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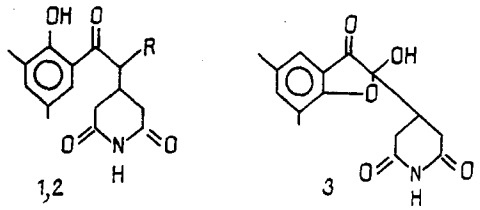
SYNTHESIS OF ACTIPHENOL AND ITS NORMETHYL ANALOGUES AND 6-HYDROXY DERIVATIVES

F. A. Lakhvich, T. N. Buravskaya, and A. A. Akhrem UDC 547.442.3+547.56+547.822.3+547.9

The synthesis has been achieved of the natural antibiotic actiphenol and its 4,6-bisnormethyl and 4,5-bisnormethyl-5-methyl analogues and also its 6-hydroxy derivatives, starting from 2-(β-glutarimidyl-acetyl)cyclohexane-1,3-diones.

The glutarimide antibiotic actiphenol (1), which has been isolated from various streptomycete species [1-3] exhibits antitumoral and fungicidal activities [4, 5]. It was considered for a long time that actiphenol was the only glutarimide antibiotic with an aromatic carbocycle [6]. However, in 1980 a report appeared on the isolation of a new glutarimide antibiotic which was given the name nong-kang 101-G and proved to be a hydroxy derivative of actiphenol in the side chain (2) [7]. Isolation of actiketal (3), which may be regarded as the semiketal of dehydro derivative of compound (2), was described in 1991 [8].

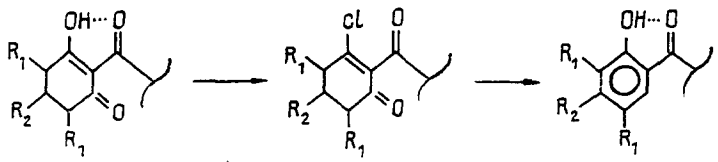
A partial synthesis of actiphenol (1) in very low yield has been effected from cycloheximide [2]. Its total synthesis [9] was based on the reaction of 2,4-dimethylphenol with β-glutarimidylacetic anhydride, followed by the rearrangement, in the presence of $AlCl_3$, of the O-acyl derivative formed.



1,2

1: R=H
2: R=OH

In the development of investigations on the total synthesis of glutarimide antibiotics [10, 11] and other natural compounds based on cyclic β-di- and β-triketones, we have achieved the synthesis of actiphenol (1) and its 4,6-bisnormethyl and 4,6-bisnormethyl-5-methyl analogues (10) and (11) and also the 6-hydroxy derivatives (14) and (15). The key compounds in these syntheses were the previously described [10, 12, 13] 2-(β-glurarimidylacetyl)cyclohexane-1,3-diones (4-6) which were then converted by interaction with oxalyl chloride into the vinylogous acid chlorides (7-9). The structures of the latter were confirmed by a combination of spectral characteristics. Thus, for example, the PMR spectra of the diketovinyl chlorides (7, 8) contained the signals of the protons of the cyclohexene and glutarimide moieties, while the signal of the proton of a chelated enolic hydroxyl in the 17-18 ppm region that is characteristic for the initial β-triketones (4, 5) was absent.



4-6 7-9 1,10,11

4,7,10: $R_1=R_2=H$
5,8,11: $R_1=H$, $R_2=CH_3$
1,6,9: $R_1=CH_3$, $R_2=H$

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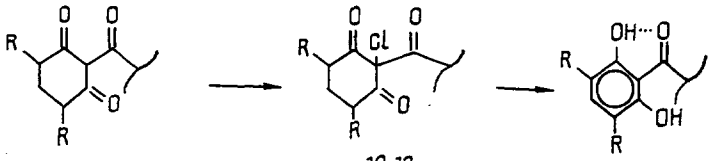
From the β-triketone (6), consisting of cis and trans isomers in a ratio of 7:1, we obtained the corresponding β-chlorovinyl ketone (9) in the form of a 1:3 mixture of cis and trans isomers.

When the diketovinyl chlorides (7, 8) were boiled with palladium black in the presence of cyclohexene as hydrogen acceptor, hydrogenolysis of the C−Cl bonds and aromatization [14] took place with the formation of the acetophenone derivatives (10, 11) in yields of about 70%. The formation of these aromatic compounds, which are the bisnor- and normethyl analogues of actiphenol, was shown by their PMR spectra. Thus, for compound (10), in addition to the signals of the protons of the ethylglutarimide moiety, the signals of four aromatic protons were observed in the form of two triplets (6.92 and 7.52 ppm) and two doublets (7.03 and 7.69 ppm). Furthermore, in the 12.03 ppm region there was the signal of the proton of a hydroxy group bound by an intramolecular hydrogen bond. For compound (11), apart from the signals of three aromatic protons consisting of two doublets (6.73 and 7.56 ppm) and a singlet and also the signal of a chelated hydroxylic proton (12.05 ppm), the signal of the protons of the methyl group of the aromatic moiety was observed in the 2.38 ppm region.

The application of this procedure for the diketovinyl chloride (9) led to actiphenol (1) with a melting point and spectral characteristics coinciding with those of the natural antibiotic and that synthesized previously [9]. The PMR spectrum of compound (1) showed two singlets of protons of methyl groups (2.23 and 2.28 ppm) and two singlets of aromatic protons (7.21 and 7.31 ppm) and also the signal of the chelated proton of a hydroxy group at 12.18 ppm.

The IR spectra of compounds (1, 10, and 11) showed characteristic absorption bands of the glutarimide (1700—1710 and 1725-1730 cm^{-1} for C−O groups and 3100 and 3200-3230 cm^{-1} for −NH bonds) and aromatic moieties.



4, 12, 14: R=H
5, 13, 15: R=CH_3

Another interesting variant of the synthesis of actiphenol analogues, which we studied with the β-triketones (4) and (6) as examples, is connected with the conversion of cyclohex-2-ene-1,3-diones into the corresponding 2-acylresorcinols. For this pupose, the β-triketones (4, 6) were subjected to the action of tert-butyl hypochlorite in chloroform [15]. This gave the non-enolized chlorotriketones (12, 13), the PMR spectra of which lacked the signals of the protons of chelated OH groups in the 17-18 ppm region that were characteristic for the initial compounds. In the IR spectra, in the region of carbonyl absorption there were bands of the C=O groups of the glutarimide and cyclohexanedione moieties (1695-1705, 1720-1725, and 1740-1745 cm^{-1}, respectively). The aromatization of the chlorotriketones (12, 13) under the action of dimethylformamide saturated with hydrogen chloride led to the formation of compounds (14, 15), which are the 6-hydroxy derivatives of actiphenol and of its bisnormethyl derivative. The PMR spectrum of compound (14) contained the signals of three aromatic protons (a two-proton singlet at 6.43 ppm and a one-proton doublet of doublets at 7.30 ppm) and also the signals of the protons of free and chelated hydroxy goups (9.48 and 11.43 ppm, respectively). For hydroxyactiphenol (15) we observed the signal of an aromatic proton (6.56 ppm) and signals of the protons of free and chelated hydroxy groups (9.51 and 10.64 ppm), and also a singlet of the protons of the two methyl groups at 2.17 ppm. Its IR spectrum exhibited the absorption band of a hydroxy group at 3470 cm^{-1}.

It must be mentioned that 2-acylresorcinols with various structures are of interest as important intermediate compounds in the synthesis of drugs. Moreover, 2-acylresorcinols have been detected in in a number of plants used used in folk medicine [16, 17].

Thus, 2-(β-glutarimidylacetyl)-cyclohexane-1,3-diones (4-6) and their vinylog acid chlorides (7-9) are convenient precursors for synthesis of glutarimide antibiotics and their analogs with an aromatic ring.

EXPERIMENTAL

Melting points were measured on a Kofler block. IR spectra were taken on a UR-20 instrument. PMR spectra were recorded on JNM-PS-100, Bruker AC-200, and WM-360-Bruker spectrometers with TMS as internal standard. The course of

the reations was monitored and the purity of the compounds obtained was checked by TLC on Silufol-UV-254 and DC-Alufolien Aluminiumoxid-UV-254 plates. Type LSL_{254} silica gel was used for preparative chromatography.

3-[2-(2-Chloro-6-oxocyclohex-1-enyl)-2-oxoethyl]glutarimides (7-9). A solution of 0.001 mole of a triketone in 5 ml of oxalyl chloride was kept at room temperature for 5-12 h. The excess of reagent was eliminated, the residue was dissolved in $CHCl_3$, and the solution was washed with water, saturated aqueous $NaHCO_3$ solution, and water again. Then it was dried with $MgSO_4$, the solvent was driven off, and the residue was crystallized from acetone. The following compounds were obtained by the method described:

3-[2-(2-Chloro-6-oxocyclohex-1-enyl)-2-oxoethyl]glutarimide (7), yield 90%, mp 187-189°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1625, 1675, 1695, 1710, 3100, 3180. PMR (360 MHz, $CDCl_3$): 2.13 (2H, m), 2.40 (2H, t, J = 7.2 Hz), 2.50 (2H, t, J = 7.2 Hz), 2.73 (2H, d, J = 6 Hz), 2.79 (3H, m), 2.84 (2H, d, J = 4.2 Hz), 8.03 (1H, s).

3-[2-(2-Chloro-4-methyl-6-oxocyclohex-1-enyl)-2-oxoethyl]glutarimide (8), yield 75%, mp 194-196°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1628, 1670, 1700, 1715, 3100, 3200. PMR (100 MHz, $CDCl_3$): 1.10 (3H, d, J = 6.6 Hz), 1.24 (1H, s), 1.38 (4H, t, J = 8.4 Hz), 2.30-2.86 (7H, m), 8.28 (1H, s).

3-[2-(2-Chloro-3,5-dimethyl-6-oxocyclohex-1-enyl)-2-oxoethyl]glutarimide (9), yield 72%, mp 153-154.5°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1620, 1670, 1690, 1710, 3110, 3240. PMR (360 MHz, $CDCl_3$): 1.15 (d), 1.18 (d), 1.33 (d), 1.43 (d) — all 6H, each J = 6.6 Hz), 1.23 (1H, m), 1.95 (2H, m), 2.07 (1H, m), 2.20 (1H, dt, J = 4.8; 13.2 Hz), 2.40 (2H, m), 2.60 (1H, m), 2.71 (2H, d, J = 6.6 Hz), 2.80 (3H, m), 8.41 (1H, s), ratio of cis/trans isomers 1:3 [12].

3-[2-(2-Hydroxyphenyl)-2-oxoethyl]glutarimides (1, 10, 11). A solution of 0.001 mole of a diketovinyl chloride in 50 ml of cyclohexene and 10 ml of THF was boiled in the presence of 0.25 g of Pd black for 6-14 h. The catalyst was filtered off and the residue after elimination of the solvent was crystallized from THF or acetone. The following compounds were obtained by the method described:

3-[2-(2-Hydroxyphenyl)-2-oxoethyl]glutarimide (10), yield 69%, mp 170-172°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1635, 1700, 1725, 3100, 3200. PMR (360 MHz, $CDCl_3$): 2.78-2.89 (5H, m), 3.13 (2H, d, J = 6 Hz), 6.92 (1H, t, J = 7.2 Hz), 7.69 (1H, d, J = 8.4 Hz), 8.28 (1H, s), 12.03 (1H, s).

3-[2-(2-Hydroxy-4-methylphenyl)-2-oxoethyl]glutarimide (11), yield 70%, mp 138-140°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1630, 1700, 1725, 3100, 3200. PMR (360 MHz, $CDCl_3$): 2.38 (3H, s), 2.73-2.91 (5H, m), 3.03 (2H, d, J = 6 Hz), 6.73 (1H, d, J = 8.4 Hz), 6.83 (1H, s), 7.56 (1H, d, J = 8.4 Hz), 8.07 (1H, s), 12.05 (1H, s).

3-[2-(2-Hydroxy-3,5-dimethylphenyl)-2-oxoethyl]glutarimide (1), yield 68%, mp 197-200°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1620, 1710, 1730, 3100, 3230. PMR (360 MHz, $CDCl_3$): 2.23 (3H, s), 2.28 (3H, s), 2.79-2.87 (5H, m), 3.12 (2H, d, J = 6 Hz), 7.21 (1H, s), 7.31 (1H, s), 8.33 (1H, s), 12.18 (1H, s).

3-[2-(1-Chloro-2,6-dioxocyclohexyl)-2-oxoethyl]glutarimides (12, 13). A solution of 0.001 mole of a triketone in dry $CHCl_3$ (20-25 ml) was kept at −5°C for an hour, and then 0.15 ml (0.0011 mole) of tert-butyl hypochlorite was added, and the mixture was left at −5°C for 12 h. Then it was evaporated. The following crystalline chloroketones were obtained by the method described:

3-[2-(1-Chloro-2,6-dioxocyclohexyl)-2-oxoethyl]glutarimide (12), yield quantitative. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1695, 1720, 1745, 3100, 3220. PMR (360 MHz, acetone-d_6): 1.94 (2H, m), 2.35-2.53 (3H, m), 2.73-2.85 (6H, m), 2.90-2.95 (2H, m), 8.03 (1H, s).

3-[2-(1-Chloro-3,5-dimethyl-2,6-dioxocyclohexyl)-2-oxoethyl]glutarimide (13), yield quantitative, mp 42-44°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1705, 1725, 1740, 3100, 3220. PMR (360 MHz, $CDCl_3$): 1.23 d, 1.26 d, 1.27 d, 1.33 d (all 6H, each, J = 6.6 Hz), 1.46 (1H, m), 1.92 (2H, m), 2.20 (1H, m), 2.25-2.43 (3H, m), 2.59-3.05 (5H, m), 3.26 (1H, m), 8.12 (1H, s), ratio of the cis/trans isomers 1:1.

3-[2-(2,6-Dihydroxyphenyl)-2-oxoethyl]glutarimides (14, 15). With protection from moisture, a chlorotriketone was slowly mixed with 5 ml of DMFA containing 0.5-2 g of dry HCl. The temperature was rapidly raised to 120-130°C and was kept there for 15-20 min. After cooling, 70-80% of the solvent was evaporated off, and the residue was extracted with 5 N aqueous HCl (5 ml) and with diethyl ether. The ethereal extracts were washed with 20 ml of 5 N HCl, dried with $MgSO_4$ and evaporated. The residue was crystallized from acetone. The following compounds were obtained by the method described:

3-[2-(2,6-Dihydroxyphenyl)-2-oxoethyl]glutarimide (14), yield 77%, mp 218-220°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1640, 1670, 1730, 3090, 3200, 3430. PMR (360 MHz, acetone-d_6): 2.74-2.83 (5H, m), 3.33 (2H, d, J = 6.6 Hz), 6.43 (2H, d, J = 7.8 Hz), 7.30 (1H, t, J = 8 Hz), 8.03 (1H, s), 9.48 (1H, s), 11.43 (1H, s).

3-[2-(2,6-Dihydroxy-3,5-dimethylphenyl)-2-oxoethyl]glutarimide (15), yield 55%, mp 249-251°C. IR spectrum, ν_{max}^{KBr} (cm^{-1}): 1625, 1690, 1715, 3100, 3200, 3470. PMR (360 MHz, acetone-d_6): 2.17 (6H, s), 2.69-2.84 (5H, m), 3.33 (2H, d, J = 6.6), 6.56 (1H, s), 8.00 (1H, s), 9.51 (1H, s), 10.64 (1H, s).

REFERENCES

1. K. V. Rao and W. P. Cullen, J. Am. Chem. Soc., **82**, No. 5, 1127 (1960).
2. R. J. Highet and V. Prelog, Helv. Chim. Acta, **42**, No. 7, 1523 (1959).
3. K. V. Rao, J. Org. Chem., **25**, No. 4, 661 (1960).
4. H. Zhang, Y. Ye, C. Zhang, and C. Zai, Weishengu Xuebao, **21**, No. 4, 464 (1981); Chem. Abstr., **96**, 118576c (1982).
5. F. Johnson, US Patent 3,152,130; Chem. Abstr., **62**, 484g (1965).
6. F. Johnson, Fortschr. Chem. Org. Naturst., **29**, 140-208 (1971).
7. J. Hua and Y. Xie, Hua Hsueh Hsueh Pao, **38**, No. 3, 275 (1980); Chem. Abstr., **93**, 219277z (1980).
8. T. Sonoda, H. Osada, J. Usawa, and K. Isono, J. Antibiot, **44**, 160 (1991).
9. F. Johnson, J. Org. Chem., **27**, No. 10, 3658 (1962).
10. A. A. Akhrem, F. A. Lakhvich, S. I. Budai, T. S. Khlebnikova, and T. N. Shcherbakova, Dokl. Akad. Nauk. SSSR, **226**, No. 6, 1326 (1976)
11. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Khim. Geterotsikl. Soedin., No. 2, 230 (1979).
12. F. A. Lakhvich, T. N. Buravskaya, and A. A. Akhrem, Vestsi Akad. Navuk Belarusi. Swer. Khim. Navuk, No. 2, 77 (1992).
13. A. A. Akhrem, F. A. Lakvich, S. I. Budai, T. S. Khlebnikova, and I. I. Petrusevich, Synthesis, No. 12, 925 (1978).
14. A. A. Akhrem, A. M. Moiseenkov, and F. A. Lakvich, Izv. Akad. Nauk SSSR. Ser. Khim., No. 11, 2625 (1970).
15. F. A. Lakvich, V. A. Kozinets, D. B. Rubinov, and A. A. Akhrem., Zh. Org. Khim., **23**, No. 12, 2626 (1987).
16. N. F. Cooray, E. R. Jansz, S. Wimalasena, et al., Phytochemistry, **26**, No. 12, 3369 (1987).
17. A. Friesz and G. Cresmely, Hungarian Patent 24,590; Chem. Abstr., **99**, 122034d (1983).