

Condensation of 4-Substituted 2-Ethoxycarbonyl-4-pentanolides with α,β -Unsaturated Compounds

T. V. Kochikyan, V. S. Arutyunyan, E. V. Arutyunyan, and A. A. Avetisyan

Yerevan State University, Yerevan, 375025 Armenia

Received August 2, 2002

Abstract—Condensation of 4-substituted 2-ethoxycarbonyl-4-pentanolides with methyl acrylate and acrylonitrile under Michael reaction conditions in the presence of sodium methylate affords 4-substituted 2-ethoxycarbonyl-2-(2-methoxycarbonyl- or cyano)ethyl-4-pentanolides. The latter were subjected to alkaline hydrolysis, and 4-substituted 2-carboxy-2-(2-carboxyethyl)-4-pentanolides were isolated which on decarboxylation yielded 4-substituted 2-(2-carboxyethyl)-4-pentanolides. The partial hydrolysis of 2-ethoxycarbonyl-2-(2-cyanoethyl)-4-pentanolides gave rise to previously unknown cyanolactones.

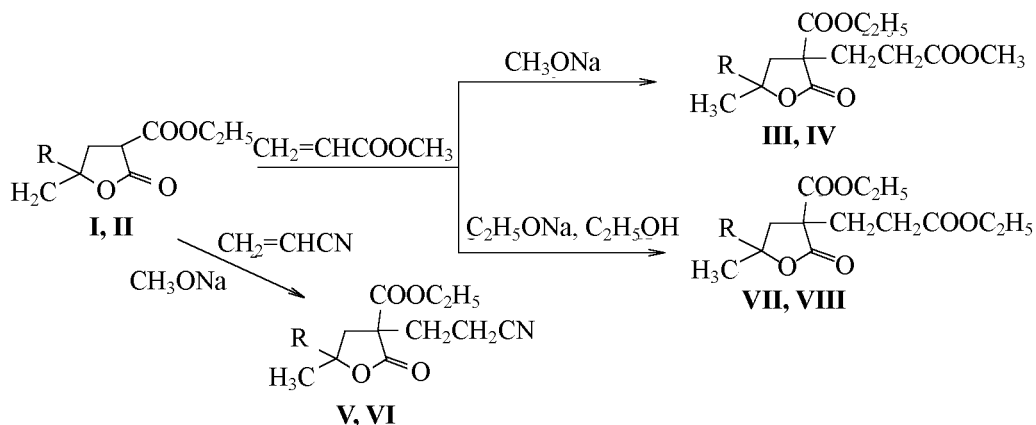
We demonstrated formerly [1–3] that 4-substituted 2-acetyl or 2-ethoxycarbonyl-4-pentanolides are good CH-acids of cyclic structure that make possible a transition to various lactone-containing compounds. In extension of the research in this field and aiming at preparation of new ester lactones of a new generation we studied the condensation of 4-substituted 2-ethoxycarbonyl-4-pentanolides **I**, **II** with methyl acrylate and acrylonitrile under Michael reaction conditions.

This reaction catalyzed with sodium methylate proceeds very vigorously and furnishes 4-substituted 2-ethoxycarbonyl-2-(2-methoxycarbonyl- or cyano)ethyl-4-pentanolides (**III**–**VI**) in high yield. It was established that when the condensation of pentanolides **I**, **II** with methyl acrylate was carried out in the presence of sodium ethylate and of sufficient amount of ethanol the reaction was accompanied with

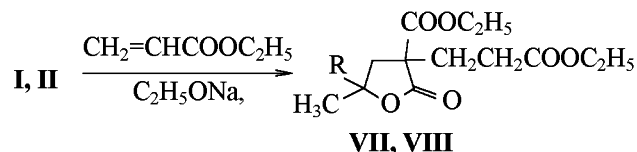
transesterification giving rise to 4-substituted 2-ethoxycarbonyl-2-(2-ethoxycarbonylethyl)-4-pentanolides (**VII**, **VIII**).

Optimal reaction conditions were developed. It was established that the best results were obtained if a mixture of pentanolide **I**, **II** and the α,β -unsaturated compound were heated to 45°C, and then sodium alcoholate was added, and the reaction was carried out at 45–50°C. The structure of ester lactones **VII**, **VIII** was proved by an independent synthesis (the condensation of lactones **I**, **II** with ethyl acrylate) affording identical compounds.

In order to prepare carboxylactones of new structure we studied the alkaline hydrolysis of alkoxy-carbonyllactones **III**, **IV**, **VII**, and **VIII**. These compounds were readily hydrolyzed with a slight excess of 30% water solution of sodium hydroxide. After

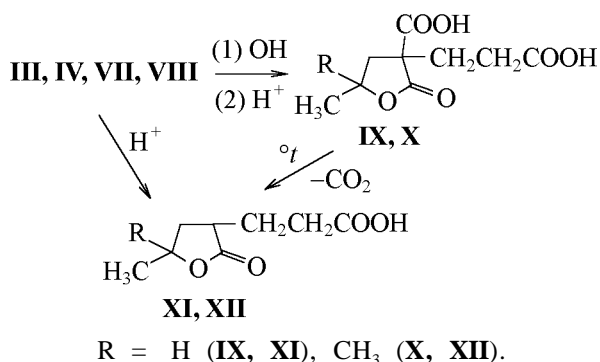


R = H (**I**, **III**, **V**, **VII**), CH_3 (**II**, **IV**, **VI**, **VIII**).

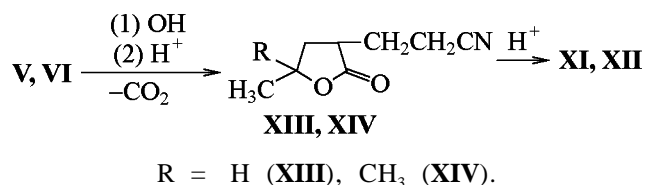


acidifying the reaction mixture we successfully isolated the corresponding dicarboxylactones, 4-substituted 2-carboxy-2-(2-carboxyethyl)-4-pentanolides (**IX, X**) which on decarboxylation furnished 4-substituted 2-(2-carboxyethyl)-4-pentanolides (**XI, XII**).

The best results of acid hydrolysis of compounds **III, IV, VII, VIII** was obtained at boiling them with diluted (1:2) hydrochloric acid for 10–12 h. Therewith the yields of (2-carboxyethyl)pentanolides **XI, XII** attained 90–94%.



Investigating the alkaline hydrolysis of cyanolactones **V, VI** we succeeded in performing a partial hydrolysis affording 4-substituted 2-(2-cyanoethyl)-4-pentanolides (**XIII, XIV**) which were hydrolyzed with acid to yield carboxylactones **XI, XII**.



It was shown that the alkaline hydrolysis should be carried out with 25% aqueous sodium hydroxide in the presence of catamine AB. Therewith the ethoxycarbonyl group is hydrolyzed under mild conditions, and the cyano group remains intact. The acid hydrolysis of cyanolactones **XIII, XIV** was successfully carried out with diluted (1:1) hydrochloric acid.

All compounds synthesized were characterized by physicochemical constants and elemental analyses, with IR spectra, and their homogeneity was proved by TLC and GLC.

EXPERIMENTAL

IR spectra of compounds **III–VIII, XIII, XIV** were recorded from thin films, those of compounds **IX–XII** from mulls in mineral oil on spectrophotometers UR-20 or Nicolet FTIR NEXUS. GLC was carried out on chromatograph Varian Model 3600 equipped with a flame-ionization detector (300°C), column DB5 (15000 × 0.25 mm, stationary phase 0.25 μ thick), oven temperature 180–250°C, carrier gas helium, flow rate 18.9 ml s⁻¹. TLC was performed on Silufol UV-254 plates, eluent ethanol–benzene–hexane, 3:3:10. Melting points were measured on a Boetius heating block.

Initial 4-substituted 2-ethoxycarbonyl-4-pentanolides were prepared by procedure [4].

4-Substituted 2-ethoxycarbonyl-2-(2-methoxycarbonyl- or cyano)ethyl-4-pentanolides (**III–VI**).

A mixture of 0.1 mol of an appropriate 4-substituted 2-ethoxycarbonyl-4-pentanolide and 0.1 mol of methyl acrylate or acrylonitrile was heated to 45°C, and dropwise was added a freshly prepared sodium methylate solution (0.2 g of sodium dissolved in 10 ml of anhydrous methanol) maintaining temperature below 50°C. After self-cooling of the mixture it was stirred for 1 h at 20–25°C and 2 h at 60–65°C. The obtained mixture was cooled, dilute hydrochloric acid was added to pH 2–3. The reaction product was extracted into ether, the combined extracts were washed with water and dried on anhydrous magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum (see table).

4-Substituted 2-ethoxycarbonyl-2-(2-ethoxycarbonyl)ethyl-4-pentanolides (**VII, VIII**).

(a) Compounds **VII, VIII** were prepared similarly to substances **III–VI** from 0.05 mol of an appropriate pentanolide **I, II**, 4.7 g (0.055 mol) of methyl acrylate, and sodium ethylate obtained by dissolving 0.1 g of metallic sodium in 10 ml of anhydrous ethanol. After self-cooling of the mixture it was stirred for 2 h at 20–25°C and 7 h at 75–80°C. The ethanol was distilled off, and the residue was worked up as described above. (b) The preparation was carried out similarly to substances **III–VI** from 0.05 mol of an appropriate pentanolide **I, II**, 5.5 g (0.055 mol) of ethyl acrylate, and sodium ethylate obtained by dissolving 0.1 g of metallic sodium in 10 ml of anhydrous ethanol. After self-cooling of the mixture it was stirred for 1 h at 20–25°C and 2 h at 60–65°C. The ethanol was distilled off, and the residue was worked up as described above.

Yields, constants, and elemental analyses of 2,4-disubstituted 2-(2-alkoxycarbonyl- or 2-cyanoethyl)-4-pentanolides **III–VIII**, **XIII**, **XIV**

Compd. no.	Yield, %	R	bp, °C, (mm Hg)	n_D^{20}	d_4^{20}	R_f	Found, %			Formula	Calculated, %		
							C	H	N		C	H	N
III	80	H	130–131(2)	1.4580	1.1702	0.49	55.95	6.80	–	C ₁₂ H ₁₈ O ₆	55.81	6.98	–
IV	79	CH ₃	129–130(1)	1.4575	1.1406	0.50	57.50	7.20	–	C ₁₃ H ₂₀ O ₆	57.35	7.35	–
V	83	H	135–136(1)	1.4635	1.1575	0.45	58.80	6.55	6.30	C ₁₁ H ₁₅ NO ₄	58.67	6.67	6.22
VI	87	CH ₃	141(1)	1.4595	1.1174	0.42	60.15	7.20	5.95	C ₁₂ H ₁₇ NO ₄	60.25	7.11	5.86
VII	76	H	135–136(2)	1.4535	1.1376	0.55	57.25	7.45	–	C ₁₃ H ₂₀ O ₆	57.35	7.35	–
VIII	90	CH ₃	134–135(1)	1.4550	1.1167	0.56	58.60	7.80	–	C ₁₄ H ₂₂ O ₆	58.74	7.69	–
XIII	80	H	111–112(1)	1.4605	1.0994	0.44	62.85	7.05	9.30	C ₈ H ₁₁ NO ₂	62.75	7.19	9.15
XIV	78	CH ₃	115–116(1)	1.4590	1.0614	0.43	64.55	7.80	8.50	C ₉ H ₁₃ NO ₂	64.67	7.78	8.38

IR spectrum of compounds **III–VIII**, ν , cm⁻¹: 1770 (C=O, lactone), 1740 (C=O, ester), 1130, 1210 (C–O–C), 2250 (C≡N).

2-Carboxy-2-(2-carboxyethyl)-4-pentanolide (IX). To 0.1 mol of 2-ethoxycarbonyl-2-(2-methoxy- or ethoxycarbonylethyl)-4-pentanolide was added dropwise at cooling 140 g of 30% water solution of sodium hydroxide, the mixture was stirred for 1 h at 20–25°C and 4 h at 75–80°C. On cooling the mixture was acidified with concn. HCl to pH 1–2. The separated crystals were filtered off, washed with a little water, and dried. Yield 16.2 g (76%), mp 113–114°C. IR spectrum, ν , cm⁻¹: 2500–3400 (OH), 1738 (C=O, lactone), 1700 (C=O, carboxy group), 1183, 1230 (C–O–C). Found, %: C 50.20; H 5.65. C₉H₁₂O₆. Calculated, %: C 50.00; H 5.56.

2-Carboxy-2-(2-carboxyethyl)-4-methyl-4-pentanolide (X) was obtained in the same way as compound **IX** from 0.15 mol of 2-ethoxycarbonyl-2-(2-methoxy- or ethoxycarbonylethyl)-4-methyl-4-pentanolide and 210 g of 30% water solution of sodium hydroxide. Yield 27.6 g (80%), mp 121–122°C. IR spectrum is identical to that of compound **IX**. Found, %: C 52.30; H 6.20. C₁₀H₁₄O₆. Calculated, %: C 52.17; H 6.09.

A weighed sample of compound **IX**, **X** is quantitatively titrated with 2 equiv of 0.1 N sodium hydroxide solution at room temperature against phenolphthalein.

2-(2-Carboxyethyl)-4-pentanolide (XI). Into a Claisen flask was charged 10.8 g (0.05 mol) of 2-carboxy-2-(2-carboxyethyl)-4-pentanolide, and the flask was heated to 250–300°C in a vacuum of a water-jet pump (15–20 mm Hg). The residue was distilled at still lower pressure. Yield 6.6 g (77%),

bp 154–155°C (1 mm Hg), mp 55–57°C. Found, %: C 55.57; H 7.10. C₈H₁₂O₄. Calculated, %: C 55.81; H 6.98.

2-(2-Carboxyethyl)-4-methyl-4-pentanolide (XII). (a) It was obtained similarly to compound **XI** from 0.05 mol of 2-carboxy-2-(2-carboxyethyl)-4-methyl-4-pentanolide. Yield 9.7 g (94%), bp 159–160°C (1 mm Hg), mp 55–57°C. Found, %: C 57.95; H 7.65. C₉H₁₄O₄. Calculated, %: C 58.06; H 7.53.

(b) A mixture of 0.15 mol of 2-ethoxycarbonyl-2-(2-methoxy- or ethoxycarbonylethyl)-4-methyl-4-pentanolide, 80 ml of concn. HCl, and 120 ml of water was heated for 12 h to weak boiling. The water was distilled off in a vacuum of a water-jet pump, the residue was distilled at a lower pressure. Yield 25.1 g (90%), bp 159–160°C (1 mm Hg), mp 55–57°C.

A weighed sample of compound **XI**, **XII** is quantitatively titrated with 1 equiv of 0.1 N sodium hydroxide solution at room temperature against phenolphthalein.

4-Substituted 2-(2-cyanoethyl)-4-pentanolides (XIII, XIV). To 0.08 mol of an appropriate 4-substituted 2-ethoxycarbonyl-2-(2-cyanoethyl)-4-pentanolide and 0.8 ml of catamine AB was added dropwise 7.2 g (0.2 mol) of sodium hydroxide as 25% water solution, maintaining the mixture temperature at 20–25°C. The stirring at this temperature was continued for 1 h, and 3 h at 55–60°C. On cooling a diluted hydrochloric acid was added to the mixture till pH 2–3. The reaction product was extracted into ether, the extracts were washed with water, and dried on anhydrous magnesium sulfate. On removing the solvent the product was subjected to decarboxylation by heating to 250–300°C in a vacuum of a water-jet

pump (15–20 mm Hg). The residue was distilled at lower pressure.

In the IR spectra of compounds **XIII**, **XIV** lacks the absorption band of the ester group, and only the following bands appear, ν , cm^{-1} : 2250 ($\text{C}\equiv\text{N}$), 1770 ($\text{C}=\text{O}$, lactone), 1130, 1210 ($\text{C}-\text{O}-\text{C}$).

Acid hydrolysis of 4-substituted 2-ethoxycarbonyl-2-(2-cyanoethyl)-4-pentanolides and 4-substituted 2-(2-cyanoethyl)-4-pentanolides. A mixture of 0.04 mol of an appropriate pentanolide and 80 ml of diluted (1 : 1) hydrochloric acid was heated to weak boiling for 5 h. On cooling the reaction product was extracted into ether. The extracts were washed with water and dried with anhydrous magnesium sulfate. On removing the solvent the residue was distilled in

a vacuum. Carboxylactones **XI**, **XII** were obtained in 78–82% yield.

The yields, constants, and elemental analyses of compounds **III–VIII**, **XIII**, **XIV** are given in the table.

REFERENCES

1. Arutyunyan, V.S., Kochikyan, T.V., and Zalianyan, M.G., *Arm. Khim. Zh.*, 1981, vol. 34, p. 1001.
2. Arutyunyan, V.S., Kochikyan, T.V., and Zalianyan, M.G., *Arm. Khim. Zh.*, 1982, vol. 35, p. 386.
3. Kochikyan, T.V., Arutyunyan, E.V., Arutyunyan, V.S., and Avetisyan, A.A., *Zh. Org. Khim.*, 2002, vol. 38, p. 411.
4. Arutyunyan, V.S., Kochikyan, T.V., Arutyunyan, E.V., and Avetisyan, A.A., *Uch. Zap. EGU*, 2002, p. 73.