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GLUTARIMIDE ANTIBIOTICS PART VI.

THE NATURE OF DEOXYCYCLOHEXIMIDE

and

EPIDEOXYCYCLOHEXIMIDE

by

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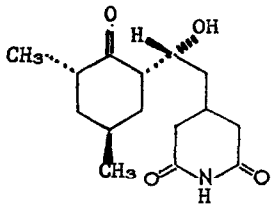
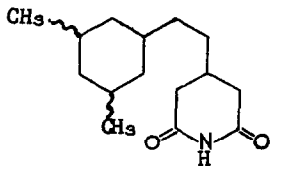
In recent publications[1,2] Schaeffer and Jain have described two procedures for the conversion of cycloheximide (I) to two different dideoxy-derivatives of general structure II.



I



II

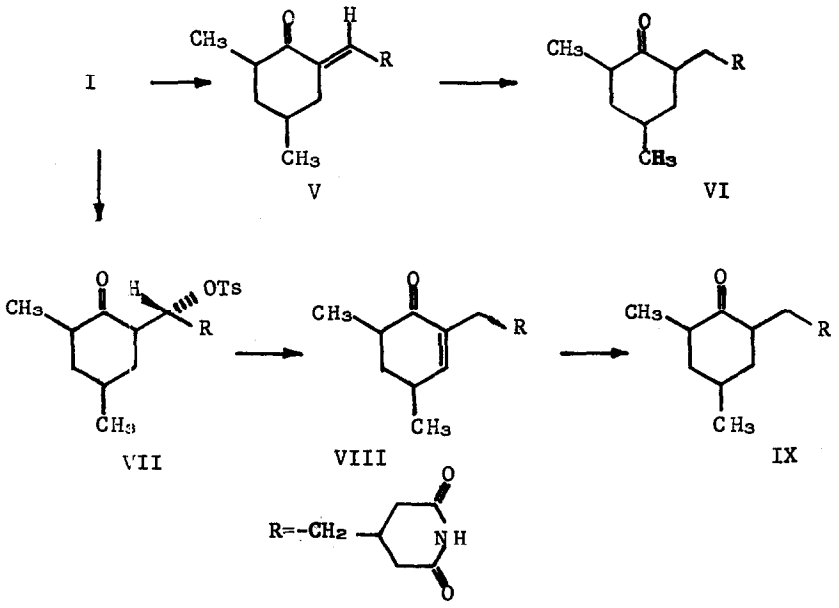
The first dideoxycycloheximide (III) reported[1], m.p. 135-136° was claimed to have trans-oriented methyl groups

(1) H. J. Schaeffer and V. K. Jain, J. Pharm. Sci., 50, 1048 (1961).

(2) H. J. Schaeffer and V. K. Jain, ibid. 52, 639 (1963).

since it was found to be optically active, and this was cited as proof of the trans-orientation of the methyl groups in cycloheximide. The second dideoxy compound (IV), m.p. 124-126°, having no optical activity, was postulated[2] to have cis methyl groups.

The preparation of III involved in the initial stage the conversion of I to anhydrocycloheximide (V) by phosphorus pentoxide dehydration. By implication[1] then, all derivatives intermediate between I and III including V must have trans-methyl groups. However, Lawes[3] had already obtained V by direct synthesis from cis-2,4-



(3) B. C. Lawes, J. Am. Chem. Soc., 82, 6413 (1960).

dimethylcyclohexanone, thus suggesting V to have cis-oriented methyl groups. In order to resolve the conflict in these results, we have examined the n.m.r. spectrum* of VI obtained from V by catalytic reduction[4] with a palladium-on-charcoal catalyst. As can be seen from the accompanying table, the

TABLE I

	Position of the methyl peaks† in $CDCl_3$		Position of the methyl peaks† in pyridine	
Compound	2 Me	4 Me	2 Me	4 Me
Isocycloheximide acetate	60.6 (6.3)	58.2(5.9)	57.4(6.2)	53.1(5.9)
α-Epiisocycloheximide acetate	58.3	58.3	58.9(6.4)	52.0(5.8)
Deoxycycloheximide	58.0(6.1)	57.7(5.8)	59.8(6.2)	50.6(5.8)
Cycloheximide acetate	58.2(6.3)	75.6(6.7)	59.4(6.4)	70.6(6.6)

†J. values given between brackets

positions of the methyl group absorptions of VI correspond very closely to those of isocycloheximide acetate and α-epiisocycloheximide acetate in which the methyl groups are cis-oriented, but not to one of the methyl group absorption of cycloheximide acetate. The lack of methyl group absorption around 70 cps definitely excludes[5] the possibility

(4) T. Okuda, Chem. and Pharm. Bull.(Japan) 7, 666 (1959).

(5) F. Johnson and N. A. Starkovsky, Tetrahedron Letters 1173 (1962).

of there being an axial methyl group in VI. In addition all attempts to isomerize VI under acidic or basic conditions failed consistently[6] (cf. cycloheximide which is very easily isomerized by base[7]). Thus we can only conclude that III, V, and VI have cis-oriented methyl groups and that the very low optical activity reported[1] for III must be due to an impurity.

The second dideoxycycloheximide (IV) was prepared[2] from cycloheximide tosylate (VII), and here the initial stages involved refluxing VII in boiling dimethylformamide whereby epianhydrocycloheximide (VIII) was obtained, followed by catalytic reduction of the latter to epideoxycycloheximide (IX). We at first thought that the differences between VI and IX might lie in the orientation of the 3-ethylglutarimide side-chain. However, the n.m.r. spectrum of IX proved to be absolutely identical with that of VI and, what was even more surprising, the solution infrared spectra of these two materials were superimposable.[8]

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(6) T. Okuda has informed us that he also has been unable to isomerize VI - private communication.

(7) T. Okuda, M. Suzuki, T. Furumai and H. Takahashi, Chem. and Pharm. Bull. (Japan) 11, 730 (1963).

(8) The two alcohols m.p. 131° and m.p. 141° obtained by platinum-catalyzed hydrogenation of VI and IX respectively, also showed identical infrared spectra.

The only rational explanation of these phenomena is that one of these two substances is the racemic form of the other. This is supported by the fact that all optical rotations quoted by Schaeffer and Jain[2] for derivatives of VIII are esentially zero. The rotation of VIII (sodium D Line), which was not reported by the above authors, we have also found to be zero. In addition the optical rotatory dispersion curve of IX showed no departure from the abscissa whereas VI gave a real curve[4], exhibiting a weak positive Cotton effect very similar to isocycloheximide as might be expected.

Thus we conclude that all compounds of the so-called epi-series reported by Schaeffer and Jain have cis-oriented methyl groups and are racemic. A plausible mechanism for racemization during the formation of VIII can be visualized through an $\alpha\beta \rightleftharpoons \beta\gamma$ double bond equilibration. The racemization is undoubtedly acid-catalyzed by the toluene sulfonic acid liberated from VII, and we have confirmed this by the conversion of both I and V to VII by strong hydrochloric acid.

We have also prepared racemic VIII by a totally synthetic route and have found it to have the same melting point (84-86°) as the material described by Schaeffer and Jain[2]. These and the above results will be presented in full in a future publication.

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

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