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Synthesis of Dehydro Derivatives of Cycloheximide and Inactone

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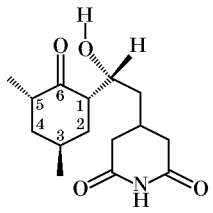
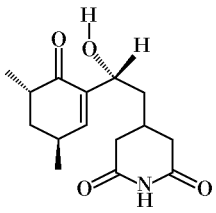
Abstract—Catalytic hydrogenation of 3-chloro-2-(2,6-dioxopiperidin-4-ylacetyl)-2-cyclohexenones over palladium catalyst leads to formation of dehydrocycloheximide derivatives. Reduction of the same compounds with Zn–Ag yields dehydroinactone derivatives.

Glutarimide antibiotics cycloheximide (**I**) [1] and inactone (**II**) [2] were isolated from *Streptomyces griseus*. The synthesis of cycloheximide was described previously [3].

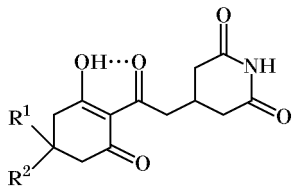


I

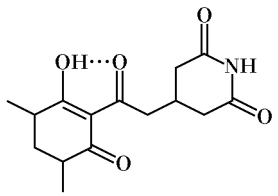


II

In the preceding publications [4, 5] we proposed schemes for the synthesis of some analogs of glutarimide antibiotics from cyclic triacylmethanes having a glutarimide fragment in the side chain. We described modifications of the β-tricarbonyl system in compounds **III**–**VI**, which are 6-oxo derivatives of dehydrocycloheximide and its 4,4-dimethyl, 4-methyl, and 3,5-bisnormethyl analogs, through regioselective transformation of one carbonyl group into enamino, the degree of oxidation of carbon atoms in the β-triketone fragment being retained. Such modifications are important for preparation of new physiologically active substances from both natural antibiotics having a β-tricarbonyl moiety [6] and numerous derivatives of synthetic β-triketones exhibiting a wide spectrum of pesticide activity [7]. On the other hand, the transformation of compounds **III**–**VI** into glutarimide antibiotics like cycloheximide, inactone, streptovitacins, and their analogs implies selective modification of the β-tricarbonyl system. It is known [8] that catalytic hydrogenation of cyclohexane-based β-triketones is not selective: It usually gives mixtures of products formed by reduction of one carbonyl group in the ring or in the side chain. Therefore, we examined different ways of reduction of diketones **VII**–**X** [4, 9]. Diketone **X** was a mixture of *cis* and *trans* isomers at a ratio of 1 : 3. The catalytic hydrogenation of compounds **VII**–**X** over 30% $Pd/BaSO_4$ resulted in reduction of of the C=C bond and hydrodechlorination to afford β-diketones **XI**–**XIV** (Scheme 1). Compounds **XI**, **XII**, and **XIII** are analogs of dehydrocycloheximide (**XIV**), differing by the number and position of methyl groups in the cyclohexene ring. Compound **XIV** was obtained previously by oxidation of cycloheximide (**I**) or by the total synthesis [3]. The structure of β-diketones **XI**–**XIV** is confirmed by the spectral data. Compound **XIII** shows in the ^1H NMR spectrum signals from the cyclohexane fragment: a singlet from two geminal methyl groups at δ 1.0 ppm and signals from methylene protons at δ 1.46, 2.17, and 2.30 ppm, and a complete set of signals from the glutarimide moiety. The spectra of **XI** and **XII** also contained signals from both structural fragments. It should be noted that all signals in the spectra of **XI**–**XIII** appear



III–**V**



VI

III, $R^1 = R^2 = H$; **IV**, $R^1 = H$, $R^2 = CH_3$; **V**, $R^1 = R^2 = CH_3$.

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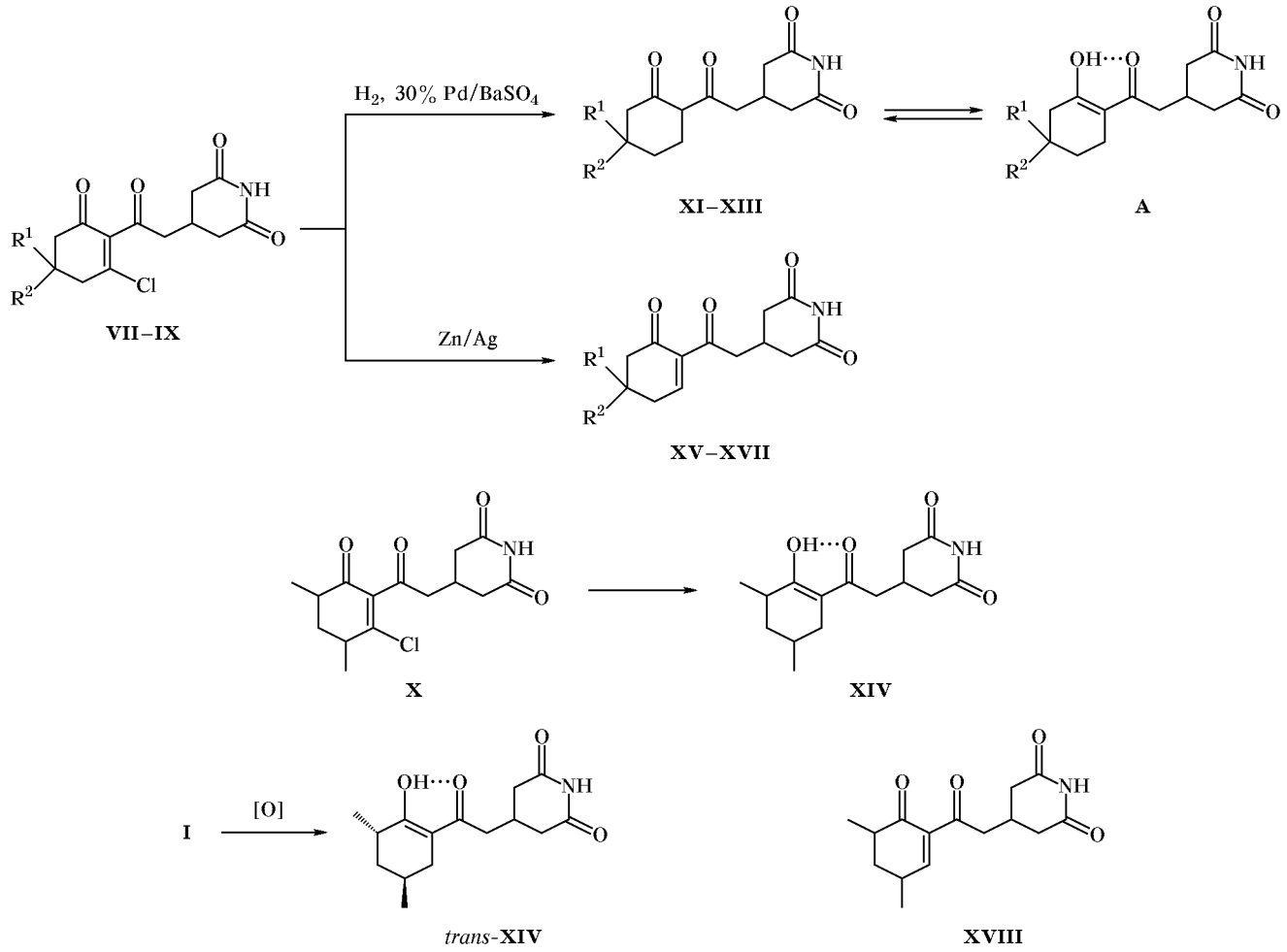
Scheme 1.



VII, **XI**, **XV**, $R^1 = R^2 = H$; **VIII**, **XII**, **XVI**, $R^1 = H$, $R^2 = CH_3$; **IX**, **XIII**, **XVII**, $R^1 = R^2 = CH_3$.

0.1 to 0.35 ppm upfield relative to those observed for initial β-triketones **III**–**V**. This pattern is explained by weaker deshielding effect of the β-dicarbonyl system as compared to β-tricarbonyl.

β-Diketones **XI**–**XIV** exist in the enol form which is stabilized by strong intramolecular hydrogen bond. This follows from the presence in their ^1H NMR spectra of a downfield signal in the region δ 15.6–16.1 ppm, which belongs to the chelated hydroxy proton. In addition, a positive test for enolic hydroxy group was obtained on treatment with a solution of iron(III) chloride. In the IR spectra absorption bands from conjugated C=C and C=O bonds were present at 1616 and 1690 cm^{-1}, respectively. According to the data of [10], 2-acylcyclohexanones **XI**–**XIV** are likely to exist as *endo*-enol tautomers **A**.

Under the same conditions the hydrogenation of diketone **X** was more difficult than the reduction of **VII**–**IX**. Products **XI**–**XIII** were formed from compounds **VII**–**IX** in 82–96% yield in 1–2 days at room temperature. The reaction with diketone **X** required heating for 5 days at 40–45°C, and the yield of **XIV** was 73%. Obviously, the presence of methyl groups in positions *3* and *5* of the cyclohexane ring hinders adsorption of the substrate on the catalyst surface.

With the goal of comparing spectroscopic parameters we have synthesized β-diketone **XIV** by oxidation of cycloheximide **I**. The product had *trans*-arranged methyl groups (*trans*-**XIV**). Its ^1H NMR spectrum contained two doublets from the methyl protons at δ 1.05 and 1.25 ppm and a downfield signal at δ 15.7 ppm from the chelated hydroxy proton. The methylene protons on C^4 gave a multiplet signal at δ 1.53 ppm. In the ^1H NMR spectrum of product **XIV** obtained by hydrogenation of diketone **X** we observed two doublets of the methyl groups, which are typical

of their *trans* arrangement, and one more doublet at δ 1.20 ppm; the intensity ratio of the doublets located at δ 1.05, 1.20, and 1.25 ppm was about 2 : 1 : 1. This means that the reduction product is a mixture of *cis* and *trans* isomers at a ratio of 1 : 1. The doublet at δ 1.20 ppm belongs to the 3-CH_3 group of the *cis* isomer of **XIV**. The upfield doublets from the 5-CH_3 groups in *cis*-**XIV** and *trans*-**XIV** coincide with each other (in both isomers the 5-methyl group is equatorial); therefore, the signal at δ 1.05 ppm has a double intensity. Signals from methyl groups that are not contiguous to the carbonyl group appear separately, for they have different configurations. The observed pattern is similar to the ^{1}H NMR spectra of the corresponding β-triketones [11]: the difference between the chemical shifts of the methyl protons in the *trans* isomer is larger than in the *cis* isomer: 0.20 and 0.15 ppm, respectively. In the downfield region of the spectrum there were two signals from the chelated hydroxy proton at δ 15.68 and 16.08 ppm, which also indicate the presence of a mixture of two isomers. The product of hydrogenation of compound **X** showed in the spectrum both C^4-methylene proton signal of *trans*-**XIV** at δ 1.53 ppm (with a halved intensity) and a multiplet at δ 1.71 ppm, typical of the equatorial methylene proton at C^4 in the *cis* isomer of **XIV**. The signal from the axial proton of the same isomer appears at δ 1.25 ppm.

Thus we have shown that catalytic hydrogenation of diketone **X** results in formation of dehydrocycloheximide (**XIV**) as a mixture of *cis* and *trans* isomers and that compounds **VII**–**IX** give rise to products **XI**–**XIII**. These compounds can also be used as precursors of cycloheximide (**I**) and its analogs.

The reduction of diketone **IX** with a Zn–Ag couple yields dehydroinactone isomer **XVII** (Scheme 1). According to the data of [12, 13], such reactions are carried out in methanol at room temperature and are accompanied by heat evolution. Taking into account poor solubility of compound **IX** in methanol, we performed the reaction in a mixture of methanol with tetrahydrofuran, and the reaction mixture was heated under reflux with stirring. As a result, we obtained two products, compound **XVII** and β-diketone **XIII** at a ratio of 1 : 2. Compound **XVII** is likely to exist in the enedione form. It gave a negative test for enolic hydroxyl with a solution of iron(III) chloride. Its structure is also confirmed by the UV and IR spectral data. In the IR spectrum we observed absorption bands at 1555 and 1680 cm^{-1}, which are characteristic of conjugated C=C and C=O bonds, respectively. The ^{1}H NMR spectrum contained a signal from vinyl proton at δ 6.43 ppm, a two-proton doublet from the C^5-methylene group (δ 2.07 ppm), and singlets from the C^3H_2 protons and geminal methyl groups at δ 2.33 and 1.13 ppm, respectively). These data are well consistent with those published in [12].

An analogous treatment of chlorodiketones **VII**, **VIII**, and **X** led to formation of mixture of the corresponding enediones (dehydroinactone **XVIII** and its analogs **XV** and **XVI**) and β-diketones **XI**, **XII**, and **XIV**. Compound **XVIII** was a mixture of *cis* and *trans* isomers. This follows from the ^{1}H NMR spectrum which contained two signals from the olefinic proton (δ 5.28 and 5.31 ppm) and signals from the C^4H_2 groups of both isomers, δ, ppm: 1.38 m (1H) and 1.78 m (1H) (*cis* isomer, axial and equatorial protons); 1.64 m (2H, *trans* isomer).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The UV spectra were measured on a Specord UV-Vis spectrophotometer in alcohol. The ^{1}H NMR spectra were obtained on a Bruker WM-360 instrument (360 MHz) using tetramethylsilane as internal reference. The melting points were determined on a Koefler device.

2-(2,6-Dioxopiperidin-4-ylacetyl)cyclohexanones XI–XIV. Diketone **VII**–**X**, 0.001 mol, in 10 ml of tetrahydrofuran was hydrogenated over 100 mg of 30% $Pd/BaSO_4$. The catalyst was separated, the solvent was removed from the filtrate, and the residue was recrystallized from ether or acetone.

***trans*-2,4-Dimethyl-6-(2,6-dioxopiperidin-4-ylacetyl)cyclohexanone (XIV).** A solution of 200 mg of CrO_3 in 10 ml of glacial acetic acid was added to a solution of 200 mg of cycloheximide (**I**) in 10 ml of glacial acetic acid. The mixture was stirred for 3 h at 5–10°C, diluted with 50 ml of ice water, and extracted with chloroform. The extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was recrystallized from methylene chloride–ethanol. Yield 170 mg.

2-(2,6-Dioxopiperidin-4-ylacetyl)-2-cyclohexenones XV–XVIII. To 1 g of zinc dust we added 5 ml of 10% hydrochloric acid, and the resulting suspension was shaken periodically. After a few minutes, the solution was separated by decanting, the remaining zinc was washed with acetone (2 × 5 ml) and ether (5 ml), a suspension of 35 mg of silver acetate in 5 ml of boiling acetic acid was added, and the mixture was stirred for 1 min. The solution was separated by decanting, and the dark zinc–silver mixture was washed with acetic acid (5 ml), ether (4 × 5 ml), and

Yields, melting points, and IR and ^{1}H NMR spectra of glutarimide derivatives **XI**–**XVIII**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz)
XI	91	134–136	1615, 1695, 1710, 1725, 3100, 3200 (KBr)	1.69 s (4H), 2.30 s (2H), 2.40 t (4H, 7.8), 2.47 d (2H, 6), 2.78 s (2H), 2.83 s (1H), 8.18 s (1H), 15.68 s (1H)
XII	96	168.5–170.5	1625, 1690, 1700, 1725, 3100, 3200 (KBr)	1.0 d (3H, 6), 1.25 s (2H), 1.78 m (2H), 1.96–2.07 m (1H), 2.26–2.52 m (6H), 2.80 m (3H), 8.1 s (1H), 15.64 s (1H)
XIII	82	136.5–139	1615, 1690, 1705, 1720, 3090, 3183 (KBr)	1.00 s (6H), 1.46 t (2H, 6.6), 2.17 s (2H), 2.30 t (2H, 6.6), 2.37 q (2H, 9), 2.49 d (2H, 6), 2.79 s (2H), 2.84 s (1H), 8.25 s (1H), 15.61 s (1H)
XIV[a]	73	165–169	1610, 1690, 1705, 1730, 3090, 3200 (KBr)	1.05 d (3H, 6), 1.20 d (1.5H, 7.2), 1.25 d (1.5H, 7.2), 1.53 m (2H), 1.71 m (H), 1.87 m (2H), 2.38 m (3H), 2.53 m (3H), 2.78 s (2H), 2.83 s (1H), 8.07 s (1H), 15.68 s (0.5H), 16.08 s (0.5H)
XIV[b]	89	170–173	1625, 1690, 1710, 1730, 3100, 3200 (KBr); 1580, 1612, 1710, 1730, 3380 ($CHCl_3$)	1.05 d (3H, 6), 1.25 d (3H, 7.2), 1.53 m (2H), 1.87 m (2H), 2.38 m (3H), 2.53 m (3H), 2.78 s (2H), 2.83 s (1H), 8.36 s (1H), 15.70 s (1H)
XV[c]	42	128–130	1580, 1675, 1705, 1730, 3100, 3230 (film)	2.36 m (6H), 2.43 d (2H, 6.6), 2.51 d (2H, 6.6), 2.76 m (3H), 5.36 s (1H), 8.43 s (1H)
XVI[d]	50	163–165	1565, 1675, 1720, 1740, 3100, 3210, (CCl_4)	1.10 d (3H, 6.6), 1.45 t (2H, 7.2), 1.75 m (2H), 1.92 m (1H), 2.17–2.66 m (4H), 2.79 m (3H), 5.97 s (1H), 8.07 s (1H)
XVII[e]	18	190–193	1555, 1680, 1705, 1725, 3100, 3220 ($CHCl_3$)	1.13 s (6H), 2.07 d (2H, 6), 2.33 s (2H), 2.66 s (2H), 2.73 d (2H, 6), 2.79 d (2H, 4.8), 2.84 s (1H), 6.43 s (1H), 7.86 s (1H)
XVIII[f]	34	170–173	1600, 1660, 1715, 1740, 3100, 3230 (CCl_4)	1.08–1.31 m (6H), 1.38 m (H), 1.64 m (2H), 1.78 m (1H), 2.08 m (2H), 2.25–2.48 m (4H), 2.69 m (3H), 5.28 s (0.5H), 5.31 s (0.5H), 8.00 s (1H)

[a] Mixture of *cis* and *trans* isomers at a ratio of 1:1.
[b] *trans* Isomer; UV spectrum, λ_{max}, nm (ε): 293 (9655).
[c] β-Diketone **XI** was also obtained (42%).
[d] β-Diketone **XII** was also obtained (21%).
[e] UV spectrum, λ_{max}, nm (ε): 239 (4670). β-Diketone **XIII** was also obtained (40%).
[f] Ratio of *cis* and *trans* isomers 1:1. β-Diketone **XIV** was also obtained (20%).

methanol (5 ml). A solution of 0.001 mol of compound **VII**–**X** in 5 ml of THF was added to the moist Zn–Ag mixture, and the resulting mixture was heated for 2–6 h at 30–40°C under vigorous stirring. The precipitate was filtered off and washed with THF. The filtrate was evaporated, the residue was treated with a mixture of ether (or chloroform) and 10% hydrochloric acid, and the aqueous phase was extracted with the corresponding solvent (5 × 10 ml). The combined extracts were washed and dried over $MgSO_4$, the solvent was removed, and the residue was recrystallized from acetone and was subjected to chromatography on silica gel to isolate β-diketones **XI**–**XIV** and enediones **XV**–**XVIII**.

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