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Structure of Jacobine Methanol Solvate, $C_{18}H_{25}NO_6.CH_4O$

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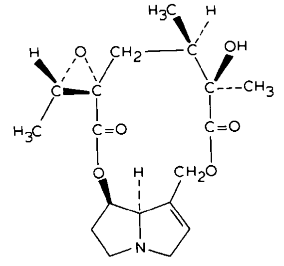
Abstract. $M_r = 383\cdot44$, orthorhombic, $P2_12_12_1$, $a = 10\cdot9903\ (8)$, $b = 20\cdot530\ (1)$, $c = 8\cdot9550\ (6)$ Å, $V = 2020\cdot5$ Å^3, $Z = 4$, $D_x = 1\cdot260$ g cm^{-3}, Ni-filtered Cu $K\alpha$, $\lambda = 1\cdot5418$ Å, $\mu = 7\cdot59$ cm^{-1}, $F(000) = 824$, $T = 257$ K, $R = 0\cdot044$ for 2373 unique reflections. The conformations of the pyrrolizidine ring system and the 12-membered macrocyclic ring in this structure are surprisingly similar to the conformations observed in three other pyrrolizidine alkaloids containing a 12-membered macrocyclic ring. This structural consistency suggests that this is a preferred conformation for this type of molecule.

Introduction. Large numbers of people have been poisoned when plants containing hepatotoxic pyrrolizidine† alkaloids, such as jacobine, have been harvested with cereal or grain crops (Mohabbat, Younos, Merzad, Srivastava, Sediq & Aram, 1976). Human exposure to these pyrrolizidine alkaloids can also occur through consumption of herbal teas or indirectly from honey or milk when foraging of plants containing these alkaloids occurs (Deinzer, Thomson, Burgett & Isaacson, 1977; Culvenor, Edgar & Smith, 1981). Some concern has also arisen over the possibility that low levels of these alkaloids in food may produce tumors (Culvenor & Jago, 1979).

Crystallographic studies on jacobine were undertaken to explore the structural and hydrogen-bonding characteristics of the molecule. These results have been used as an aid to understanding the results of positive and negative ion methane chemical ionization mass spectrometry studies of a series of pyrrolizidine alkaloid derivatives (Karchesy, Deinzer, Griffin & Rohrer, 1984).



Experimental. Colorless rod-shaped crystals grown by slow evaporation of a methanol solution yielding a crystal 0·4 × 0·4 × 0·8 mm. CAD-4 diffractometer equipped with a cool stream, 257 K, 2373 independent intensities, 2θ limit 150°, θ–2θ scan. Intensity data measured and saved as profiles of 96 intervals for each scan. 4 standard intensities used to monitor variations in intensity data, <3% variation observed. Least-squares procedure based on centered 2θ values of 25 reflections in range 70 to 80° used to refine lattice parameters. Profile intensity data converted into integrated net intensities (Blessing, 1980) and structure-factor amplitudes. h 0–13, k 0–25, l 0–11. Structure determined using direct-methods program *MULTAN* (Main, Lessinger, Woolfson, Germain & Declercq, 1977) in conjunction with the NQEST figure-of-merit

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† Pyrrolizidine is 5,6,7,7a-tetrahydro-3*H*-pyrrolizine.

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program (DeTitta, Edmonds, Langs & Hauptman, 1975). Refinement of coordinates of all atoms, anisotropic thermal parameters for non-hydrogens and isotropic thermal parameters for hydrogens with full-matrix least squares based on F. $w = (1/\sigma^2_F)$, σ_F as defined by Stout & Jensen (1968). Final R and R_w 0·044 and 0·065 for 2336 data with $F > 2\sigma_F$, final R for all 2373 data 0·044. Atomic scattering factors calculated from coefficients given in Table 2.2*B* of *International Tables for X-ray Crystallography* (Cromer & Waber, 1974). $\Delta_{\max}/\sigma = 0·8$, max. and min. heights in final difference Fourier synthesis = 0·3 and $-0·2$ e Å^{-3}.

Discussion. The final fractional atomic coordinates and equivalent isotropic thermal parameters (Hamilton, 1959) for the non-hydrogen atoms are given in Table 1,* with Fig. 1 showing the geometry and anisotropic thermal ellipsoids at the 60% level (Johnson, 1965). The bond lengths and angles are shown in Fig. 2 with the torsion angles given in Table 2. The e.s.d.'s in the bond lengths range from 0·002 to 0·004 Å, except for the methanol bond length (1·340 Å) where the e.s.d. is 0·008 Å, and the e.s.d.'s for the angles range from 0·1 to 0·2°.

The bond lengths and angles in this structure agree exceptionally well with those observed in the unsolvated crystal structure of jacobine (Pérez-Salazar, Cano & García-Blanco, 1978). In most cases, the corresponding structural parameters in the two structures agree within one e.s.d. Similarly, the conformations are essentially identical, despite the addition of a solvent molecule in the structure reported here and the change of crystal system and space group from monoclinic $P2_1$ to orthorhombic $P2_12_12_1$. This indicates that the conformation of the molecule is determined primarily by intramolecular forces and is suitable for comparison with solution and gas-phase spectral results.

The conformation of the pyrrolizidine ring system is also very similar to that observed in the crystal structures of two other pyrrolizidine alkaloids with a 12-membered macrocyclic ring: retrorsine (Stoeckli-Evans, 1979) and swazine (Laing & Sommerville, 1972). The five-membered ring formed by C(1), C(2), C(3), N(4) and C(8) has an N(4)-envelope conformation as indicated by the mirror asymmetry parameter (Duax, Weeks & Rohrer, 1976), ΔC_s(N4), value of 0·8. The other five-membered ring, N(4),C(5),C(6),C(7) and C(8), has a C(6)-envelope conformation, ΔC_s(C6) = 6·8, distorted toward a C(6)/C(7)-half-chair conformation, ΔC_2(C6/C7) = 11·5.

Table 1. *Fractional atomic coordinates* (×10^5) *and equivalent isotropic thermal parameters* (Å^2 × 10^2) *for the non-hydrogens in jacobine methanol solvate*

$$B_{\rm eq} = \tfrac{4}{3}\textstyle\sum_i\sum_j\beta_{ij}(\mathbf{a}_i.\mathbf{a}_j).$$

The e.s.d.'s are given in parentheses.

	x	y	z	$B_{\rm eq}$
C(1)	6328 (18)	75644 (9)	−4539 (22)	293 (4)
C(2)	14007 (22)	73532 (12)	−14888 (24)	358 (5)
C(3)	14273 (23)	66291 (13)	−15682 (26)	384 (5)
N(4)	4361 (15)	64197 (8)	−5375 (19)	293 (3)
C(5)	7806 (26)	59176 (11)	5627 (27)	394 (5)
C(6)	1420 (23)	61192 (10)	19979 (25)	351 (5)
C(7)	2455 (17)	68559 (9)	19625 (20)	259 (4)
C(8)	121 (16)	70032 (9)	3109 (20)	253 (4)
C(9)	2865 (22)	82586 (10)	−1924 (29)	368 (5)
O(10)	8456 (13)	85266 (7)	11517 (20)	347 (3)
C(11)	19672 (18)	87788 (9)	9591 (24)	292 (4)
C(12)	24659 (18)	90564 (9)	24228 (25)	306 (4)
C(13)	24341 (20)	85291 (9)	36532 (24)	319 (4)
C(14)	32956 (18)	79655 (9)	32437 (24)	283 (4)
C(15)	30073 (17)	73323 (9)	40464 (21)	269 (4)
C(16)	17377 (17)	70699 (9)	37981 (21)	260 (4)
O(17)	14844 (12)	70617 (7)	23298 (15)	261 (3)
O(20)	24912 (15)	87831 (9)	−2162 (19)	387 (4)
C(21)	17060 (24)	96601 (10)	28048 (34)	426 (6)
O(22)	36752 (15)	92798 (7)	21712 (21)	364 (4)
C(23)	26885 (36)	87982 (16)	51878 (34)	501 (7)
O(24)	33934 (16)	72787 (8)	55762 (17)	386 (4)
C(25)	39693 (20)	68756 (11)	44679 (27)	362 (5)
C(26)	37751 (31)	61553 (15)	46297 (53)	555 (9)
O(27)	10596 (15)	68973 (9)	47536 (17)	378 (4)
C(*M*)	58783 (54)	99796 (26)	42525 (87)	862 (15)
O(*M*)	49773 (37)	102754 (14)	35064 (67)	1035 (15)

Table 2. *Torsion angles* (°) *for the non-hydrogen atoms in jacobine*

The e.s.d.'s are given in parentheses.

C(8)C(1)C(2)C(3)	−0·7 (3)	O(20)C(11)C(12)C(21)	111·0 (2)
C(9)C(1)C(2)C(3)	−173·1 (2)	O(20)C(11)C(12)O(22)	−3·6 (3)
C(2)C(1)C(8)C(7)	113·6 (2)	C(12)C(11)O(10)C(9)	179·1 (2)
C(2)C(1)C(8)N(4)	−5·6 (2)	O(20)C(11)O(10)C(9)	−0·7 (3)
C(9)C(1)C(8)C(7)	−73·8 (2)	C(11)C(12)C(13)C(14)	64·4 (2)
C(9)C(1)C(8)N(4)	167·0 (2)	C(11)C(12)C(13)C(23)	−169·3 (2)
C(2)C(1)C(9)O(10)	−106·2 (2)	C(21)C(12)C(13)C(14)	−175·5 (2)
C(8)C(1)C(9)O(10)	82·3 (2)	C(21)C(12)C(13)C(23)	−49·2 (3)
C(1)C(2)C(3)N(4)	6·6 (3)	O(22)C(12)C(13)C(14)	−55·8 (2)
C(2)C(3)N(4)C(5)	−130·3 (2)	O(22)C(12)C(13)C(23)	70·5 (2)
C(2)C(3)N(4)C(8)	−9·9 (2)	C(12)C(13)C(14)C(15)	−159·2 (2)
N(4)C(5)C(6)C(7)	−37·6 (2)	C(23)C(13)C(14)C(15)	74·2 (2)
C(6)C(5)N(4)C(3)	140·3 (2)	C(13)C(14)C(15)C(16)	58·1 (2)
C(6)C(5)N(4)C(8)	19·6 (2)	C(13)C(14)C(15)C(25)	−147·0 (2)
C(5)C(6)C(7)C(8)	40·2 (2)	C(13)C(14)C(15)O(24)	−77·9 (2)
C(5)C(6)C(7)O(17)	−74·9 (2)	C(14)C(15)C(16)O(17)	49·3 (2)
C(6)C(7)C(8)C(1)	−146·8 (2)	C(14)C(15)C(16)O(27)	−130·5 (2)
C(6)C(7)C(8)N(4)	−28·8 (2)	C(25)C(15)C(16)O(17)	−106·3 (2)
O(17)C(7)C(8)C(1)	−30·1 (2)	C(25)C(15)C(16)O(27)	73·8 (3)
O(17)C(7)C(8)N(4)	87·9 (2)	O(24)C(15)C(16)O(17)	−172·7 (2)
C(6)C(7)O(17)C(16)	−80·6 (2)	O(24)C(15)C(16)O(27)	7·4 (3)
C(8)C(7)O(17)C(16)	168·6 (1)	C(14)C(15)C(25)C(26)	−152·4 (2)
C(1)C(8)N(4)C(3)	9·5 (2)	C(14)C(15)C(25)O(24)	105·0 (2)
C(1)C(8)N(4)C(5)	134·7 (2)	C(16)C(15)C(25)C(26)	1·7 (3)
C(7)C(8)N(4)C(3)	−119·2 (2)	C(16)C(15)C(25)O(24)	−100·9 (2)
C(7)C(8)N(4)C(5)	5·9 (2)	O(24)C(15)C(25)C(26)	102·6 (3)
C(1)C(9)O(10)C(11)	86·7 (2)	C(14)C(15)O(24)C(25)	−112·1 (2)
O(10)C(11)C(12)C(13)	54·9 (2)	C(16)C(15)O(24)C(25)	110·7 (2)
O(10)C(11)C(12)C(21)	−68·7 (2)	C(15)C(16)O(17)C(7)	−176·2 (1)
O(10)C(11)C(12)O(22)	176·6 (2)	O(27)C(16)O(17)C(7)	3·6 (3)
O(20)C(11)C(12)C(13)	−125·4 (2)	C(26)C(25)O(24)C(15)	−115·3 (3)

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39369 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The two rings are joined in a pseudo-*cis* fusion along the N(4)–C(8) bond with a 41·4 (2)° dihedral angle formed by the least-squares planes calculated for the two five-membered rings.

The similarity between the two jacobine 12-membered macrocyclic ring conformations is demonstrated by the very small value, 1·4 (1·0)°, of the average difference between the corresponding intraring torsion angles. This similarity of the 12-membered macrocyclic ring structures also extends to the conformations of the 12-membered rings in retrorsine and swazine. The intraring torsion angles for the four molecules given in Table 3 clearly show that the ring conformations have a great deal of internal consistency. The mean variation in the range of the corresponding torsion angles in the molecules is only 11·7 (7·8)°. The largest degree of flexibility involves the bonds to C(9) and C(15) where the torsion angles vary by as much as 24°. The consistency of these data provide further evidence that the ring conformations are controlled by intramolecular factors since these structures not only have packing differences but also substituent differences. Another important feature of the macrocyclic ring conformation is that it directs the two carbonyl bonds, C(11)=O(20) and C(16)=O(27), to nearly antiparallel orientations, see Fig. 1.

The hydroxyl groups on the jacobine and methanol molecules are both involved in forming hydrogen bonds. The methanol hydroxyl forms a hydrogen bond to O(22) of jacobine. In addition to accepting a hydrogen bond from the methanol, O(22) forms a hydrogen bond to N(4) of a symmetry-related molecule. Hydrogen-bond distances and angles are given in Table 4.

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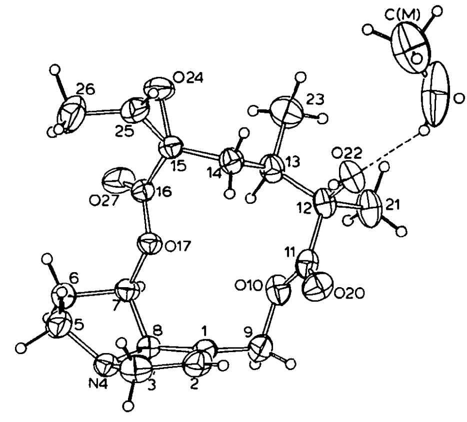

Fig. 1. Perspective drawing of the jacobine molecule. The thermal ellipsoids are drawn at the 60% probability level.

Table 3. *Intraring torsion angles* (°) *for the* 12-*membered macrocyclic ring in jacobine methanol solvate, jacobine, retrorsine and swazine*

	Jacobine methanol solvate	Jacobine	Retrorsine	Swazine	Average
C(1)C(9)O(10)C(11)	86·7	88·4	79·5	97·3	88·0
C(9)O(10)C(11)C(12)	179·1	179·2	177·5	182·4	179·6
O(10)C(11)C(12)C(13)	54·9	51·8	50·3	63·3	55·1
C(11)C(12)C(13)C(14)	64·4	63·3	59·3	60·3	61·8
C(12)C(13)C(14)C(15)	−159·2	−159·3	−157·5	−152·5	−157·1
C(13)C(14)C(15)C(16)	58·1	59·8	78·6	64·9	65·4
C(14)C(15)C(16)O(17)	49·3	50·7	36·3	28·4	41·2
C(15)C(16)O(17)C(7)	−176·2	−175·8	−175·7	−173·0	−175·2
C(16)O(17)C(7)C(8)	168·6	167·2	163·5	175·5	168·7
O(17)C(7)C(8)C(1)	−30·1	−29·3	−27·4	−30·9	−29·4
C(7)C(8)C(1)C(9)	−73·8	−75·3	−74·6	−68·4	−73·0
C(8)C(1)C(9)O(10)	82·3	85·6	93·6	69·3	82·7

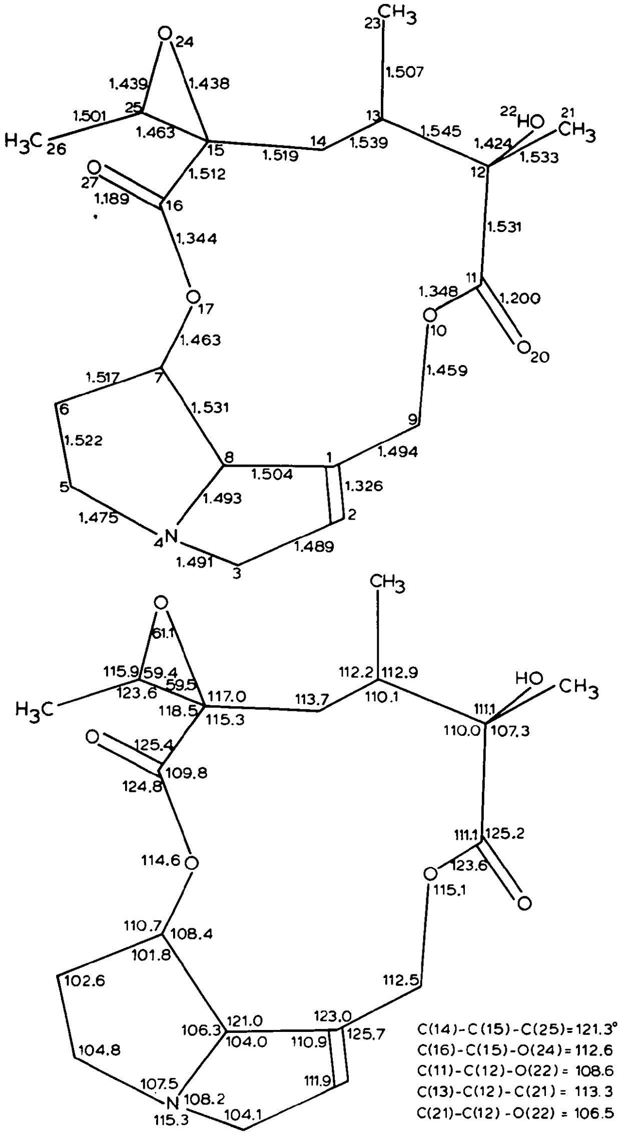

Fig. 2. Structural parameters for jacobine. (*a*) Bond distances (Å). (*b*) Bond angles (°).

Table 4. *Hydrogen-bond distances* (Å) *and angles* (°) *in the structure of jacobine methanol solvate*

The e.s.d.'s are given in parentheses.

D—H···A	D—H	H···A	D···A	∠ D—H···A
O(M)—H···O(22) [x,y,z]	0·89 (7)	2·04 (8)	2·767 (4)	139 (5)
O(22)—H···N(4) [$\frac{1}{2}+x,\frac{3}{2}-y,-z$]	0·87 (3)	1·99 (3)	2·819 (2)	159 (2)

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Structure of 2,11,20,29-Tetrathia[3.3.3.3]parabenzenophane, $C_{32}H_{32}S_4$

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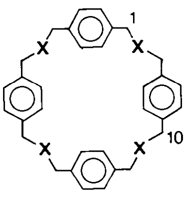
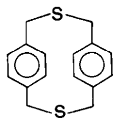
Abstract. $M_r = 544{\cdot}86$, orthorhombic, $Pccn$, $a = 20{\cdot}607\,(3)$, $b = 20{\cdot}121\,(3)$, $c = 6{\cdot}622\,(1)$ Å, $V = 2745{\cdot}7\,(7)$ Å^3, $Z = 4$, $D_m = 1{\cdot}316$ (flotation in KI/H_2O), $D_x = 1{\cdot}318$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 3{\cdot}51$ cm^{-1}, $F(000) = 1152$, $T = 295$ K, final $R_F = 0{\cdot}045$ for 2151 observed reflections. An improved synthesis of the title compound yielded a product whose m.p. of 527–529 K is 55 K higher than the literature value. The four S atoms are coplanar as are each benzene ring and its two methylene carbons. The conformation reduces the size of the central cavity. There are no unusual close contacts.

Introduction. Macrocyclic heterocyclophanes 2,11,20,29-tetrathia[3.3.3.3]parabenzenophane (I) (Tabushi, Sasaki & Kuroda, 1976) and N,N',N'',N'''-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]parabenzenophane (II) (Tabushi, Kimura & Kuroda, 1976; Tabushi, Kimura & Yamamura, 1978, 1981) have recently emerged as a novel class of compounds in the area of inclusion chemistry. The alkylatable exterior heteroatoms together with the hydrophobic cavity in these cyclic systems endow them with the unique ability to form water-soluble host molecules which exhibit marked binding capacity and catalytic specificity toward certain organic substrates. By analogy to the [2^n]paracyclophanes whose conformations in solution (Tabushi, Yamada & Kuroda, 1975) were well analyzed by variable-temperature NMR, the shapes of the cavities in both (I) and (II) were assumed to be approximately square with the benzene rings lying perpendicular to the mean plane of the four heteroatoms (Tabushi, Sasaki & Kuroda, 1976; Tabushi, Kimura & Kuroda, 1976). However, direct structural determination of these compounds has not



(I) X = S

(II) X = NCH₃



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