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Synthesis of New Carboxy Lactones and Some Their Transformations

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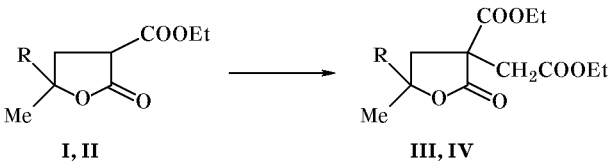
Abstract—Alkylation of 2-ethoxycarbonyl-4-pentanolides with ethyl chloroacetate gave 2-ethoxycarbonyl-2-ethoxycarbonylmethyl-4-pentanolides. Alkaline hydrolysis of the latter afforded 2-carboxymethyl-4-pentanolides which were converted into the corresponding acyl chlorides in high yield by treatment with thionyl chloride in the presence of a catalytic amount of dimethylformamide. Reaction of 2-chloroformylmethyl-4-pentanolides with thiosemicarbazide, followed by treatment with alkali, resulted in formation of 2-(5-mercapto-1,2,4-triazol-3-ylmethyl)-4-pentanolides.

The present study continues the series of our systematic investigations in the field of biologically active substances having a saturated γ-lactone ring [1–3]. We previously described [4, 5] a procedure for preparation of 4-substituted 2-ethoxycarbonyl-4-pentanolides which possess a wide synthetic potential. In the present communication we report on some transformations leading to carboxylactone esters and heterocyclic compounds having a lactone ring as substituent.

It is known that carboxylactones and esters derived therefrom are used as propellant additives [6] and in the synthesis of lactone derivatives as lubricant additives [7, 8], plasticizers [9], etc. Taking the above into account, 2-ethoxycarbonyl-4-pentanolides **I** and **II** were brought into reaction with ethyl chloroacetate in the presence of an equimolar amount of sodium ethoxide in anhydrous ethanol. The reaction gave the corresponding 2-ethoxycarbonylmethyl derivatives **III** and **IV** (Scheme 1).

Scheme 1.

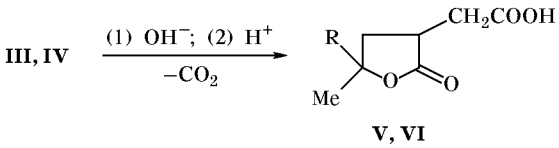


I, II **III, IV**

I, **III**, R = Me; **II**, **IV**, R = H.

Compounds **III** and **IV** were then subjected to alkaline hydrolysis. The best results were obtained when the reaction was carried out in 30% aqueous sodium hydroxide, first at room temperature and then on heating for 3 h. The yields of butanolides **V** and **VI** were 80–90% (Scheme 2).

Scheme 2.

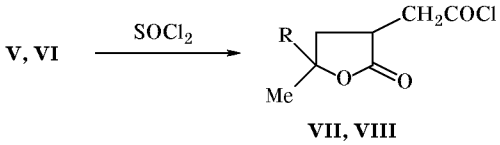


V, VI

V, R = Me; **VI**, R = H.

Carboxylic acids **V** and **VI** were converted into chlorides **VII** and **VIII** by treatment with thionyl chloride. Products **VII** and **VIII** were obtained in high yields (80–90%) when the reaction was carried out in dry benzene in the presence of a catalytic amount of dimethylformamide (Scheme 3).

Scheme 3.



VII, VIII

VII, R = Me; **VIII**, R = H.

We previously synthesized triazolyl-substituted lactones which showed a hypotensive effect [10].

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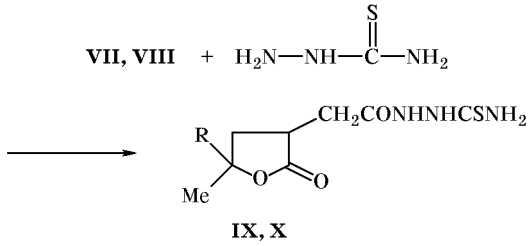
With the goal of obtaining new triazolyl lactones and studying substituent effect on their pharmacological properties we examined the reaction of acyl chlorides **VII** and **VIII** with thiosemicarbazide in dry benzene. These reactions smoothly afforded compounds **IX** and **X** in 76–87% yield (Scheme 4).

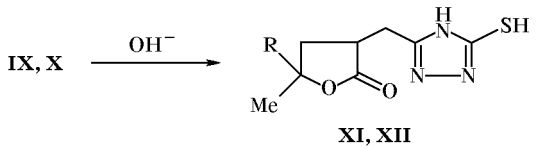
Scheme 4.



IX, R = Me; **X**, R = H.

Cyclization of thiosemicarbazides **IX** and **X** in 16% aqueous sodium hydroxide gave triazolylmethylpentanolides **XI** and **XII** (Scheme 5).

Scheme 5.



XI, R = Me; **XII**, R = H.

All the compounds prepared were characterized by physical constants, elemental analysis data, and ^{1}H and IR spectra, and their purity was proved by TLC and GLC.

EXPERIMENTAL

The IR spectra of compounds **III** and **IV** (prepared as thin films) and **V**–**XII** (dispersed in mineral oil) were recorded on a Nicolet FTIR NEXUS instrument. The ^{1}H NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz) in DMSO-d_6. Gas–liquid chromatography was performed on a Varian Model 3600 chromatograph using a DB-5 capillary column (15 m × 0.25 mm, film thickness 0.25 μm); flame ionization detector (300°C); oven temperature 180–250°C; carrier gas helium, flow rate 18.9 ml/s. Silufol UV-254 plates were used for TLC, eluent alcohol–benzene–hexane (3:3:10) (A) or alcohol–benzene (1:5) (B). The melting points of crystalline products were determined on a Boetius device. Initial compounds **I** and **II** were synthesized by the procedure described in [5].

2-Ethoxycarbonyl-2-ethoxycarbonylmethyl-4-methyl-4-pentanolide (III). A dry four-necked flask equipped with a mechanical stirrer, reflux condenser, dropping funnel, and thermometer was charged with 150 ml of anhydrous ethanol and 3.45 g (0.15 mol) of metallic sodium. When the metal dissolved, the solution was cooled to 20–25°C, and 25.8 g (0.15 mol) of butanolide **I** was added. The mixture was stirred for 0.5 h, and 20.2 g (0.165 mol) of ethyl chloroacetate was added dropwise. The mixture was stirred for 3 h at 20–25°C and was then heated under reflux until it became neutral. The solvent was distilled off, and dilute hydrochloric acid was added to the residue to pH 2–3. The mixture was extracted with ether, the extract was washed with water and dried over anhydrous magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 35.9 g (88%), bp 119–120°C (2 mm), n_D^{20} = 1.4515, d_4^{20} = 1.1239, R_f 0.7 (A). IR spectrum, ν, cm^{-1}: 1770 (C=O, lactone); 1730 (C=O, ester); 1183, 1225 (C–O–C). Found, %: C 57.45; H 7.50. $C_{13}H_{20}O_6$. Calculated, %: C 57.35; H 7.35.

2-Ethoxycarbonyl-2-ethoxycarbonylmethyl-4-pentanolide (IV) was synthesized as described above for compound **III** from 2.3 g (0.1 mol) of metallic sodium, 20 g (0.1 mol) of pentanolide **II**, and 13.5 g (0.11 mol) of ethyl chloroacetate in 100 ml of anhydrous ethanol. Yield 20.1 g (78%), bp 118–120°C (1 mm), n_D^{20} = 1.4515, d_4^{20} = 1.1464, R_f = 0.51 (A). IR spectrum, ν, cm^{-1}: 1770 (C=O, lactone); 1733 (C=O, ester); 1183, 1225 (C–O–C). Found, %: C 55.95; H 7.10. $C_{12}H_{18}O_6$. Calculated, %: C 55.81; H 6.98.

2-Carboxymethyl-4-methyl-4-pentanolide (V). A three-necked flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was charged with 70 g of 30% aqueous sodium hydroxide; the solution was cooled, and 40.8 g (0.15 mol) of pentanolide **III** was added dropwise. When the mixture became homogeneous, it was stirred for 1 h at room temperature and for 3 h at 80–85°C. The mixture was cooled, acidified with concentrated hydrochloric acid to pH 1–2, and extracted with ether. The extract was washed with a small amount of water and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was heated at 250–300°C (12–15 mm), cooled, and recrystallized from water. Yield 23.2 g (90%), mp 147–149°C. IR spectrum, ν, cm^{-1}: 3400–2500 (OH); 1738 (C=O, lactone); 1700 (C=O, COOH); 1230, 1183 (C–O–C).

^{1}H NMR spectrum, δ, ppm: 1.1–1.22 two s (6H, CH_3), 1.86–2.36 two d (2H, CH_2, ring), 2.36–2.7 two d (2H, 2-CH_2), 2.99–3.11 m (1H, CH), 12.1 br.s (1H, OH). Found, %: C 55.70; H 7.15. $C_8H_{12}O_4$. Calculated, %: C 55.81; H 6.98.

2-Carboxymethyl-4-pentanolide (VI) was synthesized as described above for compound **V** from 25.8 g (0.1 mol) of pentanolide **IV** and 46.7 g of 30% aqueous sodium hydroxide. After decarboxylation, the residue was distilled under reduced pressure. Yield 12.6 g (80%), bp 144–145°C (1 mm), n_D^{20} = 1.4690. The product crystallized on storage, mp 68–69°C (from hexane). IR spectrum, ν, cm^{-1}: 3400–2500 (OH); 1738 (C=O, lactone); 1700 (C=O, COOH); 1230, 1183 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.27 d (3H, CH_3), 1.88–2.40 d.d (2H, CH_2, ring), 2.40–2.67 d (2H, 2-CH_2), 2.96–3.15 m (1H, CH), 4.4–4.65 m (1H, CH), 12.22 br.s (1H, OH). Found, %: C 53.30; H 6.50. $C_7H_{10}O_4$. Calculated, %: C 53.16; H 6.33.

2-Chloroformylmethyl-4-methyl-4-pentanolide (VII). A round-bottomed flask was charged with 17.2 g (0.1 mol) of compound **V**, 50 ml of dry benzene, 13.1 g (0.11 mol) of thionyl chloride, and 1 ml of dimethylformamide. The mixture was left to stand for 2 h at room temperature and was then refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was distilled at 109–110°C (1 mm). Yield 16.2 g (85%). After distillation, the product crystallized, mp 68–69°C. Found, %: C 50.50; H 5.65; Cl 18.75. $C_8H_{11}ClO_3$. Calculated, %: C 50.39; H 5.77; Cl 18.64.

2-Chloroformylmethyl-4-pentanolide (VIII) was synthesized as described above for compound **VII** from 15.8 g (0.1 mol) of pentanolide **VI**, 13.1 g (0.11 mol) of thionyl chloride, and 1 ml of dimethylformamide in 50 ml of dry benzene. Yield 14.3 g (81%), bp 97°C (2 mm), n_D^{20} = 1.4735, d_4^{20} = 1.2537. Found, %: C 47.45; H 5.20; Cl 20.30. $C_7H_9ClO_3$. Calculated, %: C 47.59; H 5.10; Cl 20.11.

4-Methyl-2-(1-thiosemicarbazidocarbonyl)-4-pentanolide (IX). A three-necked flask was charged with 0.1 g (0.1 mol) of thiosemicarbazide and 40 ml of dry benzene, and a solution of 9.5 g (0.05 mol) of chloride **VII** in 10 ml of dry benzene was added dropwise. The mixture was stirred for 0.5 h at 20–25°C and was then heated for 4 h under reflux. The solvent was distilled off, and the residue was cooled and treated with water. The precipitate was filtered off, washed with water, and dried. Yield 10.7 g (87%), mp 204–206°C (aqueous alcohol, 1:1), R_f 0.50 (B). IR spectrum, ν, cm^{-1}: 3425–3100 (NH, NH_2), 1750 (C=O, lactone), 1690 (C=O, amide), 1630 (δNH_2), 1210 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.2–1.23 two s (6H, CH_3), 1.46–1.7 d.d (2H, CH_2, ring), 2.23–2.60 m (2H, 2-CH_2), 2.85–3.0 m (1H, CH), 4.45–4.63 m (1H, CH), 7.05–7.85 br.s (2H, NH_2), 8.93–9.85 br.s (2H, NH). Found, %: C 44.20; H 6.20; N 17.30; S 13.25. $C_9H_{15}N_3O_3S$. Calculated, %: C 44.08; H 6.12; N 17.14; S 13.06.

2-(1-Thiosemicarbazidocarbonylmethyl)-4-pentanolide (X) was synthesized as described above for compound **IX** from 6.8 g (0.075 mol) of thiosemicarbazide and 6.6 g (0.0375 mol) of chloride **VIII** in 40 ml of dry benzene. Yield 6.6 g (76%), mp 199–200°C (from water), R_f 0.46 (B). IR spectrum, ν, cm^{-1}: 3425–3100 (NH, NH_2), 1750 (C=O, lactone), 1690 (C=O, amide), 1630 (δNH_2), 1210 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.38 d (3H, CH_3), 1.50–1.71 d.d (2H, CH_2, ring), 2.2–2.65 m (2H, 2-CH_2), 2.9–3.07 m (1H, CH), 4.5–4.67 m (1H, CH), 7.0–7.9 br.s (2H, NH_2), 8.9–9.9 br.s (2H, NH). Found, %: C 41.70; H 5.55; N 18.30; S 13.95. $C_8H_{13}N_3O_3S$. Calculated, %: C 41.56; H 5.63; N 18.18; S 13.85.

2-(5-Mercapto-1,2,4-triazol-3-ylmethyl)-4-methyl-4-pentanolide (XI). A round-bottomed flask was charged with a 16% aqueous solution of sodium hydroxide, prepared from 3 g (0.075 mol) of NaOH, and 7.35 g (0.03 mol) of compound **IX**. The mixture was heated for 4 h on a boiling water bath, cooled, diluted with water, and acidified with hydrochloric acid to pH 2–3. The precipitate was filtered off, washed with water, and dried in air. Yield 4.8 g (71%), mp 262–263°C (from aqueous alcohol, 1:1), R_f 0.52 (B). IR spectrum, ν, cm^{-1}: 3290, 3226 (NH); 1734 (C=O, lactone); 1590 (C=N); 1240 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.17–1.24 two s (6H, CH_3), 1.8–2.36 d.d (2H, CH_2, ring), 2.58–3.08 d.d (2H, 2-CH_2), 3.15–3.35 m (1H, CH), 12.98 s (1H, NH), 13.1 s (1H, SH). Found, %: C 47.65; H 5.65; N 18.65; S 14.22. $C_9H_{13}N_3O_2S$. Calculated, %: C 47.58; H 5.73; N 18.50; S 14.10.

2-(5-Mercapto-1,2,4-triazol-3-ylmethyl)-4-pentanolide (XII) was synthesized as described above for compound **XI** from 4.6 g (0.02 mol) of compound **X** and 2 g (0.05 mol) of sodium hydroxide. Yield 3 g (70%), mp 221–223°C (from water). R_f 0.48 (B). IR spectrum, ν, cm^{-1}: 3290, 3226 (NH); 1734 (C=O, lactone); 1590 (C=N); 1240 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.3 s (3H, CH_3), 1.78–2.25 d.d (2H, CH_2, ring), 2.4–2.98 d.d (2H, 2-CH_2), 3.07–3.3 m (1H, CH), 4.5–4.63 m (1H, CH), 12.95 s (1H, NH), 13.0 s (1H, SH). Found, %: C 45.22; H 5.05; N 19.85; S 15.20. $C_8H_{11}N_3O_2S$. Calculated, %: C 45.07; H 5.16; N 19.72; S 15.02.

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