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THE CRYSTAL STRUCTURE OF OXOTUBEROSTEMONINE

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Oxotuberostemonine, one of the Stemona alkaloids, was first isolated by Kondo, Satomi and Odera (1). Edwards, Feniak and Handa (2) showed that it was related to tuberostemonine, whose structure was established (3) shortly thereafter. However, insufficient evidence was available to distinguish between several possible structures for oxotuberostemonine, and an X-ray crystal structure analysis was therefore undertaken.

The crystal data are as follows:

Oxotuberostemonine	$(C_{22}H_{31}O_5N)$
Orthorhombic cell	$\underline{a} = 10.29$, $\underline{b} = 24.50$, $\underline{c}$ 8.34Å
Space Group	$P2_12_12_1$ $Z = 4$ M.W. = 389
Density	$D_x = 1.229$ $D_m = 1.237$ gm/cm^3

The intensities of 1836 independent reflections were visually estimated from equi-inclination Weissenberg photographs which were taken with CuKα radiation about the $\underline{a}$ and $\underline{c}$ crystallographic axes.

Attempts at solving this structure were unsuccessful for several years. These included the use of direct phasing techniques such as vector search and symbolic addition procedures. Of these attempts, the latter, involving a symbolic approach to Karle and Hauptman's (4) statistical phasing methods, appeared the most promising. However, this revealed two important irregularities. Firstly, the high normalized structure factors were not distributed evenly throughout reciprocal space; there was a preponderence of terms with ℓ=0, 3 and 6, and a deficiency of h0ℓ reflections with h or ℓ odd. Secondly, in the application of the symbolic addition procedure, phase contradictions were generated at an early stage in the extension process.

The first of these irregularities indicated that the molecule has marked anisotropic thermal motion so that normalization involving the usual isotropic temperature factors is inadequate. Anisotropic temperature factor corrections were therefore estimated using an approach described by Maslen (5), and this made a considerable improvement in the distribution of E's. At this time a set of programs was being prepared for the application of Karle and Hauptman's direct phasing methods based primarily on the repeated application of the tangent formula, rather than symbolic addition procedure. The phase set is extended from the origin and enantiomorph defining phases directly, using lower E values than is customary with the conventional symbolic addition procedure. A carefully weighted iteration with the tangent formula is used to correct errors in the generated phases. Occasionally a symbol is introduced to accelerate the phase extension, but its value is not determined, non-arbitrary phases being generated only by addition and subtraction of the phase symbol. These programs, which are equally applicable to centrosymmetric or noncentrosymmetric space groups, had proved very successful in the solution of a number of a test structures. Because of its past difficulties, oxotuberostemonine was selected for the first attempt on an unknown structure.

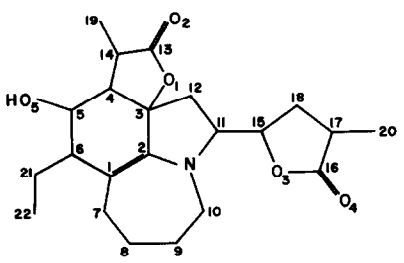
The phases of three reflections, of type Ouu, guO, and uOu, were specified in order to define the cell origin, and the phase of another reflection, uuO, was chosen to fix the enantiomorph. One undetermined symbol was used to accelerate extension of the phasing process among the larger E'S. Thre repetitive application of the tangent formula to these reflections enabled the extension and refinement of phases to reflections with E's above successively lower threshold values. Ten iteration cycles were performed for each of the five threshold values 2.0, 1.9, 1.8, 1.7, and 1.5. In the refinement the phases converged rapidly, particularly in the latter stages, providing an internally consistent set of 258 reflections.

These reflections were used to calculate a three-dimensional E-map. This enabled 26 of the 28 non-hydrogen atoms to be identified and another atom to be restricted to one of two alternative sites. A subsequent difference map resolved the two unknown atomic sites.

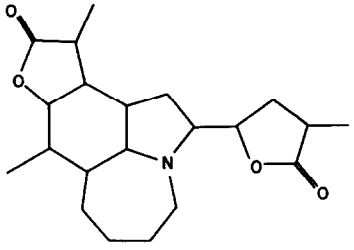
Four cycles of least-squares refinement using isotropic temperature factors followed by six cycles of least-squares calculations with anisotropic temperature factors have reduced R, the reliability index, to 0.075. The structure is thus shown to be essentially correct.

The molecular structure of oxotuberostemonine viewed along the a axis is shown in Figure 1, and it can therefore be formulated as I. The structure is similar to that of tubero-

stemonine (II), but involves the addition of an oxygen atom (at C(3)*) and the incorporation of a double bond (between C(1) and C(2)) as the empirical formula suggested.



I



II

There is also a striking and unexpected difference between the two ring systems in the region of the lactone ring which is fused to the six-membered ring. In oxotuberostemonine the γ-lactone ring involves the oxygen atom O(1), and the ring fusion is along the C(3)-C(4) bond, resulting in a spiro junction of the lactone and pyrrolidine rings at C(3). In tuberostemonine, on the other hand, oxygen atom O(5) forms part of the lactone ring, and ring fusion is along the C(4)-C(5) bond.

The formation of oxotuberostemonine from tuberostemonine, which can be accomplished by mercuric acetate oxidation (2), must involve a relactonization as well as the introduction of the oxygen atom and the double bond. The hydroxyenamine formation is of a type discovered by Leonard and co-workers (6). The location of the double bond and new carbon-oxygen bond had been suggested by Edwards (7) on the basis of this known oxidation pathway, and the fact that oxotuberostemonine was not smoothly dehydrogenated to a pyrrole. However the relactonization is unexpected. This relactonization has the effect of making the oxotuberostemonine molecule more compact than it would otherwise be. Also, in the crystal structure, it makes possible the formation of a hydrogen bond between O(5) and O(2) of adjacent molecules; the oxygen-oxygen distance is 2.8Å.

The structure of tuberostemonine, in the form of its methobromide dihydrate, has also been studied by X-ray diffraction recently, and its absolute configuration has been determined (8). By comparison of the portions of the two molecules which are unaffected by the oxidation, it can be proved that oxotuberostemonine is shown in the correct absolute configuration in Figure 1. Wherever the two structures are comparable, the configurations determined by the two analyses agree. In both molecules the lactone ring and six-membered ring are cis-fused. The

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* The numbering scheme is arbitrary.

azacycloheptene ring in oxotuberostemonine is in chair form, and the pyrrolidine ring is puckered, with C(12) deviating about 0.65Å from the mean plane through the other four atoms.

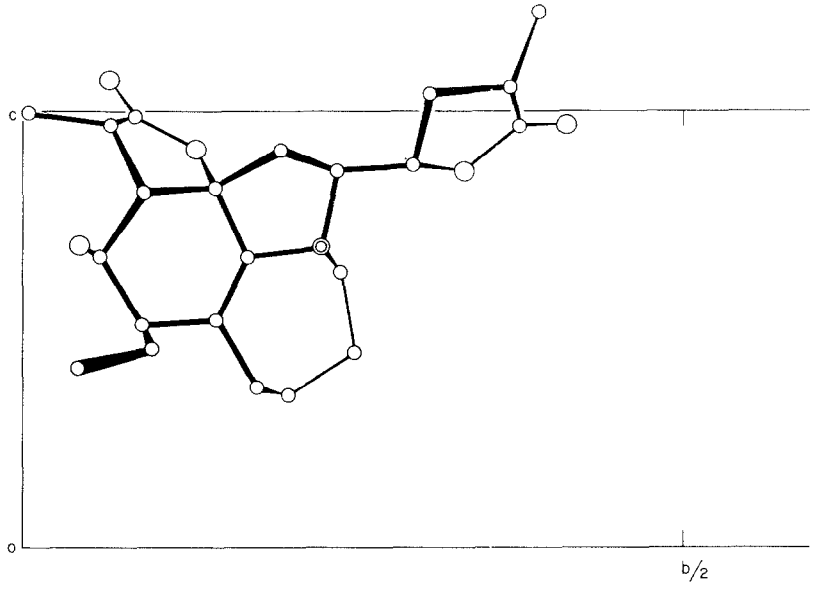

FIG. 1.

Large, small, and double circles represent oxygen, carbon, and nitrogen atoms respectively.

Acknowledgements

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References

1. H. Kondo, M. Satomi and T. Odera, Ann. Rep. ITSUU Lab. (Tokyo), 5, 99 (1954).
2. O.E. Edwards, G. Feniak and K.L. Handa, Can. J. Chem. 40, 455 (1962).
3. O.E. Edwards and G. Feniak, Can. J. Chem. 40, 2416 (1962).
4. J. Karle and H. Hauptman, Acata Cryst. 9, 635 (1956).
5. E.N. Maslen, Acta Cryst. 22, 945 (1967).
6. N.J. Leonard, L.A. Miller and P.D. Thomas, J. Am. Chem. Soc. 78, 3463 (1956).
7. O.E. Edwards, The Alkaloids, Edited by R.H.F. Manske, Vol. IX, p. 550. Academic Press, New York (1967).
8. H. Harada, H. Irie, N. Masaki, K. Osaki and S. Uyeo, Chem. Commun. 460 (1967).