Veratrum Alkaloids. Part LVI.[1] Crystal Structure and Absolute Configuration of Zygacine Acetonide Hydriodide Acetone Solvate

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A three-dimensional, single-crystal, *X*-ray analysis of the title compound has confirmed its molecular structure and absolute configuration, and thus the stereochemistry and absolute configurations of the related alkaloids, zygadenine, germine, and protoverine. Crystals are monoclinic, $a = 20{\cdot}484(3)$, $b = 8{\cdot}828(1)$, $c = 25{\cdot}208(4)$ Å, $\beta = 114{\cdot}55(1)°$, space group $C2$, $Z = 4$, and there are 8 molecules of acetone of solvation in the unit cell. The structure was solved by the heavy-atom method, and refined by least-squares methods to R 0·093 for 2564 independent reflections measured by counter diffractometry. The absolute configuration was determined by the anomalous dispersion method.

THE clinically useful hypotensive principles of plants of the *Veratrum* genus have been shown to be polyesters of the highly oxygenated alkamines germine (II) and protoverine (III).[1-3] Detailed structural and stereochemical assignments for the alkamines were based on extensive degradative studies[1] which included successive selective reductions of a derivative of protoverine to one of germine[4] and of a derivative of germine to one of zygadenine.[5,6] Although the chemical arguments in favour of these assignments were convincing, no definitive *X*-ray crystallographic study had been carried out to give conclusive proof of their correctness. We report the results of a three-dimensional, single-crystal, *X*-ray diffraction analysis of the structure of zygacine acetonide hydriodide (IV). The analysis confirms, unambiguously, the stereochemistry (I) for zygadenine, and consequently proves the correctness of the assignments (II) and (III) for germine and for protoverine.

EXPERIMENTAL

Zygacine acetonide hydriodide was prepared by treatment of zygacine in acetone solution with hydriodic acid[7] and recrystallised from acetone.

Crystal Data.—$[C_{32}H_{50}NO_8{}^+][I^-],2Me_2CO$, $M = 819{\cdot}8$. Monoclinic, $a = 20{\cdot}484(3)$, $b = 8{\cdot}828(1)$, $c = 25{\cdot}208(4)$ Å, $\beta = 114{\cdot}55(1)°$, $U = 4146$ Å^3, $D_m = 1{\cdot}36$, $Z = 4$, $D_c = 1{\cdot}31$, $F(000) = 1720$. Space group $C2$ (C_2^3, No. 5). Mo-K_α radiation, $\lambda = 0{\cdot}71069$ Å; μ(Mo-K_α) 8 cm^{-1}.

Unit-cell parameters were obtained by a least-squares fit to the observed values of $\pm 2\theta$ for 25 strong general reflections measured on the diffractometer.

Intensity Data.—Crystals of the salt lose acetone of solvation readily upon exposure to the air, the loss being complete in *ca.* 24 h, with destruction of the lattice arrangement. A crystal *ca.* $0{\cdot}6 \times 0{\cdot}8 \times 0{\cdot}2$ mm^3 was therefore mounted in a sealed thin-wall quartz capillary together with a small amount of mother liquor. After a slight decrease

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[3] S. M. Kupchan and W. E. Flacke, 'Antihypertensive Agents,' ed. E. Schlittler, Academic Press, New York, 1967, ch. XII.

[4] S. M. Kupchan, C. I. Ayres, M. Neeman, R. H. Hensler, T. Masamune, and S. Rajagopalan, *J. Amer. Chem. Soc.*, 1960, **82**, 2242.

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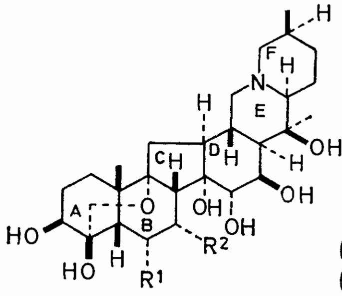
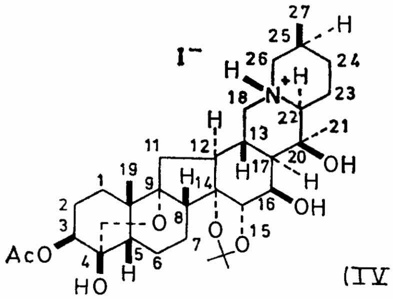
in the intensity of scattering the system reached equilibrium and no further loss in scattered intensity was apparent during the actual measurement of the diffraction pattern. Standard diffractometric methods were used, with Mo-K_α radiation, to yield intensities significantly above background for 2564 independent reflections in the monoclinic reciprocal lattice.[8]



	R¹	R²
(I)	H	H
(II)	H	OH
(III)	OH	OH



(IV)

Observed structure amplitudes and the corresponding calculated values are listed in Supplementary Publication No. 20579 (3 pp., 1 microfiche).*

Structure Determination and Refinement.—The structure was initially determined in space group $P1$, with $Z = 2$. At the end of the analysis it was seen that the two supposedly independent molecules were related by a two-fold axis of symmetry and closer inspection of the original set of intensity measurements showed that the diffraction pattern had monoclinic symmetry. After appropriate transformations of indices, co-ordinates, and cell axes had been made, the refinement of the structural parameters was completed for space group $C2$ and with a unique set of structure amplitudes corresponding to a quadrant of the monoclinic reciprocal lattice.

The structure was solved by the heavy-atom method in the usual way. With all non-hydrogen atoms located, R was 0·18 when a single overall thermal parameter, B 4·0 Å^2, was used.

Refinement of the structural parameters was by block-diagonal least-squares methods, with individual isotropic thermal parameters assumed, and gave R 0·13 at convergence. Conventional weighting schemes were used,[9] and the scattering factors were those for the neutral atoms except for iodine.[10,11]

The choice of enantiomer was made by taking account of the anomalous dispersion terms for iodine[12] ($\Delta f'$ −0·64, $\Delta f''$ 2·15) in separate structure-factor calculations for each of the two possible sets of parameters. These calculations gave R 0·125 and 0·127, enabling a distinction to be made between the two enantiomeric structures at the 99·5% confidence level.[13] The choice of enantiomer was confirmed as correct by measurement of several Friedel pairs of reflections[14] with Cu-K_α radiation so as to take advantage of the very large imaginary component of the anomalous scattering ($\Delta f'$ −1·03, $\Delta f''$ 6·68).[12] In all cases the expected differences in intensity were in good agreement with those observed.

The parameters for the chosen enantiomer were refined further, taking into account the anomalous dispersion terms for the iodide ions and allowing these atoms to assume anisotropic thermal parameters, to give R 0·103.

A three-dimensional residual electron-density synthesis was calculated and showed peaks suggesting the presence of four molecules of acetone of solvation in the triclinic cell. Both the peak heights found for the atoms of these molecules in the difference-Fourier synthesis, and the very high thermal parameters assumed by the atoms on least-squares refinement, show the acetone molecules to be present with only fractional occupancy. One third of an atom was assumed at each site indicated and the atoms were held fixed with B 4·0 Å in the final cycles of least-squares refinement to give R 0·073 for the 4128 reflections used.

After the parameters for one cation and two molecules of acetone of solvation had been transformed to correspond to the monoclinic cell, the final refinement was carried out with the unique set of 2564 structure amplitudes for the monoclinic cell. Anisotropic thermal parameters were assumed only for the iodide ion. A group of about 130 of the strongest structure amplitudes showed signs of having been underestimated and were excluded from the final refinement. For the remaining 2435 structure amplitudes R was 0·078 and R' was 0·114 $\{R' = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2]^{\frac{1}{2}}\}$, and the standard deviation of an observation of unit weight was 1·2. A final three-dimensional residual electron-density map showed no structurally significant features. For the complete set of 2564 structure amplitudes R was 0·093.

RESULTS AND DISCUSSION

The molecular structure, stereochemistry, and absolute configuration of the zygacine acetonide cation have been established. The atomic parameters defining the crystal structure are given, together with their estimated standard deviations,[15] in Table 1. The numbering scheme adopted, bond lengths, bond angles, and torsion angles about the various ring bonds are given in Figure 1.

The mean estimated standard deviation in a C–C bond distance, as calculated from the standard errors in the positional parameters given in Table 2, is 0·02 Å, and in no instance exceeds 0·035 Å. However, these errors are generally underestimates[16] and a more

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* For details see Notice to Authors, No. 7, in *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (items less than 10 pp. are sent as full size copies).

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[15] L. I. Hodgson and J. S. Rollett, *Acta Cryst.*, 1963, **16**, 329.

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realistic measure of the accuracy of the determination may be found from the root-mean-square deviation from the mean of the 33 measurements of the C–C single-bond distance in the cation.[17] The mean is 1·538 Å, and the root-mean-square deviation from the mean is 0·042 Å.

TABLE 1

Atomic parameters (× 10^4) and isotropic thermal parameters with standard deviations in parentheses

Atom	x/a	y/b	z/c	B(Å^2)
I	644(0)	57 *	−2732(0)	†
C(1)	1339(7)	−969(16)	−589(6)	3·6(2)
C(2)	982(8)	−604(17)	−166(6)	3·8(3)
C(3)	1110(7)	−1841(17)	286(6)	3·6(2)
C(4)	1028(7)	−3411(16)	16(6)	3·3(2)
C(5)	1605(7)	−3721(15)	−213(6)	3·1(2)
C(6)	1668(7)	−5402(14)	−334(6)	3·5(2)
C(7)	945(8)	−6013(18)	−762(7)	3·9(3)
C(8)	527(5)	−4895(14)	−1255(5)	2·4(2)
C(9)	562(6)	−3301(14)	−1007(5)	2·5(2)
C(10)	1320(7)	−2672(16)	−771(6)	3·3(2)
C(11)	−48(6)	−2461(14)	−1532(5)	2·5(2)
C(12)	−561(6)	−3664(14)	−1956(6)	2·7(2)
C(13)	−541(6)	−3603(12)	−2551(5)	2·1(2)
C(14)	−274(5)	−5221(16)	−1641(5)	2·7(2)
C(15)	−431(7)	−6592(16)	−2014(6)	3·2(2)
C(16)	−455(8)	−6380(17)	−2646(7)	3·6(2)
C(17)	−859(5)	−5021(23)	−2935(5)	2·9(2)
C(18)	−964(6)	−2171(15)	−2861(6)	2·8(2)
C(19)	1700(9)	−2817(21)	−1157(8)	4·8(3)
C(20)	−919(7)	−4810(16)	−3543(6)	3·7(2)
C(21)	−1232(10)	−6225(24)	−3912(8)	5·4(3)
C(22)	−1380(7)	−3372(17)	−3825(6)	3·5(2)
C(23)	−1533(11)	−3115(27)	−4478(10)	6·2(4)
C(24)	−1968(12)	−1745(29)	−4700(10)	6·7(5)
C(25)	−1491(10)	−315(25)	−4350(8)	5·9(4)
C(26)	−1425(8)	−563(16)	−3718(6)	3·8(3)
C(27)	−835(9)	47(34)	−4419(8)	6·2(4)
C(28)	2048(7)	−1895(17)	1284(6)	3·7(2)
C(29)	2826(11)	−2001(26)	1638(10)	6·1(4)
C(30)	−1137(8)	−6706(19)	−1519(7)	4·3(3)
C(31)	−1933(11)	−5995(26)	−1713(9)	6·2(4)
C(32)	−900(13)	−8155(32)	−1127(11)	7·3(5)
N	−1028(5)	−2048(13)	−3466(5)	3·0(2)
O(4)	1008(5)	−4552(11)	381(4)	3·6(2)
O(9)	377(4)	−3378(11)	−520(4)	3·0(1)
O(14)	−652(4)	−5575(10)	−1282(4)	3·3(2)
O(15)	−1118(5)	−7047(12)	−2083(5)	2·0(2)
O(16)	261(5)	−6297(12)	−2583(5)	4·1(2)
O(20)	−223(5)	−4465(12)	−3541(4)	3·9(2)
O(31)	1845(5)	−1680(13)	705(5)	4·4(2)
O(32)	1581(7)	−1817(16)	1490(6)	5·5(2)
Acetone molecules in fixed positions with B 4·0 Å^2				
C(33)	4088	2326	4088	
C(34)	3299	1999	3777	
C(35)	2856	2868	3235	
O(34)	2945	1244	4021	
C(36)	4110	−2664	4235	
C(37)	3329	−3000	3919	
C(38)	2945	−2713	3276	
O(37)	3011	−3725	4172	

* Held fixed to define the origin. † The iodide ion was assigned anisotropic thermal parameters with the exponent in the form $-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})$. Values of β (× 10^5) in that order are: 316(2), 1248(10), 301(2), −45(8), 136(2), and −7(7).

The corresponding error in a C–C–C bond-angle measurement would thus be *ca.* 2·5°. Within these limits of error, the bond distances in the cation have normal values, but certain bond angles, notably C(4)–C(5)–C(10) and C(5)–C(10)–C(9), show signs of strain because of the participation of these atoms in the A–B–H fused ring system.

A general view of the structure of the cation is given in

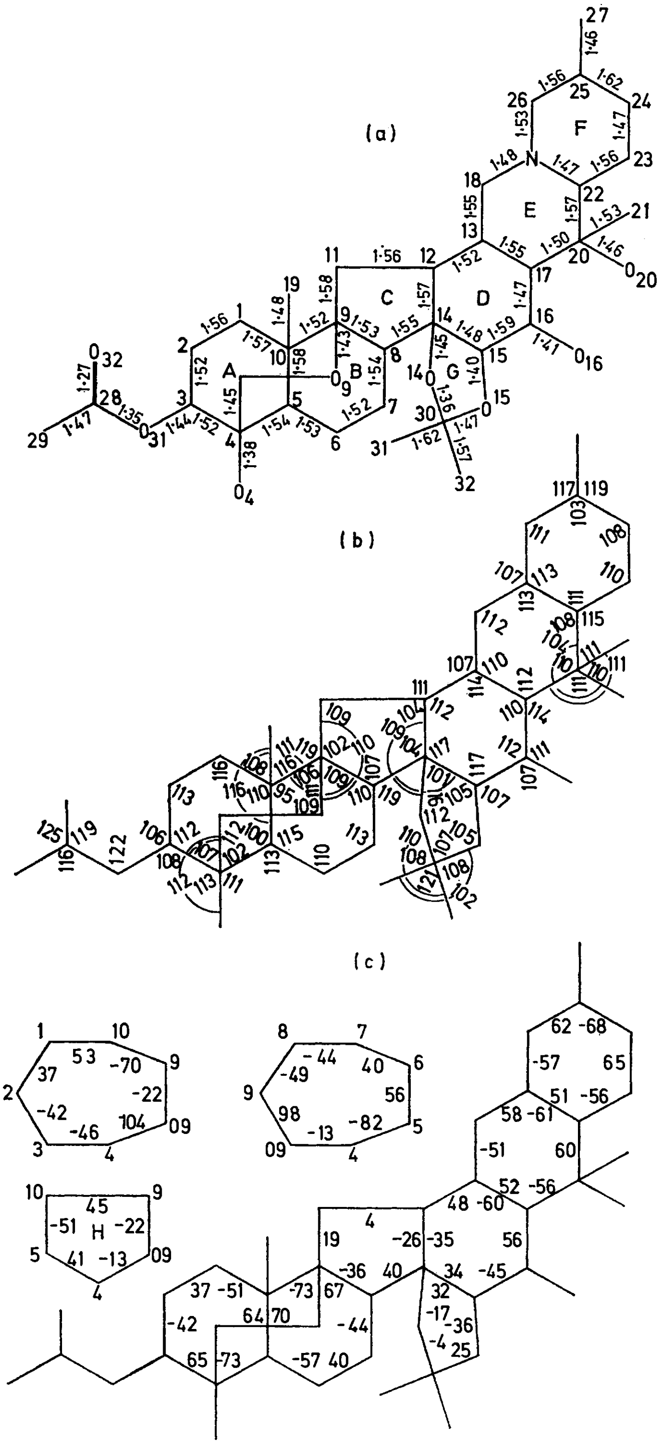

FIGURE 1 (a) Bond lengths (Å) in the cation, with the numbering scheme adopted for the atoms, and (b) bond angles (deg.). (c) Torsion angles about the bonds of the ring systems in the cation. A torsion angle is defined as positive when the uppermost atom in the grouping *A–B–C–D* must be rotated in a clockwise sense to eclipse the lowest atom. The sequence of atoms in the angles is taken in a counterclockwise direction around each ring

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Figure 2. Equations defining the least-squares mean planes through the various rings are given in Table 2. The conformations of the rings may be described in terms of the deviations of atoms from these mean planes, and the torsion angles given in Figure 1. Rings A, B, D, E, and F have chair conformations.[18] The torsion angles about the bonds in rings E and F show little or no signs of strain, but in ring D four of the six torsion angles are closed from normal values, with no compensating opening of the remaining two angles, because of the fusion of this ring with rings C and G. Rings A and B each show a compensatory symmetrical opening and closing of torsion angles from the normal unstrained values, also because of ring fusion.

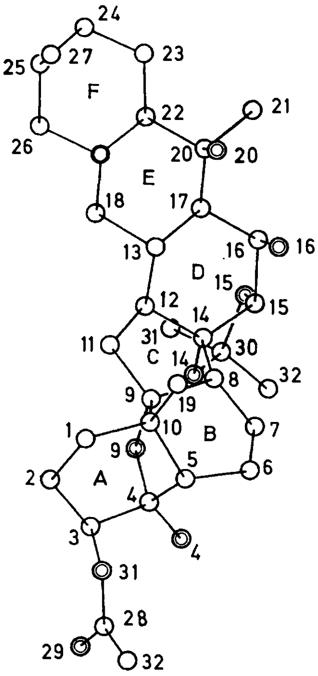

FIGURE 2 View of the molecular structure of the cation as found in the crystal. Atoms are numbered, carbon being indicated by the normal circles, oxygen by the double circles, and the single nitrogen atom by the heavy circle

TABLE 2

Equations of the mean planes of the various rings in the form $aX + bY + cZ = d$. X, Y, and Z are in Å with respect to a Cartesian axial system.* Deviations (Å) of atoms from the planes are given in square brackets

Plane	*a*	*b*	*c*	*d*
Ring A:	0·7644	0·1753	0·6204	1·4371
[C(1) −0·14, C(2) 0·10, C(3) −0·19, C(4) 0·35, C(5) −0·37, C(10) 0·26]				
Ring B:	−0·8222	0·0574	0·5663	−3·6427
[C(5) −0·29, C(6) 0·16, C(7) −0·10, C(8) 0·20, C(9) −0·35, C(10) 0·38]				
Ring C:	−0·7934	−0·0513	0·6066	−3·1739
[C(8) 0·25, C(9) −0·17, C(11) 0·04, C(12) 0·09, C(14) −0·21]				
Ring D:	0·9765	0·1049	0·1881	−0·1555
[C(12) 0·15, C(13) −0·25, C(17) 0·29, C(16) −0·22, C(15) 0·13, C(14) −0·09]				
Ring E:	0·9922	0·1197	0·0347	0·7708
[C(13) −0·20, C(18) 0·21, N, −0·25, C(22) 0·26, C(20) −0·25, C(17) 0·23]				
Ring F:	−0·9982	−0·0494	0·0336	−1·5040
[N 0·20, C(26) −0·27, C(25) 0·32, C(24) −0·33, C(23) 0·25, C(22) −0·18]				
Ring G:	0·4380	−0·6853	0·5818	1·6254
[C(14) 0·15, C(15) −0·21, O(15) 0·19, C(30) −0·08, O(14) −0·04]				
Ring H:	0·6700	0·7407	0·0509	−0·4337
[C(4) 0·40, C(5) −0·33, C(10) −0·95, C(9) 0·36, O(9) 0·95]				

* $X = x + z \cos \beta$, $Y = y$, $Z = z \sin \beta$.

The cyclopentane ring C has an envelope conformation,[18] as has ring G, but the C(4), C(9) hemiketal is α-oriented with respect to rings A and B, so that the five-membered ring H has a half-chair conformation.[18]

The two seven-membered rings formed by the hemiketal function and rings A and B are in conformations between boat and twist-boat forms,[19] but the constraints on the system are such that the torsion angles are far removed from those of any recognisable minimum-energy conformation.

The stereochemistry of the ring junctions is illustrated by Figure 3, which shows Newman projections about the ring-junction bonds. Rings A and B have a *cis*-junction with the hydrogen atom at C(5) and the methyl group at C(10) β-oriented. The junction of rings B and C is *trans*, with the hydrogen atom at C(8) β-oriented and the hemiketal group at C(9) α-oriented. The acetonide group at C(14) and C(15) is α-oriented with respect to ring D, with a *cis*-fusion of rings C and D.

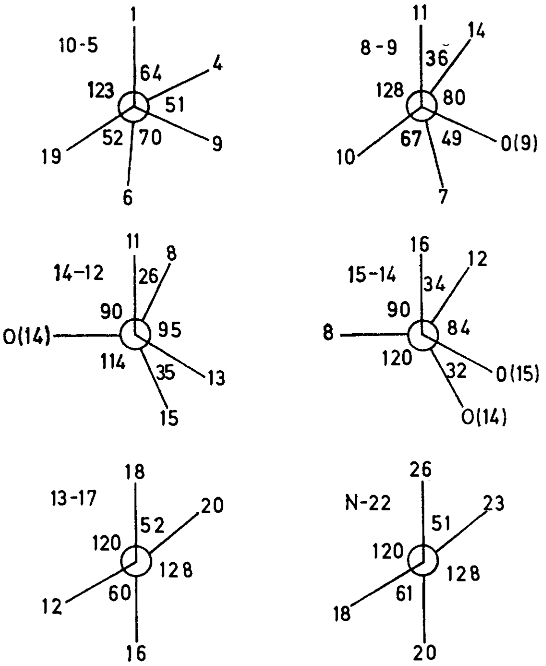

FIGURE 3 Newman projections for the bonds at the ring junctions showing the mode of fusion of the rings. Atom numbers refer to carbon unless otherwise indicated

The determination of the absolute stereochemistry of the cation confirms the stereochemistry at the 15 asymmetric centres, and thus proves the absolute stereochemistry at the common asymmetric carbon atoms in zygadenine,[6] germine,[5] and protoverine.[4]

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[18] H. J. Geise, C. Altona, and C. Romers, *Tetrahedron*, 1967, **23**, 439; 1968, **24**, 13.

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Assignment of α-orientation to the hydroxy-group at C(7) in germine was originally based on chemical and spectral arguments.[5] In addition, extensive studies of the facilitated solvolysis of germine 7-acetate esters established[20] the *cis*-1,3-diaxial relationship of the substituents at C(7) and C(14). Thus, the independent proof of the α-orientation of the C(14) substituent in zygacine acetonide (and therefore in zygadenine and germine) now confirms also the 7α-hydroxy-configuration in germine. Formation of a 6,7-acetonide derivative in the protoverine series requires that the C(6) hydroxy-group be oriented *cis* to the 7α-hydroxy-group and confirms the assignment of an α-configuration to the C(6) hydroxy-group in protoverine.[4]

A two-dimensional X-ray analysis[21] of cevine hydriodide has provided reasonably conclusive evidence for the relative configurations assigned on chemical grounds at 13 of the 14 asymmetric centres in that compound.[22] The β-configuration was favoured for the hydroxy-group at C(20), but this could not be definitely assigned from that X-ray analysis. In view of the impressive chemical and spectral evidence[1] for the congruence of the stereochemistry of rings D, E, and F in cevine with that in germine, this indirect proof of the absolute configuration of germine would strongly support the assignment of a β-orientation for the hydroxy-group at C(20) in cevine.

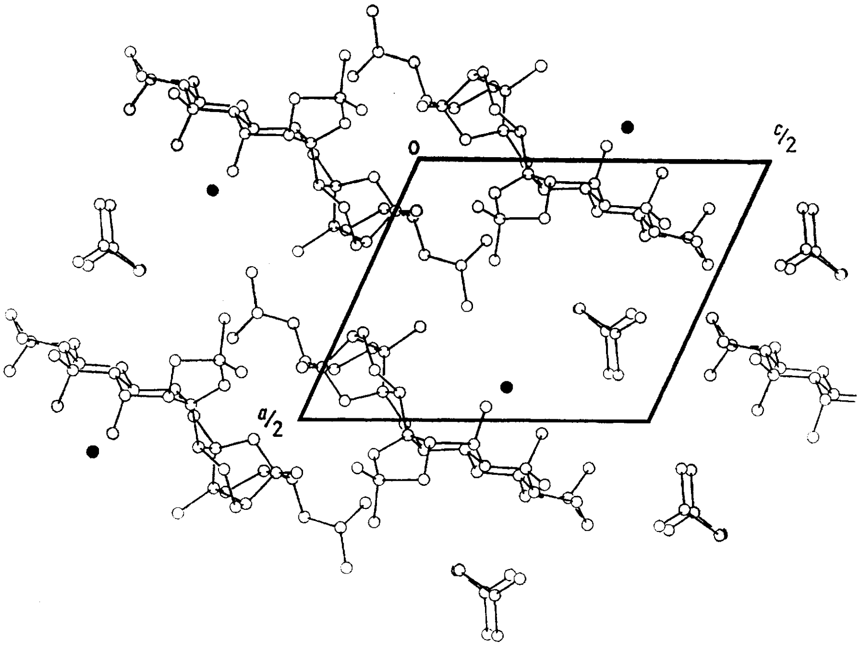

FIGURE 4 Arrangement of molecules in the unit cell. The axial system is right-handed, and the view is down *b*. Iodide anions are indicated by solid circles

A view of the arrangement of molecules in the unit cell is shown in Figure 4, and selected intermolecular approach distances are given in Table 3. The shortest contacts between the iodide ions and the cations involve the nitrogen atoms, as would be expected, and the oxygen atom of the hydroxy-group at C(16). The geometry of these latter contacts is compatible with hydrogen bonding, but is not ideal for the purpose.

TABLE 3

Selected shorter intermolecular contacts (Å)

I · · · N	3·60	I · · · O(16$^{\mathrm{I}}$)	3·47
O(4) · · · O(9$^{\mathrm{II}}$)	3·18	O(4) · · · O(14$^{\mathrm{II}}$)	2·81
C(11) · · · O(32$^{\mathrm{II}}$)	3·24	C(26) · · · O(37$^{\mathrm{II}}$)	3·29
C(12) · · · O(32$^{\mathrm{II}}$)	3·23	C(30) · · · O(4$^{\mathrm{II}}$)	3·36
C(22) · · · O(37$^{\mathrm{II}}$)	3·10	C(31) · · · O(4$^{\mathrm{II}}$)	3·35
C(31) · · · C(35$^{\mathrm{III}}$)	3·64	C(27) · · · C(21$^{\mathrm{II}}$)	3·74

Contacts are between the first atom in the reference molecule at x, y, z and the second atom in the position denoted by the Roman superscript:

I $x, 1 + y, z$ II $\bar{x}, y, \bar{z}$ III $\bar{x}, y - 1, \bar{z}$

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[20] S. M. Kupchan, S. P. Eriksen, and M. Friedman, *J. Amer. Chem. Soc.*, 1966, **88**, 343.

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