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SINGLE CRYSTAL X-RAY STRUCTURES OF CHEMOTHERAPEUTIC AGENTS II,* THE STRUCTURE OF CEPHALOTAXINE METHIODIDE

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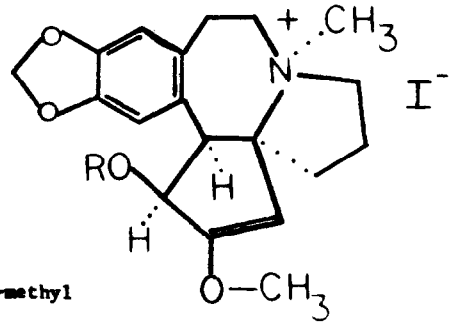
We wish to report the structure of cephalotaxine methiodide (I) elucidated by single crystal X-ray diffraction. Cephalotaxine (II) is related to an active antitumor alkaloid harringtonine (III) isolated by R. G. Powell et al. (1). The elemental formulas for



I, R = H

II, R = H,Des-N-methyl

III, R = $C_{10}H_{17}O_5$,Des-N-methyl

II ($C_{18}H_{21}NO_4$) and III ($C_{28}H_{37}NO_9$) were obtained from high resolution mass spectral measurements. The methiodide I (1) was recrystallized from methanol to give monoclinic crystals. A crystal was mounted on a Picker four-circle automatic diffractometer and the following lattice parameters obtained: a = 9.225, b = 11.456, c = 19.569 Å and β = 100°36'. The density, measured by flotation was D_m = 1.53, corresponding to four molecules per unit cell. The space

*For Paper I, see D. J. Abraham, J. S. Rutherford, and R. D. Rosenstein, J. Med. Chem. 12, 189 (1969).

group was $P2_1/n$.

Data for 1729 independent reflections, including those below the observable threshold, were collected with MoKα radiation. The low order data were measured with a continuous θ - 2θ scan to get integrated intensities, while the remainder of the intensities were found by peak count. These data were then processed in the usual manner to give relative structure factors. These were normalized, with temperature and absolute scale factors derived by Wilson statistics, and a sharpened, three-dimensional Patterson function with origin removed was calculated with the resulting E^2-1 fourier coefficients.

The three overwhelmingly highest peaks in the sharpened Patterson synthesis were easily interpreted as vectors between four symmetry-related iodine atoms in a $P2_1/n$ arrangement. A difference synthesis with the heavy atom contribution removed revealed a fused five-and seven-membered ring system. A second difference synthesis based on the iodine position and the five- and seven-membered rings gave the trial structure I for cephalotaxine. This structure was refined by isotropic least squares to a conventional R-factor of .18 and by anisotropic least squares to an R of 0.074. Since the space group is centrosymmetric, the crystal contains matched pairs of D and L isomers, that is, it is a racemate. In agreement with this, no measurable optical rotation was found for the methiodide in water.

Acknowledgment

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REFERENCES

(1) R. G. Powell, D. Weisleder, C. R. Smith Jr. and I. A. Wolff, preceding communication.