Tetrahedron Letters No.14, pp. 885-889, 1965. Pergamon Press Ltd.
Printed in Great Britain.

GLUTARIMIDE ANTIBIOTICS PART VIII[1]

A Stereoselective Synthesis of dl-α-epi-Isocycloheximide

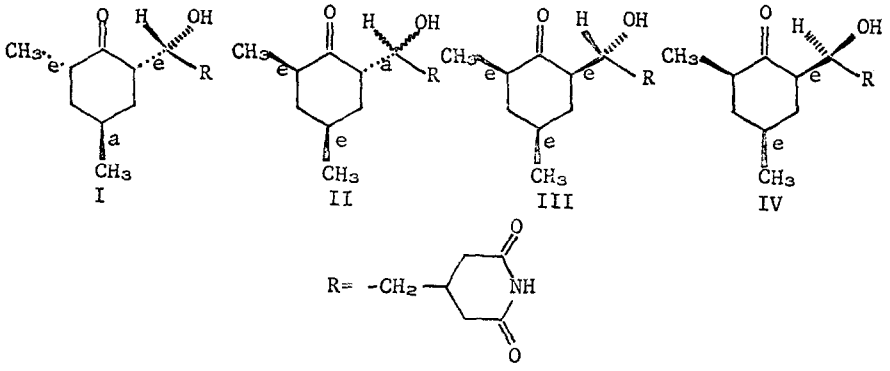
by

Francis Johnson and A. A. Carlson

Eastern Research Laboratory
Dow Chemical Company
Wayland, Massachusetts

(Received 9 February 1965)

Successful synthetic approaches to cycloheximide (I) and its isomers have led either to I itself[2], to neocycloheximide[1,3] (II) or to mixtures of isocycloheximide (III) and α-epi-isocycloheximide (IV) together with other position isomers[4]. The latter

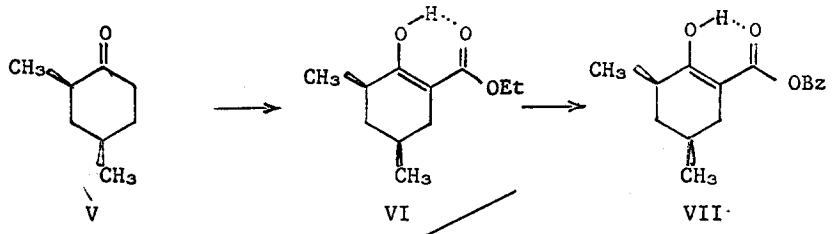


(1) Part VII submitted for publication.
(2) Francis Johnson, N. A. Starkovsky, A. C. Paton and A. A. Carlson, J. Am. Chem. Soc., 86, 118 (1964).
(3) Francis Johnson, W. D. Gurowitz and N. A. Starkovsky, Tet. Letters, 1167 (1962).
(4) T. Okuda, M. Suzuki and Y. Egawa, J. Antibiotics, 14, 158 (1961); M. Suzuki, Y. Egawa and T. Okuda, Chem. and Pharm. Bull., 11, 582 (1963); ibid p. 589.

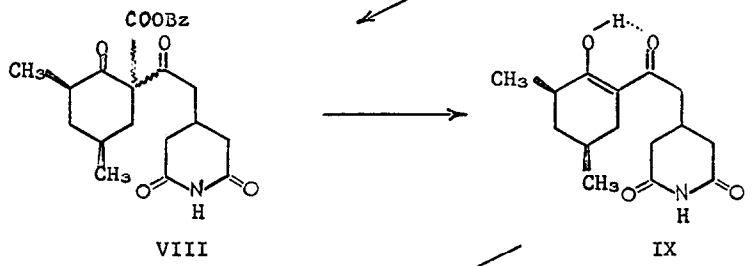
approach furnishes III and IV in yields of only ~4% in the final step and, as the separation of III from IV is also somewhat laborious, the method is not suitable for the large scale preparation of these compounds. An alternative approach[5] to III is the isomerization of cycloheximide but here again the yields and purification procedure leave something to be desired. Since we were interested in having reasonable quantities of any derivatives with cis-oriented methyl groups, we examined an alternative synthetic route outlined below. This leads stereoselectively to dl-α-epi-isocycloheximide.

Oxalylation of cis-2,4-dimethylcyclohexanone (V) followed by decarbonylation afforded the β-keto ester VI which when refluxed with benzyl alcohol led to VII b.p. 155° (0.3 mm.) $n_D^{25°}$ 1.5244 (Found: C, 74.0; H, 7.8. Calcd. for $C_{16}H_{20}O_3$. C, 73.8; H, 7.7.) Treatment of the latter substance with one equivalent of phenylmagnesium bromide in tetrahydrofuran, followed by 3-glutarimidylacetyl chloride[6] furnished VIII as an oily substance. This without purification was hydrogenated in ethyl acetate over a palladium catalyst to remove the benzyl group. The

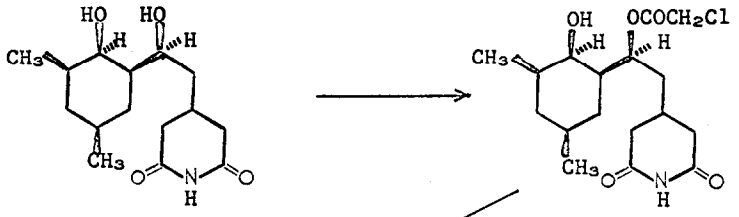
(5) T. Okuda, M. Suzuki, T. Furamai and H. Takahashi, Chem. and Pharm. Bull., 10, 639 (1962); ibid, 11, 730 (1963).
(6) Francis Johnson, J. Org. Chem., 27, 3658 (1962).



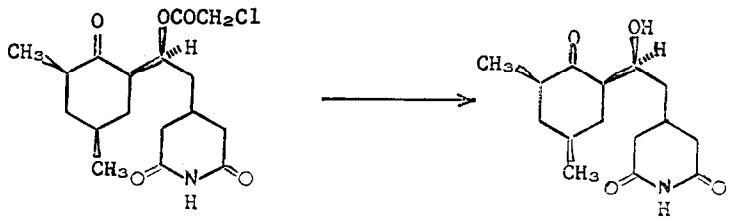
V VI VII



VIII IX



X XI



XII XIII

resulting solution of the diketo acid underwent smooth decarboxylation when refluxed and gave exclusively pure dehydroisocycloheximide (IX) m.p. 147.5-148° (Found: C, 64.6; H, 7.6; N, 5.9. Calcd. for $C_{15}H_{21}NO_4$. C, 64.5; H, 7.6; N, 5.0.) in 50-70% yields based on VII. The solution infrared spectrum of IX proved identical with a specimen prepared by the isomerization of dehydrocycloheximide according to Lemin and Ford[7]. Hydrogenation of VIII over platinum in ethyl acetate proceeded easily and furnished the dialcohol[8] X, m.p. 172° (Found: C, 63.6; H, 9.0; N, 5.0. Calcd. for $C_{15}H_{25}NO_4$. C, 63.6; H, 8.9; N, 4.9.) in 70% yield. Thus once again, as we had done in the synthesis of cycloheximide[2], we were able to establish five asymmetric centers stereoselectively in two relatively simple steps.

Monochloroacetylation of X afforded a good yield of XI m.p. 166-168° (Found: C, 56.9; H, 7.1; Cl, 10.0. Calcd. for $C_{17}H_{26}ClNO_5$; C, 56.8; H, 7.2; Cl, 9.9.). The latter on chromic acid oxidation furnished the keto-chloroacetate XII m.p. 149-150° (Found: C, 57.2; H, 6.6; Cl, 9.9. Calcd. for $C_{17}H_{24}ClNO_5$. C, 57.1; H, 6.7; Cl, 9.9). Mild alkaline hydrolysis then gave dl-α-epi-isocycloheximide (XIII) m.p. 153.5° (Found: C, 64.0; H, 8.2; N, 5.1. Calcd. for $C_{15}H_{23}NO_4$: C 64.0; H, 8.2; N, 5.0) whose solution infrared and n.m.r. spectra proved to be identical

(7) A. J. Lemin and J. H. Ford, J. Org. Chem., 25, 344 (1960).
(8) The stereochemistry assigned to this compound has been proven by n.m.r. and chemical studies which will be presented in the full paper.

with those of an authentic specimen[9], but different from those of isocycloheximide (III).

Full details of this synthesis together with additional reactions of some of the intermediates will be published at a later date.

Acknowledgement. The authors thank Dr. C. K. Fitz who performed all elemental analyses.

(9) A specimen of optically active XIII was very kindly provided by Dr. T. Okuda (Tanabe Seiyaku Co., Ltd., Tokyo.)