REACTIONS OF HALOGEN METAL ALKOXIDES

XXIII. Synthesis of Esters of α-Oxo- and of α-Hydroxyacids of the Thiophene Series*

I. I. Lapkin, Yu. P. Dormidontov, and T. A. Bidman

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The study of the thermal stability of halogen-magnesium alkoxycarbinolates was continued. The data obtained led to the development of procedures for the synthesis of esters of α-oxo and of α-hydroxyacids containing the thienyl radical. An intramolecular hydrogen bond between the sulfur atom and the hydrogen of the hydroxyl group in esters of (5-bromothienyl-2)glycolic acid was revealed. The presence of this bond was confirmed by infrared spectroscopic data and by the results of the investigation of the esters of (thienyl-3)- and (4-bromothienyl-3)glycolic acids.

As a result of previous investigations, it had been established that the thermal stability of halogen-magnesium alkoxycarbinolates, obtained by the reaction of organomagnesium compounds with oxalic acid esters, depends on the character of the radical that they contain [1–4].

This research was undertaken to study the stability of a more complete series of halogen-magnesium alkoxycarbinolates, including those carbinolates containing heterocyclic radicals.

In contradistinction to carbinolates containing aryl radicals [1], which are comparatively easily decomposed at 36°–40° C to form aldehyde and ester of α-hydroxyacid, carbinolates containing the 2-(5-bromothienyl) radical are thermally more stable and decompose at 110°–115° C, in spite of its aromatic character. This is probably explained by a weakening of the aromatic properties of the thienyl radical due to the formation of a coordinating bond between the sulfur and the magnesium atoms, and the electron shift from the sulfur atom to the magnesium atom. In this case, the 2-(5-bromothienyl) radical resembles in its properties the aliphatic radicals, which decompose at 110°–115° C. This hypothesis is substantiated by the fact that bromomagnesium alkoxycarbinolates containing the 3-thienyl and the 3-(4-bromothienyl) radicals, and in which the formation of a coordinating bond between the sulfur and the magnesium atoms is not possible, are labile and decompose at 36°–40° C, the same as carbinolates containing aryl radicals.

A knowledge of the degree of thermal stability of halogenmagnesium alkoxycarbinolates containing the previously mentioned radicals allowed us to develop methods to synthesize esters of both the α-oxo and α-hydroxyacids.

The reaction of 2-(5-bromothienyl) magnesium bromide with oxalic acid esters at 36°–40° C (boiling in ethereal solution), followed by the hydrolysis of the halogenmagnesium alkoxycarbinolates thus formed, leads to the production of esters of ketoacids (Table 1). If the reaction temperature is raised to 110°–115° C (boiling in toluene solution), the previously mentioned decomposition of the alcoholates takes place and esters of α-hydroxyacids are formed after hydrolysis (Table 2). The best yields of the latter are obtained, however, when the synthesis is conducted in two steps instead of one. To this end, the esters of α-oxoacids first obtained are treated with bromomagnesium alcoholates at 110°–115° C. This reaction leads to the formation of the same complex compound which is obtained by the interaction of Grignard reagent with oxalic acid esters:

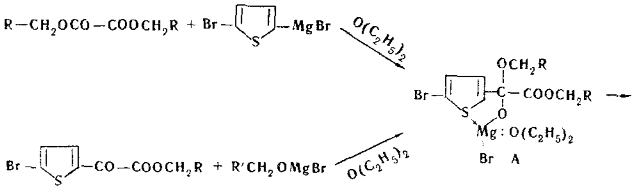

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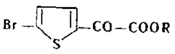
Table 1



R	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	Empirical formula	Found, % S	Found, % Br	Calculated, % S	Calculated, % Br	Yield, %
CH_3	136—137 (4)[a]	—	—	—	—	$C_7H_5BrO_3S$	12.62	31.85	12.87	32.08	28
C_2H_5	151—152 (6)[b]	—	—	—	—	$C_8H_7BrO_3S$	11.98	30.15	12.18	30.37	44
n-C_3H_7	136—137 (2,5)	1.4685	1.5297	58.26	57.32	$C_9H_9BrO_3S$	11.35	28.60	11.57	28.83	46
i-C_3H_7	135—136 (4,5)	1.4521	1.5242	58.41	57.32	$C_9H_9BrO_3S$	11.33	28.56	11.57	28.83	45
n-C_4H_9	142—143 (2)	1.4421	1.5363	62.98	61.94	$C_{10}H_{11}BrO_3S$	10.80	27.31	11.01	27.44	43
i-C_4H_9	150—151 (4)	1.4222	1.5295	63.20	61.94	$C_{10}H_{11}BrO_3S$	10.79	27.22	11.01	27.44	46
n-C_5H_{11}	170—171 (5)	1.4072	1.5425	68.31	66.55	$C_{11}H_{13}BrO_3S$	10.30	25.97	10.51	26.18	38
n-C_6H_{13}	173—174 (3)	1.3824	1.5452	73.05	71.17	$C_{12}H_{15}BrO_3S$	9.82	24.81	10.04	25.03	32
n-C_7H_{15}	185—186 (4)	1.3658	1.5487	77.57	75.78	$C_{13}H_{17}BrO_3S$	9.43	23.72	9.62	23.98	30

a) mp 83–84 (ex benzene)
b) mp 70–71 (ex ethanol)

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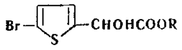
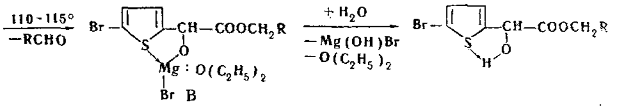
*For part XXII, see [4].

Table 2



R	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calculated, %			Yield, %
				found	calculated		S	Br	OH	S	Br	OH	
C_2H_5	148—149 (5)*	—	—	—	—	$C_8H_9BrO_3S$	11.86	29.88	6.2	12.09	30.14	6.4	52
n-C_3H_7	146—147 (3.5)	1.4523	1.5355	59.88	58.83	$C_9H_{11}BrO_3S$	11.24	28.42	5.8	11.49	28.63	6.1	55
i-C_3H_7	136—137 (2.5)	1.4374	1.5305	60.05	58.83	$C_9H_{11}BrO_3S$	11.31	28.39	5.9	11.49	28.63	6.1	68
n-C_4H_9	158—159 (5.5)	1.4168	1.5380	64.71	63.45	$C_{10}H_{13}BrO_3S$	10.73	27.05	5.7	10.94	27.26	5.8	63
i-C_4H_9	178—179 (12)	1.4112	1.5350	64.71	63.45	$C_{10}H_{13}BrO_3S$	10.72	27.00	5.7	10.94	27.26	5.8	60
n-C_5H_{11}	177—178 (4.5)	1.3859	1.5403	69.56	68.07	$C_{11}H_{15}BrO_3S$	10.23	25.76	5.3	10.44	26.01	5.5	50
n-C_6H_{13}	185—186 (5)	1.3623	1.5419	74.11	72.69	$C_{12}H_{17}BrO_3S$	9.62	24.67	5.2	9.98	24.88	5.3	48
n-C_7H_{15}	191—192 (4.5)	1.3308	1.5428	79.36	77.30	$C_{13}H_{19}BrO_3S$	9.38	23.34	4.9	9.56	23.83	5.1	43

*mp 84 (ex petroleum ether).



On the example of the synthesis of the isopropyl ester of (5-bromothienyl-2)glycolic acid, it was shown that the complete decomposition of compound A with the formation of aldehyde and carbinolate **B** takes place after a two-hour heating.*

The synthesis of the esters of (thienyl-3)- and of (4-bromothienyl-3)glycolic acids by the reaction of (thienyl-3) and of (4-bromothienyl-3) magnesium bromide with oxalic acid esters was conducted at 36°–40° C.

The IR-spectra of the compounds obtained, a broad band corresponding to the valence vibrations of the hydroxyl group, is found in the 3600–3200 cm^{-1} region and exhibits maximum absorption at about 3460 cm^{-1}. This distinguishes it from the absorption frequencies of the nonassociated OH-group (3650–3590 cm^{-1}) [5]. The lowering of the absorption frequency and the increase in the band half-width testify to the formation of a hydrogen bond. The position of the absorption band of the OH-group is not changed when the substances are dissolved in CCl_4. This points out to the intramolecular character of the hydrogen bond. This intramolecular hydrogen bond may be formed either with the sulfur atom or with the oxygen atom of the ester carbonyl group. It is formed with the sulfur atom only, and this is substantiated by the following data. Absorption frequencies of the ester carbonyl in α-hydroxy and α-oxocarboxylic acids are close together (1736 ± 6 cm^{-1}), and indication of their almost identical character. If the ester carbonyl would participate in hydrogen bond formation, as in mandelic acid esters, its absorption band would lie at about 1710 ± 5 cm^{-1} [5].

The following data testify to the participation of the sulfur atom of the thienyl radical in the formation of the hydrogen bond. It is known that the absorption bands of the α-thienyl radical lie at about 1410 and 1223 cm^{-1} [6]. These bands are present in the spectra of α-oxoacid esters. It is true that, due to the influence of the bromine atom with its +C-effect, the bands are lowered to 1400 and 1200 cm^{-1} in the spectra of the esters of the α-(α′-bromothienyl)glyoxalic acid. In the spectra of α-oxyacids esters, the 1200 cm^{-1} band turns less intense and loses definition, while the 1400 cm^{-1} band vanishes and is replaced by a weak absorption band at 1675 ± 2 cm^{-1}, which presumably may be attributed to the valence vibrations of the usual double bond.

Upon studying the spectra of the esters of (thienyl-3)- and of (4-bromothienyl-3)glycolic acids, a hydrogen bond is also observed, but of intermolecular character. This is indicated by a rise in the maximum absorption frequency of the OH-group, as well as by a rise from 3330 to 3580 cm^{-1} and from 1720 to 1739 cm^{-1} in the valence-vibrations frequencies of the ester carbonyl in the spectra of the individual compounds as recorded in a CCl_4 solution. Again absorption bands characteristic of the thienyl radical appear at 1408 and 1200 cm^{-1}, while the 1675 cm^{-1} band disappears. To the presence of a hydrogen bond in the esters of (5-bromothienyl-2)glycolic acid testifies the fact that they are very easily polymerized, and thus differ from the esters of (thienyl-3)- and of (4-bromothienyl-3)glycolic acids.

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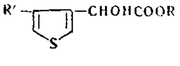
*The reaction was controlled by determining the hydroxyl group in the hydrolysis product, according to Terent'yev's procedure.

Table 3



R	R′	Mp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calculated, %			Yield, %
					found	calculated		S	Br	OH	S	Br	OH	
C_2H_5	H	122—123 (5)	1.1597	1.4925	46.62	46.45	$C_8H_{10}O_3S$	17.01	—	8.8	17.22	—	9.1	48
n-C_3H_7	H	113—114 (2)	1.1415	1.4972	51.35	51.07	$C_9H_{12}O_3S$	15.78	—	8.2	16.01	—	8.5	53
C_2H_5	Br	142—143 (5)	1.4603	1.5125	54.51	54.21	$C_8H_9BrO_3S$	11.97	29.91	6.3	12.09	30.14	6.4	45
n-C_3H_7	Br	154—155 (6,5)	1.4248	1.5146	59.03	58.83	$C_9H_{11}BrO_3S$	11.41	28.48	6.0	11.49	28.62	6.1	51

EXPERIMENTAL

Esters of (5-bromothienyl-2)glyoxalic acid. Grignard reagent was prepared by adding an ethereal solution of α, α'-dibromothiophene and ethyl bromide (molar ratio 2:1) dropwise, while cooling in ice water, to magnesium shavings. The reagent was poured into an equimolar quantity of an ethereal solution of an oxalic acid ester. After heating the reaction mixture for 2 hr, it was hydrolized with a 10% acetic acid solution. The ethereal layer was separated from the aqueous, washed first with a 10% $NaHCO_3$ solution, then with water, and dried over anhydrous sodium sulfate. The reaction product was purified by distillation under vacuum (Table 1). (5-Bromothienyl-2)-glyoxalic acid was separated by the hydrolysis of the esters. Mp 121°–122° C (ex benzene). Found, %: Br 33.79; S 13.42; COOH 19.00. Calculated for $C_6H_3BrO_3S$, %: Br 34.00; S 13.64; COOH 19.15.

In distinction from the synthesis of (5-bromothienyl-2)glyoxalic acid esters, the (5-bromothienyl-2)glycolic acid esters were synthesized at 110°–115° C (ether was replaced by toluene). The heating lasted 3 hr. As already mentioned, it is more convenient to obtain these compounds from the esters of (5-bromothienyl-2)glyoxalic acid by reducing their halogenmagnesium alcoholates at the same temperature (110°–115° C) and in the same solvent (toluene). The heating lasted 3 hr. The halogenmagnesium alcoholate radicals and the ester groups were always identical. (5-Bromothienyl-2)glycolic acid was separated by the hydrolysis of the esters. Mp 131°–132° C (ex petroleum ether). Found, %: Br 33.51; S 13.32; COOH 18.73. Calculated for $C_6H_5BrO_3S$, %: Br 33.71; S 13.53; COOH 19.00.

Esters of (thienyl-3)- and of (4-bromothienyl-3)glycolic acids. The reaction between β-bromo- and β,β'-dibromothiophenes [7] and magnesium were carried out in the presence of ethyl bromide also. The ratio of bromothiophene to ethyl bromide was 1:2. Under stirring and cooling, the ethereal solution of the organomagnesium compound was added to the ethereal solution of the oxalic acid ester. The reaction mixture was heated for an hour on a water-bath. The further treatment of the reaction mixture was as previously described. Table 3 presents the results obtained.

The following acids were separated after the hydrolysis of their esters: β-thienylglycolic, mp 84°–85° C (ex petroleum ether). Found, %: S 20.27; COOH 28.30. Calculated for $C_6H_6O_3S$, %: S 20.17; COOH 28.46, (4-bromothienyl-3)glycolic acid, mp 133°–134° C (ex petroleum ether). Found, %: Br 33.54; S 13.28; COOH 18.80. Calculated for $C_6H_5BrO_3S$, %: Br 33.71; S 13.53; COOH 19.00.

The IR-spectrum of the (5-bromothienyl-2)glyoxalic acid ethyl ester was recorded in a vaseline oil dispersion in a UR-10 apparatus. The spectra of the other esters of thienylglycolic and of thienylglyoxalic acids were recorded on a 0.05% solution in CCl_4 (10 mm cuvette).

REFERENCES

1. I. I. Lapkin, Zhur. Obshch. Khim., 16, 721, 1946; 17, 1332, 1339, 1947.
2. I. I. Lapkin and N. A. Karavanov, Zhur. Obshch. Khim., 30, 1638, 2677, 1960.
3. I. I. Lapkin and Yu. S. Andrichikov, Zhur. Obshch. Khim., 34, 3183, 1964.
4. I. I. Lapkin and Yu. P. Dormidontov, (KhGS) Chemistry of Heterocyclic Compound, 857, 1967.
5. L. J. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], Moscow, 1963.
6. E. M. Popov, F. M. Stoyanovich, B. P. Fedorov, and G. M. Andrianov, Zhur. Obshch. Khim., 64, 478, 1963.
7. S. Gronowitz, Acta Chem. Scand., 13, 1045, 1959; Ref. Zhur. Khim., 200, 1960.

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Gor'kii Perm State University