SYNTHESIS AND SOME REACTIONS OF SULFIDES OF THE THIOPHENE SERIES

XVI. The Direction of the Dealkylation of α, β-Bis(alkylthio)thiophenes with Sodium in Liquid Ammonia*

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The action of two equivalents of sodium in liquid ammonia on bis(alkylthio)thiophenes of types **Ia** and **b** leads to the splitting off of the alkyl group from the sulfur atom in the α-position of the thiophene ring and the formation of the corresponding α-mercaptothiophenes II and III. The PMR spectra of the compounds obtained are given.

In the preceding communication [1] it was shown that the action of four equivalents of sodium in liquid ammonia on α,β-bis(alkylthio)thiophenes of type I leads to the formation of the corresponding dimercapto derivatives. It was of interest to ascertain whether there is a definite sequence in the splitting out of the alkyl groups from the sulfur atoms in positions 2 and 3 of the thiophene ring or whether the rates of dealkylation of these groups are so similar that the question of the direction of the process cannot be answered unambiguously.

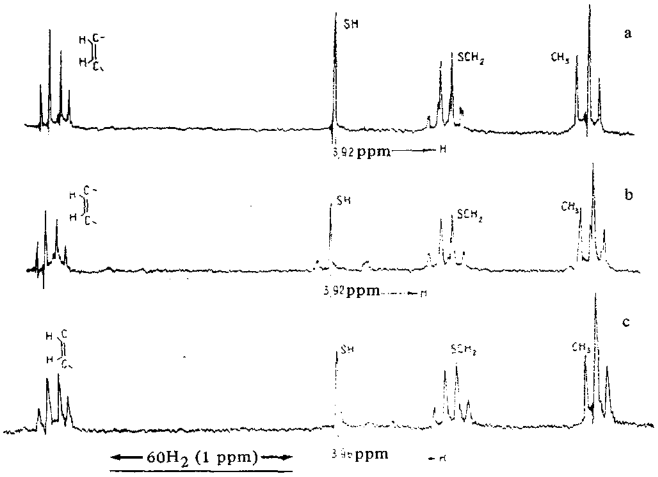

Fig. 1. PMR spectra of 3-ethylthio-2-mercaptothiophene (**II**), obtained: a) by the action of 2 equiv. of Na/NH_3 on **Ia**; b) by method [1]; c) by the action of 2 equiv. of Na/NH_3 on **XI**.

According to ideas existing at the present time [2, 3], the direction of the cleavage of an organic sulfide with alkali metals depends to a considerable extent on the numerical values of the acidity of the mercaptide ions and carbanions formed. Thus, on cleavage alkyl aryl sulfides give an aromatic thiol and an aliphatic hydrocarbon, since the aromatic thiols are $\sim 10^4$ times more acidic than aliphatic thiols [3]. In the case of bis(alkylthio)thiophenes of type I, which may be regarded as one of the types of alkyl aryl sulfides and are not distinguished by the aliphatic radicals connected to the non-ring sulfur atoms, the main factor determining the direction of cleavage is apparently the stability of the 2- or 3-thiophenethiolates arising. Obviously, the first of them is stabilized to a greater extent, since the delocalization of the negative charge is distributed over the whole of the aromatic ring, while in the 3-isomer it is limited to the 1, 3-π system [4]:

Thus, it may be assumed that the action of two equivalents of sodium on bis-sulfides of type I will lead, at least predominantly, to the dealkylation of the α-alkylthio group. To elucidate the influence on the course of the process of the presence of an alkyl group in the second α-position, experiments were carried out both with unsubstituted 2,3-bis(ethylthio)thiophene **Ia** and with 5-ethyl-2,3-bis(ethylthio)thiophene **Ib**. The mercaptosulfides II and III were obtained with yields of about 80% in the form of mobile light-colored liquids distilling in vacuum with slight decomposition.

In order to establish the structure of these mercaptosulfides, we selected the method of comparing the crystalline bis-sulfones formed from them with bis-sulfones of definite structure IV–IX (see scheme) obtained by the reactions described in the experimental part.

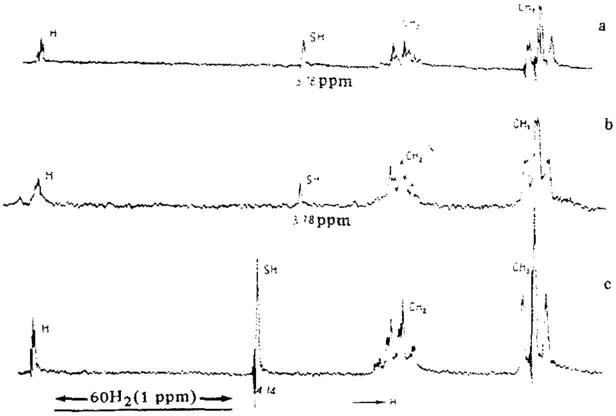

Fig. 2. PMR spectra of 5-ethyl-3-ethylthio-4-mercaptothiophene (III) obtained: a) by method [1]; by the action of 2 equiv. of Na/NH_3 on Ib; c) 5-ethyl-2-ethylthio-3-mercaptothiophene (**X**).

As can be seen from the scheme and Table 1, the sulfone obtained from the cleavage products of **Ia**

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*For part XV, see [1].

Table 1

Bis(alkylsulfonyl)thiophenes

Compound	Name	Initial mercaptothiophene and method for its production	Alkyl halide	Mp, °C (solvent)	Empirical formula	Found, %			Calculated, %		
						C	H	S	C	H	S
IV	3-Ethylsulfonyl-2-methylsulfonylthiophene*	II, action of 2 equiv. of Na/NH_3 on Ia	CH_3I	113.5—114.5 (50% ethanol)	$C_7H_{10}O_4S_3$	33.03	4.07	37.89	33.05	3.96	37.82
		" " on IX	" "	113—114	" "	33.20	3.98	37.68	33.05	3.96	37.82
		II, action of C_4H_9Li and S on ethyl 3-thienylsulfide [1]	" "	112.5—114	" "	32.74	3.92	37.90	33.05	3.96	37.82
VII	2-Ethylsulfonyl-3-methylsulfonylthiophene*	—	—	127—129	" "	33.17	4.09	37.79	33.05	3.96	37.82
V	5-Ethyl-3-ethylsulfonyl-2-methylsulfonylthiophene	III, action of 2 equiv. of Na/NH_3 on Ib	CH_3I	92—93 (50% ethanol nonane)	$C_9H_{14}O_4S_3$	38.28	4.90	33.91	38.28	5.00	34.06
		III, action of C_4H_9Li and S on 2-ethyl-4-ethylthiothiophene	" "	95—96	" "	38.50	5.16	33.88	38.28	5.00	34.06
VIII	5-Ethyl-2-ethylsulfonyl-3-methylsulfonylthiophene	X, obtained by method [1]	" "	80—82	" "	38.73	5.10	33.52	38.28	5.00	34.06
VI	2-Benzylsulfonyl-5-ethyl-3-ethylsulfonylthiophene	III, action of 2 equiv. of Na/NH_3 on Ib	$C_6H_5CH_2Cl$	102—103 (50% ethanol, heptane)	$C_{15}H_{18}O_4S_3$	50.34	4.97	26.82	50.25	5.06	26.83
		III, action of C_4H_9Li and S on 2-ethyl-4-ethylthiothiophene	" "	103—104	" "	50.57	5.01	26.49	50.25	5.06	26.83
IX	3-Benzylsulfonyl-5-ethyl-2-ethylsulfonylthiophene	X, obtained by method [1]	" "	104—105 (50% ethanol)	" "	50.03	5.10	26.72	50.25	5.06	26.83

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*Obtained by the oxidation of 2-ethylthio-3-methylthiothiophene with 30% H_2O_2 in glacial acetic acid [1].

Table 2

Chemical Shifts (ppm) and Spin-Spin Coupling Constants (Hz) in Alkylmercaptothiophenethiols and 2,3-Bis(ethylthio)thiophene

Compound	Name	δ_{3H}	δ_{4H}	δ_{5H}	$I_{4,5}$	δ_{2SH}	δ_{4SH}	δ_{5SH}	I_{3H-2CH_2}	δ_{2SCH_2}	δ_{4SCH_2}	δ_{5SCH_2}	δ_{3SCH_2}	δ_{2CH_2}	δ_{2CH_3}	δ_{3SCH_3}	δ_{4SCH_3}	δ_{5SCH_3}	I_{SH-4H}	I_{SH-2CH_2}	δ_{2SCH_3}
II	3-Ethylthio-2-mercaptothiophene	—	6.85	7.04	5.7	3.92	—	—	—	—	—	—	2.73	—	—	1.20	—	—	0.2	—	—
X	5-Ethyl-2-ethylthio-3-mercaptothiophene	6.48	—	—	—	—	4.14	—	1.05	—	—	2.65	—	2.67	1.22	—	—	1.21	—	—	—
III	5-Ethyl-3-ethylthio-2-mercaptothiophene	6.53	—	—	—	—	—	3.78	1.05	—	2.73	—	—	2.65	1.23	—	1.21	—	—	0.2	—
Ia	2,3-Bis(ethylthio)thiophene	—	6.92	7.22	5.0	—	—	—	—	2.77	—	—	2.83	—	—	1.19	—	—	—	—	1.19

Table 3

Alkylthiothiophenethiols

Compound	Name	Method of preparation	Bp, °C (mm)	n_D^{20}	Empirical formula	Found, %			Calculated, %			Yield, % (after redistillation)
						C	H	S	C	H	S	
II	3-Ethylthio-2-mercaptothiophene	Action of 2 equiv. of Na/NH_3 on Ia	90—91 (3)	1.6365	$C_6H_8S_3$*	41.00	4.55	54.79	40.87	4.57	54.56	77
		Action of 2 equiv. of Na/NH_3 on XI	96—97 (4)	1.6443	$C_6H_8S_3$	40.08	4.75	55.52	40.87	4.57	54.56	65
		By method [1].	86—91 (3)	1.6370	$C_6H_8S_3$	40.66	4.60	54.35	40.87	4.57	54.56	—
III	5-Ethyl-3-ethylthio-2-mercaptothiophene	Action of 2 equiv. of Na/NH_3on Ib	112—113 (3)	1.6010	$C_8H_{12}S_3$	47.29	5.86	46.57	47.01	5.92	47.07	75
		Action of C_4H_9Li and S on 2-ethyl-4-ethylthiothiophene	112—113 (3)	1.6010	$C_8H_{12}S_3$	47.41	5.97	47.18	47.01	5.92	47.07	65.5

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*2,4-Dinitrophenyl 3-ethylthio-2-thienyl sulfide, mp 92–93° C (from ethanol). Found, %: C 42.09; H 2.94; S 28.10. Calculated for $C_{12}H_{10}N_2P_4$, %: C 41.83; H 3.17; S 27.86. A mixture with the material described previously [1] gave no depression.

proved to be identical in melting point with 3-ethylsulfonyl-2-methylsulfonylthiophene (IV) and differed from the isomeric bis-sulfone VII. In just the same way, the product of the cleavage of Ib gave bis-sulfone identical with the bis-sulfones V and VI respectively.

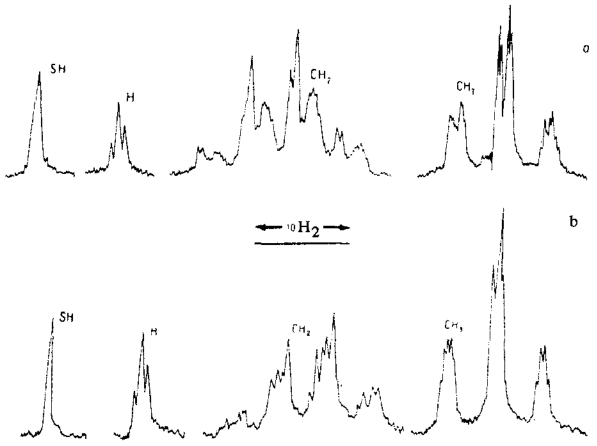
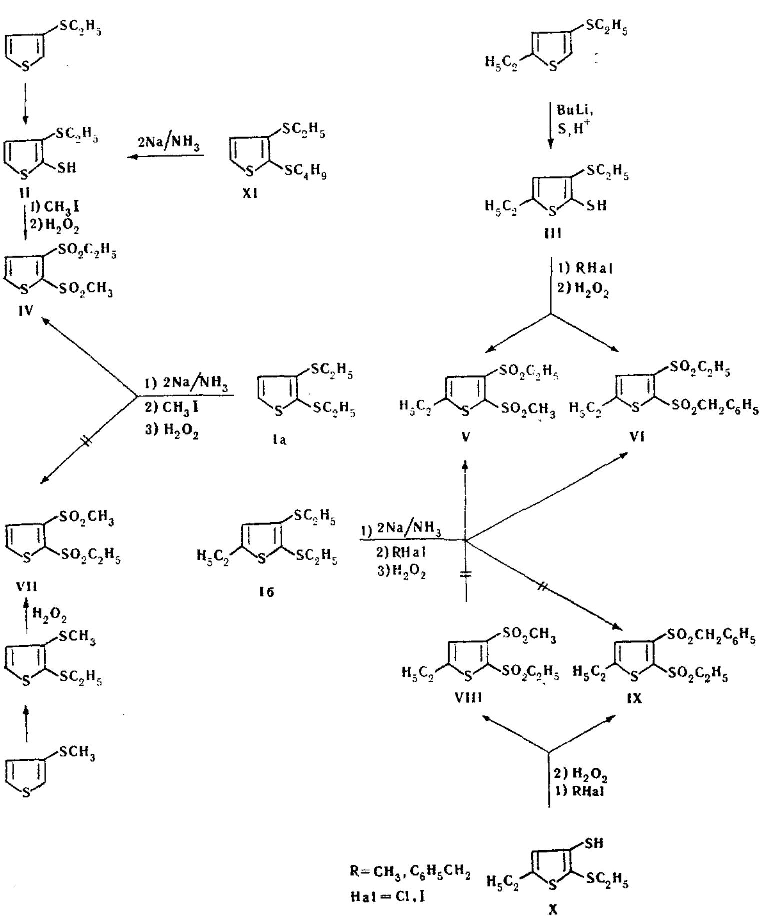


Fig. 3. NMR spectra: a) 5-ethyl-3-ethylthio-2-mercaptothiophene (III); b) 5-ethyl-2-ethylthio-3-mercaptothiophene (X).

A mixture of the bis-sulfone VI with the isomeric 3-benzylsulfonyl-5-ethyl-2-ethylsulfonylthiophene IX (see Table 1) gave a depression of the melting point.



It may, therefore, be concluded that the action of two equivalents of sodium in liquid ammonia on bis-sulfides, both **Ia** and **Ib**, is directed predominantly to the alkylthio group in the α-position of the thiophene ring.

The structure of the cleavage products as α-mercapto derivatives of thiophene was also confirmed by the results of studies of the PMR spectra of the mercaptosulfides obtained and corresponding synthetic samples of 3-ethylmercapto-2-mercaptothiophene (II) [1], 5-ethyl-3-ethylthio-2-mercaptothiophene (III), and 5-ethyl-2-ethylmercapto-3-mercaptothiophene (X) [1].

The spectra were recorded in CCl_4 solutions (concentrations 7–26 mole-%) at a frequency of 60 MHz (RS-60 spectrometer [5]). The chemical shifts were measured relative to an internal standard—hexamethyldisiloxane—by means of calibration using the side-band method (accuracy of the measurements ∓ 0.02 ppm). It must be mentioned that the determination of the structure of di- and tri-substituted thiophenes by the NMR method is a comparatively complex analytical problem. Even the extremely fundamental investigations of substituted thiophenes carried out by Gronowitz's group [6] have left considerable uncertainties in the approach to the structural analysis of thiophene derivatives.

The study of the chemical shifts of the protons of the SH groups in compounds III and X in solutions of different concentrations showed that the chemical shift does not substantially depend on the concentration and is characteristic for the position of the SH group (for example, $\delta \simeq 4.14$ ppm in position 3 and $\simeq 3.78$–3.92 ppm in position 2).

The study of the spin-spin coupling constants can also be useful to establish the structure of isomeric thiophene derivatives. For example, we detected coupling between the protons of the 2-CH_2 group and 3-H with J = 1.05 Hz. By using an estimate based on the relative intensities of the signals (proposed by N. M. Sergeev [7]) it is possible to suggest the presence of the interaction $J_{SH-4H} \simeq 0.2$ Hz (in compound **II**) and $J_{SH-2CH_2} \simeq 0.2$ Hz (in compound **III**) (Table 2, Figs. 1 and 2). Of course, a final assignment of the lines and an accurate determination of the values and signs of the spin-spin coupling constants requires the use of double resonance. We may mention an interesting feature of the NMR spectra of compounds **X** and **III.** It consists in a remarkable coincidence of the chemical shifts of the methyl and methylene groups, respectively, for 2-C_2H_5 and 5- (or 4-) SC_2H_5. The difference in the chemical shifts between SCH_2 and CH_2 in **X** is (ν = 60 MHz) about 2 Hz and in **III** about 3 Hz (while for the CH_3 group it is 0.5 and 1.2 Hz, respectively); the narrower line of the SCH_2 group is located in the stronger field in X and the weaker field in III (Fig. 3). Another feature of these spectra is the small value of the chemical shift between CH_2 and CH_3 (of the order of 90–92 Hz), which leads to a considerable magnitude of the second-order splitting in the spectra of CH_2-CH_3 [8] $(J^2_{CH_2-CH_3})/(\nu_{\delta\, CH_2-CH_3}) \simeq 0.55$ Hz, which can be seen from the spectra (Fig. 3).

A comparison of the spectra of the product of the cleavage of 5-ethyl-2,3-bis(ethylthio)thiophene with the spectra of compounds III and X showed that in the magnitude of the chemical shifts and the nature of the spectrum (Fig. 2, a, b) the cleavage product is identical with 5-ethyl-3-ethylthio-2-mercaptothiophene (III). The spectra of 3-ethylthio-2-mercaptothiophene (**II**) and the thiol obtained by the cleavage of 2,3-bis(ethylthio)thiophene also proved to be identical (Figs. 1, a, b).

In the spectrum of 2,3-bis(ethylthio)thiophene (**Ia**), it is interesting to note the presence of a chemical shift of 0.06 ppm between the protons of the SCH_2 groups (Fig. 4) which apparently shows a difference in the electronegativity of the sulfur atoms in positions 2 and 3 of the thiophene ring.

The delocalization effect (see above) apparently plays a decisive part in determining the direction of the cleavage of the bis-sulfides of the thiophene series with different alkylthio substituents, for example 2-butylthio-3-ethylthio-thiophene (**XI**). If it is assumed that the ease of cleavage of primary alkyl groups in the form of carbanions falls in the sequence $CH_3 > C_2H_5 > C_4H_9$ [3], then in the case of the sulfide **XI** the cleavage of the ethyl group could take place predominantly with the formation of 2-butylthio-3-mercaptothiophene. However, in this case the sole reaction product isolated was 3-ethylthio-2-mercaptothiophene (**II**), the NMR spectrum of which proved to be identical with that of an authentic sample of 3-ethylthio-2-mercaptothiophene and the product of the cleavage of **Ia** (Fig. 1, a, c). The bis-sulfone obtained from it by the successive action of methyl iodide and H_2O_2 did not differ in melting point from a sample of 3-ethylsulfonyl-2-methylsulfonylthiophene (**IV**).

EXPERIMENTAL

Action of 2 g-atoms of sodium in liquid ammonia on the bis(alkylthio)thiophenes Ia, Ib, and XI. In the manner described previously [1], 0.025 mole of a bis-sulfide was treated with 0.05 g-atom of sodium. After the addition of the last portion of sodium (no blue color appeared), the ammonia was evaporated off, the residue was treated with benzene and water, and the corresponding thiophenethiols were extracted from the aqueous layer in the usual way. The yields, constants, and analyses of the compounds obtained are given in Table 3.

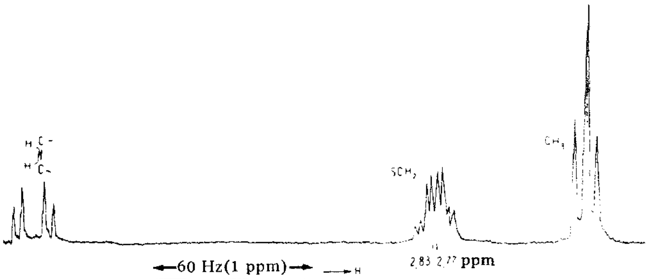


Fig. 4. PMR spectrum of 2,3-bis(ethylthio)thiophene Ia.

2-Ethyl-4-ethylthiothiophene. This was obtained with a yield of 68% by a published method [9] from 23 g of 4-bromo-2-ethylthiophene [10], an ethereal solution of 8.7 g of butyllithium, and 16.5 g of diethyl disulfide. Bp 132°–134° C (26 mm); d_4^{20} 1.0847, n_D^{20} 1.5590. Found, %: 55.66; H 7.02; S 36.90; MR_D 51.29. Calculated for $C_8H_{12}S_2$, %: C 55.76; H 7.02; S 37.22; MR_D 52.02.

5-Ethyl-3-methylthio-2-mercaptothiophene (III). This was obtained from 10 g of 2-ethyl-4-ethylthiothiophene, an ethereal solution of 4.1 g of butyllithium, and 2.1 g of sulfur as described previously [1] for 3-ethylthio-2-mercaptothiophene. The yield, analytical data, and constants are given in Table 3.

The bis(alkylsulfonyl)thiophenes IV–VI, VIII, IX. To a solution of 0.005 mole of an alkylthiothiophenethiol in 10 ml of methanol containing 0.005 mole of KOH was added 0.006 mole of an alkyl halide. The mixture was boiled for 4 hr, the methanol was distilled off, the residue was diluted with water and extracted with ether, the extract was washed with 10% NaOH solution and with water and was dried with $CaCl_2$, the ether was driven off, and the sulfide was distilled in vacuum and oxidized with 30% H_2O_2 in glacial acetic acid as described previously [1]. The bis-sulfones were isolated in the form of crystalline or oily products which were recrystallized from suitable solvents (Table 1).

2-Ethylthio-3-methylthiothiophene. This was obtained with a yield of 60% by the previously-described method [1] from 6.8 g of 3-methylthiothiophene, an ethereal solution of 3.3 g of butyllithium, 1.7 g of sulfur, and 9 g of ethyl iodide, bp 112°–113° C (3 mm); d_4^{20} 1.2028; M_D^{20} 1.6209. Found, %: C 43.86; H 5.08; S 50.14; MR_D 55.66. Calculated for $C_7H_{10}S_3$, %: C 44.16; H 5.30; S 50.54; MR_D 56.602.

2-Butylthio-3-ethylthiothiophene (XI). To an 18.5-g solution of 3-ethylthio-2-thiothiothiophene was added 14.4 g butyl bromide in 60 ml of a 10% KOH solution in methanol. The mixture was boiled for 6 hr and was treated as described earlier [1], for 4,5-bis(ethylthio)-2-ethylthiophene. Yield: 14.1 g (58%) 3-ethylthio-2-butylthiothiophene, bp 136°–137° C (3 mm); d_4^{20} 1.1024, n_D^{20} 1.5800. Found, %: C 52.01; H 6.92; S 40.72. Calculated for $C_{10}H_{16}S_3$, %: C 51.67; H 6.94; S 41.39; MR_D 70.456.

2-Butylsulfonyl-3-ethylsulfonylthiophene, mp 65.5°–67.5° C (from 50% ethanol). Found, %: C 40.88; H 5.68; S 32.59. Calculated for $C_{10}H_{16}O_4S_3$, %: C 40.52; H 5.44; S 32.45.

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