UDC 615.779.931-011

119. **Tomoharu Okuda** : Studies on Streptomyces Antibiotic, Cycloheximide. V.[1] Synthesis and Stereochemistry of Deoxycycloheximide.

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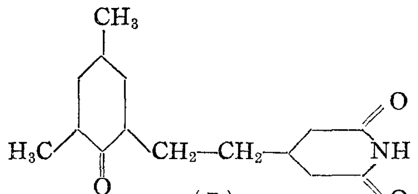
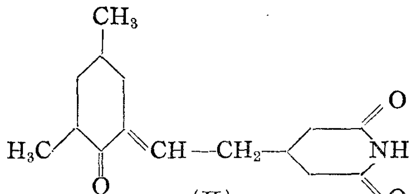
The present paper describes the synthesis and stereochemistry of 2,4-dimethyl-6-β-(2,6-dioxo-4-piperidinyl)ethylcyclohexanone (deoxycycloheximide) (I) derivable from anhydrocycloheximide (II).



(I)

Plane structure of deoxycycloheximide

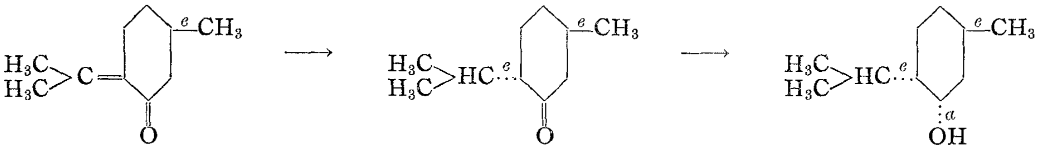


(II)

Plane structure of anhydrocycloheximide

In the previous paper[1] configurations of Naramycin-A (identified with cycloheximide) and its stereoisomeric Naramycin-B were respectively shown to have (4S:6S)- and (4S:6R)-configuration by elucidating the sign of the Cotton effect shown in the rotatory dispersion (R.D.) curves of the two antibiotics. The elucidation was made only by close examination of the R.D. curves of numerous compounds mainly reported by Prof. C. Djerassi of the Wayne State University, U.S.A. It seemed necessary, therefore, to have a proper model compound for reference.

Anhydrocycloheximide which is derivable from both Naramycins by dehydration is thought to have the most stable conformation, e.g. 2*e*,4*e*-conformation, formulated as (III). If so, catalytic reduction of anhydrocycloheximide in acid medium should effect addition of hydrogen atoms in the same manner as in the case of the reduction of pulegone. Pulegone gave menthone predominantly[2] and menthone gave neomenthol as a sole product.[3] Therefore, it is expectable that on catalytic reduction anhydrocycloheximide would give 4*e*,6*e*-deoxycycloheximide and its dihydrogenated compound having axial 1-hydroxyl group. If this consideration on R.D. curves is correct, the deoxycylohexinide thus obtained should exhibit a positive Cotton-effect curve, because this deoxycycloheximide has a configuration similar to Naramycin-B.



Pulegone Menthone Neomenthol

The following two procedures were adopted for the synthesis of deoxcycloheximide, viz. (1) oxidation of dihydrodeoxycycloheximide derived from anhydrocycloheximide by catalytic reduction over platinum oxide in acid medium, and (2) partial reduction of anhydrocycloheximide.

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[1] Part IV. T. Okuda : This Bulletin, **7**, 659(1959).

[2] cf. J.L. Simonsen : "The Terpenes," 2nd Ed., **1**, 230(1947). The Cambridge University Press, London.

[3] W. Hückel : Chem. Ber., **91**, 311(1958).

By catalytic reduction of anhydrocycloheximide (III) in glacial acetic acid using platinum oxide catalyst, crude hydrogenated compound (m.p. 120.5～121.5°) was obtained (yield, 83%), which, on fractional recrystallization from dehyd. ether, separated into two isomeric dihydrodeoxycycloheximides, colorless prisms (IV) of m.p. 130～131° and colorless prisms (V) of m.p. 117～118°.[*2]

The production ratio of (IV) and (V) was 1:16. On oxidation of dihydrodeoxycycloheximides (IV and V) with chromium trioxide in glacial acetic acid, two kinds of deoxycycloheximides, (VI) (m.p. 123～124°; oxime, m.p. 137～137.5°) and (VII) (m.p. 109.5～110.5°; oxime, m.p. 148.5～149.5°), were obtained in ca. 50% yield. By partial reduction of anhydrocycloheximide (III) in ethanol-benzene at room temperature using 2% $Pd\text{-}SrCO_3$ as a catalyst, a deoxycycloheximide was obtained as a sole product (yield, 83～84%) and this

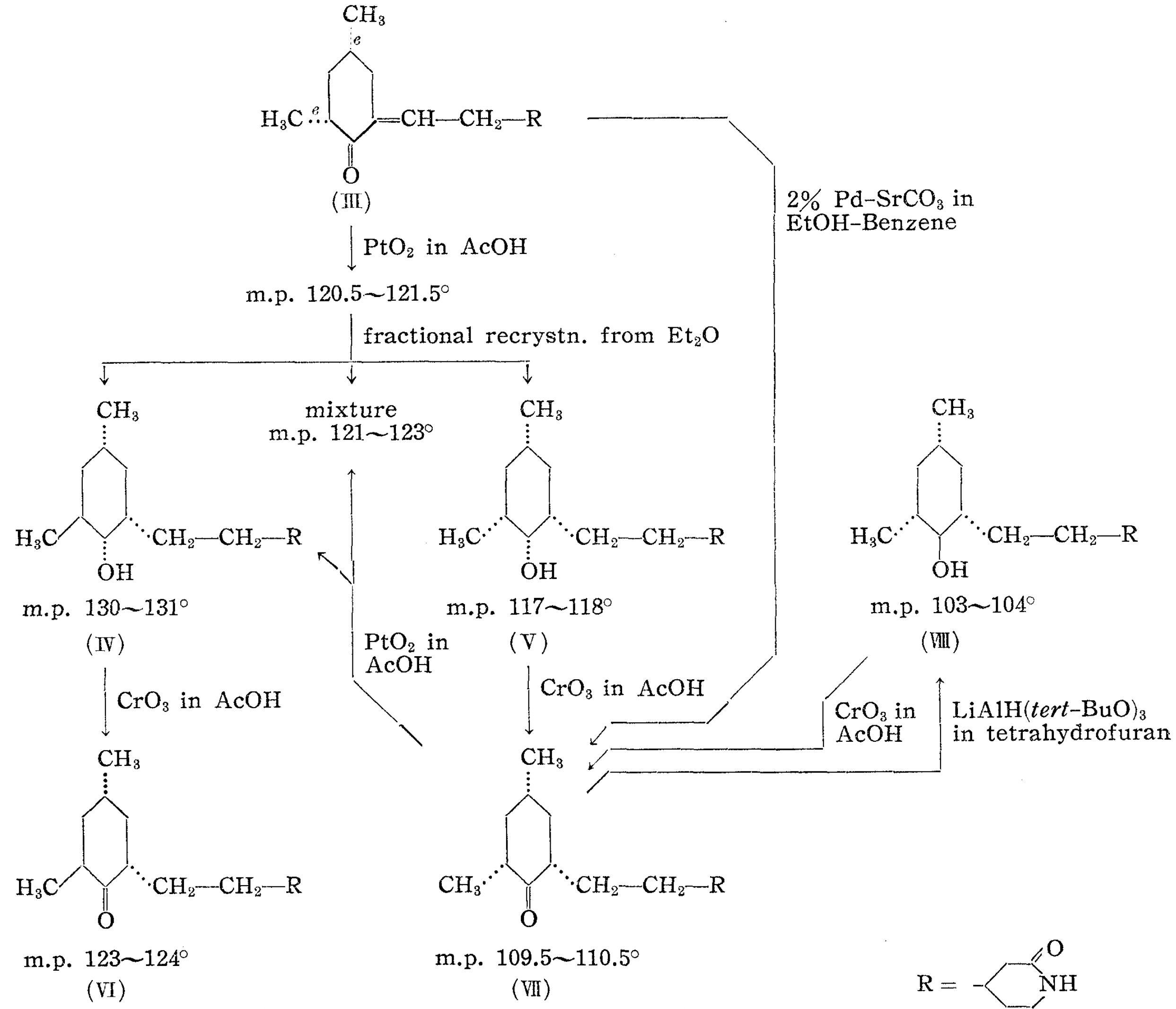

Chart 1.

[*2] Kornfeld, *et al.* reported on catalytic hydrogenation of anhydrocycloheximide. They obtained crystals of m.p. 125～126°(corr.) by recrystallization of the crude hydrogenated product from benzene-petr. ether. It was impossible to separate the crude hydrogenated product into two components by only recrystallization from the above solvent. Only by means of fractional recrystallization from dry ether were two isomers successfully obtained. cf. E. C. Kornfeld, R. G. Jones, T. V. Parke: J. Am. Chem. Soc., 71, 150(1949).

product was found to be identical with the above-mentioned deoxycycloheximide (VII). Deoxycycloheximide (VII) produced another kind of dihydrodeoxycycloheximide (VIII) (m.p. 103~104°) by reduction with LiAlH(*tert*-BuO)$_3$[4] in tetrahydrofuran. This product returned to the starting deoxycycloheximide (VII) by oxidation with chromium trioxide. The catalytic reduction of deoxycycloheximide (VII) gave a mixture of dihydrodeoxycycloheximides (IV and V), from which (V) was isolated in a pure state. The above reductions are summarized in Chart 1.

It is evident from the above reactions that deoxycycloheximide (VII) is the expected product which is thought to have 2*e*,4*e*,6*e*-conformation. The R. D. curve of deoxycycloheximide (VII) was measured through the courtesy of Prof. C. Djerassi. As illustrated in Fig. 1, this deoxycycloheximide exhibited a weak but distinct single positive Cotton-effect curve as expected, in spite of the fact that the starting anhydrocycloheximide showed a multiple negative Cotton-effect curve.

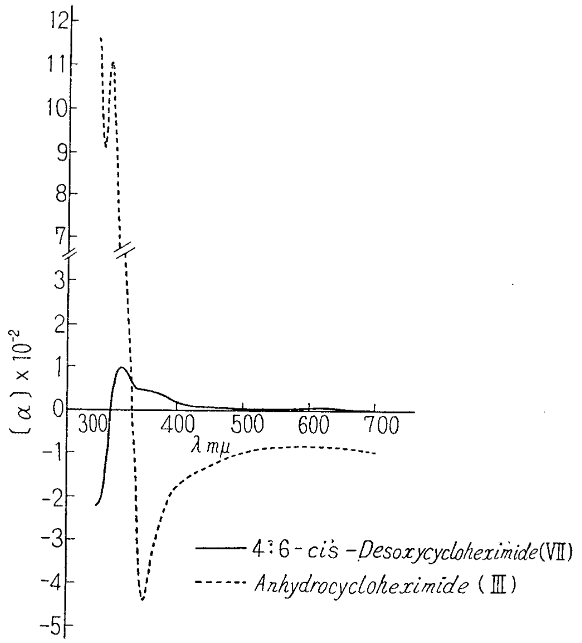

Fig. 1.

An attempt was made to measure the R. D. curve of another deoxycycloheximide (VI) but unfortunately this compound was not soluble in methanol and was slightly soluble in dioxane, so that the full chart of the R. D. curve was not obtained but it is noteworthy that this compound also showed a tendency to increase dextrorotatory value toward a shorter wave length. Therefore, this compound is thought to have (4:6)-*cis*-configuration and to have 2*a*-methyl group. The full chart of R. D. curve, if obtained, would make it possible to testify the conformation of 2-methyl group in deoxycycloheximides (VI and VII).

Two dihydrodeoxycycloheximides (V and VIII) are isomeric to each other as to the conformation of 1-hydroxyl group. According to Wheeler and Mateos,[5] the conformation of 1-hydroxyl group in dihydrodeoxycycloheximide (VIII) is presumably equatorial and therefore, that of 1-hydroxyl group in isomeric dihydrodeoxycycloheximide (V) would be axial. It seemed interesting that, in infrared spectrum of dihydrodeoxycycloheximide (VIII), $\nu_{\text{C-OH}}$ was observed at 1058 cm^{-1} (Nujol mull). Infrared spectra of these compounds described in this paper will be reported elsewhere and the reduction process with LiAlH(*tert*-BuO)$_3$ will be described in a later paper.

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[4] H. C. Brown, R. F. McFarlin: J. Am. Chem. Soc., **78**, 252(1956).

[5] O. H. Wheeler, J. L. Mateos: Chem. & Ind. (London), **1957**, 395.

The author expresses his deep gratitude to Professor C. Djerassi of the Wayne State University, U. S. A., for the measurement of rotatory dispersion curves and for his instructive and valuable suggestions through private communications. The author appreciates the kind guidance of Professor S. Sugasawa, University of Tokyo, and the encouragement of Dr. S. Yamada, the Director of this Laboratory. The author is also grateful to Messrs. M. Suzuki and Y. Egawa for their enthusiastic collaboration throughout the course of this work, to Mr. K. Kotera for infrared analysis, and to Mrs. F. Hisamichi, and Messrs. T. Yoda and T. Kōno for elementary analysis.

Experimental

(All m.p.s are not corrected. All $[\alpha]$ values were measured in dehyd. MeOH)

Catalytic Reduction of Anhydrocycloheximide (III) : Dihydrodeoxycycloheximides (IV and V)—Anhydrocycloheximide (3 g.) was reduced at atmospheric pressure in 60 cc. of glacial AcOH using 850 mg. of PtO_2 as a catalyst. Reduction was completed after 2 moles of H_2 had been absorbed (about 0.5 hr.). The solution was filtered and AcOH was removed *in vacuo*. Water was added to the residue, which solidified. A crude hydrogenated product, m.p. 120.5~121.5°, was obtained (yield, 85%). The crude product was dissolved in 25 volumes of warm ether and kept in a refrigerator over night. A small amount of crystals (m.p. 127~128°) crystallized out, which was removed, the ethereal solution was evaporated slowly, and the residual concentrate was kept in a refrigerator again. The same crystals as above crystallized out. By repeating the above procedure, crystals melting at 127~128° were collected and were recrystallized from ether to pure dihydrodeoxycycloheximide (IV), as colorless prisms, m.p. 130~131°; $[\alpha]_{366.4}^{21}$ +3.5°(c=0.2). *Anal.* Calcd. for $C_{15}H_{25}O_3N$: C, 67.42; H, 9.36; N, 5.24. Found : C, 67.55; H, 9.12; N, 5.27.

From the final ethereal mother liquor, crystals melting at 113~115° were obtained. These were recrystallized from ether to pure dihydrodeoxycycloheximide (V) as colorless prisms, m.p. 117~118°; $[\alpha]_{366.4}^{21}$ +80.2°(c=0.2). Analytical data were also in accord with dihydrodeoxycycloheximide. *Anal.* Found : C, 67.41; H, 9.41; N, 5.59.

From the ethereal mother liquor used for the recrystallization of (IV) and (V), a mixture of (IV) and (V) (m.p. 121~123°) was obtained. The formation ratio of (IV), (V), and their mixture was 1:16:3.

Oxidation of Dihydrodeoxycycloheximides (IV and V) : Deoxycycloheximides (VI and VII)—To a solution of 65 mg. of dihydrodeoxycycloheximide (IV) (m.p. 130~131°) dissolved in 1.7 cc. of glacial AcOH, a solution of 20 mg. of CrO_3 in 0.25 cc. of water was added, the reaction mixture was warmed for a few minutes on a steam bath and allowed to stand at room temperature for 2 hr. The solvent was then removed *in vacuo*, water was added to the residue, and the product was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. Ether was added to the residual syrup and 32 mg. of crude deoxycycloheximide (VI) melting at 122~123° was obtained. The crude product was recrystallized from benzene-hexane mixture to colorless prisms, m.p. 123~124°. *Anal.* Calcd. for $C_{15}H_{23}O_3N$: C, 67.92; H, 8.68; N, 5.28. Found : C, 67.78; H, 8.57; N, 5.49.

Treatment of (VI) with $NH_2OH \cdot HCl$ and anhyd. AcONa gave the oxime, m.p. 137~137.5°, as recrystallized from 50% MeOH.

By a similar procedure, dihydrodeoxycycloheximide (V) gave deoxycycloheximide (VII) (yield, 50%). The crude product was recrystallized from benzene-hexane mixture to colorless fine prisms, m.p. 109.5~110.5°. This oxidized product agreed with deoxycycloheximide derived by partial reduction of anhydrocycloheximide as will be described in the following section. The oxime of (VII) melted at 148.5~149.5° (from 50% MeOH) and also agreed with the oxime mentioned below.

Partial Reduction of Anhydrocycloheximide : Deoxycycloheximide (VII)—Anhydrocycloheximide (830 mg.) was reduced at atmospheric pressure in 30 cc. of EtOH and 6 cc. of benzene, using 500 mg. of 2% Pd-$SrCO_3$ catalyst. Reduction was completed after 1.06 moles of H_2 had been absorbed (about 30 min.). The solution was filtered, the solvent was removed *in vacuo*, and the residue was treated with dehyd. ether. 740 mg. of the crude deoxycycloheximide (VII) (m.p. 103.5~105°) so obtained (yield, 89%) was recrystallized twice from ether to colorless small prisms, m.p. 109.5~110.5°; $[\alpha]_D^{29}$ +1.2 (c=1.0). *Anal.* Calcd. for $C_{15}H_{23}O_3N$: C, 67.92; H, 8.68; N, 5.28. Found : C, 67.86; H, 8.62; N, 5.49. Other isomers were not detected in the ethereal mother liquor.

Pure deoxycycloheximide (VII) (133 mg.) was dissolved in a small amount of MeOH and aqueous solution of 35 mg. of $NH_2OH \cdot HCl$ and 41 mg. of anhyd. AcONa was added. After being warmed for a few minutes, the mixture was allowed to stand in a refrigerator overnight, the white precipitate was collected, and recrystallized from 50% MeOH to 96 mg. of pure oxime, m.p. 148.5~149.5°. *Anal.* Calcd. for $C_{15}H_{24}O_3N_2$: C, 64.29; H, 8.57; N, 10.00. Found : C, 64.66; H, 8.79; N, 10.15.

Reduction of Deoxycycloheximide (VII) with $LiAlH(\textit{tert}\text{-}BuO)_3$ and Reoxidation of the Hydrogenated Product (VIII)—To a solution of $LiAlH_4$ (20 mg.) dissolved in 3 cc. of dehyd. tetrahydrofuran, 120 mg. of *tert*-BuOH was added dropwise at room temperature (25°) and the mixture was stirred for 1 hr. to produce the solution of $LiAlH(\textit{tert}\text{-}BuO)_3$. A solution of 133 mg. of deoxycycloheximide (VII) dissolved in 6 cc. of dehyd. tetrahydrofuran was added dropwise into the above solution under ice cooling (−5° to 0°). The mixture was stirred for 1 hr. at 3~5° and a small amount of water was added to the mixture to decompose an excess of reducing agent. The solution was slightly acidified with 20% AcOH and 6 cc. ether was added. Inorganic substance was filtered off and the filtrate, was concentrated *in vacuo*. Ether-hexane was added to the residual syrup and 107 mg. of crude dihydrodeoxycycloheximide (VIII) was recrystallized twice from benzene-hexane mixture to 86 mg. of pure crystals. Colorless prisms, m.p. 103~104°; $[\alpha]_{366.4}^{21}$ +43.2°(c=0.2). *Anal.* calcd. for $C_{15}H_{25}O_3N$: C, 67.42; H, 9.36; N, 5.24. Found: C, 67.39; H, 9.16; N, 5.64.

This dihydrodeoxycycloheximide (VIII) is an isomer of the above-mentioned (IV) and (V). Other isomers were not isolated from this crystal nor from the mother liquor.

Oxidation of (VIII) with CrO_3 in a similar manner as above gave colorless prisms, m.p. 109~110° (from ether). This product agreed with the starting deoxycycloheximide (VII), no m.p. depression being observed on admixture. The oximes of both deoxycycloheximides were also in accord with each other.

Catalytic Reduction of Deoxycycloheximide (VII)—400 mg. of deoxycycloheximide (VII) was reduced at atmospheric pressure in 8 cc. of glacial AcOH using 100 mg. of PtO_2 as a catalyst. By treating the solution as described above, 370 mg. of hydrogenated product was obtained. By fractional recrystallization of the product from ether, crystals melting at 127~129° and 123~124° were obtained in a ratio of 1:5. The former showed no melting point depression on admixture with (IV). The latter was not successfully purified further, but this seemed to be a mixture of dihydrodeoxycycloheximides, (IV), and (V).

R. D. Curves of Deoxycycloheximides (VI and VII)—R. D. curve of deoxycycloheximide (VII) was measured by Prof. C. Djerassi of the Wayne State University, U. S. A. R. D. in MeOH (c=0.0765): $[\alpha]_{700}^{29}$ ca. 0°, $[\alpha]_{589}$ +8°, $[\alpha]_{400}$ +13°, $[\alpha]_{350}$ +43°, $[\alpha]_{330}$ +42°, $[\alpha]_{315\sim310}$ +98°(peak), $[\alpha]_{295}$ −54°, $[\alpha]_{280}$ −216°.

Full chart of R. D. curve of deoxycycloheximide (VI) was not obtained because of its insolubility in MeOH and of its low solubility in dioxane, but dextrorotatory value of this compound tended to increase toward a shorter wave length.

R. D. Curve of Anhydrocycloheximide (III)—R. D. in MeOH (c=0.0575): $[\alpha]_{700}^{30}$ −100°, $[\alpha]_{589}$ −80°, $[\alpha]_{500}$ −100°, $[\alpha]_{400}$ −175°, $[\alpha]_{375}$ −310°, $[\alpha]_{351}$ −435°(trough), $[\alpha]_{333}$ −175°, $[\alpha]_{315}$ +570°, $[\alpha]_{312.5}$ +760°, $[\alpha]_{305}$ +780°, $[\alpha]_{300}$ +925°, $[\alpha]_{295}$ +1120°(peak), $[\alpha]_{292.5}$ +910°(trough), $[\alpha]_{280}$ +1160°.

Summary

Deoxycycloheximide (VII), obtained as the main product of catalytic reduction of anhydrocycloheximide, was thought to have $2e,4e,6e$-conformation and exhibited a single positive Cotton-effect curve. This fact verifies the correctness of the author's consideration for elucidation of the R. D. curves of Naramycins.

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