Tetrahedron Letters No. 25, pp. 1167-1171, 1962. Pergamon Press Ltd.
Printed in Great Britain.

GLUTARIMIDE ANTIBIOTICS. PART II. THE SYNTHESIS AND STEREOCHEMISTRY OF dl-NEOCYCLOHEXIMIDE, A NEW ISOMER OF CYCLOHEXIMIDE

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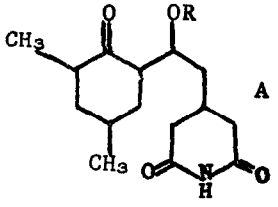
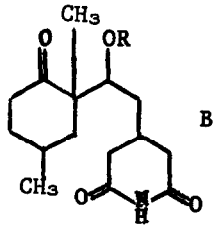
(Received 19 September 1962)

Recently T.Okuda et al.[1] have reported their work on the aldol condensation of optically active cis-2,4-dimethylcyclohexanone with 3-glutarimidylacetaldehyde in an attempt to synthesize cycloheximide (I) (Structural type A).

Three materials were obtained, two of which were assigned structures of type A (R = H), the other being of type B[2] (R = H). Both of the former materials were assumed to have the large substituent of the cyclohexanone ring in an equatorial position. One of these proved to be identical with isocycloheximide[3] (II).

When racemic cis-2,4-dimethylcyclohexanone was used,[2] only an irresolvable syrup was obtained. However, acetylation led to a material m.p. 134-135° claimed to be the dl- form of isocycloheximide acetate. In addition, two other acetates were isolated and were considered to be structural isomers of the general form B (R = Ac).

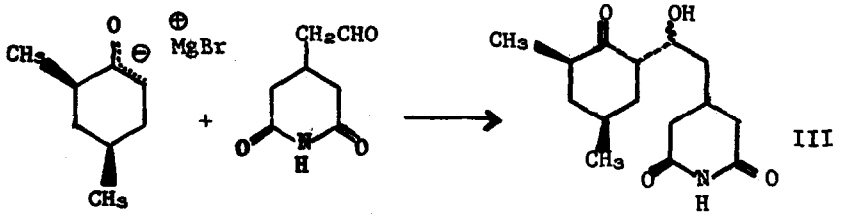




1. T. Okuda, M. Suzuki and Y. Egawa, J. Antibiotics 14, 158 (1961)
2. T. Okuda and M. Suzuki, Yakagaku Kenkyu 33, 371 (1961).
3. A. J. Lemin and J. H. Ford, J. Org. Chem. 25, 344 (1960).

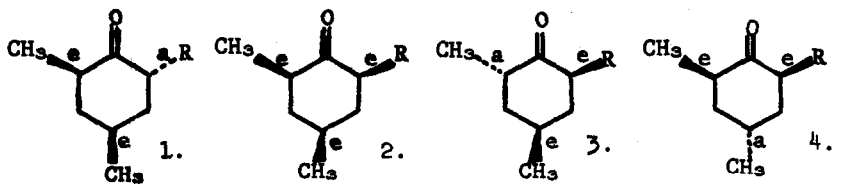
As part of our synthetic program in this area, we have also examined the Nielsen condensation[4] of 3-glutarimidylacetaldehyde with the magnesiobromide salt of racemic cis-2,4-dimethylcyclohexanone in tetrahydrofuran.

Extensive chromatography of the crude product, contrary to the above results, afforded a highly crystalline substance in 12% yield m.p. 195-196° (Found: C, 63.8; H, 8.3; N, 5.0. Calcd. for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0%). We have assigned the name dl-neocycloheximide (III) to this material.



Its infrared spectrum (Nujol mull) showed bands at 2.91 (hydroxyl) 3.11, 3.23 (imide NH) and at 5.82 and 5.94μ (ketone and imide carbonyl). Acetylation with pyridine/acetic anhydride produced a monoacetate m.p. 131-132° (Found: C, 63.0; H, 7.7; N, 4.2. Calcd. for $C_{17}H_{25}NO_5$: C, 63.1; H, 7.8; N, 4.3%) which appears to be the same as that obtained by the Japanese,[2] for acetylation of the crude condensation product followed by repeated crystallization led to the same acetate.

That the isomer we have isolated has the ring stereochemistry depicted in III and is not racemic isocycloheximide, is supported by the evidence presented below and in the following article.



R = hydroxyethylglutarimide group

4. A. T. Nielsen, C. Gibbons and C. A. Zimmerman, J. Am. Chem. Soc. 73, 4696 (1951).

Of the four stereoisomers (1-4)[5] possible for the 2,4,6-trisubstituted cyclohexanone system of these antibiotics structures 2, 3 and 4 have been assigned to isocycloheximide, naramycin B, and cycloheximide respectively, by Okuda, et al,[6] after much vacillation[7,8] using optical rotatory dispersion methods.

On the basis of convincing chemical evidence Lawes[9] and Schaeffer and Jain[10] have demonstrated that the methyl groups in I are trans to one another and Lawes has expressed the opinion that structure 3 represents cycloheximide while favoring 2 for isocycloheximide.

Previously, it has been impossible to destroy the asymmetric centre of the side-chain R, without simultaneously affecting the adjacent asymmetric carbon atom of the ring. This has prevented a direct chemical correlation of the ring stereochemistry of the various natural and synthetic isomers of these antibiotics. We have now found that this difficulty can be avoided by a careful chromic acid oxidation of the hydroxy-ketones to the 1,3-diketones. Although the latter easily are converted to the enolic forms, they can be kept long enough to carry out comparison of physical properties.

Oxidation of III with chromic acid afforded a stable diketone (V) m.p. 100-101°C. (Found: C, 64.4; H, 7.6; N, 5.0. Calcd. for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.6; N, 5.0%) in 95% yield which only developed a purple color slowly (12 hours) with ferric chloride solution, and could be recrystallized unchanged from hot ethyl acetate. However, heating at 100° for a short period effected quantitative conversion to the enolic form of dl-dehydroisocycloheximide (VI) m.p. 146.5-147.5° (mixed m.p. 146.5-148°) which gave an immediate color with ferric chloride. In addition, treatment of V with copper acetate slowly afforded a chelate whose infrared

5. Absolute stereochemistry is not implied in these diagrams.
6. T. Okuda and M. Suzuki, Chem. and Pharm. Bull. (Japan) 9, 1041 (1961).
7. T. Okuda, ibid. 7, 659 (1959).
8. T. Okuda, M. Suzuki and Y. Egawa, ibid. 8, 335 (1960).
9. B. C. Lawes, Abstracts of 139th A. C. S. Meeting, St. Louis, March 1961, p. 33N; J. Am. Chem. Soc. 84, 239 (1962).
10. H. J. Schaeffer and V. K. Jain, J. Pharm. Sci., 1048 (1961).

spectrum was identical with the copper chelate from VI. On the other hand, low temperature oxidation of isocycloheximide with chromic acid led to an unstable diketone (VII), $[\alpha]^{25}D$ -6.3° m.p. 104-106° (crude product) resolidifies at 106° and remelts at 149°, which we have been unable as yet to recrystallize without its isomerizing to the enolic optically active form of VI.[2] It developed a ferric chloride color within 10 minutes and its solution infrared spectrum in chloroform was different from that of V. The mode of synthesis of III leaves little doubt that its methyl groups have a cis relationship and permits, with the above information, a similar assignment to II (a separate and stereospecific synthesis of enolic VI in 60% yield pure, which will be reported later, also lends great weight to this argument). Therefore, II and III must differ in the orientation of the side-chain, R.

Careful oxidation of cycloheximide afforded a new unstable diketone (VIII), $[\alpha]^{25}D$ -40.8 (C = 1.0) m.p.[11] 99-101° resolidifies 101° and remelts 176°. (Found: C, 64.3; H, 7.5; N, 5.0%). The diketo form could only be recrystallized at low temperatures, and quickly isomerized quantitatively to the enolic form[12] of dehydrocycloheximide (IX), m.p. 177-179°, $[\alpha]^{23}D$ -28.40° (C = 0.94, $CHCl_3$), in methylene chloride solution just above room temperature. The infrared spectra of V, VII and VIII showed differences in the infrared in the 8-13 cps region.

We ascribe the similarity in the behavior of VII and VIII to an identity in orientation of the hydroxyethylglutarimide group, and feel that the hydrogen atom at this junction has an axial conformation while the reverse holds for V. A consideration of the transition states for acid- or base-catalyzed enolization suggests that the former configuration would permit more facile enolization of either ketone.[13]

11. Both VII and VIII are stable enough in the solid state to give fairly satisfactory melting points.

12. E. C. Kornfeld, R. G. Jones, and T. V. Parke, J. Am. Chem. Soc. 71, 150 (1949).

13. Pertinent to this is the work of Corey and Sneen (J. Am. Chem. Soc. 78, 6269 (1956)) who showed that in a rigid

These conclusions allow the assignment of structure 2 to isocycloheximide and of 1 to neocycloheximide,[14] while permitting the side-chain R of cycloheximide to be designated equatorial (i.e., 3 or 4).

These results and further reactions of neocycloheximide will be reported in full at a later date.

ACKNOWLEDGMENT

The authors would like to thank Dr. A. J. Lemin of the Upjohn Co. (Kalamazoo) who provided a specimen of isocycloheximide for the oxidation study, Messrs. A. A. Carlson and C. A. Brown for technical help and Dr. C. K. Fitz for elemental analyses.

14. N. L. Allinger, L. A. Frieberg and S.-E. Hu, [J. Am. Chem. Soc. 84, 2836 (1962)] have suggested that an axial isopropyl group is sterically less hindered than a methyl group.

Provided it can be assumed that the isopropyl group and the hydroxyethylglutarimide group have similar steric requirements in the vicinity of the ring then the possibility that neocycloheximide has the 2a, 4a, 6e-configuration, can be neglected. The n.m.r. evidence also mitigates strongly against this assignment. This is presented below.

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cyclic system, a hydrogen atom adjacent to a ketone is removed at a faster rate when it is in an axial, as opposed to an equatorial position, in an enolization process.