÖHLICH, R. & TEBBE, K.-F. (1982). *Acta. Cryst.* B**38**, 115–120.

HÖNLE, W. & VON SCHNERING, H. G. (1978*a*). *Z. Anorg. Allg. Chem.* **440**, 171–182.

HÖNLE, W. & VON SCHNERING, H. G. (1978*b*). *Z. Anorg. Allg. Chem.* **442**, 92–94.

HÖNLE, W. & VON SCHNERING, H. G. (1978*c*). *Z. Anorg. Allg. Chem.* **442**, 107–111.

International Tables for X-ray Crystallography (1974). Bd. IV. Birmingham: Kynoch Press.

JOHNSON, C. K. (1976). *ORTEP*II. Bericht ORNL-5138. Oak Ridge National Laboratory, Tennessee, V. St. A.

ROBINSON, E. A. & GILLESPIE, R. J. (1980). *J. Chem. Educ.* **57**, 329–333.

SHELDRICK, G. M. (1976). *SHELX*76. Programme für die Strukturbestimmung. Univ. Cambridge, England (unveröffentlicht).

TEBBE, K.F. (1980). *Z. Anorg. Allg. Chem.* **468**, 202–212.

TEBBE, K.-F. & FRÖHLICH, R. (1979). *IREFL* und *DATNEU*. Programme zur Analyse von CAD-4-Daten und zur Datenreduktion. Univ. zu Köln, Bundesrepublik Deutschland (unveröffentlicht).

TEBBE, K.-F. & FRÖHLICH, R. (1982). *Z. Naturforsch. Teil B*, **37**, 534–541.

TEBBE, K.-F. & HEINLEIN, TH. (1984). *Z. Anorg. Allg. Chem.* Im Druck.

Acta Cryst. (1984). C**40**, 1882–1887

Derivatives of the Anti-Leprosy Drug Clofazimine: 7- and 8-Chloroclofazimine, $C_{27}H_{21}Cl_3N_4$, and 4,9-Dichloroclofazimine, $C_{27}H_{20}Cl_4N_4$

BY M. BETH HUMPHREY BROOM, URSZULA RYCHLEWSKA* AND DEREK J. HODGSON†

Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514, *USA*

(*Received* 4 *April* 1984; *accepted* 15 *June* 1984)

Abstract. 7-Chloroclofazimine [7-chloro-3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-(isopropylimino)phenazine], $M_r = 507{\cdot}8$, triclinic, $P\bar{1}$, $a = 12{\cdot}152$ (4), $b = 12{\cdot}598$ (6), $c = 8{\cdot}699$ (6) Å, $\alpha = 91{\cdot}68$ (5), $\beta = 98{\cdot}49$ (4), $\gamma = 108{\cdot}64$ (3)°, $V = 1244$ (2) Å^3, $Z = 2$, $D_m = 1{\cdot}34$ (3), $D_x = 1{\cdot}356$ Mg m^{-3}, Mo $K\alpha$ radiation ($\lambda K\alpha_1 = 0{\cdot}70926$, $\lambda K\alpha_2 = 0{\cdot}71354$ Å), $\mu = 0{\cdot}39$ mm^{-1}, $F(000) = 524$, $T = 293$ K, $R = 0{\cdot}052$ for 3097 unique observed data. 8-Chloroclofazimine, $M_r = 507{\cdot}8$, monoclinic, $P2_1/a$, $a = 9{\cdot}245$ (13), $b = 24{\cdot}403$ (6), $c = 11{\cdot}015$ (4) Å, $\beta = 101{\cdot}55$ (10)°, $V = 2435$ (6) Å^3, $Z = 4$, $D_m = 1{\cdot}38$ (2), $D_x = 1{\cdot}385$ Mg m^{-3}, Mo $K\alpha$ (see above), $\mu = 0{\cdot}40$ mm^{-1}, $F(000) = 1048$, $T = 292$ K, $R = 0{\cdot}050$ for 1897 unique observed data. 4,9-Dichloroclofazimine, $M_r = 542{\cdot}3$, monoclinic, $C2/c$, $a = 41{\cdot}078$ (10), $b = 5{\cdot}575$ (12), $c = 22{\cdot}975$ (3) Å, $\beta = 108{\cdot}68$ (2)°, $V = 4984$ (16) Å^3, $Z = 8$, $D_m = 1{\cdot}42$ (3), $D_x = 1{\cdot}445$ Mg m^{-3}, Mo $K\alpha$ (see above), $\mu = 0{\cdot}50$ mm^{-1}, $F(000) = 2224$, $T = 292$ K, $R = 0{\cdot}064$

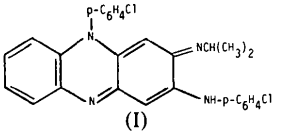
* Permanent Address: Faculty of Chemistry, A. Mickiewicz University, ul. Grunwaldzka 6, 60-780 Poznań, Poland.

† Author to whom correspondence should be addressed.

0108-2701/84/111882-06$01.50

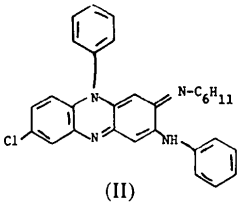
for 1619 unique observed data. The structures of the two mono-substituted compounds are substantially similar, each consisting of an approximately planar dihydrophenazine moiety with the *p*-chlorophenyl group at N(10) approximately perpendicular to the phenazine plane and the *p*-chloroanilino group at C(3) inclined at approximately 30° to the phenazine plane. In the dichloro analogue, this latter value is increased to 56·3° as the result of steric interactions involving the chlorine substituent at C(4).

Introduction. The substituted iminophenazine clofazimine (I)



(I)

is widely used in leprosy therapy (Jacobson, 1981; Browne, Harman, Waudby & McDougall, 1981), but the details of the mode of action of this and related iminophenazines remain unknown. Morrison & Marley (1976) have demonstrated that clofazimine binds to the G:C regions of DNA, and that it does not act as an intercalator, but the molecular basis for the marked difference in activity (Conalty, 1982; Levy, 1981) among various related iminophenazines remains unclear. Levy (1981) has noted that the two *p*-chloro substituents in clofazimine are of importance, but the absence of such substituents in other active analogues, notably B1912 (II)



(II)

(Shepard, Ellard, Levy, Opromolla, Pattyn, Peters, Rees & Waters, 1976; Levy, 1981), demonstrates that their presence is not imperative. Among the halogen-substituted clofazimines, the 7-chloro analogue is active both *in vitro* and *in vivo*, the 8-chloro derivative is active *in vitro* but inactive *in vivo*, and the 4,9-dichloro analogue is inactive both *in vitro* and *in vivo* (Conalty, 1982).

We have recently begun a comprehensive examination of the structural and electronic properties of clofazimine and its derivatives and analogues in the hope of eventually establishing structure–activity relationships for this important class of molecules (Eggleston, Marsh & Hodgson, 1984; Rychlewska, Broom & Hodgson, 1984). We here report the structures of the 7- and 8-chloro and 4,9-dichloro derivatives of clofazimine.

Experimental. Samples generously donated by Dr M. L. Conalty; crystals of 4,9-dichloro derivative grown from hexane–ethyl acetate solution, others from acetone solutions; D_m measured by flotation; Enraf–Nonius CAD-4 diffractometer, Mo $K\alpha$ radiation; programs from CAD-4/*SDP* (Enraf–Nonius, 1979); all structures solved by direct methods; absorption corrections not applied; atomic scattering factors from *International Tables for X-ray Crystallography* (1974); weights as defined by Corfield, Doedens & Ibers (1967) with $p = 0{\cdot}01$ for 7- and 8-chloro, $p = 0{\cdot}02$ for 4,9-dichloro compound. Other experimental parameters as listed in Table 1.

Discussion. The atomic parameters for 7-chloroclofazimine, 8-chloroclofazimine and 4,9-dichloroclofazimine, along with their standard deviations as estimated from the inverse matrix, are listed in Tables 2,3 and 4, respectively.*

Views of 7-chloroclofazimine, 8-chloroclofazimine and 4,9-dichloroclofazimine are shown in Figs. 1, 2 and 3, respectively. Selected bond distances and angles in the three molecules are listed in Tables 5 and 6.

In all three molecules, the pattern of bond lengths observed is entirely consistent with the bond orders suggested in (I). Thus, the formally double bond N(5)–C(13) [1·293 (2)–1·316 (6) Å] is very much shorter than the formally single N(5)–C(12), N(10)–C(11), and N(10)–C(14) bonds [1·366 (6)–1·392 (4) Å]. Similarly, the formal double bonds C(1)–C(14) and C(3)–C(4) [1·317 (7)–1·358 (7), average 1·337 (14) Å] are shorter than the adjacent single bonds C(1)–C(2) and C(4)–C(13) [1·431 (5)–1·444 (2), average 1·436 (5) Å]. In all cases, the chlorine substitution on the aromatic phenazine ring leads to widening of the angle at which the substitution takes place. In the 8-chloro compound the 14-membered dihydrophenazine is surprisingly planar, the largest deviation from the least-squares plane being 0·054 (3) Å. The other two compounds show much larger deviations from planarity, and are better viewed as two planar six-member carbon rings which form a butterfly at the N(5)–N(10) axis; the butterfly angles in the 7-, 8-, and 4,9-substituted compounds are 3·0, 1·3, and 6·3°, respectively.

As can be seen in the figures, the *p*-chlorophenyl ring at N(10) is almost perpendicular to the dihydrophenazine plane in all three molecules. The torsion angles τ_1 around N(10)–C(15) [defined by C(14)–

* Lists of observed and calculated structure amplitudes, hydrogen-atom coordinates, bond lengths and angles in the aromatic rings and anisotropic thermal parameters for all three compounds have been deposited with the British Library Lending Division as Supplentary Publication No. SUP 39593 (60 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Experimental parameters for 7-chloroclofazimine, 8-chloroclofazimine, and 4,9-dichloroclofazimine*

	7-Chloro	8-Chloro	4,9-Dichloro
Crystal shape and size	Red rod, 1·00 × 0·60 × 0·40 mm	Red–orange rod, 0·80 × 0·30 × 0·40 mm	Orange rod 0·06 × 0·13 × 1·20 mm
No. and range of reflections used to calculate cell constants	25 reflections, $15 < \theta(\text{Mo}) < 17°$	25 reflections, $15 < \theta(\text{Mo}) < 17{\cdot}5°$	25 reflections, $8{\cdot}5° < \theta(\text{Mo}) < 14{\cdot}5°$
Max. $(\sin\theta)/\lambda$	0·651 Å^{-1}	0·651 Å^{-1}	0·528 Å^{-1}
Range of h,k,l	$-15 \le h \le 15$ $-16 \le k \le 16$ $0 \le l \le 11$	$0 \le h \le 12$ $0 \le k \le 31$ $-14 \le l \le 14$	$-43 \le h \le 43$ $0 \le k \le 5$ $0 \le l \le 24$
Standard reflections and max. deviation in F	$\bar{6}55$ (3·0%) 182 (2·2%) 383 (3·0%)	$2,\bar{1}9,2$ (3·1%) $5\bar{4}5$ (2·2%) 2,16,5 (2·8%)	935 (7·4%) $13,1\bar{5}$ (9·7%) 24,0,10 (7·9%)
No. reflections measured	6085	6059	3132
No. unique reflections	5712	5572	3030
No. unobserved reflections $[I < n\sigma(I)]$	2615 ($n = 3$)	3672 ($n = 3$)	1411 ($n = 2{\cdot}5$)
Location and refinement of hydrogen atoms	Positions calculated, isotropic refinement	Located on ΔF map, isotropic refinement	Positions calculated, isotropic refinement on H(3) only
Parameters refined (LS refinement on F)	Scale factor, 34 anisotropic non-hydrogen atoms, 21 isotropic hydrogen atoms (391 variables)	Same as 7-chloro	Scale factor, 35 anisotropic atoms, 1 isotropic hydrogen atom (320 variables)
R	0·052	0·050	0·064
wR	0·048	0·038	0·061
S	3·03	1·86	2·42
Final LS shift/error	0·54	0·43	0·59
Max. height in final difference Fourier map	0·14 e Å^{-3}	0·18 e Å^{-3}	0·25 e Å^{-3}

Table 2. *Atomic positional and equivalent isotropic thermal parameters for 7-chloroclofazimine* (*B*1509)

$U_{eq} = (1/6\pi^2)\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}(Å^2)
Cl(7)	1·41753 (8)	0·94122 (8)	1·1998 (1)	0·0979 (2)
Cl(18)	1·21017 (9)	1·64926 (6)	1·0804 (1)	0·0859 (3)
Cl(24)	0·46955 (9)	0·44972 (8)	0·2064 (1)	0·0924 (3)
N(2)	0·7741 (2)	1·1350 (2)	0·4801 (3)	0·058 (1)
N(3)	0·7288 (2)	0·9221 (2)	0·4331 (3)	0·059 (1)
N(5)	1·0642 (2)	0·9415 (2)	0·8095 (3)	0·049 (1)
N(10)	1·1000 (2)	1·1672 (2)	0·8953 (3)	0·043 (1)
C(1)	0·9385 (2)	1·1590 (2)	0·6939 (3)	0·049 (1)
C(2)	0·8440 (2)	1·0979 (2)	0·5705 (3)	0·047 (1)
C(3)	0·8248 (2)	0·9750 (2)	0·5450 (3)	0·047 (1)
C(4)	0·8994 (2)	0·9296 (2)	0·6218 (3)	0·050 (1)
C(6)	1·2328 (3)	0·9507 (2)	0·9952 (4)	0·059 (1)
C(7)	1·3246 (2)	1·0083 (2)	1·1087 (4)	0·058 (1)
C(8)	1·3442 (2)	1·1198 (2)	1·1555 (4)	0·057 (1)
C(9)	1·2704 (2)	1·1728 (2)	1·0860 (3)	0·049 (1)
C(11)	1·1760 (2)	1·1160 (2)	0·9697 (3)	0·041 (1)
C(12)	1·1569 (2)	1·0030 (2)	0·9238 (3)	0·045 (1)
C(13)	0·9959 (2)	0·9919 (2)	0·7398 (3)	0·043 (1)
C(14)	1·0097 (2)	1·1109 (2)	0·7746 (3)	0·040 (1)
C(15)	1·1212 (2)	1·2853 (2)	0·9364 (3)	0·042 (1)
C(16)	1·0805 (2)	1·3159 (2)	1·0644 (4)	0·052 (1)
C(17)	1·1071 (3)	1·4296 (2)	1·1070 (4)	0·060 (1)
C(18)	1·1722 (2)	1·5067 (2)	1·0245 (4)	0·053 (1)
C(19)	1·2112 (3)	1·4764 (2)	0·8943 (4)	0·057 (1)
C(20)	1·1851 (3)	1·3630 (2)	0·8522 (3)	0·053 (1)
C(21)	0·6709 (2)	0·8088 (2)	0·3866 (3)	0·051 (1)
C(22)	0·6764 (3)	0·7226 (2)	0·4763 (3)	0·056 (1)
C(23)	0·6140 (3)	0·6123 (2)	0·4220 (4)	0·059 (1)
C(24)	0·5448 (3)	0·5889 (2)	0·2778 (4)	0·061 (1)
C(25)	0·5356 (3)	0·6730 (3)	0·1877 (4)	0·062 (1)
C(26)	0·5996 (3)	0·7832 (2)	0·2404 (4)	0·053 (1)
C(27)	0·7872 (3)	1·2546 (3)	0·4910 (4)	0·070 (1)
C(28)	0·8806 (4)	1·3171 (3)	0·3998 (5)	0·099 (1)
C(29)	0·6673 (3)	1·2656 (3)	0·4323 (6)	0·116 (1)

Table 3. *Atomic positional and equivalent isotropic thermal parameters for 8-chloroclofazimine* (*B*1480)

$U_{eq} = (1/6\pi^2)\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}(Å^2)
Cl(8)	−0·1304 (2)	0·30339 (6)	0·2585 (1)	0·0691 (3)
Cl(18)	0·1866 (2)	0·56981 (6)	0·5589 (2)	0·0951 (3)
Cl(24)	0·9608 (2)	0·03565 (6)	1·1998 (2)	0·0934 (3)
N(2)	0·7557 (4)	0·3526 (1)	0·9281 (3)	0·041 (1)
N(3)	0·7671 (4)	0·2481 (1)	0·9693 (3)	0·051 (1)
N(5)	0·3476 (4)	0·2191 (1)	0·6461 (3)	0·038 (1)
N(10)	0·3128 (4)	0·3327 (1)	0·6112 (3)	0·038 (1)
C(1)	0·5298 (5)	0·3462 (2)	0·7677 (4)	0·040 (1)
C(2)	0·6506 (5)	0·3253 (2)	0·8588 (4)	0·039 (1)
C(3)	0·6544 (4)	0·2646 (2)	0·8768 (4)	0·037 (1)
C(4)	0·5561 (5)	0·2322 (2)	0·8056 (4)	0·041 (1)
C(6)	0·1353 (5)	0·2050 (2)	0·4864 (4)	0·044 (1)
C(7)	0·0209 (5)	0·2238 (2)	0·3968 (4)	0·048 (1)
C(8)	0·0090 (5)	0·2790 (2)	0·3763 (4)	0·045 (1)
C(9)	0·1015 (5)	0·3160 (2)	0·4453 (4)	0·044 (1)
C(11)	0·2152 (4)	0·2973 (2)	0·5367 (4)	0·038 (1)
C(12)	0·2349 (5)	0·2409 (2)	0·5584 (4)	0·038 (1)
C(13)	0·4395 (5)	0·2534 (2)	0·7120 (4)	0·035 (1)
C(14)	0·4298 (4)	0·3131 (2)	0·6988 (4)	0·035 (1)
C(15)	0·2864 (5)	0·3909 (2)	0·5989 (4)	0·039 (1)
C(16)	0·3380 (5)	0·4206 (2)	0·5117 (4)	0·056 (1)
C(17)	0·3064 (5)	0·4765 (2)	0·4997 (5)	0·062 (1)
C(18)	0·2247 (5)	0·4999 (2)	0·5746 (4)	0·055 (1)
C(19)	0·1739 (6)	0·4711 (2)	0·6628 (5)	0·064 (1)
C(20)	0·2088 (5)	0·4161 (2)	0·6744 (4)	0·056 (1)
C(21)	0·8076 (5)	0·1969 (2)	1·0224 (4)	0·039 (1)
C(22)	0·7074 (5)	0·1554 (2)	1·0263 (4)	0·054 (1)
C(23)	0·7549 (5)	0·1052 (2)	1·0809 (5)	0·067 (1)
C(24)	0·8988 (5)	0·0987 (2)	1·1322 (4)	0·054 (1)
C(25)	0·9987 (5)	0·1392 (2)	1·1322 (4)	0·044 (1)
C(26)	0·9524 (5)	0·1885 (2)	1·0770 (4)	0·041 (1)
C(27)	0·7627 (5)	0·4116 (2)	0·9169 (4)	0·050 (1)
C(28)	0·8503 (6)	0·4261 (2)	0·8194 (5)	0·081 (1)
C(29)	0·8309 (6)	0·4367 (2)	1·0413 (5)	0·069 (1)

N(10)—C(15)—C(16)] are 101·0 (2), 96·5 (5), and 79·2 (8)° in the 7-, 8-, and 4,9-substituted compounds, respectively. The observation of approximately equal deviations from 90° in the 7-chloro and 4,9-dichloro derivatives suggests that the 9-chloro substituent does not introduce any additional steric constraint around this bond. It is, however, noteworthy that all three exocyclic bond angles C(15)—N(10)—C(11), N(10)—C(11)—C(9), and C(11)—C(9)—Cl(9) have opened up in the 4,9-dichloro derivative. Thus, these exocyclic angles at N(10) and C(11) are 3·6 and 4·2°, respectively, larger in the 4,9-dichloro derivative than the average values in the 7- and 8-chloro compounds, which are in the normal range (Eggleston *et al.*, 1984; Rychlewska *et al.*, 1984; Rychlewska, Broom, Eggleston & Hodgson, unpublished observations); similarly, the C(11)—C(9)—Cl(9) angle of 121·3 (5)° in

Table 4. *Atomic positional and equivalent isotropic thermal parameters for* 4,9-*dichloroclofazimine* (*B*1493)

$U_{eq} = (1/6\pi^2) \sum_i \sum_j \beta_{ij} \mathbf{a}_i . \mathbf{a}_j .$

	x	*y*	*z*	U_{eq}(Å²)
Cl(4)	0·65651 (5)	0·2008 (4)	0·68308 (9)	0·070 (1)
Cl(9)	0·71898 (6)	1·3222 (4)	0·53618 (10)	0·080 (1)
Cl(18)	0·64477 (6)	1·2372 (5)	0·29515 (10)	0·099 (1)
Cl(24)	0·54747 (7)	−0·0511 (7)	0·81613 (10)	0·129 (1)
N(2)	0·5610 (1)	0·504 (1)	0·5024 (2)	0·061 (2)
N(3)	0·5820 (1)	0·228 (1)	0·5961 (3)	0·070 (2)
N(5)	0·6931 (1)	0·593 (1)	0·6528 (2)	0·060 (2)
N(10)	0·6731 (1)	0·882 (1)	0·5484 (2)	0·053 (2)
C(1)	0·6168 (2)	0·702 (1)	0·5217 (3)	0·054 (2)
C(2)	0·5925 (2)	0·542 (1)	0·5338 (3)	0·054 (2)
C(3)	0·6062 (2)	0·387 (1)	0·5904 (3)	0·053 (3)
C(4)	0·6386 (2)	0·402 (1)	0·6251 (3)	0·052 (3)
C(6)	0·7474 (2)	0·781 (2)	0·6875 (3)	0·068 (4)
C(7)	0·7701 (2)	0·952 (2)	0·6830 (3)	0·067 (4)
C(8)	0·7602 (2)	1·111 (2)	0·6335 (3)	0·070 (3)
C(9)	0·7291 (2)	1·095 (1)	0·5907 (3)	0·054 (3)
C(11)	0·7048 (2)	0·919 (1)	0·5922 (3)	0·053 (3)
C(12)	0·7152 (2)	0·762 (1)	0·6440 (3)	0·056 (3)
C(13)	0·6616 (2)	0·578 (1)	0·6143 (3)	0·052 (3)
C(14)	0·6494 (2)	0·731 (1)	0·5603 (3)	0·051 (3)
C(15)	0·6650 (2)	0·968 (1)	0·4862 (3)	0·047 (3)
C(16)	0·6427 (2)	1·152 (1)	0·4657 (3)	0·058 (3)
C(17)	0·6355 (2)	1·236 (2)	0·4069 (4)	0·073 (3)
C(18)	0·6519 (2)	1·131 (1)	0·3688 (3)	0·061 (3)
C(19)	0·6728 (2)	0·941 (1)	0·3885 (3)	0·064 (3)
C(20)	0·6803 (2)	0·857 (1)	0·4488 (3)	0·062 (3)
C(21)	0·5758 (2)	0·157 (1)	0·6512 (3)	0·054 (3)
C(22)	0·5849 (2)	0·304 (2)	0·7019 (3)	0·065 (3)
C(23)	0·5764 (2)	0·240 (2)	0·7533 (3)	0·080 (4)
C(24)	0·5580 (2)	0·035 (2)	0·7511 (3)	0·069 (4)
C(25)	0·5490 (2)	−0·113 (1)	0·7021 (3)	0·064 (3)
C(26)	0·5582 (2)	−0·048 (1)	0·6512 (3)	0·062 (3)
C(27)	0·5451 (2)	0·642 (2)	0·4463 (3)	0·064 (3)
C(28)	0·5169 (3)	0·497 (2)	0·4037 (4)	0·136 (5)
C(29)	0·5302 (3)	0·853 (2)	0·4610 (4)	0·149 (4)

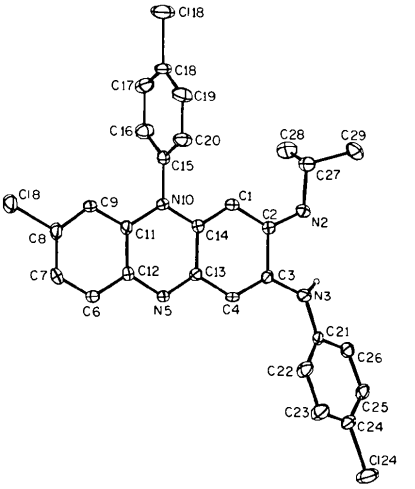


Fig. 2. View of a single molecule of 8-chloroclofazimine, drawn as in Fig. 1.

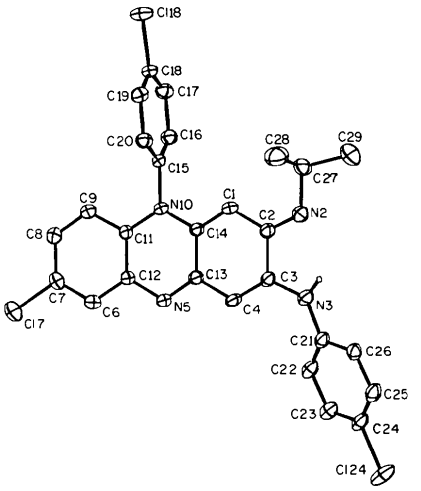


Fig. 1. View of a single molecule of 7-chloroclofazimine. Atom H(3) is shown as a sphere of arbitrary size, and other hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at the 25% probability level.

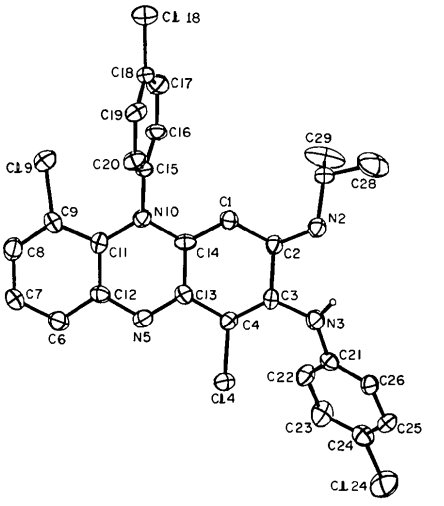


Fig. 3. View of a single molecule of 4,9-dichloroclofazimine, drawn as in Fig. 1.

the 4,9-dichloro compound is much larger than the C(8)–C(9)–Cl(9) angle of only 115·5 (5)°. All of these increased exocyclic angles serve to reduce the interaction between Cl(9) and the *p*-chlorophenyl ring.

Table 5. *Selected bond distances* (Å) *in 7-chloro-, 8-chloro-, and 4,9-dichloroclofazimine*

	7-Chloro	8-Chloro	4,9-Dichloro
C(1)–C(2)	1·444 (2)	1·438 (5)	1·431 (7)
C(1)–C(14)	1·337 (2)	1·343 (5)	1·358 (7)
C(2)–C(3)	1·494 (2)	1·492 (5)	1·512 (7)
C(2)–N(2)	1·280 (2)	1·294 (4)	1·280 (6)
C(3)–C(4)	1·331 (2)	1·335 (5)	1·317 (7)
C(3)–N(3)	1·372 (2)	1·364 (4)	1·369 (7)
C(4)–C(13)	1·433 (2)	1·431 (5)	1·438 (7)
N(5)–C(12)	1·387 (2)	1·378 (4)	1·366 (6)
N(5)–C(13)	1·293 (2)	1·305 (4)	1·316 (6)
C(6)–C(12)	1·383 (2)	1·397 (5)	1·382 (7)
C(6)–C(7)	1·363 (3)	1·374 (5)	1·360 (7)
C(7)–C(8)	1·385 (3)	1·366 (5)	1·396 (7)
C(8)–C(9)	1·366 (3)	1·364 (5)	1·343 (7)
C(9)–C(11)	1·393 (2)	1·379 (5)	1·407 (7)
N(10)–C(11)	1·385 (2)	1·392 (4)	1·384 (6)
N(10)–C(14)	1·389 (2)	1·383 (4)	1·377 (6)
N(10)–C(15)	1·450 (2)	1·442 (4)	1·442 (6)
C(11)–C(12)	1·404 (2)	1·403 (5)	1·426 (7)
C(13)–C(14)	1·471 (2)	1·464 (5)	1·458 (7)
N(2)–C(27)	1·462 (2)	1·447 (4)	1·465 (6)
C(27)–C(28)	1·505 (4)	1·512 (7)	1·494 (8)
C(27)–C(29)	1·522 (4)	1·518 (6)	1·413 (9)
N(3)–C(21)	1·391 (2)	1·399 (5)	1·423 (7)
C(7)–Cl(7)	1·734 (2)	—	—
C(8)–Cl(8)	—	1·740 (3)	—
C(4)–Cl(4)	—	—	1·716 (5)
C(9)–Cl(9)	—	—	1·736 (6)

Table 6. *Selected bond angles* (°)

	7-Chloro	8-Chloro	4,9-Dichloro
C(2)–C(1)–C(14)	122·4 (2)	122·1 (4)	123·5 (6)
C(1)–C(2)–C(3)	115·9 (2)	116·1 (4)	115·6 (6)
N(2)–C(2)–C(1)	128·5 (2)	128·0 (4)	129·5 (6)
N(2)–C(2)–C(3)	115·5 (2)	115·9 (3)	114·9 (6)
C(2)–C(3)–C(4)	120·5 (2)	120·9 (4)	120·7 (6)
N(3)–C(3)–C(2)	112·2 (2)	112·8 (3)	111·8 (5)
N(3)–C(3)–C(4)	127·2 (2)	126·2 (4)	127·3 (6)
C(3)–C(4)–C(13)	122·9 (1)	122·4 (4)	122·1 (6)
C(13)–N(5)–C(12)	118·3 (2)	117·3 (3)	120·1 (5)
C(12)–C(6)–C(7)	120·4 (2)	121·5 (4)	121·4 (6)
C(6)–C(7)–C(8)	121·3 (2)	118·3 (4)	118·5 (5)
C(7)–C(8)–C(9)	119·2 (2)	122·6 (4)	121·1 (6)
C(8)–C(9)–C(11)	120·8 (2)	119·3 (4)	122·9 (6)
C(11)–N(10)–C(14)	121·7 (1)	121·3 (3)	120·5 (5)
C(11)–N(10)–C(15)	118·9 (1)	118·6 (3)	122·3 (5)
C(14)–N(10)–C(15)	119·2 (1)	120·1 (3)	116·7 (5)
N(10)–C(11)–C(9)	122·5 (2)	122·3 (4)	126·6 (6)
N(10)–C(11)–C(12)	118·1 (2)	117·5 (3)	118·4 (6)
C(9)–C(11)–C(12)	119·4 (2)	120·2 (4)	115·0 (6)
C(11)–C(12)–C(6)	119·0 (2)	118·1 (4)	121·1 (6)
C(11)–C(12)–N(5)	122·3 (2)	123·6 (3)	120·7 (6)
N(5)–C(12)–C(6)	118·7 (2)	118·3 (4)	118·1 (6)
N(5)–C(13)–C(4)	119·1 (2)	118·8 (3)	119·3 (6)
N(5)–C(13)–C(14)	124·1 (2)	124·2 (3)	122·0 (6)
C(4)–C(13)–C(14)	116·8 (2)	117·0 (3)	118·8 (6)
C(13)–C(14)–C(1)	121·0 (2)	121·4 (4)	118·9 (6)
C(13)–C(14)–N(10)	115·4 (2)	116·0 (3)	117·0 (5)
C(1)–C(14)–N(10)	123·6 (2)	122·6 (4)	123·7 (5)
C(3)–N(3)–C(21)	131·5 (2)	132·7 (4)	127·4 (6)
C(2)–N(2)–C(27)	120·3 (2)	120·2 (3)	119·5 (5)
N(2)–C(27)–C(28)	109·7 (2)	109·5 (4)	108·9 (5)
N(2)–C(27)–C(29)	107·7 (2)	110·0 (4)	109·3 (6)
C(28)–C(27)–C(29)	112·9 (3)	111·2 (5)	107·6 (7)
C(6)–C(7)–Cl(7)	120·0 (2)	—	—
C(8)–C(7)–Cl(7)	118·7 (2)	—	—
C(7)–C(8)–Cl(8)	—	118·9 (3)	—
C(9)–C(8)–Cl(8)	—	118·6 (3)	—
C(3)–C(4)–Cl(4)	—	—	121·9 (5)
C(13)–C(4)–Cl(4)	—	—	115·9 (5)
C(8)–C(9)–Cl(9)	—	—	115·5 (5)
C(11)–C(9)–Cl(9)	—	—	121·3 (5)

The major differences between the disubstituted derivative and the monosubstituted compounds are at the anilino nitrogen atom N(3). As is the case in the other clofazimine analogues whose structures have been reported (Eggleston *et al.*, 1984; Rychlewska *et al.*, 1984), the aromatic ring at N(3) is inclined at approximately 30° to the phenazine ring; the values of 29·8 and 30·1° for this interplanar angle in the 7- and 8-chloro derivatives, respectively, lie in the range of 29 to 38° reported for other analogues. These angles are evidently large enough to minimize steric interactions between the *ortho* hydrogen atoms of the *p*-chloroanilino ring and the phenazine hydrogen at C(4), yet they are small enough to allow considerable overlap between the π-systems of the two rings and the p_z orbital of N(3). In 4,9-dichloroclofazimine, however, this interplanar angle is 56·3°, which is more than 20° larger than observed in the monosubstituted cases. The reason for this difference is presumably the increased steric interaction between the 4-chloro substituent and the anilino ring hydrogen atoms. The distortion can also be described in terms of the torsion angles τ_2 and τ_3 around C(3)–N(3) [defined by C(4)–C(3)–N(3)–C(21)] and N(3)–C(21) [defined by C(3)–N(3)–C(21)–C(22)], respectively. These angles are 11·3 (3) and 22·4 (3)° in the 7-chloro and 5·3 (5) and 28·0 (5)°, respectively, in the 8-chloro derivative. In the 4,9-dichloro compound the corresponding values are 44·1 (8) and 24·0 (8)°, respectively. Thus, the major difference in this region is the very large value of τ_2 in the 4,9-dichloro compound. In the related compounds B673 and B741, in which there is no chloro substituent on the phenazine ring, the τ_2 values are 9·5 (5) and 11·0 (5)°, respectively, while the τ_3 values are 27·0 (5) and 33·2 (5)° (Rychlewska *et al.*, 1984). Thus, the τ_3 value of 24·0 (8)° in the 4,9-dichloro compound appears to be normal, while the τ_2 angle of 44·1 (8)° is clearly far from the range of 5·3–11·3° observed for these compounds which are unsubstituted at C(4).

Intramolecular hydrogen-bond formation involving five approximately coplanar atoms has been postulated in a variety of systems. Thus, in 4-hydroxy-L-proline there is neutron diffraction evidence for N–H···O hydrogen bonding of this type (Koetzle, Lehmann & Hamilton, 1973), and in 1-methylamino-7-methylimino-1,3,5-cycloheptatriene there is both IR (Brasen, Holmquist & Benson, 1961) and X-ray diffraction (Goldstein & Trueblood, 1967) evidence for intramolecular N–H···N hydrogen bonding. One impact of this enhanced τ_2 angle in the 4,9-dichloro compound is to rotate the hydrogen atom H(3) out of the plane defined by N(2)–C(2)–C(3)–N(3). Such a rotation presumably prevents the formation of an intramolecular N(3)–H(3)···N(2) hydrogen bond; a hydrogen bond of this kind has been proposed for other compounds of this type (Rychlewska *et al.*, 1984). Thus, if the N(3)–H(3) bond length were adjusted from its observed value of

0·72 (4) Å to an idealized value of 1·03 Å, atom H(3) would be calculated to lie 0·29 (5) Å out of the plane defined above.

Since the structures of the 7- and 8-chloro derivatives appear to be substantially similar, little can be concluded concerning the difference between *in vitro* active molecules which are also active *in vivo* and those which are not. Evidently, 8-chloro substitution hinders absorption or transport without effecting a significant structural change.

The inactivity of the 4,9-dichloro compound is readily rationalized in the light of these observations. Evidently, it is the 4-chloro substituent which introduces the major structural changes, and these changes occur at or near the presumed active site. Although the active site in these molecules is not known, it is reasonable to assume that it involves the chemically active sites N(2), N(3), and/or N(5). As is apparent from Figs. 1 and 2, approach to these sites is relatively unhindered in the 7- and 8-chloro derivatives, as it is in the other analogues which have been studied (Eggleston *et al.*, 1984; Rychlewska *et al.*, 1984). It has been determined that *N,N*-dimethylformamide, a small acceptor molecule, can interact strongly with N(3) of clofazimine in the solid state (Eggleston *et al.*, 1984) and it seems feasible that small donor molecules could easily approach N(2) and/or N(5). Thus, in all of these active (*in vitro*) analogues, approach to the nitrogen atoms is unhindered and the geometry at N(3) is approximately constant. In the inactive 4,9-dichloro analogue, however, approach to N(5) is presumably hindered by the presence of Cl(4) (see Fig. 3), and the geometry and potential hydrogen-bonding capacity of the N(3) site are entirely different than in these other compounds. Structural and theoretical studies on other active and inactive analogues which are currently in progress should permit us to determine which of these features is of the greater significance.

We are indebted to Dr M. L. Conalty of the Medical Research Council of Ireland for the generous gift of the samples used in this analysis. This research was supported by the University Research Council of the University of North Carolina through grant No. 43566.

References

BRASEN, W. R., HOLMQUIST, H. E. & BENSON, R. E. (1961). *J. Am. Chem. Soc.* **83**, 3125–3135.

BROWNE, S. G., HARMAN, D. J., WAUDBY, H. & MCDOUGALL, A. C. (1981). *Int. J. Lepr.* **49**, 167–176.

CONALTY, M. L. (1982). Private communication.

CORFIELD, P. W. R., DOEDENS, R. J. & IBERS, J. A. (1967). *Inorg. Chem.* **6**, 197–204.

EGGLESTON, D. S., MARSH, W. E. & HODGSON, D. J. (1984). *Acta Cryst.* C**40**, 288–292.

Enraf–Nonius (1979). *Structure Determination Package.* Enraf–Nonius. Delft.

GOLDSTEIN, P. & TRUEBLOOD, K. N. (1967). *Acta Cryst.* **23**, 148–156.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press.

JACOBSON, R. R. (1981). *Int. J. Lepr.* **49**, 510.

KOETZLE, T. F., LEHMANN, M. S. & HAMILTON, W. C. (1973). *Acta Cryst.* B**29**, 231–236.

LEVY, L. (1981). *Lepr. Rev.* **52**, 23–26.

MORRISON, N. E. & MARLEY, G. M. (1976). *Int. J. Lepr.* **44**, 475–481.

RYCHLEWSKA, U., BROOM, M. B. H. & HODGSON, D. J. (1984). *Acta Cryst.* C**40**, 1004–1007.

SHEPARD, C. C., ELLARD, G. A., LEVY, L., OPROMOLLA, V. A., PATTYN, S. R., PETERS, J. H., REES, R. J. W. & WATERS, M. F. R. (1976). *Bull. W.H.O.* **53**, 425–433.

Acta Cryst. (1984). C**40**, 1887–1890

(±)-2,3-Dihydroxy-2,3-dimethylbutanedioic Acid [(±)-Dimethyltartaric Acid], $C_6H_{10}O_6$

BY EILEEN N. DUESLER, MINERVA MONDRAGON AND ROBERT E. TAPSCOTT

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131, *USA*

(*Received* 27 *February* 1984; *accepted* 18 *June* 1984)

Abstract. $M_r = 178·2$, triclinic, $P\bar{1}$, $a = 8·632$ (4), $b = 10·064$ (3), $c = 10·505$ (3) Å, $\alpha = 114·22$ (2), $\beta = 106·71$ (2), $\gamma = 92·92$ (3)°, $V = 782·1$ (5) Å^3, $Z = 4$, $D_x = 1·51$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0·13$ mm^{-1}, $F(000) = 376$, $T = 293$ (2) K, final $R = 0·058$ for 2086 observed unique reflections. The poorly staggered conformations are (−)-synclinal and (+)-synclinal for *R,R* and *S,S* molecules respectively. The torsion-angle deviation from perfect staggering of about 17° is toward a closer contact for the methyl substituents. As also found for the *R,S* (*meso*) modification, the C–C bond lengths are significantly greater than those which have been determined for the parent compound, tartaric acid.

0108-2701/84/111887-04$01.50