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Crystal and Molecular Structure of 19,20-epoxy-15-hydroxy-icajine

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The crystal and molecular structure of the title compound has been determined by X-ray crystallographic methods using 2123 reflections observed by counter methods. The crystals are orthorhombic, space group $P\,2_12_12_1$ with unit cell dimensions at 143 K: a=10.314(2) Å, b=10.843(3) Å and c=16.039(3) Å. The structure was refined to a conventional R-factor of 4.1 %. Estimated standard deviations are 0.004 Å and 0.2° in interatomic distances and angles when hydrogen atoms are not involved. A transannular interaction between N···C=O is observed.

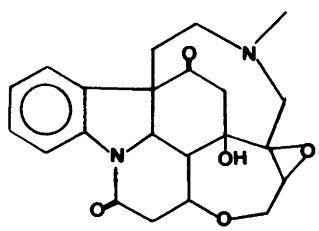
The presence of transannular interactions between a tertiary nitrogen atom and a carbonyl group, showing short N···C=O distances of 2.24 Å and 2.46 Å has been established for some strychnos alkaloids by X-ray analysis.[1,2] In view of the possible relationship between this type of intramolecular interaction and the biological activity of these compounds, the significance of the variation in chemical structure for the N···C=O interaction is studied further in the present structure analysis of 19,20-epoxy-15-hydroxy-icajine.

EXPERIMENTAL

A sample of the compound was supplied by D. Rob Verpoorte at Gorlaeus Laboratorium der R.U., Leiden. The compound was in the form of colourless needle-shaped crystals which could readily be cut to a size suitable for the X-ray experiments. The experimental conditions are given in the table below. Cell parameters were determined by a least-squares fit to the diffractometer settings for 15 general reflections.

The standard deviations for the intensities were calculated from $\sigma(I)=|C_T+(0.002\,C_N)^2|^{\frac{1}{2}}$ where C_T is the total number of counts and C_N is the scan count minus background count. The usual corrections were made for Lorentz and polarization effects, no correction was made for absorption or extinction.

Scattering factors used were those of Doyle and Turner for O, N and C,[3] and of Stewart, Davidson and Simpson for H.[4] Descriptions of the computer programs applied are given in Refs. 5 and 6. The quality minized in the least-squares calculations was $\sum w\Delta F^2$ where w is the inverse of the variance of the observed structure factors.



0302-4369/85 $2.50

Table 1. Fractional atomic coordinates. Estimated standard deviations in parentheses.

Atom	*x*	*y*	*z*
O25	−0.0575(2)	0.0738(1)	0.7520(1)
O26	0.1247(1)	0.1936(1)	0.5818(1)
O27	0.2957(2)	0.0447(1)	0.3535(1)
O28	−0.2143(2)	−0.2617(1)	0.5007(1)
O29	0.0890(2)	−0.1100(1)	0.6975(1)
N1	0.0970(2)	0.0050(2)	0.4088(1)
N4	−0.2824(2)	−0.0355(2)	0.5859(1)
C2	0.0064(2)	0.0083(2)	0.4818(1)
C3	−0.1431(2)	−0.1776(2)	0.5214(1)
C5	−0.2782(2)	0.0624(2)	0.5235(1)
C6	−0.2338(2)	0.0044(2)	0.4418(1)
C7	−0.1103(2)	−0.0748(2)	0.4570(1)
C8	−0.0680(2)	−0.1294(2)	0.3736(1)
C9	−0.1296(3)	−0.2169(2)	0.3246(1)
C10	−0.0717(3)	−0.2517(2)	0.2491(1)
C11	0.0421(3)	−0.1966(3)	0.2231(1)
C12	0.1043(3)	−0.1066(2)	0.2707(1)
C13	0.0476(2)	−0.0761(2)	0.3471(1)
C14	−0.0682(2)	−0.1872(2)	0.6032(1)
C15	0.0014(2)	−0.0697(2)	0.6338(1)
C16	0.0838(2)	−0.0285(2)	0.5587(1)
C17	0.1835(2)	0.0736(2)	0.5737(1)
C18	0.0741(3)	0.2172(2)	0.6634(1)
C19	−0.0565(3)	0.1598(2)	0.6824(1)
C20	−0.0932(2)	0.0281(2)	0.6700(1)
C21	−0.2365(2)	−0.0019(2)	0.6688(1)
C22	0.2749(2)	0.0791(2)	0.4994(1)
C23	0.2238(2)	0.0431(2)	0.4139(1)
C2	−0.4059(3)	−0.1009(2)	0.5881(1)
H2	−0.026(2)	0.091(2)	0.489(1)
H51	−0.218(2)	0.129(2)	0.543(1)
H52	−0.359(2)	0.105(2)	0.518(1)
H61	−0.210(2)	0.068(2)	0.399(1)
H62	−0.302(2)	−0.051(2)	0.419(1)
H9	−0.209(2)	−0.252(2)	0.340(1)
H10	−0.111(2)	−0.316(2)	0.217(1)
H11	0.075(3)	−0.226(3)	0.170(2)
H12	0.183(3)	−0.063(2)	0.255(1)
H141	0.001(2)	−0.245(2)	0.596(1)
H142	−0.126(2)	−0.224(2)	0.644(1)
H16	0.139(2)	−0.103(2)	0.548(1)
H17	0.238(2)	0.057(2)	0.627(1)
H181	0.062(3)	0.311(2)	0.665(1)
H182	0.141(3)	0.188(2)	0.706(1)
H19	−0.129(2)	0.220(2)	0.683(1)
H211	−0.252(2)	−0.074(2)	0.706(1)
H212	−0.289(2)	0.068(2)	0.695(1)
H221	0.319(2)	0.165(2)	0.495(1)
H222	0.344(3)	0.017(3)	0.508(1)
H241	−0.393(2)	−0.174(2)	0.620(1)
H242	−0.432(2)	−0.117(2)	0.527(1)
H243	−0.475(3)	−0.045(3)	0.616(1)
H29	0.087(3)	−0.061(2)	0.737(1)

EXPERIMENTAL CONDITIONS

Instrument	SYNTEX PĪ
Radiation	Graphite crystal monochromated Mo$K\alpha$ λ=0.71069 Å
Crystal dimensions/mm	0.2×0.2×0.3
Scanning mode	$\theta/2\theta$
Scan speed/° min^{-1}	3–4
Scan range	$2\theta_{\alpha 1}-1.0$ to $2\theta_{\alpha 2}+1.0$
Background counts	For 0.35 of scan time at scan limits
Temperature/K	143
2θ range	2.5–60.0
Number of reflections	2510
Number of reflections $I>2.5\sigma(I)$	2123
Number of standard reflections	3
Number of reflections between standard reflections	97

CRYSTAL DATA

19,20-epoxy-15-hydroxy-icajine. $C_{22}N_2O_5H_{24}$, orthorhombic, a=10.314(2) Å, b=10.843(3) Å, c=16.039(3) Å, V=1793.6 Å^3, M=396, Z=4 $F(000)$=840, space group: $P2_12_12_1$ (No. 19).

STRUCTURE DETERMINATION

The structure was solved by direct methods using the program assembly MULTAN;[6] hydrogen atomic positional parameters were calculated from stereochemical considerations. The refinement by least-squares calculations included positional parameters for all atoms,

Table 2. Bond lengths in 19,20-epoxy-15-hydroxy-icajine. C–H distances are between 0.941 and 1.02 Å, mean distance being 0.981(2) Å.

Distance	(Å)	Distance	(Å)
O26–C17	1.4421(3)	O26–C18	1.433(3)
O27–C23	1.221(3)	O28–C3	1.217(3)
O29–C15	1.432(3)	N1–C13	1.419(3)
N1–C23	1.374(4)	N4–C5	1.459(3)
N4–C21	1.457(3)	N4–C24	1.458(4)
C2–C7	1.554(4)	C2–C16	1.523(4)
C3–C7	1.556(4)	C5–C6	1.524(4)
C6–C7	1.556(4)	C7–C8	1.526(3)
C9–C10	1.402(4)	C12–C13	1.398(4)
C14–C15	1.543(4)	c15–C16	1.540(4)
C15–C20	1.554(4)	C17–C22	1.521(4)
C19–C20	1.491(4)	C22–C23	1.519(4)
N1–C2	1.498(3)	C3–C14	1.526(4)
C8–C9	1.386(4)	C8–C13	1.392(4)
C10–C11	1.381(5)	C11–C12	1.395(5)
C16–C17	1.529(4)	C18–C19	1.515(4)
C20–C21	1.512(4)	C18–C19	1.515(4)

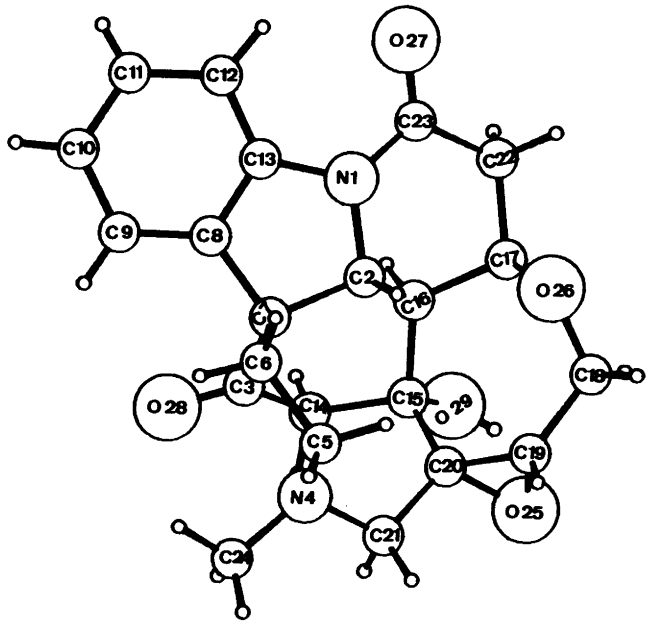


Fig. 1. 19,20-Epoxy-15-hydroxy-icajine.

anisotropic thermal parameters for the heavier atoms and isotropic thermal parameters for hydrogen atoms; it converged to a conventional R-factor of 0.041, R_w=0.035 and $S=|\sum w\Delta F^2/(n-m)|^{\frac{1}{2}}=1.98$.

Final parameters are given in Table 1, structural data are listed in Tables 2, 3 and 4. The structure factor listing and thermal parameters may be obtained from the authors.

Standard deviations given are calculated from the variance-covariance matrix.

DESCRIPTION AND DISCUSSION

A drawing of the molecule as seen perpendicular to the benzene ring plane is shown in Fig. 1, where the numbering of the atoms also is indicated. The only differences in chemical

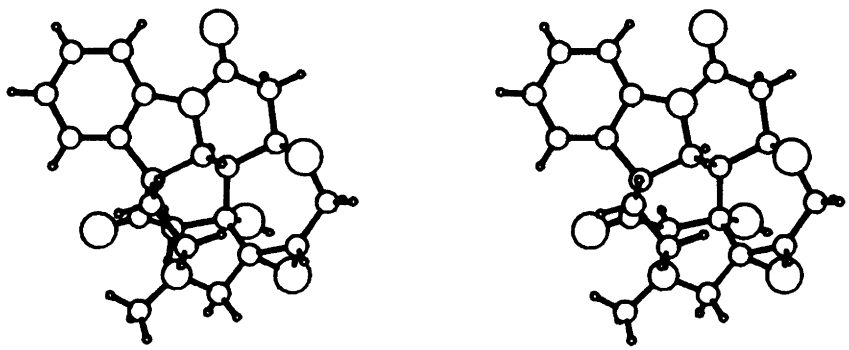


Fig. 2. Stereoscopic drawing of the 19,20-epoxy-15-hydroxy icajine molecule.

Table 3. Angles in 19,20-epoxy-15-hydroxy-icajine.

Angle	(°)	Angle	(°)
C2–N1–C13	109.6(2)	C5–N4–C21	115.7(2)
C5–N4–C24	113.4(2)	C21–N4–C21	112.5(2)
N1–C2–C16	107.4(2)	O28–C3–C7	119.1(2)
N4–C5–C6	107.3(2)	C2–C7–C3	114.5(2)
C3–C7–C6	108.7(2)	C17–O26–C18	113.3(2)
C2–N1–C23	122.7(2)	C13–N1–C23	124.8(2)
N1–C2–C7	105.7(2)	C7–C2–C18	117.5(2)
O28–C3–C14	119.3(2)	C7–C3–C14	120.6(2)
C5–C6–C7	109.9(2)	C2–C7–C6	110.7(2)
C2–C7–C8	103.2(2)	C3–C7–C8	111.5(2)
C6–C7–C8	108.1(2)	C7–C8–C9	129.2(3)
C7–C8–C13	110.6(2)	C9–C8–C13	120.3(3)
C8–C9–C10	118.8(3)	C9–C10–C11	120.4(3)
C10–C11–C12	121.9(3)	C11–C12–C13	116.9(3)
N1–C13–C8	110.6(2)	N11–C13–C12	127.4(3)
C8–C13–C12	121.9(3)	C3–C14–C15	116.9(2)
O29–C15–C14	105.6(2)	C29–C15–C20	109.8(2)
C14–C15–C16	104.3(2)	C14–C15–C20	112.9(2)
C16–C15–C20	116.2(2)	C2–C16–C15	114.8(2)
C2–C16–C17	106.9(2)	C15–C16–C17	117.2(2)
O26–C17–C16	112.6(2)	C16–C17–C22	108.8(2)
C18–C19–C20	126.3(3)	O25–C20–C15	114.3(2)
O25–C20–C21	109.5(2)	C15–C20–C19	122.9(2)
O27–C23–C22	120.2(3)		
C19–C20–C25	59.2(2)	C20–C19–C25	59.1(2)
C20–C25–C19	61.7(2)		

Table 4. Some torsional angles in 19,20-epoxy-15-hydroxy-icajine in the crystal state.

Dihedral angle	(°)	Dihedral angle	(°)
C2–N1–C12–C12	−178.6(3)	C5–C6–C7–C3	59.7(3)
C13–N1–C2–C7	−3.0(3)	C5–C6–C7–C8	−179.2(3)
C13–N1–C2–C16	−123.1(2)	C2–C7–C8–C9	175.2(3)
C2–N1–C23–O27	−177.1(2)	C3–C7–C8–C9	51.9(4)
C2–N1–C23–C22	5.4(4)	C6–C7–C8–C13	110.8(3)
C23–N1–C–C7	−164.4(2)	C7–C8–C9–C10	179.2(3)
C23–N1–C2–C16	−38.3(3)	C7–C8–C13–C12	−177.4(3)
C13–N1–C23–C27	−24.4(4)	C13–C8–C9–C10	1.1(5)
C13–N1–C23–C22	−153.1(3)	C3–C14–C15–O29	−165.6(2)
C23–N1–C13–C8	159.8(3)	C3–C14–C15–C20	74.5(3)
C21–N4–C5–C6	140.1(2)	O29–C15–C20–C25	11.5(3)
N1–C2–C7–C3	126.8(2)	O29–C15–C20–C19	79.3(3)
N1–C2–C16–C15	−161.8(2)	O29–C15–C20–C21	−118.9(3)
C7–C2–C16–C17	−174.9(2)	C14–C15–C16–C2	63.7(3)
C16–C2–C7–C3	7.1(3)	C14–C15–C16–C17	−169.6(2)
C16–C2–C7–C6	130.4(2)	C14–C15–C20–O25	129.0(2)
C16–C2–C7–C8	−114.2(2)	C20–C15–C16–C2	−61.3(3)
C14–C3–C7–C2	3.0(4)	O26–C17–C22–C23	−91.6(3)
C14–C3–C7–C6	−121.3(3)	C16–C17–C22–C23	30.4(4)
CC14–C3–C7–C8	119.8(3)	O26–C18–C19–O25	119.8(3)
N4–C5–C6–C7	−49.2(3)	C17–C22–C23–O27	−178.7(3)
C5–C6–C7–C2	−66.8(3)		

Table 5. Conformational differences between 19,20-epoxy-15-hydroxy-icajine and icajine. The data for icajine have been given signs as to be compatible with the enantiomeric form in which the present molecule is presented.

		HEI	ICAJINE
C14–C15–C20–C19	(°)	−163	178
C16–C15–C20–C19	(°)	−43	58
C19–C20–C21–N4	(°)	109	129
C20–C19–C18–O	(°)	51	67
Distances from the plane (C9, C11, N1): (Å)			
C22		0.978	0.416
C17		1.080	1.064
O		−0.129	0.1825
C18		0.004	0.702
C19		−0.076	0.275
C20		0.700	0.700
C21		0.188	0.225
N4		−0.374	−0.309
Distance of C20 from C15, C19, C21 plane (Å)		0.14	0.015
Distance of C2 from benzene ring plane (Å)		0.13	0.014

Table 6. Comparison of geometrical data concerning the N···C=O interaction. The calculated values for the out-of-plane distance for C3 was obtained from the expression suggested by Dunitz: $d_1 = -1.701 \log n + 1.479$ Å where d_1 is the N···C distance, $n = \Delta/0.437$ Å and Δ is the out-of-plane displacement of the carbonyl C-atom.

	HEI	ICAJIN	STRY–BRA
Distances (Å)			
N4···C3	2.347	2.456	2.24
N4 out of C5, C21, C24 plane	0.37	0.36	0.44
C3 out of C7, C14, O plane (Obs)	0.08	0.05	0.13
C3 out of C7, C14, O plane (Calc)	0.13	0.12	0.16
Angles (°)			
Lone-pair–N4···C3	8	10	13
O–C2···N4	104	102	102
C5, C21, C24 plane and O, C27, C14 plane	11	14	12

structure between this molecule and that of icajine[2] are the presence of the hydroxy group at C15 and the exchange of the 19–20 double bond in icajine for the 19–20 epoxy group in 15-hydroxy-19–20-epoxy icajine (HEI). Accordingly, the overall conformation of the present molecule, illustrated in Fig. 2, is very close to that observed for icajine. However, even if the C19–C20 distance is about the same in the two compounds, the shift from a C19–C20 double bond to a C19–C2 epoxy group introduces changes of about 20° in some of the torsion angles involving the C19–C20 bond. The most significant differences between the geometries of icajine and HEI are given in Table 5. The decrease in the values for the first three torsion angles in the table seems reasonable from the change in the C19–C20

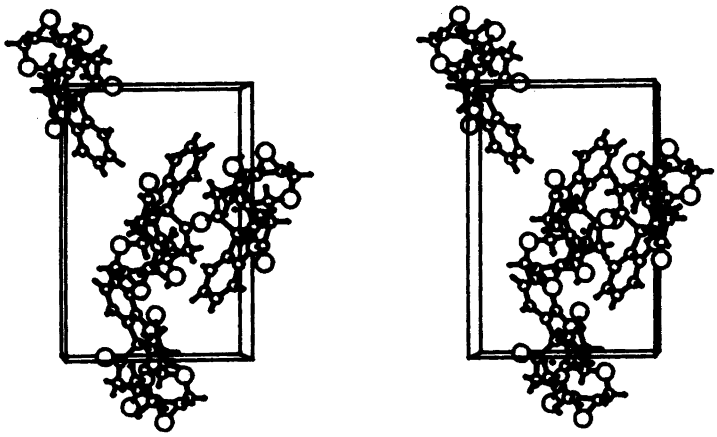


Fig. 3. Molecular packing of 19,20-epoxy-15-hydroxy-icajine molecules in the crystal as seen down the *a*-axis.

bonding. The decrease in the C20–C19–C18–O angle also seems to be caused by the shift in positions of atoms C18, C19 and the oxygen atom O26 (O17 in icajine) relative to the indole ring plane as shown in Table 5. Nevertheless, the conformation of the nine membered ring N4, C5, C6, C7, C3, C14, C15, C20, C21 is quite close to that found in icajine, and the transannular interaction between N4 and the C=O group is evident also in the present structure. The N4 atom exists in sp^3 condition, the axis of the lone pair pointing towards the C3 atom in such a way as to form an angle of 7.5° with a line through the two atoms. The N4···C3 distance is found to be 2.347 Å. As in icajine, the conformation about the N4···C3 bonding is eclipsed, the rotation being about 7°. The C3 atom is 0.08 Å out of the O28, C7, C14 plane and in the direction of the N4-atom. A displacement of a carbonyl-C atom out of the sp^2-plane as a result of a nucleophilic N···C=O interaction has tentatively been described by an expression given by Dunitz.[7] Table 6 gives a comparison between the displacements calculated by this expression and the findings from the structural analyses of 14-hydroxy-strychnobrasiline, icajine and HEI together with other geometrical data concerning the transannular interaction.

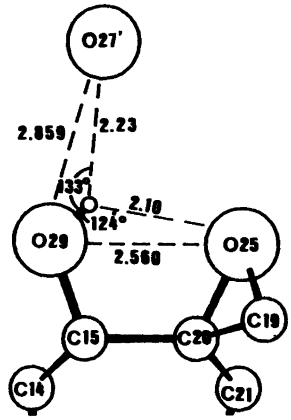


Fig. 4. Hydrogen bonding in the 19,20-epoxy-15-hydroxy icajine molecule.

The geometry of the epoxy group is as normally found in such rings, the C–O bonds being close to 1.45 Å and the C–C bond 1.49 Å.

The packing of the molecules in the crystal is illustrated in Fig. 3. There is one intermolecular hydrogen bond in the present structure, namely between atoms O29 (donor) and O27 ($\frac{1}{2}-x,-y,\frac{1}{2}+z$) (acceptor), the distance between the two oxygen atoms being 2.859 Å. However, the hydrogen atom at O29 also seems to be involved in an *intra*-molecular interaction with the epoxy-oxygen atom. The situation is displayed in Fig. 4.

The hydrogen bonded molecular chains along the z-axis are held together by van der Waals' forces. The shortest intermolecular contact appears to exist between O28 and H16 ($x+\frac{1}{2},\frac{1}{2}-y,-z$) the distance being 2.25 Å. Other such contacts between oxygen or aromatic carbon atoms and hydrogen atoms are at distances of 2.60 to 2.80 Å.

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