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SYNTHESIS AND SOME TRANSFORMATIONS OF 4-ALKOXYMETHYL-2-ETHOXYCARBONYL-2-ETHOXYCARBONYLMETHYLBUTANOLIDES

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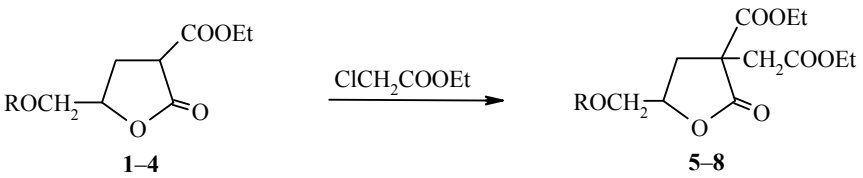
A method was developed for the production of 4-alkoxy-2-ethoxycarbonyl-2-ethoxycarbonyl-methylbutanolides. The latter were subjected to alkaline and acid hydrolysis, leading to 4-alkoxymethyl-2-carboxymethylbutanolides, from which lactone-containing thioureas and amides of carboxylactones with novel structures were obtained.

Keywords: amides, carboxylactone, thioureas, lactone esters.

Derivatives of carboxylactones, which have a wide spectrum of valuable characteristics, are well known. In particular, the esters of carboxylactones with various structures are used as additives for propellants [1] and are the starting materials for the synthesis of heterocyclic compounds [2]. Some amides of carboxylactones exhibit antitumor activity, a hypotensive effect [3], and a inhibiting effect on Ehrlich's ascitic tumor and melanoma B-16 [4]. The few described representatives of lactone-containing acylureas exhibit anti-inflammatory, anticonvulsive, and muscle-relaxing activity [3]. The information presented above demonstrates the importance of research in this field.

Earlier we reported on methods for the production of various ester and carboxy lactone structures [5, 6]. While continuing research in this field, in order to develop a new method for the production of ester lactones based on readily obtainable raw material we studied the alkylation of 4-alkoxymethyl-2-ethoxycarbonylbutanolides **1-4** with ethyl monochloroacetic acid, leading to 4-alkoxymethyl-2-ethoxycarbonyl-2-ethoxycarbonylmethylbutanolides **5-8**.



1–4 **5–8**

5 R = *i*-Pr, **6** R = *i*-Bu, **7** R = Am, **8** R = *i*-Am

The optimum reaction conditions, giving high yields of the desired products, were determined. It was shown that alkylation of the butanolides **1-4** takes place smoothly in the presence of an equimolar amount of sodium ethoxide in absolute ethanol.

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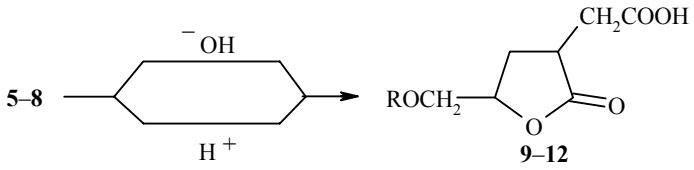
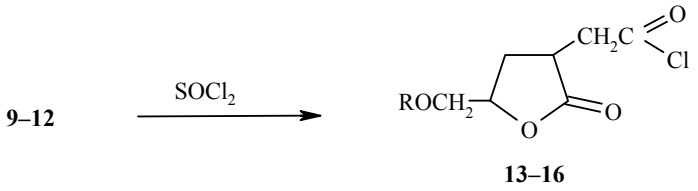
The alkaline hydrolysis of compounds **5-8** was carried out. It was shown that the best results were obtained with a small excess of 30% aqueous sodium hydroxide solution. The yields of the required 4-alkoxymethyl-2-carboxymethylbutanolides **9-12** here amounted to 78-87%.



9 R = *i*-Pr, **10** R = *i*-Bu, **11** R = Am, **12** R = *i*-Am

High yields (77-87%) of the products **9-12** were obtained during the acid hydrolysis of compounds **5-8** with dilute hydrochloric acid (1:2).

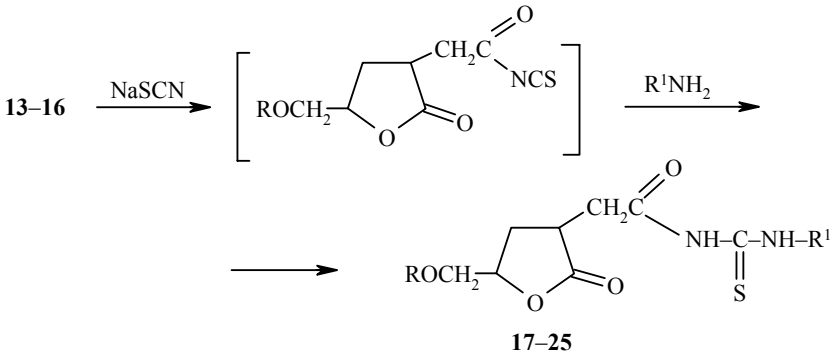
In order to obtain various carboxy lactone derivatives the products were converted into the acid chlorides by reaction of the acids **9-12** with thionyl chloride.



13 R = *i*-Pr, **14** R = *i*-Bu, **15** R = Am, **16** R = *i*-Am

High yields (91-95%) of the desired compounds are obtained when the reaction is carried out in absolute benzene in the presence of small amounts of DMF.

In view of the high biological activity of lactone-containing thioureas, the molecules of which contain two pharmacophoric groups, we synthesized some new compounds of this type **17-25** by reaction of the obtained acyl isothiocyanates with various amines. The yields of the products **17-25** amounted to 70-93%.



17–**20** R = *i*-Pr, **21**, **22** R = *i*-Bu, **23**–**25** R = Am; R^1 – see Table 2

In order to look for more effective biologically active substances and to extend the arsenal of carboxy lactone amides we synthesized certain amides of the acids **9-12** by reaction of the acid chlorides **13-16** with amines. To obtain comparative data we also used the sulfamide products streptocide, albucide, and norsulfazole that are widely used in medical practise. The reaction was carried out in absolute acetone for 2 h. The yields of the amides **26-34** amounted to 77-90%.

TABLE 1. 4-Alkoxy-2-ethoxycarbonyl-2-ethoxycarbonylmethylbutanolides **5-8**, 4-Alkoxymethyl-2-carboxymethyl-butanolides **9-12**, and the Acid Chlorides of 4-Alkoxymethyl-2-carboxymethylbutanolides **13-16**

Compound	n_D^{20}	d_4^{20}	Empirical formula	Found, % / Calculated, %			bp, °C (mm Hg.)	R_f	Yield, %
				C	H	Cl			
5	1.4520	1.1225	$C_{15}H_{24}O_7$	57.10 / 56.96	7.40 / 7.59	—	148-150 (2)	0.59 (A)	77
6	1.4515	1.1006	$C_{16}H_{26}O_7$	58.35 / 58.18	7.75 / 7.87	—	143 (1)	0.61 (A)	79
7	1.4520	1.0898	$C_{17}H_{28}O_7$	59.20 / 59.30	8.25 / 8.13	—	170 (2)	0.65 (A)	87
8	1.4510	1.0851	$C_{17}H_{28}O_7$	59.40 / 59.30	8.00 / 8.13	—	161 (1)	0.63 (A)	87
9	1.4638	1.1680	$C_{10}H_{16}O_5$	55.59 / 55.56	7.55 / 7.40	—	184 (3)	—	78
10	1.4630	1.1310	$C_{11}H_{18}O_5$	57.60 / 57.39	7.55 / 7.83	—	170 (1)	—	87
11	1.4655	1.1129	$C_{12}H_{20}O_5$	59.00 / 59.02	8.10 / 8.20	—	178 (1)	—	81
12	1.4650	1.1183	$C_{12}H_{20}O_5$	59.30 / 59.02	8.10 / 8.20	—	192-193 (3)	—	80
13	1.4646	1.1760	$C_{10}H_{15}ClO_4$	51.00 / 51.17	6.00 / 6.40	15.50 / 15.14	133 (1)	—	94
14	1.4652	1.1492	$C_{11}H_{17}ClO_4$	53.50 / 53.12	6.60 / 6.84	14.00 / 14.29	138 (1)	—	95
15	1.4664	1.1355	$C_{12}H_{19}ClO_4$	54.60 / 54.86	7.40 / 7.24	13.80 / 13.52	153 (2)	—	91
16	1.4665	1.1335	$C_{12}H_{19}ClO_4$	56.65 / 54.86	7.45 / 7.24	13.75 / 13.52	152 (2)	—	93

TABLE 2. 1-Substituted 3-(4'-Alkoxymethylbutanolidyl-2'-methylcarbonyl)thioureas **17-25** and the Amides of 4-Alkoxymethyl-2-carboxymethylbutanolides **26-34**

Compound	R^1	Empirical formula	Found, % / Calculated, %				mp, °C	R_f	Yield, %
			C	H	N	S			
1	2	3	4	5	6	7	8	9	10
17	*p*-$O_2NC_6H_4$	$C_{17}H_{21}N_3O_6S$	51.55 / 51.65	5.45 / 5.32	10.75 / 10.63	8.25 / 8.10	149-150	0.56 (B)	89
18	*m*-$O_2NC_6H_4$	$C_{17}H_{21}N_3O_6S$	51.60 / 51.65	5.50 / 5.32	10.75 / 10.63	8.20 / 8.10	120-121	0.61 (B)	93
19	Bn	$C_{18}H_{24}N_2O_4S$	59.25 / 59.34	6.70 / 6.59	7.75 / 7.69	8.90 / 8.79	122-123	0.56 (B)	75
20	5-Cl-Pyridyl	$C_{16}H_{21}ClN_3O_4S$	49.95 / 49.81	5.05 / 5.19	11.00 / 10.89	8.50 / 8.30	164-165	0.63 (B)	83
21	C_6H_{11}	$C_{18}H_{30}N_2O_4S$	58.34 / 58.38	8.10 / 8.11	7.70 / 7.57	8.50 / 8.65	155	0.54 (B)	77
22	*o*-ClC_6H_4	$C_{18}H_{23}ClN_2O_4S$	54.40 / 54.20	5.45 / 5.77	7.20 / 7.03	8.30 / 8.05	163-164	0.56 (B)	76
23	C_6H_{11}	$C_{19}H_{32}N_2O_4S$	59.00 / 59.38	8.50 / 8.33	7.40 / 7.29	8.50 / 8.33	154	0.51 (B)	75
24	*p*-$H_2NSO_2C_6H_4$	$C_{19}H_{27}N_3O_6S_2$	50.05 / 49.89	6.10 / 5.91	9.30 / 9.19	14.20 / 14.00	160-162	0.47 (B)	73

TABLE 2 (continued)

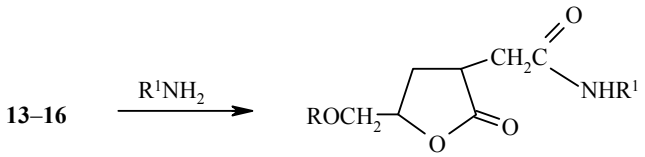
1	2	3	4	5	6	7	8	9	10
25	*p*-(2-Thiazolyl)NHSO$_2$C$_6$H$_4$	$C_{22}H_{28}N_4O_4S_3$	49.95 48.89	5.30 5.19	10.55 10.37	17.90 17.78	175-177	0.49 (B)	70
26	*p*-H$_2$NSO$_2$C$_6$H$_4$	$C_{17}H_{24}N_2O_6S$	58.90 57.90	6.60 6.81	8.10 7.95	9.20 9.09	160-162	0.60 (B)	78
27	*p*-(2-Thiazolyl)NHSO$_2$C$_6$H$_4$	$C_{20}H_{25}N_3O_6S_2$	51.30 51.40	5.50 5.35	9.15 8.99	13.85 13.70	185-187	0.52 (A)	77
28	*p*-H$_3$CCONHSO$_2$C$_6$H$_4$	$C_{18}H_{26}N_2O_7S$	53.70 53.52	6.00 6.10	6.80 6.57	7.65 7.51	176-177	0.57 (A)	78
29	*p*-(2-Thiazolyl)NHSO$_2$C$_6$H$_4$	$C_{21}H_{27}N_3O_6S_2$	52.20 52.39	5.80 5.61	9.00 8.73	13.45 13.30	142-144	0.58 (B)	80
30	*p*-H$_3$CCONHSO$_2$C$_6$H$_4$	$C_{19}H_{28}N_2O_7S$	54.70 54.54	6.20 6.36	6.55 6.36	7.10 7.27	113-115	0.56 (B)	80
31	*p*-MeC$_6$H$_4$	$C_{19}H_{27}NO_4$	68.65 68.46	8.00 8.10	4.35 4.20	—	93-95	0.52 (B)	90
32	*p*-O$_2$NC$_6$H$_4$	$C_{18}H_{24}N_2O_6$	59.20 59.34	6.75 6.59	7.80 7.60	—	117-118	0.48 (B)	89
33	Bn	$C_{17}H_{23}NO_4$	67.00 66.89	7.65 7.54	4.70 4.59	—	69-70	0.49 (A)	80
34	5-Cl-Pyridyl-2	$C_{15}H_{19}ClNO_4$	55.08 55.13	6.00 5.82	8.70 8.58	—	139-140	0.57 (A)	81

TABLE 3. ^{1}H NMR Spectra of Compounds **17-25**.

Atoms H	Chemical shifts, δ, ppm (*J*, Hz)								
	17	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
CH_3	1.16 t (*J* = 6.0)	1.14 t (*J* = 5.9)	1.04 t (*J* = 5.8)	1.08 t (*J* = 5.8)	0.91 t (*J* = 6.7)	0.91 t(*J* = 6.7)	0.92 t (*J* = 7.0)	0.95 t (*J* = 7.0)	0.93 t (*J* = 7.0)
CH in ring, m	1.80-2.17	1.80-2.15	1.81-2.17	1.80-2.15	1.86-1.87	1.83-2.00	1.82-2.03	2.74	2.72
CH outside ring, m	2.00	1.95	1.94	1.94	1.95	1.93	—	—	—
CH_2 in ring, m	2.46-2.58	2.40-2.51	2.45-2.57	2.44-2.56	2.37-2.58	2.35-2.57	2.38-2.56	2.40-2.60	2.41-2.62
CH_2 at pos. 2, m	2.89-3.08	2.85-3.00	2.80-3.09	2.79-3.00	2.85-3.01	2.85-3.01	2.85-3.01	3.49-3.67	3.29-3.57
CH_2 outside ring	—	—	—	—	—	—	1.33 and 1.56 m	1.36 and 1.58 m	1.35 and 1.59 m
CHO in ring, m	4.54-4.42	4.51-4.62	4.53-4.62	4.54-4.62	4.73	4.73	4.72	4.71	4.72
OCH_2, m	3.50-3.62	3.48-3.60	3.48-3.59	3.46-3.58	3.59-3.63	3.59-3.63	3.58-3.63	3.56-3.60	3.55-3.61
CH_2O	—	—	—	—	3.39 br.	3.41 br.	3.47 br.	3.45 br.	3.44 br.
H_{Ar}	7.83 m and 8.12 m	7.48, 7.83, 7.88, 7.98 m	7.08-7.19 m	7.77, 8.31, 8.88 m	—	7.05-7.22 m	—	7.83-7.91 m	7.80-7.90 m
C_6H_{11}, m	—	—	—	—	1.45-1.97	—	1.45-1.97	1.45-1.97	—
$CH_2C_6H_5$	—	—	3.09-3.15 br.	3.09-3.15 br.	—	—	—	—	—
NCH	—	—	—	—	4.56 s	4.56 s	4.56 s	—	6.20 br.
NH	11.64 and 3.02 s	11.64 and 13.02 s	11.42 and 13.12 s	11.64 and 13.12 s	11.53 and 13.12 s	11.53 and 13.12 s	11.48 and 12.98 s	11.51 and 12.98 s	6.95 s, 9.98 and 12.05 s
NH_2, s	—	—	—	—	—	—	—	7.09	—

TABLE 4. The ^{1}H NMR Spectra of Compounds **26-34**

Atoms H	Chemical shifts, δ, ppm. (*J*, Hz)								
	26	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**
CH_3	0.91 (t, *J* = 6.7)	0.95 (t, *J* = 6.8)	0.96 (t, *J* = 6.9)	0.92 (t, *J* = 7.0)	0.94 (t , *J* = 6.8)	0.94 (t, *J* = 6.7)	0.92 (t, *J* = 6.7)	1.16 (t, *J* = 6.0)	1.14 (t, *J* = 5.9)
CH in ring, m	2.70	2.72	2.71	2.73	2.76	2.74	2.72	3.08	2.98
CH outside ring., m	1.86	1.83	1.84	—	1.85	1.83	1.85	1.90	1.87
CH_2 in ring e	1.50 br. d and 2.00 br. d	1.51 br. d and 2.15 br. d	1.48 br. d and 2.05 br. d	2.38 br. d and 2.56 br. d	2.39 br. d and 2.53 br. d	2.37 (d, *J* = 8.4) and 2.50 (d, *J* = 7.1)	2.35 (d, *J* = 8.2) and 2.51 (d, *J* = 7.0)	1.81-2.17 m	1.80-2.05 m
CH_2 in pos. 2, m	3.56-3.67	3.51-3.60	3.49-3.61	3.58-3.63	3.58-3.63 m	3.55-3.61 m	3.51-3.60	3.50-3.62	3.50-3.61
CH_2 outside ring., m	—	—	—	1.56	1.54	1.58	1.55	—	—
CHO in ring., m	4.73	4.70	4.71	4.75	4.75	4.73	4.75	4.54–4.62 m	4.52–4.60
OCH_2	2.80 br. d and 3.05 m	2.27 br. d and 3.00 br. d	2.33 br. d and 2.91 br. d	2.85 br. d and 3.25 (d, *J* = 6.7)	2.85 br. d and 3.22 (d, *J* = 6.8)	2.90 br. d and 3.28 (d, *J* = 6.2)	3.00 br. d and 3.26 (d, *J* = 6.2)	2.15 br. d and 2.54 br. d	1.98 br. d and 2.22 br. d
CH_2O	3.25 (d, *J* = 6.7)	3.29 (d, *J* = 6.8)	3.27 (d, *J* = 6.7)	3.47 (d, *J* = 6.5)	3.49 (d, *J* = 6.2)	3.47(d, *J* = 6.2)	3.45 (d, *J* = 6.2)	—	—
ArH	7.83-7.91 m	7.80-7.90 m	7.86-7.94 m	7.81-7.92 m	7.78-7.91 m	7.05-7.24 m	7.92-8.05 m	7.18-7.32 m	7.77, 8.31, 8.88 br.
$C\underline{H}_2C_6H_5$	—	—	—	—	—	—	—	3.10 br.	—
NCH	—	6.20 br.	—	6.33 br.	—	—	—	–	—
NH, s	11.51	6.95, 9.98	10.45, 10.62	7.05, 10.05	10.55, 11.68	9.55	10.25	10.40	10.46
NH_2, s	7.09	—	—	—	—	—	—	—	—
OCH_3, s	—	—	1.95	—	1.97	—	—	—	—



26–34

26–**28** R = *i*-Bu, **29** R = Am, **30**–**32** R = *i*-Am, **33**, **34** R = *i*-Pr; R^1 – see Table 2.

All the synthesized compounds were characterized by their physicochemical constants and by data from the IR and ^{1}H NMR spectra, and the purity was checked by TLC (Tables 1-4).

EXPERIMENTAL

The IR spectra of liquid films of compounds **5-16** or suspensions of compounds **17-34** in vaseline oil were obtained on a UR-20 or Nicolet FTIR NEXUS instrument. The ^{1}H NMR spectra of compounds **17-34** were recorded in deuterochloroform on a Varian Mercury-300 instrument (300 MHz) with TMS as internal standard. Thin-layer chromatography was performed on Silufol UV-254 plates in the 3:3:10 alcohol–benzene–hexane (A) and 1:1 alcohol–benzene (B) systems with development in iodine vapor. The melting points were recorded on a Boetius microheater bench.

The initial compounds **1-4** were synthesized according to [7].

4-Alkoxymethyl-2-ethoxycarbonyl-2-ethoxycarbonylmethylbutanolides 5-8. To a cooled solution of sodium ethoxide, prepared from absolute ethanol (50 ml) and metallic sodium (2.3 g, 0.1 mol), at 20-25°C we added dropwise the respective 4-alkoxymethyl-2-ethoxycarbonylbutanolide (0.1 mol). After 30 min we added ethyl monochloroacetate (13.5 g, 0.11 mol) to the mixture drop by drop. The mixture was stirred at room temperature for 1 h and at 75-80°C for 4 h. After distillation of the ethanol the mixture was cooled, and acidified water (HCl) was added to the residue. The product was extracted with ether, and the extracts were washed with water and dried with anhydrous magnesium sulfate. The solvent was distilled, and the residue was distilled under vacuum. IR spectrum, ν, cm^{-1}: 1760 (lactone C=O); 1730, 1725, (ester C=O); 1220, 1180 (C–O–C).

4-Alkoxymethyl-2-carboxymethylbutanolides 9-12. A. To a solution of sodium hydroxide (8.4 g, 0.21 mol) in water (19.6 ml) we added dropwise the respective compound **5-8** (0.06 mol). The mixture was stirred without heat for 1 h and on a boiling water bath for 4 h. It was then cooled, concentrated hydrochloric acid was added to pH 1-2, and the product was extracted with ether. The extracts were washed with water and dried with anhydrous magnesium sulfate, and the solvent was distilled. The residue was decarboxylated at 250-300°C (12-13 mm Hg) and distilled under vacuum.

B. A mixture of the respective ester **5-8** (0.05 mol) and dilute (1:2) hydrochloric acid (180 ml) was heated with gentle boiling for 12 h, cooled, and extracted with ether. The extracts were washed with water and dried with anhydrous magnesium sulfate, and the solvent was distilled. The residue was distilled under vacuum. IR spectrum, ν, cm^{-1}: 1760 (C=O lactone); 1725 (acid C=O); 1220, 1180 (C–O–C); 3200-3400 (assoc. OH).

Acid Chlorides of 4-Alkoxymethyl-2-carboxymethylbutanolides 13-16. A mixture of the respective acid **9-12** (0.05 mol), absolute benzene (55 ml), DMF (0.5 ml), and thionyl chloride (6.5 g, 0.055 mol) was left at room temperature for 1 h, and the temperature was then brought to the boiling point of the solvent over 3 h. The mixture was kept under these conditions for 1 h, the solvent was removed under vacuum, and the residue was distilled. IR spectrum, ν, cm^{-1}: 1760 (lactone C=O); 1730 (anhydride C=O); 1220, 1180 (C–O–C).

1-Substituted 3-(4'-alkoxymethylbutanolidyl-2'-methylcarbonyl)thioureas 17-25. To potassium thiocyanate (5.8 g, 0.06 mol) in absolute acetone (20 ml) with cooling we added the respective acid chloride **13-16** (0.03 mol) in absolute acetone (20 ml), and we stirred the mixture at room temperature for 0.5 h. We added the respective amine (0.03 mol) and stirred the mixture at 20-25°C for 30 min and at 55-60°C for 1 h. The

acetone was distilled, the mixture was cooled, and water was added. The crystals that separated were filtered off, washed with water, and recrystallized from aqueous alcohol (1:2). IR spectrum, ν, cm^{-1}: 1750 (lactone C=O); 1680, 1690 (amide C=O); 1140, 1180 (C–O–C); 1580 (C=N); 1600 (ar.); 3050 (ar. =CH); 3200, 3270 (NH).

Amides of 4-Alkoxymethyl-2-carboxymethylbutanolides 26-34. To a solution of the amine (0.08 mol) in absolute acetone (60 ml) with stirring we added dropwise the respective acid chloride **13-16** (0.04 mol) in absolute acetone (40 ml). The mixture was stirred at 20-25°C for 2 h and at the boiling point of acetone for 1 h. The acetone was distilled, the residue was cooled, and water was added. The crystals that separated were filtered off, washed with acidified water (HCl) and then with water and dried. The product was recrystallized from aqueous alcohol. IR spectrum, ν, cm^{-1}: 1760 (lactone C=O); 1690 (amide C=O); 1140, 1180 (C–O–C); 1590 (C=N); 1600 (ar.); 3050 (ar. =CH); 3250 (NH).

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