ACTION OF ALKALI METALS IN LIQUID AMMONIA ON SUBSTITUTED THIOPHENE DERIVATIVES. COMMUNICATION 8*. PREPARATION OF DIALKYLAMINO-s-TRANS-2(E),4(E)-ALKADIENOIC ACIDS BY REDUCTIVE SPLITTING OF 5-DIALKYLAMINOALKYL-2-THIOPHENECARBOXYLIC ACIDS

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In the preceding article [1] we showed that during the action of solvated electrons on alkylthiophene-2-carboxylic acids, regio- and stereoselective opening takes place of the thiophene ring with the formation of δ-mercapto-β,γ(Z)-alkenoic acids. To make use of this reaction for the synthesis of aminomercaptocarboxylic acids, we studied the action of liquid ammonia on 5-dialkylaminoalkyl-2-thiophenecarboxylic acids (I).

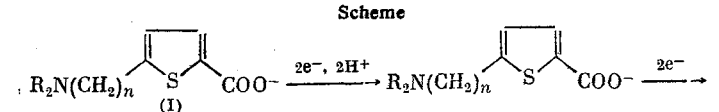
When the Na-salt of 5-dimethylaminomethyl-2-thiophenecarboxylic acid (Ia) was treated with 8 equivalents of Na in liquid NH_3 and alcohol, followed by alkylation with benzyl chloride, and esterification of the reaction product, instead of the expected ethyl ester of 5-benzylthio-6-dimethylamino-3-hexenoic acid (IIa), the ethyl ester of 6-dimethylamino-s-trans-2(E),4(E)-hexadienoic acid (IIIa) was isolated (63%), as well as dibenzyl sulfide (IV) and dibenzyl disulfide. Dibenzyl sulfide was isolated by distillation in a yield of 30%.

5-Diethylaminoethyl-2-thiophenecarboxylic acid (Ib) undergoes a similar splitting with the formation (60%) of ethyl ester of 7-diethyl-amino-s-trans-2(E),4(E)-heptadienoic acid (III). Similar treatment of 5-(4-diethylaminobutyl)-2-thiophenecarboxylic acid (Ic) gave a mixture of esters containing, according to the chromatomass-spectrometry data, besides the ester of the initial (Ic), also the esters of acids (IIc) and (IIIc)† in a ratio of ~5:2.

In discussing these results, we should note that dialkylaminoalkadienoic acids (III) are formed also when the reaction mixture is not treated by alkylating agent. In other words, sulfur is split in the form of S^{2-}, and only then does the compound become alkylated.

The experimental data show that sulfur elimination proceeds most smoothly only in those cases when the substituted amino group is separated from the S atom by two or three carbon atoms. If the distance between these groups is larger, for example, in the case of (Ic), the acid (II) predominates, and the path of reduction of acid (Ic) in principle does not differ from the reduction of alkyl-2-thiophenecarboxylic acids, which we have already studied [1]. Even in the presence of excess of metal, the reaction ceases at the stage of the formation of carbanion A (see scheme), because the negative charge, located between the carboxylic group and the double bond is then stabilized to the greatest extent.

Scheme



(I)

R = Me; n = 1 (Ia); R = Et, n = 2 (Ib), R = Et, n = 3 (Ic).

*Communication 7, see [1]. See also [2].

†The steric structure of 9-diethylamino-2,4-nonadienoic acid was not determined, but in analogy with the above examples, it can be assumed that it has the structure of (IIIc).

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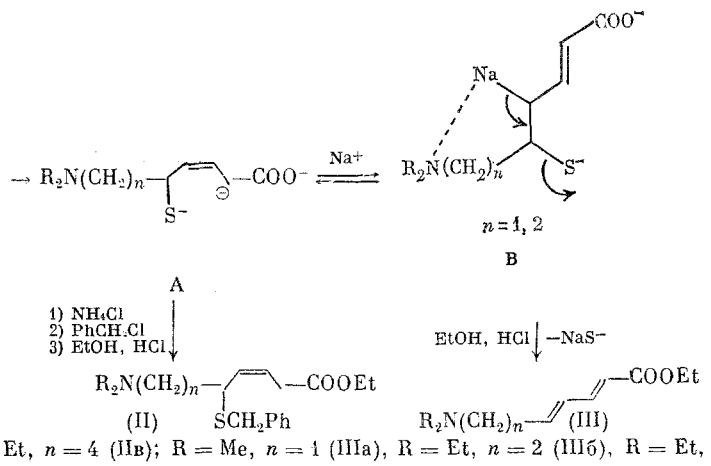

R = Et, $n = 4$ (IIв); R = Me, $n = 1$ (IIIa), R = Et, $n = 2$ (IIIб), R = Et, $n = 4$ (IIIв).

However, if in the side chain there is an amino group able to participate in intramolecular coordination with metal with the formation of thermodynamically favorable five- or six-membered rings, the transition of carbanion A into the tautomeric form B becomes probable, and this causes the appearance of free rotation around the β,γ-bond, and the trans-illumination of the sulfur anion is possible.

Thus, not only the readiness of the sulfur elimination from carbanion B can be explained, but also the formation of acids (IIIa) and (IIIb) in the s-trans-2(E),4(E)-geometry.

EXPERIMENTAL

Infrared spectra were run on the UR-20 spectrometer (in liquid film, KBr). Mass spectra were obtained on the "Varian CH-6" and "Varian MAT-111" apparatus. PMR spectra were measured on the BS-497 (100 MHz) and "Bruker WM-250" (250 MHz) spectrometers in CCl_4 and $CDCl_3$, using HMDS as standard. Chemical shifts (CS) are given with reference to TMS. GLC analysis was carried out on the LKhM-8 MD chromatograph (air separating apparatus, with helium as carrier gas at a flow rate of 24 ml/min). Column A: 100 × 0.3 cm, 5% Apiezone L on Celite 545, modified by 1% Na_3PO_4; column B: 150 × 0.3 cm, 5% SE-30 on Chromatone N-AW-HMDS; column C: 200 × 0.3 cm, 5% PFMS-4 on Chromosorb G, AW-HMDS. Na salts of the initial acids (I) used in the synthesis were obtained by alkaline hydrolysis of ethyl esters of the corresponding acids with the calculated amount of alkali.

Ethyl Esters of 5-Dimethylaminomethyl-2-thiophenecarboxylic Acid (Ia). A 55-ml portion of an ether solution of 0.095 mole of n-butyllithium was added at 15-20°C over 20 min to a solution stirred in an inert gas atmosphere of 12.7 g (0.09 mole) of 2-dimethylaminomethylthiophene in 50 ml of absolute ether. After 1.5 h of stirring at the same temperature, the mixture was poured into dry ice in ether, and after attaining room temperature, the precipitate which separated out was filtered off, washed with ether, and dried in vacuo to a constant weight. The precipitate was dissolved in 200 ml of absolute ethanol, the solution saturated with dry HCl, boiled for 4 h, and evaporated to dryness in vacuo. The residue was dissolved again in absolute ethanol, and the above operation was repeated. The residue after the removal of the solvent was diluted with 100 ml of ether, and shaken with 100 ml of saturated sodium carbonate solution. The ether layer was separated, washed with a saturated solution of K_2CO_3, and after removal of solvent and twice repeated distillation, 11.6 g (60%) of (Ia), bp 99-102°C (0.05 mm), n_D^{20} 1.5220 were obtained. Found: C 56.91% H 7.21; N 6.39; S 14.67%. $C_{10}H_{15}NO_2S$. Calculated: C 56.30; H 7.09; N 6.57; S 15.03%.

Ethyl ester of 5-(2-diethylaminoethyl)-2-thiophenecarboxylic acid (Ib) was obtained similarly to the ester of acid (Ia) from 2-(2-diethylaminoethyl)thiophene in a yield of 56%, bp 101-102°C (0.03 mm), n_D^{20} 1.5144. Found: C 61.05; H 8.38; N 5.18; S 12.67%. $C_{13}H_{21}NO_2S$. Calculated: C 61.14; H 8.29; N 5.49; S 12.53%.

Ethyl ester of 5-(4-diethylaminobutyl)-2-thiophenecarboxylic acid (Ic) was obtained similarly to the ester of acid (Ia) in a yield of 68%, bp 121-122°C (0.05 mm), n_D^{20} 1.5074. Found: C 63.84; H 8.53; N 5.04; S 11.61%. $C_{15}H_{25}NO_2S$. Calculated: C 63.56; H 8.89; N 4.94; S 11.31%.

In the PMR spectra of esters (Ia)-(Ic), the CS for the thiophene ring protons have the values (δ, ppm): 6.70 (H^4) and 7.51 (H^3); $J_{3,4}$ = 3.9 Hz [3].

Ethyl Ester of 6-Dimethylamino-s-trans-2(E),4(E)-hexadienoic Acid (IIIa). Sodium, 4.6 g (0.2 g-atom), was added slowly to a solution stirred at −40°C of 5.2 g (0.025 mole) of the Na salt of acid (Ia) in 150 ml of liquid NH_3 and 50 ml of absolute ethanol. The mixture was stirred for 1 h, and then 5.35 g (0.1 mole) of NH_4Cl was added. The mixture was cooled to −80°C, and 9.4 g (0.075 mole) of benzyl chloride was added. After 30 min, cooling was stopped, NH_3 was evaporated off, and 50 ml of water and 50 ml of ether was added to the residue. By distillation of the ether layer, 2.2 g of a mixture of benzyl chloride and benzylamine were isolated (GLC, column C, 83°C) as well as 1.61 g (30%) of dibenzyl sulfide, mp 46-48°C (from ether) [4], mol. wt. 214 (mass spectrum). After bringing the aqueous layer to pH 9 with dilute H_2SO_4, it was evaporated to a volume of 15 ml, filtered from precipitated salts, and the filtrate evaporated to dryness. The residue was extracted with absolute ethanol, and the extract evaporated. The residue was dissolved in 50 ml of absolute ethanol, the solution saturated with dry HCl, and further treated as in the case of acid (Ia). By distillation, 2.9 g (63%) of (IIIa), bp 87°C (0.1 mm), n_D^{20} 1.4952 was isolated. Found: 65.68; H 9.71; N 7.99% $C_{10}H_{17}NO_2$. Calculated: C 65.60; H 9.35; N 7.65: PMR spectrum (250 MHz, δ, ppm): 1.29 t (3H, CH_3C), 2.23 s (6H, $(CH_3)_2N$), 3.02 d (2H, NCH_2), 4.20 q (2H, CH_2O), 5.84 d (1H, H^2), 6.12 d. t (1H, H^5), 6.31 d. d (1H, H^4), 7.28 d. d (1H, H^3), $J_{2,3} = J_{4,5}$ = 15.5 Hz, $J_{3,4}$ = 10.7 Hz. The obtained values of constants determine the s-trans-2(E),4(E)-geometry of (IIIa). UV spectrum (in alcohol, λ_{max} (ε)): 255 (29,460). Mass spectrum, m/z (relative intensity, %), fragment: 183 (33), $[M]^+$, 110 (100), $[M-COOEt]^+$, 58 (60), $[Me_2NCH_2]^+$. IR spectrum (ν, cm^{-1}): 1715 (C=O), 1265, 1150 (C–O–C).

Ethyl ester of 7-diethylamino-s-trans-2(E),4(E)-heptadienoic acid (IIIb) was obtained from 5.0 g (0.02 mole) of the Na salt of (Ib), 3.5 g (0.16 g-atom) of Na in 50 ml of absolute ethanol and 150 ml of liquid NH_3 by the method described above for (IIIa). Yield 2.7 g (60%) of (IIIb), bp 98°C (0.05 mm), n_D^{20} 1.4941. Found: 69.50; H 10.14; N 6.28%. $C_{13}H_{23}NO_2$. Calculated: C 69.29; H 10.29; N 6.22%. PMR spectrum (δ, ppm): 1.04 t (6H, CH_3 in Et_2N), 1.29 t (3 H, CH_3 in EtO), 2.33 d. t (2H, CH_2C=), 2.55 q (6H, CH_2N), 4.20 q (2H, CH_2O), 5.80 d (1H, H^2), 6.12 d. t (1H, H^5), 6.21 d. d (1H, H^4), 7.27 d. d (1H, H^3), $J_{2,3} = J_{4,5}$ = 15.5 Hz, $J_{3,4}$ = 10.0 Hz. UV spectrum (in alcohol), λ_{max} (ε): 262 (21,580). Mass spectrum, m/z (relative intensity, %): 225 (4) $[M]^+$, 86 (100) $[Et_2NCH_2]^+$, 58 (60), $[EtNHCH_2]^+$. IR spectrum ν, cm^{-1}: 1715 (C=O), 1140 (C–O–C). From the ether extract of the hydrolyzed reaction mixture, 2.0 g of a mixture of benzyl chloride and benzylamine were isolated, as well as 1.94 g (36%) of dibenzyl sulfide.

Reductive Splitting of Na-Salt of 5-(4-Diethylaminobutyl)-2-Thiophenecarboxylic Acid (Ic). By the method used for (IIIa), from 3.4 g (0.012 mole) of Na salt (Ic) and 2.0 g (0.084 g-atom) of Na in liquid NH_3 and absolute ethanol, 3.12 g of a mixture were obtained consisting according to the chromatomass-spectral data and GLC, of ethyl esters of acid (Ic), 5-benzylthio-9-diethylamino-3-nonenoic acid (IIc) and 9-diethylamino-2,4-nonadienoic acid (IIIc) in a ratio of 3:5:2. Mass spectra, m/z (relative intensity, %), fragments: (Ic) – 283 (7) $[M]^+$, 86 (100), $[Et_2NCH_2]^+$, 58 (32), $[EtNHCH_2]^+$; (IIc) – 123 (10) $[PhCH_2S]^+$, 91 (26) $[PhCH_2]^+$, 86 (100), 58 (33); (IIIc) – 253 (2) $[M]^+$, 86 (100); 58 (33). Besides these, small amounts of dibenzyl disulfide, and, in the ether part, of dibenzyl sulfide were identified. The mixture components could not be isolated in a pure state by distillation and preparative TLC.

CONCLUSION

1. Reductive splitting of 5-dialkylaminoalkyl-2-thiophenecarboxylic acids by sodium and alcohol in liquid ammonia leads in a good yield and regio- and stereoselectivity to dialkylamino-s-trans-2(E),4(E)-alkadienoic acids, if the amino group is separated from the thiophene ring by one or two methylene groups.

2. The high regio- and stereoselectivity of the thiophene ring opening is explained by intramolecular coordination of the metal in the intermediately formed organometallic compound with the nitrogen atom of the amino group.

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SYNTHESIS AND TRANSFORMATIONS OF SULFIDES IN THIOPHENE SERIES. COMMUNICATION 37. SYNTHESIS AND PROPERTIES OF 2-METHOXY-5-METHYLTHIOPHENES, SUBSTITUTED BY BROMINE OR ALKYLTHIO- AND ALKYLSULFONYL GROUPS

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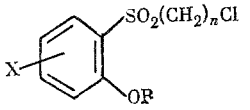
During the recent decade, the biological properties of compounds in the thiophene series have been widely studied, particularly, in the fields of pesticides, medicinal and veterinary preparations. This is indicated by several reviews and patents [1-5], in which substituted thiophene derivatives appear as the principal structural fragment of the physiologically active compounds. All this stimulates further research among different classes of thiophene derivatives, containing, particularly halide, methoxy, alkylthio, or alkylsulfonyl groups [6, 7]. Especially interesting can be the study of polyfunctional derivatives, containing functional groups at various positions of the thiophene ring. In this connection should be noted the recent paper [8, 9] on the useful properties of certain benzene derivatives containing methoxy and chloroalkylsulfonyl groups, having cytostatic properties, especially against cancerous cells.



X = Cl, Alk, R = Me, $n = 2, 3$

In the present work, we describe the synthesis and certain properties of β-Br- and β-SH-, SR-, SO_2R-, $SO_2(CH_2)_3Cl$-derivatives of 2-methoxy-(5-methylthio)thiophene (I), which we already obtained [10]. These derivatives can be of independent interest for testing their physiological properties, and as starting materials in the synthesis of various polyfunctional compounds in the thiophene series.

To introduce bromine in the molecule of (I), we used the reaction with N-bromosuccinimide (NBS). In the reaction of methoxysulfide (I) with 1 mole of NBS, a mixture is formed containing (according to TLC data) up to 80% of monobromides (II) and (III), a little dibromide (IV), and initial (I), from which a narrow boiling fraction of monobromides was isolated,

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