Studies of Cycloheximide-Related Compounds. II. The Acid-catalyzed Condensation of Glutarimide-β-acetaldehyde with Ketones*

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Cycloheximide, a mold metabolite, has been known for many years, having been first isolated from the culture of streptomycin-producing Streptomyces griseus by Whiffen et al.[1] The antibiotic has been used as an agricultural fungicide and possesses antitumor and rodent-repellent activities. We have now undertaken a program of synthesis with the intention of preparing new compounds related to cycloheximide, meanwhile improving the biological activities of the antibiotic.

One approach to the synthesis of cycloheximide-related compounds is to condense carbonyl compounds with glutarimide-β-acetaldehyde (GAA) by aldol reaction. Lawes[2] successfully synthesized anhydrocycloheximide by condensing 2,4-dimethyl-6-formylcyclohexanone with GAA in the presence of potassium carbonate. However, since our preliminary experiments showed that basic catalysts, such as sodium hydroxide, carbonate, bicarbonate and cyanides of sodium and potassium, caused a cleavage of the imide ring in GAA during the aldol reaction, it was thought advisable to investigate condensation by the aid of acid catalysts.

We have successfully condensed GAA with ketones by the use of dry hydrogen chloride (method A) or concentrated sulfuric acid in acetic acid (method B) to give cycloheximide-related compounds. When GAA is sparingly soluble in ketone component, method B is preferable to A.

The glutarimide-β-acetaldehyde was prepared from diethyl β-ketoglutarate and cyanoacetic acid by way of diethyl β-cyanomethylglutarate by the method of Egawa et al.[3]

The condensation of acetone and ethyl methyl ketone with GAA by method A gave 3-(4-oxo-2-*n*-pentenyl)glutarimide (I) and 3-(3-methyl-4-oxo-2-*n*-pentenyl)glutarimide (II) respectively. Woodward's ultraviolet rule[4] predicted the values of the absorption maxima of I and II.

The reaction of methyl isopropyl ketone with GAA by method A resulted in the formation

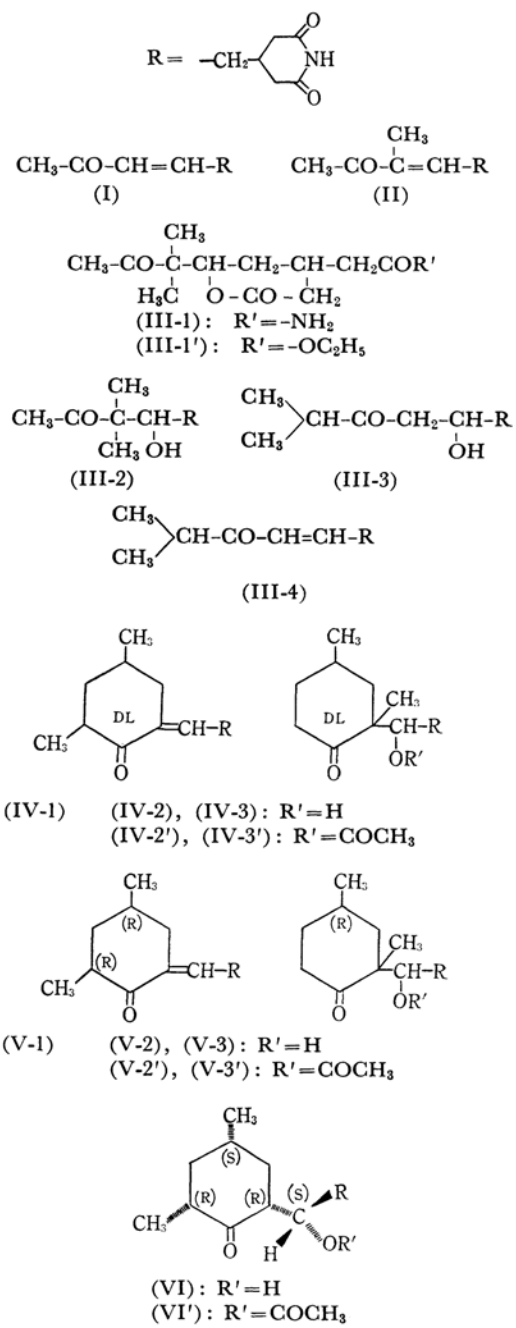

Chart 1.

* This constitutes Part XXIII of a series entitled "Studies of Antibiotics and Related Substances," by S. Umezawa; a portion of this paper was presented at the 16th Annual Meeting of the Chemical Society of Japan, Tokyo, March, 1963.

1) A. J. Whiffen, N. Bohonos and R. L. Emerson, *J. Bacteriol.*, **52**, 610 (1946).
2) B. C. Lawes, *J. Am. Chem. Soc.*, **82**, 6413 (1960).
3) Y. Egawa, M. Suzuki and T. Okuda, *Chem. Pharm. Bull. (Tokyo)*, **11**, 598 (1963).
4) R. B. Woodward, *J. Am. Chem. Soc.*, **64**, 76 (1942).

TABLE I. CYCLOHEXIMIDE-RELATED COMPOUNDS

Compound	M. p. C	UV absorption* mμ (ε)	Formula	Analyses, % Calcd. C	H	N	Found C	H	N	Yield % (Method)
I	112.5—113	223(15560)	$C_{10}H_{13}O_3N$	61.51	6.67	7.18	61.39	6.46	7.21	34 (A), 5(B)
II	81—81.5	230(8210)	$C_{11}H_{15}O_3N$	63.14	7.23	6.69	63.02	7.05	6.73	28 (A), 5(B)
III-1	164—164.5	—	$C_{12}H_{19}O_4N$	59.73	7.94	5.81	59.90	7.73	5.89	37 (A)
III-2	112.5—113	—	$C_{12}H_{19}O_4N$	59.73	7.94	5.81	59.75	7.79	5.70	2.7(A),16(B)
III-2′	143.5—144	—	$C_{14}H_{21}O_5N$	59.35	7.49	4.49	59.42	7.32	4.86	—
III-3	96.5—97	—	$C_{12}H_{19}O_4N$	59.73	7.94	5.81	59.75	7.72	5.91	1.0
IV-1	113—114	240(6700)	$C_{15}H_{21}O_3N$				—			1.1(B)
IV-2	142.5—143	—	$C_{15}H_{23}O_4N$	64.03	8.24	4.98	64.23	7.97	4.90	1.5(B)
IV-2′	174—175	—	$C_{17}H_{25}O_5N$				—			—
IV-3	182—182.5	—	$C_{15}H_{23}O_4N$	64.03	8.24	4.98	63.90	8.10	4.94	10 (B)
IV-3′	207—208	—	$C_{17}H_{25}O_5N$	63.14	7.79	4.33	63.01	7.62	4.49	—
V-1	135—136	242(7360)	$C_{15}H_{21}O_3N$				—			1.0(B)
V-2	156—156.5	—	$C_{15}H_{23}O_4N$	64.03	8.24	4.98	63.81	8.14	4.86	4 (B)
V-2′	145—147	—	$C_{17}H_{25}O_5N$				—			—
V-3	—	—	$C_{15}H_{23}O_4N$				—			9 (B)
V-3′	164.5—165	—	$C_{17}H_{25}O_5N$				—			—

* Methanol solution

of δ-(1, 1-dimethyl-2-oxo-*n*-propyl)-β-carbamoylmethyl-δ-valerolactone (III-1) and 3-(2-hydroxy-3, 3-dimethyl-4-oxo-*n*-pentyl)glutarimide (III-2) in yields of 37 and 2.7% respectively. When the reaction was carried out by method B, III-2 was obtained as the main product. The ultraviolet spectrum of III-1 indicated the absence of the α, β-unsaturated ketone system. The infrared spectrum of III-1 showed the disappearance of bands at 3200 and 3100 cm^{-1} characteristic of glutarimide moiety and the appearance of new bands at 3442, 3225 and 1630 cm^{-1} and at 1737 cm^{-1} which indicate the presence of primary amide and of a δ-lactone ring respectively. The presence of a terminal CH_3CO-group in III-1 was demonstrated by a positive iodoform reaction. In order to further establish that III-1 contains the carbamoyl group, the ethanolysis of III-1 in the presence of a catalytic amount of concentrated sulfuric acid was carried out; an ester derivative (III-1′) was thus obtained.

It is noteworthy that either method, A or B, resulted in the formation of an isomer (III-2) of 3-(2-hydroxy-5-methyl-4-oxo-*n*-hexyl)glutarimide (III-3), the product which was obtained by Nielsen's aldol condensation procedure.[3] The latter (III-3) easily afforded an anhydro-derivative, 3-(5-methyl-4-oxo-2-*n*-hexenyl)glutarimide (III-4) on dehydration with phosphorus pentoxide in dry benzene and showed a negative iodoform reaction, while the former (III-2) resisted dehydration, showed a positive iodoform reaction, and afforded an *O*-acetate derivative (III-2′) by the usual acetylation.

In a preliminary attempt to synthesize cycloheximide,[5] DL-2, 4-dimethylcyclohexanone was caused to react with GAA by method B, however no stereoisomers of cycloheximide were obtained, while DL-anhydrocycloheximide (IV-1) and two stereoisomers (IV-2, IV-3) of DL-*gem*-cycloheximide were produced in poor yields. An analogous condensation of (2R : 4R)-2, 4-dimethylcyclohexanone[6] prepared from natural cycloheximide by alkaline degradation with GAA afforded anhydrocycloheximide[2] (V-1) and two stereoisomers (V-2, V-3) of *gem*-cycloheximide.

The resorcinol color reactions[7] of IV-2, IV-3, V-2 and V-3 were negative, suggesting the presence of the –CO–C(–)–CH(OH)– ketol system, while those of IV-1 and V-1 were positive, indicating the presence of the –CO–C(–)=CH– anhydro-system, which was further judged to be present by the absorption band near 240 mμ in the ultraviolet spectra. The melting points of these compounds corresponded well to those previously reported for the substances prepared by an alternative method.[3,8] The ketol compounds (IV-2, IV-3, V-2, V-3) were additionally characterized by having been led to their acetates. The identities were ascertained by analyses, by infrared spectra determination and by their failure to depress the melting points of authentic samples respectively.

Table I lists the melting point, absorption maxima, analyses and yields of the above-mentioned products.

5) The total synthesis of cycloheximide was recently achieved by F. Johnson, N. A. Starkovsky, A. C. Paton and A. A. Carlson, *J. Am. Chem. Soc.*, **86**, 118 (1964).
6) T. Okuda, *Chem. Pharm. Bull.* (*Tokyo*), **7**, 659 (1959).
7) M. Takeshita, H. Takahashi and T. Okuda, ibid., **10**, 304 (1962).
8) M. Suzuki, Y. Egawa and T. Okuda, ibid., **11**, 582 (1963).

In connection with the above synthesis, several attempts were made to effect the hydration of the ethylene linkage of the anhydrocycloheximide (V-1); however, this attempt resulted in no more than the formation of a small quantity of *α-epi*-isocycloheximide[8] (VI).

The results of preliminary screening studies of the antimicrobial, antitumor and rodent-repellent activities of the above-mentioned compounds will be reported elsewhere.

Experimental

General Procedures.—*Method A* (Condensation by hydrogen chloride). — Glutarimide - β - acetaldehyde (GAA) was dissolved in excess ketone saturated with dry hydrogen chloride at room temperature, and then the mixture was allowed to stand overnight. After the excess ketone and hydrogen chloride had been removed by evaporation under reduced pressure, the residue was washed with ether and further purified by chromatography.

Method B (Condensation by concentrated sulfuric acid in acetic acid).—A large excess of a ketone and GAA (5—10 mmol.) were dissolved in glacial acetic acid (2—4 ml.). Into the solution, concentrated sulfuric acid (0.3 ml.) was added drop by drop under stirring at room temperature, and the mixture was allowed to stand overnight. Volatile ketones were removed by evaporation under reduced pressure. In the case of nonvolatile ketones, the reaction mixture was diluted with water, and, after neutralization with sodium carbonate, the solution was extracted with ethyl acetate. The removal of the solvent after drying over anhydrous sodium sulfate, gave a residue; this residue was then washed with *n*-hexane and further purified by chromatography.

Acetylation.—By the usual procedure, using acetic anhydride and pyridine at room temperature overnight.

3-(4-Oxo-2-*n*-pentyl)glutarimide (I).—The crude product (2.83 g.) obtained from GAA (1.55 g., 10 mmol.) and acetone (14 g.) by method A was dissolved in acetone (2 ml.), poured onto a column of acid-treated alumina (42 g.), and eluted with 3% methanol-benzene. After the eluate had been concentrated, dry ether was added and the mixture was kept standing in a refrigerator; thereupon separated crude crystals, which were washed with a small quantity of ether (yield 658 mg. (34%)). Recrystallization from ethyl acetate gave colorless prisms, m. p. 112.5—113°C. Infrared bands (Nujol): 3210, 3100 (NH), 1732, 1700, 1685 (C=O), 1652 cm^{-1} (conjugated C=C).

2, 4-*Dinitrophenylhydrazone*: Red prisms, m. p. 203.5—205°C. Found: C, 50.90; H, 4.60; N, 18.50. Calcd. for $C_{16}H_{17}O_4N_5$: C, 51.20; H, 4.53; N, 18.67%.

3-(3-Methyl-4-oxo-2-*n*-pentenyl)glutarimide (II).—The crude product (806 mg.) obtained from GAA (775 mg., 5 mmol.) and ethyl methyl ketone (14.4 g., 0.5 mol.) by method A was dissolved in benzene (3 ml.) and chromatographed over acid-treated alumina (16 g.) using 3% methanol-benzene as a solvent. After the solvent had been removed by evaporation, the resulting syrup (642 mg.) was mixed with ether and allowed to stand in a refrigerator to give crude crystals (288 mg., 28%). Recrystallization from ethyl acetate gave colorless prisms, m. p. 81—81.5°C. Infrared bands (Nujol): 3200, 3100 (NH), 1732, 1702, 1675 (C=O), 1650 cm^{-1} (conjugated C=C).

2, 4-*Dinitrophenylhydrazone*: Red prisms, m. p. 242—244°C (decomp.). Found: C, 52.74; H, 4.88; N, 17.99. Calcd. for $C_{17}H_{19}O_4N_5$: C, 53.00; H, 4.76; N, 17.75%.

δ-(1, 1-Dimethyl-2-oxo-*n*-propyl)-β-carbamoylmethyl-δ-valerolactone (III-1).—GAA (1.55 g., 10 mmol.) in acetic acid (2 ml.) was added drop by drop into methyl isopropyl ketone (8.6 g., 100 mmol.) containing hydrogen chloride (1.8 g., 51 mmol.) and stirred at room temperature. The crude product (3.65 g.) was then dissolved in acetone-benzene (1 : 1), poured onto a column of acid-treated alumina (50 g.), and eluted with 3% methanol-benzene. The viscous residue (985 mg.) obtained was caused to crystallize from acetone; yield 890 mg. (37%). Two recrystallizations from hot acetone gave colorless prisms, m. p. 164—164.5°C. Infrared bands (Nujol): 3442, 3225 (NH), 1737, 1685, 1665 (C=O), 1630 cm^{-1} (NH).

Found: C, 59.90; H, 7.73; N, 5.87. Calcd. for $C_{12}H_{19}O_4N$: C, 59.73; H, 7.94; N, 5.81%.

δ-(1, 1-Dimethyl-2-oxo-*n*-propyl)-β-ethoxycarbonylmethyl-δ-valerolactone (III-1′).—A sample (120 mg.) of III-1 was dissolved in 95% ethanol (4 ml.). A solution of concentrated sulfuric acid (0.4 ml.) in 95% ethanol (2 ml.) was then added to the solution, and the mixture was allowed to stand at room temperature. After evaporation under reduced pressure, the resulting residue was diluted with a small amount of water, neutralized with 5% aqueous sodium carbonate, and extracted with ethyl acetate. Washing this with water, drying it over anhydrous sodium sulfate, and evaporating it left a syrup, which was then dissolved in *n*-hexane and allowed to stand in a refrigerator. There were deposited colorless prisms of III-1′ (35 mg.), m. p. 52—53°C. The infrared spectrum (Nujol) contained bands at 1750, 1740, 1715 (C=O), 1245, 1130 cm^{-1} (C-O).

Found: C, 62.32; H, 8.68. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%.

2, 4-*Dinitrophenylhydrazone*: Red prisms, m. p. 166—166.5°C (decomp.).

Found: C, 53.11; H, 5.82; N, 12.15. Calcd. for $C_{20}H_{26}O_8N_4$: C, 53.33; H, 5.82; N, 12.44%.

3-(2-Hydroxy-3,3-dimethyl-4-oxo-*n*-pentyl)glutarimide (III-2).—*By Method A.*—A syrup (810 mg.) obtained by the evaporation of the mother liquor left after isolation of III-1 was chromatographed over acid-treated alumina (16 g.) with 3% methanol-benzene. After concentration under reduced pressure, the resulting syrup (450 mg.) was dissolved in ethyl acetate - ether and kept standing in a refrigerator to give crude crystals of III-2 (150 mg., 2.7%). Recrystallization from ethyl acetate gave colorless prisms, m. p. 112—112.5°C.

By Method B.—The crude product (660 mg.) obtained from GAA (775 mg., 5 mmol.) and methyl isopropyl ketone (4.3 g., 50 mmol.) was dissolved in acetone-benzene (1 : 1) and chromatographed on acid-treated alumina (16 g.). Elution with 3% methanol-benzene gave crude crystals of III-3 (190 mg., 16%). Recrystallization from ethyl acetate gave colorless prisms, m. p. 112.5—113°C. No depression in melting point

was observed upon its admixture with the sample prepared by method A.

2, 4-Dinitrophenylhydrazone: Red prisms, m. p. 227—227.5°C (decomp.). Found: C, 51.59; H, 5.56; N, 16.75. Calcd. for $C_{18}H_{23}O_7N_5$: C, 51.30; H, 5.50; N, 16.62%.

Acetate of III-2 (III-2′).—A crude sample (28 mg.) of III-2 was acetylated to give the acetate (11 mg.). Recrystallization from isopropanol gave colorless prisms, m. p. 143.5—144°C.

3-(2-Hydroxy-5-methyl-4-oxo-*n*-hexyl) glutarimide (III)-3.—The ethyl acetate solution obtained from *N*-methylanilinomagnesium bromide (33 mmol.), methyl isopropyl ketone (3.01 g., 35 mmol.) and GAA (1.86 g., 12 mmol.) by the procedure previously[3] reported was concentrated to give a syrup; this syrup was then washed with *n*-hexane to remove the unchanged ketone. The insoluble residue (900 mg.) was chromatographed on acid-treated alumina (18 g.). Elution with 3% methanol-benzene again gave a syrup (150 mg.); when this syrup was taken up in dry ether and kept in a refrigerator, it gave crude crystals (28 mg., 1.0%). Recrystallization from ethyl acetate afforded colorless prisms, m. p. 96.5—97°C. The ultraviolet spectrum in methanol showed end absorption. The infrared spectrum (Nujol) contained bands at 3540 (OH), 3220, 3110 (NH), 1733, 1708 and 1685 cm^{-1} (C=O).

3-(5-Methyl-4-oxo-2-*n*-hexenyl) glutarimide (III-4) (Anhydro-derivative of III-3).—A sample of III-3 (20 mg.) dissolved in benzene (5 ml.) was mixed with phosphorus pentoxide (100 mg.), slowly heated to boiling, and then cooled. Evaporation under reduced pressure gave a residue which was recrystallized from dry ether to afford colorless prisms (3 mg.), m. p. 46—48°C. The ultraviolet spectrum in methanol showed a maximum at 224 mμ (ε 15200). The infrared spectrum (KBr) contained bands at 3200, 3080 (NH), 1737 sh, 1715, 1675 (C=O) and 1630 cm^{-1} (conjugated C=C).

DL-Anhydrocycloheximide (IV-1).—A crude product (2.84 g.) prepared from DL-2, 4-dimethylcyclohexanone[9] (6.3 g., 50 mmol.) and GAA (1.55 g., 10 mmol.) by method B was dissolved in benzene-methanol (8 : 1), and the solution was poured onto acid-treated alumina (56 g.) and eluted with 3% methanol-benzene. When a syrup obtained from the early fractions was taken up in dry ether and allowed to stand in a refrigerator, it afforded crude IV (yield 30 mg., 1.1%). Recrystallization from ethyl acetate gave colorless prisms (12 mg.), m. p. 113—114°C. No depression in melting point was observed in admixture with an authentic specimen (m. p. 114—115°C) previously[3] reported.

DL-*gem*-Cycloheximide I (IV-2).—The mother liquor left after the isolation of IV-1 was concentrated under reduced pressure. The resulting syrup (1.01 g.) was charged on a column of silica gel (50 g.) and eluted with isopropyl ether - ethyl acetate (9 : 1, 7 : 3, 1 : 1 and 1 : 3) and ethyl acetate successively. The early fractions obtained with 30% ethyl acetate - isopropyl ether were concentrated to give a syrup which was caused to crystallize from ether; yield, 40 mg., m. p. 112—113°C. The product was identical with VI-1 in all respects.

A syrup (108 mg.) obtained from the early fractions with 50% ethyl acetate - isopropyl ether was caused to crystallize from ethyl acetate to give crude IV-2 (42 mg., 1.5%). Two recrystallizations from the same solvent gave colorless prisms, m. p. 142.5—143°C, which showed a negative resorcinol reaction.[7] The product has a higher melting point than that of a sample of DL-*gem*-cycloheximide I previously obtained,[3] which has now been found to be impure. The identity was ascertained by both samples leading to the same acetate, as will be described below.

Acetate of IV-2 (IV-2′).—A sample of IV-2 (15 mg.) was acetylated to give colorless prisms (10 mg.), m. p. 174—175°C. The acetate was found to be identical with the DL-*gem*-cycloheximide I acetate (reported m. p. 174—175°C) previously reported[3] by a mixed melting point determination and by a comparison of the infrared spectra.

DL-*gem*-Cycloheximide II (IV-3).—The later fractions with 3% methanol - benzene and all fractions with 5% methanol - benzene (see DL-anhydrocycloheximide (IV-1)) were collected and concentrated to dryness, and the residue (783 mg.) was caused to crystallize from ethyl acetate to give crude crystals of IV-3 (280 mg., 10%). Recrystallization from methanol gave colorless prisms, m. p. 182—182.5°C, which showed a negative resorcinol reaction. The product has a higher melting point than that of DL-*gem*-cycloheximide II previously obtained,[3] a product which has now been found to be impure. The identity was confirmed by both products leading to acetate, as will be described below.

Acetate of IV-3 (IV-3′).—A sample of IV-3 (26 mg.) was acetylated to give crude acetate (22 mg.). Recrystallization from isopropanol gave colorless prisms (15 mg.), m. p. 207—208°C, undepressed by admixture with an authentic specimen (m. p. 200—202°C) previously obtained.[3]

Anhydrocycloheximide (V-1).—The crude product (1.93 g.) obtained by the reaction of optically-active (2R : 4R)-2, 4-dimethylcyclohexanone (3.2 g., 25 mmol.) with GAA (775 mg., 5 mmol.) was chromatographed over acid-treated alumina (38 g.) with 3% methanol - benzene. The eluate was then evaporated under reduced pressure, and the resulting residue (481 mg.) was dissolved in ethyl acetate, poured onto a column of silica gel (25 g.) and eluted with the same solvent systems as were used for the isolation of IV-1. A syrup obtained from the early fractions with ethyl acetate - isopropyl ether (1 : 1) was caused to crystallize from ether; crude crystals (12 mg.) (1.0%). Recrystallization from methanol gave colorless prisms, m. p. 135—136°C. The product was found to be identical with anhydrocycloheximide (reported m. p. 136.5—138°C) by a mixed melting point determination. Additionally, they had identical ultraviolet and infrared spectra.

***gem*-Cycloheximide II (V-2) and Its Acetate (V-2′).**—When a residue (197 mg.) obtained from the middle fractions with 50% ethyl acetate - isopropyl ether in the above chromatography was taken up in ether and allowed to stand at room temperature, there separated crystals of V-2 (60 mg., 4%). Recrystallization from ethyl acetate afforded colorless prisms, m. p. 156—156.5°C. The product showed a negative resorcinol color reaction, indicating that the product

9) H. E. Ungnada and A. D. McLaren, *J. Org. Chem.*, **10**, 29 (1945).

was a diastereoisomer[10] of the *gem*-cycloheximide. The product has been led to its acetate (colorless prisms; m. p. 145—147°C) by the general procedure. The infrared spectrum (KBr) contained bands at 3270, 3100w (NH), 1745sh, 1715, 1700 (C=O) and 1250 cm^{-1} (C-O).

***gem*-Cycloheximide (V-3) and Its Acetate (V-3').** —The mother liquor left after the isolation of V-2 was evaporated to give crude V-3, which could not be caused to crystallize. Then, the residue (50 mg.) was acetylated by the general procedure to give a crude solid (20 mg.). Recrystallization from isopropanol gave colorless prisms of V-3' (10 mg.), m. p. 164.5—165°C. The product was found to be identical in all respects with the *gem*-cycloheximide I acetate (reported m. p. 166—166.5°C) previously[8] reported.

***α-epi*-Isocycloheximide (VI) and Its Acetate (VI') (The Hydration of Anhydrocycloheximide).** —Into a mixture of anhydrocycloheximide (V-1) (4.21 g., 16 mmol.) and acetic acid (12 ml.), 75% sulfuric acid (2.34 g., 17.6 mmol.) was added drop by drop and stirred at room temperature. Stirring was continued for 2 hr. to give a clear solution, and then the mixture was stirred for an additional 3 hr. The reaction mixture was diluted with water (12 ml.) and neutralized with sodium carbonate, followed by extraction with ethyl acetate. After it had been washed with water, aqueous 5% sodium bicarbonate and water, and dried over anhydrous sodium sulfate, the extract was evaporated to remove the solvent. The resulting yellow syrup was treated with ether in order to precipitate unchanged anhydrocycloheximide (2.2 g., m. p. 133—135°C). The ethereal solution was evaporated to give a residue (2.45 g.), which was then taken up in dry benzene, poured onto acid-treated alumina (60 g.), and eluted with 3% methanol-benzene. The later fractions showed a significant activity in reaction to *Saccharomyces sake*. The resulting residue (950 mg.) was similarly rechromatographed to afford crude VI (240 mg.), which was taken in ethyl acetate and again chromatographed over silica gel (32 g.) with ethyl acetate - isopropyl ether (1 : 1). The evaporation of the later fractions again afforded a gummy solid (210 mg.). The minimum inhibitory concentration of the product against *S. sake* was found to be 30 mg./ml. by a dilution method.

Found: C, 63.95; H, 8.06; N, 4.95. Calcd. for $C_{15}H_{23}O_4N$: C, 64.03; H, 8.24; N, 4.98%.

10) M, Suzuki et al. described a diastereomer with a m. p. of 141—145°C. See Ref. 8.

The product (100 mg.) was acetylated by the general procedure. The crude acetate was purified by chromatography over silica gel (3 g.) with 30% ethyl acetate - isopropyl ether. Recrystallizations from ether and isopropyl ether gave colorless prisms, 30 mg., m. p. 177.5—178°C. No depression in melting point was observed upon admixture with an authentic specimen of *α-epi*-isocycloheximide acetate.[8] Additionally, the product was identical in infrared spectra with the authentic specimen.

Summary

1) Glutarimide-β-acetaldehyde has been condensed with several aliphatic ketones by acid-catalysts to give mainly α, β-unsaturated keto-derivatives. The condensation with methyl isopropyl ketone has given δ-(1, 1-dimethyl-2-oxo-*n*-propyl)-β-carbamoylmethyl-δ-valerolactone (III-1) and 3-(2-hydroxy-3, 3-dimethyl-4-oxo-*n*-pentyl)-glutarimide (III-2). It has been found that the latter is an isomer of the product prepared by Nielsen's aldol condensation procedure.

2) An analogous condensation with DL-2,4-dimethylcyclohexanone has given DL-anhydrocycloheximide and two stereoisomers of DL-*gem*-cycloheximide. The condensation with (2R:4R)-2, 4-dimethylcyclohexanone has given a similar result.

3) It has been shown that the acid-catalyzed hydration of anhydrocycloheximide affords *α-epi*-isocycloheximide.

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