The authors express their deep gratitude to Prof. T. Reichstein of the Organisch-chemische Anstalt der Universität Basel for his supply of valuble samples, and to Prof. K. Meyer of the Pharmazeutische Anstalt der Universität Basel for his donation of precious specimens and his favor for information on his recent investigation before publication. They are grateful to Dr. K. Takeda, Director of this Laboratory, for his unfailing guidance. They are also indebted to Dr. Y. Nozaki for his help in microbiological work, to the members of the Analysis Room for elemental analytical data, and to the members of the Section of Physical Chemistry for measurements of optical rotation, and ultraviolet and infrared spectra.

Summary

Fissions of 14α,15α-epoxy ring in a cardenolide with perchloric acid and with hydrogen chloride were found to afford 14β-steroids. With the use of these reactions, some D-ring-transformed compounds of digitoxigenin, e.g. 15α-hydroxydigitoxigenin, and 14-chloro-3β,15α-dihydroxy- and-3β-hydroxy-14β,15β-epoxy-cardenolides, were synthesized.

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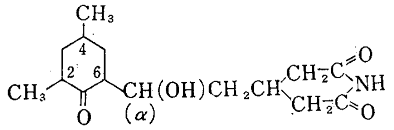
102. Makoto Suzuki, Yoshiyuki Egawa, and Tomoharu Okuda :

Studies on Streptomyces Antibiotic, Cycloheximide. XV.[1] Hydroxycarbonylation of Optically Active 2,4-Dimethylcyclohexanones with Glutarimide-β-acetaldehyde. (Synthesis of Isocycloheximide and its Isomers.)[*1]

(*Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.*[*2])

It is a recent tendency in an antibiotic field to synthesize a compound of the proposed structure of an antibiotic to confirm its molecular architecture and to find a key to elucidate the structure and activity relationships. However, notwithstanding the fact that the plane structure of cycloheximide had been proposed as (1) by Kornfeld, *et al.*[2] in 1949, papers concerning the synthesis had not been published until Phillips, *et al.*[3] suggested the way to synthesize this antibiotic by aldol condensation of 2,4-dimethylcyclohexanone with glutarimide-β-acetaldehyde in 1959. Soon later, Lawes[4] tried the condensation of 6-formyl-2,4-dimethylcyclohexanone with glutarimide-β-acetaldehyde and obtained successfully anhydrocycloheximide identical with the dehydration product



(1)

[*1] Presented before the 81st Annual Meeting of the Pharmaceutical Society of Japan (July 20, 1961). Preliminary Note : T. Okuda, M. Suzuki, Y. Egawa : J. Antibiotics, **14A**, 158 (1961).

[*2] Toda-machi, Kitaadachi-gun, Saitama-ken (鈴木真言, 頴川吉之, 奥田朝晴).

1) Part XIV : T. Okuda, M. Suzuki, Y. Egawa : Yakugaku Kenkyu, **33**, 530 (1961).

2) E.C. Kornfeld, J.H. Ford, A.J. Whiffen : J. Am. Chem. Soc., **71**, 150 (1949).

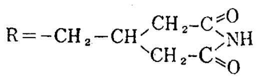
3) D.D. Phillips, M.A. Acitelli, J. Meinwald : *Ibid.*, **79**, 3513 (1959).

4) B.C. Lawes : *Ibid.*, **82**, 6413 (1960).

derived from cycloheximide. Although it was to be attributed to Lawes that the structure proposed to cycloheximide was confirmed synthetically, total synthesis of cycloheximide remained unachieved.

The present paper concerns the hydroxycabonylation of optically active (2R:4R)- and (2S:4R)-2,4-dimethylcyclohexanones with glutarimide-β-acetaldehyde and refers to the configuration of one of the products named as *α-epi*-isocycloheximide. Synthesis of cycloheximide analogous compounds and an improved synthesis of starting glutarimide-β-acetaldehyde will be reported in the next paper.5)

Model experiments6) suggested that optically active 2,4-dimethylcyclohexanone might condense with glutarimide-β-acetaldehyde with the aid of N-methylanilinomagnesium bromide to afford cycloheximide itself or its stereoisomers. Thus, the condensation of (2R:4R)-2,4-dimethylcyclohexanone or (2S:4R)-isomer with glutarimide-β-acetaldehyde was carried out in tetrahydrofuran-benzene mixture. After the repeated trials using (2R:4R)-2,4-dimethylcyclohexanone,7,8) an alkaline degradation product of cycloheximide, I, II, V, and VI illustrated in Table I were obtained as a mixture, which was separated into each of isomers by means of acid-treated alumina and silicic acid chromatography. The ratio and the yield of the products varied in each of trials. According to the resorcinol color reaction9) which is characteristic to cycloheximide and its stereoisomers, the condensation products illustrated in Table I were classified into two types, *normal*-type showing positive color reaction as cycloheximide and *gem*-type exhibiting negative one. This characterization shows that a product of *normal*-type has the same plane structure as cycloheximide, whereas that of *gem*-type has 2,2-disubstituents in the molecule.



$$\mathrm{R=-CH_2-CH}\left\langle\begin{matrix}\mathrm{CH_2-C{=}O}\\ \mathrm{CH_2-C{=}O}\end{matrix}\right\rangle\mathrm{NH}$$

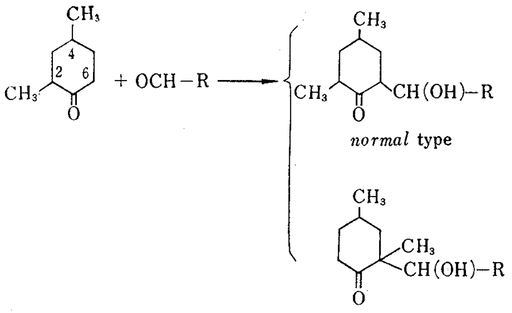


Chart 1.

Condensation at 6-position of the 2,4-dimethylcyclohexanone gives *normal*-type products and that at 2-position affords *gem*-type as shown in Chart 1. I and II belong to *normal*-type, while V and VI to *gem*-type.

Among the products listed in Table I, I and II gave the same dehydrated compound on dehydration with phosphorus pentoxide in benzene. This dehydrated compound was identical with that derived from cycloheximide. I and its acetate (I-Ac) were found to be identical with isocycloheximide and its acetate respectively, because

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5) Part XVI. Y. Egawa, M. Suzuki, T. Okuda: This Bulletin, **11**, 589 (1963).
6) M. Suzuki: *Ibid.*, 8, 706 (1960).
7) E. J. Eisenbraun, J. Osiecki, C. Djerassi: J. Am. Chem. Soc., **80**, 1261 (1958).
8) J. Osiecki: Dissertation Abstracts, **21** (5) Mic. 60-3824 (1960).
9) Part XIII. M. Takeshita, H. Takahashi, T. Okuda: This Bulletin, **10**, 304 (1962).

Table I. Physicochemical Properties of Synthetic Cycloheximide Isomers

Type	Product	Crystal form (m.p.[a]) (°C)	Analytical data[b] (Found)	Infrared spectra[c] (Nujol, cm^{-1})	RD curve[d] (c=0.1, MeOH) Sign of Cotton effect	RD curve[d] (c=0.1, MeOH) [α] at peak, mμ	Relative value of colorimetry[e] (%)
Normal-Type	I (Isocycloheximide)	Colorless prism (95~96)	C, 63.85 H, 8.22 N, 5.18	ν_{OH} : 3220 ν_{NH} : 3080 $\nu_{C=O}$: 1710, 1692	Positive	+349° at 317.5	96.0
	I-Acetate	〃 (167~167.5)	C, 63.03 H, 7.46 N, 4.31	ν_{NH} : 3179, 3071 $\nu_{C=O}$: 1729, 1709, 1694	〃	+177° at 322.5 and +178° at 307.5	96.0
	Ⅱ (*α-epi*-iso-Cycloheximide)	〃 (112~114)	C, 64.02 H, 8.25 N, 5.06	ν_{OH} : 3442 ν_{NH} : 3192, 3052w $\nu_{C=O}$: 1230sh, 1712, 1663	〃	+373° at 317.5	92.5
	Ⅱ-Acetate	〃 (177~178)	C, 62.66 H, 7.56 N, 4.41	ν_{NH} : 3259 $\nu_{C=O}$: 1735, 1700	〃	+139° at 315	95.0
	Ⅲ	〃 (106~107)	C, 63.95 H, 8.08 N, 5.26	ν_{OH} : 3470 ν_{NH} : 3215, 3100w $\nu_{C=O}$: 1718, 1702, 1688	〃	+122° at 317.5	86.6
	Ⅳ	〃 (168~170)	C, 63.87 H, 8.03 N, 5.02	ν_{OH} : 3420 ν_{NH} : 3200, 3065w $\nu_{C=O}$: 1722, 1710, 1678	Negative	−1980° at 312.5 (trough)	99.4
Gem-Type	Ⅴ	〃 (99~101)	C, 64.19 H, 8.08 N, 4.76	ν_{OH} : 3260 ν_{NH} : 3190sh, 3060w $\nu_{C=O}$: 1704, 1695sh	Positive	+1377° at 322.5	16.8
	Ⅴ-Acetate	〃 (166~166.5)	C, 62.99 H, 7.70 N, 4.46	ν_{NH} : 3270 $\nu_{C=O}$: 1731, 1715, 1701	〃	+1482° at 322.5	0.4
	Ⅵ	〃 (141~145)		ν_{OH} : 3470, 3380w ν_{NH} : 3190, 3080 $\nu_{C=O}$: 1738, 1695	〃	+697° at 320	10.2

a) Melting points were measured in H_2SO_4 bath and uncorrected.

b) *Anal.* calcd. for cycloheximides ($C_{15}H_{23}O_4N$) : C, 64.03; H, 8.24; N, 4.98.
Anal. calcd. for cycloheximide-acetates ($C_{17}H_{25}O_5N$) : C, 63.14; H, 7.79; N, 4.33.

c) Measured with JASCO IR-S Spectrometer (NaCl prism).

d) Zirconium lamp was used as a source of light.

e) The values listed were obtained from the following equation.[9]

$$100\times\frac{\text{Molar extinction coefficient shown by the sample}}{\text{Molar extinction coefficient shown by pure cycloheximide (naramycin-A)}}\ (\text{at } 400\ \text{m}\mu)$$

the infrared spectra of the formers were perfectly identical with those of the latters (Fig. 1), and the formers showed the similar type of optical rotatory dispersion curve (positive Cotton curve) as the latters. The amplitude shown by I in its optical rotatory dispersion curve was slightly different from that of isocycloheximide due to the difference of minor contaminant(s) coexisted, but the optical rotatory dispersion curve shown by acetate (I-Ac) was similar to that of isocycloheximide acetate,[*3] as shown in Fig. 2.

The another isomer (Ⅱ) was deduced to be C^{α}-epimer of isocycloheximide according to the following reasons and named as *α-epi*-isocycloheximide.

[*3] After the paper (part Ⅶ[10]) had been published, it was found that iso-cycloheximide acetate showed the positive Cotton curve with the double peaks, when the optical rotatory dispersion curve was measured using Zirconium lamp as a light source. On the other hand, isocycloheximide, Naramycin-B and Naramycin-B acetate showed the same optical rotatory dispersion curve (the positive Cotton curve with a single peak) as described in Part Ⅶ.

10) Part Ⅶ. T. Okuda, M. Suzuki, Y. Egawa : This Bulletin, 8, 335 (1960).

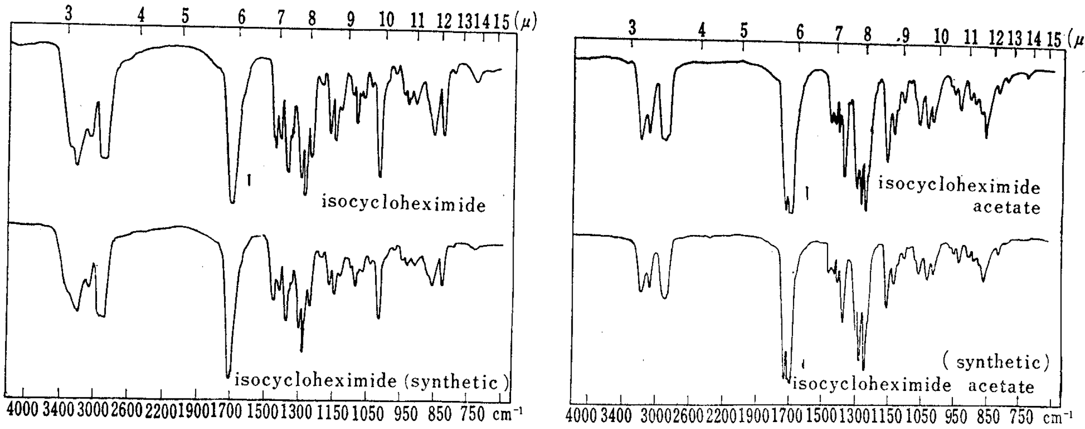

Fig. 1. IR Spectra of Synthetic and Natural Isocycloheximides and their Acetates

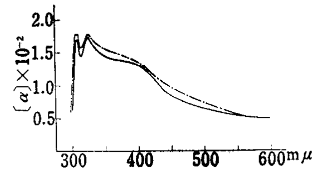

Fig. 2. Optical Rotatory Dispersion Curve of Synthetic and Natural Isocycloheximide Acetate

——— : Natural isocycloheximide acetate

- - - - : Synthetic isocycloheximide acetate

1) As described in Part XVIII,[11] II was recovered intact in its isomerization study using sodium methoxide as an isomerizing agent, as I was. This finding shows that II has the conformation as stable as I.

2) In the infrared spectra in Nujol mull, II showed the stretching-vibration band of hydroxyl group at 3442 cm^{-1} (Fig. 3), and in diluted solution at 3490~3500 cm^{-1}.

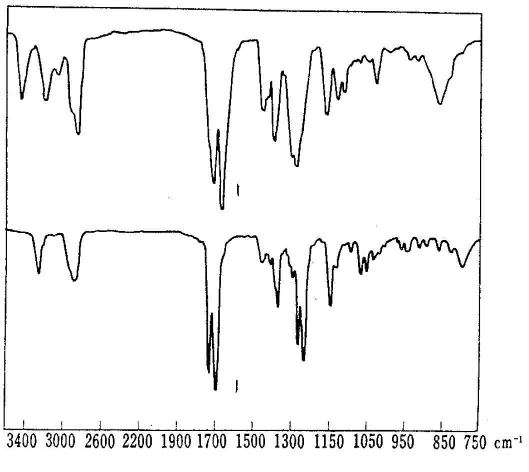

Fig. 3. IR Spectra of α-*epi*-Isocycloheximide and its Acetate

Upper : α-*epi*-Isocycloheximide

Lower : α-*epi*-Isocycloheximide acetate

These absorption bands are ascribed to the intramolecular hydrogen bonded hydroxyl group. This phenomenon suggests that the long substituent at C^6 existing in II orients equatorially to the cyclohexanone ring and the spatial relationship between hydroxyl group and carbonyl function is *cis*-like, according to the previous discussion[12] and this spatial relation is similar to that of cycloheximide but opposit to those of isocycloheximide and Naramycin-B.

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[11] Part XVIII : Preliminary Note, T. Okuda, M. Suzuki; The Bulletin, **10**, 639 (1962).

[12] Part VI. T. Okuda : *Ibid.*, **7**, 671 (1959).

3) The fact that the sign of Cotton effect shown by II is positive suggests that II has (4:6)-*cis* configuration based upon a previous consideration.[13)] *4 Moreover, when II was derived to its acetate, the definite amplitude reduction was observed in their optical rotatory dispersion curves as shown in Fig. 4. This characteristic is opposite to those observed in other stereoisomers and suggests that the configuration of II at its C^{α}-position where hydroxyl group attached is opposite to those of cycloheximide, Naramycin-B and isocycloheximide.

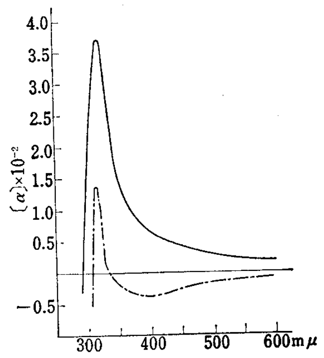
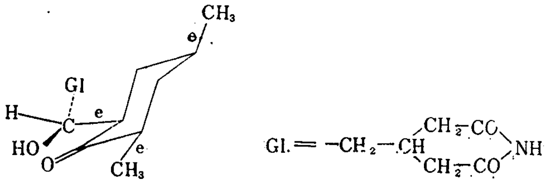


Fig. 4. Optical Rotatory Dispersion Curve of α-*epi*-Isocycloheximide and its Acetate

——— : α-*epi*-Isocycloheximide

—·—·— : α-*epi*-Isocycloheximide acetate

The above mentioned considerations led to the conclusion that II has the (2R:4S:6R:αR)-configuration depicted as (2) which only does explain consistently all of the findings observed on II.



α-*epi*-isocycloheximide (2)

Hydroxycarbonylation of (2S:4R)-2,4-dimethylcyclohexanone, a thermal degradation product of cycloheximide,[15)] with glutarimide-β-acetaldehyde gave α-*epi*-isocycloheximide of 2:4:6-(*cis, cis*) configuration as a main product. This phenomenon was well explained by the fact that cycloheximide was not isomerized under the Nielsen's reaction condition, whereas (2S:4R)-2,4-dimethylcyclohexanone was epimerized into (2R:4R)-isomer during the reaction, particularly in the course of preparing carbanion ion complex with N-methylanilinomagnesium bromide. Because, actually when the reaction was discontinued after carbanion formation, (2R:4R)-2,4-dimethylcyclohexanone was recovered in 66～80% yield.

Besides α-*epi*-isocycloheximide, small amounts of other two isomers (III and IV) were obtained from the reaction mixture, though isocycloheximide or *gem*-type of isomers was not isolated. III (m.p. 106～107°) and IV (m.p. 168～170°) had the same plane structure as cycloheximide and seemed to have 4:6-*cis* and -*trans* configuration respectively, because III showed the positive Cotton curve and IV did the negative one.

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*4 The relationships between the sign of the Cotton effect shown by cycloheximides and the absolute configurations of asymmetric centers on cyclohexanone is well explained by adapting the Octant rule.[14)] (cf. Abstract Paper of the 6th Symposium on the Chemistry of Natural Products, p. 39 (1962)).

13) Part IV. T. Okuda: This Bulletin, **7**, 660 (1959).

14) C. Djerassi: "Optical Rotatory Dispersion" p. 178 (McGraw Hill Co. 1960).

15) B.C. Lawes: J. Am. Chem. Soc., **84**, 239 (1962).

Experimental

(2R:4R)-2,4-Dimethylcyclohexanone——This *cis*-ketone was prepared by an alkaline degradation of cycloheximide according to the procedure reported by Kornfeld, *et al.*[2] and purified through its semicarbazone (m.p. 205°(decomp.)), b.p. 176～177°, $[\alpha]_D^{16}$ +10.8°(c=5, MeOH). Yield : 68～70 %.

(2S:4R)-2,4-Dimethylcyclohexanone——This *trans*-ketone was prepared by a thermal degradation of cycloheximide by the method of Lawes,[15] b.p. 177～178°, $[\alpha]_D^{22}$ +59.2°(c=5, MeOH), $[\alpha]_{312.5}^{22.6}$ +771° (peak). Semicarbazone, m.p. 171～172°, $[\alpha]_D^{23}$ +151° (c=1, Dimethylformamide). *Anal.* Calcd. for $C_9H_{17}ON_3$: C, 59.98; H, 9.35; N, 22.93. Found : C, 58.98; H, 8.97; N, 22.59.

Glutarimide-β-acetaldehyde——This aldehyde was prepared from diethyl β-oxoglutarate and cyanoacetic acid *via* 5 steps (Over-all yield : 53.7 %). The details will be reported in the succeeding paper.[5]

Modified Nielsen's Condensation of (2R:4R)-2,4-Dimethylcyclohexanone with Glutarimide-β-acetaldehyde. : Preparation of I, II, V and VI——1) To the solution of N-methylanilinomagnesium bromide in Et_2O-benzene mixture[6] (prepared from 4.0 g. (36.4 m*M*) of EtBr, 0.8 g. (33.0 m*M*) of Mg ribbon and 3.26 g. (30.5 m*M*) of N-methylaniline) was added dropwise 6 cc. of benzene solution of 4.41 g. (35 m*M*) of (2R:4R)-2,4-dimethylcyclohexanone and the reaction mixture was kept at 25° for 30 min. To the mixture, 1.86 g. (12.0 m*M*) of glutarimide-β-acetaldehyde dissolved in 60 cc. of dehyd. tetrahydrofuran was added at −15～−10° within 15 min. under continuous stirring and it was kept at −3±1° for 2.5 hr. After the decomposition of MgBr-complex with 7.5% HCl at −20°, the reaction mixture was extracted repeatedly with AcOEt and the AcOEt solution was washed with 7.5% HCl to remove N-methylaniline and basic by-products and with H_2O, dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to syrup, which was washed with hexane to remove excess of ketone and dried in desiccator. The product (3.51 g.) thus obtained was dissolved in benzene, poured onto a column filled with 80 g. of acid treated Al_2O_3 (pH 5.0) and chromatographed. For the development of the column, benzene and MeOH-benzene mixture were used successively. 1.25 g. of syrup recovered from 3% MeOH-benzene fraction was further purified chromatographically on SiO_2, using iso-Pr_2O containing 10～30% AcOEt as eluting solvent, and thus, 410 mg. of crude isocycloheximide (m.p. 90～92°; yield, 12.2 %) and 640 mg. of crude α-*epi*-isocycloheximide (m.p. 103～105°; yield, 20 %) were obtained. The former (I) was recrystallized from AcOEt-Et_2O to give colorless prisms, m.p. 112～114°.

The 5% MeOH-benzene fraction obtained from Al_2O_3 column was found to be the mixture of I, II and V after the SiO_2 chromatography, but each component was not separated successfully.

2) When the experiment was run with the same molecular ratio of the starting materials as example 1 but with the different reaction temperature (−3～−0°), the products were not always the same as those in example 1.

3.87 g. of caramel-like residue recovered from AcOEt extract of condensation reaction mixture was chromatographed over 80 g. of acid-treated Al_2O_3. The 3% MeOH-benzene fraction gave 1.37 g. of residue, from which 410 mg. (yield, 12.2 %) of *gem*-cycloheximide (V) of m.p. 99～101° was recovered by treating with Et_2O, and from the remaining liquor 280 mg. (yield, 8.4%) of α-*epi*-isocycloheximide (m.p. 110～111°), 520 mg. (yield, 15.6 %) of isocycloheximide (m.p. 93～95°) and *gem*-cycloheximide (V) were recovered with the aid of SiO_2 chromatography followed by recrystallization from AcOEt-Et_2O.

The 5% MeOH-benzene fraction obtained by the Al_2O_3 chromatography gave 600 mg. of residue, which was chromatographed on SiO_2 followed by recrystallization from AcOEt to give 310 mg. (yield, 9.3 %) of second *gem*-isomer (VI) of m.p. 141～145°.

The physicochemical properties of synthetic isocycloheximide, α-*epi*-isocycloheximide, *gem*-cycloheximides (V) and (VI) were illustrated in the Table I, together with those of acetates.

Identification of synthetic I with natural isocycloheximide was made by direct comparison of the product and also by deriving into derivatives (acetate, N-phenylmercuri-compound), with the aid of mixed m.p., IR, and ORD measurement. The physicochemical properties of derivatives were already reported.[16]

Condensation of (2S:4R)-2,4-Dimethylcyclohexanone with Glutarimide-β-acetaldehyde : Preparation of II, III and IV——Aldolization of (2S:4R)-2,4-dimethylcyclohexanone with glutarimide-β-acetaldehyde was carried out similarly as described in the example 1 of the foregoing experiment, using 4.41 g. (35.0 m*M*) of *trans*-ketone.

3.0 g. of caramel-like residue obtained from AcOEt extract of the reaction mixture was chromatographed over 80 g. of acid-treated Al_2O_3 (pH 5.0) and eluted with MeOH-benzene mixture. From the 1% MeOH-benzene fraction, 310 mg. (yield, 9.5 %) of anhydrocycloheximide (m.p. 134～136°) was recovered.

The residue obtained from the 30% MeOH-benzene fraction was further purified, chromatographically over SiO_2 followed by recrystallization from AcOEt-Et_2O mixture to give 720mg. (yield, 21.4 %)

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[16] Part XIV. T. Okuda, M. Suzuki, Y. Egawa, K. Kotera : Yakugaku Kenkyu, **33**, 530 (1961). cf. T. Okuda, M. Suzuki : *Ibid.*, **33**, 371 (1961).

of *α-epi*-isocycloheximide (Ⅱ) (m.p. 111-113°) and 80 mg. (yield, 2.4 %) of Ⅲ (m.p. 106-107°).

The residue obtained from 5% MeOH-benzene fraction in Al_2O_3 chromatography was purified as above and 60 mg. (yield, 1.8%) of Ⅳ (m.p. 168-170°) was obtained. Some of the physicochemical properties of Ⅲ and Ⅳ are illustrated in Table 1.

Ⅲ : IR ν_{max}^{Nujol} cm^{-1}: 3470, 3215, 3100w-sh, 1718 s-sh, 1702 s, 1688 s, 1403m, 1360m-sh, 1300, 1281, 1260m, 1238, 1177w, 1150, 1135m-sh, 1122w, 1105m, 1078, 1051w, 1030, 1012, 945, 935, 922, 835m, 825.

ORD in MeOH : $[\alpha]_{589}^{25}$ +2°, $[\alpha]_{400}$ +23°, $[\alpha]_{330}$ +80°, $[\alpha]_{317.5}$ +122°(peak), $[\alpha]_{312.5}$ +111°, $[\alpha]_{305}$ +63°, $[\alpha]_{300}$ −44°, $[\alpha]_{285}$ −111°. (c=0.1, MeOH, Xe)

Ⅳ : IR ν_{max}^{Nujol} cm^{-1}: 3420, 3200, 3065w-sh, 1722 s-sh, 1710 s, 1678 s, 1415w, 1350w, 1300, 1270 s, 1220, 1190w, 1175w, 1152w, 1132w, 1104w, 1080, 1062m, 1030m, 1010w, 1000w, 970, 955, 940, 925, 877m, 870m, 842m.

ORD in MeOH : $[\alpha]_{589}^{25}$ −79°, $[\alpha]_{400}$ −284°, $[\alpha]_{350}$ −600°, $[\alpha]_{330}$ −1100°, $[\alpha]_{317.5}$ −1822°, $[\alpha]_{312.5}$ −1980°(trough), $[\alpha]_{307.5}$ −1922°, $[\alpha]_{300}$ −1200°(c=0.1, MeOH, Xe).

Isomerization of (2S:4R)-2,4-Dimethylcyclohexanone under Nielsen's Reaction Condition——(2S:4R)-2,4-Dimethylcyclohexanone ($[\alpha]_D^{22}$ +59.2°) dissolved in 2 cc. of benzene was added dropwise to the ethereal benzene solution of N-methylanilinomagnesium bromide freshly prepared from 1.22 g. of EtBr, 0.245 g. of Mg ribbon and 1.0 g. of N-methylaniline, and the reaction mixture was kept at 23～25° for 30 min. with continuous stirring. It was then treated similarly as in the Nielsen's reaction, and final purification was made by distillation. The 2,4-dimethylcyclohexanone (b.p. 176～177°) thus recovered showed $[\alpha]_D^{22.8}$ +20.8° and $[\alpha]_{312.5}^{23.5}$ +175°(peak), this values indicating that the recovered ketone consists of 20～34 % of *trans*-(2S:4R)-ketone and 80～66 % of *cis*-(2R:4R)-ketone.

Isomerization Study of Cycloheximide under Nielsen's Reaction Condition——The solution prepared by dissolving 2.11 g. (7.5 m*M*) of cycloheximide in 20 cc. of dehyd. tetrahydrofuran was added dropwise at −15～−10° with stirring to the Et_2O-benzene solution of N-methylanilinomagnesium bromide freshly prepared from 2 g. (18.2 m*M*) of EtBr, 0.4 g. (16.5 m*M*) of Mg ribbon and 1.63 g. (15.3 m*M*) of N-methylaniline and it was kept at 0±1° for 2.5 hr. under continuous agitation.

The mixture was then treated similarly as in the Nielsen's reaction. AcOEt extract remained 84.6% of initial potency against *S. cerevisiae*. And the substance recovered from this solvent was purified with the aid of acid-treated Al_2O_3 chromatography followed by recrystallization from AcOPr(iso). The resulting crystal, m.p. 115～116°, was identified with cycloheximide by mixed melting point determination and IR and ORD determination.

The authors express their sincere gratitude to Emeritus Professor S. Sugasawa of Tokyo University for his interest and kind advices. They are also appreciative of the encouragement of Dr. K. Abe, the Superintendent of this laboratory, and grateful to Mrs. F. Hisamichi and her associates for their analytical helps.

Summary

Hydroxycarbonylation of optically active 2,4-dimethylcyclohexanone with glutarimide-β-acetaldehyde was carried out using N-methylanilinomagnesium bromide as a condensation agent, isocycloheximide, *α-epi*-isocycloheximide and other isomers of cycloheximide being obtained.

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