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# SYNTHESIS OF NEW α-SPIROHETERYL-FUSED BUTANOLIDES

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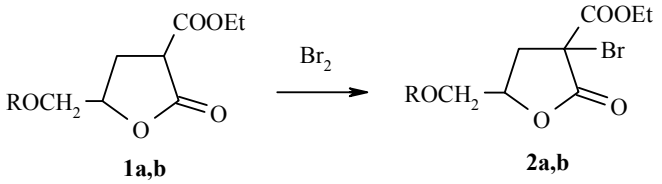
*4-Alkoxymethyl-2-bromo-2-ethoxycarbonylbutanolides were obtained with good yields by the bromination of 4-alkoxymethyl-2-ethoxycarbonylbutanolides with bromine in dry carbon tetrachloride. Reaction of the products with thiourea and aryl-substituted thioureas gave spiroheteryl-fused lactones of a new generation – 8-alkoxymethyl-3-amino(arylamino)-7-oxa-4-thia-2-azaspiro[4,4]-2-nonene-1,6-diones.*

**Keywords:** benzimidazole, halolactones, heterocycles, spirolactones.

Halogen-substituted butanolides [1-3] provide a good raw-material base for the synthesis of various types of compounds that are of certain biological interest [4-7]. While continuing our investigations in the series of 4-alkoxymethylbutanolides [3], we realized the bromination of 4-alkoxymethyl-2-ethoxycarbonylbutanolides **1a**,**b** with bromine in dry carbon tetrachloride at room temperature with the formation of high yields (88-89%) of the corresponding 2-bromo derivatives **2a**,**b**.




**1a,b** **2a,b**

**1, 2 a** R = Pr, **b** R = Bu

Such compounds can be used as synthons for the synthesis of various spiro-fused butanolide-containing heterocycles, among which highly biologically active compounds [8, 9] and also natural compounds of plant origin [10, 11] have been found.

In fact, in the reaction of equimolar amounts of the bromides **2a**,**b** with thiocarbamide or its monoaryl-substituted derivative in dry acetone under mild conditions (20°C for 1 h, boiling for 1 h) high yields of previously undescribed spiroheteryl-fused butanolides with a new structure, 8-alkoxymethyl-3-amino- or 8-alkoxymethyl-3-(R-amino)-7-oxa-4-thia-2-azaspiro[4,4]-2-nonene-1,6-diones, were obtained.

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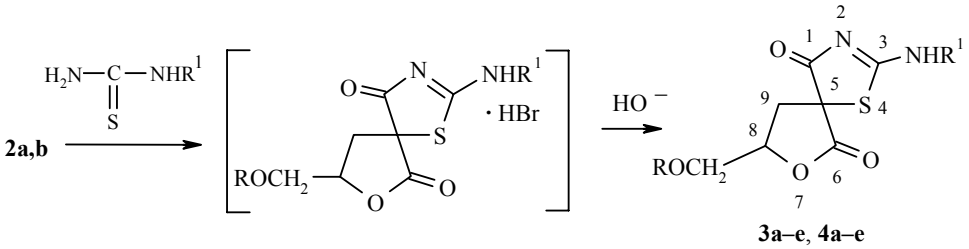

**3 a-e** R = Pr, **a** $R^1$ = H, **b** $R^1$ = Ph, **c** $R^1$ = 4-$MeC_6H_4$, **d** $R^1$ = 3-$MeOC_6H_4$, **e** $R^1$ = 4-$EtOC_6H_4$;
**4 a-e** R = Bu, **a** $R^1$ = H, **b** $R^1$ = Ph, **c** $R^1$ = 4-$MeC_6H_4$, **d** $R^1$ = 2-$MeC_6H_4$, **e** $R^1$ = 4-$EtOC_6H_4$

However, only the sulfide **5** (yield 75%) was obtained in the reaction of the bromide **2a** with 2-mercaptobenzimidazole without the formation of the spiro product.

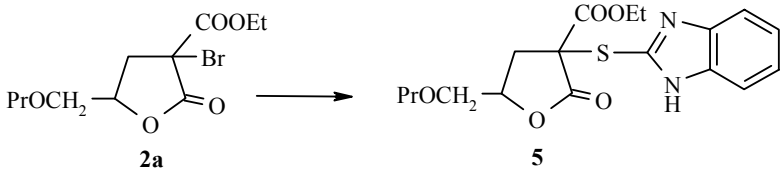

TABLE 1. The Characteristics of the Synthesized Compounds

| Compound | Empirical formula | Found, % / Calculated, % | | | | mp, °C | $R_f$ | Yield, % |
|---|---|---|---|---|---|---|---|---|
| | | C | H | N | S | | | |
| **3a** | $C_{10}H_{14}N_2O_4S$ | 46.65 / 46.51 | 5.30 / 5.42 | 11.00 / 10.85 | 12.50 / 12.40 | 182-184 | 0.39 | 76 |
| **3b** | $C_{16}H_{18}N_2O_4S$ | 57.35 / 57.48 | 5.25 / 5.39 | 8.50 / 8.38 | 9.70 / 9.58 | 220-222 | 0.55 | 91 |
| **3c** | $C_{17}H_{20}N_2O_4S$ | 58.45 / 58.62 | 5.60 / 5.74 | 8.20 / 8.04 | 9.30 / 9.19 | 236-238 | 0.57 | 95 |
| **3d** | $C_{17}H_{20}N_2O_5S$ | 56.15 / 56.04 | 5.35 / 5.49 | 7.80 / 7.69 | 8.65 / 8.79 | 198-200 | 0.57 | 80 |
| **3e** | $C_{18}H_{22}N_2O_5S$ | 57.00 / 57.14 | 5.65 / 5.82 | 7.50 / 7.41 | 8.60 / 8.46 | 145-147 | 0.54 | 80 |
| **4a** | $C_{11}H_{16}N_2O_4S$ | 48.40 / 48.53 | 6.00 / 5.88 | 10.40 / 10.29 | 11.85 / 11.76 | 173-174 | 0.35 | 84 |
| **4b** | $C_{17}H_{20}N_2O_4S$ | 58.75 / 58.62 | 5.60 / 5.74 | 8.15 / 8.04 | 9.35 / 9.19 | 214-215 | 0.64 | 82 |
| **4c** | $C_{18}H_{22}N_2O_4S$ | 59.50 / 59.66 | 6.20 / 6.08 | 7.90 / 7.73 | 8.95 / 8.83 | 235-237 | 0.64 | 93 |
| **4d** | $C_{18}H_{22}N_2O_4S$ | 59.55 / 59.66 | 5.95 / 6.08 | 7.85 / 7.73 | 8.75 / 8.83 | 159-160 | 0.48 | 85 |
| **4e** | $C_{19}H_{24}N_2O_5S$ | 58.30 / 58.16 | 6.00 / 6.12 | 7.20 / 7.14 | 8.30 / 8.16 | 196-198 | 0.50 | 87 |

TABLE 2. The $^1$H NMR Spectra of Compounds **3a-e** and **4a-e**

| Compound | Chemical shifts, δ, ppm (*J*, Hz)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $CH_3$, t | $CH_2$, outside ring | $CH_2$, in ring, dd | $CH_2O$ | $OCH_2$ | CH in ring | Ar-H | NH |
| **3a** | 0.94 (*J* = 7.4) | 1.62 (dd, *J* = 7.4, *J* = 6.6) | 2.49 (*J* = 13.5, *J* = 5.1), 3.02 (*J* = 13.5, *J* = 8.1) | 3.44 (d, *J* = 6.6, *J* = 2.0) | 3.64 (dd, *J* = 10.9, *J* = 2.7) | 4.90 (dddd, *J* = 8.2, *J* = 5.1, *J* = 3.4, *J* = 2.7) | — | 9.33 (br.) |
| **3b** | 0.96 (*J* =7.4) | 1.66 (sext., *J* = 7.1) | 2.57 (*J* = 13.6, *J* = 4.4), 3.08 (*J* = 13.6, *J* = 8.2) | 3.36-3.70 (m) | | 4.96 (ddt, *J* = 8.2, *J* = 5.1, *J* = 3.0) | 7.35 (m), 7.76 (m) | 11.26 (br.) |
| **3c** | 0.96 (*J* = 7.4) | 1.65 (sext., *J* = 7.1) | 2.56 (*J* = 13.6, *J* = 5.2), 3.07 (*J* = 13.8, *J* = 8.3) | 3.37-3.70 (m) | | 4.95 (ddt, *J* = 8.3, *J* = 5.2, *J* = 3.0) | 7.05 (m), 7.62 (m) | 11.19 (s) |
| **3d***[2] | 0.97 (*J* = 7.4) | 1.66 (sext., *J* = 7.1) | 2.57 (*J* = 13.5, *J* = 4.9), 3.08 (*J* = 13.5, *J* = 8.1) | 3.37-3.70 (m) | | 4.96 (m) | 6.65 (m), 7.29 (m) | 11.23 (br.) |
| **3e***[3] | 0.96 (*J* = 7.4) | 1.65 (br., *J* = 7.1) | 2.55 (*J* = 13.6, *J* = 5.1), 3.07 (*J* = 13.6, *J* = 8.2) | 3.47-3.70 (m) | 4.95 (m) | (d, *J* = 9.0), 7.64 (d, *J* = 9.0) | 11.14 (br.) | — |
| **4a** | 0.95 (*J* = 7.3) | 1.38 (m), 1.58 (m) | 2.49 (*J* = 13.5, *J* = 5.2), 3.01 (*J* = 13.5, *J* = 8.1) | 3.48 (t, *J* = 6.5) | 3.63 (dd, *J* = 11.0, *J* = 2.7) | 4.89 (dddd, *J* = 8.2, *J* = 5.2, *J* = 3.5, *J* = 2.7) | — | 9.33 (br.) |
| **4b** | 0.95 (*J* = 7.4) | 1.28 (m), 1.50 (m) | 2.37 (*J* = 13.5, *J* = 5.0), 3.09 (*J* = 13.5, *J* = 8.1) | 3.46-3.71 (m) | | 4.87 (m) | 7.10 (m), 7.76 (m) | 11.26 (br.) |
| **4c** | 0.96 (*J* = 7.3) | 1.23-1.65 (m) | 2.55 (*J* = 13.5, *J* = 5.2), 3.06 (*J* = 13.5, *J* = 8.2) | 3.39-3.69 (m) | | 4.95 (ddt, *J* = 8. 2, *J* = 5.2, *J* = 3.0) | 7.13 (d, *J* = 8.4), 7.62 (d, *J* = 8.4) | 11.17 (br.) |
| **4d** | 0.78 (*J* = 7.3) | 1.17 (m), 1.31 (m) 1.34-1.43 (m) | 2.43 (*J* = 13.8, *J* = 4.1), 3.15 (*J* = 13.8, *J* = 8.5) | 3.38 (t, *J* = 6.3) | 3.59 (dd, *J* = 11.0, *J* = 2.5) | 4.88 (dddd, *J* = 8.5, *J* = 4.1, *J* = 3.0, *J* = 2.5) | 7.01 (d, *J* = 7.5), 7.06-7.22 (m) | 11.94 (br.) |
| **4e***[3] | 0.96 (*J* = 7.4) | 1.23-1.66 (m) | 2.55 (*J* = 13.6, *J* = 5.3), 3.05 (*J* = 13.6, *J* = 8.1) | 3.42-3.69 (m) | | 4.86-4.98 (m) | 6.84 (d, *J* = 9.0), 7.64 (d, *J* = 9.0) | 11.14 (br.) |

* Compounds **3c**, **4c** and **4d**, δ, ppm: 2.34 (s, Ar–$CH_3$), 2.35 (s, Ar–$CH_3$), 2.26 (s, Ar–$CH_3$) respectively.

*[2] δ, ppm: 3.81 (s, $OCH_3$).

*[3] Compounds **3e** and **4e**, δ, ppm (*J*, Hz): 4.02 (q, *J* = 7.0, O<u>$CH_2$</u>$CH_3$), 1.40 (t, *J* = 7.0, $OCH_2$<u>$CH_3$</u>).

## EXPERIMENTAL

The IR spectra were obtained in thin layers (for compounds **2a**,**b**) and in suspensions in vaseline oil (for compounds **3** and **4**) on a Nicolet FTIR Nexus instrument. The $^1$H NMR spectra were obtained on a Varian Mercury-300 spectrometer (300 MHz) in deuterochloroform with TMS as internal standard. Silufol UV-254 plates and 1:5 ethanol–benzene were used for TLC with development in iodine vapor. The melting points were determined on heated Boethius apparatus. The initial 4-alkoxymethyl-2-ethoxycarbonylbutanolides were obtained according to [12].

**2-Bromo-2-ethoxycarbonyl-4-propoxymethylbutanolide (2a).** To a mixture of butanolide **1a** (23 g, 100 mmol) and dry carbon tetrachloride (70 ml) we added dropwise a solution of bromine (16 g, 0.1 mol) in carbon tetrachloride (30 ml). The rate of addition of the bromine was monitored by the decolorization of the solution. The mixture was stirred for 15 min in the cold, the hydrogen bromide was removed, the solvent was distilled under the vacuum of a water-jet pump, and the residue was distilled. Yield 27.2 g (88%); bp 134-135°C (1 mm Hg), $n_D^{20}$ 1.4760, $d_4^{20}$ 1.3676, $R_f$ 0.71.Found %: C 42.85; H 5.35; Br 25.95. $C_{11}H_{17}BrO_5$. Calculated %: C 42.72; H 5.50; Br 25.89.

**2-Bromo-4-butoxymethyl-2-ethoxycarbonylbutanolide (2b).** This compound was obtained similarly from the butanolide **1b** (18.3 g, 75 mmol) and bromine (12 g, 75 mmol) in dry carbon tetrachloride (25 ml). Yield 21.6 g (89%); bp 138-139°C (1 mm Hg), $n_D^{20}$ 1.4720, $d_4^{20}$ 1.3231. $R_f$ 0.70. Found %: C 44.45; H 5.95; Br 24.90. $C_{12}H_{19}BrO_5$. Calculated %: C 44.58; H 5.75; Br 24.77.

The IR spectra of compounds **2a**,**b** contain absorption bands at, ν, cm$^{-1}$: 1780 (lactone C=O); 1725 (ester C=O); 1125, 1170, 1275 (C–O–C); 945 (C–Br).

**8-Butoxymethyl-3-phenylamino-7-oxa-4-thia-2-azaspiro[4,4]-3-nonene-1,6-dione Hydrobromide (4b·HBr).** A mixture of 2-bromobutanolide **2b** (2.4 g, 7.5 mmol) and thiourea (0.6 g, 7.5 mmol) in absolute acetone (5 ml) was stirred at room temperature for 1 h and with gentle boiling for 1 h. The mixture was cooled, and the crystals that separated were filtered off, washed with absolute ether, and dried. Yield 3.1 g (97%); mp 169-171°C. IR spectrum, ν, cm$^{-1}$: 1783, (lactone C=O); 1125, 1697 (amide C=O); 1170 (C–O–C); 1610 (aromatic C–C); 1528 (C=N); 3080 (aromatic CH=); 3130, 3300 (NH, $NH_2$). Found %: C 47.45; H 5.00; Br 18.75; N 6.70; S 7.35. $C_{17}H_{21}BrN_2O_4S$. Calculated %: C 47.55; H 4.90; Br 18.65; N 6.53; S 7.46.

**8-Butoxymethyl-3-phenylamino-7-oxa-4-thia-2-azaspiro[4,4]-2-nonene-1,6-dione (4b).** A. The compound was obtained like the previous compound and in the same quantities except that after separation of the acetone the residue was dissolved in water and made alkaline to pH 9-10 with aqueous ammonia. The crystals that separated were filtered off, washed with water, and dried. Yield 2.1 g (82%); mp 214-215°C. $R_f$ 0.64. Found %: C 58.75; H 5.60; N 8.15; S 9.35. $C_{17}H_{20}N_2O_4S$. Calculated %: C 58.62; H 5.74; N 8.04; S 9.19.

B. A solution of the **4b** hydrobromide (2.1 g, 5 mmol) in water (50 ml) was made alkaline to pH 9-10 with aqueous ammonia with stirring. The crystals that separated after 2 h were filtered off, washed to a neutral reaction with water, and dried. The yield was quantitative; mp 214-215°C. $R_f$ 0.64. The compounds obtained by methods A and B were identical and did not give a melting point depression.

**Compounds 3a,c-e and 4a,c-e.** The compounds were obtained similarly by method A (Tables 1 and 2). Their IR spectra contain the following absorption bands, ν, cm$^{-1}$: 1783 (lactone C=O); 1697 (amide C=O); 1125, 1170 (C–O–C); 1610 (aromatic C=C); 1528 (C=N); 3080 (aromatic CH=); 3130, 3300 (NH, $NH_2$).

**2-(2'-Benzimidazolylthio)-2-ethoxycarbonyl-4-propoxymethylbutanolide (5).** A mixture of the bromide **2a** (1.6 g, 5 mmol) and 2-mercaptobenzimidazole (0.8 g, 5 mmol) in absolute acetone (5 ml) was stirred at room temperature for 1 h and with gentle boiling of the solvent for 1 h. The mixture was cooled, water was added, and the mixture was made alkaline to pH 9-10 with aqueous ammonia. The crystals that separated were filtered off, washed, and dried. Yield 1.4 g (75%); mp 96-97°C. $R_f$ 0.62. IR spectrum, ν, cm$^{-1}$: 1770 (lactone C=O); 1730 (ester C=O); 1125, 1170, 1230 (C–O–C); 1528 (C=N); 1610 (aromatic C=C); 1528 (C=N); 3080

(aromatic CH=); 3130-3300 (NH). $^1$H NMR spectrum, δ, cm$^{-1}$: 0.95 (3H, t, *J* = 7.4, γ-$CH_3$); 1.40 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 1.58 (2H, dd, *J* = 7.4, *J* = 6.5, β-$CH_2$); 2.45 and 3.10 (2H, dd, *J* = 2.0, $CH_2$ in ring); 3.43 (2H, d, *J* = 6.5, $CH_2O$); 3.80 (2H, d, *J* = 10.9, *J* = 6.5, $OCH_2$); 4.25 (2H, dd, *J* = 7.1, $O\underline{CH_2}CH_3$); 4.80 (1H, m, 5-CH); 7.10 (2H, m, $C_6H_4$); 7.43 (2H, m, $C_6H_4$); 12.45 (1H, s, NH). Found %: 5 57.24; H 6.00; N 7.55; S 8.55. $C_{18}H_{22}N_2O_5S$. Calculated %: C 57.14; H 5.82; N 7.41; S 8.47.

## REFERENCES


1. A. Richard, C. Marcello de Moura, and L. Kenneth, *J. Am. Chem. Soc.*, **75**, 1044 (1953).
2. V. Zebic, V. Skaric, Z. Ruzic-Toros, and B. Kojic-Prodic, *Croat. Chem. Acta*, **59**, 491 (1986).
3. V. S. Arutyunyan, T. V. Kochikyan, Z. Yu. Nalbandyan, M. A. Samvelyan, and A. A. Avetisyan, *Zh. Org. Khim.*, **37**, 119 (2001).
4. D. F. Dickel and G. De Stevans, US Patent 3528223; *Chem. Abstr.*, **74**, 22694 (1971).
5. D. F. Dickel and G. De Stevans, US Patent 3686211; *Chem. Abstr.*, **77**, 151925 (1972).
6. V. S. Arutyunyan, T. V. Kochikyan, T. V. Kochikyan, L. I. Bugaeva, and M. G. Antadze, *Arm. Khim. Zh.*, **38**, 688 (1985).
7. V. S. Arutyunyan, T. V. Kochikyan, A. A. Avetisyan, and I. G. Korpakova, Armenian Patent 1114, *Ofits. Byul. Promyshlennoi Sobstvennosti*, **1** (2002).
8. I. M. Gella, L. Yu. Sernienko, and A. N. Cherevko, *Khim.-Farm. Zh.*, **24**, 29 (1990).
9. H. Ferai, M. Craire, A. Rondot, A. Aumelas, and G. Aizou, *J. Chem. Soc, Perkin Trans. 2*, 3045 (1990).
10. H. Avchibasi, H. Anil, and M. Toprak, *Phytochemistry*, **26**, 2852 (1987).
11. H. Itakava, H. Morita, K. Osawa, K. Watanabe, and Y. Itaka, *Chem. Pharm. Bull.*, **35**, 2849 (1987).
12. V. S. Arutyunyan, T. V. Kochikyan, N. S. Egiazaryan, and A. A. Avetisyan, *Arm. Khim. Zh.*, **47**, 91 (1994).