

## The Structure of the Bisbenzylisoquinoline Alkaloid Methylwarifteine

BY NIVEDITA BORKAKOTI AND REX A. PALMER

Department of Crystallography, Birkbeck College, University of London, Malet Street, London WC1E 7HX, England

(Received 8 August 1977; accepted 23 September 1977)

The crystal structure of the bisbenzylisoquinoline alkaloid methylwarifteine,  $C_{37}H_{38}N_2O_6$ , has been determined by direct methods, using Cu  $K\alpha_1$  diffractometer data. The compound crystallizes in the orthorhombic space group  $P2_12_12_1$ , with unit-cell dimensions  $a = 17.539$  (4),  $b = 12.224$  (3),  $c = 14.393$  (3) Å,  $Z = 4$ . The structure was refined by full-matrix least-squares methods to  $R = 0.057$ , for 2508 observed reflections. The phenyl rings of the isoquinoline groups are planar and the nitrogen-containing rings are both in similar half-chair conformations, with the pseudo twofold axis bisecting two C–C bonds. The benzyltetrahydroisoquinoline residue is in an extended conformation while the benzylidihydroisoquinoline residue is folded. The two halves of the molecule thus formed are joined by an ether linkage on one side and a methoxy linkage on the other side. The dihedral angle between the two benzyl groups is  $111.3^\circ$ .

### Introduction

A number of tertiary bisbenzylisoquinoline bases were isolated (Gorinsky, Colyer & Walker, 1970) from the dried rhizomes of the plant *Cissampelos ovalifolia* D. C. Chemical and mass spectral analysis of these bases (Snedden, Parker & Gorinsky, 1970), referred to as warifteine (I), methylwarifteine (II) and dimethylwarifteine (III) (Fig. 1), have been made and the crystal structure analyses of (II) (this paper) and (III) (Borkakoti & Palmer, 1978) have been successfully completed. The alkaloid cissampereine isolated from the related plant *Cissampelos pareira* Linn., and characterized by Kupchan, Kubota, Fujita, Kobayashi, Block & Telang (1966) is isomeric with methylwarifteine. Dimethylwarifteine has been shown by Snedden *et al.* (1970), on the basis of melting point and

NMR spectra, to be identical with *O*-methylcissampereine. Against human carcinoma cells of the nasopharynx in cell culture, (II) has shown significant and reproducible inhibitory activity (Kupchan, Patel & Fujita, 1965). Biological testing of the warifteines was also reported to be in progress by Gorinsky, Colyer & Walker (1970). The absolute configuration, Fig. 1, has been chemically determined (Kupchan *et al.*, 1966).

### Experimental

Methylwarifteine (MEW) was crystallized from methanol, in the form of needles elongated along **b** (Reynolds, 1974). The crystals were found to be unstable in air and it was necessary to mount the crystals for X-ray diffraction in thin-walled capillary tubes with a little mother liquor to minimize decomposition. Preliminary cell parameters were derived from Weissenberg photographs, and the space group was determined to be  $P2_12_12_1$ , with  $Z = 4$  (Reynolds, 1974). Accurate cell parameters were determined by least-squares calculations from 20  $\theta$  values measured on a Hilger & Watts Y290 computer-controlled four-circle diffractometer. Intensities for  $\theta < 70^\circ$  were measured on the same instrument, employing the  $\omega$ - $2\theta$  scanning mode. 3217 independent intensities were measured, of which 709 with  $I \leq 3\sigma(I)$  were classified as unobserved. Three reference reflections, measured periodically, showed no significant change in intensities over the period of data collection. Lorentz and polarization corrections were applied but no absorption correction was made [ $\mu(\text{Cu } K\alpha) = 5.57 \text{ cm}^{-1}$ ]. Crystal data are given in Table 1.

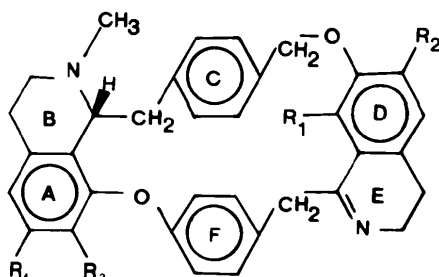


Fig. 1. Structural formulae of the compounds (I) warifteine,  $R_1 = R_3 = \text{OH}$ ;  $R_2 = R_4 = \text{OCH}_3$ ; (II) methylwarifteine,  $R_1 = \text{OH}$ ;  $R_2 = R_3 = R_4 = \text{OCH}_3$ ; and (III) dimethylwarifteine,  $R_1 = R_2 = R_3 = R_4 = \text{OCH}_3$ .

Table 1. *Crystal data for MEW*

Molecular formula	C <sub>37</sub> H <sub>38</sub> N <sub>2</sub> O <sub>6</sub>	$D_c$	1.31 g cm <sup>-3</sup>
Crystal system	Orthorhombic	$F(000)$	1288
Space group	$P2_12_12_1$	$\lambda(\text{Cu } K\alpha_1)$	1.5405 Å
FW	606.357	$\mu(\text{Cu } K\alpha)$	5.566 cm <sup>-1</sup>
$V$	3085.812 Å <sup>3</sup>	Crystal size	0.2 × 0.3 × 0.3 mm
$Z$	4	Systematic absences	
Unit cell		$h00$	$h = 2n + 1$
$a$	17.539 (4) Å	$0k0$	$k = 2n + 1$
$b$	12.224 (3)	$00l$	$l = 2n + 1$
$c$	14.393 (3)	$\omega$ axis	$b$

Table 2. *Final positional parameters and, for H, isotropic thermal parameters*E.s.d.'s are in parentheses.  $\overline{U}^2$  is the mean-square amplitude of atomic vibration (Å<sup>2</sup>).

	$x$	$y$	$z$		$x$	$y$	$z$	$\overline{U}^2$
C(1)	0.9764(2)	0.3455(4)	0.3784(3)	H(3)	0.8629	0.1230	0.3951	0.054
C(2)	0.9563(2)	0.2368(4)	0.3937(3)	H(7)	0.7900	0.5419	0.3376	0.054
C(3)	0.8810(3)	0.2048(4)	0.3922(3)	H(8)	0.6384	0.3100	0.3894	0.093
C(4)	0.8255(3)	0.2799(4)	0.3704(4)	H(82)*	0.7054	0.3545	0.4653	0.093
C(5)	0.8427(3)	0.3873(4)	0.3467(3)	H(9)	0.7349	0.1839	0.4179	0.081
C(6)	0.9201(3)	0.4195(3)	0.3538(3)	H(92)	0.7275	0.2201	0.3047	0.081
C(7)	0.7807(3)	0.4642(4)	0.3116(3)	H(101)	0.6758	0.5955	0.3704	0.096
C(8)	0.6932(5)	0.3346(9)	0.3957(9)	H(102)*	0.6157	0.5017	0.4197	0.096
C(9)	0.7423(3)	0.2475(5)	0.3718(5)	H(103)*	0.7036	0.5207	0.4658	0.096
C(10)	0.6781(6)	0.5180(10)	0.4070(8)	H(111)	1.1370	0.4037	0.4600	0.086
C(11)	1.0806(3)	0.3891(5)	0.4705(5)	H(112)	1.0490	0.4439	0.5093	0.086
C(12)	1.0026(3)	0.0535(4)	0.4082(4)	H(113)	1.0780	0.3113	0.5039	0.086
C(13)	0.9134(2)	0.6145(3)	0.3706(3)	H(121)	1.0510	0.0104	0.4249	0.068
C(14)	0.8818(3)	0.6124(4)	0.4569(4)	H(122)	0.9588	0.0320	0.4544	0.068
C(15)	0.8487(2)	0.7083(4)	0.4925(3)	H(123)	0.9849	0.0329	0.3411	0.068
C(16)	0.8492(3)	0.8049(4)	0.4408(4)	H(14)	0.8750	0.5350	0.4749	0.063
C(17)	0.8836(2)	0.8047(3)	0.3559(4)	H(15)	0.8310	0.7023	0.5559	0.051
C(18)	0.9162(2)	0.7107(3)	0.3181(4)	H(17)	0.8849	0.8734	0.3120	0.062
C(19)	0.8121(3)	0.9080(4)	0.4806(5)	H(18)	0.9420	0.7070	0.2530	0.056
C(20)	0.7327(3)	0.8873(5)	0.5140(5)	H(19)	0.8526	0.9340	0.5291	0.077
C(21)	0.6468(5)	0.8502(9)	0.6369(5)	H(192)	0.8082	0.9585	0.4191	0.077
C(22)	0.6144(5)	0.7112(8)	0.5777(6)	H(211)	0.6501	0.8299	0.7039	0.108
C(23)	0.6096(3)	0.7961(5)	0.4814(5)	H(212)	0.6181	0.9024	0.6354	0.108
C(24)	0.6696(3)	0.8626(4)	0.4489(4)	H(221)	0.5601	0.7412	0.6014	0.119
C(25)	0.6637(3)	0.8896(4)	0.3561(4)	H(222)	0.6480	0.6905	0.5808	0.119
C(26)	0.6020(3)	0.8705(4)	0.3021(5)	H(28)	0.5077	0.7154	0.4552	0.093
C(27)	0.5454(3)	0.8022(4)	0.3354(5)	H(29)	0.4031	0.6683	0.2438	0.138
C(28)	0.5507(3)	0.7655(5)	0.4268(5)	H(292)	0.4181	0.6845	0.3597	0.138
C(29)	0.4460(5)	0.6759(7)	0.2947(8)	H(293)	0.4800	0.6095	0.2957	0.138
C(30)	0.5936(11)	0.8491(4)	0.1329(5)	H(30)	0.5278	0.8312	0.1234	0.088
C(31)	0.6436(3)	0.7495(5)	0.1394(4)	H(302)	0.6075	0.8925	0.0733	0.088
C(32)	0.6111(3)	0.6471(4)	0.1462(4)	H(32)	0.5543	0.6321	0.1373	0.072
C(33)	0.6512(3)	0.5555(4)	0.1628(4)	H(33)	0.6298	0.4810	0.1655	0.067
C(34)	0.7343(3)	0.5658(4)	0.1735(3)	H(35)	0.8209	0.6802	0.1625	0.073
C(35)	0.7665(3)	0.6681(5)	0.1614(4)	H(36)	0.7404	0.8297	0.1441	0.073
C(36)	0.7213(3)	0.7593(4)	0.1453(4)	H(37)	0.8336	0.4850	0.1776	0.068
C(37)	0.7813(3)	0.4708(4)	0.2050(3)	H(372)	0.7630	0.3992	0.1773	0.068
N(1)	0.7028(3)	0.4360(5)	0.3412(4)	H(4)	0.7052	0.9914	0.2482	0.081
N(2)	0.7227(4)	0.8852(5)	0.6031(4)					
O(1)	1.0168(2)	0.1685(2)	0.4140(2)					
O(2)	1.0511(2)	0.3792(2)	0.3806(3)					
O(3)	0.9439(2)	0.5230(2)	0.3269(2)					
O(4)	0.7168(2)	0.9688(3)	0.3210(3)					
O(5)	0.4877(2)	0.7747(4)	0.2756(4)					
O(6)	0.6003(2)	0.9193(3)	0.2147(3)					

\* Calculated position.

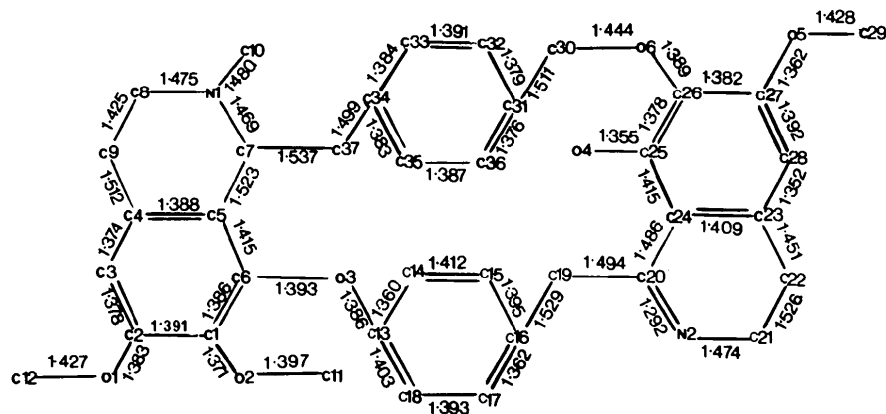


Fig. 2. Bond distances (Å) in MEW; e.s.d.'s are in the range 0.004 to 0.013 Å.

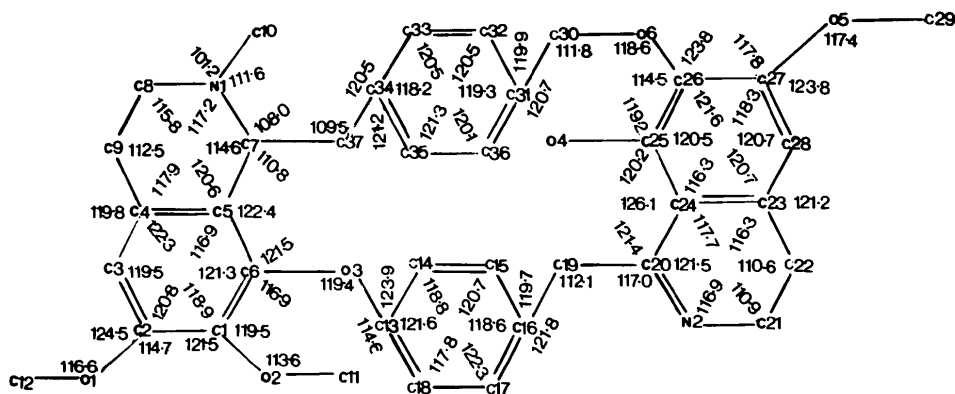


Fig. 3. Bond angles (°) in MEW; e.s.d.'s are in the range 0.2 to 0.7°.

### Structure determination and refinement

The structure was determined by direct methods using the tangent formula (Karle & Hauptman, 1956) as implemented by Germain, Main & Woolson (1971) in the program *MULTAN*. Using 228  $E$  values with  $E \geq 1.70$  and 2000  $\Sigma_2$  interactions, 16 phase sets were generated. The phase set having the second-highest figure of merit (0.96) and the lowest  $R_k$  (22.5) produced an  $E$  map with geometrically acceptable sites among the highest 60 peaks, and 36 of the 45 non-hydrogen atoms were thus provisionally identified. The remaining nine atoms were located from an electron density synthesis. The  $R$  factor for this trial structure, calculated with isotropic temperature factors  $\bar{U}^2 = 0.04 \text{ \AA}^2$  for all atoms, was 0.35.

Isotropic full-matrix least-squares refinement reduced  $R_{\text{obs}}$  to 0.16. Anisotropic thermal parameters for all non-hydrogen atoms were then introduced. All 405 parameters could not be refined in one cycle and consequently in a given cycle the positional and thermal parameters of only a selected number of atoms plus the overall scale factor were varied; the remaining atoms

were treated as 'fixed' atom contributors. Four complete passes of refinement reduced  $R_{\text{obs}}$  to 0.079. A difference electron density map then revealed the positions of 35 of the 38 H atoms in stereochemically feasible positions. The remaining three H-atom positions were calculated from known positions of other C and H atoms, with C-H distances of 1.04 Å and C-C-H angles of 109.5°. H atoms were included in all subsequent structure factor calculations with assigned isotropic temperature factors corresponding to those of the heavy atoms to which they were bonded. No attempt was made to refine the H-atom parameters. After two further passes of refinement the analysis was terminated at  $R_{\text{obs}} = 0.057$ ,  $R' = 0.087$ ,  $R = 0.073$ .\* A final difference map revealed no significant regions of density. Relative weights were assigned using the function  $w = [1 - \exp(-a \sin^2 \theta / \lambda^2)](1 + b|F_o| + c|F_o|^2 + d|F_o|^3)^{-1}$ , where  $a = 20$ ,  $b = 40$ ,  $c = 0.01$ ,

\* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33049 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

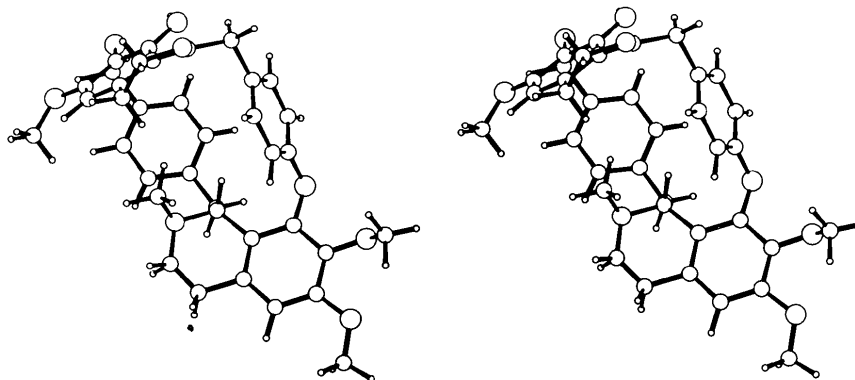


Fig. 4. Stereoscopic view of the molecule looking along *c*; the circles in increasing order of size represent H, C, N and O.

$d = 0.01$ . Using this weighting scheme the mean value of  $w(|F_o| - |F_c|)^2$  was approximately constant over the ranges of  $\sin \theta/\lambda$  and  $|F_o|$  in the final cycles of refinement.

Final positional parameters are given in Table 2. Figs 2 and 3 illustrate the numbering scheme and show the bond distances and bond angles involving the non-hydrogen atoms. C—H bond lengths are in the range 0.92 to 1.10 Å.

### Results and discussion

The overall shape of the molecule is illustrated in Fig. 4, which is a stereoscopic diagram of the molecule viewed along *c*. The average C—C bond lengths in the phenyl rings *A*, *C*, *D* and *F* are 1.389, 1.383, 1.388 and 1.387 Å respectively. The bonds C(23)—C(28), 1.352(9) Å, in ring *D*, and C(13)—C(14), 1.360(7) Å, in ring *F* are lower than the average C—C bonds by  $4\sigma$ . The heterocyclic rings *B* and *E* have average C—C bonds of 1.487 and 1.488 Å respectively. In ring *B*, C(8)—C(9) has a value of 1.425(11) Å, which is  $6\sigma$  smaller than the average value. The three C—N distances range from 1.469 to 1.480 Å (mean 1.475 Å). The average C—N bond distance is in good agreement with the value found in other alkaloids, for example 1.467 Å in tetrandrine (Gilmore, Bryan & Kupchan, 1976), and 1.50 Å in (+)-tubocurarine dichloride (Codding & James, 1973). The C=N double bond in the 3,4-dihydroisoquinoline ring is 1.292(7) Å, which compares well with the value of 1.288(13) Å found in dimethylwarifteine (Borkakoti & Palmer, 1978). Average C—C—C angles are  $120.0^\circ$  in all the phenyl rings. The average N—C—C angle for ring *B* is  $110.0^\circ$ , which is in good agreement with the average values obtained for tetrandrine ( $111.4^\circ$ ) and (+)-tubocurarine dibromide ( $110.3^\circ$ ) (Reynolds & Palmer, 1976). The C—C single bonds in the methylene linkages vary from 1.464 to 1.537 Å (mean 1.514 Å). The seven  $C_{\text{arom}}-\text{O}$  bonds have an average value of 1.377 Å. The mean value for the four  $C(sp^3)-\text{O}$  bonds is 1.428 Å, which,

Table 3. *Least-squares planes*

ATOMS MARKED (=) HAVE NOT BEEN INCLUDED IN THE CALCULATION OF THE PLANE

A) EQUATIONS OF THE LEAST-SQUARES PLANES

THE EQUATIONS FOR THE LEAST-SQUARES ARE IN THE FORM  $PX + QY + RZ = S$

PLANE	P	Q	R	S
A	0.1174	-0.2336	-0.9859	-4.3117
B	0.5060	-0.8049	-0.3100	-4.5658
C	0.0922	-0.1414	-0.9857	-2.2207
D	0.8762	0.2443	0.4153	18.0935

X, Y, Z ARE THE COORDINATES IN Å REFERRED TO THE AXES *a*, *b*, *c*.

B) DISTANCES (IN Å) OF THE ATOMS FROM THE LEAST-SQUARES PLANES

PLANE A		PLANE B	
ATOM	DEVIATION	ATOM	DEVIATION
C(1)	-0.0263	C(23)	-0.0150
C(2)	0.0350	C(24)	0.0081
C(3)	-0.0098	C(25)	0.0060
C(4)	-0.0235	C(26)	-0.0138
C(5)	0.0307	C(27)	0.0072
C(6)	-0.0061	C(28)	0.0073
C(7)=	0.1793	C(29)=	0.5489
C(8)=	-0.2858	C(30)=	0.8759
C(9)=	-0.1117	C(22)=	-0.0582
C(10)=	-1.5203	C(20)=	0.0354
C(11)=	-1.2274	C(21)=	-0.9103
C(12)=	-0.4434	C(19)=	-0.6841
C(37)=	-1.6440	N(2)=	-0.4304
O(1)=	0.0623	O(4)=	-0.0474
O(2)=	-0.0074	O(5)=	-0.0322
O(3)=	0.1197	O(6)=	-0.1195
N(1)=	-0.3034		
PLANE C		PLANE D	
ATOM	DEVIATION	ATOM	DEVIATION
C(31)	-0.0314	C(13)	-0.0140
C(32)	0.0175	C(14)	0.0112
C(33)	0.0133	C(15)	0.0018
C(34)	-0.0303	C(16)	-0.0120
C(35)	0.0187	C(17)	0.0097
C(36)	0.0142	C(18)	0.0034
O(8)=	-1.4423	O(3)=	-0.0790
C(30)=	-0.1655	C(19)=	-0.0352
C(37)=	0.2376		

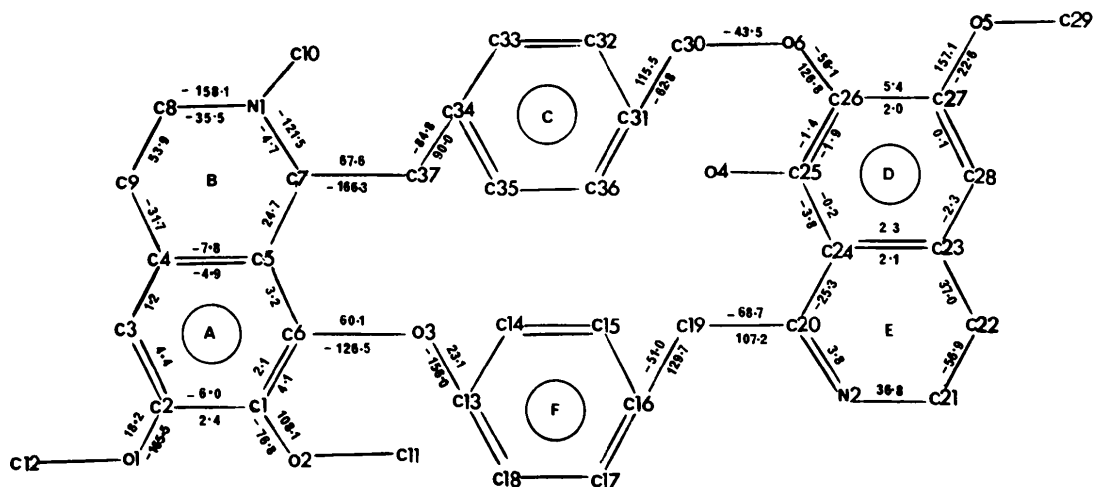
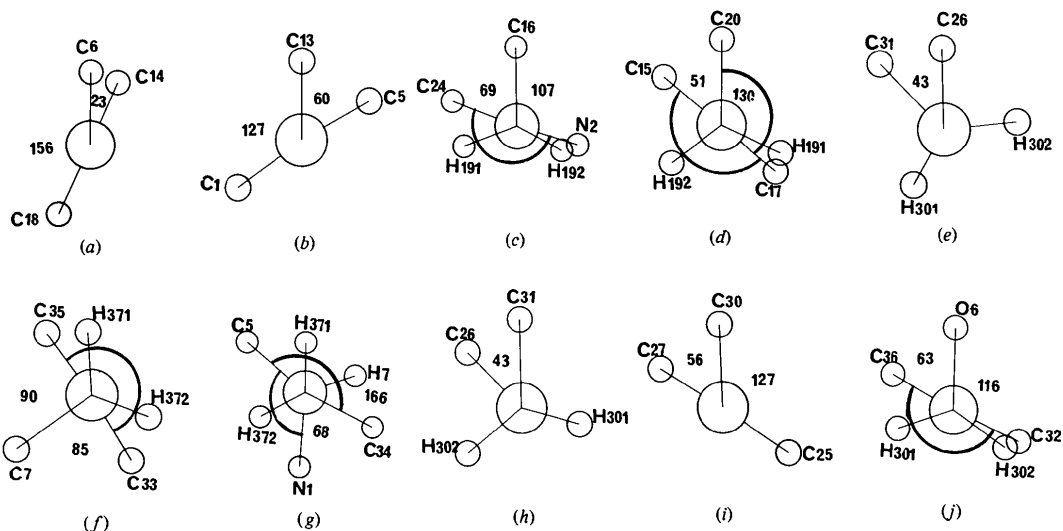
Fig. 5. Selected torsion angles ( $^{\circ}$ ) in MEW.

Fig. 6. Newman projections along bonds (a) O(3)–C(13), (b) O(3)–C(6), (c) C(19)–C(20), (d) C(19)–C(16), (e) O(6)–C(30), (f) C(37)–C(34), (g) C(37)–C(7), (h) C(30)–O(6), (i) O(6)–C(26), (j) C(30)–C(31).

though slightly larger than the average value of 1.408 Å for dimethylwarifteine, is smaller than the average values of 1.452 Å for (+)-tubocurarine dibromide, and 1.467 Å for tetrandrine.

Selected torsion angles are shown in Fig. 5. The methyl group attached to the N atom of the tetrahydroisoquinoline ring is axial. Details of the least-squares planes through the phenyl rings *A*, *C*, *D*, and *F* and the distances of the relevant atoms from these planes are given in Table 3. The rings *B* and *E* are in

the half-chair conformation with N(1) and C(8)  $-0.32$  and  $-0.79$  Å from the plane of ring *A*, and N(2) and C(21)  $-0.43$  and  $0.91$  Å from the plane of ring *D*. The pseudo twofold axis bisects bond C(8)–C(9) in ring *B* and bond C(21)–C(22) in ring *E*. The asymmetry parameters are  $\Delta C_2^{8,9} = 3.5^{\circ}$  and  $\Delta C_2^{21,22} = 2.7^{\circ}$  (Duax & Norton, 1975). The benzyl groups are rigorously planar, the maximum deviation of the atoms from plane *C* being  $-0.03$  Å and from plane *F*,  $-0.01$  Å. Of the three methoxy groups, those at O(1) and

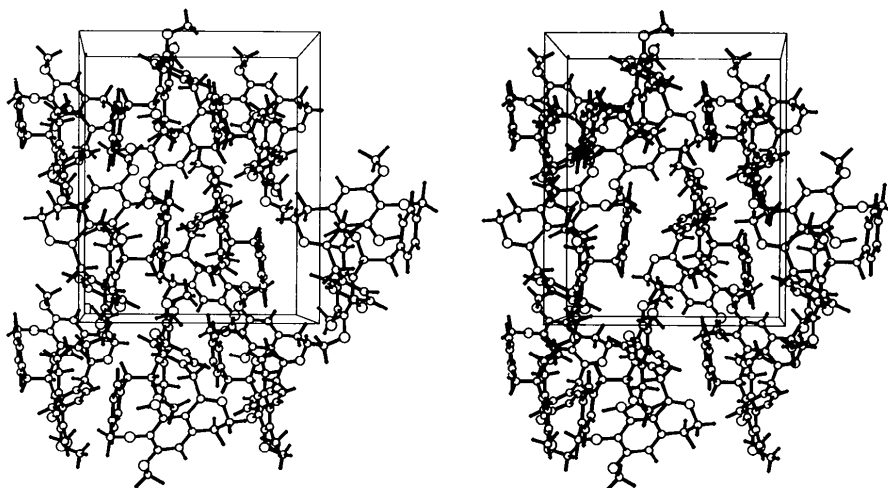


Fig. 7. Stereoscopic diagram illustrating the molecular packing as seen along *b*.

O(5) have the C atom close to the ring plane, while the methyl group attached to O(2) is out of the plane of the aromatic residue.

The conformations about the methylene, ether and methoxy linkages are shown in the Newman projections in Fig. 6. It can be seen that the conformations about the single bonds C(37)–C(7) and C(19)–C(20) are considerably different, indicating quite distinct orientations of the phenyl rings *C* and *F* with respect to the corresponding isoquinoline residue (Fig. 6*g* and *c* respectively).

Fig. 4, which is a stereodiagram of the molecule seen along *c*, shows that the O atoms of the molecule are grouped on two halves of the molecule, three [O(1), O(2), O(3)] on the upper-left and three others [O(4), O(5), O(6)] on the lower-right side of the molecule. A stereoview of the packing of the molecules along *b* is given in Fig. 7. The crystal structure is loosely held together by a small number of van der Waals contacts.

The overall conformation of the molecule is best described in terms of the torsion angles about the bonds linking the semi-rigid isoquinoline groups and the rigid phenyl units (Fig. 5). Folding of the molecule is predominantly governed by the torsion angle C(16)–C(19)–C(20)–C(24) =  $-68.7^\circ$ , whereas C(1)–C(6)–O(3)–C(13) =  $-126.5^\circ$ , C(5)–C(7)–C(37)–C(34) =  $-166.3^\circ$  and C(25)–C(26)–O(6)–C(30) =  $126.8^\circ$  constrain three sides of the molecule in a fairly open conformation.

All calculations were carried out on the CDC 6600 computer of London University. Programs used are

from the Birkbeck College Crystallography Department.

We wish to thank Dr C. Gorinsky for supplying the crystals. One of us (NB) was the recipient of a grant from the Science Research Council during the course of this work.

#### References

- BORKAKOTI, N. & PALMER, R. A. (1978). *Acta Cryst.* **B34**, 482–489.
- CODDING, P. W. & JAMES, M. N. G. (1973). *Acta Cryst.* **B29**, 935–942.
- DUAX, W. L. & NORTON, D. A. (1975). *Atlas of Steroid Structure*. London: Plenum.
- GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* **A27**, 368–376.
- GILMORE, C. J., BRYAN, R. F. & KUPCHAN, S. M. (1976). *J. Am. Chem. Soc.* **98**, 1947–1952.
- GORINSKY, C., COLYER, R. M. & WALKER, K. (1970). Personal communication.
- KARLE, J. & HAUPTMAN, H. (1956). *Acta Cryst.* **9**, 635–651.
- KUPCHAN, S. M., KUBOTA, S., FUJITA, E., KOBAYASHI, S., BLOCK, J. H. & TELANG, S. A. (1966). *J. Am. Chem. Soc.* **88**, 4212–4218.
- KUPCHAN, S. M., PATEL, A. C. & FUJITA, E. (1965). *J. Pharm. Sci.* **54**, 580–583.
- REYNOLDS, C. D. (1974). PhD Thesis, Univ. of London.
- REYNOLDS, C. D. & PALMER, R. A. (1976). *Acta Cryst.* **B32**, 1431–1439.
- SNEDDEN, W., PARKER, R. B. & GORINSKY, C. (1970). *Org. Mass. Spectrom.* **4**, 607–614.