Crystal and Molecular Structure of Pseudostrychnine

Arvid Mostad

Department of Chemistry, University of Oslo, N-0315 Oslo 3, Norway

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The crystal and molecular structure of pseudostrychnine (3-hydroxystrychnine: $C_{21}O_3N_2H_{22}$) has been determined by X-ray methods at low temperature ($T = 133$ K) using 1637 reflections. The crystals are orthorhombic, space group $P2_12_12_1$, cell dimensions $a = 11.814(5)$, $b = 11.817(5)$, $c = 12.052(5)$. The structure was refined to a conventional R factor of 0.051. Estimated standard deviation in bond lengths and angles not including hydrogen atoms are 0.005 Å and 0.3°, respectively. The 3-hydroxy-tautomeric form of the compound is found to exist in the crystals, and the hydroxy group is involved in a hydrogen bond to the ethereal oxygen in the oxacycloheptane ring rather than to the N4 atom. A simple linear relationship between the N4−C3 distances and the distances of C3 from the C7, C17, O plane in strychnos alkaloids is given.

Dedicated to Professor Otto Bastiansen on his 70th birthday

Strong, non-bonded intramolecular interactions between a carbon atom in a carbonyl group and a nitrogen atom having lone-pair electrons have been observed in various types of molecules, and described in general by Birnbaum[1] and by Dunitz.[2] Such interactions have also been shown to exist in a number of strychnos alkaloids.[3-5] In some compounds, as for instance in strychnine, the N4−C3 bond is formally established, whereas in others, such as icajine, there is only a non-bonded interaction. The non-bonded N−C interaction in strychnos alkaloids is of interest for several reasons. The interaction conserves the same molecular conformation as found in compounds where the N−C bond is formally established. This may thus be of importance to their biological activity. Furthermore, the study of such interactions in a number of different molecules may illuminate details of an intramolecular nucleophilic reaction. In the latter context Dunitz has proposed a formula which includes the length of a "normal" C−N bond and describes a relation between the planarity of the $R_1R_2C = O$ group and the N−C distance. However, in strychnine, where the N−C bond is established, the bond length is shown to be influenced by the protonation of the nitrogen atom as well as by the

conformation about the N−C bond,[6,7] and a "normal" value for the bond length is not easily given. Moreover, as the non-bonded N−C interactions in strychnos alkaloids involve oxygen-substituted carbon atoms, whereas the substituent on the carbon atom in strychnine (where the N−C bond is established) is hydrogen, it appears to be of interest to examine also the possible effect of an oxygen-substituted carbon on the formal N−C bond length. Pseudostrychnine presents an opportunity for doing this (Scheme 1). Furthermore this compound may exist in the two tautomeric forms:

$$HO-C-N: \leftrightarrow O = C:NH$$
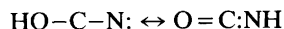
and even though infrared spectroscopy strongly indicates that the hydroxy-form exists in the solid phase,[8] it was of interest to investigate this as well.

Experimental

A few milligrams of pseudostrychnine, supplied by Dr. R. Verpoorte at the Gorlaeus Laboratoire in Leiden, were recrystallized from acetonitrile, giving coalesced crystal lumps containing small

ICAJINE   STRYCHNINE   PSEUDOSTRYCHNINE
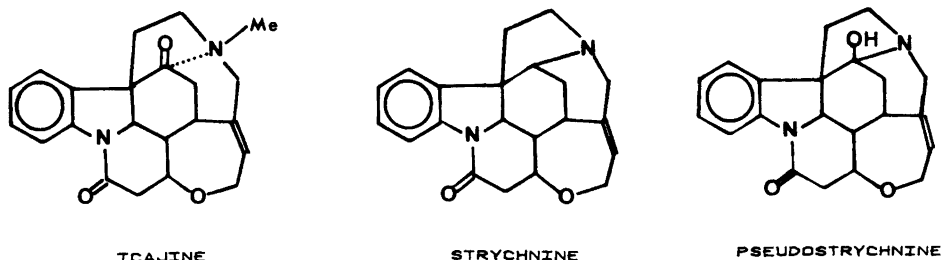
Scheme 1.

plate-like single crystals. A crystal of dimensions 0.35 × 0.30 × 0.15 mm was cut and used for the X-ray experiments. Cell parameters were determined from a least-squares fit to the diffractometer settings for 21 general reflections (2θ range: 16.0–35.0°). The standard deviations for the intensities were calculated from: $\sigma(I) = [C_T + (0.002C_N)^2]^{1/2}$, where C_T is the total number of counts and C_N is the scan count minus the background counts. Corrections were made for Lorentz and polarization effects, but not for absorption or extinction. The fluctuations of the test reflections were less than 2 % and no corrections were made on this basis. The data collection procedure is summarized in Table 1.

Table 1. Crystal and experimental data.

Compound	$C_{21}O_3N_2H_{22}$
Melting point	–
Diffractometer	NICOLET P3/F
Crystal size/mm	0.35×0.30×0.15
Radiation	Graphite cryst. monochrom. MoKα (λ = 0.71069 Å)
Crystal system	Orthorhombic
a/Å	11.814(5)
b/Å	11.817(5)
c/Å	12.052(5)
V/Å³	1682(1)
Temp./°C	−140
Space group	$P2_12_12_1$ (No. 19)
M	336.2
Z	4
F(000)	736
D_x/g cm^{-3}	1.327
μ(MoKα)/cm^{-1}	1.0
Scan mode	$\theta/2\theta$
Scan speed (2θ)/°min^{-1}	3.0
Scan range (2θ)/°	$2\theta\alpha_1$ −1.2 to $2\theta\alpha_2$+1.0
Maximum sinθ/λ/Å^{-1}	0.65
No. of indep. meas.	1834
No. with $I > 3\sigma(I)$	1637
Correction for absorption	No
Method for solving structure	Direct (MITHRIL)
No. of parameters refined	323
$R = \Sigma|F_o-F_c|/\Sigma F_o$	0.051
$R_w = [\Sigma w(F_o-F_c)^2/\Sigma wF_o^2]^{1/2}$ [a]	0.047
$S = [\Sigma w(F_o-F_c)^2/(n-m)]^{1/2}$	1.98

[a] w is the inverse of the variance of the observed structure factors.

Table 2. Fractional atomic coordinates for Pseudostrychnine. Estimated standard deviations in parentheses. $U_{eq} = (U_{11}+U_{22}+U_{33})/3$.

| Atom	x	y	z	U_{eq}
O3	−.0298(3)	.6972(2)	.6533(3)	.030
O17	.2483(3)	.2566(2)	.7692(2)	.026
O23	.1751(3)	.2422(3)	.3850(3)	.040
N1	.0734(3)	.3434(3)	.5114(3)	.022
N4	−.0168(3)	.5697(3)	.8051(3)	.024
C2	.0753(3)	.3928(3)	.6261(3)	.018
C3	.0252(4)	.5966(3)	.6925(4)	.023
C5	−.0907(4)	.4672(4)	.8020(4)	.025
C6	−.1221(4)	.4587(4)	.6787(4)	.023
C7	−.0119(3)	.4930(3)	.6198(3)	.021
C8	−.0293(3)	.5091(3)	.4963(3)	.022
C9	−.0903(4)	.5911(4)	.4389(4)	.030
C10	−.1049(4)	.5801(5)	.3242(4)	.038
C11	−.0617(4)	.4863(5)	.2674(4)	.036
C12	−.0006(3)	.4031(4)	.3256(4)	.027
C13	.0150(3)	.4166(4)	.4375(4)	.025
C14	.1514(4)	.6202(4)	.6913(4)	.024
C15	.2130(4)	.5159(4)	.7375(4)	.026
C16	.2003(3)	.4228(3)	.6493(3)	.020
C17	.2671(4)	.3125(4)	.6638(4)	.023
C18	.2910(4)	.3182(4)	.8649(4)	.030
C19	.2033(4)	.3972(4)	.9090(4)	.026
C20	.1671(4)	.4861(4)	.8521(4)	.027
C21	.0738(4)	.5637(4)	.8900(4)	.028
C22	.2274(4)	.2253(4)	.5770(4)	.027
C23	.1591(4)	.2695(3)	.4816(3)	.023
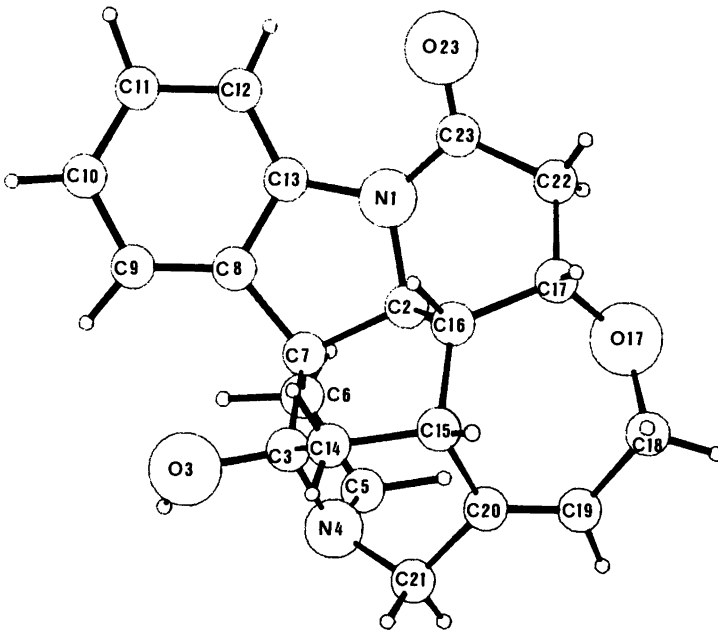
Fig. 1. Pseudostrychnine.

Table 3. Bond lengths (Å) and angles (°) in pseudostrychnine. Estimated standard deviations in parentheses. The C−H distances are all between 0.83 and 1.13 Å.

Bond lengths

O3−C3	1.436(5)	O17−C17	1.449(6)
O17−C18	1.455(6)	O23−C23	1.222(6)
N1−C2	1.500(6)	N1−C13	1.423(6)
N1−C23	1.385(6)	N4−C3	1.480(6)
N4−C5	1.492(7)	N4−C21	1.484(7)
C2−C7	1.571(6)	C2−C16	1.544(6)
C3−C7	1.568(7)	C3−C14	1.515(7)
C5−C6	1.534(7)	C6−C7	1.537(7)
C7−C8	1.515(7)	C8−C9	1.391(7)
C8−C13	1.404(7)	C9−C10	1.399(8)
C10−C11	1.397(8)	C11−C12	1.407(8)
C12−C13	1.368(7)	C14−C15	1.537(7)
C15−C16	1.535(7)	C15−C20	1.526(7)
C16−C17	1.535(7)	C17−C22	1.541(7)
C18−C19	1.491(7)	C19−C20	1.324(7)
C20−C21	1.504(7)	C22−C23	1.497(7)

Bond angles

C17−O17−C18	114.5(4)	C2−N1−C13	110.4(4)
C2−N1−C23	118.3(4)	C13−N1−C23	125.2(4)
C3−N4−C5	110.4(4)	C3−N4−C21	113.5(4)
C5−N4−C21	113.7(4)	N1−C2−C7	103.9(4)
N1−C2−C16	105.7(4)	C7−C2−C16	117.5(4)
O3−C3−N4	109.1(4)	O3−C3−C7	109.6(4)
O3−C3−C14	106.9(4)	N4−C3−C7	104.4(4)
N4−C3−C14	112.4(4)	C7−C3−C14	114.4(4)
N4−C5−C6	102.7(4)	C5−C6−C7	103.0(4)
C2−C7−C3	112.2(4)	C2−C7−C6	109.5(4)
C2−C7−C8	103.3(4)	C3−C7−C6	100.7(4)
C3−C7−C8	119.2(4)	C6−C7−C8	111.8(4)
C7−C8−C9	130.2(5)	C7−C8−C13	110.4(4)
C9−C8−C13	118.9(5)	C8−C9−C10	119.3(5)
C9−C10−C11	120.9(6)	C10−C11−C12	119.8(5)
C11−C12−C13	118.5(5)	N1−C13−C8	109.7(4)
N1−C13−C12	127.7(5)	C8−C13−C12	122.6(5)
C3−C14−C15	108.3(4)	C14−C15−C16	106.1(4)
C14−C15−C20	110.3(4)	C16−C15−C20	115.2(4)
C2−C16−C15	112.6(4)	C2−C16−C17	108.5(4)
C15−C16−C17	118.7(4)	O17−C17−C16	114.0(4)
O17−C17−C22	104.1(4)	C16−C17−C22	109.5(4)
O17−C18−C19	110.7(4)	C18−C19−C20	122.5(5)
C15−C20−C19	122.4(5)	C15−C20−C21	113.2(4)
C19−C20−C21	124.3(5)	N4−C21−C20	110.4(4)
C17−C22−C23	116.9(4)	O23−C23−N1	121.7(5)
O23−C23−C22	123.8(5)	N1−C23−C22	114.5(4)

Structure determination

The structure was solved by direct methods using the program assembly MITHRIL,[9] which imme- diately indicated the positions of all non-hydro- gen atoms. The hydrogen atoms were introduced in calculated positions, and full-matrix least- squares refinements resulted in final parameters
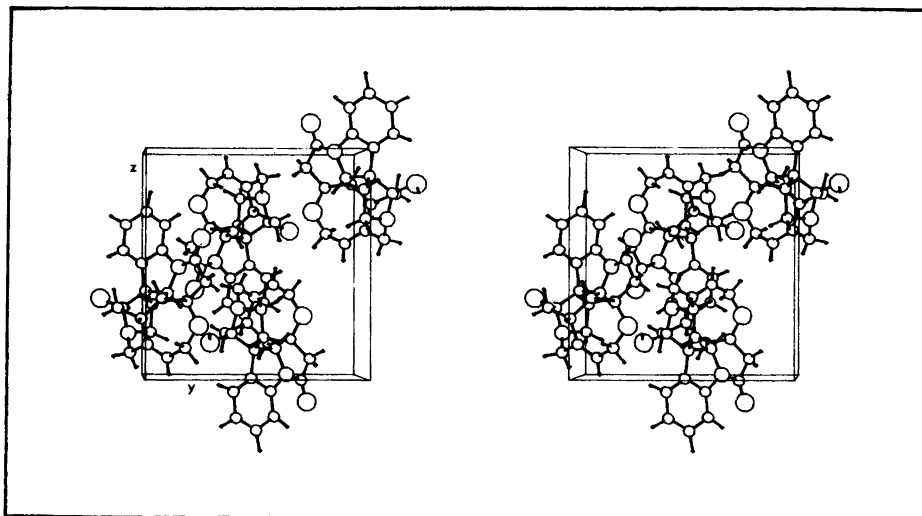
Fig. 2. Stereoscopic drawing of the packing of pseudostrychnine molecules in the crystal.

given in Table 2. During the final refinements, the non-hydrogen atoms were given anisotropic thermal parameters and the hydrogen atoms isotropic thermal parameters. The standard deviations calculated from the variance—covariance matrix are 0.007 Å in interatomic distances and 0.4° in angles not involving hydrogen atoms. Bond lengths and angles have standard deviations about ten times those given above when hydrogen atoms are involved. Lists of structure factors, thermal parameters and hydrogen atom positions may be obtained from the author on request. The quantity minimized in the least-squares calculations was $\Sigma w(\Delta F)^2$, where w is the inverse of the variance of the observed structure factors. Atomic scattering factors were taken from Ref. 10. Computer programs used are described in Ref. 11.

Description and discussion

A drawing of the pseudostrychnine molecule is shown in Fig. 1, where the numbering of the atoms is also indicated. Bond lengths and angles are given in Table 3, and the packing of the molecules is depicted in Fig. 2. The molecule exists in the crystals in the form where N4 has a formal bond to C3, which has a hydroxy group substituent; the conclusion from the infrared experiments is thus confirmed. The hydroxy group

constitutes the only hydrogen donor in the molecule. It is interesting to note that it is the ethereal oxygen atom in the oxacycloheptane ring that is involved as acceptor in the hydrogen bond and not the N4 atom with its lone-pair electrons. This may be a consequence of reduced availability of the N4 lone-pair electrons, which is also reflected by the decreased value of pK_a. (5.50 in pseudostrychnine and 7.37 in strychnine).[12] The distance between O3 and O17 in the molecule at $(-x, 1/2+y, 3/2-z)$ is 2.83 Å (HO3—O17 = 1.86 Å, angle O3—HO3—O17 = 160°). The hydrogen atom H3 is positioned in a tetrahedral arrangement about the acceptor O17. In a systematic study of hydrogen bonds[13] it is concluded that linear hydrogen bonds in which ethereal oxygen atoms are acceptors are relatively rare. However, the geometry given for such bonds is in good agreement with that found in the present study. Thus, the hydrogen atom is found to be close to the lone-pair plane of the acceptor oxygen (0.3 Å) and the donor oxygen atom a little further away from that plane (0.6 Å). Hydrogen-bonded molecular chains are established in the direction of the b axis and these chains are held together by van der Waals forces only. The closest contact between neighbouring molecules, except for the hydrogen bond, occurs between O23 and the HC10—C10 group $(-x, y-1/2, 1/2-z)$ where the distance O23—C10 is 3.273 Å (O23—HC10 =

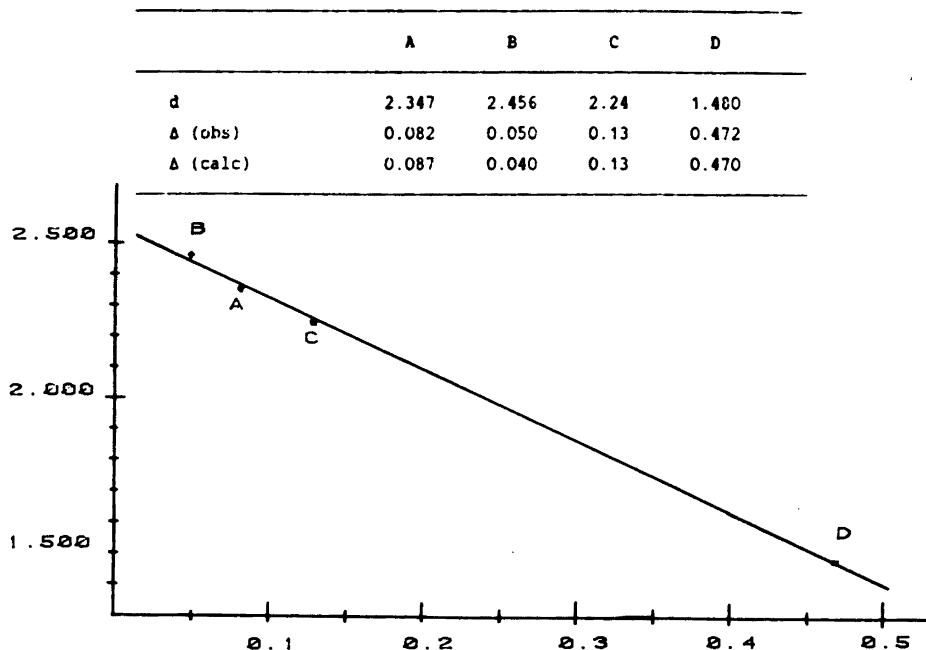|	A	B	C	D
d	2.347	2.456	2.24	1.480
Δ (obs)	0.082	0.050	0.13	0.472
Δ (calc)	0.087	0.040	0.13	0.470

Fig. 3. The relationship between the N4−C3 (d) distances and the distances of C3 from the C7, C14, O plane (Δ) in epoxyicajine (A), icajine (B), strychnobrasiline (C) and pseudostrychnine (D). Δ = −0.441d + 1.123.

2.39 Å, angle O23−HC10−C10 = 146°). The next shortest distance between neighbouring molecules exists between N4 and C22 (−x, y+1/2, 3/2−z), the distance being 3.404 Å (N4−H122 = 2.44 Å, angle N4−H122−C22 = 165°). Strychnine is metabolized by substitution at the C10 atom, and a substituent in this position seems to reduce the biological activity of such compounds.[12] In this context it is interesting that it is the HC10 atom that is involved in intermolecular contacts in both strychnine and dihydrostrychnine (where there are no formal hydrogen bonds), as well as in the present structure where the hydrogen bonding might be believed to be a dominant factor in the molecular packing. The conformation of the molecule is found to be almost identical to that of strychnine. The differences in conformational angles are less than 4.0° (C3−C7−C8−C9). Differences in bond lengths and angles are found to be less than 0.03 Å and 2°, respectively. The N−C bond length in strychnine is 1.49(2) Å, and 1.480(6) Å in pseudostrychnine. Thus, the effect of the C3- hydroxy group on the C3−N4 bond length appears to be

less than effects from protonation of the N4 atom and from the conformation about the N4−C3 bond. The N4−C3 distances and the distances of C3 from the C7, C14, O plane in the structures of icajine, epoxyicajine, strychnobrassiline and pseudostrychnine are given in Fig. 3. It may be seen that the data are well represented by a straight line: Δ = −0.441d + 1.123, where Δ is the C3 "out of the plane" distance and d is the N4−C3 distance.

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