The Structure of Anisomycin

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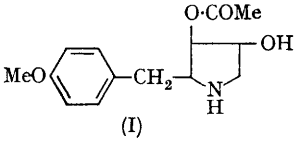
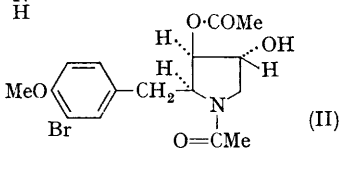
THE antibiotic anisomycin (I) is a fermentation product produced by various species of *Streptomyces* and has been shown to have widespread activity against certain pathogenic protozoa.[1,2] Early chemical studies indicated that (I) had a formula corresponding to $C_{14}H_{19}NO_4$ and possessed a methoxyl group, an acetyl group, and two active hydrogens.[1,3] The basicity of (I) (pK_a = 7·75) indicated that the compound was an amine and subsequent degradation confirmed the presence of a pyrrolidine ring.[3] Further studies[3] established that the gross structural features of anisomycin are best represented by the formula (I).



(I)



(II)

To decide the relative stereochemical relationships of the substituents on (I), a complex series of transformations of the hydroxyl and acetate groups was undertaken and as a result of these studies the groups on the pyrrolidine ring were assigned the all-*trans* configuration. More recent studies[4] have, however, led to results which are difficult to rationalize in terms of this configuration for (I) and, as a result, we have determined the

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crystal structure of a derivative of (I), *N*-acetylbromoanisomycin, to clarify any ambiguity which may exist in the stereochemical assignments. It has proved to have the stereochemistry of (II).

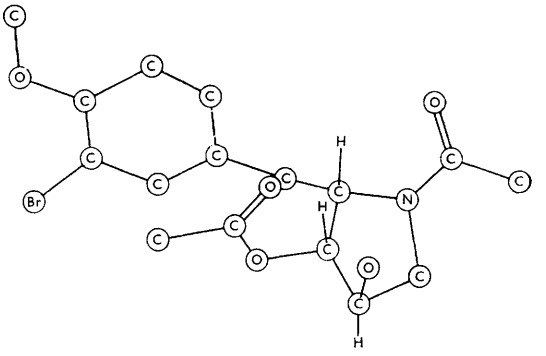
Crystals of (II) (m.p. 177°) were grown from ethyl acetate as colourless needles elongated along [*b*] and have the following crystallographic characteristics:

$C_{16}H_{20}NO_5Br$, $M = 386{\cdot}2$. Monoclinic, $a = 11{\cdot}254 \pm 0{\cdot}017$, $b = 7{\cdot}160 \pm 0{\cdot}013$, $c = 11{\cdot}439 \pm 0{\cdot}018$ Å, $\beta = 112{\cdot}8 \pm 0{\cdot}2°$. $U = 849{\cdot}7$ Å^3, $D_m = 1{\cdot}501$, $D_c = 1{\cdot}506$, $Z = 2$, $F(000) = 394$. Space group $P2_1$ (C_2^2, No. 4).

Equi-inclination Weissenberg photographs of the levels $h(0–4)l$ were taken with Cu-K radiation, and the relative intensities estimated. Reflexions which were too weak to be observed were included at one half the local minimum observable value. A total of 1000 independent reflexions was recorded.

The structure was solved by the heavy-atom technique. The co-ordinates of the bromine atom were found from a three-dimensional Patterson synthesis, and the positions of the lighter atoms obtained from successive two- and three-dimensional Fourier syntheses. Refinement was carried out by differential synthesis until R had dropped to a final value of 10·5%. Hydrogen atoms were ignored throughout. All calculations were carried out on an IBM 7072 computer with programmes written in Prof. G. A. Jeffrey's laboratory at the University of Pittsburgh.

The Figure shows a molecule of (II) as viewed in a *b*-axis projection. An examination of the structure reveals that, although the two oxygen atoms on the pyrrolidine ring are *trans*, the relative stereochemical assignment previously given to the *p*-methoxybenzyl group is incorrect since this group is *cis* to the adjacent acetate function. Since the conversion of anisomycin into (II) did not utilize any reactions which could have involved a rearrangement, it follows that anisomycin must also have this stereochemical arrangement of groups on the pyrrolidine ring.‡



N-*Acetylbromoanisomycin*

FIGURE

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‡ We thank Dr. Kenneth Butler for supplying us with a sample of (II) and for bringing this problem to our attention.

[1] B. A. Sobin and F. W. Tanner, jun., *J. Amer. Chem. Soc.*, 1954, **76**, 4053.
[2] J. E. Lynch, A. R. English, H. Bauck, and H. Deliganis, *Antibiot. Chemotherapy*, 1954, **4**, 844.
[3] J. J. Beereboom, K. Butler, F. C. Pennington, and I. A. Solomons, *J. Org. Chem.*, 1965, **30**, 2334.
[4] K. Butler, private communication.