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# Crystal and Molecular Structure of the Strychnos Alkaloid Icajine

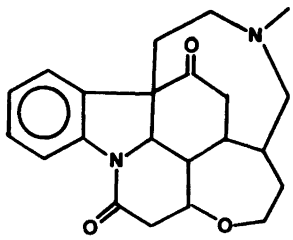
ARVID MOSTAD

University of Oslo, Department of Chemistry, Blindern, Oslo 3, Norway

The crystal and molecular structure of the natural strychnos-alkaloid, icajine, has been determined at room temperature by X-ray crystallographic methods, using 1230 reflections observed by counter methods. The crystals are orthorhombic, space group $P2_12_12_1$ with unit cell dimensions $a$=8.058 (2) Å, $b$=14.237 (2) Å, $c$=15.665 (4) Å. The structure was refined to a conventional $R$-factor of 0.057. A transannular interaction involving a N···C=O distance of 2.456 Å is discussed. Estimated standard deviations are less than 0.01 Å and 0.7° in interatomic distances and angles when hydrogen atoms are not involved.

The crystal structure analysis of 14-hydroxy-strychnobrasiline[1] revealed the existence of a short non-bonded distance of 2.24 Å between a tertiary nitrogen atom and the carbon atom in a carbonyl group, both atoms included in a nine-membered ring. In order to further study the presence of such interactions in similar compounds, a number of compounds related to strychnos alkaloids are under investigation at our laboratory and in the present work the results of the structure analysis of the natural compound icajine (Scheme 1) is presented.

The compound has been supplied by Dr. R. Verpoorte at Gorlaeus Laboratoria der Rijks-universiteit, Leiden.




*Scheme 1.*

## EXPERIMENTAL AND STRUCTURE SOLUTION

From a sample of only a few mg of relatively small colourless prismatic crystals, a single crystal of the dimensions 0.2×0.2×0.3 mm was selected and used for the collection of X-ray data. The experimental conditions are given in the table below.

Cell parameters were determined by a least squares fit to the diffractometer settings for 25 general reflections. The intensity data were corrected for Lorentz and polarization effects, and the scattering factors used were those of Doyle and Turner[2] for O, N and C atoms and of Stewart, Davidson and Simpson[3] for the H-atoms. The structure was solved by direct methods using the program assembly MULTAN[4] and refined to a conventional $R$ factor of 0.051 ($R_w$=0.040) and a goodness of fit $S=(\sum w\Delta^2/m-n)^{\frac{1}{2}}=1.7$, using the program library described in Ref. 5. The hydrogen atoms were introduced from stereochemical considerations and the parameters were refined by least squares calculations. The atomic coordinates are given in Tables 1 and 2. Temperature factors as well as tables of observed and calculated structure factors are available from the author.

## EXPERIMENTAL CONDITIONS

| | |
|---|---|
| Instrument | NICOLET P3/F |
| Radiation | Graphite crystal monochromated Mo$K\alpha$ $\lambda$=0.71069 Å |
| Crystal dimensions/mm | 0.2×0.2×0.3 |
| Scanning mode | $\theta/2\theta$ |
| Scan speed/°min$^{-1}$ | 2–4 |
| Scan range/° | $2\theta_{\alpha_1}-0.8$ to $2\theta_{\alpha_2}+0.8$ |

0302-4369/84 $2.50

*Table 1.* Fractional atomic coordinates for the non-hydrogen atoms. Estimated standard deviations in parentheses.

| ATOM | X | Y | Z |
|---|---|---|---|
| O5 | -.1459( 5) | 1.0869( 2) | .0859( 2) |
| O17 | .0628( 5) | .8244( 2) | -.2224( 2) |
| O25 | -.0200( 6) | .6565( 2) | .0181( 2) |
| N1 | .0352( 6) | .7924( 3) | .0199( 2) |
| N4 | .0857( 6) | 1.1265( 3) | -.0591( 2) |
| C2 | .0417( 7) | .8850( 3) | -.0288( 3) |
| C3 | -.1112( 7) | 1.0551( 4) | .0276( 3) |
| C5 | .2502( 8) | 1.0706( 4) | -.0575( 4) |
| C6 | .1961( 7) | 1.0176( 4) | .0449( 4) |
| C7 | .0311( 7) | .9617( 3) | .0401( 3) |
| C8 | .0076( 7) | .9068( 4) | .1228( 3) |
| C9 | -.0096( 9) | .9597( 5) | .2054( 3) |
| C10 | -.0214( 9) | .8745( 6) | .2718( 4) |
| C11 | -.0181(10) | .7808( 6) | .2557( 4) |
| C12 | -.0055( 9) | .7451( 5) | .1787( 4) |
| C13 | .0111( 6) | .8110( 3) | .1081( 3) |
| C14 | -.2202( 7) | 1.0288( 4) | -.0511( 4) |
| C15 | -.1482( 7) | .9765( 4) | -.1282( 3) |
| C16 | -.0969( 7) | .8782( 3) | -.0944( 3) |
| C17 | -.0606( 8) | .8022( 4) | -.1597( 4) |
| C18 | .0094(12) | .8962( 5) | -.2806( 4) |
| C19 | .0559( 9) | .9920( 4) | -.2471( 3) |
| C20 | -.0149( 8) | 1.0286( 3) | -.1776( 3) |
| C21 | .0567(10) | 1.1250( 4) | -.1492( 4) |
| C22 | .0122(12) | .7158( 4) | -.1159( 4) |
| C23 | .0026( 8) | .7096( 4) | -.0205( 4) |
| C24 | .0854(11) | 1.2205( 4) | -.0211( 5) |

*Table 2.* Fractional atomic coordinates for the hydrogen atoms. Estimated standard deviations in parentheses.

| ATOM | X | Y | Z |
|---|---|---|---|
| H2 | .150( 4) | .884( 2) | -.056( 2) |
| H51 | .358( 6) | 1.110( 3) | -.052( 3) |
| H52 | .266( 5) | 1.028( 3) | -.079( 2) |
| H61 | .186( 5) | 1.064( 3) | .090( 2) |
| H62 | .285( 6) | .978( 3) | .058( 3) |
| H9 | .005( 8) | 1.009( 5) | .217( 3) |
| H10 | -.020( 7) | .909( 3) | .327( 3) |
| H11 | -.013( 8) | .729( 4) | .302( 3) |
| H12 | .016( 6) | .672( 3) | .165( 3) |
| H141 | -.247( 5) | 1.096( 3) | -.067( 2) |
| H142 | -.317( 6) | .999( 2) | -.029( 2) |
| H15 | -.251( 7) | .965( 3) | -.172( 3) |
| H16 | -.194( 5) | .857( 3) | -.066( 2) |
| H17 | -.161( 6) | .782( 3) | -.190( 3) |
| H181 | -.118( 8) | .892( 4) | -.295( 3) |
| H182 | .073( 8) | .881( 4) | -.336( 3) |
| H19 | .148( 6) | 1.025( 5) | -.277( 3) |
| H211 | -.054( 5) | 1.165( 3) | -.154( 3) |
| H212 | .128( 6) | 1.150( 3) | -.182( 3) |
| H221 | -.059( 6) | .662( 3) | -.138( 3) |
| H222 | .151( 8) | .714( 4) | -.136( 4) |
| H241 | -.022( 8) | 1.252( 4) | -.055( 3) |
| H242 | .188( 8) | 1.262( 4) | -.048( 4) |
| H243 | .114( 8) | 1.217( 3) | .044( 3) |

| | |
|---|---|
| Background counts | For 0.35 of scan time at scan limits |
| Temperature/K | 294 |
| $2\theta$ range | 2.5–55.0 |
| Number of reflections | 1930 |
| Number of reflections $I>2.5\sigma(I)$ | 1230 |
| Number of standard reflections | 3 |
| Number of reflections between standard reflections | 97 |

## CRYSTAL DATA

ICAJINE, $C_{22}N_2O_3H_{24}$, orthorhombic, $a$=8.058 (2) Å, $b$=14.237 (2) Å, $c$=15.665 (4) Å, $V$=1797.3 Å$^3$, $M$=364.25, $Z$=4, $F_{000}$=776., space group No 19. $P2_12_12_1$.

## DESCRIPTION AND DISCUSSION

Bond lengths and angles are given in Tables 3 and 4 and some of the torsional angles in Table 5, whereas the numbering of the atoms is given in Fig. 1. The packing of the molecules is entirely determined by van der Waals' forces and the situation is illustrated in Fig. 2. The shortest intermolecular contacts are found between O23 and the C6 atom in a neighbour molecule ($x-\frac{1}{2}$, $1.5-y$, $-z$), the distance being 2.323 Å (O23–H62′=2.56 Å) and between O23 and the C14 atom in another neighbour molecule ($x+\frac{1}{2}$, $1.5-y$, $-z$), where the distance is 3.412 Å (O23–H142′=2.54 Å). The shortest distance between neighbour molecules related by screw axes in the $y$-direction exists between O17 and C21′: 3.570 Å (O17–H21′=2.98 Å). All other intermolecular distances between non hydrogen atoms are larger than 3.700 Å. It is, however, interesting to note that the O17 atom is pointing towards the aromatic ring in an adjacent mole-

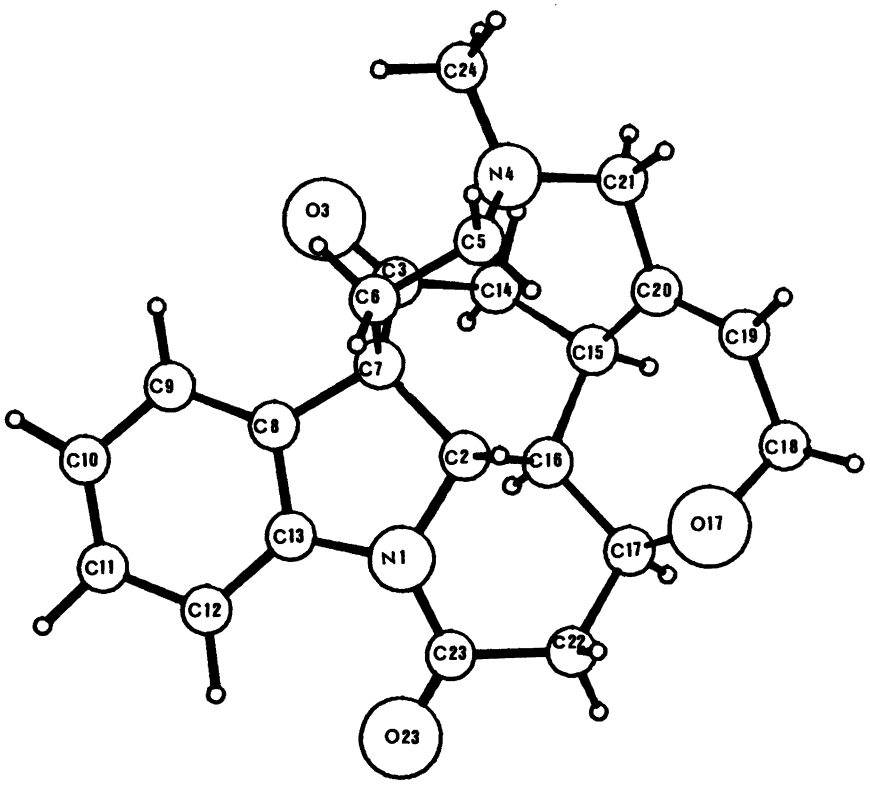



*Fig. 1.* The numbering of the atoms in the icajine molecule.

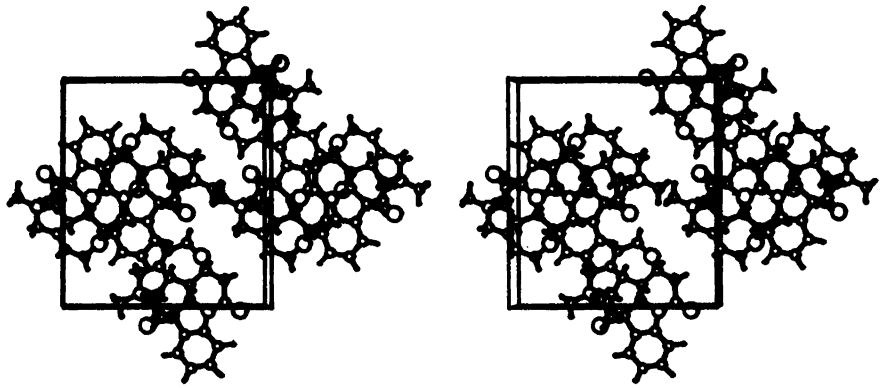


*Fig. 2.* A stereoscopic drawing of the molecular packing of icajine molecules as seen along the *a*-axis.

*Table 3.* Bond lengths in icajine. Estimated standard deviations in parentheses. The C–H distances vary between 0.93 and 1.10 Å, the mean value being 1.00(6) Å.

| DISTANCE | (Å) | DISTANCE | (Å) |
|---|---|---|---|
| O5 - C5 | 1.221( 6) | O17 - C17 | 1.455( 7) |
| O17 - C18 | 1.454( 8) | O25 - C25 | 1.218( 7) |
| N1 - C2 | 1.500( 7) | N1 - C15 | 1.417( 7) |
| N1 - C25 | 1.361( 6) | N4 - C5 | 1.485( 8) |
| N4 - C21 | 1.461( 8) | N4 - C24 | 1.465( 7) |
| C2 - C7 | 1.559( 7) | C2 - C16 | 1.519( 7) |
| C5 - C7 | 1.545( 8) | C5 - C14 | 1.515( 8) |
| C5 - C6 | 1.522( 8) | C6 - C7 | 1.544( 8) |
| C7 - C8 | 1.525( 7) | C8 - C9 | 1.385( 7) |
| C8 - C15 | 1.385( 7) | C9 - C10 | 1.392( 9) |
| C10 - C11 | 1.357(10) | C11 - C12 | 1.386( 9) |
| C12 - C13 | 1.397( 8) | C14 - C15 | 1.554( 8) |
| C15 - C16 | 1.550( 8) | C16 - C20 | 1.519( 8) |
| C16 - C17 | 1.518( 7) | C17 - C22 | 1.549( 9) |
| C18 - C19 | 1.504( 9) | C19 - C20 | 1.328( 8) |
| C20 - C21 | 1.502( 8) | C22 - C23 | 1.500( 9) |

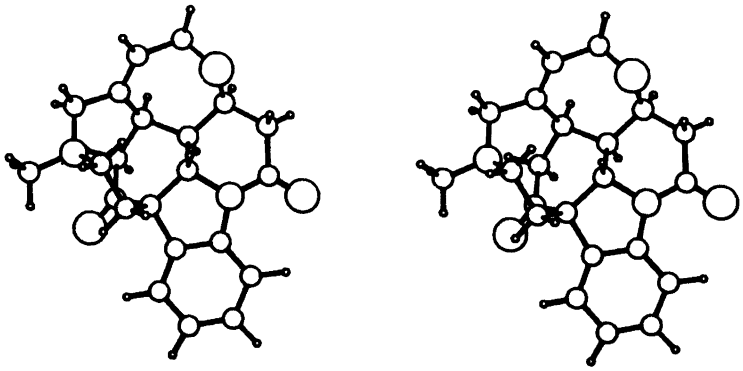


*Fig. 3.* Stereoscopic view of the icajine molecule.

*Table 4.* Bond angles in icajine. Estimated standard deviations in parentheses.

| ANGLE | (°) | ANGLE | (°) |
|---|---|---|---|
| C17 - O17 - C18 | 112.6( 5) | C2 - N1 - C15 | 110.0( 4) |
| C2 - N1 - C25 | 121.2( 4) | C15 - N1 - C25 | 126.2( 5) |
| C5 - N4 - C21 | 115.1( 5) | C5 - N4 - C24 | 115.5( 6) |
| C21 - N4 - C24 | 114.1( 5) | N1 - C2 - C7 | 105.2( 4) |
| N1 - C2 - C16 | 105.8( 4) | C7 - C2 - C16 | 117.1( 5) |
| O5 - C5 - C7 | 118.5( 5) | O5 - C5 - C14 | 120.6( 6) |
| C7 - C5 - C14 | 120.5( 5) | N4 - C5 - C6 | 108.1( 5) |
| C5 - C6 - C7 | 111.9( 5) | C2 - C7 - C5 | 115.2( 5) |
| C2 - C7 - C6 | 110.9( 5) | C2 - C7 - C8 | 105.1( 4) |
| C5 - C7 - C6 | 107.7( 4) | C5 - C7 - C8 | 110.7( 5) |
| C6 - C7 - C8 | 109.2( 5) | C7 - C8 - C9 | 129.5( 5) |
| C7 - C8 - C15 | 111.2( 4) | C9 - C8 - C15 | 119.5( 5) |
| C8 - C9 - C10 | 118.1( 7) | C9 - C10 - C11 | 121.5( 7) |
| C10 - C11 - C12 | 122.0( 7) | C11 - C12 - C15 | 116.5( 7) |
| N1 - C15 - C8 | 110.1( 5) | N1 - C15 - C12 | 127.0( 6) |
| C8 - C15 - C12 | 122.5( 6) | C5 - C14 - C15 | 116.2( 5) |
| C14 - C15 - C16 | 105.7( 4) | C14 - C15 - C20 | 115.1( 5) |
| C16 - C15 - C20 | 115.5( 5) | C2 - C16 - C15 | 112.7( 4) |
| C2 - C16 - C17 | 110.5( 5) | C15 - C16 - C17 | 117.6( 5) |
| O17 - C17 - C16 | 116.0( 5) | O17 - C17 - C22 | 102.7( 5) |
| C16 - C17 - C22 | 110.7( 5) | O17 - C18 - C19 | 110.7( 5) |
| C18 - C19 - C20 | 122.9( 7) | C15 - C20 - C19 | 121.5( 5) |
| C15 - C20 - C21 | 119.6( 6) | C19 - C20 - C21 | 119.1( 6) |
| N4 - C21 - C20 | 111.8( 5) | C17 - C22 - C25 | 117.1( 6) |
| O25 - C25 - N1 | 122.7( 5) | O25 - C25 - C22 | 122.1( 6) |
| N1 - C25 - C22 | 114.7( 6) | | |

cule, the distance to C11′ and C12′ being 3.731 and 3.713 Å, respectively.

The present molecule is different from strychnobrasiline (stry-bra) in several ways. Thus in icajine, the acetyl group on the N1 atom in stry-bra is included in a piperidine ring. The pyranose ring present in stry-bra is in the icajine molecule enlarged to a 7-membered ring by including C19 in the ring system and the double bond between C20 and C21 is shifted to be between C20 and C19, and thus no longer present in the 9-membered ring (C14, C15, C20, C21, N4, C5, C6, C7, C3). The conformation of the icajine molecule as it appears in the crystalline state is illustrated by the stereoscopic drawing in Fig. 3 and described by the torsional angles in Table 5. The changes in molecular conformation brought about by the changes in chemical structure described above, are illuminated by the data in Table 6. It seems reasonable to anticipate that the changes in chemical structure from stry-bra to icajine should have an effect on the conformation of the 9-membered ring, and hence on the transannular interaction between N4 and C3. The conformation of the 9-membered ring in icajine appears indeed to be somewhat different from the one found in stry-bra. The "5-membered ring" (C3, N4, C5, C6, C7) may in both structures be considered to exist in an envelope form with the C7 atom being 0.6–0.7 Å out of a least square plane through C3, C6, C5 and N4. However, whereas the deviations of the atoms used for the definition of the plane are less than 0.05 Å in stry-bra, the largest deviation in icajine is 0.17 Å. Moreover, the "6-membered ring" C3, C14, C15, C20, C21, N4 which in the stry-bra existed in a flattened chair form, is found to exhibit a slightly twisted boat form, the atoms C3, N4, C20, C15 being planar within 0.05 Å and C14 and C21 being respectively 0.760 and 0.527 Å out of the plane on the same side.

The interaction between N4 and C3, however, seems to be only little influenced by the differences in conformation described above. The N4···C3 distance is found to be 2.456 Å and the direction of the lone pair on N4 deviates from the N4···C3 direction with only 9.6°. It may be noticed that the relative orientation of the two groups as described by the rotation about the N4···C3 direction is almost eclipsed, the rotation

*Table 5.* Some torsional angles in icajine.

| DIHEDRAL ANGLE | (°) |
|---|---|
| C17 - O17 - C16 - C15 | 69.4( 7) |
| C16 - O17 - C17 - C16 | -69.5( 8) |
| C16 - O17 - C17 - C22 | 170.8( 5) |
| C2 - N1 - C15 - C9 | -1.2( 8) |
| C2 - N1 - C15 - C12 | 178.8( 7) |
| C15 - N1 - C2 - C7 | 2.7( 7) |
| C15 - N1 - C2 - C16 | -122.2( 5) |
| C2 - N1 - C25 - O25 | -175.1( 7) |
| C2 - N1 - C25 - C22 | 11.4( 9) |
| C25 - N1 - C2 - C7 | 166.4( 5) |
| C25 - N1 - C2 - C16 | 40.5( 7) |
| C15 - N1 - C25 - O25 | -15.4(10) |
| C15 - N1 - C25 - C22 | 171.1( 5) |
| C25 - N1 - C15 - C9 | -162.8( 5) |
| C25 - N1 - C15 - C12 | 18.0(10) |
| C5 - N4 - C21 - C20 | 64.4( 9) |
| C21 - N4 - C5 - C6 | -157.1( 5) |
| C21 - N4 - C5 - C8 | 69.0( 7) |
| C24 - N4 - C21 - C20 | -162.1( 6) |
| N1 - C2 - C7 - C5 | -125.7( 5) |
| N1 - C2 - C7 - C8 | 115.8( 5) |
| N1 - C2 - C7 - C9 | -5.0( 6) |
| N1 - C2 - C16 - C15 | 159.5( 4) |
| N1 - C2 - C16 - C17 | -68.9( 6) |
| C7 - C2 - C16 - C15 | 42.5( 7) |
| C7 - C2 - C16 - C17 | 176.1( 5) |
| C16 - C2 - C7 - C5 | -6.4( 7) |
| C16 - C2 - C7 - C8 | -129.0( 5) |
| C16 - C2 - C7 - C9 | 114.5( 5) |
| O5 - C5 - C7 - C2 | 169.2( 5) |
| O5 - C5 - C7 - C6 | -67.6( 7) |
| O5 - C5 - C7 - C9 | 51.7( 7) |
| O5 - C5 - C14 - C15 | 166.6( 5) |
| C7 - C5 - C14 - C15 | -20.4( 8) |
| C14 - C5 - C7 - C2 | -4.8( 7) |
| C14 - C5 - C7 - C8 | 119.5( 6) |

| DIHEDRAL ANGLE | (°) |
|---|---|
| C14 - C5 - C7 - C9 | -121.5( 6) |
| N4 - C5 - C8 - C7 | 52.2( 7) |
| C5 - C8 - C7 - C2 | 64.4( 6) |
| C5 - C8 - C7 - C5 | -62.4( 6) |
| C5 - C8 - C7 - C9 | 177.4( 5) |
| C2 - C7 - C8 - C9 | -180.0(*) |
| C2 - C7 - C9 - C15 | 2.5( 7) |
| C5 - C7 - C9 - C9 | -56.5( 6) |
| C5 - C7 - C9 - C15 | 126.2( 5) |
| C8 - C7 - C9 - C9 | 62.1( 6) |
| C8 - C7 - C9 - C15 | -115.5( 6) |
| C5 - C14 - C15 - C16 | 55.4( 7) |
| C5 - C14 - C15 - C20 | -75.5( 7) |
| C14 - C15 - C16 - C2 | -64.6( 6) |
| C14 - C15 - C16 - C17 | 165.4( 5) |
| C14 - C15 - C20 - C19 | -178.0( 6) |
| C14 - C15 - C20 - C21 | -.1(29) |
| C16 - C15 - C20 - C19 | 59.2( 7) |
| C16 - C15 - C20 - C21 | -125.8( 6) |
| C20 - C15 - C16 - C2 | 64.2( 6) |
| C20 - C15 - C16 - C17 | -65.8( 7) |
| C2 - C16 - C17 - O17 | -75.7( 6) |
| C2 - C16 - C17 - C22 | 40.8( 7) |
| C15 - C16 - C17 - O17 | 55.5( 7) |
| C15 - C16 - C17 - C22 | 172.0( 6) |
| O17 - C17 - C22 - C25 | 156.5( 7) |
| C16 - C17 - C22 - C25 | 11.9(10) |
| O17 - C19 - C19 - C20 | -67.1(10) |
| C19 - C19 - C20 - C15 | -1.7(10) |
| C19 - C19 - C20 - C21 | -179.7( 7) |
| C15 - C20 - C21 - N4 | 55.2( 8) |
| C19 - C20 - C21 - N4 | -129.8( 6) |
| C17 - C22 - C25 - O25 | 144.7( 7) |
| C17 - C22 - C25 - N1 | -59.8(10) |

*Table 6.* Conformational differences between icajine and strychnobrasiline.

| | Icajine | Stry-bra. |
|---|---|---|
| Distance from benzene ring-plane to C2 (Å) | 0.014 | 0.43 |
| Distance from benzene ring-plane to C23 (Å) | 0.330 | 0.66 |
| Distance from plane C13,C2,C23 to Ni | 0.133 | 0.13 |
| Distance from plane N1,O23,C22 to C23 | 0.031 | 0.01 |
| Distance from plane C15,C19,C21 to C20 | 0.015 | 0.14 |
| Distance from plane C5,C21,C24 to N4 | 0.359 | 0.44 |
| Distance from plane O3,C7,C14 to C3 | 0.050 | 0.13 |
| Distance O17···C15 | 3.131 | 2.859 |
| Distance O17···C20 | 3.057 | 2.400 |
| Distance N4···C3 | 2.456 | 2.24 |
| Angle (°) O3–C3···N4 | 102 | 102 |
| Angle (°) Lone-pair-N4···C3 | 10 | 13 |
| Angle between planes (°) C5,C21,C24 and O3,C7,C14 | 14 | 12 |
| Angle between planes (°) C15,C16,C7 and C15,C3,C7 | 39 | 26 |
| Conf. of cyclohexane ring | twisted chair | twisted chair |
| Conf. of piperidine ring | twisted boat | twisted chair |

angle being about 9° as compared to the 30° found in stry-bra, and this may partly be the reason for the longer N4···C3 distance found in the present structure.

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