Title	Synthetic studies on cycloheximide-related compounds
Sub Title	
Author	頴川, 吉之(Egawa, Yoshiyuki)
Publisher	慶応義塾大学藤原記念工学部
Publication year	1967
Jtitle	Proceedings of the Fujihara Memorial Faculty of Engineering Keio University (慶応義塾大学藤原記念工学部研究報告). Vol.20, No.81 (1967.) ,p.303(127)- 305(129)
JaLC DOI	
Abstract	
Notes	Summaries of Doctor and Master Theses
Genre	Departmental Bulletin Paper
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=KO50001004-00200081-0127

Synthetic Studies on Cycloheximide-Related Compounds

Yoshiyuki EGAWA*

So called "glutarimide antibiotic" including cycloheximide (3-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl] glutarimide) and its related antibiotics are known to be active against yeast, phytopathogenic fungi, protozoa and tumors. Moreover, cycloheximide is found to be the strongest rodent-repellent so far as examined. However, the utility of these antibiotics is limited to a minor extent due to their toxicity to animals and plants. The present study was carried out to synthesize useful compounds structually related to cycloheximide.

The studies by the author are concerned with the condensation of aliphatic and aromatic ketones with glutarimide-β-acetaldehyde in acidic and basic conditions to synthesize cycloheximide-related compounds. The experiments are also done to examine the biological activities of the synthetic compounds.

Outlines and the results of the present studies are summarized as follows.

1) Synthesis of glutarimide-β-acetaldehyde was first examined, which was an indispensable starting material in the present study. A new synthetic procedure which started from diethyl β-oxoglutarate and cyanoacetic acid gave the aimed compound via five steps. The total yield (53.7%) was greater than that (6.6—14%) of a method reported by Phillips. This result made it possible to carry out the next synthesis.

2) Condensation of (2R : 4R)-2,4-dimethylcyclohexanone with glutarimide-β-acetaldehyde with the aid of N-methylanilinomagnesium bromide gave four isomers of cycloheximide. Two of them were found to be stereoisomers of cycloheximide and the other two were position-isomers of cycloheximide. One of the stereoisomers was identified as isocycloheximide found as a metabolite of Streptomyces sp. The another (m.p. 112—114°C) was named α-epi-isccycloheximide (I) and its absolute configuration was determined to be (2R : 4S : 6R ; 2eq : 4eq : 6eq ; αS). Both position-isomers found to be gem-cycloheximides and determined to be 3-[2-(1,3-dimethyl-6-oxocyclohexyl)-2-hydroxyethyl] glutarimide. The absolute configurations of these isomers were further inferred, the one (m.p. 99—101°C) to be (2R : 4R)-configuration with 2- and 4- methyl equatorially oriented and the other (m.p. 141—145°C) (2S : 4R)-configuration with axial 2-methyl and equatorial 4-methyl.

By an analogous reaction, (2S : 4R)-2,4-dimethylcyclohexanone gave two stereoisomers (m.p. 106—107°C, 168—170°C) of cycloheximide with 4 : 6-cis and 4 : 6-trans

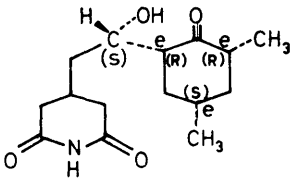
*頴 川 吉 之

configuration.

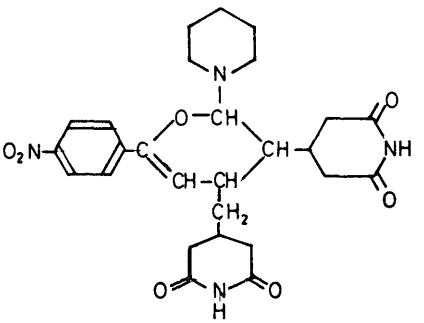
3) Condensation of aliphatic and alicyclic ketones with glutarimide-β-acetaldehyde under acidic conditions, namely by using dry hydrogen chloride or concentrated sulfuric acid as a condensing agent, gave some cycloheximide-related compounds including anhydrocycloheximide identical with the product derived from cycloheximide by dehydration.

4) In connection with the above synthesis, an attempt was made to effect the hydration of the ethylene linkage of anhydrocycloheximide. Application of 75% sulfuric acid as a hydration agent resulted in the formation of α-epi-isocycloheximide.

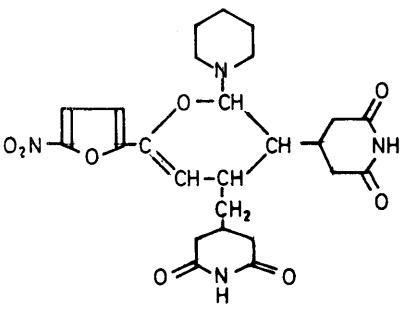
5) It has been found that aromatic nitroketones such as p-nitroacetophenone or 5-nitro-2-acetylfuran, which failed to react with glutarimide-β-acetaldehyde in the presence of acid catalysts, was caused to react with aldehydes in the presence of secondary amines (piperidine, morpholine, pyrrolidine or diethylamine) to afford an interesting product. The products have been shown by degradation and infrared, NMR and ultraviolet spectral studies to have a 2,3-dihydro-γ-pyran skeleton. The re-



(I)



(II)



(III)

action of p-nitroacetophenone in the presence of piperidine gave 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-6-(4-nitrophenyl)-2-piperidino-2,3-dihydro-γ-pyran (II) m.p. 199—199.5°C(dec.). The analogous reaction of 5-nitro-2-acetylfuran gave 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-6-(5-nitro-2-furyl)-2-piperidino-2,3-dihydro-γ-pyran (III), m.p. 145—145.5°C (dec.). The probable reaction mechanism of this unique reaction was further inferred to include a new reaction of Mannich type. The scope of the reaction has been defined.

6) A number of esters and O-glycoside of cycloheximide were synthesized. The formers were obtained by the reaction of the corresponding acid chloride with cycloheximide in the presence of pyridine. The latter was synthesized by condensing acetobromoglucose and cycloheximide with the aid of mercuric cyanide as a catalyst, followed by deacetylation of the condensation product with triethylamine in 90 % methanol.

7) Biological activities of the above-mentioned cycloheximide-related compounds were examined. 3-(3-Glutarimidyl)-4-(3-glutarimidylmethyl)-6-(5-nitro-2-furyl)-2-piperidino-2,3-dihydro-γ-pyran (III) was found to have significant antitumor-activity and low toxicity. Cycloheximide cinnamate was found to have inhibitory effect against Piricularia oryzae, a phytopathogenic fungi to a rice-plant and anti-toxoplasmic activity.