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X-RAY ANALYSIS OF THE STRUCTURE OF GELSEMINE HYDROHALIDES

F. M. Lovell, R. Pepinsky and A. J. C. Wilson*

Dept. of Physics, The Pennsylvania State University, Philadelphia, Pa.

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THE alkaloid gelsemine, in the form of two crystalline hydrohalides, has been subjected to X-ray analysis. The resulting structure satisfies all crystallographic criteria of correctness, and is chemically reasonable.

The structure of gelsemine is of importance in the understanding of biogenetic processes in the parent plant, Gelsemium sempervirens (yellow jasmine). A considerable amount of chemical information has been gathered about the alkaloid, but no acceptable structural model was available to us throughout the present study. The stoichiometric formula, $C_{20}H_{22}N_2O_2$, was known;[1] and evidence existed for the presence of 3,3'-disubstituted oxindole group,[2,3] a tertiary, basic nitrogen atom, bearing one methyl group,[2] **in a five-membered ring,**[2a] **one reactive double bond in a vinyl side** chain,[4] and a cyclic ether grouping containing the **second oxygen atom.**[5] **The**

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* Dept. of Physics, University College, Cardiff.

[1] C. W. Moore, J. Chem. Soc. **97**, 2223 (1910); **99**, 123 (1911).

[2] L. Marion, Canad. J. Res. **21B**, 247 (1943).

[2a] T. Habgood and L. Marion, Canad. J. Chem. **33**, 604 (1955).

[3] M. Kates and L. Marion, Canad. J. Res. **29**, 27 (1951).

[4] L. Marion and K. Sargeant, J. Amer. Chem. Soc. **78**, 5127 (1956).

[5] R. Robinson and M. S. Gibson, Chem. & Ind. 93 (1951).

nature of the remaining ring system was unknown.

Two crystalline salts, the hydrochloride and the hydroiodide, were used in the present investigation. Both salts crystallize in the orthorhombic space group $P2_12_12_1$, with 4 molecules in the cell. The hydrochloride has dimensions $\underline{a}$ = 7.30 A, $\underline{b}$ = 9.00 A, $\underline{c}$ = 26.40 A, with d_{calc} = 1.35 g/cc and d_{obs} = 1.37 g/cc; the hydroiodide has $\underline{a}$ = 7.80 A, $\underline{b}$ = 9.17 A, $\underline{c}$ = 26.90 A, d_{calc} = 1.54 g/cc and d_{obs} = 1.55 g/cc.

Multifilm equi-inclination Weissenberg photographs were used to collect full three-dimensional X-ray data about the $\underline{a}$ and $\underline{b}$ axes of the iodide crystal, and about the $\underline{a}$ axis of the chloride. Cylindrical specimen 0.15 mm in diameter were used, with CuKα radiation, absorption corrections being applied for the hydroiodide ($\mu = 144\ cm^{-1}$) but not for the hydrochloride ($\mu = 21\ cm^{-1}$).

The hydroiodide was considered first, and the iodine position was found from a three-dimensional Patterson function. The coordinates so obtained were $\underline{x}$ = 0.181, $\underline{y}$ = 0.150, $\underline{z}$ = 0.250. Due to the value of the $\underline{z}$ coordinate, the three-dimensional electron density synthesis, computed with coefficients having iodine phases, contained <u>pseudo</u> mirror planes at $z = \pm 1/4$. Thus is became necessary to disentangle the true structure from its superposed mirror image. A set of peaks could be selected for the atoms of the indole group; and these were introduced into a new structure factor calculation. An electron-density synthesis based on these structure factors confirmed the indole group location, and showed several more atoms. These were in turn included in another cycle. After several cycles of this sort, all atoms were included in a reasonable trial structure.

This structure was subjected to least-squares refinement using the

IBM 704 program of Vand and Pepinsky.[6] The first disagreement factor

$$R = \frac{\Sigma \left| |F_{obs}| - |F_{calc}| \right|}{\Sigma |F_{obs}|}$$

was 0.24; subsequent stages of refinement lowered the R-factor to 0.14 for 1500 symmetry-unrelated reflections, and resulted in a structure which is chemically reasonable.

The hydrochloride structure was derived by assuming it to be roughly isomorphous with the above structure, and subjecting the coordinates to

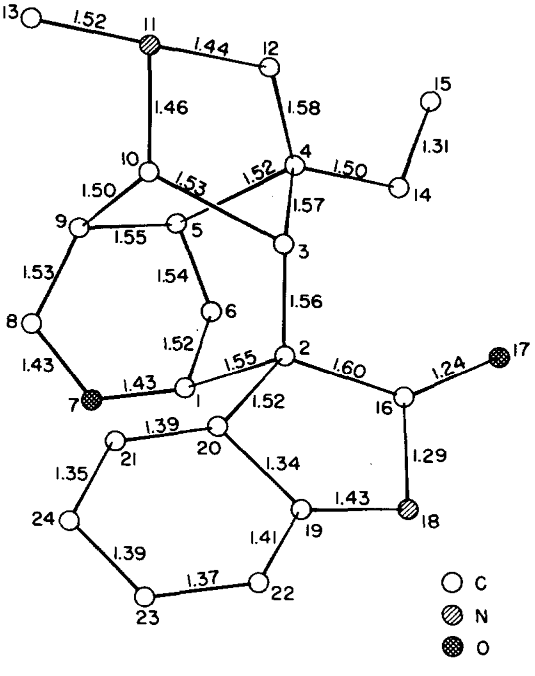

FIG. 1. Bond distances in gelsemine ion, as established from X-ray analysis of gelsemine hydrochloride.

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[6] V. Vand and R. Pepinsky, Z. Krist. 111, 46 (1958).

repeated least-squares refinement cycles. The positions of the halogen and organic components were found to differ significantly in the two derivatives; but least-squares coordinate adjustments in the hydrochloride eventually led to an R value of 0.17 for that structure.

The structure of the organic ion, as derived in the hydrochloride crystal, is shown in Fig. 1. Bond distances, which have standard deviations ranging from 0.01 to 0.03 A, are shown in the figure. A full discussion of the analyses of both crystals, with supporting X-ray data, and a description of the stereochemistry and resonance state of the molecule, will be submitted shortly to this journal. Meanwhile, a table of bond angles, and several figures showing these, are available from the second author (R. P.), as an aid in model construction.

We are delighted to report that the structure given here agrees with one privately reported to us by R.B. Woodward of Harvard University on February 26, 1959, without knowledge of our conclusions. Professor Woodward's arguments made use of biogenetic considerations in conjunction with new chemical evidence, privately communicated to him by Professor Harold Conroy of Yale University, which showed that the vinyl group of gelsemine is attached to a quaternary carbon atom β to $\underline{N}^{b}$. Professor Conroy's similar, independent deduction, as well as other new physical and chemical evidence which is confirmatory of our structure, are reported in his accompanying communication with Dr. J. K. Chakrabarti.[7] We are grateful to Professor Conroy for the opportunity to read his manuscript in advance of publication.

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[7] H. Conroy and J. K. Chakrabarti, Tetrahedron Letters No. 4, 6 (1959).

This X-ray analysis was initiated in the Viriamu Jones Laboratory, University College, Cardiff, by the first and third authors (F. M. L. and A. J. C. W.), and proceeded there successfully from data collection through location of the oxindole group in the hydroiodide. The remainder of the analysis, essentially straightforward from that point, was supported at The Pennsylvania State University by Grant No. A228 from the Institute for Arthritis and Metabolic Diseases, National Institutes of Health. Extensive computations on X-RAC were supported by Contract No. N6onr-26916 with the Office of Naval Research, Physics Branch; and IBM 704 calculations were supported by the Atomic Energy Commission under Contract No. AT(30-1)-1516, and through the generosity of the Curtiss-Wright Corporation at Quehanna, Pa.

We are grateful indeed for the invaluable advice and aid of our colleagues at Penn State: Prof. V. Vand in IBM 704 programming and Prof. Y. Okaya in the structure elucidation.