The Crystal and Molecular Structure of 7-Chloro-5-(2,4-dichlorophenyl)-4,5-dihydro-1,4-dimethyl-3H-1,4-benzodiazepin-2-one, $C_{17}H_{15}Cl_3N_2O$

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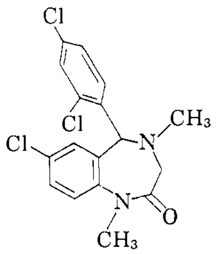
Abstract: The compound crystallizes in the triclinic space group, P1, with two molecules per unit cell. The cell parameters are: $a = 8.84$, $b = 10.18$, $c = 10.80$ A, $\alpha = 93° 51'$, $\beta = 112° 33'$, $\gamma = 101° 39'$. The seven-membered ring contains two nitrogen atoms, one of which is pyramidal and the other planar. The -C(CO)(NCH_3)C- group is nearly planar but is rotated by 50° from the adjacent benzo group. The structure analysis was performed with the use of the symbolic addition procedure for phase determination.

Derivatives of 1,4-benzodiazepine are compounds which show psychotherapeutic properties. Many of these materials have been synthesized.[1] From a structural point of view it was desirable to establish the configuration of the seven-membered ring, especially since the two nitrogen atoms have a different basicity and each can be alkylated independently of the other.[1] The particular compound chosen for this X-ray diffraction analysis was



mp 150–153°

Experimental Section

The material, which was kindly supplied by Dr. R. I. Fryer of Hoffmann-LaRoche, Inc., crystallizes from hexane as colorless slender prisms elongated parallel to the *a* axis. The crystal belongs to the triclinic system, and its cell parameters as determined from precession photographs are: $a = 8.84 \pm 0.02$ A, $b = 10.18 \pm 0.02$ A, $c = 10.80 \pm 0.02$ A; $\alpha = 93° 51' \pm 20'$, $\beta = 112° 33' \pm 20'$, $\gamma = 101° 39' \pm 20'$. The density calculated for two molecules in the unit cell is 1.414 g cm^{-3}, while that determined by flotation in a $AgNO_3$ solution is 1.410 g cm^{-3}.

Intensity data were collected photographically for a crystal of size 0.7 × 0.1 × 0.1 mm mounted on the *a* axis for the 0 through the sixth layer with the multiple film, equiinclination Weissenberg technique using Cu radiation with a Ni filter. Because of the crystal habit, satisfactory photographs along other axes could not be obtained for cross-correlation of intensities. Accordingly, the layer photographs along the *a* axis were taken under controlled conditions of exposure and development. The crystal scattered strongly to the limit of the reciprocal sphere. The total number of reflections recorded was 2310 of which 1784 were assigned intensity values greater than zero. The intensities were estimated by visual comparison to a calibrated film strip. Corrections were made for spot size and Lorentz and polarization factors. Both structure factor magnitudes, $|F|$, and normalized structure factor magnitudes, $|E|$, were computed. The largest $|F|$ recorded was for the $0\bar{2}2$ reflection with a value of 185 as compared to 390 for F_{000}. For the normalized structure factor magnitudes, the averages were $\langle|E|\rangle = 0.75$ and $\langle|E^2 - 1|\rangle = 0.98$, indicating that the crystal has a center of symmetry and that the space group is $P\bar{1}$.

Structure Analysis

The structure was solved by obtaining phases directly from the structure factor magnitudes with the use of the symbolic addition procedure,[2,3] a method for implementing the phase-determining formula (34) of Karle and Hauptman[4] by means of probability measures. To carry out the procedure, three reflections with large $|E|$, $0\bar{6}7$, $1\bar{4}6$, and $1\bar{3}\bar{2}$, were assigned + signs to fix the origin of the unit cell, and symbols *p*, *q*, and *r* were assigned to represent the signs of $0\bar{2}2$, $3\bar{6}\bar{6}$, and 1,2,10, respectively. With these six assignments, the signs of nearly all the reflections with $|E| > 1.5$ were determined as + or functions of *p*, *q*, and *r*. During the course of the determination many relationships indicated that $r \equiv +$ and $p \equiv r$. The most consistent model would then have the assignment $p \equiv +$, $q \equiv -$, and $r \equiv +$, where *q* was assigned the − sign to avoid all positive phases. The most consistent set of phases, however, was incorrect. This is a frequent occurrence, and other examples of determinations where the most consistent set of phases was not the correct solution were those of the structures of jamine,[5] β-fumaric acid,[6] and auramine perchlorate.[7] The correct assignment in this investigation was $p \equiv -$, $q \equiv -$, and $r \equiv +$. An *E* map computed with 270 terms ($|E| > 1.5$) revealed the coordinates of all the atoms.

The coordinates were refined by means of a least-squares program in which the function $\Sigma(F_o - F_c)^2$ was minimized. The atomic scattering factors were taken from the International Tables for X-ray Crystallography.[8] During the isotropic refinement the scale factors for individual layers were allowed to vary. For the anisotropic refinement, the scale factors were kept constant. There was no further improvement in the isotropic refinement at $R = 0.17$. The isotropic thermal factors are listed in the last column of Table I. Several cycles of refinement with anisotropic thermal parameters decreased the *R* factor to 13.6%. At this point, a difference map was computed which is illustrated on the left-hand side of Figure 1. Contours

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[1] *E.g.*, R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, 7, 386 (1964).

[2] I. L. Karle and J. Karle, *Acta Cryst.*, 16, 969 (1963).

[3] J. Karle and I. L. Karle, *ibid.*, 21, 849 (1966).

[4] J. Karle and H. Hauptman, *ibid.*, 3, 181 (1950).

[5] I. L. Karle and J. Karle, *ibid.*, 17, 1356 (1964).

[6] A. Bednowitz and B. Post, *ibid.*, 21, 566 (1966).

[7] A. V. Fratini, I. L. Karle, and J. Karle, to be published.

[8] "International Tables for X-Ray Crystallography," The Kynoch Press, Birmingham, England, 1962.

Table I. Fractional Coordinates for 7-Chloro-5-(2,4-dichlorophenyl)-4,5-dihydro-1,4-dimethyl-3H-1,4-benzodiazepin-2-one[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	B
Cl(1)	1.4726	1.0311	0.7356	126	183	144	−31	60	60	5.1
Cl(2)	0.8063	0.8840	0.6143	103	138	66	26	7	69	3.0
Cl(3)	0.9436	0.3175	0.5484	186	91	94	51	59	−3	3.5
C(1)	1.3039	0.9445	0.7726	52	84	90	−38	27	24	2.8
C(2)	1.1426	0.9524	0.6938	128	74	63	9	20	19	2.7
C(3)	1.0123	0.8784	0.7208	69	79	32	27	−15	19	1.8
C(4)	1.0356	0.7986	0.8240	102	47	59	18	31	28	1.8
C(5)	1.2067	0.7997	0.9048	100	51	99	7	11	42	2.5
C(6)	1.3403	0.8701	0.8813	94	79	110	20	22	24	3.2
C(7)	0.8893	0.7175	0.8491	87	52	44	3	10	24	1.3
C(8)	0.8137	0.5758	0.7629	42	69	22	13	−8	27	1.2
C(9)	0.9071	0.5191	0.7026	57	52	34	27	−5	18	1.4
C(10)	0.8286	0.3905	0.6241	79	67	64	31	26	27	2.0
C(11)	0.6700	0.3229	0.6044	120	66	65	12	−10	−8	2.3
C(12)	0.5798	0.3769	0.6644	130	85	112	−35	30	3	3.3
C(13)	0.6569	0.5048	0.7485	72	83	46	23	33	30	1.7
N(14)	0.5677	0.5609	0.8148	76	96	66	26	34	45	2.8
C(15)	0.3815	0.5496	0.7412	39	238	119	75	41	63	4.3
C(16)	0.6413	0.6112	0.9519	133	88	88	45	71	61	2.7
O(17)	0.5655	0.6594	1.0103	176	148	85	102	91	48	3.7
C(18)	0.8253	0.5980	1.0204	101	75	59	35	39	50	1.6
N(19)	0.9494	0.7043	0.9979	110	57	33	37	3	27	1.6
C(20)	0.9752	0.8356	1.0790	290	51	59	1	35	3	2.7
				Standard deviations						
Cl	0.0006	0.0004	0.0003	10	4	4	5	5	4	
C	0.0019	0.0011	0.0010	30	11	11	16	16	10	
N	0.0014	0.0009	0.0008	25	10	8	13	12	7	
O	0.0014	0.0009	0.0008	28	12	10	15	14	9	

[a] These coordinates are so chosen that they may be substituted directly in eq 1–4. The thermal parameters are of the form $T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$. Each thermal parameter is multiplied by 10^4. The last column lists the isotropic thermal parameter obtained before anisotropic refinement.

Table II. Bond Distances and Angles

Bond	Distance, A	Angle	Deg
C(1)–Cl(1)	1.769	Cl(1)–C(1)–C(2)	118.6
		Cl(1)–C(1)–C(6)	118.8
C(3)–Cl(2)	1.756	Cl(2)–C(3)–C(2)	116.7
		Cl(2)–C(3)–C(4)	119.3
C(10)–Cl(3)	1.764	Cl(3)–C(10)–C(9)	117.2
		Cl(3)–C(10)–C(11)	120.4
C(1)–C(2)	1.374	C(1)–C(2)–C(3)	117.4
C(2)–C(3)	1.384	C(2)–C(3)–C(4)	124.0
C(3)–C(4)	1.399	C(3)–C(4)–C(5)	115.4
C(4)–C(5)	1.424	C(4)–C(5)–C(6)	122.9
C(5)–C(6)	1.372	C(5)–C(6)–C(1)	117.6
C(6)–C(1)	1.408	C(6)–C(1)–C(2)	122.6
C(4)–C(7)	1.514	C(3)–C(4)–C(7)	122.4
		C(5)–C(4)–C(7)	122.2
		C(4)–C(7)–N(19)	109.0
C(7)–C(8)	1.532	C(4)–C(7)–C(8)	112.8
		N(19)–C(7)–C(8)	109.5
C(8)–C(9)	1.411	C(8)–C(9)–C(10)	116.5
C(9)–C(10)	1.396	C(9)–C(10)–C(11)	122.4
C(10)–C(11)	1.359	C(10)–C(11)–C(12)	121.3
C(11)–C(12)	1.372	C(11)–C(12)–C(13)	118.1
C(12)–C(13)	1.412	C(12)–C(13)–C(8)	120.4
C(13)–C(8)	1.372	C(13)–C(8)–C(9)	121.2
		C(7)–C(8)–C(9)	119.9
		C(7)–C(8)–C(13)	118.9
C(13)–N(14)	1.421	C(8)–C(13)–N(14)	120.4
		C(12)–C(13)–N(14)	119.1
N(14)–C(15)	1.503	C(13)–N(14)–C(15)	120.4
N(14)–C(16)	1.379	C(13)–N(14)–C(16)	121.8
		C(15)–N(14)–C(16)	117.2
C(16)–O(17)	1.226	N(14)–C(16)–O(17)	122.4
C(16)–C(18)	1.545	N(14)–C(16)–C(18)	112.4
		O(17)–C(16)–C(18)	125.2
C(18)–N(19)	1.481	C(16)–C(18)–N(19)	113.6
N(19)–C(20)	1.474	C(18)–N(19)–C(20)	110.1
N(19)–C(7)	1.510	C(18)–N(19)–C(7)	110.5
		C(20)–N(19)–C(7)	109.9

which correspond to the positions of 14 of the 15 hydrogen atoms are plotted at the 0.50- and 0.75-electron/A^3 levels. Seven other peaks of the same order of magnitude as those corresponding to hydrogen atoms also occurred in the difference map. Three of these peaks corresponded to the positions of the three chlorine atoms indicating that the scattering factor used for chlorine was not completely compatible with the physical situation. Three other extra peaks occurred at large distances from the molecule and could be considered entirely spurious. The seventh extra peak occurred near the expected position of H(7), the missing hydrogen atom, but at too great a distance for a C–H bond. Inclusion of 14 hydrogen atoms as constant parameters in the least-squares refinement reduced the R factor to 12.8%.[9]

The coordinates of the atoms are listed in Table I. The general shape of the molecule can be seen in Figures 1 and 2, and the bond distances and angles are shown in Figures 3a and b and Table II. The standard deviations range from 0.018 A for C–Cl bonds to 0.024 A for C–C bonds. For the angles, the standard deviations are of the order of 1.0 to 1.4°.

Least-squares planes have been computed[10] for atoms C(1) through C(6) (I), for atoms C(8) through C(13) (II), for the N(CO)C group (III), and for N(14) and the three adjacent carbon atoms (IV). The equations for

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[9] Observed and calculated structure factors have been deposited as Document No. 9084 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington, D. C. A copy may be secured by citing the document number and by remitting $2.50 for photoprints, or $1.25 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

[10] V. Schomaker, J. Waser, R. E. Marsh, and G. Bergman *Acta. Cryst.*, 12, 600 (1959).

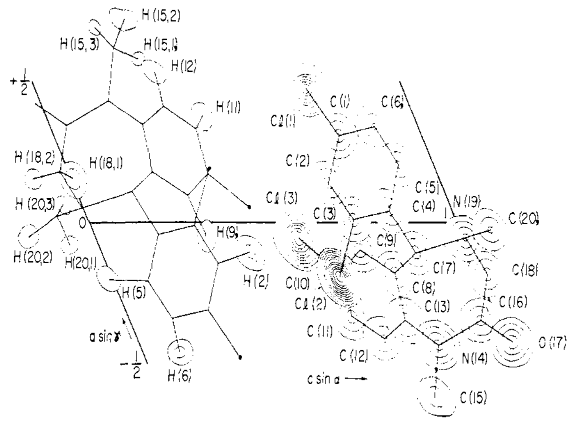


Figure 1. The contents of a unit cell projected on the (010) plane. The direction of the *b* axis is up. The final electron density map is represented on the right where the contours are spaced by 2 e A^{-3} beginning with the 2 e A^{-3} level. On the left is the difference map from which the hydrogen atoms were located. The contours are 0.50 and 0.75 e A^{-3}.

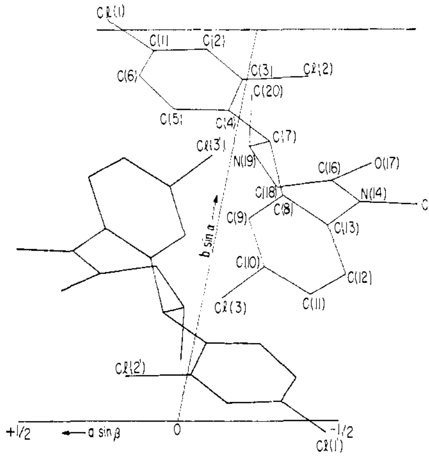


Figure 2. The contents of a unit cell projected on the (001) plane. The direction of the *c* axis is down.

these planes, referred to the triclinic axes, are

$$\text{(I)} \quad -2.9542x + 7.6898y + 6.4496z = 8.4104 \quad (1)$$

$$\text{(II)} \quad 1.7192x - 6.0264y + 7.9898z = 4.0440 \quad (2)$$

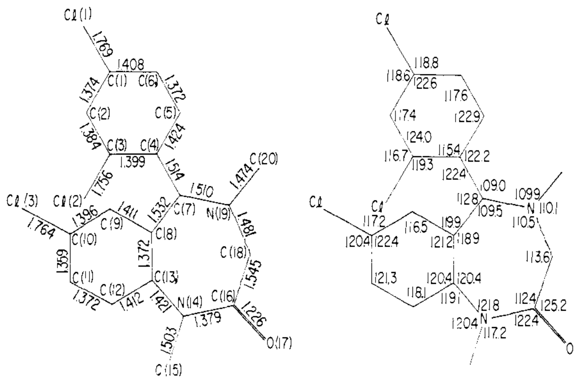
$$\text{(III)} \quad 2.2816x + 8.9105y - 4.4622z = 2.6587 \quad (3)$$

$$\text{(IV)} \quad 1.6040x + 9.1297y - 4.6533z = 2.1948 \quad (4)$$

where the value on the right is the origin-to-plane distance in Ångstrom units. Figure 4 illustrates the deviations of atoms from three of these planes.

Discussion

Nitrogen atoms in saturated aliphatic compounds such as hexamethylenediamine[11] and jamine (**1**)[5] assume the pyramidal configuration with C–N bond lengths of 1.46–1.50 A. On the other hand, nitrogen atoms adjacent to C═S, C═O, and C═C, for example, tend to be in the planar configuration with foreshortened C–N bond lengths in the range 1.34–1.40 A. Some examples are uric acid (**2**),[12] which is completely planar with C–N bonds ranging from 1.36 to 1.40 A; antabuse (**3**),[13]



(a) (b)

Figure 3. (a) Bond distances. (b) Bond angles.

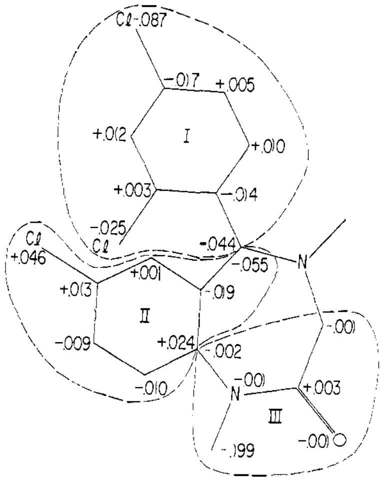
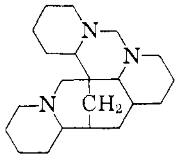


Figure 4. Deviations in Ångstrom units from least-squares planes: plane I, through atoms C(1) to C(6); plane II, through atoms C(8) to C(13); plane III, through the atoms N(CO)C. The dihedral angle between planes I and II is 87.5°, and between planes II and III it is 50.3°.

where each nitrogen atom is planar and the C–N bonds adjacent to the C═S groups are 1.33 and 1.36 A; and tetramethyl-*p*-phenylenediamine (**4**),[14] which is planar



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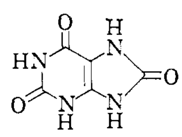

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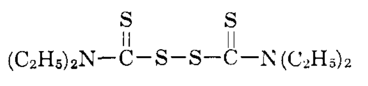
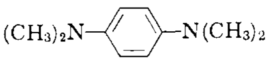
except for the methyl hydrogen atoms, and the C–N distance adjacent to the phenyl group is 1.37 A. A derivative of **5**[15] has two different kinds of nitrogen atoms.



$$(C_2H_5)_2N{-}\overset{\overset{\large S}{\|}}{C}{-}S{-}S{-}\overset{\overset{\large S}{\|}}{C}{-}N(C_2H_5)_2$$

3



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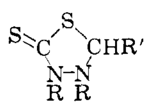

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(11) C. J. Brown, *Acta. Cryst.*, **21**, 185 (1966).

(12) H. Ringertz, *ibid.*, **20**, 397 (1966).

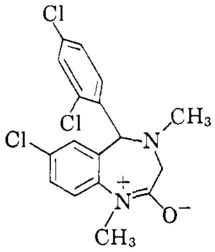
(13) I. L. Karle, J. A. Estlin, and K. Britts, *ibid.*, in press.

(14) A. W. Hanson, *ibid.*, **19**, 610 (1965).

(15) I. L. Karle and J. Karle, *ibid.*, **19**, 92 (1965).

The nitrogen atom adjacent to the CHR′ group is in the pyramidal configuration with a C–N bond length of 1.51 A, while the nitrogen atom adjacent to the C═S group is planar with a much shorter C–N bond length of 1.36 A.

Similarly in the present investigation, the two nitrogen atoms in the seven-membered ring are quite different. N(19) is surrounded by three saturated carbon atoms. The three C–N–C angles involving N(19) are 109.9, 110.1, and 110.5°, which are very close to the tetrahedral value. Furthermore, the three C–N bonds involving N(19) are 1.474, 1.481, and 1.510 A with standard deviations of the order of 0.02 A, values which are usually observed for C–N single bonds. On the other hand, N(14) is located between a benzene ring and a C═O group. On the basis of the previous discussion, one may assume that N(14) may be planar with C–N bonds shorter than the single bond value. In fact, the three C–N–C angles involving N(14) are 117.2, 120.4, and 121.8°. The deviation from coplanarity of N(14) from the plane of the three adjacent carbon atoms is 0.06 A. The C–N bond length between N(14) and the CH_3 group is 1.50 A, a normal single bond. However, the C–N bond length between N(14) and the C═O group is only 1.38 A, a value in agreement with those found for comparable bonds in molecules like uric acid[12] and alloxan.[16] The short C–N bond length suggests contributions to the total structure from conjugation effects of the type



The least-squares planes involving N(14) are III (atoms N(14), C(16), O(17) C(18)) and IV (atoms C(13), N(14), C(15), C(16)). They are almost coplanar, the dihedral angle between them being 5° 20′. In Figure 4 the deviations from plane III are shown not only for the four atoms used to compute the equation of the plane but C(13) and C(15) as well. The 0.2-A deviation of the methyl carbon atom C(15) from plane III may in part be accounted for by the large anisotropic thermal motion of this atom.

It is interesting to note that plane III is not coplanar with plane II, the plane of the adjacent benzene ring, but is rotated about the C(13)–N(14) bond by 50.3°. The rotation is probably caused by the constraints imposed by closing the seven-membered ring. Accordingly, bond C(13)–N(14), which is adjacent to the benzene ring, is 1.42 A, not as short as the C(16)–N(14) bond although considerably shorter than the single bond value. The differences in the structural features of the two nitrogen atoms N(14) and N(19) seem to be reflected in their chemical behavior. The two nitrogen atoms have a different basicity, and each can be alkylated independently of the other.[1]

The configuration of the seven-membered ring is of particular interest since molecular structures have not been determined for many compounds containing seven-membered rings. Unsaturated seven-membered rings as in azulene[17] are planar. In longifolene[18] the saturated seven-membered ring is in the boat configuration with angles ranging from 114 to 118°, and in diazobicyclooctylpyridine[19] the seven-membered ring is also a boat, but the angles range from 104 to 113°. In the present molecule the configuration can be seen best in Figure 2. It can be described approximately as having a fold between atoms C(8) and C(18) and then having the N(19) end twisted with respect to the N(14) end. At the N(19) end where both N(19) and the adjacent C(7) have tetrahedral angles, the phenyl group on C(7) and the methyl group on N(19) occur in the *trans* configuration with respect to each other.

Planes I and II, Figure 4, which describe the two benzene rings, show that the two rings are reasonably planar, within 0.02 A. The atoms attached to the ring, however, deviate from coplanarity by as much as 0.09 A for Cl(1). Molecules such as *p*-dichlorobenzene[20] and 1,3,5-trichlorobenzene[21] were found to be completely planar with deviations from coplanarity within 0.01 A at liquid air temperatures. The deviations of the chlorine atoms from coplanarity with the benzene rings in the present molecule appear to be associated with the thermal factors. Cl(1) has the largest thermal factor and the largest deviation.

The dihedral angle between planes I and II is 87°. This large rotation about the C(4)–C(7) bond allows Cl(2) and Cl(3) to be separated by 4.38 A. In fact, in the packing of the molecules, all the chlorine separations, both intra- and intermolecular, are much larger than 4 A except for Cl(3)–Cl(3′) at 3.96 A and Cl(1)–Cl(2′) at 3.90 A. The lighter atoms in adjacent molecules approach each other more closely. The distance through a center of symmetry between O(17) and O(17″) is only 3.18 A. Other close approaches are 3.24 A between C(6) and O(17‴) at $1 + x, y, z$, and 3.41 A between C(2) and Cl(3′).

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(16) C. Singh, *Acta. Cryst.*, **19**, 759 (1965).

(17) J. M. Robertson, H. M. M. Shearer, G. A. Sim, and D. G. Watson, *ibid.*, **15**, 1 (1962).

(18) A. F. Cesur and D. F. Grant, *ibid.*, **18**, 55 (1965).

(19) I. L. Karle and K. Britts, *ibid.*, 21, 532 (1966).

(20) E. Frasson, C. Garbuglio, and S. Bezzi, *ibid.*, **12**, 126 (1959).

(21) H. J. Milledge and L. M. Plant, *ibid.*, **13**, 285 (1960).