Tetrahedron Letters No. 27, pp. 2527-2529, 1971. Pergamon Press. Printed in Great Britain.

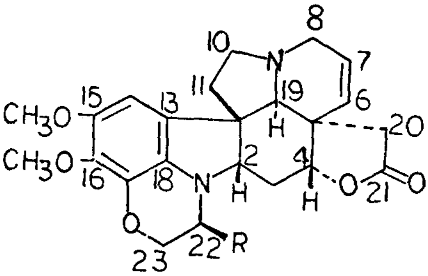
ALKALOID STUDIES LXV.[1] CONFIRMATION OF THE HEPTACYCLIC STRUCTURE OF THE ASPIDOSPERMA OBSCURINERVIUM ALKALOIDS THROUGH X-RAY ANALYSIS OF OBSCURINERVINE HYDROBROMIDE

J. Kahrl, T. Gebreyesus[2] and Carl Djerassi

Department of Chemistry, Stanford University, Stanford, California 94305

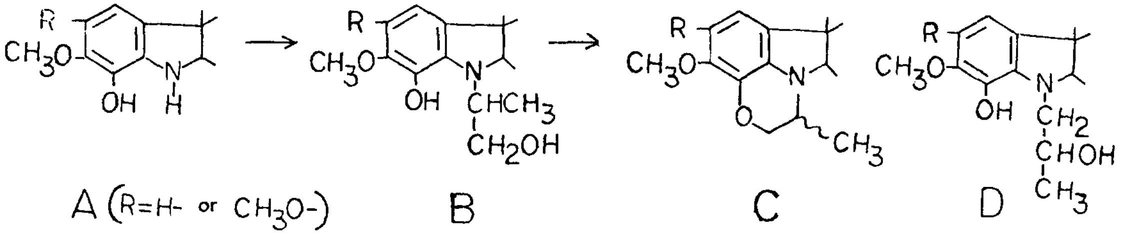
(Received in USA 19 April 1971; received in UK for publication 8 June 1971)

The Brazilian Apocynaceae species *Aspidosperma obscurinervium* Azembuja is the hitherto unique source of four indole alkaloids - obscurinervine (I), obscurinervidine (II) and their dihydro analogs III and IV - whose heptacyclic structure was proposed[3] on the basis of extensive nmr and mass spectral measurements as well as certain chemical transformations.



I $R = C_2H_5$
II $R = CH_3$
III $R = C_2H_5$; 6,7-dihydro
IV $R = CH_3$; 6,7-dihydro

The most unusual feature of these alkaloids is the cyclic ether which incorporates the indolic nitrogen atom and the phenolic hydroxyl group. Its structure assignment was based[3] on a partial synthesis involving condensation of the appropriate dihydroindole precursor (partial structure A) with 2-iodo-1-propanol, separation of the resulting two epimers of the presumed structure B and finally cyclization of the monobrosylate of one of these epimers to yield C.



A more detailed examination[4] of the condensation reaction (A→B) disclosed that the supposed two epimers of structure B were actually isomers of structure B and D, respectively. Isomer D apparently arose from prior cyclization of 2-iodopropanol in the reaction medium to propylene oxide, since in a separate experiment, condensation of A with propylene oxide led to D. That isomer B is indeed one of the constituents of the reaction resulting from the condensation of A with 2-iodopropanol was confirmed[4] by reaction of A with methyl α-bromopropionate followed by reduction with lithium aluminum hydride.

In any event, this complication in one of the key hemisynthetic sequences and the unique nature of the heptacyclic skeleton of these alkaloids, suggested that independent structure proof by X-ray analysis was desirable For this purpose, obscurinervine (I) was transformed into its hydrobromide in ether solution and recrystallized from ethanol to give orthorhombic plates of m.p. 228-230°(dec.). The space group is $P2_12_12_1$ with unit cell dimensions $a = 9.179 \pm 0.005$, $b = 33.51 \pm 0.01$, $c = 7.994 \pm 0.005$ A; $V = 2459.2$ A^3. The density, which was measured by density gradient in carbon tetrachloride and 1,2-dichloroethane, was 1.46 ± 0.01 g/cm^3. The calculated density assuming four molecules per unit cell is $1{,}400 \pm 0{,}001$ g/cm^3.

A total of 2,074 unique diffraction intensities was collected by a Hilger-Watts Model Y290 automatic diffractometer using intensity-weighted Cu $K\alpha$ radiation. Of the total of 2,074 unique diffraction intensities collected, 2,045 were not systematically absent. However, only 1,382 of the diffraction intensities were larger than the background by more than one σ. The large number of zero intensities and the large discrepancy between the calculated and observed densities seem to indicate that solvent molecules are trapped in an unordered fashion in the crystal. The unique bromine position was located from a sharpened, origin-removed, three-dimensional Patterson function. Two cycles of full-matrix least-squares refinement of the positions and anisotropic thermal parameters of the bromine, using all of the data, was performed prior to calculation of a bromine-phased difference electron density map. The positions of all of the atoms in the alkaloid molecule were located from this map. Several cycles of full-matrix least-squares refinement, using the 1,382 diffraction intensities above background, reduced the discrepancy factor ($R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$) to 12.6%. A difference electron density map based on the final structure (see Fig. 1 for three-dimensional projection) failed to reveal any peaks large enough to be considered solvent atoms. The structure and relative stereochemistry proposed originally[3] is thus confirmed in all respects.

REFERENCES

1. For paper LXIV see N. C. Ling and C. Djerassi, Tetrahedron Letters, 3015 (1970).
2. *Recipient of an AFGRAD fellowship from the African-American Institute.*

3. K. S. Brown, Jr., and C. Djerassi, J. Amer. Chem. Soc., **86**, 2451 (1964).

4. P. L. Bachman, unpublished observations from this laboratory.

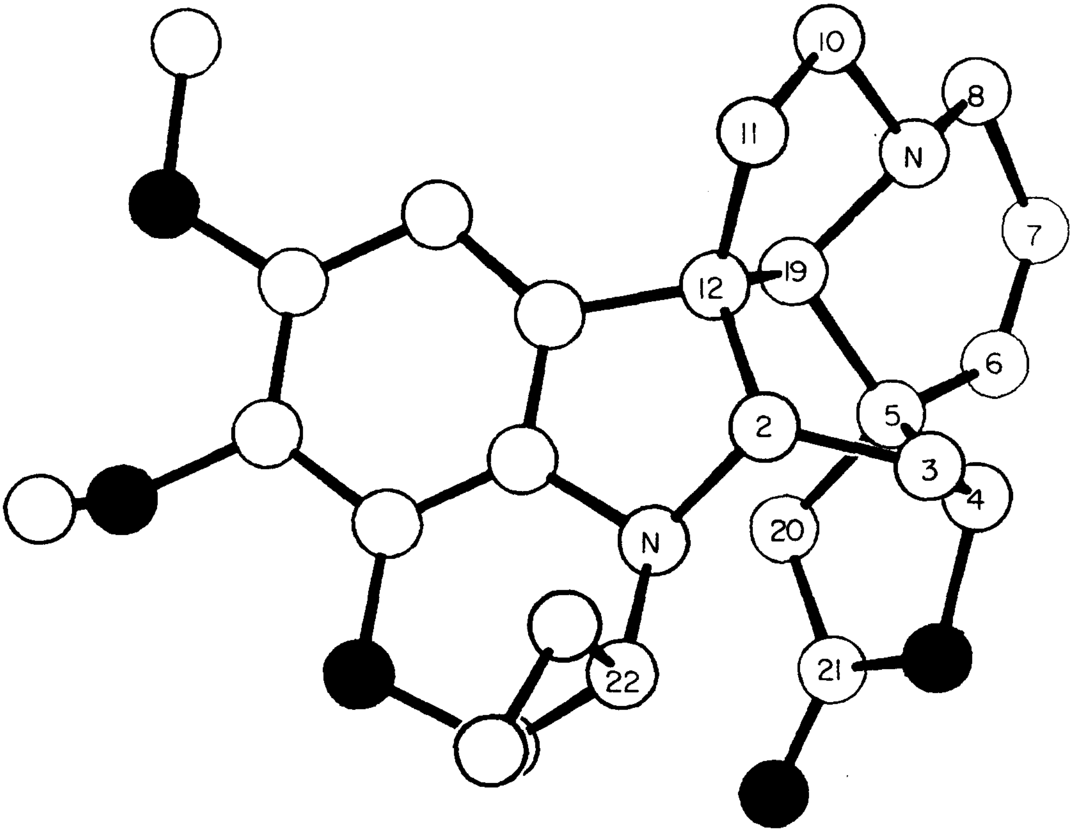


Fig. 1. Three-dimensional projection of (-)-obscurinervine (I) hydrobromide. Double bonds are not indicated and solid circles denote oxygen atoms. Key carbon atoms are numbered as in I.