

Crystal and Molecular Structure of 19,20-Dihydrostrychnine

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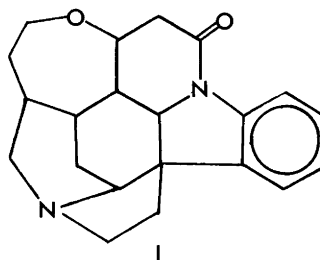
The crystal and molecular structure of 19,20-Dihydrostrychnine was determined by X-ray methods at about 133 K, using 2346 reflections. The crystals are tetragonal, space group $P4_1$, and cell dimensions $a = b = 7.251(1)$ Å and $c = 31.422(4)$ Å. The structure was refined to a conventional R -factor of 0.044. Estimated standard deviations in bond lengths and angles when hydrogen atoms are not involved are $(3-4) \times 10^{-3}$ and 0.2° respectively. Changes in conformation and bond lengths induced by the hydration of the C19–C20 bond are discussed.

Introduction

In the effort to elucidate the characteristics of the molecular structures of *Strychnos* alkaloids, the crystal and molecular structure of 19,20-dihydrostrychnine (I) was determined by X-ray methods. It is of interest to study the changes in molecular conformation when the state of hybridisation for the C19 and C20 atoms is transformed from sp^2 to sp^3 , and the influence of this change on the N4–C3 bond as indicated in the structural study of strychnine.¹ Finally, in view of the biological effects of *strychnos* alkaloids, it is of interest to study the intermolecular interactions of such molecules.

Experimental

A small sample of I from the laboratory of Dr. R. Verpoorte at the Gorlaeus Laboratoire in Leiden was recrystallized from chloroform. The process produced a few fairly large crystals from which a smaller piece was cut and used for the X-ray experiments. Cell parameters were determined by least squares fit to the diffractometer settings for 20 general reflections. The standard deviations for the intensities were calculated from $\sigma(I) = [C_T + (0.002 C_N)^2]^{1/2}$, 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, whereas no corrections were made for absorption or extinction. Scattering factors used were those of Doyle & Turner for O, N and C², and of Stewart Davidson & Simpson for H³. Other experimental conditions are given below.

Experimental conditions

Instrument	NICOLET P3/F
Radiation	Graphite crystal monochromated MoK α . $\lambda = 0.71069$
Crystal dimensions/mm	0.4 \times 0.3 \times 0.3
Scanning mode	$\theta/2\theta$
Scan speed $^\circ/\text{min}^{-1}$	3.0 (2 θ)
Scan range $^\circ$	± 1.0
Back ground counts	For 0.35 of scan time at scan limita

Table 1. Fractional coordinates of 19,20-dihydrostrychnine. Estimated standard deviations in parentheses.

Atom	X	Y	Z
O17	0.0800(3)	0.2946(2)	0.3696(0)
O23	0.4768(3)	0.7872(3)	0.3322(1)
N1	0.2507(3)	0.6679	0.2901(1)
N4	-0.1682(3)	0.2826(3)	0.2269(1)
C2	0.1156(3)	0.5156(3)	0.2850(1)
C3	0.0245(4)	0.3312(3)	0.2172(1)
C5	-0.2654(4)	0.4550(4)	0.2165(1)
C6	-0.1393(4)	0.6152(4)	0.2316(1)
C7	0.0552(3)	0.5261(3)	0.2375(1)
C8	0.2081(3)	0.6404(3)	0.2181(1)
C9	0.2483(4)	0.6725(4)	0.1756(1)
C10	0.3952(4)	0.7895(4)	0.1653(1)
C11	0.4977(4)	0.8736(4)	0.1970(1)
C12	0.4597(3)	0.8421(3)	0.2397(1)
C13	0.3145(3)	0.7245(3)	0.2495(1)
C14	0.1581(4)	0.1825(3)	0.2316(1)
C15	0.1426(4)	0.1591(4)	0.2798(1)
C16	0.2172(3)	0.3403(3)	0.2990(1)
C17	0.2410(4)	0.3499(4)	0.3472(1)
C18	0.0454(5)	0.1001(4)	0.3688(1)
C19	-0.1010(5)	0.0512(5)	0.3365(1)
C20	-0.0573(4)	0.0997(4)	0.2896(1)
C21	-0.1973(4)	0.2365(4)	0.2722(1)
C22	0.2797(4)	0.5509(4)	0.3619(1)
C23	0.3482(4)	0.6796(3)	0.3273(1)
H2	-0.001(4)	0.535(4)	0.306(1)
H3	0.030(4)	0.345(4)	0.186(1)
H15	-0.388(4)	0.460(4)	0.230(1)
H25	-0.276(4)	0.463(4)	0.183(1)
H16	0.347(4)	0.353(4)	0.286(1)
H26	-0.135(4)	0.705(4)	0.212(1)
H9	0.168(4)	0.618(4)	0.153(1)
H10	0.423(4)	0.812(4)	0.138(1)
H11	0.593(4)	0.950(4)	0.190(1)
H12	0.530(4)	0.896(4)	0.261(1)
H114	0.287(4)	0.217(4)	0.222(1)
H214	0.125(4)	0.064(4)	0.216(1)
H15	0.225(4)	0.062(4)	0.291(1)
H16	-0.182(4)	0.673(4)	0.258(1)
H17	0.345(4)	0.265(4)	0.356(1)
H118	0.012(4)	0.070(4)	0.398(1)
H218	0.166(4)	0.035(4)	0.363(1)
H119	-0.220(4)	0.113(4)	0.343(1)
H219	-0.122(4)	-0.074(4)	0.338(1)
H20	-0.077(4)	0.001(4)	0.275(1)
H121	-0.204(4)	0.351(4)	0.291(1)
H221	-0.321(4)	0.183(4)	0.277(1)
H122	0.361(4)	0.562(4)	0.387(1)
H222	0.158(4)	0.594(4)	0.373(1)

Temperature / K	133
at crystal site	
2 θ range	2.0 – 55.0
Number of reflections	2837
Number of reflections with $I > 2.5\sigma(I)$	2346
Number of standard reflections	3
Number of reflections between standard reflections	57

Crystal data

Dihydrostrychnine, $C_{21}O_2N_2H_{24}$, tetragonal $a = b = 7.251(1)$ Å, $c = 31.422(4)$, $V = 1652.5$, $M = 336.2$, $Z = 4$, $F_{(000)} = 720$, Space group $P4_3$ (NO 78).

Structure determination

The structure of I was solved by direct methods using the MITHRIL program assembly⁴, which indicated a recognizable fraction of the molecule. Positions of all the non-hydrogen atoms were determined by Fourier methods and refined by least-squares calculations. Positions of the hydrogen atoms were introduced from stereochemical considerations and the final refinement by least-squares methods included positional parameters for all atoms (except the Z coordinate for the O17 atom), and anisotropic thermal parameters for the non-hydrogen atoms.

Sixty-seven reflections with small intensities, but where the measurements were influenced by neighbour reflections, were excluded from the intensity data. The final statistical parameters were: $R = 0.044$, $R_w = 0.043$ and $S = [\omega(\Delta F)^2/(n-m)]^{1/2} = 2.1$. Standard deviations given are calculated from the variance-covariance matrix. The structure factor listing and thermal parameters may be obtained from the author. The quality minimized in the least squares calculations was $\sum w(\Delta F)^2$, where w is the inverse of the variance of the observed structure factors. Description of the computer programs applied is given in Ref. No. 5.

Table 2. Bond lengths and angles in 19,20-dihydrostrychnine. Estimated standard deviations in parentheses. The C–H distances are all between 1.07 Å and 0.87 Å with standard deviation of $4 \cdot 10^{-2}$ Å.

Distance	(Å)	Distance	(Å)
O17–C17	1.421(3)	O17–C18	1.432(3)
O23–C23	1.225(3)	N1–C2	1.485(3)
N1–C13	1.418(3)	N1–C23	1.367(3)
N4–C3	1.472(4)	N4–C5	1.472(4)
N4–C21	1.478(4)	C2–C7	1.557(3)
C2–C16	1.534(3)	C3–C7	1.566(3)
C3–C14	1.518(4)	C5–C6	1.553(4)
C6–C7	1.562(3)	C7–C8	1.513(4)
C8–C9	1.384(4)	C8–C13	1.394(3)
C9–C10	1.400(4)	C10–C11	1.384(4)
C11–C12	1.390(4)	C12–C13	1.388(3)
C14–C15	1.529(4)	C15–C16	1.544(3)
C15–C20	1.543(4)	C16–C17	1.527(4)
C17–C22	1.554(4)	C18–C19	1.511(5)
C19–C20	1.548(5)	C20–C21	1.521(4)
C22–C23	1.518(4)		
Angle	(°)	Angle	(°)
C17–O17–C18	114.4(2)	C2–N1–C13	109.4(2)
C2–N1–C23	118.7(2)	C13–N1–C23	125.5(2)
C2–N4–C5	101.8(2)	C3–N4–C21	112.9(2)
C5–N4–C21	109.8(2)	N1–C2–C7	104.7(2)
N1–C2–C16	105.6(2)	C7–C2–C16	116.8(2)
N4–C3–C7	105.5(2)	N4–C3–C14	112.0(2)
C7–C3–C14	115.4(2)	N4–C5–C6	106.6(2)
C5–C6–C7	105.0(2)	C2–C7–C3	112.7(2)
C2–C7–C6	112.9(2)	C2–C7–C8	101.9(2)
C3–C7–C6	101.4(2)	C3–C7–C8	115.7(2)
C6–C7–C8	112.7(2)	C7–C8–C9	129.4(2)
C7–C8–C13	111.1(2)	C9–C8–C13	119.5(2)
C8–C9–C10	119.1(3)	C9–C10–C11	120.5(2)
C10–C11–C12	121.1(3)	C11–C12–C13	117.7(2)
N1–C13–C8	109.3(2)	N1–C13–C12	128.6(2)
C8–C13–C12	122.1(2)	C3–C14–C15	109.0(2)
C14–C15–C16	105.5(2)	C14–C15–C20	107.3(2)
C16–C15–C20	119.3(2)	C2–C16–C15	115.1(2)
C2–C16–C17	107.5(2)	C15–C16–C17	117.8(2)
O17–C17–C16	112.7(2)	O17–C17–C22	105.4(2)
C16–C17–C22	111.0(2)	O17–C18–C19	111.5(3)
C18–C19–C20	116.3(2)	C15–C20–C19	116.5(3)
C15–C20–C21	111.9(2)	C19–C20–C21	110.6(3)
N4–C21–C20	113.4(3)	C17–C22–C23	115.0(2)
O23–C23–N1	122.7(2)	O23–C23–C22	123.4(2)
N1–C23–C22	113.9(2)		

Description and discussion

The 19,20-dihydrostrychnine molecule is depicted in Fig. 1 where the numbering of the atoms is also given. To simplify comparison between structures, all figures have been drawn to represent the natural chirality of the molecule, whereas the coordinates represents the enantiomer.

The hydration of the C19–C20 bond in the strychnine molecule brings about a change in the state of hybridization of the two involved atoms from sp^2 to sp^3 . Consequently, the C19–C20 bond length is observed to increase from 1.330 Å in strychnine to 1.551 Å in dihydrostrychnine. Accordingly, a decrease in bond angles involving these atoms are found in dihydrostrychnine relative to the values presented for strychnine¹ C18–C19–C2 from 122.5° to 116.3°, C19–C20–C15 from 122.2° to 116.5°, C19–C20–C21 from 123.5° to 110.6° and C15–C20–C21 from 114.2° to 111.9°.

The three dimensional structure is illustrated in Fig. 2, and the conformational characteristics of the different parts of the molecule is compared to those of strychnine in Table 4. It may be seen from this Table that there are only small changes in the conformation of the oxacycloheptane ring.

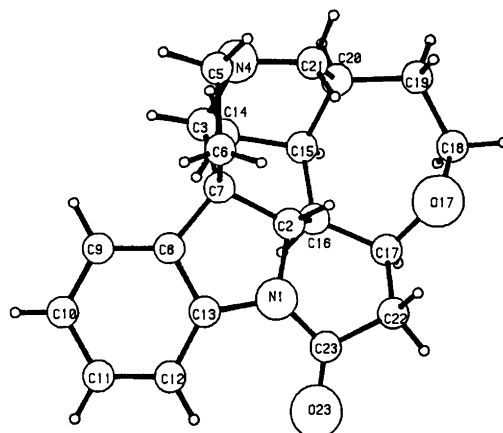


Fig. 1. 19,20-dihydrostrychnine.

It may be noticed, however, that O17 is moved away from the C15–C20–C19–C18 plane by the hydration and also in fact away from the phenyl ring plane by 0.35 Å relative to the position in strychnine.

Changes in the twisted boat-conformation of the 2-oxo-piperidine ring are also small, but the effect on the O23 atom is to move it 0.30 Å closer to the phenyl ring plane.

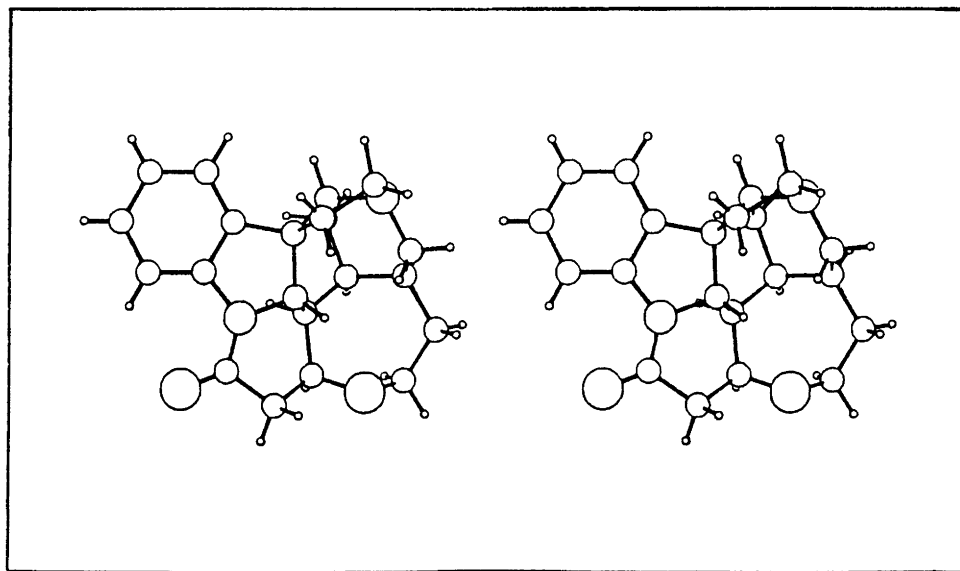


Fig. 2. Stereoscopic drawing of 19,20-dihydrostrychnine.

Table 3. Dihedral angles in 19,20-dihydrostrychnine. Estimated standard deviations in parentheses.

Dihedral angle	(°)	Dihedral angle	(°)
C17-O17-C18-C19	-100.9(3)	C14-C3-C7-C6	-158.0(2)
C18-O17-C17-C16	73.3(3)	C14-C3-C7-C8	79.7(3)
C18-O17-C17-C22	-165.5(2)	N4-C5-C6-C7	17.4(3)
C2-N1-C13-C8	9.7(2)	C5-C6-C7-C2	-111.2(3)
C2-N1-C13-C12	-169.6(2)	C5-C6-C7-C3	9.6(3)
C13-N1-C2-C7	-17.7(2)	C5-C6-C7-C8	133.9(3)
C13-N1-C2-C16	106.1(2)	C2-C7-C8-C9	168.4(2)
C2-N1-C23-O23	171.3(3)	C2-C7-C8-C13	-13.4(2)
C2-N1-C23-C22	-10.1(3)	C3-C7-C8-C9	45.7(3)
C23-N1-C2-C7	-171.3(2)	C3-C7-C8-C13	-136.1(2)
C23-N1-C2-C16	-47.5(3)	C6-C7-C8-C9	-70.4(3)
C13-N1-C23-O23	22.3(4)	C6-C7-C8-C13	107.9(2)
C13-N1-C23-C22	-159.1(2)	C7-C8-C9-C10	177.9(2)
C23-N1-C13-C8	161.0(2)	C7-C8-C13-N1	3.0(3)
C23-N1-C13-C12	-18.2(4)	C7-C8-C13-C12	-177.7(2)
C3-N4-C5-C6	-38.6(3)	C9-C8-C13-N1	-178.6(2)
C5-N4-C3-C7	45.4(3)	C3-C14-C15-C16	-67.3(3)
C5-N4-C3-C14	171.8(2)	C3-C14-C15-C20	60.9(3)
C3-N4-C21-C20	-48.7(3)	C14-C15-C16-C2	58.6(3)
C21-N4-C3-C7	-72.2(3)	C14-C15-C16-C17	-172.8(2)
C21-N4-C3-C14	54.1(3)	C14-C15-C20-C19	174.9(2)
C5-N4-C21-C20	-161.6(2)	C14-C15-C20-C21	-56.4(3)
C21-N4-C5-C6	81.2(3)	C16-C15-C20-C19	-65.4(3)
N1-C2-C7-C3	142.9(2)	C16-C15-C20-C21	63.3(3)
N1-C2-C7-C6	-103.1(2)	C20-C15-C16-C2	-62.0(3)
N1-C2-C7-C8	18.1(2)	C20-C15-C16-C17	66.5(3)
N1-C2-C16-C15	-155.4(2)	C2-C16-C17-O17	81.2(2)
N1-C2-C16-C17	71.1(2)	C2-C16-C17-C22	-36.8(3)
C7-C2-C16-C15	-39.5(3)	C15-C16-C17-O17	-50.8(3)
C7-C2-C16-C17	-173.0(2)	C15-C16-C17-C22	-168.8(2)
C16-C2-C7-C3	26.5(3)	O17-C17-C22-C23	-141.7(2)
C16-C2-C7-C6	140.6(2)	C16-C17-C22-C23	-19.4(3)
C16-C2-C7-C8	-98.2(2)	O17-C18-C19-C20	61.0(4)
N4-C3-C7-C2	87.1(2)	C18-C19-C20-C15	10.8(4)
N4-C3-C7-C6	-33.8(3)	C18-C19-C20-C21	-118.5(3)
N4-C3-C7-C8	-156.1(2)	C15-C20-C21-N4	50.8(3)
N4-C3-C14-C15	-61.1(3)	C19-C20-C21-N4	-177.5(2)
C7-C3-C14-C15	59.6(3)	C17-C22-C23-O23	-135.4(3)
C14-C3-C7-C2	-37.1(3)	C17-C22-C23-N1	46.0(3)

The most significant difference between the structure of I and that of strychnine is found in the piperidine ring conformation, which is changed from a boat form in strychnine to a chair form in the dihydro derivative. Furthermore, the conformation about the N4-C3 bond which in strychnine is almost eclipsed (C-N4-C3-C $\sim 8^\circ$) is found in I to be only about 10° away from staggered, as illustrated in Fig. 3. This gives a reason-

able explanation for the shortening of about $2 \cdot 10^{-2}$ Å in the N4-C3 bond from 1.491 Å in strychnine to 1.473 Å in dihydrostrychnine. Accordingly, there is also a change in the pyrrolidine ring conformation in that the envelope conformation with the C7 atom 0.619 Å out of the N4, C5, C6, C3 plane is present in the strychnine molecule, whereas the dihydro derivative exhibit a similar ring conformation, but with the N4

Table 4. Comparison of conformational characteristics of 19,20-dihydrostrychnine and strychnine. Distances given in Å.

	I	Strychnine
The oxacycloheptane ring		
Planarity of C15, C20, C19, C18	± 0.953	± 0.053
Distance from plane to C16	1.090	1.014
Distance from plane to C17	1.229	1.085
Distance from plane to O17	1.282	1.082
The oxo-piperidine ring		
Distance from plane C16, C17, C23, to C22	0.259	0.155
Distance from plane C16, C17, C23 to N1	0.530	0.628
	1.071	1.111
The piperidine ring		
	Chair conformation	Boat conformation
Planarity of N4, C3, C15, C20	0.015	0.033
Distance from plane to C14	0.729	0.710
Distance from plane to C21	-0.580	0.613
The pyrrolidine ring		
Planarity of N4, C5, C6, C23	± 0.234	± 0.100
Distance from plane to C7	0.372	0.619
Planarity of C3, C5, C6, C7	± 0.059	± 0.264
Distance from plane to N4	0.615	0.063

atom 0.727 Å out of the C3, C5, C6, C7 plane. An increase in the three bond lengths C5–C6, C6–C7 and C7–C3 of about $2 \cdot 10^{-2}$ Å is observed and finally the N4 atom is shifted from a position 0.009 Å away from the phenyl ring plane in strychnine to be 0.305 Å away from this plane in dihydrostrychnine.

The molecular packing in the crystal is shown in Fig. 4 and appears to be governed by van der Waals' forces alone. Thus the shortest intermolecular distances found are those between mole-

cules related by the fourfold screw axis, namely between O23 and H9' ($y, 1-x, \frac{1}{4}+z$): 2.478 Å, (O23...C9: 3.272 Å). Furthermore, the shortest

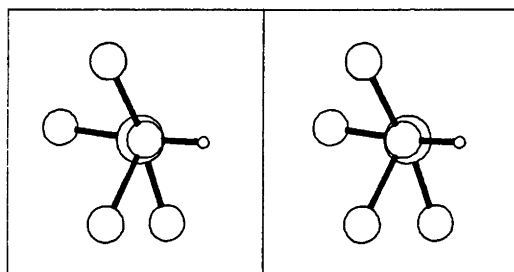


Fig. 3. Stereoscopic illustration of the rotation about the C3–N4 bond as seen in that direction.

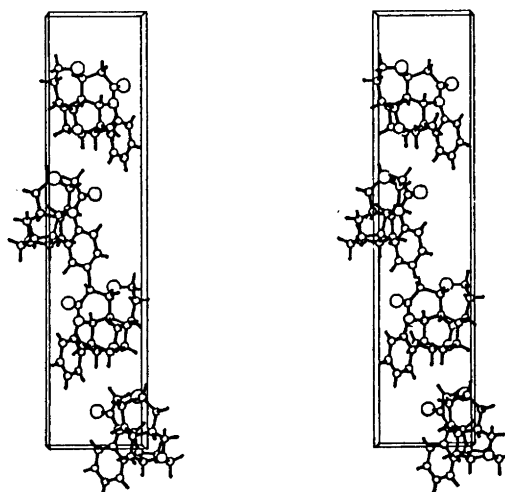


Fig. 4. Molecular packing of 19,20-dihydrostrychnine molecules in the crystal.

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distances between the helices along the fourfold screw-axes are found between 017 and the hydrogen atoms at C10 and C11 displaced by: $y-1$, $1-x$, $Z+\frac{1}{4}$, the distances being 2.882 Å and 2.544 Å respectively. (017··C10: 3.399 Å, and 017··CH: 3.228 Å). In this way the two oxygen atoms and the phenyl ring seem to play the main role in binding the molecules together. All intermolecular N4···H distances are above 3.0 Å.

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