

Crystal and Molecular Structure of Mesembranol

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Single-crystal *X*-ray analysis has established the conformation of mesembranol (III). Crystals are monoclinic, space group $P2_1$, with $Z = 2$ in a cell of dimensions $a = 13.45$, $b = 7.84$, $c = 7.68$ Å, $\beta = 104.6^\circ$. The structure was solved from photographic data by direct phase-determining methods, and the molecular parameters refined by full-matrix least-squares calculations to R 0.082 over 1598 independent reflections.

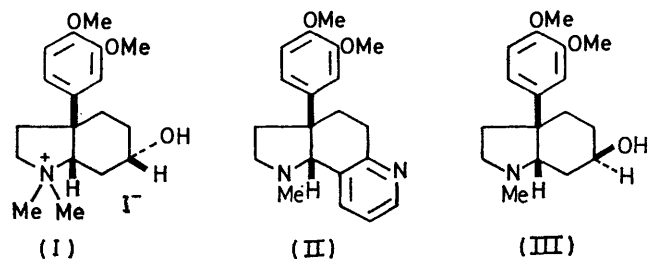
PREVIOUS crystal-structure analyses of 6-*epi*-mesembranol methiodide¹ (I) and Sceletium Alkaloid A₄² (II) have defined the absolute configuration of mesembrine

¹ P. Coggon, D. S. Farrier, P. W. Jeffs, and A. T. McPhail, *J. Chem. Soc. (B)*, 1970, 1267.

alkaloids and permitted the detailed conformations of these two compounds to be examined. In (I), the

² P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Comm.*, 1971, 1466; P. A. Luhan and A. T. McPhail, *J.C.S. Perkin II*, 1972, 2006.

presence of the quaternary nitrogen atom forced the cyclohexane ring to adopt a slightly twisted boat conformation in order to reduce non-bonded intramolecular



interactions, whereas the fusion of the pyridine moiety resulted in a half-chair conformation for the ring in (II). We now report on the preferred conformation of mesembranol (III) wherein the cyclohexane ring is free from such constraints and it is thus able to adopt a chair conformation.

EXPERIMENTAL

Crystal Data.— $C_{17}H_{24}NO_3$, $M = 290.4$, m.p. 143–145°, $[\alpha]_D -32^\circ$. Monoclinic, $a = 13.45(2)$, $b = 7.84(1)$, $c = 7.68(1)$ Å, $\beta = 104.6(2)^\circ$, $U = 784$ Å, $D_m = 1.22$, $Z = 2$, $D_c = 1.230$, $F(000) = 314$. Cu- K_α X-rays, $\lambda = 1.542$ Å; $\mu(\text{Cu-}K_\alpha) = 6.8$ cm $^{-1}$. Space group $P2_1(C_2^2)$ from systematic absences $0k0$ when $k \neq 2n$, and mesembranol is a chiral molecule.

Crystallographic Measurements.—Unit cell dimensions were evaluated from precession photographs taken with Mo- K_α ($\lambda = 0.7107$ Å) radiation and from $h0l$ Weissenberg photographs taken with Cu- K_α radiation. Intensities were estimated visually from equi-inclination multiple-film Weissenberg photographs of the layers $h0-7l$ taken with Cu- K_α radiation. Spot-shape corrections and the usual Lorentz and polarization factors were applied, and 1598 independent observed structure amplitudes obtained. No correction was made for absorption.

Structure Analysis.—The structure was solved by direct phase-determining methods. Initial phases for a selected set of reflections with large $|E|$ values were determined by the symbolic addition procedure³ for non-centrosymmetric crystals. For the present analysis 3,0,6, $|E| = 3.29$, $\phi = 0$; 10,0,7, $|E| = 2.91$, $\phi = 0$; and 1,7,3, $|E| = 2.48$, $\phi = 0$, were selected as the origin-defining reflections, and symbols a and b were assigned to the phases of two other reflections 2,5,4, $|E| = 2.41$, $\phi = a$; and 11,6,3, $|E| = 2.67$, $\phi = b$. These 5 reflections were expanded into a set of 18 reflections for which $|E_H \cdot E_K \cdot E_{H-K}| > 10.0$. The values of a ($0 \leq a \leq \pi$) and b ($0 \leq b \leq 2\pi$) were allowed to vary by increments of $\pi/4$ and these were input to the tangent formula⁴ using a local version of the iterative program originally written by Drew⁵ and amended by Larson and Motherwell.⁶ The largest 200 $|E|$ values were refined for 7 cycles and 495 were refined for 5 cycles. In any cycle a phase assignment was rejected if the consistency index, $t = \sqrt{A^2 + B^2} / \sum_K |E_K| \cdot |E_{H-K}|$ was < 0.40 , and the value of $\alpha = |E_K| / \sqrt{A^2 + B^2}$ was < 6.0 . At the end of the tangent

refinement cycles, inspection of the $R_K [= \sum_H |E_H|_{\text{obs}} - |E_H|_{\text{calc}}] / \sum_H |E_H|_{\text{obs}}$ values revealed that starting set $a = \pi/4$, $b = -3\pi/4$ was one of the lowest with $R_K = 0.11$. This set also used a large number of Σ_2 values and assigned phases to a larger number of reflections than other sets. An E map was computed from the phase angles derived from this set, and although it contained an almost exact pseudo-mirror plane of symmetry, the peaks could be interpreted to give a chemically reasonable model. The derived approximate atomic positions, with assumed B 3.5 Å², were

TABLE I
Fractional atomic co-ordinates* ($\times 10^4$) with estimated standard deviations in parentheses

Atom	x/a	y/b	z/c
N(1)	8317(3)	7550(—)	5997(5)
C(2)	8144(5)	8165(9)	7705(8)
C(3)	8065(4)	6621(8)	8820(6)
C(3a)	8181(3)	5047(7)	7681(5)
C(4)	9328(3)	4450(8)	8155(5)
C(5)	9543(3)	3261(7)	6747(6)
C(6)	9351(3)	4172(7)	4942(5)
C(7)	8237(3)	4748(7)	4340(5)
C(7a)	7883(3)	5788(6)	5760(5)
C(8)	7852(4)	8662(9)	4488(9)
O(9)	9515(2)	3094(6)	3533(4)
C(1')	7682(3)	2826(8)	9701(5)
C(2')	7019(4)	1593(8)	10067(6)
C(3')	6178(3)	1041(7)	8755(6)
C(4')	6020(3)	1699(7)	7019(6)
C(5')	6661(3)	2959(7)	6649(5)
C(6')	7498(3)	3563(6)	7999(5)
O(10)	5558(3)	-200(6)	9183(5)
C(11)	4526(4)	356(10)	9078(7)
O(12)	5213(2)	1029(5)	5736(4)
C(13)	5088(4)	1523(8)	3920(6)
H(2 α)	874	897	838
H(2 β)	742	886	743
H(3 α)	867	665	1002
H(3 β)	734	658	914
H(4 α)	981	554	827
H(4 β)	949	379	943
H(5 α)	1033	286	714
H(5 β)	906	217	662
H(6)	985	525	510
H(7a)	706	587	532
H(7 α)	814	549	313
H(7 β)	775	363	403
H(8 α)	817	992	468
H(8 β)	706	866	440
H(8 γ)	801	806	334
H(9)	1026	290	370
H(1')	832	322	1071
H(2')	714	110	1137
H(5')	654	345	534
H(11 α)	406	-61	942
H(11 β)	425	82	776
H(11 γ)	462	137	1004
H(13 α)	447	101	293
H(13 β)	591	118	362
H(13 γ)	501	288	393

* Hydrogen atoms, labelled according to the carbon atom to which they are bonded, have fractional co-ordinates expressed ($\times 10^3$).

used to compute structure factors for which R was 0.423. The positional and isotropic thermal parameters were then refined for nine cycles of full-matrix least-squares calculations which reduced R to 0.167. At the end of this refinement the temperature factor for C(11) was unreasonably large, suggesting that this atom had been misplaced too far in the original model for the least-squares to

⁶ See e.g., O. Kennard, D. L. Wampler, J. C. Coppola, W. D. S. Motherwell, D. G. Watson, and A. C. Larson, *Acta Cryst.*, 1971, **B**, 27, 1116.

³ J. Karle and I. L. Karle, *Acta Cryst.*, 1966, **21**, 849.

⁴ J. Karle and H. Hauptmann, *Acta Cryst.*, 1956, **9**, 635.

⁵ See e.g., M. G. B. Drew, D. H. Templeton, and A. Zalkin, *Acta Cryst.*, 1969, **B**, 25, 261.

refine it into position. Structure factors were calculated omitting C(11) which was relocated in a subsequent difference-Fourier synthesis. A further three cycles of isotropic refinement reduced R to 0.127. Evaluation of a three-dimensional difference electron-density map indicated that there was significant density at all positions calculated for the hydrogen atoms assuming C-H 1.07 Å, O-H 1.0 Å. Inclusion of 24 hydrogen atoms with B 4.0 Å² in the next structure-factor calculation decreased R significantly to 0.116. Atomic positional and anisotropic thermal parameters of the non-hydrogen atoms were adjusted for five cycles of least-squares calculations which brought the refinement to convergence at R 0.082.

For all structure-factor calculations, scattering factors for neutral atoms were taken from ref. 7. During the least-squares calculations the y co-ordinate of N(1) was held constant to define the space-group origin. The weighting scheme used in these calculations was $\sqrt{w} = 1$ for $|F_o| \leq 5.0$ and $\sqrt{w} = |F_o|/5.0$ for $|F_o| > 5.0$. At the end of the refinement analysis of $\langle w\Delta^2 \rangle$ in ranges of $|F_o|$ and $\sin \theta$ showed no systematic dependence on these values.†

RESULTS AND DISCUSSION

Final atomic positional and thermal parameters are given in Tables 1 and 2, and interatomic distances and angles in Table 3. The numbering scheme employed is shown in Figure 1 which illustrates the conformation

TABLE 2

Anisotropic thermal parameters * ($\times 10^4$) with estimated standard deviations in parentheses

Atom	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
N(1)	32(2)	58(6)	140(5)	-2(5)	46(5)	-38(10)
C(2)	79(3)	113(11)	202(8)	-5(10)	124(8)	-108(16)
C(3)	57(2)	105(8)	151(7)	-44(8)	91(6)	-150(13)
C(3a)	27(2)	92(8)	99(6)	-6(6)	22(5)	-51(11)
C(4)	28(2)	128(9)	80(5)	-11(7)	6(5)	26(13)
C(5)	32(2)	98(9)	131(7)	32(7)	26(6)	41(13)
C(6)	24(2)	96(9)	95(6)	20(6)	29(5)	-18(11)
C(7)	35(2)	74(8)	77(5)	10(6)	17(5)	-11(11)
C(7a)	24(2)	64(8)	106(6)	-15(6)	31(5)	-4(10)
C(8)	50(3)	108(10)	225(11)	24(9)	30(9)	98(18)
O(9)	37(1)	142(7)	115(5)	38(6)	28(4)	-86(10)
C(1')	38(2)	117(9)	82(5)	2(7)	32(5)	-2(12)
C(2')	48(2)	110(9)	91(6)	36(8)	43(6)	34(13)
C(3')	48(2)	68(8)	113(6)	0(8)	67(5)	0(12)
C(4')	34(2)	92(8)	105(6)	12(7)	40(5)	-2(12)
C(5')	33(2)	63(7)	87(6)	-9(6)	7(5)	4(11)
C(6')	24(2)	68(8)	92(5)	6(6)	19(5)	-21(10)
O(10)	65(2)	111(7)	168(6)	-29(7)	81(5)	73(11)
C(11)	61(3)	214(14)	182(8)	-85(10)	106(7)	-17(19)
O(12)	53(2)	140(7)	102(5)	-104(6)	15(5)	11(10)
C(13)	59(2)	141(11)	108(7)	-69(9)	13(7)	15(15)

* These are the values of b_{ij} in the expression: $B \sin^2\theta/\lambda^2 = b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl$. An isotropic temperature factor, B 4.0 Å², was assigned to all the hydrogen atoms.

adopted by mesembranol in the crystal. The absolute configuration was defined earlier by our X-ray analysis of (I). Displacements of various atoms from least-squares planes calculated through selected groups of atoms are presented in Table 4.

Torsion angles⁸ for the *cis*-octahydroindole ring system are provided in Figure 2. From these, and the

† Final observed and calculated structure factors are listed in Supplementary Publication No. SUP 20555 (10 pp., 1 microfiche). For details see Notice to Authors No. 7 in *J. Chem. Soc. (A)*, 1970, Issue No. 20.

TABLE 3

Interatomic distances (Å) and angles (deg.), with estimated standard deviations in parentheses

(a) Intramolecular distances

N(1)-C(2)	1.470(7)	C(7)-C(7a)	1.531(6)
N(1)-C(7a)	1.492(5)	C(11)-C(2')	1.392(7)
N(1)-C(8)	1.459(7)	C(1')-C(6')	1.393(6)
C(2)-C(3)	1.501(9)	C(2')-C(3')	1.381(6)
C(3)-C(3a)	1.544(7)	C(3')-C(4')	1.395(6)
C(3a)-C(4)	1.565(6)	C(3')-O(10)	1.374(6)
C(3a)-C(7a)	1.541(6)	C(4')-C(5')	1.388(7)
C(3a)-C(6')	1.539(6)	C(4')-O(12)	1.373(6)
C(4)-C(5)	1.510(7)	C(5')-C(6')	1.406(6)
C(5)-C(6)	1.523(6)	O(10)-C(11)	1.438(7)
C(6)-C(7)	1.521(6)	O(12)-C(13)	1.416(6)
C(6)-O(9)	1.433(6)		

C(3) ... C(1')	3.12	C(5) ... C(5')	3.86
C(4) ... C(1')	3.04	C(7a) ... C(5')	2.94
		C(11) ... O(12)	2.99
H(1') ... H(3 α)	2.80	H(5') ... H(5 β)	3.43
H(1') ... H(3 β)	3.06	H(5') ... H(7 β)	2.12
H(1') ... H(4 β)	2.10	H(5') ... H(7a)	2.02

(b) Valency angles

C(2)-N(1)-C(7a)	105.5(4)	N(1)-C(7a)-C(3a)	103.5(3)
C(2)-N(1)-C(8)	112.3(4)	N(1)-C(7a)-C(7)	113.5(3)
C(7a)-N(1)-C(8)	112.3(4)	C(3a)-C(7a)-C(7)	115.4(4)
N(1)-C(2)-C(3)	107.1(5)	C(2')-C(1')-C(6')	120.4(4)
C(2)-C(3)-C(3a)	106.8(4)	C(1')-C(2')-C(3')	121.3(4)
C(3)-C(3a)-C(4)	110.0(4)	C(2')-C(3')-C(4')	118.7(4)
C(3)-C(3a)-C(6')	111.4(3)	C(2')-C(3')-O(10)	118.8(4)
C(3)-C(3a)-C(7a)	101.6(4)	C(4')-C(3')-O(10)	122.4(4)
C(4)-C(3a)-C(6')	109.3(4)	C(3')-C(4')-C(5')	120.4(4)
C(4)-C(3a)-C(7a)	109.8(3)	C(3')-C(4')-O(12)	116.5(4)
C(6')-C(3a)-C(7a)	114.6(3)	C(5')-C(4')-O(12)	123.0(4)
C(3a)-C(4)-C(5)	111.9(3)	C(4')-C(5')-C(6')	120.8(4)
C(4)-C(5)-C(6)	110.1(4)	C(3a)-C(6')-C(1')	119.4(4)
C(5)-C(6)-C(7)	110.1(3)	C(3a)-C(6')-C(5')	122.4(4)
C(5)-C(6)-O(9)	112.8(4)	C(1')-C(6')-C(5')	118.2(4)
C(7)-C(6)-O(9)	105.8(3)	C(3')-O(10)-C(11)	114.0(5)
C(6)-C(7)-C(8)	113.6(3)	C(4')-O(12)-C(13)	118.6(4)

(c) Intermolecular distances < 3.60 Å

O(9) ... N(1 ^I)	2.88	O(9) ... C(2 ^I)	3.51
C(13) ... O(10 ^{II})	3.46	O(9) ... C(8 ^I)	3.51
O(9) ... C(6 ^I)	3.50	C(13) ... O(12 ^{II})	3.57

Roman numeral superscripts refer to the following transformations of the co-ordinates of Table 1:

$$\text{I } 2 - x, -\frac{1}{2} + y, 1 - z \quad \text{II } 1 - x, \frac{1}{2} + y, 1 - z$$

TABLE 4

Displacements (Å) of some atoms from various planes. Atoms not included in the derivation of the plane are italicized

Plane (A): N(1) -0.004, C(2) 0.006, C(3) -0.005, C(3a) 0.003, C(7a) 0.582

Plane (B): C(3a) 0.001, C(4) -0.001, C(6) 0.001, C(7) -0.001, C(5) 0.710, C(7a) -0.544, O(9) 0.653

Plane (C): C(1') 0.017, C(2') 0.005, C(3') -0.017, C(4') 0.022, C(5') 0.001, C(6') -0.022, O(10) -0.005, O(12) 0.086, C(3a) -0.148, C(11) -1.193, C(13) 0.271, C(3) -1.486

displacements recorded in Table 4, the five-membered heterocyclic ring is shown to adopt an envelope conformation with C(7a) 0.582 Å out of the plane through N(1)-C(3a). This conformation differs from either of the half-chair forms found in (I) or (II). The *cis*-fused substituted cyclohexane ring has a chair conformation

⁷ 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

⁸ W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.

slightly flattened at C(7a) as evidenced by the smaller mean torsion angle of 46° around C(7a) compared with the mean of 61° around C(5). The hydroxy-group is equatorial to the ring and the 3,4-dimethoxyphenyl substituent is axially oriented.

The dihedral angle between the plane through C(1')—(6'), O(10) and that through C(7a), C(3a), C(6') is 5° , slightly smaller than the corresponding angle of 10° in (II). In (III) the H(7a) \cdots H(5') separation of 2.02 \AA

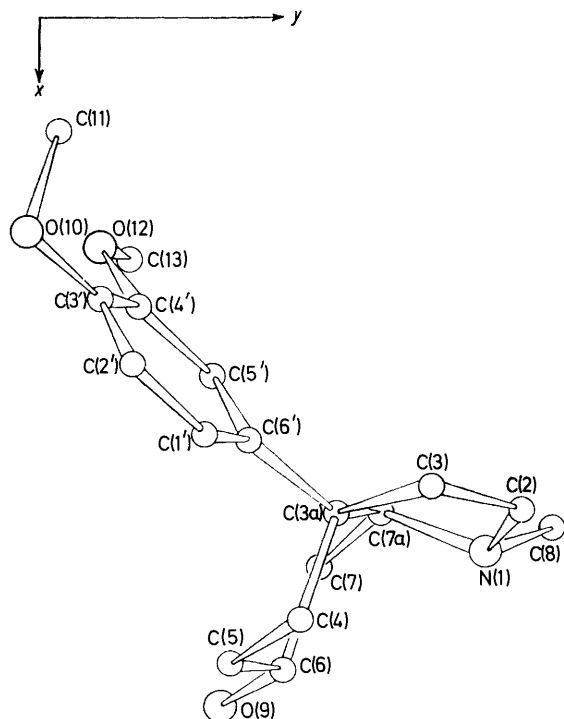


FIGURE 1 Molecular conformation and atom numbering

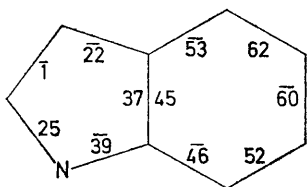


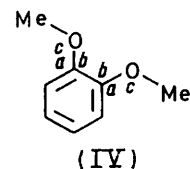
FIGURE 2 Torsion angles (deg.) for the *cis*-octahydroindole rings

is close to that of 2.17 \AA in (II) but is in contrast to 1.76 \AA found in (I). Thus, the C(3a)—C(6')—C(1') and C(3a)—C(6')—C(5') angles have approximately equal values in (II) and (III) whereas they differ significantly (116.8 and 125.2°) in (I) to reduce non-bonded interactions.

From our analysis of (II) we noted that C(3a) was displaced by 0.118 \AA from the mean plane calculated through C(1')—(6'), O(13), O(15), and we ascribed this to reduction in non-bonded interactions between the phenyl ring and hydrogen atoms on C(3) and C(7a). In addition to these interactions in (III) there is present an H(7 β) \cdots H(5') interaction which is absent in (I), where the cyclohexane ring adopts a boat conformation,

and in (II), where the pyridine ring is fused at C(6)—C(7). Consequently, in (III) while the phenyl ring is also bent back to reduce interactions, the bending is in the opposite sense (Table 4) to that observed in (II), where C(3a) and C(3) were displaced to the same side of the corresponding plane.

A survey of the preferred geometries at methoxy-substituents on phenyl rings reveals that the oxygen and methyl carbon atoms generally lie close to the phenyl-ring plane, and the angles a and c (IV) are enlarged from normal values while the angle b is correspondingly reduced. These deformations occur in order to decrease



the H(Ph) \cdots H(Me) non-bonded interactions.^{1,9} When methoxy-substituents are on adjacent carbon atoms these features are still maintained in general, and the C \cdots O vectors bend toward each other. From the present analysis we find that these geometries are not all preserved in the dimethoxyphenyl group of crystalline mesembranol. The pattern of angles at one methoxy-group is consistent with the normal situation in which C(5')—C(4')—O(12) 123.0° and C(4')—O(12)—C(13) 118.6° are both enlarged while C(3')—C(4')—O(12) 116.5° is reduced from 120° . At the other methoxy-group, however, the pattern of angles is $b > a$ [C(4')—C(3')—O(10) 122.4° , C(2')—C(3')—O(10) 118.8°] and the angle c [C(3')—O(10)—C(11) 114.0°] is normal. These values are a consequence of the fact that C(11) is significantly displaced, $\Delta 1.193 \text{ \AA}$, from the phenyl-ring plane with the C(2')—C(3')—O(10)—C(11) torsion angle 114° . We ascribe this unusual geometry to crystal packing forces, for if the torsion angle were nearly zero then C(11) would be *ca.* 3.2 \AA from C(13) on an adjacent molecule. By rotation out of the phenyl plane this separation is increased to a more normal van der Waals distance of 3.72 \AA . With this orientation, the C(Ph)—O—C(Me) angle may assume a normal value and, with the removal of the unfavourable H(Ph) \cdots H(Me) interaction, the C(Ph)—O(methoxy) bond is bent away from the other C—O bond to give an O \cdots O separation of 2.74 \AA in (III) compared to 2.59 \AA in (II). Adoption of this orientation introduces a C(11) \cdots O(12) intramolecular interaction which is relieved by bending the C(4')—O(12) bond to the opposite side of the phenyl ring plane from C(11) so that O(12) is displaced 0.086 \AA from the plane and gives a C(11) \cdots O(12) distance of 2.99 \AA .

The mean C(sp^3)—C(sp^3) and aromatic C—C lengths (1.539 and 1.393 \AA) agree well with the standard values ¹⁰ [$1.537(5)$ and $1.394(5) \text{ \AA}$]. The C(3a)—C(6') bond length [$1.539(6) \text{ \AA}$] is not significantly different from the corre-

⁹ P. Coggon, A. T. McPhail, and S. C. Wallwork, *J. Chem. Soc. (B)*, 1970, 884 and references therein.

¹⁰ *Chem. Soc. Special Publ.*, No. 18, 1965.

sponding distance [1.534(8) Å] in (II), and these bonds are significantly longer than the normal $C(sp^3)-C(Ph)$ length [1.505(5) Å] as a result of steric overcrowding in

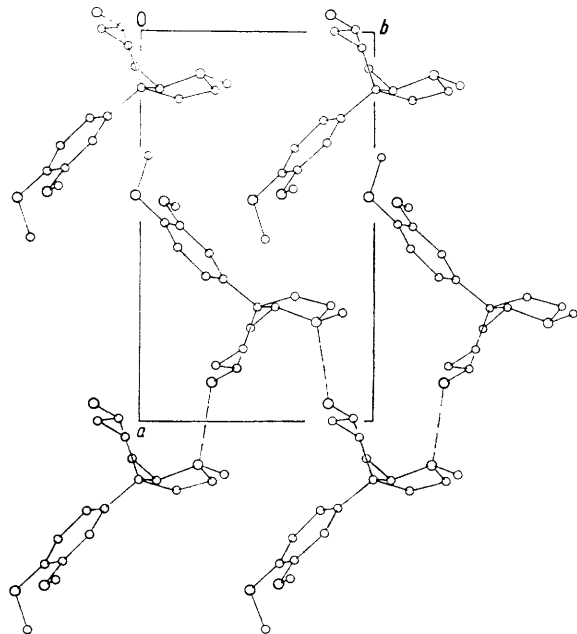


FIGURE 3 The crystal structure, viewed in projection along c^* . Hydrogen bonds are denoted by broken lines

this region. The mean $C(sp^3)-N$ bond length (1.474 Å) agrees with the accepted value [1.472(5) Å] for such bonds. The internal angle at the nitrogen atom [$C(2)-N(1)-C(7a)$ 105.5°] is significantly smaller than tetrahedral (109.5°) while the mean exocyclic angle is

112.3°. Mean bond lengths involving oxygen atoms, $C(sp^3)-O$ 1.429, and $C(Ph)-O$ 1.374 Å, are close to the corresponding distances of 1.411 and 1.362 Å in (II), and 1.426 and 1.371 in cryptopine.¹¹

The crystal structure as seen in projection along c^* is shown in Figure 3. Intermolecular distances < 3.6 Å are quoted in Table 3. The shortest of these [$O(9) \cdots N(1)$ 2.88 Å] is typical for a hydrogen bond¹² and the hydroxy-proton lies close to the line of centres, for the $C(6)-O(9)-N(1)$ angle is 109.7°, and $O(9)$ lies near to the local C_3 axis at the nitrogen atom, $C(2)-N(1)-O(9)$ 102.9, $C(7a)-N(1)-O(9)$ 120.4, and $C(8)-N(1)-O(9)$ 103.1°. Other intermolecular separations correspond to normal van der Waals distances.

This analysis and the earlier studies on (I) and (II) show that despite the variations in conformation of the five- and six-membered *cis*-fused rings, the phenyl substituent consistently adopts an orientation such that non-bonded interactions are minimized and the $C(5')-H(5')$ bond points over the $C(7)-C(7a)$ bond [alternatively, $H(1')$ is sandwiched between the hydrogen atoms on $C(3)$ and $C(4)$].

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¹² W. C. Hamilton and J. A. Ibers, 'Hydrogen Bonding in Solids,' Benjamin, New York, 1968; G. C. Pimentel and A. L. McClellan, 'The Hydrogen Bond,' Freeman, San Francisco, 1964.