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THE ABSOLUTE MOLECULAR STRUCTURE OF (-)-PODOPETALINE

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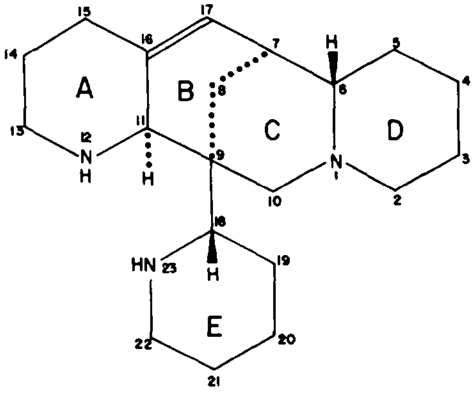
Abstract—X-ray analysis of crystals of podopetaline hydrobromide, $C_{20}H_{33}N_3 \cdot HBr$, has established the absolute structure of podopetaline, an alkaloid from *Podopetalum ormondii* F. Muell. The crystals are orthorhombic, with unit cell dimensions, $a = 6{\cdot}619$, $b = 10{\cdot}907$, $c = 26{\cdot}806$ Å, $Z = 4$, the space group being $P2_12_12_1$. The intensity data were measured with CuKα radiation on a single-crystal diffractometer. The crystal structure was solved by the heavy atom method and refined by difference and least-squares procedures to a final R index of 0·069 for the 849 observed terms. The absolute chirality has been defined by Bijvoet's technique. Podopetaline (I) therefore provides an absolute chirality reference for *Ormosia* alkaloids which was not previously available.

(-)-Podopetaline, $C_{20}H_{33}N_3$, is a major alkaloid occurring in the Australian plant *Podopetalum ormondii* F. Muell. (family Leguminosae). Alkaloids related to a $C_{20}H_{35}N_3$ pentacyclic parent structure[1] have also been isolated from species of *Ormosia* indigenous to the tropical regions of the Americas and South-East Asia[2-7] and from species of *Piptanthus*.[8,9] Structural assignment, however, within the group has been difficult because of the large number of possible stereoisomers differing in relative or absolute configuration or both.[10] Extensive chemical evidence[8-13] and subsequent synthesis[14] have established the structure of the base (-)-piptanthine, $C_{20}H_{35}N_3$, isolated from *P. nanus*.[9] The isomeric base ormosanine, $C_{20}H_{35}N_3$, isolated from species of *Ormosia* in both optically active[3,4] and *racemic*[15] form and from species of *Piptanthus*[8] has also been the subject of much chemical study.[12,16,17] Its structure given as (2) was deduced finally from an X-ray analysis of the related alkaloid (+)-jamine,[18] $C_{21}H_{35}N_3$, (3), which can be obtained from ormosanine by reaction with formaldehyde.[15] Piptanthine is therefore an epimer of ormosanine differing only in relative configuration at C(6). These two alkaloids recently have been isolated in *racemic* form from the Asian species of *Ormosia semicastrata*,[7] together with 18-epiormosanine[19] and a fourth base, originally named ormocastrine, but now known to be podopetaline hydrochloride.[20]



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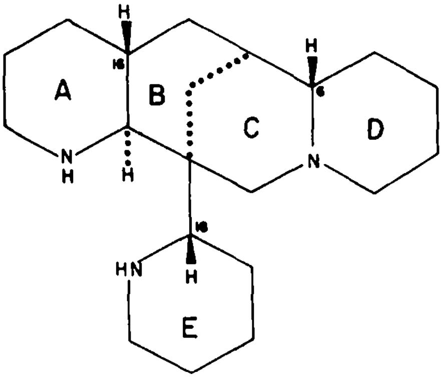

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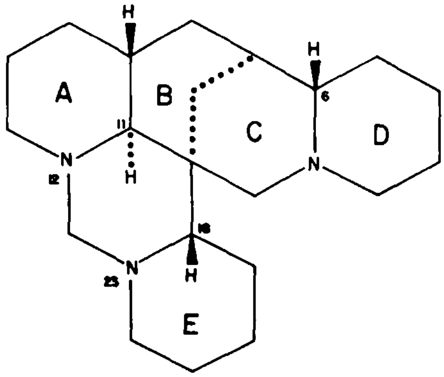
To determine the absolute molecular structure of podopetaline and thus establish the absolute chirality of other alkaloids in this group, an X-ray analysis of the hydrobromide salt of podopetaline was undertaken. A brief report has been presented earlier.[21]



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STRUCTURE AND DISCUSSION

A perspective view of the podopetaline cation is given in Fig. 1 while the conventional representation of the absolute molecular structure is shown as 1 (see also Fig. 2).

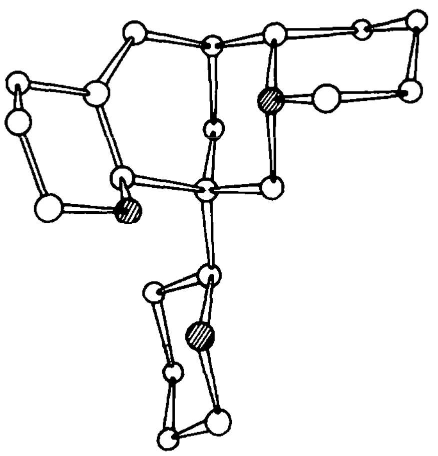

Fig. 1. A perspective view of the podopetaline cation.

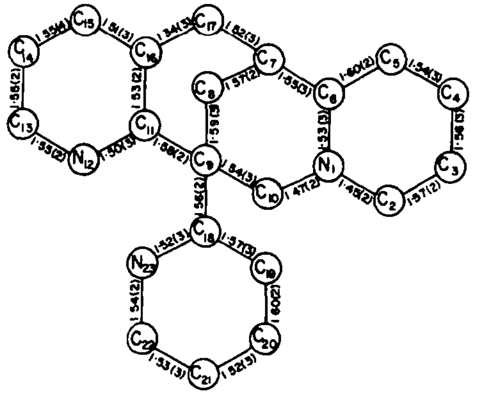

Fig. 2. (a) Bond lengths (Å); estimated standard deviations in brackets;

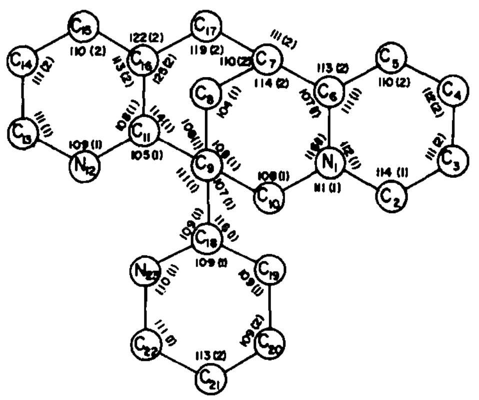

Fig. 2. (b) Bond angles; estimated standard deviations in brackets.

Podopetaline has a molecular skeleton composed of five 6-membered rings. Rings A, B, C and D are fused and thus form a rigid framework, while ring E linked to C(9) at the junction of rings B and C is free to rotate about the bond C(9)–C(18). The three reduced rings, C, D and E, have a regular chair conformation while ring A deviates a little from a regular chair because of the sp^2 hybridization at C(16). The cyclohexene ring B, with the double bond between atoms C(16) and C(17), instead of the expected half-chair form is constrained by its fusion with rings A and C to adopt a sofa conformation in which the five ring atoms C(11), C(16), C(17), C(7) and C(9) are nearly coplanar (mean deviation 0·02 Å) with C(8) lying 0·83 Å from the plane. Other examples of this conformation have been noted in codeine,[22] bromomiroestrol[22] and kreysiginine.[23] Ring C is *cis*-fused to ring D and ring E is oriented relative to the fused ring system so that the dihedral angles associated with the groups of atoms C(19), C(18), C(9), C(8) and N(23), C(18), C(9), C(11) are 55·5 and 62·7° respectively. The three nitrogen atoms in the molecule N(1), N(12) and N(23) occupy positions mutually δ to one another.

The saturated C–C bonds have an average value of 1·56 Å (mean deviation 0·02 Å). The double bond C(16)–C(17) is 1·34 Å and the mean of seven C–N bond lengths is 1·51 Å (mean deviation 0·03 Å). The average value of the five C–N–C bond angles is 111·5° (mean deviation 1·6°) which is not significantly different from the value expected for a tetrahedral angle.

The molecular packing in the crystal is illustrated in Fig. 3. The T-shaped molecules are interleaved to form a bilayer structure which is held together by ionic forces between the bromine ions and ionic $>N^+H_2$ groups. Each bromine ion lies approximately mid-way between the nitrogen atoms of rings E of two adjacent molecules, the Br--N(23) distances being 3·27 and 3·35 Å respectively. N(23) obviously carries the protonic charge. By contrast, the Br approach to N(12) is 3·82 Å. There is no close approach of Br to N(1). Other intermolecular approaches less than 3·90 Å are given in Table 2. The forces between the bilayer units are van der Waals, no close approaches being involved (see Fig. 3).

Podopetaline is found to have the same relative configuration at C(6), C(11) and C(18) as the related alkaloid jamine shown in 3. In the latter, N(12) and N(23) are bridged by a methylene group so that the molecule has a rigid framework in which six 6-membered ring systems are fused together. The chair conformation for ring C in podopetaline and the *cis* junction at rings C and D are in contrast to the situation in jamine and the related base panamine[24] in which ring C is in the boat conformation and the junction at rings C and D is *trans*. It has been suggested that the *trans* conformation noted in jamine[21] and presumably panamine has arisen because of steric interaction between the H atom at C(16) and the lone pair of electrons on N(1). In podopetaline, the absence of hydrogen at C(16) allows the *cis* conformation to occur. This results in ring C adopting the chair conformation. A similar situation to that noted in jamine probably also occurs in the reduced base ormosanine.

The absolute structure determined for podopetaline, which has five asymmetric carbon atoms in the molecule at C(6), C(7), C(9), C(11) and C(18), provides a reference absolute chirality for other alkaloids in this series.

EXPERIMENTAL

Colourless orthorhombic needles of (-)-podopetaline hydrobromide, $C_{20}H_{33}N_3 \cdot HBr$, were found from Weissenberg photographs to belong to the space group $P2_12_12_1$. The unit cell parameters, determined from diffractometer settings, were $a = 6{\cdot}619(3)$, $b = 10{\cdot}907(4)$, $c = 28{\cdot}806(6)$ Å, $U = 1935{\cdot}2$ Å^3. The density, D_m = 1·34 g.cm^{-1}, measured by flotation in a mixture of bromoform and xylene is in accord with the value, D_x = 1·36, calculated on the basis

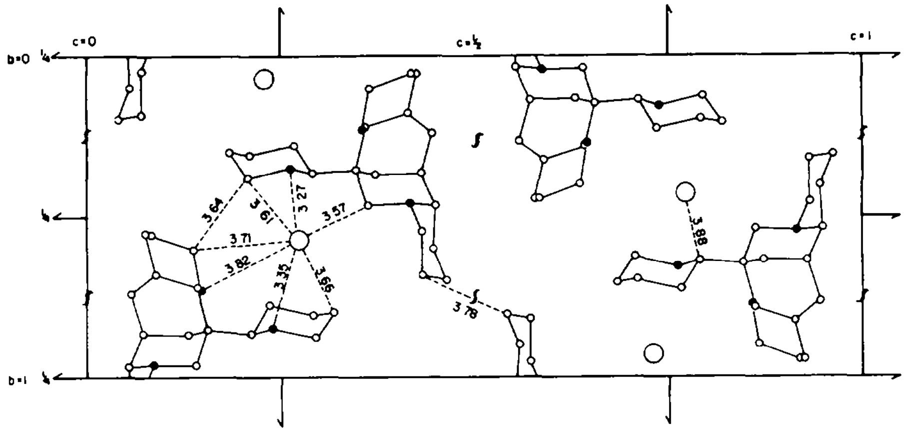

Fig. 3. Projection of the structure down the *a* axis. Selected approach distances are indicated.

Table 1. Atomic parameters of the absolute structure with their estimated standard deviation, all × 10^4, referred to a right-handed set of axes. The thermal parameters are in the form given by the expression $\exp[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})]$

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	9212(3)	0699(2)	2287(1)	0388(6)	0077(1)	0020(0)	0030(4)	0003(2)	-0002(1)
N(1)	7541(23)	4582(10)	4155(5)	0364(51)	0038(13)	0018(2)	0014(22)	-0001(10)	-0005(4)
C(2)	9039(34)	5469(13)	4308(6)	0383(58)	0054(15)	0023(3)	-0002(34)	-0006(14)	-0003(5)
C(3)	8262(37)	6830(17)	4300(6)	0547(90)	0147(24)	0015(3)	-0008(38)	0006(14)	-0004(6)
C(4)	6261(33)	6956(15)	4605(6)	0371(80)	0098(19)	0020(3)	-0005(34)	-0008(14)	-0001(6)
C(5)	4676(35)	6002(14)	4446(6)	0521(87)	0072(19)	0021(3)	+0044(32)	0005(14)	-0012(6)
C(6)	5641(34)	4662(13)	4476(6)	0317(61)	0080(17)	0024(3)	0011(34)	0037(15)	0003(6)
C(7)	4183(37)	3643(15)	4289(6)	0448(66)	0100(17)	0018(3)	-0019(40)	0016(16)	-0004(6)
C(8)	3737(30)	3683(14)	3714(5)	0446(76)	0101(16)	0016(3)	0015(33)	0008(12)	-0008(6)
C(9)	5906(36)	3527(15)	3464(5)	0419(68)	0130(19)	0011(3)	0002(41)	0040(14)	-0002(6)
C(10)	7206(34)	4634(12)	3612(5)	0635(80)	0068(17)	0009(2)	-0062(31)	-0009(12)	-0014(5)
C(11)	6710(28)	2198(15)	3597(5)	0372(67)	0108(19)	0011(2)	0065(30)	0010(11)	0009(6)
N(12)	8964(25)	2297(12)	3555(5)	0373(53)	0120(15)	0013(2)	0003(32)	0018(10)	0000(5)
C(13)	9910(32)	1017(14)	3652(6)	0627(96)	0103(20)	0018(3)	0094(32)	-0028(13)	-0001(6)
C(14)	9361(45)	0546(18)	4182(6)	0647(96)	0128(22)	0018(3)	-0037(55)	0001(16)	-0000(7)
C(15)	7044(40)	0536(17)	4253(7)	0634(97)	0084(21)	0023(4)	0055(39)	-0007(16)	0027(7)
C(16)	6195(38)	1778(17)	4126(7)	0472(89)	0115(21)	0022(4)	-0024(41)	0006(16)	-0007(7)
C(17)	4956(33)	2381(17)	4439(7)	0447(95)	0107(22)	0023(4)	-0105(33)	-0000(15)	0005(7)
C(18)	5511(30)	3643(15)	2893(5)	0289(59)	0170(17)	0013(3)	-0037(34)	0009(12)	-0006(5)
C(19)	3902(29)	2740(13)	2664(6)	0377(59)	0108(16)	0013(2)	-0005(32)	-0032(14)	-0006(6)
C(20)	3586(35)	3063(15)	2089(6)	0494(87)	0093(18)	0018(3)	-0030(33)	-0009(14)	-0008(6)
C(21)	5607(34)	2969(16)	1822(5)	0349(60)	0145(20)	0014(3)	-0031(42)	0002(15)	-0012(7)
C(22)	7229(31)	3773(14)	2059(5)	0453(71)	0082(17)	0009(2)	0011(31)	-0005(11)	-0005(5)
N(23)	7494(26)	3473(10)	2617(5)	0564(62)	0056(12)	0013(3)	-0013(25)	-0020(11)	-0007(5)

of four molecules in the unit cell. Three-dimensional intensity data to 0·85 Å were recorded with CuKα radiation on a Picker automatic single-crystal four-circle diffractometer. Recorded intensity values for 1558 of a possible 1732 non-equivalent terms were made of which 849 had values significantly greater than the background scatter. The intensities were corrected for Lorentz and polarization factors but not for absorption, $\mu(\mathrm{CuK}\alpha) = 32{\cdot}2\ \mathrm{cm}^{-1}$. All scattering factors used in the analysis were those given in *International Tables for X-ray Crystallography.*[25]

The structure was solved by the heavy-atom method. The Br atom site parameters derived from an, 'unsharpened' 3-dimensional Patterson synthesis were $x = 0{\cdot}077$, $y = 0{\cdot}069$, $z = 0{\cdot}227$. Light-atom sites were selected from a Fourier map phased on the bromine contribution to the structure factor. The atomic sites selected, when assembled with the aid of a ball-on-spoke model, corresponded to nineteen of the twenty-three atoms comprising the molecular skeleton. The sites of the remaining four skeletal atoms, C(10), C(14), C(15) and C(16) (see Fig. 2), were located from the subsequent Fourier synthesis, and a difference map allowed differentiation of the C and N atom sites. After isotropic full-matrix least-squares refinement, calculation of bond lengths and angles and the spatial disposition of the associated atoms established the position of the double bond to be between C(16)–C(17). The R index for the 1558 measured terms was 0·138 for $R = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$. Final least-squares refinement cycles were carried out in which all the atoms were refined anisotropically. The final R index for the 849 observed terms was 0·069. All terms were given unit weight.

Atomic parameters together with their estimated standard deviations are listed in Table 1. Derived bond lengths and angles are given in Fig. 2, while some short intermolecular approach distances are given in Table 2 and Fig. 3. Tables listing a comparison of measured and calculated structure amplitudes have not been included, but are available on request from the authors.

The absolute configuration of the structure has been determined by Bijvoet's method,[26] utilizing the anomalous dispersion of CuKα radiation by the bromine atoms, for which $\Delta f' = -0{\cdot}9$, and $\Delta f'' = 1{\cdot}5$.[25] Comparison of observed intensity of selected Friedel pairs with the calculated values has shown that the absolute structure is defined by parameters listed in Table 1 when these are referred to a right-handed set of axes. Table 3 lists a comparison of the difference in observed intensity of the selected Friedel pairs with the corresponding calculated difference expressed as the percentage $100\,\Delta I(\mathrm{calc})/I(\mathrm{calc})$, where I(calc) refers to the calculated intensity uncorrected for anomalous dispersion.

Table 2. Intermolecular approach distances < 3·90 Å

ATOMS	d(Å)
Br ...... $N(12)^{I}$	3.82
Br ...... $C(13)^{I}$	3.71
Br ...... $C(22)^{I}$	3.65
Br ...... $N(23)^{I}$	3.35
Br ...... $C(21)^{I}$	3.66
Br ...... $C(19)^{II}$	3.83
Br ...... $C(20)^{II}$	3.81
Br ...... $C(18)^{II}$	3.88
Br ...... $C(22)^{III}$	3.61
Br ...... $C(10)^{III}$	3.57
Br ...... $N(23)^{III}$	3.27
C(13) ...... $C(22)^{III}$	3.64
N(12) ...... $C(8)^{IV}$	3.53
C(13) ...... $C(8)^{IV}$	3.86
C(2) ...... $C(5)^{IV}$	3.79
C(6) ...... $C(14)^{V}$	3.70
C(3) ...... $C(4)^{VI}$	3.78

Symmetry codes :			
I;	x	y	z
II;	1-x	-½+y	½-z
III;	2-x	-½+y	½-z
IV;	1+x	y	z
V;	-½+x	½-y	1-z
VI;	½+x	½-y	1-z

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Table 3. Comparison of ΔI(obs), the difference in intensity of selected Friedel pairs, with the corresponding calculated difference expressed as the percentage difference 100 ΔI(calc)/I(calc), where I(calc) refers to the calculated intensity uncorrected for anomalous dispersion

h	*k*	*l*		100 ΔI(calc)/I(calc)
1	4	5	-	-24
1	5	4	+	+18
1	4	2	-	-21
1	1	11	+	+21
2	4	5	-	-19
2	1	11	+	+32
2	4	3	-	-33
2	6	1	+	+23
1	10	2	-	-11
1	2	18	+	+22
1	8	3	+	+14
2	1	19	-	-20
2	1	18	-	-21
2	1	14	-	-29
3	2	17	+	+24

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