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THE STRUCTURE OF CELEBIXANTHONE

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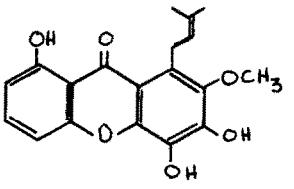
IN the course of our continuing study of the products of the botanical family Guttiferae, we have examined the Philippine tree Cratoxylon celebicum. Extraction of finely ground bark with n-pentane for 100 hr deposited in the pot a semi-crystalline precipitate which was sublimed at 150° and ca. 5×10^{-3} mm, and the sublimate crystallized from dichloromethane-cyclohexane to give an optically inactive yellow crystalline product which we have named celebixanthone, m.p. 219-220° [Found: C, 66.4; H, 5.3; OCH_3, 8.7. Calc. for $C_{18}H_{15}O_5$ (OCH_3): C, 66.6; H, 5.3; OCH_3, 9.05%]. Acetylation with acetic anhydride-pyridine gave a triacetate, m.p. 164-165° [Found: C, 63.8; H, 5.3; CH_3CO, 23.6. Calc. for $C_{18}H_{12}O_2$ (OCH_3) ($COCH_3$)$_3$: C, 64.1; H, 5.2; CH_3CO, 27.5%. U.V.: 247 mμ (38,000), 272 mμ (12,000), 345 mμ (7800)].

The near identity of the U.V. spectra of our triacetate and xanthone left no doubt as to the nature of the ring system in our product. Further, the NMR spectrum of the triacetate showed the unmistakable presence of the side chain $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C = CH\text{-}CH_2\text{-}Ar$ as well as one $-OCH_3$ and three $CH_3\overset{O}{\overset{\|}{C}}O$-groups, thus accounting for all of the atoms of the formula. In addition, the NMR spectrum of celebixanthone itself demonstrated the presence of one strongly hydrogen bonded hydroxyl group and three adjacent aromatic protons.

Treatment of celebixanthone with hot formic acid gave a product m.p.

183-185° in which the elements of formic acid had added to the side chain double bond (Found: C, 62.1; H, 5.23. Calc. for $C_{20}H_{20}O_8$: C, 61.9; H, 5.19%), showing that the side chain was not adjacent to a free hydroxyl group.[1] Reaction with HI, however, led to simultaneous demethylation and cyclization to a 2,2-dimethylchroman derivative, which gave a triacetate whose ultraviolet spectrum markedly resembled that of 2-methoxyxanthone.

Two of the hydroxyl groups were suggested to be ortho to each other by the ready oxidation of celebixanthone with Tolens reagent and by a positive catechol test with GeO_2 and indicator.[2] Based on the above evidence, the structure I was proposed as the only satisfactory explanation.



I

Concurrently with our chemical investigations, we undertook the determination of the structure of celebixanthone by X-ray crystallographic methods. Crystals from ethanol/water gave cell dimensions a = 15.73 Å, b = 14.65 Å, c = 7.49 Å, β = 100°0' with the space group $P2_1/c$ and four molecules of molecular weight 341 (Calc. for $C_{19}H_{18}O_6$, 342) per cell.

Three dimensional diffraction data were collected photometrically from integrated Weissenberg photographs, 2540 reflections being included. Two- and three-dimensional Patterson functions confirmed the chemical evidence that the molecule consisted mainly of a flat, polycyclic aromatic system. Attempts to use the direct phase determination methods which were so successful in the case of rubrofusarin[3] led only to a regular hexagonal network

[1] P. Yates and G.H. Stout, J. Amer. Chem. Soc. 80, 1691 (1958).

[2] P. Berillard, Bull. Soc. Chim. Fr. 296 (1954).

[3] G.H. Stout, D.L. Dreyer and L.H. Jensen, Chem. & Ind. 289 (1961); G.H. Stout and L.H. Jensen, Acta Cryst. 15, 451 (1962).

of points on the 001 plane, some, but not all, of which represented locations occupied by atoms in the final structure.

In order to permit rapid evaluation of the effects of superimposing chemically reasonable models on this regular grid, a special program was written for the IBM 709. This program calculates general structure factors for a given model with respect to an arbitrary local origin and then uses these to compute Fc's for any desired position of the local origin in the cell. The time required to calculate 70 Fc's at each of 70 test points in the cell is approximately 2 min.

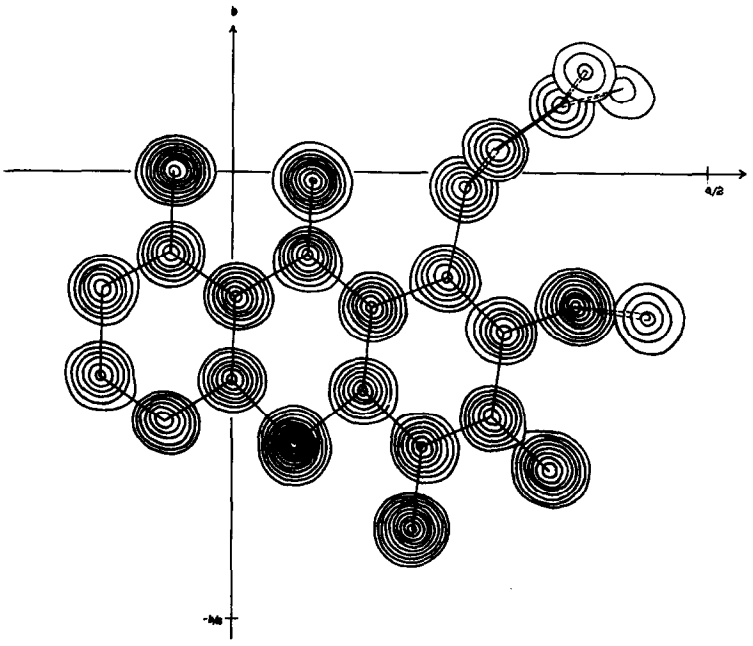


FIG. 1

Composite electron density distribution of celebixanthone, projected on the (001) plane.

Using the model suggested by the chemical data, one molecular location proved significantly superior to all others. Using the rough coordinates

from the trial structure, one cycle of structure factor and three dimensional Fourier calculations improved the positions of the ring atoms and a second defined clearly the location of all the atoms in the five carbon side chain. Subsequent refinement by full matrix and block diagonal least squares methods, coupled with difference Fourier syntheses, identified the oxygen atoms and has allowed the location of all hydrogens. The residual index R for the observed reflections including hydrogen atoms and anisotropic temperature factors is currently 8.2 per cent. The structure found is shown in Fig. 1 and is in complete agreement with our deductions from the chemical evidence.

Celebixanthone represents one of the largest natural products whose structure has been solved by X-ray methods without recourse to a heavy-atom derivative. Its solution demonstrates the increasing importance of these techniques as adjuncts to as well as replacements for classical chemical analysis.

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