UDC 615.779.931-011

103. Yoshiyuki Egawa, Makoto Suzuki, and Tomoharu Okuda : Studies on Streptomyces Antibiotic, Cycloheximide. XVI.[1] Synthesis of Cycloheximide Analogous Compounds.*[1]

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

The previous paper[1] concerned the synthesis of isocycloheximide and other stereoisomers by the condensation of optically active 2,4-dimethylcyclohexanones with glutarimide-β-acetaldehyde. The present paper concerns the improved synthesis of glutarimide-β-acetaldehyde which is an indispensable starting material for synthetic studies, and also deals with the synthesis of cycloheximide analogous compounds by the hydroxycarbonylation of several ketones with glutarimide-β-acetaldehyde.

The synthesis of glutarimide-β-acetaldehyde was first reported by Phillips, *et al.*[2] starting from dimethyl glutaconate *via* trimethyl α-cyanomethanetriacetate, glutarimide-β-acetic acid and glutarimide-β-acetyl chloride (over-all yield: 6.6~14 %). This method had much to be improved, especially in the procedure of acidic hydrolysis of trimethyl α-cyanomethanetriacetate to glutarimide-β-acetic acid, because this procedure, as pointed out by the reporters, was hard to control and the yield varied from 26 to 55 %. Later, Lawes[3] tried to improve this procedure and obtained glutarimide-β-acetic acid with a fair yield starting from triethyl α-cyanomethanetriacetate *via* methanetriacetic acid followed by the pyrolysis of triammonium salt thereof.

After an effort to find out a profitable synthetic method, the authors succeeded to synthesize glutarimide-β-acetaldehyde with considerablly better yield (over-all yield : 53.7 %), according to the reaction sequence illustrated in Chart 1.*[3]

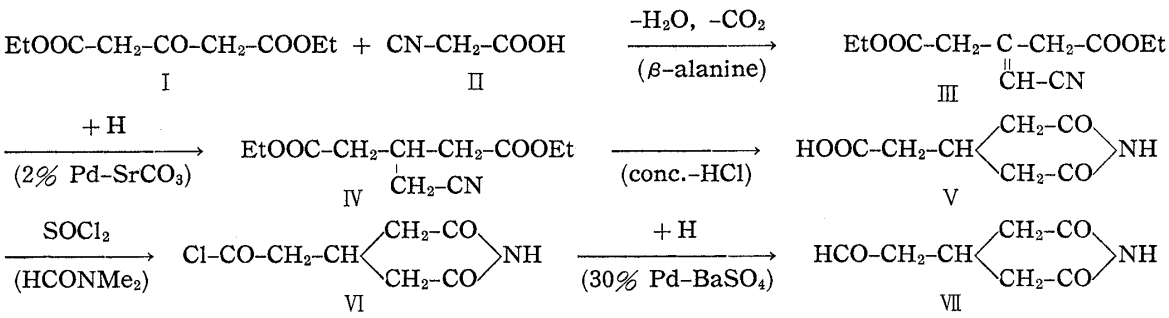


Chart 1.

Under the conditions of Cope condensation, diethyl β-oxo-glutarate (I) condensed with cyanoacetic acid (II) with the aid of β-alanine and glacial acetic acid in benzene. The resulting diethyl β-cyanomethyleneglutarate (III) was catalytically hydrogenated in ethanol using 2% palladium-strontium carbonate as a catalyst to give diethyl β-cyanomethylglutarate (IV). Treatment of IV with hot concentrated hydrochloric acid caused hydrolysis and cyclization to glutarimide-β-acetic acid (V). V was transformed to the corresponding acid chloride (VI) with thionyl chloride and then hydrogenated over 30%

*1 Presented before the 81st Annual Meeting of the Pharmaceutical Society of Japan, July 20, 1961.

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

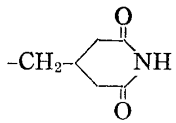
*3 Dr. F. Johnson of the Dow Chemical Co. has informed us (private communication) that his group has also used the similar route to ours to obtain V. (cf. F. Johnson : J. Org. Chem., **27**, 3658 (1962)).

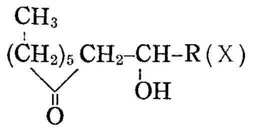
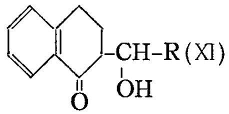
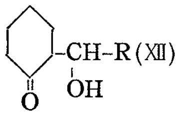
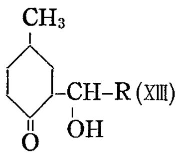
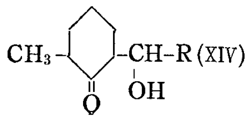
1) Part XV : This Bulletin, **11**, 582 (1960); Preliminary Note : T. Okuda, M. Suzuki, Y. Egawa : J. Antibiotics, **14A**, 158 (1961).

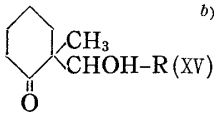
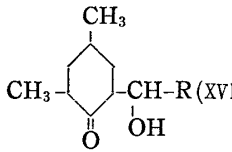
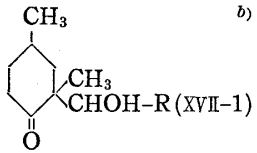
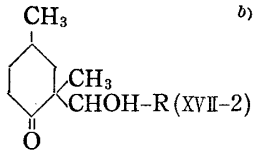
2) D.D. Phillips, M.A. Acitelli, J. Meinwald : J. Am. Chem. Soc., **79**, 3517 (1957).

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

Table I. Physicochemical Properties of Aldolization Products and their Derivatives

R = 

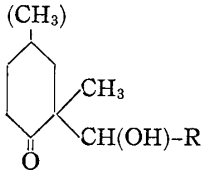
Compound	Formula	Crystal form	m.p. (°C)	Analysis Calcd.	Analysis Found	UV[a) mμ (ε)	IR ν_{max}^{Nujol} cm^{-1}
 (X)	$C_{15}H_{25}O_4N$	Colorless leafret	76～ 78	C, 63.60 H, 8.83 N, 4.95	C, 63.69 H, 9.00 N, 5.00	end	ν_{OH} : 3450 ν_{NH} : 3220, 3100 $\nu_{C=O}$: 1728, 1670
 (XI)	$C_{17}H_{19}O_4N$	Colorless prism	164～164.5	C, 67.77 H, 6.31 N, 4.65	C, 68.20 H, 6.36 N, 4.74	249 (7224)	ν_{OH} : 3530 ν_{NH} : 3220, 3120 $\nu_{C=O}$: 1715, 1700, 1675
Acetyl-XI	$C_{19}H_{21}O_5N \cdot \frac{1}{2}H_2O$	〃	165～167	C, 64.77 H, 6.25 N, 3.98	C, 64.14 H, 6.61 N, 3.57	—	ν_{NH} : 3160, 3060 $\nu_{C=O}$: 1735, 1703, 1680 ν_{C-O} : 1240
Anhydro-XI	$C_{17}H_{17}O_3N$	〃	130.5～132.5	C, 72.08 H, 6.01 N, 4.95	C, 72.19 H, 6.20 N, 4.79	270 (10188)	ν_{NH} : 3200, 3110 $\nu_{C=O}$: 1722sh, 1707, 1675 $\nu_{C=C(Conj)}$: 1618
 (XII)	$C_{13}H_{19}O_4N$	〃	84～ 86	C, 61.66 H, 7.51 N, 5.53	C, 61.69 H, 7.18 N, 5.57	end	ν_{OH} : 3490 ν_{NH} : 3195, 3090 $\nu_{C=O}$: 1726, 1700, 1690
Acetyl-XII	$C_{15}H_{21}O_5N$	〃	175.5～176.5	C, 61.02 H, 7.12 N, 4.75	C, 60.90 H, 6.77 N, 4.87	〃	ν_{NH} : 3195, 3090 $\nu_{C=O}$: 1732, 1701, 1680sh ν_{C-O} : 1234
Anhydro-XII	$C_{13}H_{17}O_3N$	〃	156～156.5	C, 66.38 H, 7.23 N, 5.96	C, 66.32 H, 7.12 N, 6.19	243 (11765)	ν_{NH} : 3200, 3100 $\nu_{C=O}$: 1725, 1690 $\nu_{C=C(Conj)}$: 1625
 (XIII)	$C_{14}H_{21}O_4N$	〃	143～144	C, 62.92 H, 7.87 N, 5.24	C, 62.63 H, 7.57 N, 5.32	end	ν_{OH} : 3495 ν_{NH} : 3230, 3100 $\nu_{C=O}$: 1725sh, 1710, 1695sh
Acetyl-XIII	$C_{16}H_{23}O_5N$	〃	150.5～151	C, 62.14 H, 7.44 N, 4.53	C, 61.84 H, 7.18 N, 4.62	〃	ν_{NH} : 3195, 3100 $\nu_{C=O}$: 1735, 1705sh, 1690 ν_{C-O} : 1237
Anhydro-XIII	$C_{14}H_{19}O_3N$	〃	111～113	C, 67.53 H, 7.69 N, 5.63	C, 67.27 H, 7.41 N, 5.72	244 (8090)	ν_{NH} : 3200, 3082 $\nu_{C=O}$: 1725, 1690 $\nu_{C=C(Conj)}$: 1622
 (XIV)	$C_{14}H_{21}O_4N$	〃	115～115.5	C, 62.92 H, 7.87 N, 5.24	C, 62.68 H, 7.80 N, 5.63	end	ν_{OH} : 3470 ν_{NH} : 3190, 3080 $\nu_{C=O}$: 1720sh, 1708, 1690

Acetyl-XIV	$C_{16}H_{23}O_5N$	〃	151～152	C, 62.14 H, 7.44 N, 4.53	C, 62.39 H, 7.03 N, 4.72	〃	ν_{NH} : 3240, 3090 $\nu_{C=O}$: 1728, 1705, 1690sh ν_{C-O} : 1255
Anhydro-XIV	$C_{14}H_{19}O_3N$	〃	137～139	C, 67.53 H, 7.69 N, 5.63	C, 67.41 H, 7.39 N, 5.51	240 (7542)	ν_{NH} : 3190, 3085 $\nu_{C=O}$: 1720sh, 1700, 1685 $\nu_{C=C(Conj)}$: 1622
 *b)*	$C_{14}H_{21}O_4N$	〃	140～142	C, 62.92 H, 7.87 N, 5.24	C, 62.82 H, 7.66 N, 5.46	end	ν_{OH} : near 3300 ν_{NH} : 3195, 3070 $\nu_{C=O}$: 1715sh, 1705, 1690
Acetyl-XV	$C_{16}H_{23}O_5N$	〃	214～216	C, 62.14 H, 7.44 N, 4.53	C, 61.94 H, 7.21 N, 4.91	〃	ν_{NH} : 3180, 3090 $\nu_{C=O}$: 1733, 1708, 1685sh ν_{C-O} : 1245
 *c)* (*rac*-Isocycloheximide)	$C_{15}H_{23}O_4N$	Syrupy	—	C, 64.03 H, 8.24 N, 4.98	—	〃	ν_{OH} : 3484 ν_{NH} : 3333 $\nu_{C=O}$: 1709, 1698
Acetyl-XVI	$C_{17}H_{25}O_5N \cdot \frac{1}{2}H_2O$	Colorless prism	134～135	C, 61.45 H, 7.83 N, 4.22	C, 61.88 H, 7.42 N, 4.07	〃	ν_{NH} : 3180, 3085 $\nu_{C=O}$: 1729, 1712, 1695 ν_{C-O} : 1240
Anhydro-XVI	$C_{15}H_{21}O_3N$	〃	114～115	C, 68.41 H, 8.04 N, 5.32	C, 68.08 H, 7.58 N, 5.27	240 (6524)	ν_{NH} : 3185, 3068 $\nu_{C=O}$: 1720, 1705, 1680 $\nu_{C=C(Conj)}$: 1621
 *b)*	$C_{15}H_{23}O_4N$	〃	70～ 73	C, 64.03 H, 8.24 N, 4.98	C, 63.68 H, 8.56 N, 4.58	end	ν_{OH} : 3482 ν_{NH} : 3238, 3120 $\nu_{C=O}$: 1732sh, 1711, 1685
Acetyl-XVII-1	$C_{17}H_{25}O_5N$	〃	174～175	C, 63.14 H, 7.79 N, 4.33	C, 63.53 H, 7.50 N, 4.28	〃	ν_{NH} : 3210, 3080 $\nu_{C=O}$: 1733, 1700sh, 1690 ν_{C-O} : 1230
 *b)*	$C_{15}H_{21}O_4N$	〃	126～128	C, 64.03 H, 8.24 N, 4.98	C, 63.80 H, 7.84 N, 4.72	〃	ν_{OH} : 3430 ν_{NH} : 3210, 3070 $\nu_{C=O}$: 1728, 1708, 1695
Acetyl-XVII-2	$C_{17}H_{25}O_5N$	〃	200～202	C, 63.14 H, 7.79 N, 4.33	C, 62.88 H, 8.01 N, 4.22	〃	ν_{NH} : 3255 $\nu_{C=O}$: 1735, 1705 ν_{C-O} : 1260

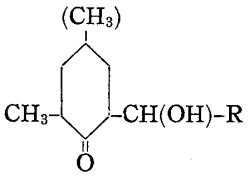
a) K-Band was only illustrated here.
b) The corresponding anhydro-compound was not obtained by dehydration with P_2O_5 in benzene.
c) IR spectrum was measured in $CHCl_3$ solution.

palladium-barium sulfate to give the desired glutarimide-β-acetaldehyde (Ⅶ). The yields of last two steps were much increased by using dimethylformamide as a catalyst in chlorination step and by applying dioxane-xylene mixture as a solvent in hydrogenation procedure. Melting points of Ⅴ, Ⅵ, and Ⅶ (176~176.5°, 138.5~139°, and 124.5~125° respectively) were higher than those reported respectively.

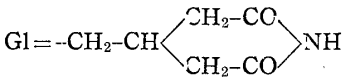
Cycloheximide analogous compounds were successfully synthesized by condensing aliphatic or alicyclic ketones with glutarimide-β-acetaldehyde (Ⅶ) with the aid of N-methylanilinomagnesium bromide. The products and their physicochemical properties are summarized in Table I. As experienced in the condensation of an optically active 2,4-dimethylcyclohexanone with Ⅶ,[1] the product obtained by the condensation of *dl*-2-methylcyclohexanone with Ⅶ consisted of two types of isomers. The one, which was classified as *gem*-type (Ⅷ), showed negative resorcinol color reaction,[4] while the other (*normal*-type : Ⅸ) did positive one. The situation was quite the same as the products obtained from *dl*-2,4-dimethylcyclohexanone. In this case the only isomer belonging to *normal*-type resisted to solidify, but on acetylation gave a corresponding acetate, whose infrared spectrum was identical with that of isocycloheximide acetate (Fig. 1). Thus, this acetate was identified with *rac*-isocycloheximide acetate. Contrary to the expectation, however, most of the condensation products showed no or only weak biological activities against *Saccharomyces cerevisiae.*



Gem-type
Ⅷ



Normal-type
Ⅸ



Experimental*4

Diethyl β-Cyanomethyleneglutarate (III)——A solution of 50 g. of diethyl β-oxoglutarate, 23.3 g. of cyanoacetic acid, 1.74 g. of β-alanine and 7.5 cc. of glac. AcOH in 50 cc. of dehyd. benzene was refluxed in an oil bath at 140~150° and H_2O liberated during the reaction was removed out of reaction mixture continuously. 0.75 g. of β-alanine and 2.5 cc. of glac. AcOH was added about 11 hr. later. Thus, the reaction mixture was kept on boiling for 18 hr., during which about 6 cc. of H_2O was liberated. After being cooled, 50 cc. of benzene was added to the reaction mixture and it was washed with H_2O, 5% $NaHCO_3$ aq. solution and H_2O successively, separated from lower layer, and dried over anhyd. Na_2SO_4. The solvent was removed and the remaining substance was distilled *in vacuo.* Thus, 41.8 g. of diethyl β-cyanomethyleneglutarate ($b.p_1$ 120~126°) was obtained, which was redistilled to give 40 g. of pure substance ($b.p_3$ 145°) (Yield : 75%). *Anal.* Calcd. for $C_{11}H_{15}O_4N$: N, 6.22. Found : N, 5.95.

Diethyl β-Cyanomethylglutarate (IV)——Catalytic hydrogenation of 40 g. of Ⅲ dissolved in 320 cc. of EtOH was carried out under atmospheric pressure using 4 g. of 2% Pd-$SrCO_3$ as a catalyst. After the absorption of H_2 gas ceased (about 50 min.), the solution was filtered and concentrated *in vacuo.* The remaining syrup was distilled under reduced pressure to give 39 g. of diethyl β-cyanomethylglutarate (b.p. 145°) (Yield : 96.6%). *Anal.* Calcd. for $C_{11}H_{17}O_4N$: N, 6.17. Found : N, 6.33.

Glutarimide-β-acetic Acid (V)——A solution of 20 g. of Ⅳ dissolved in 80 cc. of conc. HCl was heated on a water bath for 45 min. (bath temp. 85~90°). After cool, 40 cc. of H_2O was added to the reaction mixture and it was concentrated *in vacuo* at a temperature as low as possible. The remaining colorless syrup turned to white solid on treatment with 60 cc. of Me_2CO. The solid was collected and Me_2CO

*4 Melting points were corrected and determined using H_2SO_4 bath unless otherwise noticed. IR spectra were measured by JASCO IR-S double beam spectrometer equipped with a rock-salt prism. The physicochemical properties of the condensation products and their derivatives were illustrated in Table I.

4) Part XIII : M. Takeshita, H. Takahashi, T. Okuda : This Bulletin, **10**, 304 (1962).

solution, from which crude product was removed, gave further crops of solid product on concentration followed by refrigeration. Solid product was combined and extracted with hot Me_2CO to remove insoluble NH_4Cl. On evaporation of the extract, 10.7 g. of glutarimide-β-acetic acid crystallized out as colorless prisms, m.p. 173~174°. Syrupy substance obtained by the evaporation of Me_2CO mother liquor was hydrolyzed again with conc. HCl and treated as above. Thus, further 1.6 g. of crude V was obtained, which gave 1.4 g. of pure substance (m.p. 176~176.5°) on recrystallization from Me_2CO. Total yield of glutarimide-β-acetic acid, was 80.2 % of the theory. *Anal.* Calcd. for $C_7H_9O_4N$: C, 49.12, H, 5.30, N, 8.18. Found : C, 49.28; H, 5.24; N, 8.01. IR ν_{max}^{Nujol} cm^{-1} : ν_{NH} 3255, ν_{OH} near 3100, $\nu_{C=O}$ 1726, 1678.

Glutarimide-β-acetyl Chloride (VI)——Ten grams of V was mixed with 12 cc. of $SOCl_2$ and heated in an oil bath kept at 100° for 15 min. After being cooled to room temp., 3 drops of dimethylformamide was added to the reaction mixture and it was refluxed for 15 min. in an oil bath at 125~130°, during which vigorous evolution of HCl and SO_2 gas was observed and the solution turned to black. On chilling, VI crystallized out, which was collected after 30 min., washed with ice-cooled benzene followed with 50% Me_2CO-benzene mixture and dried in desiccator. Thus, 10.1 g. of colorless chloride, mp. 138.5~139° was obtained. (Yield, 91 %). *Anal.* Calcd. for $C_7H_8O_3NCl$: C, 44.34; H, 4.25; N, 7.39; Cl, 18.73. Found : C, 44.40; H, 4.03; N, 7.57; Cl, 18.97. IR ν_{max}^{Nujol} cm^{-1} : ν_{NH} 3192, 3110, $\nu_{C=O}$ 1816, 1697.

Glutarimide-β-acetaldehyde (VII)——Ten grams of VI was dissolved in 50 cc. of dehyd. dioxane, added with 50 cc. of dehyd. xylene and 0.5 g. of 30% Pd-$BaSO_4$, and saturated with H_2 gas. The reaction mixture was refluxed in an oil bath kept at 120~130° with continuous introduction of H_2 gas, and HCl gas evolved was passed into a vessel containing aq. solution of equimolecular NaOH added with Congo-red as an indicator. When the color of the NaOH solution turned from red to blue (about 50 min. later), the reaction mixture was ceased to heat, freed from the catalyst by filteration using glass filter precoated with cellite, and, while hot, concentrated *in vacuo* to about 30 cc. during which colorless crystals deposited. After chilled in refrigerator, crystals were collected and dried in a desiccator. Thus, 7.9 g. of glutarimide-β-acetaldehyde (VII), m.p. 124.5~125° was obtained. From the mother liquor, further 0.3 g. of VII was obtained on concentration. (Yield, 8.2 g., 99.5 % of the theory). This aldehyde was used in following aldol condensation reaction without recrystallization. *Anal.* Calcd. for $C_7H_9O_3N$: C, 54.19; H, 5.84; N, 9.03. Found : C, 54.26; H, 5.95; N, 8.95. IR ν_{max}^{Nujol} cm^{-1} : ν_{NH} 3195, 3090, $\nu_{CH(aldehyde)}$ 2740, $\nu_{C=O}$ 1720, 1685.

Hydroxycarbonylation of Ketones with Glutarimide-β-acetaldehyde : General Procedures——Aldol condensation of several ketones with glutarimide-β-acetaldehyde was carried out with the aid of N-methylanilinomagnesium bromide according to the method developed by Nielsen, *et al.*[5] with some modification as reported in Part VIII[6] and in previous part.[1] The general procedure adopted was as follows. To 2 cc. of an Et_2O solution of EtMgBr (prepared from 1 g. of EtBr and 0.2 g. of fresh Mg ribbon), a solution of 0.815 g. of freshly distilled dry methylaniline in 2.5 cc. of dehyd. benzene was added in N_2 atmosphere with chilling (5°) and stirring. Reaction mixture turned with foaming of ethane into viscous liquid with pale brownish tinge. To this solution, was added dropwise a solution of 8.8 m*M* of a ketone dissolved in 1.5 cc. of dehyd. benzene during 10 to 15 min., while keeping the temp. at ca. 15°. The solution was allowed to stand for 30 min. at 15~20°, and then 0.465 g. (3.02 m*M*) of glutarimide-β-acetaldehyde dissolved in 20 cc. of dehyd. tetrahydrofuran was added dropwise, and allowed to stand for 2 hr. at −3~0° with continuous stirring.

The reaction mixture was chilled to −20~−30°, and acidified with 7.5% HCl. The organic layer was separated from aqueous layer and the latter was extracted repeatedly with AcOEt. The organic layer and AcOEt extracts were combined, washed with dil. HCl, H_2O, aq. $NaHCO_3$ solution and H_2O successively, and dried over anhyd. Na_2SO_4. From the solution thus obtained, reaction product was isolated as described below.

3-(2-Hydroxy-4-oxodecyl)glutarimide (X)——The AcOEt solution prepared from 1.12 g. of methyl hexylketone and 0.465 g. of glutarimide-β-acetaldehyde was concentrated *in vacuo* and remaining oil was washed with hexane to remove excess ketone. Insoluble substance (0.3 g.) was dissolved in dehyd. benzene, poured onto 6 g. of acid-treated Al_2O_3 and eluted with 1% MeOH-benzene. The eluate was concentrated *in vacuo*, added with dehyd. Et_2O and kept in refrigerator overnight. Desired product X came out as 30 mg. of colorless leaflet, m.p. 76~78°.

On dehydration with P_2O_5, X gave the anhyro-X, which resisted to solidify, but showed λ_{max} at 222 mμ (ε, 17225) in its UV spectrum in MeOH. Considering from the Woodward calculation, this value suggests that the condensation took place at methyl side.

3-[2-Hydroxy-2-(1-oxo-1,2,3,4-tetrahydro-2-naphthyl)ethyl]glutarimide (XI)——AcOEt solution prepared from 1.28 g. of 1-tetralone and 0.465 g. of glutarimide-β-acetaldehyde was concentrated *in vacuo* to give 0.6 g. of syrupy residue, which turned to solid on treatment with Et_2O. Solid product (0.55 g.)

5) A. T. Nielsen, C. Gibbons, C. A. Zimmerman : J. Am. Chem. Soc., **73**, 4696 (1951).
6) Part VIII. M. Suzuki : This Bulletin, 8, 706 (1960).

was collected and recrystallized from dehyd. EtOH to give 0.47 g. of X as colorless prisms, m.p. 164～165°.

XI (50 mg.) was acetylated with Ac_2O and pyridine as usual, and the crude acetate was recrystallized from iso-PrOH to give 39 mg. of pure O-acetate, m.p. 165～167°. On dehydration with P_2O_5 in dehyd. benzene, 100 mg. of XI gave 25 mg. of anhydro-XI of m.p. 130.5～132.5°.

***dl*-3-[2-Hydroxy-2-(2-oxocyclohexyl)ethyl]glutarimide (XII)**——AcOEt extract obtained from the reaction mixture of 3.43 g. (35 m*M*) of cyclohexanone and 1.86 g. (12.0 m*M*) of glutarimide-β-acetaldehyde was concentrated *in vacuo*. Hexane was added and insoluble syrupy substance (2.9 g.) was separated from hexane by decantation, dissolved in dehyd. benzene-MeOH mixture (9:1), poured onto acid-treated Al_2O_3 column and eluted successively with benzene containing 0.5, 1.0, 3.0, 5.0 and 10% (v/v) of MeOH. Each of fractions was collected in every 75 cc. of portions.

From 1% MeOH-benzene fraction (Fraction Nos. 5 and 6) and from the earlier part of 3% MeOH-benzene fraction (Fraction Nos. 7 and 8), 0.11 g. of crystals (m.p. 156～156.5° (from AcOEt)) was obtained, which was identical with the anhydro-XII mentioned below. The later parts of 3% MeOH-benzene fractions (Nos. 9 to 11) and 5% MeOH-benzene fractions (Nos. 12 and 13) showed a slight activity against *S. cerevisiae* and gave 0.72 g. of oily residue on evaporation *in vacuo*. 290 mg. of oily substance obtained from Fraction No. 9 was mixed with Et_2O and kept in the refrigerator overnight. Thus, 180 mg. of crude XII was obtained, which was recrystallized from AcOEt to give pure XII as colorless prisms, m.p. 84～86°.

According to the usual method, 70 mg. of XII was acetylated with 1.4 cc. of Ac_2O in 1.4 cc. of pyridine. Crude acetate (59 mg.) was recrystallized from iso-PrOH to give 50 mg. of acetyl-XII as colorless prisms, m.p. 175.5～176.5°.

Dehydration of XII with P_2O_5 in dehyd. benzene gave anhydro-XII which was recrystallized from AcOEt to give a pure sample as colorless prisms, m.p. 156～156.5°.

***dl*-3-[2-Hydroxy-2-(5-methyl-2-oxocyclohexyl)ethyl]glutarimide (XIII)**——AcOEt solution prepared from 3.92 g. of 4-methylcyclohexanone and 1.86 g. of glutarimide-β-acetaldehyde was concentrated *in vacuo*. Hexane was added and 1.35 g. of the resultant syrup was fractionally chromatographed on acid-treated Al_2O_3 (27 g.) by similar technique described above. From the initial benzene eluate (Fraction No. 2, 40 cc.), 80 mg. of anhyd. XIII was obtained. From the 3% MeOH-benzene fraction the desired aldolization product was obtained as follows. 410 mg. of syrupy substance recovered from 3% MeOH-benzene fraction (Fraction Nos. 8, 9; each 40 cc.) was mixed with dehyd. Et_2O and kept in the refrigerator overnight to give ca. 200 mg. of solid product, which was recrystallized from AcOEt to give 120 mg. of pure XIII as colorless prisms, m.p. 143～144°. This product showed positive resorcinol color reaction[4] and 60 mg. of this sample gave 35 mg. of acetate, m.p. 150.5～151° on treatment with Ac_2O in pyridine. Anhydro-XIII of m.p. 111～113° as colorless prisms was derived from XIII by dehydration with P_2O_5 in benzene.

***dl*-3-[2-Hydroxy-2-(3- and 1-methyl-2-oxocyclohexyl)ethyl]glutarimide (XIV and XV)**——AcOEt extract, obtained from the reaction mixture of 3.92 g. of 2-methylcyclohexanone and 1.86 g. of glutarimide-β-acetaldehyde, was concentrated *in vacuo*. Hexane was added and 2.28 g. of the resultant syrup was chromatographed on acid-treated Al_2O_3, and 3% MeOH-benzene fraction (Nos. 8, 9 and 10) showed a weak activity against *S. cerevisiae*. The desired condensation products (XIV and XV) were obtained as crystals from fraction Nos. 9 and 10 as described below.

500 mg. of syrup obtained from fraction No. 9 (60 cc.) on treatment with Et_2O gave 33 mg. of crystals as colorless prisms, and this was found to be identical with the main product (XIV) obtained from fraction No. 10. The above mentioned ethereal mother liquor was concentrated to dryness and the resultant syrup was treated again with Et_2O to give 260 mg. of solid substance of m.p. 102～106°, which was recrystallized from AcOEt to give 100 mg. of crystalline (XV) as colorless prisms, m.p. 140～142°. XV gave acetyl-XV on treatment with Ac_2O in pyridine in the yield of 57.5%, which was recrystallized from iso-PrOH to afford a pure sample as colorless prisms, m.p. 214～216°. XV resisted to dehydration with P_2O_5 in benzene and showed almost negative reaction to resorcinol colorimetry. Thus, XV was assumed to have the structure belonging to *gem*-type.

From the fraction No. 10 (200 cc.), corresponding to the last parts of 3% MeOH-benzene effluent, 380 mg. of syrup was obtained, which turned to solid on treatment with Et_2O. The solid product was collected and recrystallized from AcOEt to give 200 mg. of pure XIV as colorless prisms, m.p. 115～115.5°. XIV showed the positive reaction to resorcinol color test and gave anhydro-XIV as colorless prisms, m.p. 137～139° with the yield of 45.4% by treating with P_2O_5 in benzene. XIV gave the corresponding acetate of m.p. 151～152° (yield: 69.5%).

Condensation of *rac*-2,4-Dimethylcyclohexanone with Glutarimide-β-acetaldehyde; Preparation of (XVI, XVII-1 and-2)——AcOEt solution obtained by condensing *rac*-2,4-dimethylcyclohexanone with 2.79 g. of glutarimide-β-acetaldehyde was concentrated *in vacuo* to syrup, and washed with hexane to remove the excess of starting ketone. The crude condensation product (3.0 g.) thus obtained was dissolved in 9 cc. of benzene, poured onto a column containing 75 g. of acid-treated alumina, and eluted successively with hexane-Et_2O (1:1), dehyd. benzene, 0.5, 1, 3, 5, and 10% MeOH-bezene and MeOH. From the fractions

eluted by 3% MeOH-benzene and 5% MeOH-benzene, 1.21 g. and 0.75 g. of syrup were recovered respectively and these syrup showed an activity against *S. cerevisiae*.

1. 3-[2-Hydroxy-2-(2-oxo-1,5-dimethylcyclohexyl)ethyl]glutarimide (XVII-1)——The above mentioned 1.21 g. of syrup obtained from 3% MeOH-benzene fraction was dissolved in 0.3 cc. of MeOH, diluted with 13 cc. of the upper layer of mixed solvent of 55% aq. MeOH and iso-Pr_2O, and fractionated chromatographycally over 85 g. of silica gel (28~200 mesh, pre-washed with 55% aq. MeOH) modifying the method reported by Rao.[7] Silica gel column was washed and eluted with 48 cc. of 30% AcOEt-iso-Pr_2O, and 1080 cc. of 60% AcOEt-Pr_2O successively. The latter fraction was collected, concentrated *in vacuo*, dissolved in small amount of Et_2O and kept standing in a refrigerator overnight. Thus, 440 mg. of gummy substance was obtained, which, on recrystallization from dehyd. Et_2O, gave 350 mg. of XVII-1 as colorless prisms, m.p. 70~73°. This compound showed the negative resorcinol color reaction and resisted to dehydration. Thus, this compound was assumed to have the structure belonging to *gem*-type.

Acetylation of 100 mg. of XVII-1 with Ac_2O in pyridine gave a crude acetate, which was recrystallized twice from iso-PrOH to afford 50 mg. of acetate as colorless prisms, m.p. 174~175°.

2. *rac*-Isocycloheximide Acetate (XVI)——The ethereal mother liquor from which gummy (XVII-1) had been removed as much as possible was concentrated *in vacuo*, and the syrupy residue (480 mg.) was fractionated chromatographically over silica gel by similar procedure described above. After a column had been washed with 200 cc. of iso-Pr_2O, the fraction eluted with each 200 cc. of 5 and 10% AcOEt-iso-Pr_2O was collected and concentrated *in vacuo* to syrup. The syrupy residue (250 mg.) resisted to solidify, so that 100 mg. of this syrup was acetylated by an usual procedure. 70 mg. crude acetate thus obtained was recrystallized twice from iso-PrOH to give 40 mg. of pure acetate as colorless prisms, m.p. 134~135°, which showed the positive resorcinol color reaction. The IR spectrum of this acetate was almost completely identical with that of authentic isocycloheximide acetate (Fig. 1) and differed from that of *α-epi*-isocycloheximide acetate. Thus, this acetate was confirmed as *rac*-isocycloheximide acetate. By dehydrating with P_2O_5 in hot dehyd. benzene, the syrupy substance, from which *rac*-isocycloheximide acetate was derived, gave a dehydrated product, e.g. *rac*-anhydroisocycloheximide, as colorless prisms, m.p. 114~115°.

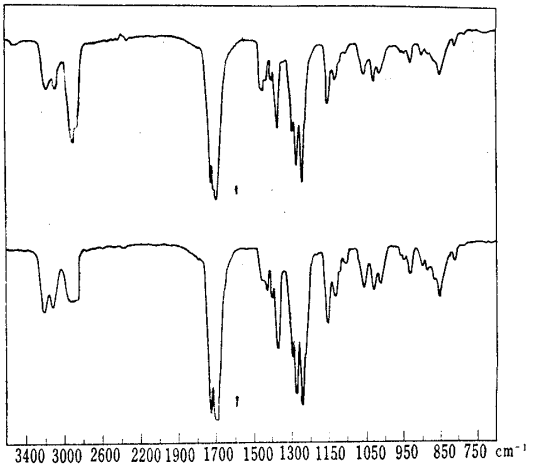


Fig. 1. Infrared Spectra of Synthetic (*Racemic*) and Natural Isocycloheximide Acetates

Upper : synthetic isocycloheximide acetate
Lower : natural isocycloheximide acetate

3. 3-[2-Hydroxy-2-(2-oxo-1,5-dimethylcyclohexyl)ethyl]glutarimide (XVII-2)——The 5% MeOH-Benzene fraction obtained by the fractionation over alumina of crude condensation product was concentrated *in vacuo* and the remaining syrup (0.75 g.) was fractionated over 52.5 g. of silica gel according to the procedure described before. Fractions obtained by eluting with 30 and 60% AcOEt-iso-Pr_2O were collected and concentrated *in vacuo*. The residue (300 mg.) was dissolved in Et_2O-hexane mixture and kept standing in a refrigerator overnight. Thus, 100 mg. of XVII-2 crystallized out as colorless prisms, m.p. 126~128°, showing the negative resorcinol color reaction. 100 mg. of XVII-2 was acetylated by an usual procedure to give 50 mg. of crude acetate, which gave 25 mg. of pure acetate as colorless prisms, m.p. 200~202°, on twice recrystallization from iso-PrOH.

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7) K. V. Rao, W. P. Cullen : J. Am. Chem. Soc., 82, 1127 (1960).

Summary

By condensing aliphatic and alicyclic ketones with glutarimide-β-acetaldehyde, several cycloheximide analogous compounds listed in Table I were synthesized.

The paper also dealt with improved synthesis of glutarimide-β-acetaldehyde.

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104. Mitsuru Furukawa and Takeo Uede: Syntheses of 4,6-Diamino-*s*-triazine-2-carboxamide Derivatives.

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As described in the previous report,[1] there was no effective compound against viruses among the alkylated diaminodihydro-*s*-triazines and diamino-*s*-triazines synthesized.

Later, some derivatives of 4,6-diamino-*s*-triazine-2-carboxamide were synthesized and their antiviral activity was examined, giving interesting results. This paper is concerned with the syntheses of 4,6-diamino-*s*-triazine-2-carboxamide derivatives.

As described in the previous report,[2] the reaction of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)guanidine prepared by the condensation of 1-(*p*-tolyl)biguanide with diethyl oxalate, with an alcohol gave 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate, while reaction with an amine gave 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamide.

This finding suggested that the objective derivatives of 4,6-diamino-*s*-triazine-2-carboxamide could be synthesized by reacting 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine with various amines.

First, the synthesis of 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine was examined. These compounds of various types were prepared in a good yield by the reaction of equimolar amounts of 1-substituted biguanide and diethyl oxalate in dehydrated ethanol, as shown in Chart 1.

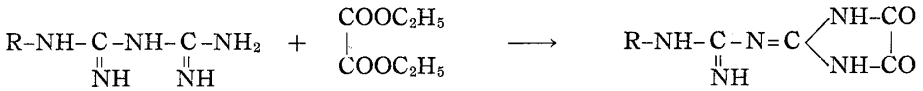
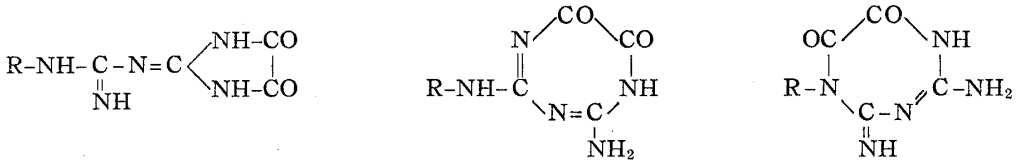


Chart 1.

The compounds obtained were assumed to have one of the following three structures from their analytical data.



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1) M. Furukawa, Y. Seto, S. Toyoshima: This Bulletin, **9**, 914 (1961).

2) M. Furukawa: *Ibid.*, **10**, 1216 (1962).