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GLUTARIMIDE ANTIBIOTICS PART V.
THE ABSOLUTE CONFIGURATION OF THE SIDE-CHAIN ASYMMETRIC CENTER OF CYCLOHEXIMIDE

by

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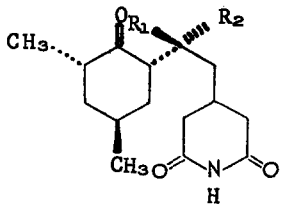
The asymmetric center of the 3-ethylglutarimide side-chain of cycloheximide (I) has been assigned the (S)-configuration (i.e. I; R_1=OH; R_2=H) by Okuda.[1] We would like to present evidence that this center has in fact the (R)-configuration (I; R_1=H; R_2=OH.).



I

The original assignment was based on two pieces of evidence.[1] The first relied on the fact that the boric acid complex (II) of dihydrocycloheximide (III)

(1) T. Okuda. Chem. and Pharm. Bull. (Japan) 7, 671 (1959).

differed little in optical rotation from the parent diol (III). The latter substance obtained by platinum catalyzed hydrogenation of I was assumed to have its ring hydroxyl group equatorially oriented. The second piece of evidence involved an infrared study of the differences in hydrogen bonding between two diol monoacetates (IV and V). One of these (IV) prepared by sodium borohydride reduction of cycloheximide acetate (IV) was claimed to have an equatorial ring-hydroxyl group while V, produced by platinum-catalyzed reduction of VI, was presumed to have its ring-hydroxyl group axially oriented.

We now have reexamined the reduction products of I and its acetate VI. Whereas catalytic hydrogenation of I leads exclusively to the diol III, both platinum-catalyzed hydrogenation and sodium borohydride reduction of VI give mixtures of the two diol monoacetates (V and IV) and not single products from each reaction as originally claimed.[1]

Of greatest significance is the fact that all three substances III, IV and V give the same diacetate (VII) m.p. 90-3°(Anal.: Found: C, 62.0; H, 8.1; N, 4.1). $[\alpha]_D^{CHCl_3}$ + 13° (C, 3.9) on mild acetylation. The simplest interpretation of the data is that reductions

of VI are accompanied by some acetyl transfer[2] from the side-chain hydroxyl to that of the ring. An examination of the n.m.r. spectrum* of the diol (III) revealed the presence of two peaks due to hydrogen attached to hydroxyl-bearing carbon atoms at 233 and 246 cps. The first was fairly sharp and showed little resolution and can be assigned to an equatorial proton[3,4,5] whereas the latter which was quite broad belongs to the CH proton of the asymmetric center of the side-chain. Thus the above reduction products can be represented as shown in Chart I.

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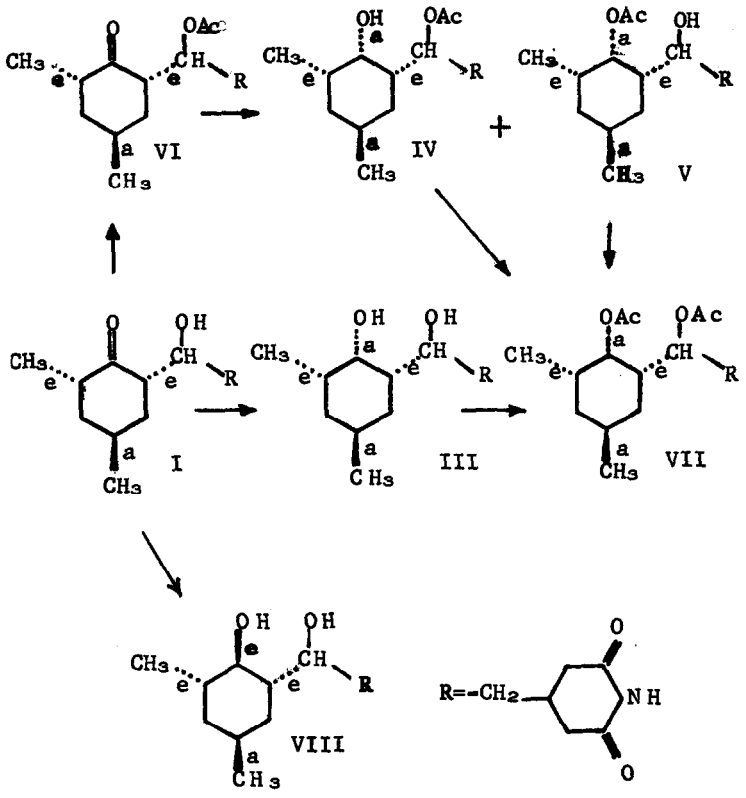
(2) This has been verified independently by an oxidation study of the diol-monoacetates. This will be reported in the full publication at a later date.

(3) The absorption peak due to the α-H of rigid axial amines has also been observed to be fairly sharp and unresolved at 60 megacycles (H. Booth and N. Franklin, Chem. and Ind. 954 (1963)).

(4) Its position is also indicative of this orientation. E. L. Eliel, M. H. Gianni and T. H. Williams, Tetrahedron Letters, 741 (1962).

(5) An n.m.r. study of the tri-, di- and mono-acetates of III and VIII, and of the two alcohols derived from deoxycycloheximide, confirms these assignments.

CHART I



In an attempt to obtain the missing diol (i.e. with the ring hydroxyl equatorially oriented) I was reduced with diphenyltin dihydride.[6] This afforded a quantitative yield of a mixture of diols which was resolved by chromatography into III (90% yield) and a diol[7] m.p. 163° (10 % yield) (Anal. Found: C, 63.4; H, 8.9; N, 5.2). $[\alpha]_D^{CH_3OH}$ 0° (C, 1.0). The n.m.r. spectrum*of this compound showed only two broad multiplets at 268 and 209cps. (each corresponding to one H atom) which can be ascribed to the hydrogen atoms of the hydroxyl-bearing carbons of the side-chain and the ring, respectively. The shape of the latter absorption is what could be expected if the hydroxyl of the ring is equatorial.[4,5] Thus, this diol is represented by VIII.

The absolute configuration of the side-chain asymmetric center can now be deduced from the observations that diol III forms an acetonide with great ease in 80% yield m.p. 142° (Anal. Found: C, 67.0; H, 9.2; N, 4.6)

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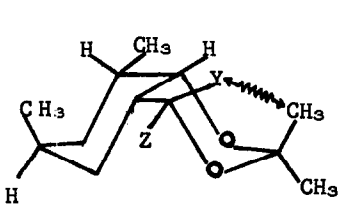
(6) This neutral reducing agent eliminates the possibility of isomerizing the base-sensitive I during reduction.

(7) This diol appears to have been obtained previously by M. Suzuki [Chem. Pharm. Bull. (Japan) 8, 778 (1960)] by the lithium aluminum hydride reduction of cycloheximide. He presumed that ring isomerization had taken place during the reduction and that the diol belonged to the naramycin-B series of compounds. However, we were able to reproduce this work only when lithium tri-t- butoxyaluminum hydride was used as the reducing agent.

$[\alpha]_D^{CHCl_3}$ 0° (C, 2.0), whereas diol VIII does not. In the latter case only starting material was recovered under all conditions tried. A consideration of the stereochemistry of the acetonides which could be expected from diol III strongly suggests that only that case (IX) where



IX

Y=H and Z=R, could form easily, since the alternative (IX; Y=R; Z=H) has a severe 1,3-diaxial interaction. This leads to the (R)-configuration for the side-chain asymmetric carbon atom of cycloheximide,[8] (i.e. I; R_1=H; R_2=OH). On this basis the acetonide from diol VIII would be represented by X (Y=R; Z=H). Since there is present in this molecule a severe 1,3-diaxial interaction, lack of its formation supports the assignment of the (R)-configuration to the center in question.

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(8) The geometry of diol III on this basis would still accommodate the Japanese data concerning its borate ester.[1]

Additional evidence confirming our arguments has been obtained from a similar study of the two diols derived from isocycloheximide. These results together with those reported above will be presented in full at a later date.

* N.M.R. spectra were recorded in pyridine solution with a Varian Associates Model A-60 analytical spectrometer. Chemical shifts are in cps relative to tetramethylsilane used as an interval standard, and are taken to be positive for protons on the low field side of the T.M.S. peak.

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