

ein Ag(3) in 3,07 Å und ein Ag(2) in 3,09 Å auf. Die Temperaturkoeffizienten der Ag sind gross und stark anisotrop (grosse Schwingungsamplituden normal zur Ebene der drei koordinierten S).

S(1) weist ein stark deformiertes, S(3) ein ziemlich regelmässiges tetraedrisches und S(2) ein polares, einseitiges Koordinationsschema auf. Die (S–Ag, As)-Abstände sind aus Tabelle 4 ersichtlich.

Diese Modifikation von Ag_3AsS_3 ist offensichtlich instabiler als Proustit (selteneres Vorkommen von Xanthokon, dreierlei kristallographisch verschiedene Ag-Atome mit z.T. ungewöhnlicher Koordination).

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The Crystal Structure of the Alkaloid Reserpine, $\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_9$

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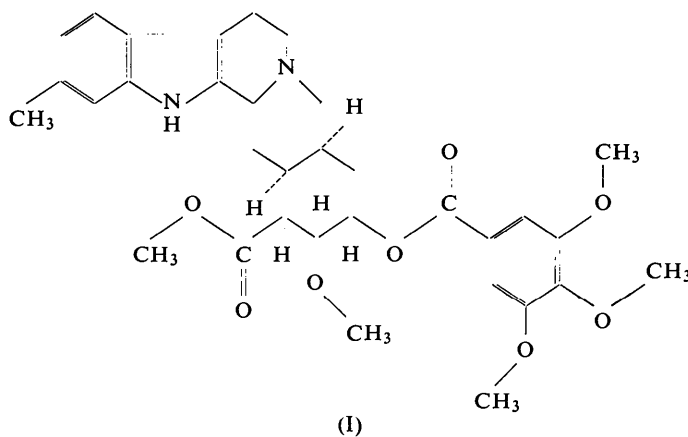
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Reserpine crystallizes in space group $P2_1$ with $Z=2$ and cell parameters $a=14.45$, $b=8.98$, $c=13.37$ Å and $\beta=115.2^\circ$. The asymmetric unit contains forty-four atoms (excluding hydrogen) of nearly equal atomic number. The structure was solved by obtaining phases directly from the magnitudes of the structure factors. The application of the symbolic addition procedure yielded a partial structure and the further use of the tangent formula based upon a recycling procedure using the partial structure yielded the complete structure. The configuration (not absolute) of the molecule as determined by chemical means is confirmed by the X-ray results.

Introduction

The Indian snake-root, *Rauwolfia serpentina* Benth., contains a large number of closely related alkaloids. One of these, reserpine, has been found to be an important and effective drug for the treatment of hypertensive, nervous and mental disorders. Reserpine was isolated in 1952 (Müller, Schlittler & Bein) and its structural formula (I) was established soon afterwards (Dorfman, Huebner, MacPhillamy, Schlittler & St. André, 1953; Dorfman, Furlenmeier, Huebner, Lucas, MacPhillamy, Mueller, Schlittler, Schwyzer & St. André, 1954). The stereochemistry has been established by chemical means (Aldrich, Diassi, Dickel, Dylion, Hance, Huebner, Korzun, Kuehne, Liu, MacPhillamy, Robb, Roychaudhuri, Schlittler, St. André, van Tamelen, Weissenborn, Wenkert & Wintersteiner, 1959) and a total synthesis has been performed (Woodward, Bader, Bickel, Frye & Kierstead, 1958). There remained to show only the spatial arrangement of the atoms in the molecule and the crystal.



This problem provided an opportunity to apply the symbolic addition procedure for noncentrosymmetric space groups (Karle & Karle, 1966a) which yielded a partial structure. Using the phase information from the partial structure in a recycling procedure (Karle, 1968) with the tangent formula (Karle & Hauptman,

1956) the complete structure was obtained. The facility with which the structure was obtained for this molecule possessing forty-four atoms exclusive of hydrogen and without a heavy atom substituent, indicates that the limit of the method has not been reached.

Experimental

Commercially available reserpine was recrystallized from hot ethanol to form colorless prisms. The cell dimensions were obtained from precession photographs taken with Cu $K\alpha$ radiation. They were:

$$\begin{aligned} a &= 14.45 \pm 0.02 \text{ \AA} \\ b &= 8.98 \pm 0.02 \\ c &= 13.37 \pm 0.02 \\ \beta &= 115^\circ 12' \pm 15'. \end{aligned}$$

These values differ from those obtained by Rose (1954) from a powder pattern which were: $a = 14.57$, $b = 8.81$, $c = 13.54 \text{ \AA}$, $\beta = 115^\circ 08'$. The computed density from the precession values is 1.287 g.cm^{-3} for two molecules in the unit cell while the density measured by flotation is 1.298 g.cm^{-3} (Rose, 1954). Systematic absences occurred only for $0k0$ reflections with k odd; hence the space group $P2_1$ was assigned.

Intensity data were collected by the multiple-film, equi-inclination Weissenberg technique. The intensities of the diffraction spots were estimated visually by comparison with a calibrated film strip. All available layers on all three axes were recorded and read. However, the full sphere of data for copper radiation was not obtained since the diffraction patterns faded at $\theta \sim 65^\circ$. The number of independent data was 2788. The data from all three axes were corrected for spot size, and Lorentz and polarization factors. The data were cross-correlated and placed on an absolute scale by means of a K curve. Both structure factor magnitudes $|F|$ and normalized structure factor magnitudes $|E|$ were computed. The values of the statistical averages for $\langle |E| \rangle$ and $\langle |E^2 - 1| \rangle$ for the noncentrosymmetric reflections were 0.851 and 0.780 as compared with 0.886 and 0.736, the theoretical values for noncentrosymmetric space groups.

Phase determination

The initial phases were determined by the symbolic addition procedure for noncentrosymmetric crystals as described previously (Karle & Karle, 1964, 1966*a,b*). The formula for starting the phase determination is

$$\varphi_h \approx \langle \varphi_k + \varphi_{h-k} \rangle_{k_r}. \quad (1)$$

To implement the use of (1), three phases were assigned to specify the origin (Hauptman & Karle, 1956) and during the determination four other reflections were assigned symbols to denote the phase. The assignments are listed in Table 1. Symbols a and b must be 0 or π to satisfy the space group requirements whereas symbols p and s can have values anywhere between $-\pi$ and π .

Table 1. Phase assignments for specifying the origin and implementing equation (1)

h	φ_h	$ E_h $
0 0 3	0	3.54
1 0 2	π	2.87
$\bar{1}\bar{2}$ 1 8	0	4.94
$\bar{1}\bar{2}$ 0 4	a	2.79
1 0 3	b	2.71
$\bar{6}$ 7 2	p	2.50
$\bar{1}\bar{1}$ 1 1	s	3.18

In the course of applying equation (1) to obtain 76 new phases ($|E| > 1.9$) from those already known in terms of 0, π , a , b , p or s , it soon became obvious that $a = \pi$, $b = 0$, and $s \approx 0$ or π . There were no strong indications for the value of p . Since we are dealing with a noncentrosymmetric crystal, it is expected that a number of phases should be near $\pm \pi/2$. Accordingly, p was assigned the value $+\pi/2$ which also effectively specified the enantiomorph.

The next step was to reiterate the determination of the initial 83 phases for the two cases, $s = 0$ and $s = \pi$, and to obtain additional phases by the use of the tangent formula (Karle & Hauptman, 1956)

$$\tan \varphi_h \approx \frac{\sum_k |E_k E_{h-k}| \sin(\varphi_k + \varphi_{h-k})}{\sum_k |E_k E_{h-k}| \cos(\varphi_k + \varphi_{h-k})}. \quad (2)$$

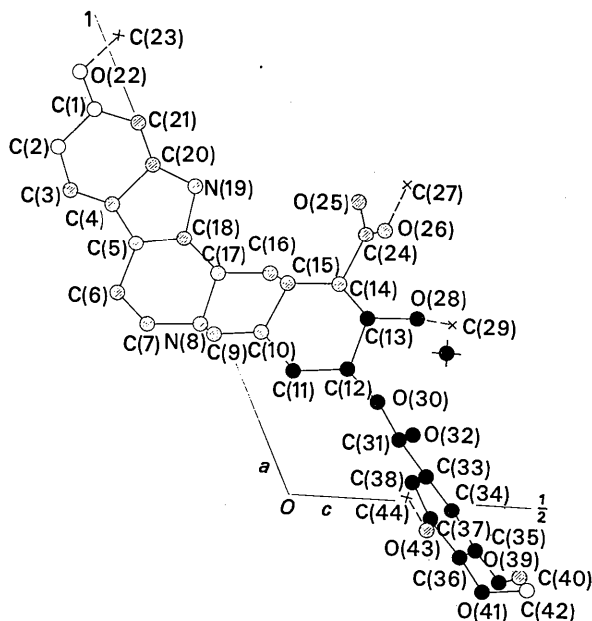


Fig. 1. The order of appearance of atoms in successive E maps. The solid circles mark atoms which appeared in the initial E map based on phases from the symbolic addition procedure. The shaded circles, open circles and \times 's mark the atoms as they appeared in three successive E maps based on phases obtained from the partially known structure and refined and expanded by recycling with the tangent formula. The \odot mark indicates a spurious peak which disappeared in the later E maps.

A total of ~ 710 phases with $|E| > 1.1$ was obtained from which the first E maps were computed. The map with $s=0$ was not meaningful, whereas the map with $s=\pi$ contained a recognizable portion of the molecule. The 16 largest peaks from this map are shown as full circles in Fig. 1. Fifteen of these peaks corresponded to atoms whereas the circle with a cross denotes a peak which proved to be spurious. There were eight other slightly weaker peaks which also corresponded to atoms but it was not obvious that they were meaningful at this stage of the analysis since they were not bonded to each other and therefore they were not included in the next step.

A procedure for obtaining the remainder of a structure by a recycling technique using the tangent formula (2) once a partial structure is known, has been described (Karle, 1968). Structure factors were computed on the basis of the 16 peaks, all weighted as carbon atoms, derived from the first E map. The phases were accepted for those reflections if both $|E| > 1.5$ and $|F_c| > 0.33|F_o|$. By use of the tangent formula (2) the values of these phases were recalculated and additional phases were obtained for those reflections with $|E| > 1.1$. An examination of the E map based on these new phases showed that of the 39 strongest peaks, 16 were identical with those chosen from the first map, 21 additional peaks were identified as corresponding to atoms and two rather weak peaks were obviously spurious. The positions of the 21 new atoms are denoted by the shaded circles in Fig. 1.

The procedure was repeated by computing structure factors based on 37 atoms, all weighted as carbon atoms, and accepting those phases if both $|E| > 1.5$ and $|F_c| > 0.6|F_o|$. The new set of phases was recomputed and additional phases for $|E| > 1.1$ were obtained through the use of the tangent formula. Additional atoms located in the E map computed from the third set of phases are shown as open circles in Fig. 1. In addition, the spurious peak, indicated by a circle with a cross, which had been included in the last two cycles, became quite weak and its position was moving toward the position of C(29), not yet located in the E maps.

One more cycle was needed to locate the remaining atoms. The atoms found in the last cycle, indicated by \times 's in Fig. 1, were several of the carbon atoms of peripheral methyl groups which have relatively large thermal factors.

After the structure was refined it was of interest to make some comparisons between the phases from the

refined structure and the phases as determined in the initial and intermediate stages. Table 2 shows the progress of the value of the phase expressed in radians for several reflections with large $|E|$ magnitudes. For the last two reflections listed, 844 and $\bar{3}, 3, 12$, the phase was not obtained from the use of equation (1) but from the initial application of the tangent formula. An examination of the 83 phases initially obtained by equation (1) showed that the average error in phase was 0.45 radians. After using the tangent formula the average error decreased slightly to 0.42 radians. For phases based on the partial structure of 16 atoms which were recomputed with the tangent formula, the average error for the 83 phases decreased to 0.31 radians and to 0.12 radians for those based on the 37 atom structure.

One difficulty encountered in the determination should be mentioned. The first attempt with the symbolic addition procedure using equation (1) did not succeed in that the initial E maps appeared to be meaningless. The procedure was repeated with a different choice for one of the reflections to which an unknown symbol was assigned and proved to be successful. Once the structure was known, the first attempt was reexamined and the difficulty was readily discovered. It concerned the failure of equation (1) for the $\bar{4}73$ reflection in the following manner:

	$ E $	Symbolic addition	Actual (radians)
$\bar{1}0\ 1\ 9$	2.45	π	2.59
$6\ 6\ \bar{6}$	2.11	$+\pi/2$	1.32
$\bar{4}\ 7\ 3$	2.28	$-\pi/2$	-2.37 (should be +0.74)
$\bar{9}\ 1\ 12$	2.02	π	2.84
$5\ 6\ \bar{9}$	1.94	$+\pi/2$	2.16
$\bar{4}\ 7\ 3$	2.28	$-\pi/2$	-1.28 (should be +0.74)

The phase indicated for $\bar{4}73$ was in error by nearly π . This error propagated others. The different starting point for implementing equation (1) avoided these particular interactions.

Refinement

The coordinates of the 44 C, N and O atoms as obtained from the last E map (Fig. 1) were subjected to a least-squares refinement in a modified ORFLS program (Busing, Martin & Levy, 1962) in which all the parameters could be accommodated. The quantity

Table 2. Comparison of phases (expressed in radians) at various stages of the structure determination

$h\ k\ l$	7 6 2	$\bar{1}\bar{3}\ 1\ 3$	$\bar{1}\ 2\ 1$	9 4 5	$\bar{4}\ 7\ 3$	8 4 4	$\bar{3}\ 3\ 12$
$ E $	(2.54)	(2.43)	(2.42)	(2.40)	(2.28)	(2.18)	(1.93)
eq. (1)	-1.57	3.14	3.14	1.57	1.57		
eq. (1) + eq. (2)	-1.59	-3.09	-3.13	1.43	1.59	-1.61	1.22
16 atoms + eq. (2)	-1.43	-3.07	2.98	1.37	1.18	-1.87	2.08
37 atoms + eq. (2)	-1.70	-2.88	2.25	1.24	0.80	-1.72	2.40
least-squares on 44 atoms	-1.90	-2.97	2.14	1.18	0.74	-1.61	2.51

$\Sigma(F_o - F_c)^2$ was minimized and the atomic scattering factors used were those listed in *International Tables for X-ray Crystallography*. The initial R value was 26%, which was readily reduced to 15% with isotropic refinement. In space group $P2_1$, it is ordinarily necessary to keep the y coordinate of some atom constant in order to fix the origin along the b axis. In the absence of a heavy atom in the molecule, it was found that keeping the y coordinate of one atom constant was not sufficient. Hence the y coordinates of six adjacent atoms were held constant. A different set of six atoms was held constant in different cycles.

The anisotropic refinement was performed in two sections. Parameters for atoms 1 through 11 and 14 through 27 were varied in one cycle and those for atoms 11 through 14 and 28 through 44 were varied in a succeeding cycle. Atoms 11 and 14 were evidently refined in each cycle. After several cycles refinement ceased at $R=11.3\%$. A difference map computed at this point is illustrated in Fig. 2. Eighteen hydrogen atoms were readily found. These are the hydrogen atoms which are attached to the central portion of the molecule which has the least thermal motion. Each of the six methyl carbon atoms has a rather high thermal motion and none of the hydrogen atoms associated with them could be located with any degree of certainty. When coordinates for the eighteen hydrogen atoms were included in the structure factor computation, the R value for the observed reflections decreased to 10.7%. The observed and calculated structure factors and the calculated phase φ are listed in Table 3.

Structure

The trimethoxybenzoxy group is nearly perpendicular to the remainder of the reserpine molecule. In order to illustrate the electron density map without undue overlap, the contours for atoms 1 through 29 are shown in the (010) projection in Fig. 3 and the contours for atoms 30 through 44 are shown in the (001) projection in Fig. 4. Table 4 contains the fractional coordinates, isotropic and anisotropic thermal parameters. Fig. 5 illustrates the contents of a unit cell and Fig. 6 shows stereodiagrams of the molecule (Johnson, 1965). The results of the crystal structure determination confirm the stereochemistry derived by chemical means.

The indole group is planar, only C(7) and N(8) are out of the plane in the adjacent ring, and the next two rings are in the chair conformation. Atom N(8) is pyramidal with bond angles near 111° . In the trimethoxybenzoxy group, steric effects prevent all three methoxy groups from being in or near the plane of the benzene ring. The methoxy groups containing atoms C(40) and C(44) are oriented in opposing directions and lie fairly close to the plane of the benzene ring, while the methoxy group containing C(42) is rotated 80° out of the plane of the benzene ring, *i.e.* 80° from its closest possible approach to C(37). There is no hydrogen bonding and the molecules pack in the unit

cell so as to have the many methyl groups in the vicinity of each other, especially near $z=\frac{1}{2}$ (Fig. 5). Nearest intermolecular approaches are 3.21 \AA between O(25) and C(40'), 3.55 \AA between O(25) and C(6'), and 3.32 \AA between O(28) and C(27'). The next nearest approaches are of the order of 3.70 \AA and greater between the layers of molecules in the b direction.

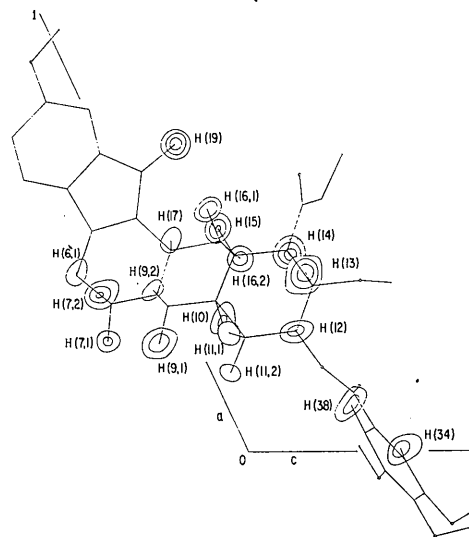


Fig. 2. Sections from a three-dimensional difference map. The contours are at $0.1 \text{ e.}\text{\AA}^{-3}$, beginning with the $0.2 \text{ e.}\text{\AA}^{-3}$ contour.

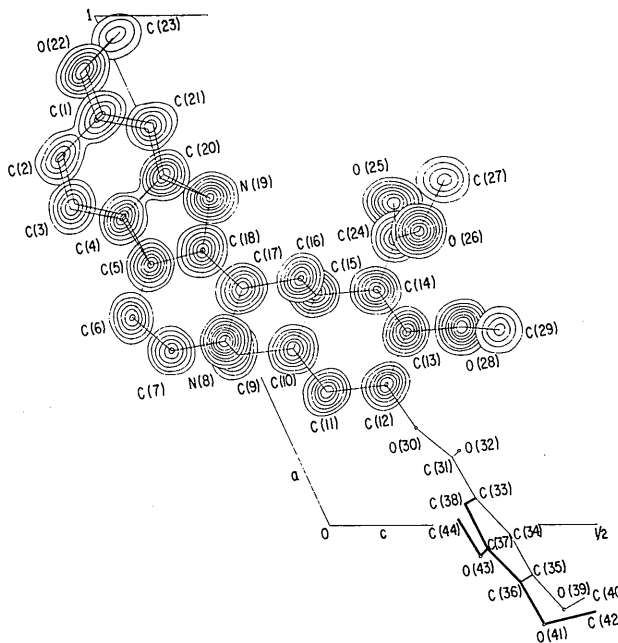


Fig. 3. Sections from a three-dimensional electron density map projected down the b axis. Contours are equally spaced at $1 \text{ e.}\text{\AA}^{-2}$, starting with the $1 \text{ e.}\text{\AA}^{-3}$ contour.

Table 3. Observed and calculated structure factors
 Successive columns contain I , $|F_{obs}|$, $|F_{calc}|$, and ϕ_{calc} (radians).

-18 0 L	4 6.8	3.1 -2.16	10 8.3	8.0 -1.14	4 2.1	2.2 1.43	10 8 L	5 3.8	3.6 -0.14	-8 8 L
5 3.0	2.9 0.00	7 3.2	3.0 -1.87	10 8.3	8.0 -1.14	4 2.1	2.2 1.43	5 3.8	3.6 -0.14	-8 8 L
6 4.0	2.6 0.00	8 3.2	3.1 1.16	11 10.5	10.3 -0.84	5 4.4	4.3 -0.25	6 3.8	3.9 -0.67	1 2.4
7 5.0	3.5 0.14	9 3.2	3.0 1.16	12 9.8	11.5 -2.31	6 7.5	4.3 0.08	7 3.0	4.4 2.79	2 3.9
8 6.5	5.7 0.00	10 4.0	2.0 -1.52	13 10.6	12.1 3.04	7 8.0	7.6 -1.38	8 3.0	2.7 0.32	3 3.1
9 8.0	1.1 0.00	11 5.0	4.0 -3.00	14 13.5	14.7 2.91	8 9.1	8.7 -0.81	9 2.0	3.6 -0.21	4 1.7
		12 6.1	2.6 -0.42	15 15.0	16.6 2.91	9 10.2	9.8 -1.11	10 0.0	4.3 -1.06	5 6.8
		13 4.4	3.4 1.24	16 17.0	19.1 3.10	10 11.3	10.8 -1.11	11 4.2	4.3 -0.17	6 8.0
		14 5.0	4.0 1.24	17 19.0	22.1 3.10	11 12.4	12.1 -1.11	12 4.2	4.3 -0.17	7 8.0
		15 6.0	4.0 1.24	18 21.0	25.1 3.10	12 13.5	13.2 -1.11	13 4.2	4.3 -0.17	8 8.0
		16 7.0	4.0 1.24	19 23.0	28.1 3.10	13 14.6	14.0 -1.11	14 4.2	4.3 -0.17	9 8.0
		17 8.0	4.0 1.24	20 25.0	31.0 3.10	14 15.7	14.8 -1.11	15 4.2	4.3 -0.17	10 8.0
		18 9.0	4.0 1.24	21 27.0	34.0 3.10	15 16.8	15.6 -1.11	16 4.2	4.3 -0.17	11 8.0
		19 10.0	4.0 1.24	22 29.0	37.0 3.10	16 17.9	16.4 -1.11	17 4.2	4.3 -0.17	12 8.0
		20 11.0	4.0 1.24	23 31.0	40.0 3.10	17 19.0	17.2 -1.11	18 4.2	4.3 -0.17	13 8.0
		21 12.0	4.0 1.24	24 33.0	43.0 3.10	18 20.1	18.0 -1.11	19 4.2	4.3 -0.17	14 8.0
		22 13.0	4.0 1.24	25 35.0	46.0 3.10	19 21.2	18.8 -1.11	20 4.2	4.3 -0.17	15 8.0
		23 14.0	4.0 1.24	26 37.0	49.0 3.10	20 22.3	19.6 -1.11	21 4.2	4.3 -0.17	16 8.0
		24 15.0	4.0 1.24	27 39.0	52.0 3.10	21 23.4	20.4 -1.11	22 4.2	4.3 -0.17	17 8.0
		25 16.0	4.0 1.24	28 41.0	55.0 3.10	22 24.5	21.2 -1.11	23 4.2	4.3 -0.17	18 8.0
		26 17.0	4.0 1.24	29 43.0	58.0 3.10	23 25.6	22.0 -1.11	24 4.2	4.3 -0.17	19 8.0
		27 18.0	4.0 1.24	30 45.0	61.0 3.10	24 26.7	22.8 -1.11	25 4.2	4.3 -0.17	20 8.0
		28 19.0	4.0 1.24	31 47.0	64.0 3.10	25 27.8	23.6 -1.11	26 4.2	4.3 -0.17	21 8.0
		29 20.0	4.0 1.24	32 49.0	67.0 3.10	26 28.9	24.4 -1.11	27 4.2	4.3 -0.17	22 8.0
		30 21.0	4.0 1.24	33 51.0	70.0 3.10	27 30.0	25.2 -1.11	28 4.2	4.3 -0.17	23 8.0
		31 22.0	4.0 1.24	34 53.0	73.0 3.10	28 31.1	26.0 -1.11	29 4.2	4.3 -0.17	24 8.0
		32 23.0	4.0 1.24	35 55.0	76.0 3.10	29 32.2	26.8 -1.11	30 4.2	4.3 -0.17	25 8.0
		33 24.0	4.0 1.24	36 57.0	79.0 3.10	30 33.3	27.6 -1.11	31 4.2	4.3 -0.17	26 8.0
		34 25.0	4.0 1.24	37 59.0	82.0 3.10	31 34.4	28.4 -1.11	32 4.2	4.3 -0.17	27 8.0
		35 26.0	4.0 1.24	38 61.0	85.0 3.10	32 35.5	29.2 -1.11	33 4.2	4.3 -0.17	28 8.0
		36 27.0	4.0 1.24	39 63.0	88.0 3.10	33 36.6	30.0 -1.11	34 4.2	4.3 -0.17	29 8.0
		37 28.0	4.0 1.24	40 65.0	91.0 3.10	34 37.7	30.8 -1.11	35 4.2	4.3 -0.17	30 8.0
		38 29.0	4.0 1.24	41 67.0	94.0 3.10	35 38.8	31.6 -1.11	36 4.2	4.3 -0.17	31 8.0
		39 30.0	4.0 1.24	42 69.0	97.0 3.10	36 39.9	32.4 -1.11	37 4.2	4.3 -0.17	32 8.0
		40 31.0	4.0 1.24	43 71.0	100.0 3.10	37 41.0	33.2 -1.11	38 4.2	4.3 -0.17	33 8.0
		41 32.0	4.0 1.24	44 73.0	103.0 3.10	38 42.1	34.0 -1.11	39 4.2	4.3 -0.17	34 8.0
		42 33.0	4.0 1.24	45 75.0	106.0 3.10	39 43.2	34.8 -1.11	40 4.2	4.3 -0.17	35 8.0
		43 34.0	4.0 1.24	46 77.0	109.0 3.10	40 44.3	35.6 -1.11	41 4.2	4.3 -0.17	36 8.0
		44 35.0	4.0 1.24	47 79.0	112.0 3.10	41 45.4	36.4 -1.11	42 4.2	4.3 -0.17	37 8.0
		45 36.0	4.0 1.24	48 81.0	115.0 3.10	42 46.5	37.2 -1.11	43 4.2	4.3 -0.17	38 8.0
		46 37.0	4.0 1.24	49 83.0	118.0 3.10	43 47.6	38.0 -1.11	44 4.2	4.3 -0.17	39 8.0
		47 38.0	4.0 1.24	50 85.0	121.0 3.10	44 48.7	38.8 -1.11	45 4.2	4.3 -0.17	40 8.0
		48 39.0	4.0 1.24	51 87.0	124.0 3.10	45 49.8	39.6 -1.11	46 4.2	4.3 -0.17	41 8.0
		49 40.0	4.0 1.24	52 89.0	127.0 3.10	46 50.9	40.4 -1.11	47 4.2	4.3 -0.17	42 8.0
		50 41.0	4.0 1.24	53 91.0	130.0 3.10	47 52.0	41.2 -1.11	48 4.2	4.3 -0.17	43 8.0
		51 42.0	4.0 1.24	54 93.0	133.0 3.10	48 53.1	42.0 -1.11	49 4.2	4.3 -0.17	44 8.0
		52 43.0	4.0 1.24	55 95.0	136.0 3.10	49 54.2	42.8 -1.11	50 4.2	4.3 -0.17	45 8.0
		53 44.0	4.0 1.24	56 97.0	139.0 3.10	50 55.3	43.6 -1.11	51 4.2	4.3 -0.17	46 8.0
		54 45.0	4.0 1.24	57 99.0	142.0 3.10	51 56.4	44.4 -1.11	52 4.2	4.3 -0.17	47 8.0
		55 46.0	4.0 1.24	58 101.0	145.0 3.10	52 57.5	45.2 -1.11	53 4.2	4.3 -0.17	48 8.0
		56 47.0	4.0 1.24	59 103.0	148.0 3.10	53 58.6	46.0 -1.11	54 4.2	4.3 -0.17	49 8.0
		57 48.0	4.0 1.24	60 105.0	151.0 3.10	54 59.7	46.8 -1.11	55 4.2	4.3 -0.17	50 8.0
		58 49.0	4.0 1.24	61 107.0	154.0 3.10	55 60.8	47.6 -1.11	56 4.2	4.3 -0.17	51 8.0
		59 50.0	4.0 1.24	62 109.0	157.0 3.10	56 61.9	48.4 -1.11	57 4.2	4.3 -0.17	52 8.0
		60 51.0	4.0 1.24	63 111.0	160.0 3.10	57 63.0	49.2 -1.11	58 4.2	4.3 -0.17	53 8.0
		61 52.0	4.0 1.24	64 113.0	163.0 3.10	58 64.1	50.0 -1.11	59 4.2	4.3 -0.17	54 8.0
		62 53.0	4.0 1.24	65 115.0	166.0 3.10	59 65.2	50.8 -1.11	60 4.2	4.3 -0.17	55 8.0
		63 54.0	4.0 1.24	66 117.0	169.0 3.10	60 66.3	51.6 -1.11	61 4.2	4.3 -0.17	56 8.0
		64 55.0	4.0 1.24	67 119.0	172.0 3.10	61 67.4	52.4 -1.11	62 4.2	4.3 -0.17	57 8.0
		65 56.0	4.0 1.24	68 121.0	175.0 3.10	62 68.5	53.2 -1.11	63 4.2	4.3 -0.17	58 8.0
		66 57.0	4.0 1.24	69 123.0	178.0 3.10	63 69.6	54.0 -1.11	64 4.2	4.3 -0.17	59 8.0
		67 58.0	4.0 1.24	70 125.0	181.0 3.10	64 70.7	54.8 -1.11	65 4.2	4.3 -0.17	60 8.0
		68 59.0	4.0 1.24	71 127.0	184.0 3.10	65 71.8	55.6 -1.11	66 4.2	4.3 -0.17	61 8.0
		69 60.0	4.0 1.24	72 129.0	187.0 3.10	66 72.9	56.4 -1.11	67 4.2	4.3 -0.17	62 8.0
		70 61.0	4.0 1.24	73 131.0	190.0 3.10	67 74.0	57.2 -1.11	68 4.2	4.3 -0.17	63 8.0
		71 62.0	4.0 1.24	74 133.0	193.0 3.10	68 75.1	58.0 -1.11	69 4.2	4.3 -0.17	64 8.0
		72 63.0	4.0 1.24	75 135.0	196.0 3.10	69 76.2	58.8 -1.11	70 4.2	4.3 -0.17	65 8.0
		73 64.0	4.0 1.24	76 137.0	199.0 3.10	70 77.3	59.6 -1.11	71 4.2	4.3 -0.17	66 8.0
		74 65.0	4.0 1.24	77 139.0	202.0 3.10	71 78.4	60.4 -1.11	72 4.2	4.3 -0.17	67 8.0
		75 66.0	4.0 1.24	78 141.0	205.0 3.10	72 79.5	61.2 -1.11	73 4.2	4.3 -0.17	68 8.0
		76 67.0	4.0 1.24	79 143.0	208.0 3.10	73 80.6	62.0 -1.11	74 4.2	4.3 -0.17	69 8.0
		77 68.0	4.0 1.24	80 145.0	211.0 3.10	74 81.7	62.8 -1.11	75 4.2	4.3 -0.17	70 8.0
		78 69.0	4.0 1.24	81 147.0	214.0 3.10	75 82.8	63.6 -1.11	76 4.2	4.3 -0.17	71 8.0
		79 70.0	4.0 1.24	82 149.0	217.0 3.10	76 83.9	64.4 -1.11	77 4.2	4.3 -0.17	72 8.0
		80 71.0	4.0 1.24	83 151.0	220.0 3.10	77 85.0	65.2 -1.11	78 4.2	4.3 -0.17	73 8.0
		81 72.0	4.0 1.24	84 153.0	223.0 3.10	78 86.1	66.0 -1.11	79 4.2	4.3 -0.17	74 8.0
		82 73.0	4.0 1.24	85 155.0	226.0 3.10	79 87.2	66.8 -1.11	80 4.2	4.3 -0.17	75 8.0
		83 74.0	4.0 1.24	86 157.0	229.0 3.10	80 88.3	67.6 -1.11	81 4.2	4.3 -0.17	76 8.0
		84 75.0	4.0 1.24	87 159.0	232.0 3.10	81 89.4	68.4 -1.11	82 4.2	4.3 -0.17	77 8.0
		85 76.0	4.0 1.24	88 161.0	235.0 3.10	82 90.5	69.2 -1.11	83 4.2	4.3 -0.17	78 8.0
		86 77.0	4.0 1.24	89 163.0	238.0 3.10	83 91.6	70.0 -1.11	84 4.2	4.3 -0.17	79 8.0
		87 78.0	4.0 1.24	90 165.0	241.0 3.10	84 92.7	70.8 -1.11	85 4.2	4.3 -0.17	80 8.0
		88 79.0	4.0 1.24	91 167.0	244.0 3.10	85 93.8	71.6 -1.11	86 4.2	4.3 -0.17	81 8.0
		89 80.0	4.0 1.24	92 169.0	247.0 3.10	86 94.9	72.4 -1.11	87 4.2	4.3 -0.17	82 8.0
		90 81.0	4.0 1.24	93 171.0	250.0 3.10	87 96.0	73.2 -1.11	88 4.2	4.3 -0.17	83 8.0
		91 82.0	4.0 1.24	94 173.0	253.0 3.10	88 97.1	74.0 -1.11	89 4.2	4.3 -0.17	84 8.0
		92 83.0	4.0 1.24	95 175.0	256.0 3.10	89 98.2	74.8 -1.11	90 4.2	4.3 -0.17	85 8.0
		93 84.0	4.0 1.24	96						

Bond lengths and bond angles are shown in Table 5 and Fig. 7. All the values are quite normal except those for C(1)–C(2), C(4)–C(20) and O(22)–C(23). These values are respectively 1.51 and 1.49 Å, too large for aromatic bonds, and 1.34 Å, too small for a single O–C bond. The explanation of these erratic values may lie in a possible disorder at the indole end of the molecule as indicated in Fig. 3. Relatively high thermal motions have been found for C(1) and C(2), as well as the six methyl groups, C(23), C(27), C(29), C(40), C(42), and C(44). Similarly high thermal parameters for methyl groups and the end of the indole group were observed in the structure determination of villalstonine (Nordman & Kumra, 1965).

Table 5. Bond lengths and angles

Lengths		Angles		
C(1)–C(2)	1.509 Å	C(1) C(2) C(3)	119.9°	
C(2)–C(3)	1.387	C(2) C(3) C(4)	118.7	
C(3)–C(4)	1.427	C(3) C(4) C(5)	133.7	
		C(3) C(4) C(20)	119.9	
C(4)–C(20)	1.494	C(4) C(20) C(21)	121.2	
		C(4) C(20) N(19)	106.8	
C(4)–C(5)	1.464	C(5) C(4) C(20)	106.4	
		C(4) C(5) C(6)	129.6	
		C(4) C(5) C(18)	105.8	
C(5)–C(18)	1.395	C(5) C(18) N(19)	111.9	
		C(5) C(18) C(17)	121.5	
C(5)–C(6)	1.444	C(6) C(5) C(18)	124.6	
		C(5) C(6) C(17)	109.7	
C(6)–C(7)	1.552	C(6) C(7) N(8)	115.1	
C(7)–N(8)	1.453	C(7) N(8) C(9)	111.2	

Table 4. Fractional coordinates, isotropic and anisotropic temperature factors for reserpine

The anisotropic thermal parameters ($\times 10^4$) are of the form $T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

	<i>x</i>	<i>y</i>	<i>z</i>	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	<i>B</i>
C(1)	0.7986	0.1805	-0.0747	79	212	131	28	71	23	5.6
C(2)	0.7161	0.1792	-0.1917	111	188	147	20	98	10	6.1
C(3)	0.6171	0.2207	-0.2126	107	175	100	13	74	12	5.3
C(4)	0.5964	0.2681	-0.1223	76	115	83	6	46	9	4.1
C(5)	0.5037	0.3168	-0.1129	78	122	78	-7	51	-11	4.1
C(6)	0.4005	0.3310	-0.1975	71	229	61	-3	19	10	5.1
C(7)	0.3333	0.4115	-0.1494	87	191	78	31	45	42	5.4
N(8)	0.3523	0.3684	-0.0375	71	121	64	2	26	11	4.1
C(9)	0.3305	0.2106	-0.0318	82	120	71	-18	41	-7	4.2
C(10)	0.3362	0.1693	0.0829	73	131	76	-6	45	1	4.0
C(11)	0.2532	0.2486	0.1071	63	189	83	13	46	15	4.3
C(12)	0.2677	0.2038	0.2248	48	206	75	2	37	1	4.3
C(13)	0.3726	0.2541	0.3100	61	180	48	3	29	12	3.8
C(14)	0.4530	0.1654	0.2878	46	156	57	5	19	5	3.7
C(15)	0.4492	0.2058	0.1725	49	140	65	-6	28	-3	3.7
C(16)	0.4804	0.3674	0.1610	77	115	74	-20	49	-12	4.0
C(17)	0.4594	0.4070	0.0410	79	100	111	-1	62	11	4.3
C(18)	0.5335	0.3458	-0.0009	84	99	84	-3	51	5	4.3
N(19)	0.6377	0.3201	0.0616	55	123	78	4	28	11	4.0
C(20)	0.6805	0.2711	-0.0079	62	131	87	5	47	2	4.0
C(21)	0.7796	0.2290	0.0126	61	241	93	3	45	21	4.9
O(22)	0.8891	0.1312	-0.0719	91	407	116	62	71	19	7.1
C(23)	0.9612	0.0835	0.0245	83	505	110	53	32	7	8.5
C(24)	0.5593	0.1936	0.3759	72	167	82	-6	46	-4	4.7
O(25)	0.6286	0.1059	0.3993	61	214	121	21	11	-14	6.6
O(26)	0.5732	0.3300	0.4223	69	222	93	0	29	-30	5.6
C(27)	0.6755	0.3687	0.5119	69	351	125	-25	20	-29	7.5
O(28)	0.3831	0.1990	0.4194	103	225	86	6	57	37	5.8
C(29)	0.3741	0.3233	0.4847	140	378	88	-3	66	-66	7.8
O(30)	0.1891	0.2820	0.2461	60	155	98	5	49	6	4.3
C(31)	0.1318	0.2062	0.2849	57	153	82	5	40	9	4.1
O(32)	0.1436	0.0728	0.3047	107	196	153	16	95	42	6.1
C(33)	0.0506	0.2967	0.2943	62	178	62	-1	29	0	4.1
C(34)	-0.0167	0.2170	0.3271	49	233	85	-13	43	-8	4.5
C(35)	-0.0986	0.2922	0.3338	52	265	74	-8	28	-15	5.0
C(36)	-0.1141	0.4479	0.3052	56	217	72	24	33	-1	4.6
C(37)	-0.0458	0.5158	0.2728	71	168	91	15	40	16	4.7
C(38)	0.0387	0.4472	0.2689	80	163	73	4	40	15	4.6
O(39)	-0.1676	0.2296	0.3643	75	268	157	-4	79	20	6.5
C(40)	-0.1451	0.0813	0.4112	86	244	153	-21	74	22	6.2
O(41)	-0.1977	0.5125	0.3070	67	261	109	38	46	11	5.5
C(42)	-0.1782	0.6006	0.4036	161	375	110	119	80	20	8.1
O(43)	-0.0638	0.6662	0.2544	102	211	148	42	67	19	6.9
C(44)	0.0124	0.7566	0.2443	139	292	228	-30	133	63	8.2
Standard error										
O	0.0006	0.0012	0.0007	8	18	8	9	7	11	
N	0.0007	0.0011	0.0007	6	13	6	8	5	8	
C(<i>B</i> < 5.2)	0.0008	0.0014	0.0009	7	18	8	10	7	11	
C(<i>B</i> > 5.2)	0.0011	0.0020	0.0011	11	31	13	16	10	18	

Table 5 (cont.)

Lengths		Angles	
N(8)—C(17)	1.495	C(7) N(8) C(17)	110.3
N(8)—C(9)	1.462	C(9) N(8) C(17)	111.7
		N(8) C(9) C(10)	111.3
C(9)—C(10)	1.545	C(9) C(10) C(11)	112.3
		C(9) C(10) C(15)	107.5
C(10)—C(11)	1.543	C(11) C(10) C(15)	112.7
		C(10) C(11) C(12)	108.2
C(10)—C(15)	1.595	C(10) C(15) C(16)	111.5
C(11)—C(12)	1.549	C(11) C(12) O(30)	107.0
		C(11) C(12) C(13)	110.0
C(12)—C(13)	1.527	O(30) C(12) C(13)	108.6
		C(12) C(13) O(28)	106.6
		C(12) C(13) C(14)	107.2
C(13)—C(14)	1.538	C(13) C(14) C(15)	110.9
		C(13) C(14) C(24)	111.4
		C(14) C(13) O(28)	104.3
C(14)—C(15)	1.561	C(15) C(14) C(24)	109.2
		C(14) C(15) C(10)	106.8
		C(14) C(15) C(16)	115.2
C(15)—C(16)	1.546	C(15) C(16) C(17)	112.6
C(16)—C(17)	1.541	C(16) C(17) N(8)	111.3
		C(16) C(17) C(18)	116.5
C(17)—C(18)	1.508	N(8) C(17) C(18)	109.9
		C(17) C(18) N(19)	126.4
C(18)—N(19)	1.396	C(18) N(19) C(20)	109.1
N(19)—C(20)	1.388	N(19) C(20) C(21)	132.0
C(20)—C(21)	1.390	C(20) C(21) C(1)	118.6
C(21)—C(1)	1.379	C(21) C(1) C(2)	121.7
		C(21) C(1) O(22)	127.8
C(1)—O(22)	1.366	C(2) C(1) O(22)	110.5
O(22)—C(23)	1.336	C(1) O(22) C(23)	118.3
C(13)—O(28)	1.490	C(13) O(28) C(29)	109.6
O(28)—C(29)	1.456		
C(14)—C(24)	1.506	C(14) C(24) O(25)	123.4
C(24)—O(25)	1.206	C(14) C(24) O(26)	114.6
C(24)—O(26)	1.355	O(25) C(24) O(26)	121.9
O(26)—C(27)	1.490	C(24) O(26) C(27)	118.8
C(12)—O(30)	1.462	C(12) O(30) C(31)	119.5
O(30)—C(31)	1.336	O(30) C(31) O(32)	122.1
		O(30) C(31) C(33)	113.6
C(31)—O(32)	1.224	O(32) C(31) C(33)	124.3
C(31)—C(33)	1.476	C(31) C(33) C(34)	115.0
		C(31) C(33) C(38)	122.4
C(33)—C(34)	1.419	C(34) C(33) C(38)	122.5
		C(33) C(34) C(35)	119.1
C(34)—C(35)	1.399	C(34) C(35) C(36)	119.5
		C(34) C(35) O(39)	124.9
C(35)—C(36)	1.442	C(36) C(35) O(39)	115.7
		C(35) C(36) C(37)	117.5
		C(35) C(36) O(41)	116.8
C(36)—C(37)	1.378	C(37) C(36) O(41)	125.6
		C(36) C(37) C(38)	125.0
		C(36) C(37) O(43)	112.6
C(37)—C(38)	1.388	C(38) C(37) O(43)	122.1
C(38)—C(33)	1.387	C(37) C(38) C(33)	116.3
C(35)—O(39)	1.350	C(35) O(39) C(40)	117.1
O(39)—C(40)	1.448		
C(36)—O(41)	1.350	C(36) O(41) C(42)	114.8
O(41)—C(42)	1.435		
C(37)—O(43)	1.378	C(37) O(43) C(44)	118.8
O(43)—C(44)	1.421		

Least-squares planes were computed for the indole group and the benzoxy group. The dihedral angle between these planes is 82° . Deviations of atoms from the planes are listed in Table 6.

We wish to thank Mr Stephen Brenner for programming the cycling procedure employing the tangent formula.

Table 6. Deviations of atoms from least-squares planes

Plane I		Plane II	
	Δ		Δ
C(1)	-0.025 Å	*O(30)	-0.180 Å
C(2)	0.006	*C(31)	-0.087
C(3)	0.003	*O(32)	-0.132
C(4)	0.010	C(33)	-0.006
C(5)	-0.007	C(34)	-0.007
*C(6)	-0.044	C(35)	0.010
*C(17)	0.054	C(36)	0.001
C(18)	-0.012	C(37)	-0.015
N(19)	0.006	C(38)	0.017
C(20)	0.010	*O(39)	0.017
C(21)	0.009	*C(40)	0.252
*O(22)	-0.063	*O(41)	-0.049
*C(23)	-0.484	*C(42)	1.200
		*O(43)	0.066
		*C(44)	0.353

* These atoms were not used in calculating the plane.

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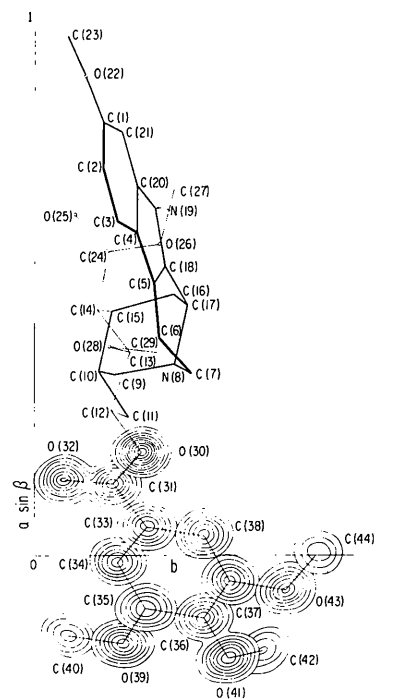


Fig. 4. Sections from a three-dimensional electron density map projected down the c axis. Contours are equally spaced at $1 \text{ e.}\text{\AA}^{-3}$, starting with the $1 \text{ e.}\text{\AA}^{-3}$ contour. The c axis is down.

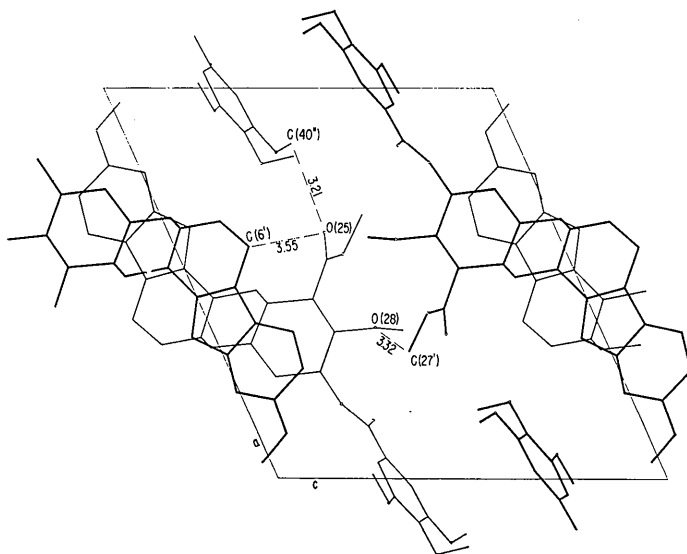


Fig. 5. The contents of a unit cell of reserpine.

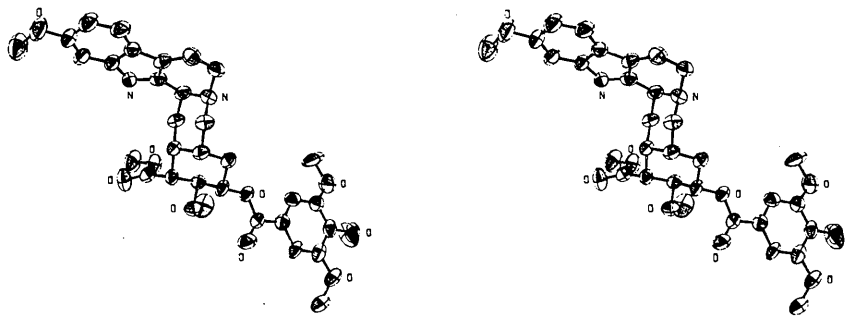


Fig. 6. Stereodiagrams of reserpine.

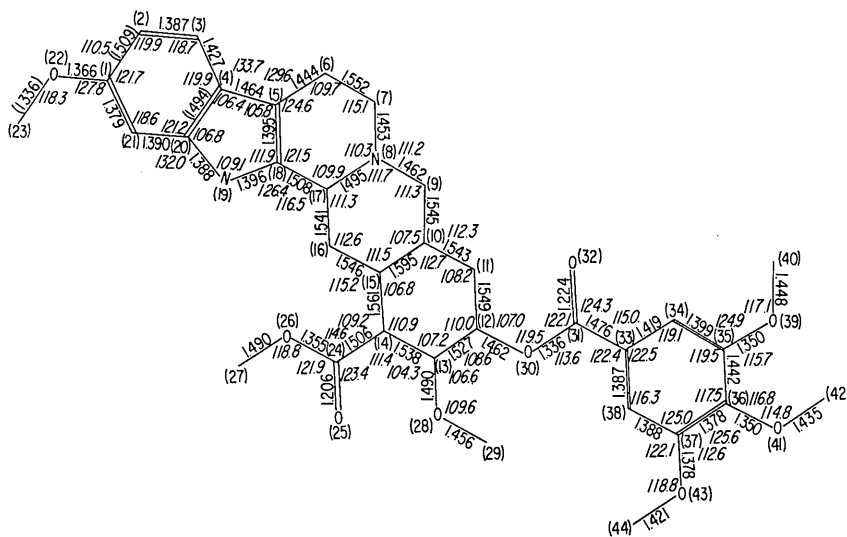


Fig. 7. Bond lengths and bond angles. The standard deviations as computed by the least-squares program are ~ 0.017 Å for most bond lengths except for those involving carbon atoms with large thermal factors ($B > 5.2$) where the value increases up to 0.022 Å. The standard deviations for the bond angles are $1.0 - 1.3^\circ$. If all experimental factors were taken into account the values of the standard deviations would increase.

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On the Application of Phase Relationships to Complex Structures

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For complex centrosymmetric structures the symbolic addition method has two weak links; the first is in the initial few steps when single sign relationships must be trusted and the second is in the acceptance of relationships between sign symbols. A systematic multi-solution symbolic addition procedure is described which greatly reduces the risk of taking a wrong step and offers the possibility of solving structures with up to 400 atoms in the unit cell. A computer program is described which incorporates some of the proposals. Several alternative procedures are also described for extending the application of phase-determining techniques to non-centrosymmetric structures and the result of applying one of these methods is given. The basis of these procedures is that initial phase allocations in the correct quadrant ($\pi/4$, $3\pi/4$, $5\pi/4$, $7\pi/4$) to a few reflexions is sufficient to derive new phases and to refine them by the usual tangent formula.

Introduction

For centrosymmetric structures the point has now been reached where, for equal-atom structures with no special features, direct methods are at least as effective as other methods of solving crystal structures. After many years in which various types of sign-determining formula have been proposed it has become clear that the simplest one of all, the triple-product sign relationship (t.p.s.r.) is the most powerful and the most useful. The method of using these relationships which has proved to be very powerful is based on that proposed by Zachariasen (1952) in his contribution to the trio of pioneer papers by himself, Sayre (1952) and Cochran (1952). Zachariasen showed that if inequality relationships enabled the signs of some structure factors to be related and if signs, where unknown, were represented by letter symbols then subsequent use of the relationship

$$s(\mathbf{h}) \approx s\left\{ \sum_{\mathbf{h}'} s(\mathbf{h}') s(\mathbf{h} - \mathbf{h}') \right\} \quad (1)$$

could lead to a knowledge of signs (perhaps in terms of symbols) for more reflexions and could also often

enable the signs corresponding to the symbols to be determined. It is assumed in (1) that all the signs are those of large unitary structure factors.

It was suggested by Woolfson (1961) that a 'hit-or-miss' version of Zachariasen's method could be tried even when inequality relationships were not available. If a number of the strongest t.p.s.r.'s were accepted as inviolable then further progress could be made by the use of relationship (1).

However, the main credit for demonstrating the full power of this type of method must go to Karle & Karle, who have developed a systematic approach to the use of sign symbols which they call the 'symbolic addition' method. These workers and their associates have solved a number of fairly complex structures (e.g. Karle & Karle, 1964a; Karle, Karle, Owen & Hoard, 1965) and their process is now widely used by crystallographers everywhere.

The process of using symbols has also been extended to the solution of non-centrosymmetric structures. The applications which have been made (Karle & Karle, 1964b; Karle & Karle, 1966a) have relied to some extent on the presence of centrosymmetric projections