We are indebted to Dr I. J. Good for drawing our attention to one of the families of surface tessellations described in this paper. Realizing that only six equilateral triangles can meet at a point on a plane surface he investigated the nature of the (curved) surface which may be divided into equilateral triangles in such a way that eight meet at every point, and in this way derived one of the 6-tunnel {3, 8} polyhedra. Special thanks are due to our colleague Mr E. Young and his staff for preparing the numerous stereoscopic photographs.

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The Crystal and Molecular Structure of (+)-Hetisine Hydrobromide*

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(+)-Hetisine hydrobromide, $C_{20}H_{27}O_3N.HBr$, crystallizes in the monoclinic system,

$$a = 9{\cdot}75,\ b = 10{\cdot}84,\ c = 9{\cdot}46\ \text{Å},\ \beta = 114°40',$$

the space group being $P2_1$ with two molecules per unit cell. The structure was solved from a three-dimensional Fourier synthesis based on phases of the contribution of the bromine atom. The determination of the molecular structure was carried out solely on the empirical formulae, except that the nitrogen atom was identified with the help of chemical work on this alkaloid. The absolute configuration was investigated by reference to the anomalous dispersion of the Cu $K\alpha$ radiation by the Br atom.

Introduction

Hetisine, $C_{20}H_{27}O_3N$, was isolated from *Aconitum heterophyllum* by Jacobs & Craig (1942) and its first preliminary structural investigation by chemical methods was undertaken by Jacobs & Huebner (1947). It was followed by an extensive chemical study, which led to the proposal of two structures (Solo & Pelletier, 1959; Wiesner & Valenta, 1958), given in Fig. 1(*a*) and (*b*), neither of which, however, accounted satisfactorily for the accumulated evidence. Hetisine appeared to have an unusual heptacyclic skeleton, capable of a facile and interesting rearrangement. In view of this, and the limited amount available for chemical study, Dr O. E. Edwards suggested an X-ray analysis of the alkaloid.

The structure shown in Fig. 1(*c*) represents the result of this determination. It proved valuable in establishing in detail the stereochemistry of the carbon–nitrogen skeleton and in locating all the substituents.

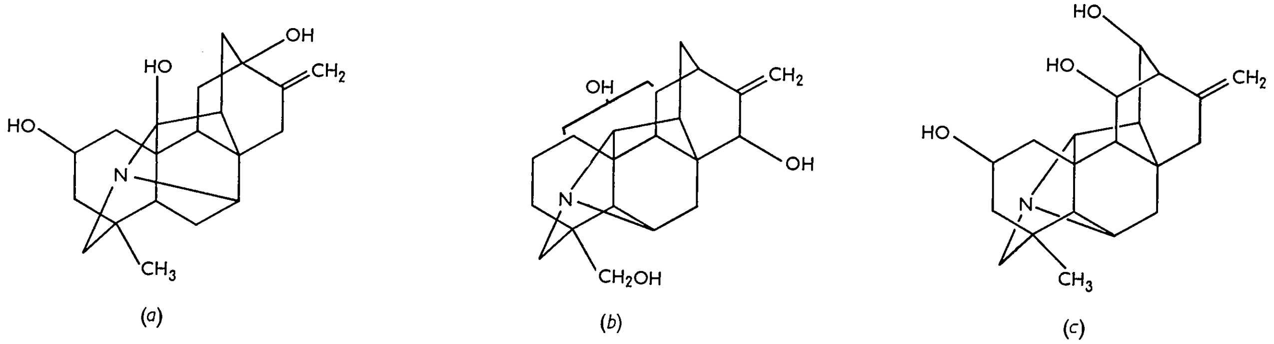

Fig. 1. (*a*) The structure of hetisine proposed by Solo & Pelletier.
(*b*) The structural formula of Wiesner & Valenta. (*c*) Hetisine proven by the X-ray analysis.

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No chemical evidence was used in the solution of this structure, except that it helped to distinguish at the initial stages of refinement the nitrogen atom from the carbon atoms of the skeleton. Hetisine is the first compound with this unusual molecular structure fully analysed by X-rays, and this investigation should assist in elucidation of structures of related alkaloids.

Experimental

A sample of hetisine was kindly provided by Dr O. E. Edwards and the hydrobromide derivative was prepared by Dr G. Feniak, who also measured the optical rotation:

$$[\alpha]_D^{29} = +10 \pm 1° \text{ (}c\text{, 2·03 in methanol).}$$

The salt was crystallized from absolute methanol, and it melted with decomposition at 266–9 °C. The crystals were found to be elongated along the *b* (unique) axis with (001) and $(10\bar{1})$ faces prominently developed and with small (100) pinacoids.

There are two molecules per unit cell. Since it was found that the *0k0* reflections are absent when *k* is odd, the space group is $P2_1(C_2^2)$. The unit-cell constants are:

$$a = 9·75 \pm 0·02,\ b = 10·84 \pm 0·02,$$
$$c = 9·46 \pm 0·02 \text{ Å},\ \beta = 114° 40' \pm 5'.$$

The calculated density is 1·50 g.cm^{-3} and the measured value, obtained by flotation in toluene and carbon tetrachloride is 1·48 g.cm^{-3}. The number of electrons per unit cell, $F(000)$, is 428, and the absorption coefficient for Cu $K\alpha$ radiation is $\mu = 33·6$ cm^{-1}.

The three-dimensional data were collected from equi-inclination Weissenberg films of *h0l*...*h9l* levels, multiple-film packs of up to five films being used. The *0kl* and *hk0* reflections were also measured. The total number of observed reflections amounted to 1877, which constitutes 87% of all those available with Cu $K\alpha$ radiation. The intensities were estimated visually from a set of timed exposures of a single reflection. All crystals were cylindrical, and since most of them were about 0·30 mm in diameter absorption corrections were not applied. The overall scale and temperature factors ($B \simeq 2·0$ Å^2) were derived by Wilson's (1942) method.

Structure analysis

Two Patterson syntheses using the *h0l* and *hk0* data were evaluated and the *x* and *z* coordinates of the bromine atom were derived from them. A three-dimensional Fourier synthesis was subsequently carried out for eight sections perpendicular to the *b* axis, the axes being divided into 30 parts. The phases for this synthesis were based only on the contribution made by the bromine atom, which was placed at $y = 0·25$. This procedure imparted the symmetry of the centrosymmetric space group $P2_1/m$, causing the superposition of the real atoms with their related mirror-image peaks.

The electron-density contours were plotted on Perspex sheets and assembled together to give a three-dimensional model. By studying the angles and distances between peaks of that model it was possible to arrive at a complete molecular structure of this compound. Only three weaker spurious peaks were present, but since they lay directly beneath the heavy atom, along the *b* axis, they were recognized as diffraction effects caused by the termination of the Fourier series.

A first set of coordinates consisted in addition to the bromine atom of 21 light atoms, all of which were treated as carbon atoms. It is interesting that even at this early stage of investigation the $C=CH_2$ bond length was found to be 1·29 Å and all the oxygen atoms could be readily recognized by comparing the peak heights. The subsequent examination of the $\varrho_o - \varrho_c$ maps for the three axial zones confirmed the position of the remaining three atoms and led to the assignment of the atom types, C, N and O.

Since the evidence for distinguishing the nitrogen from carbon atoms was not conclusive at this stage of the work, chemical study was also taken into account. The nitrogen atom has appeared only at one location in the related diterpenoid alkaloids of known structure. Since this position is not inconsistent with the chemistry of hetisine (Pelletier, 1961), it seemed quite legitimate, in order to speed the refinement, to use this information in selecting the site for the nitrogen atom. It should be emphasized, however, that the electron-density values for that peak were studied throughout the process of refinement and were always found in agreement with the chemical evidence.

At the beginning of the refinement, the overall 3D reliability factor, the unobserved reflections having been omitted, was 0·22.

A three-dimensional Fourier synthesis which was then carried out fully confirmed the structure, as all the false mirror-image peaks had disappeared, and the ϱ values were found to be in agreement with the positions assigned to the nitrogen and oxygen atoms.

The structure was subsequently refined by seven differential syntheses, the final *R* factor for all 3D data, including the unobserved reflections, being 0·11. In all of these cycles the back-shift corrections and the factor of 1·7 for the lack of centre of symmetry were applied, with the exception that the latter was not used with the last set of atomic shifts. These last corrected shifts gave average values of 0·0014 Å in the directions of *x* and *z*, and 0·0016 Å along *y*.

The refinement process was rather slow, until different *B* factors were used for the different atoms, and until a correction was made for the anisotropic motion of the bromine atom. The progress was further slowed down by the fact that a few peaks, which lay directly under the bromine atom, along the *b* axis,

Table 1. *Fractional atomic coordinates*

Atom	x	y	z	B (Å^2)	ϱ_o (e.Å^{-3})	ϱ_c (e.Å^{-3})
C(1)	0·2822	0·7009	0·4139	2·3	9·97	10·06
C(2)	0·3588	0·8083	0·3665	2·9	8·94	9·06
C(3)	0·2585	0·9218	0·2956	2·4	9·67	9·87
C(4)	0·1054	0·8837	0·1742	2·3	10·20	10·38
C(5)	−0·2486	0·8219	−0·0141	2·2	10·18	10·28
C(6)	−0·3579	0·8618	0·0519	2·2	9·74	9·95
C(7)	−0·4592	0·7529	0·0411	3·0	9·17	9·23
C(8)	−0·3640	0·6378	0·1133	2·9	9·04	9·11
C(9)	−0·1081	0·5670	0·2941	2·5	9·50	9·63
C(10)	0·0576	0·6000	0·3793	2·2	9·78	9·81
C(11)	0·1335	0·6722	0·2864	2·4	9·65	9·83
C(12)	0·0200	0·7799	0·2227	1·5	11·70	11·91
C(13)	−0·1283	0·7309	0·0979	1·7	10·73	10·60
C(14)	−0·2015	0·6754	0·2006	1·8	10·66	10·65
C(15)	0·3932	0·5936	0·4595	3·8	7·90	8·01
C(16)	0·2403	0·7335	0·5478	2·3	9·79	9·97
C(17)	−0·0114	0·8105	0·3674	1·6	10·69	10·68
C(18)	−0·2774	0·8946	0·2225	2·2	9·84	10·01
C(19)	−0·1790	0·7828	0·3141	1·6	10·98	11·22
C(20)	−0·6076	0·7547	−0·0139	4·3	6·99	7·16
N	0·0733	0·7096	0·4821	1·8	13·37	13·72
O(1)	0·2462	0·9905	0·4172	2·8	13·46	13·69
O(2)	−0·1928	0·9267	−0·0620	2·7	13·56	13·78
O(3)	−0·1933	1·0078	0·2462	2·9	13·09	13·33
Br	0·0598	0·2500	0·2568	2·2	75·38	75·94

were affected considerably by large errors due to the termination of the series. Their back-shift corrections were very high and changed appreciably from one cycle of refinement to another. The final fractional atomic coordinates, temperature factor constants and electron density values are listed in Table 1.

Owing to the pronounced anisotropic vibration of the bromine atom (B=2·2, 3·1 and 5·0 Å^2 along the ellipsoid axes), the four bromine atoms of $\frac{1}{4}$ weight (Kartha & Ahmed, 1960) were later replaced with a resultant improvement by six anisotropic thermal parameters (Vos & Smits, 1961). They were used with the isotropic temperature factor of 2·2 Å^2, and are listed in Table 2.

Table 2. *The anisotropic thermal parameters of the bromine atom*

x	y	z	p
0·0929	0·2593	0·2806	0·09
0·0929	0·2407	0·2806	0·09
0·0267	0·2593	0·2330	0·09
0·0267	0·2407	0·2330	0·09
0·0598	0·2593	0·2568	0·31
0·0598	0·2407	0·2568	0·31

The scattering curves of Freeman (1959) were used for the light atoms and that of Thomas & Umeda (1957) for the bromine atom. The hydrogen atoms were not included in any of the structure-factor calculations.

At first the refinement was carried out by means of the IBM 650 computer; during the course of this work, however, the IBM 1620 machine became available and it was used for all computations with the exception of the differential synthesis. All the programs were kindly provided by Dr F. R. Ahmed (1961) and the computing was carried out under his guidance.

The (010) projection of the structure is given in Fig. 2, while Fig. 3 shows the structure projected along the c axis.

Vorbrueggen & Djerassi (1962) using optical rotatory-dispersion methods, and ApSimon & Edwards (1962) by direct comparison with compounds of known stereochemistry, rigorously established the absolute stereochemistry of the *Garrya* and atisine groups of alkaloids. Since atisine and hetisine have related structures and occur side by side in *Aconitum heterophyllum*, it is reasonable to assume that the basic perhydrophenanthrene system common to the two alkaloids would have the same absolute stereochemistry.

The study of the absolute configuration of (+)-hetisine hydrobromide was undertaken by means of the anomalous scattering of the Cu $K\alpha$ radiation by the bromine atom. The films were obtained by inclining the Weissenberg camera in opposite ways with respect to the X-ray beam. They were exposed for exactly the same interval of time and processed simultaneously. All the factors described by Peerdeman & Bijvoet (1956) were taken into account in indexing. The absolute configuration of hetisine was found in agreement with the investigations of related compounds and is represented by all the structural drawings in this publication and by the atomic set of coordinates listed in Table 1 referred to a right-handed system of axes. Because the f'' value for Br and Cu $K\alpha$ radiation is only +1·5 (Dauben & Templeton, 1955), the differences between the intensities of seven studied hkl reflections and their corresponding $\bar{h}\bar{k}\bar{l}$ values amounted to about 12%. Despite

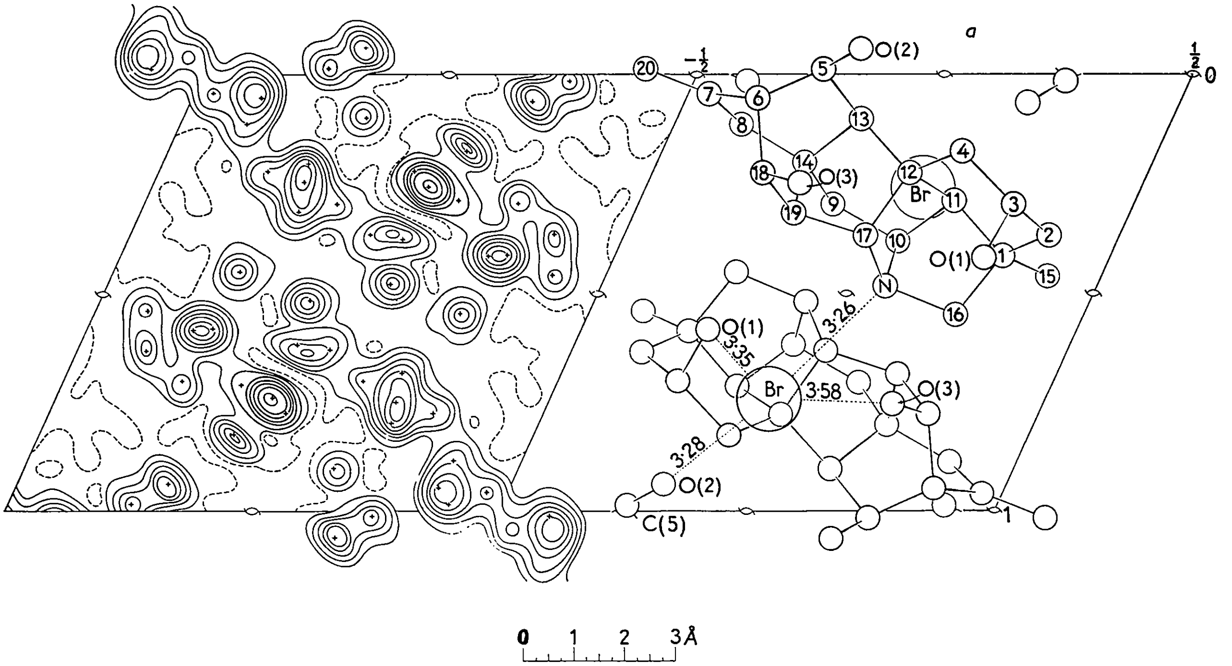

Fig. 2. A projection of the structure of (+)-hetisine hydrobromide along the *b* axis. Light-atom contours are drawn at intervals of 2 e.Å^{-2}, starting with a broken line at 2 e.Å^{-2}. The bromine-atom heavier contours are at 10 e.Å^{-2}.

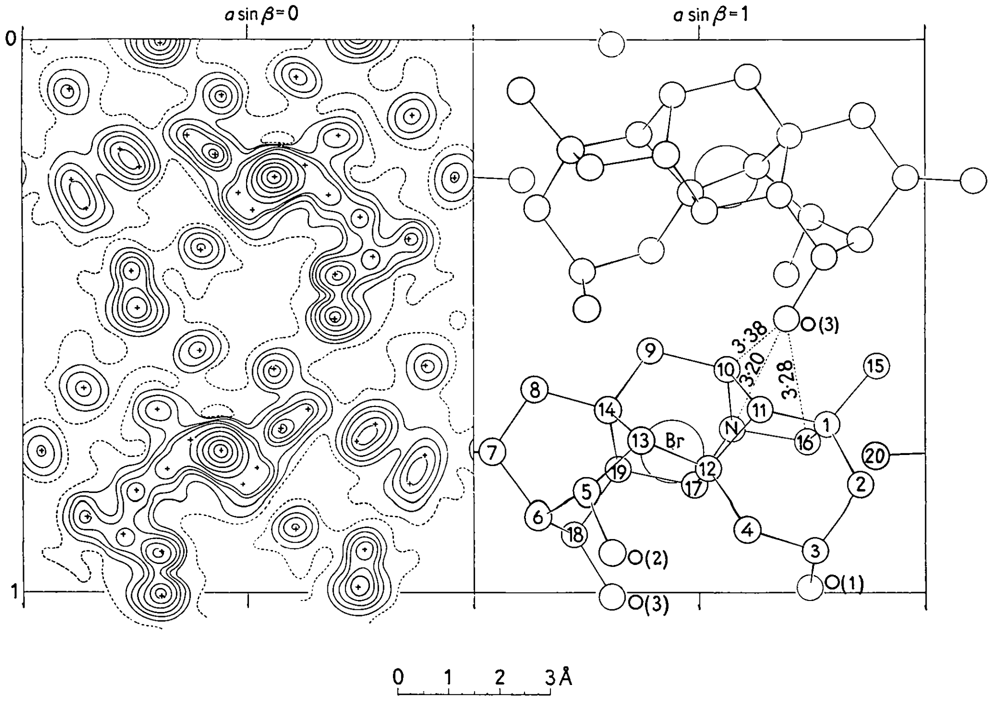

Fig. 3. The structure viewed along the *c* axis. Contour interval is 2 e.Å^{-2} and for the bromine atom 10 e.Å^{-2}, starting at 10 e.Å^{-2}. The first broken line is at 2 e.Å^{-2}.

the fact that the contribution made by the hydrogen atoms was not included and the anisotropic motion of the bromine was only roughly corrected, it seems unlikely that this result is incorrect in view of the above indirect evidence.

Discussion

Fig. 4 gives the bond lengths and the valency angles are listed in Table 3. The standard deviations of the atomic coordinates were calculated by Cruickshank's equations for a monoclinic cell (1949), a factor of 1·8 being included to allow for the absence of a centre of symmetry. Their r.m.s. values for the light atoms other than hydrogen vary from 0·010 Å to 0·015 Å with the exception of C(15) and C(20) which have values of 0·018 Å and 0·021 Å respectively. These two carbon atoms are outside the C–N skeleton, and their markedly greater thermal vibration (*cf. B* values in Table 1) is probably responsible for lowering the accuracy.

The average r.m.s. value for all light atoms is 0·013 Å and for the bromine atom 0·002 Å, and the e.s.d. of a bond is 0·019 Å. It follows that for the 5% significance level, deviations as high as ±0·04 Å in these bonds from their theoretical values should not be considered as significant (Cruickshank & Robertson, 1953). All bonds were found to have values within this limit, with the exception of the C(1)–C(11) bond which is only 1·48 Å. It should be mentioned, however, that the adjoining C(11)–C(10) bond is 1·57 Å, and this indicates that the true position of C(11) may be closer to C(10), leading to an appreciable lengthening of the C(1)–C(11) bond.

The e.s.d. of valency angles were estimated to be close to 1°. The average angle for five-membered rings was found to be 101·2° and for six-membered 111·5°. Two of the angles at the nitrogen atom common to five-membered rings are 102° and 103°, whereas the third one, C(16)–N–C(17), is 110° and is, as expected, closer to the theoretical tetrahedral value.

Table 3. *Valency angles*

Angles	Value	Angles	Value
C(2)–C(1)–C(11)	110·4°	C(12)–C(13)–C(14)	100·7°
C(2)–C(1)–C(15)	106·6	C(8)–C(14)–C(9)	110·3
C(2)–C(1)–C(16)	113·3	C(8)–C(14)–C(13)	114·6
C(11)–C(1)–C(15)	114·1	C(9)–C(14)–C(13)	110·1
C(11)–C(1)–C(16)	102·4	C(8)–C(14)–C(19)	113·5
C(15)–C(1)–C(16)	110·3	C(9)–C(14)–C(19)	107·6
C(1)–C(2)–C(3)	115·6	C(13)–C(14)–C(19)	100·1
C(2)–C(3)–C(4)	111·0	C(1)–C(16)–N	103·7
C(3)–C(4)–C(12)	116·6	C(12)–C(17)–C(19)	104·1
C(6)–C(5)–C(13)	111·2	C(12)–C(17)–N	103·1
C(5)–C(6)–C(7)	107·6	C(19)–C(17)–N	106·4
C(5)–C(6)–C(18)	111·6	C(6)–C(18)–C(19)	109·5
C(7)–C(6)–C(18)	106·8	C(14)–C(19)–C(17)	101·6
C(6)–C(7)–C(8)	110·3	C(14)–C(19)–C(18)	108·9
C(7)–C(8)–C(14)	109·1	C(17)–C(19)–C(18)	110·8
C(10)–C(9)–C(14)	111·9	C(6)–C(7)–C(20)	126·3
C(9)–C(10)–C(11)	117·7	C(8)–C(7)–C(20)	123·2
C(9)–C(10)–N	109·2	C(4)–C(12)–C(13)	117·8
C(11)–C(10)–N	91·4	C(5)–C(13)–C(12)	120·3
C(1)–C(11)–C(10)	100·3	C(10)–N–C(16)	101·8
C(1)–C(11)–C(12)	117·2	C(10)–N–C(17)	103·2
C(10)–C(11)–C(12)	99·6	C(16)–N–C(17)	110·1
C(4)–C(12)–C(11)	105·8	C(2)–C(3)–O(1)	108·7
C(4)–C(12)–C(17)	115·1	C(4)–C(3)–O(1)	111·7
C(11)–C(12)–C(17)	100·9	C(6)–C(5)–O(2)	109·6
C(11)–C(12)–C(13)	109·3	C(13)–C(5)–O(2)	116·4
C(13)–C(12)–C(17)	106·4	C(6)–C(18)–O(3)	112·0
C(5)–C(13)–C(14)	105·0	C(19)–C(18)–O(3)	113·4

The equation of the plane passing through C(6), C(7) and C(8) was evaluated and the atom C(20) was found to be at a distance of 0·06 Å from this plane. The position of the C=CH$_2$ bond agreed with the chemical evidence (Pelletier, 1961), and its length,

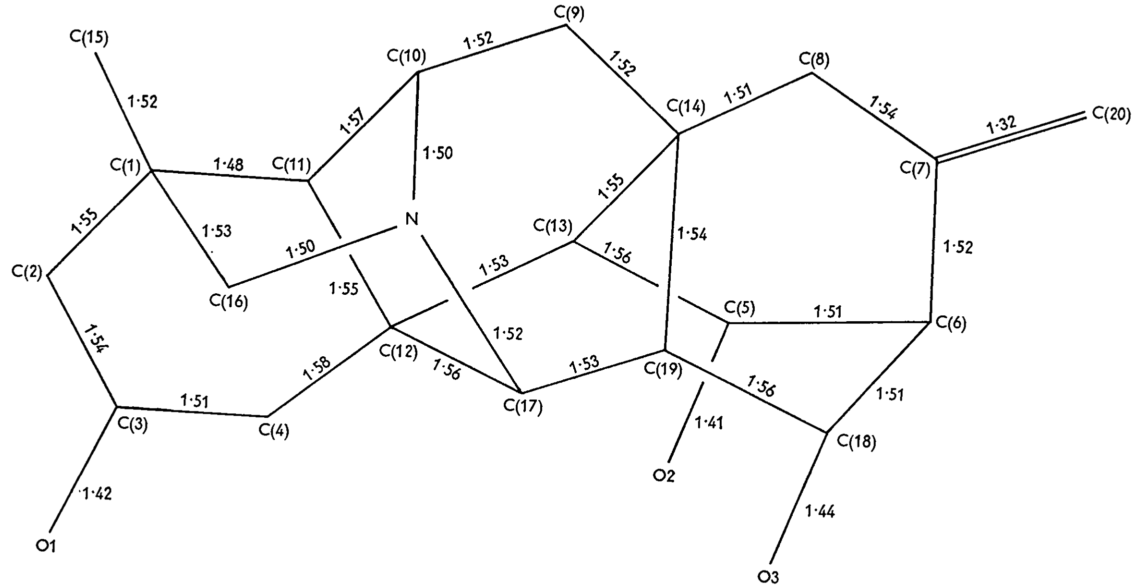

Fig. 4. Bond lengths.

1·32 Å, with the theoretical value (1·33 Å). The C–OH bonds vary between 1·41 and 1·44 Å. This result together with the ϱ_0 values (Table 1) confirm the presence of oxygen atoms in sites assigned to them.

The O(1) is attached axially, while the other two hydroxyl groups are directed the same way, preserving the symmetry of half of the molecule with the [2,2,2]-bicyclo-octane system with respect to the plane passing through the $C=CH_2$ double bond and its adjoining carbon atoms.

The intramolecular distances

$$C(16) \cdots O(1),\ C(17) \cdots O(1),\ O(2) \cdots O(3)$$

are about 3·06 and C(4) ··· O(2) is 2·87 Å, whereas all these in an undistorted model would be 2·5 Å. The larger O(2) ··· O(3) and C(4) ··· O(2) separations are achieved mainly by an increase in the angle C(13)–C(5)–O(2) to 116°.

All the C ··· C intermolecular distances can be considered as normal, as only five of them were found below 4 Å, the shortest of these being 3·72 Å. The closest C ··· O approaches of 3·28 and 3·38 Å are depicted in Fig. 3, while all others are above 3·40 Å. The only $N^+ \cdots O$ contact below 4 Å is also shown in Fig. 3. It is 3·20 Å and since the angle $C(18)–O(3) \cdots N^+$ was found to be 134·5°, a very weak hydrogen bonding may be present.

The $Br^- \cdots C$ contacts are greater than 3·58 Å. The closest $Br^- \cdots O$ approaches are given in Fig. 2. The two smaller distances to O(1) and O(2′) are 3·35 and 3·28 Å respectively and the corresponding angles, $C(3)–O(1) \cdots Br^-$ and $C(5')–O(2') \cdots Br^-$ are close to 90°, suggesting that the H-bonds may play an important role in intermolecular packing. The $Br^- \cdots N^+$ distance, also shown in Fig. 2, is 3·26 Å. It compares well with similar hydrogen bonds found in ibogaine hydrobromide (3·23 and 3·34 Å) and strychnine hydrobromide dihydrate (3·17 Å), whereas angles $C(10)–N^+ \cdots Br^-$, $C(16)–N^+ \cdots Br^-$ and $C(17)–N^+ \cdots Br^-$ which are 128, 92 and 105° respectively, are compatible with the conclusion that the hydrogen atom attached to N^+ is directed towards the bromine ion. The direction of vibration of bromine, which was found to be perpendicular to the line joining the bromine and nitrogen atoms, is also in agreement with the hydrogen bond.

I wish to express my sincere gratitude to Dr F. R. Ahmed for his invaluable computational assistance. I am indebted to Dr O. E. Edwards for suggesting this investigation and for helpful discussions and to Dr Léo Marion for his full support and unfailing encouragement. I also wish to acknowledge with thanks the assistance of Mrs C. Mackey.

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