SYNTHESIS OF GLUTARIMIDE ANTIBIOTICS AND THEIR ANALOGS THROUGH 1,3-CYCLOADDITION OF 3-GLUTARIMIDYLACETONITRILE OXIDE TO 2-CYCLOHEXENONES*

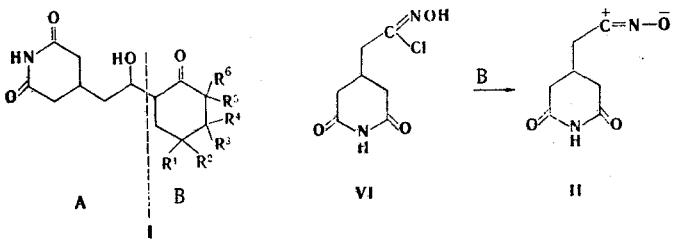
A. A. Akhrem, F. A. Lakhvich,
V. A. Khripach, and I. B. Klebanovich

UDC 542.91+615.779.9

A mixture of 4,4-dimethyl-9-(3-methylglutarimidyl)-2-oxo-7-oxa-8-azabicyclo[4.3.0]non-8-ene and 3-(3-methylglutarimidyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenz-[d]isoxazole was obtained by in situ 1,3-dipolar cycloaddition of 3-glutarimidylacetonitrile oxide to 5,5-dimethylcyclohex-2-en-1-one. Reductive cleavage of these compounds by catalytic hydrogenation over Pd catalysts gives 3-[2-amino-2,2-(4,4-dimethyl-2-oxocyclohexylene)ethyl]glutarimide and the known 3-[2-amino-2,2-(4,4-dimethyl-2,6-dioxocyclohexylene)ethyl]glutarimide, respectively, in quantitative yield. Hydrolysis of the latter leads to 3-[2-oxo-2-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]glutarimide. The ketones obtained are analogs of glutarimide antibiotics and polyfunctional intermediates in their synthesis.

The glutarimide antibiotics produced by actinomycetes have a broad spectrum of biological activity [2, 3]. The I structure of most compounds of this class includes two principal fragments: ethylglutarimide (A) and 4,6-dimethylcyclohexane (B) fragments. In this connection, the scheme of the total synthesis of glutarimide antibiotics should logically include a step involving the production of both structural fragments A and B and a method for their fusion with the imparting of the necessary stereochemistry of the molecule. Because of the lability of glutarimide antibiotics under the conditions of many chemical reactions, their synthesis is a complex task and is accomplished only in the case of the simplest representatives — actiphenol and cycloheximide [5]. The proposed methods for synthesis in this case do not make it possible to obtain a number of interesting representatives of the indicated class of substances such as the antitumorigenic antibiotic E-73, streptovitacins, and inactone, which display high biological activity [3], particularly antitumorigenic activity. The accessibility of 4,5-cyclohexanoisoxazoles by cycloaddition of nitrile oxides to unsaturated cyclohexane derivatives and the methods that have been found for the selective transformation of the indicated heterocycles to β-di- and β-tricarbonyl derivatives of cyclohexane [6-9] have made it possible to predict the promising character of the use of this cycloaddition reaction for the construction of the molecular skeleton of glutarimide antibiotics. With this in mind, we undertook the synthesis of the previously unknown 3-glutarimidylacetonitrile oxide (II), which is the A fragment. The accessible 5,5-dimethylcyclohexenone (III) was selected as a model of the B fragment. The 1,3-cycloaddition of nitrile oxide dipole II to enone III is also a method for the fusion of the indicated fragments.

We accomplished the synthesis of nitrile oxide II from 3-glutarimidylacetaldehyde (IV) by chlorination at −50°C of its oxime (V) to give hydroxamoyl chloride VI.†



*See [1] for a preliminary communication.

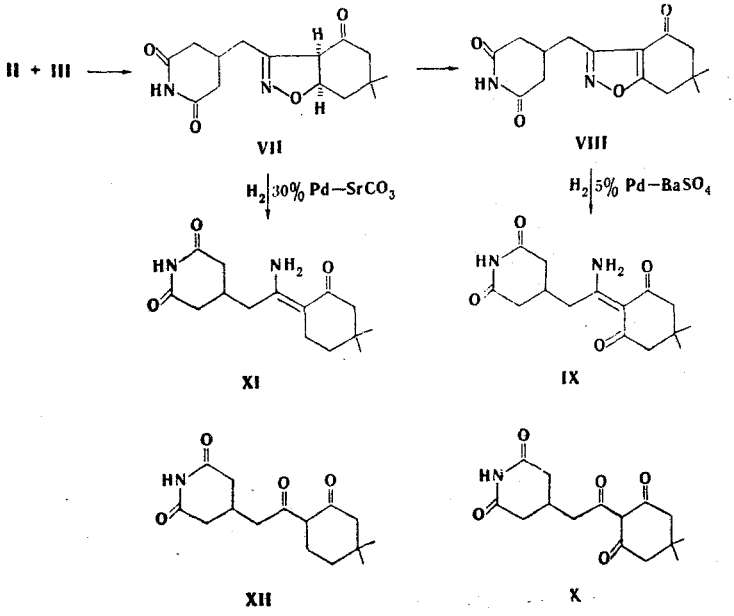
†In view of the low solubility of the oxime in chloroform or ether, which makes the use of traditional methods [10] difficult, ethanol was used as the solvent in the chlorination.

Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk 220600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 230-234, February, 1979. Original article submitted February 27, 1978.

 0009-3122/79/1502-0194$07.50

Nitrile oxide II, which was obtained from VI by the action of bases, was isolated and characterized. It was found to be relatively stable: The time required for its complete dimerization in chloroform solution at 20°C is ∿ 100 h. The lifetime of the nitrile oxide was measured by IR spectroscopy from the decrease in the intensity of the C ≡ N absorption band at 2310 cm^{-1}.

The reaction of nitrile oxide II with dimethylcyclohexenone III was accomplished by the slow addition of a dilute solution of triethylamine in chloroform to a thoroughly stirred mixture of chloride VI and enone III. The use of the nitrile oxide in situ and the use of a significant excess of the dipolarophile made it possible to avoid the effect of undesirable oxide autocondensation processes on the yields of the desired products.

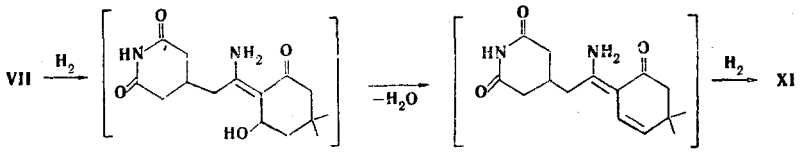


The principal reaction product was isoxazoline VII, and the regioisomeric product of "reverse" addition (5-acylisoxazoline) was not recorded. As in the case of previously examined [7, 8] simpler nitrile oxides, the high regioselectivity of the process is evidently due to the favorable combination of electronic and steric factors in the dipolarophile and 1,3-dipole molecules.

Chromatographic separation of the reaction mixture with a column filled with silica gel gives, in addition to the desired isoxazoline VII, a significant amount of its dehydro derivative (VIII). The overall yield of VII and VII was 70% based on starting VI. The application of the method of rapid chromatography under pressure made it possible to isolate isoxazoline VII as the only product of the cycloaddition of nitrile oxide II to enone III. There is no doubt that the formation of isoxazole VIII occurs as a result of the dehydrogenating effect of the sorbent during the isolation of isoxazoline VII. Isoxazole VIII was also obtained in 94% yield by refluxing isoxazoline VII in solution in tert-butyl alcohol in the presence of chloranil. The tendency of the isoxazoline to undergo dehydrogenation so readily is evidently due to the presence of a carbonyl group in the carbocyclic part of the VII molecule and to the formation of a stable conjugated tetrahydrobenzisoxazolone system (VIII) as a result of the reaction.

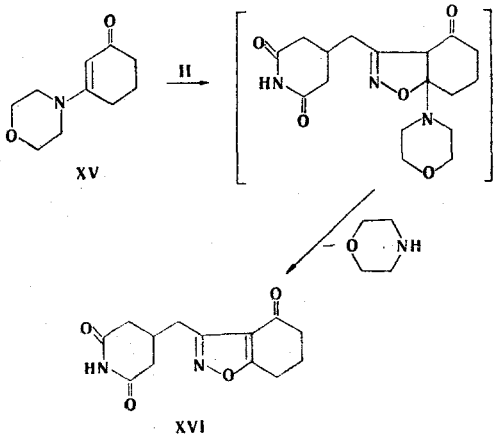
The 4-acylisoxazoline structure of adduct VII follows from the chemical shifts and the character of the spin—spin splitting of the signals of the methylidyne 4-H and 5-H protons of isoxazoline in the PMR spectrum: 3.68 (d) and 5.02 ppm (m), respectively. In the case of the isomeric 5-acylisoxazoline the position and multiplicity of the signals of the 4-H and 5-H signals would have been reversed. The further chemical transformations of isoxazoline VII provide unambiguous chemical evidence for its structure. Thus isoxazole VIII, obtained by dehydrogenation of VII, was subjected to reductive cleavage under catalytic hydrogenation conditions over 5% $Pd/BaSO_4$, and enamino diketone IX was obtained in quantitative yield; hydrolysis of the latter gave β-triketone X, which was identical to a sample obtained by an independent method [11]. Compounds IX and X are analogs of glutarimide antibiotics and poly-

functional intermediates in their synthesis [11]. In addition, one should particularly emphasize that the hydrogenation of isoxazoline VII over 30% $Pd/SrCO_3$ proceeds quantitatively to give enamino ketone XI. In analogy with [9], it may be assumed that the formation of the latter under catalytic hydrogenation conditions includes the realization of successive steps involving cleavage of the N—O bond of the heteroring of VII, dehydration of secondary alcohol XIII, and reduction of the endocyclic double bond in keto dienamine XIV. Enamino ketone XI can be thoroughly hydrolyzed subsequently to diketone XII, which is the gem-dimethyl isomer of the dehydrocycloheximide obtained by Johnson and co-workers via their proposed scheme for the total synthesis of cycloheximide [5].



XIII XIV

The use of enol derivatives of cyclohexane-1,3-diones as the dipolarophiles in cycloaddition with glutarimidylacetonitrile oxide (II) [12] proved to be less effective. Thus, for example, adduct XVI was obtained in only 18% yield in the reaction of nitrile oxide II with the morpholine enamine (XV) of dihydroresorcinol.



XV XVI

The application of the examined transformations to adducts of nitrile oxide II with suitably substituted cyclohexenones may provide a route to streptovitacins and several other glutarimide antibiotics and their analogs, particularly to the antitumorigenic antibiotic E-73.

EXPERIMENTAL

The melting points were measured with a Koffler block. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in deuterochloroform were recorded with a JNM-PS-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian MAT-311 spectrometer at an ionizing-electron energy of 70 eV. Woelm, LSL-254, and $H_2SiO_3 \cdot nH_2O$ silica gels and Silufol UV-254 plates were used for thin-layer and column chromatography.

3-(β-Oximinoethyl)glutarimide (V). A solution of 0.18 g (4.50 mmole) of NaOH and 0.326 g (4.69 mmole) of hydroxylamine hydrochloride in 5 ml of water was added to a solution of 0.7 g (4.51 mmole) of aldehyde IV [13] in 3.5 ml of ethanol, and the mixture was refluxed for 15 min. It was then concentrated and cooled, and the precipitated crystals were separated and dried in vacuo to give 0.6 g (78%) of oxime V with mp 156-158°C. IR spectrum: 1680, 1730, 3100, and 3200 cm^{-1} (broad band). Mass spectrum, m/e (relative intensity): 170 (M^+, 26%), 153 (77%), and 112 (100%). Found: C 49.4; H 5.9; N 16.4%. $C_7H_{10}N_2O_3$. Calculated: C 49.4; H 5.9; N 16.5%.

3-Glutarimidylacetylhydroxamoyl Chloride (VI). A stream of dry chlorine was bubbled through a cooled (to −50°C) solution of 1.05 g (6.17 mmole) of oxime V in 40 ml of ethanol for 30 min until the increase in weight was 0.433. The temperature of the mixture was raised

to 0°C in the course of 1.5 h, and the solvent was removed to give 1.26 g (100%) of chloride VI with mp 145°C (dec.). IR spectrum: 710, 1680, 1730, and 3100-3400 cm^{-1} (broad band).

Reaction of Nitrile Oxide II with Cyclohexenone III. A) A solution of 3.03 g of triethylamine in 200 ml of ether was added dropwise in the course of 5 h to a mixture of 2.0 g (10 mmole) of acid chloride VI, 50 g (0.4 mole) of dimethylcyclohexenone III, 60 ml of ethanol and 200 ml of ether, after which stirring was continued for another 3 h, and the mixture was allowed to stand overnight. The solvents and excess enone were removed in vacuo, and the residue (11 g) was chromatographed with a column filled with silicic acid (150 mesh) and gradient elution with a hexane—ether system to give 1.05 g (36%) of 3-(3-methylglutarimidyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenz[d]isoxazole (VIII) with mp 198-201°C. IR spectrum: 1600, 1700 (broad band), 3100, and 3200 cm^{-1}. PMR spectrum: 1.18 (6H, s, CH_3), 2.20-3.10 (11H, m, CH_2, CH), and 8.86 ppm (broad s, NH). Found: C 62.0; H 6.3; N 9.8%; M 290 mass spectrometry $C_{15}H_{18}N_2O_4$. Calculated: C 62.0; H 6.3; N 9.7%; M 290.31.

Subsequent elution gave 0.98 g (34%) of 4,4-dimethyl-9-(3-methylglutarimidyl)-2-oxo-7-oxa-8-azabicyclo[4.3.0]non-8-ene (VII) with mp 184-186°C. IR spectrum: 1690, 1710 (broad band), 3110, and 3230 cm^{-1}. PMR spectrum: 1.00 (6H, s, CH_3), 1.91 (2H, m, 5-CH_2), 3.66 (1H, d, J = 11 Hz, 1-H), 5.02 (1H, m, 6-H), and 8.67 ppm (broad s, NH). Found: C 61.8; H 6.8; N 9.4%; M 292 by mass spectrometry. $C_{15}H_{20}N_2O_4$. Calculated: C 61.6; H 6.9; N 9.6%; M 292.33.

The overall yield of the adduct based on oxime IV was 70%.

B) A solution of 0.5 g (5 mmole) of triethylamine in 50 ml of ether and a solution of 1.1 g (5.4 mmole) of hydroxamoyl chloride VI in 50 ml of ether were added dropwise simultaneously from two dropping funnels in the course of 2 h to a solution of 0.62 g (5 mmole) of enone III in 100 ml of ether. After 3 days, the precipitated triethylamine hydrochloride was separated, and the solvent was removed in vacuo. The oily residue was chromatographed with a column filled with silicic acid (150 mesh). Elution with ether gave 0.58 g (40%) of isoxazoline VII, which was identical to a sample of the compound obtained above with respect to its melting point and TLC and PMR data.

Oxidation of Isoxazoline VII with Chloranil. A 90-mg (0.3 mmole) sample of isoxazoline VII was refluxed in 10 ml of tert-butyl alcohol in the presence of 150 mg (0.6 mmole) of chloranil for 15 h, after which the mixture was cooled, and the solvent was removed in vacuo. The oily residue was chromatographed with a column filled with silica gel (150 mesh) with gradient elution with a hexane—ether system to give 85 mg (94%) of isoxazole VIII.

3-[2-Amino-2,2-(4,4-dimethyl-2,6-dioxocyclohexylene)ethyl]glutarimide (IX). An 85-mg sample of isoxazole VIII was hydrogenated in 20 ml of ethanol at room temperature and normal pressure in the presence of 50 mg of 5% $Pd/BaSO_4$ until hydrogen absorption was complete. The catalyst was then removed by filtration, and the solvent was removed in vacuo to give 86 mg (100%) of enamino diketone IX with mp 234-236°C, which was identical to an authentic sample [11].

3-[2-Oxo-2-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]glutarimide (X). A 100-mg sample of enamino diketone IX in 10 ml of ethanol was treated with 6 ml of 10% hydrochloric acid, and the reaction mixture was heated on a water bath for 30 min. The usual workup gave β-triketone X with mp 169-172°C, which was identical to an authentic sample [11].

3-[2-Amino-2,2-(4,4-dimethyl-2-oxocyclohexylene)ethyl]glutarimide (XI). A 60-mg sample of isoxazoline VII was hydrogenated in 15 ml of ethanol at room temperature and normal pressure in the presence of 50 mg of 30% $Pd/SrCO_3$ until hydrogen absorption was complete. The catalyst was removed by filtration, and the solvent was removed in vacuo to give 57 mg (100%) of enamino ketone XI with mp 220-225°C. IR spectrum: 1600, 1680-1710 (broad band), 3100, 3200, and 3340 cm^{-1}. Found: C 64.6; H 8.0; N 9.9%; M 278 by mass spectrometry. $C_{15}H_{22}N_2O_3$. Calculated: C 64.7; H 8.0; N 10.1%; M 278.34.

3-(3-Methylglutarimidyl)-4-oxo-4,5,6,7-tetrahydrobenz[d]isoxazole (XVI). A solution of 0.14 ml (1 mmole) of triethylamine in 100 ml of chloroform and a solution of 190 mg (0.9 mmole) of hydroxamoyl chloride VI in a mixture of 20 ml of ethanol and 80 ml of chloroform were added dropwise simultaneously from two dropping funnels in the course of 5 h to 362 mg (2 mmole) of enamine XV in 50 ml of chloroform. After 24 h, the solvents were removed in vacuo, and preparative TLC of the residue on silica gel (5-40 μ) yielded 43 mg (18%) of isoxazole XVI with mp 193-195°C. IR spectrum: 1600, 1700 (broad band), 3100, and 3230 cm^{-1}.

Found: C 59.5; H 5.4; N 10.7%; M 262 by mass spectrometry. $C_{13}H_{14}N_2O_4$. Calculated: C 59.5; H 5.4; N 10.7%; M 262.26.

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SYNTHESIS AND STEREOCHEMISTRY OF N-SUBSTITUTED 3,5-DIBENZOYL-4-PHENYLPIPERIDINES*

M. V. Denisenko, G. V. Pavel', and M. N. Tilichenko

UDC 547.828.829.07:541.63

The addition of methyl-, benyl-, cyclohexyl, and 2-hydroxyethylamines and hydroxylamine to 2,4-dibenzoyl-3-phenyl-1,4-pentadiene in dimethylformamide leads to the formation of stereoisomers of the corresponding N-substituted 3,5-dibenzoyl-4-phenylpiperidines in almost quantitative yields. The configurations of the stereoisomers obtained were determined by PMR spectroscopy, and their interconversions under the influence of alkali were studied.

In a preliminary communication [2] we described the formation of the α and β forms of N-substituted 3,5-dibenzoyl-4-phenylpiperidines (II, III) by the reaction of, respectively, methyl- and benzylamine with 2,4-dibenzoyl-3-phenyl-1,4-pentadiene (I). In the present paper we present data on the addition of primary amines and hydroxylamine to diketone I and on the stereochemistry and interconversions of the resulting stereoisomeric piperidines II-VI.

*Communication 34 from the series "Reactions of 1,5-Diketones." See [1] for communication 33.

Far Eastern State University, Vladivostok 690600.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 235-239, February, 1979. Original article submitted April 24, 1978.

0009-3122/79/1502-0198$07.50