REACTIONS OF AROMATIC AND HETEROAROMATIC COMPOUNDS BEARING ELECTRON-ACCEPTOR SUBSTITUENTS

IX.* SPECIFICITY OF THE NITRATION AND BROMINATION OF DIMETHYL(2-THIENYL)SULFONIUM SALTS

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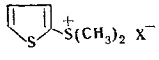
The specificity of the nitration and bromination of dimethyl(2-thienyl)sulfonium salts was studied. It was found that, in contrast to methyl 2-thienyl sulfide, which reacts to form 3- and 5-substituted derivatives, the sulfonium salts give a mixture of 4- and 5-substituted products. Total suppression of the activity of the α position under the influence of the sulfonium grouping is not observed.

Methods for changing the specificity of electrophilic substitution reactions in the thiophene and furan series have been developed in our labaratory. The methods are based on increasing the electron-acceptor capacity of the substituent (acyl or sulfonyl groups) as a result of complexing with aluminum chloride [2-5] or protonation [6-9]. In striving to find other functions capable of overcoming the α-orienting effect of the heteroatom and thereby opening up a path to difficult-to-obtain β-substituted compounds of the thiophene series, we decided to study some reactions of dimethyl(2-thienyl)sulfonium salts (I), the synthesis of which we described in a previous paper [1].



I

$X = NO_3, ClO_4$

It is known that the sulfonium grouping is a meta orienter that is stronger than the $\overset{+}{N}R_3$ group; this is explained by the presence of an additional −M effect due to the d orbitals of the sulfur atom [10-12]. If the meta orienting effect of the $\overset{+}{S}(CH_3)_2$ group were stronger than the influence of the heteroatom that activates the α position, one might obtain 4-substituted products, and the corresponding sulfides, the synthesis of which is extremely difficult, might be obtained from them by demethylation [1].

In this paper, we present the results of experiments on the bromination and nitration of salts of the I type and, for comparison, the results of the same reactions of methyl 2-thienyl sulfide. The 5 and 3 positions in the sulfide are naturally the most active ones (see [13]). The electron-acceptor capacity of the sulfonium group, as we have established, is insufficient to completely suppress substitution in the free α position of the thiophene ring. For example, the bromination of sulfonium salt I ($X = ClO_4$) gives a mixture of 4- and 5-monobromo- and 4,5-dibromo-substituted products.

The product of the bromination of the sulfonium salt was demethylated [1] to identify the compounds obtained, and the composition of the resulting mixture of sulfides was determined by gas-liquid chromatography (GLC) using authentic samples. For this, we synthesized methyl 5-bromo-2-thienyl sulfide from methyl 2-thienyl sulfide by the action of a bromide–bromate mixture, as well as methyl 3,5-dibromo-2-thienyl sulfide by the action of 2 moles of bromine in chloroform on methyl 2-thienyl sulfide. In addition,

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*See [1] for communication VIII.

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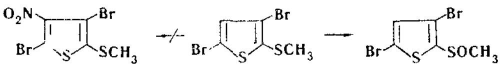
the previously described [14] methyl 4-bromo-2-thienyl sulfide was used for GLC; we obtained the sample of methyl 4,5-dibromo-2-thienyl sulfide necessary for this purpose by brominating this compound. Unfortunately, the dibromo compound could not be isolated in the analytically pure state: it contained appreciable amounts of unchanged starting compound and the 3,5-dibromo-substituted product formed as a result of bromination of methyl 3-bromo-2-thienyl sulfide, which is an impurity in the starting methyl 4-bromo-2-thienyl sulfide [14].

A mixture (in a ratio of close to 2 : 1) of 4- and 5-nitro-substituted products is formed in the nitration of salt I ($X = ClO_4$). The PMR spectrum of this mixture of perchlorates (recorded in dimethyl sulfoxide–acetone) contains signals with δ 3.48 ppm [singlet, $(CH_3)_2\overset{+}{S}$]; 8.28, and 8.12 ppm (doublets of 3-H and 4-H of the 5-nitro-substituted compound, $J_{3,4} = 5$ Hz); 8.75, and 9.20 ppm (doublets of the ring protons of the 4-substituted products, $J_{3,5} = 1.5$ Hz). The mixture obtained by demethylation of the product of the nitration of salt I contained two isomeric sulfides (in a ratio of 3 : 2), one of which, judging from the results of GLC and the PMR spectrum (in CCl_4), was the 4-nitro-substituted compound (CH_3S singlet at 2.55 ppm and 3-H doublets at 7.48 ppm, 5-H 8.20 ppm, $J_{3,5} = 1.5$ Hz), and the other was the 5-substituted product (CH_3S singlet at 2.46 ppm, 3-H doublet at 6.85 ppm, and 4-H doublet at 7.71 ppm, $J_{3,4} = 4$ Hz). We separated this mixture on aluminum oxide and isolated the pure 4- and 5-nitro sulfides, but the melting point of the 5-nitro compound was ~25°C lower than the literature value [15] (81-82°C). Our attempts to obtain a sample of methyl 5-nitro-2-thienyl sulfide by the method in [15] were unsuccessful because of pronounced resinification. By carrying out the nitration of methyl 2-thienyl sulfide at −70°C (instead of at −10°C as in [15]), we were able to isolate a nitration product, but it proved to be a mixture of two isomeric sulfides. Judging from the PMR spectrum, this mixture consisted of methyl 5-nitro-2-thienyl sulfide and methyl 3-nitro-2-thienyl sulfide (in a ratio of ~2 : 1): the spectrum of a CCl_4 solution contains signals of the 5-nitro isomer (CH_3S singlet at 2.64 ppm, 3-H doublet at 6.87 ppm, and 4-H doublet at 7.75 ppm, $J_{3,4} = 4$ Hz) and of the 3-nitro isomer (CH_3S singlet at 2.60 ppm, 5-H doublet at 7.11 ppm, and 4-H doublet at 7.57 ppm, $J_{4,5} = 5.5$ Hz). According to the PMR spectrum, the first of the nitro sulfides corresponds to the 5-nitro derivative observed in the mixture of 4- and 5-nitro isomers obtained by demethylation of the product of the nitration of the sulfonium salt (see above). The assignment of the isomers is in agreement with the data of Hoffman and Gronowitz [16], who, using a large amount of data, demonstrated that the spin–spin coupling constants range from 1.25 to 1.70 Hz in 2,4-disubstituted thiophenes, from 3.45 to 4.35 Hz in 2,5-disubstituted thiophenes, and from 4.90 to 5.80 Hz in 2,3-disubstituted thiophenes (see also [17]).* Individual samples were isolated from the mixture of 5- and 3-nitro sulfides by chromatography on Al_2O_3. The first of them (mp 57-57.5°C) is methyl 5-nitro-2-thienyl sulfide, according to PMR spectroscopy, while the second (mp 81-82°C) is methyl 3-nitro-2-thienyl sulfide. The latter was apparently isolated by Cymerman-Craig and co-workers [15] and described (without structural proof) as the 5-nitro isomer. The fact that it is actually the 3-nitro compound follows also from a recently published paper [19] in which methyl 3-nitro-2-thienyl sulfide was obtained by a cyclization that does not raise any doubts about its structure and was described as a substance with mp 84-85°C.

We also contemplated a route for the "alternative" synthesis of a third isomeric nitro sulfide–methyl 4-nitro-2-thienyl sulfide – by nitration of methyl 3,5-dibromo-2-thienyl sulfide and subsequent debromination of the dibromonitro sulfide. However, under the nitration conditions, we obtained a reaction product that does not contain nitrogen from methyl 3,5-dibromo-2-thienyl sulfide and were able to assign the methyl 3,5-dibromo-2-thienyl sulfoxide structure to it on the basis of the analytical data and PMR spectrum.



Our other attempt consisted in the nitration of dimethyl(5-bromo-2-thienyl)sulfonium perchlorate to the dimethyl(5-bromo-4-nitro-2-thienyl)sulfonium salt, the demethylation of which gave methyl 5-bromo-

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*An additional proof of the correctness of the assignment of the 3- and 5-nitro sulfide structures that we made on the basis of the PMR spectra is a comparison of the data discussed above with the PMR spectra of the similarly constructed formylthiophenes. According to [16], the spectrum of 2-methylmercapto-3-formylthiophene contains 4-H and 5-H signals (superimposed) at 5.3 ppm relative to acetone with $J_{4,5} = 5.35$ Hz. We recorded the spectrum of 5-methylmercapto-2-formylthiophene obtained by the method in [18]. It contains 3-H signals at 5.66 ppm and 4-H signals at 4.94 ppm (relative to acetone) with $J_{3,4} = 4$ Hz. Thus, as in the case of the nitro sulfides the signals of the 2,3-disubstituted derivatives are situated between the signals of the 2,5-disubstituted isomer.

4-nitro-2-thienyl sulfide. The debromination of the latter with copper in propionic acid made it possible to isolate a very low yield of a substance that was identical (according to GLC) to methyl 4-nitro-2-thienyl sulfide, which is formed in the demethylation of the product of the nitration of the dimethyl(2-thienyl)sulfonium salts (see above).

EXPERIMENTAL

The PMR spectra of the sulfonium salts and sulfides were recorded with an RS-60 spectrometer [Special Design Office of the Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR (SDO IOC AS USSR)] with hexamethyldisiloxane as the internal standard. The chemical shifts are given on the δ scale.

The chromatographic analyses were performed with an LKhM-4 chromatograph (SDO IOC AS USSR) with a thermal conductivity detector and an LKhM-8m chromatograph (Mosneftekip Plant) with a thermal conductivity and flame ionization detector. The gas carriers were helium and nitrogen, and the flow rate was 30-60 ml/min. The column temperature was 140-170° C. The columns were made of stainless steel and had an inner diameter of 3 mm: 1) a 3-m-long column with 0.5% polyethylene glycol adipate on NaCl; 2) the same with polyethyleneglycol adipate on glass spheres; 3) a 2-m-long column with 20% polyethylene glycol adipate on Chromosorb-W; 4) a 3-m-long column with 5% SE-30 on Chromaton N-AW. Columns 3 and 4 were used to analyze the bromo derivatives, and columns 1, 2, and 4 were used to analyze the nitro derivatives. (Column 3 can also be used, but the temperature must be 200° C.)

Bromination of Dimethyl(2-thienyl)sulfonium Perchlorate. A solution of 2.45 g (0.01 mole) of dimethyl-(2-thienyl)sulfonium perchlorate in 10 ml of 57% $HClO_4$ was added at 20° C to a solution of 1.55 g (0.005 mole) of silver sulfate in 40 ml of 57% $HClO_4$. When 0.5 ml (~ 0.01 mole) of bromine was added to the resulting solution, the color disappeared rapidly and AgBr precipitated. The mass was stirred for 20 min, the AgBr was separated by decantation, and the solution was poured over crushed ice to precipitate 0.94 g of a product with mp 98-107° C. Recrystallization from methanol – ether gave a product with mp 103-105° C. Judging from elementary analysis, it was a mixture of bromides with unchanged starting sulfonium salt. A solution of 0.65 g of the crude bromination product in 500 ml of methanol was passed through a column packed with the acetate form of ÉDÉ-10p anion-exchange resin (see [1]). Evaporation of the eluate gave 0.41 g of a mixture containing methyl 2-thienyl sulfide, methyl 4-bromo-2-thienyl sulfide, methyl 5-bromo-2-thienyl sulfide, and methyl 4,5-dibromo-2-thienyl sulfide, according to GLC.

Bromination of 2.45 g of dimethyl(2-thienyl)sulfonium perchlorate with 0.02 mole of bromine in $HClO_4$ in the presence of 0.01 mole of Ag_2SO_4 for 20 h at 20° C gave 0.58 g of a product that melted at 202-204° C after recrystallization from methanol – ether and, judging from its elementary analysis, was a mixture of mono- and dibromides. Decomposition of this salt on ÉDÉ-10p resin gave a mixture of the same compounds as in the experiment described above, with the exception of methyl 2-thienyl sulfide. It is interesting to note that the ratio of the 4- and 5-monobromides and 4,5-dibromide changes only slightly as a function of the amount of bromine used and is close to 1 : 1.2 : 2.2 in both cases (from the areas of the peaks when a thermal conductivity detector is used).

Methyl 5-Bromo-2-thienyl Sulfide. A total of 34 ml of concentrated hydrochloric acid was added to a solution of 3.83 g (0.0294 mole) of methyl 2-thienyl sulfide in 65 ml of benzene, and 65 ml of a 0.93 N solution of a bromide – bromate mixture was then added dropwise with stirring and cooling (0-2° C) to the mixture. The mixture was then stirred for 3 h at room temperature, and the organic layer was separated, washed with water, 10% NaOH solution, and water, and evaporated. Distillation of the residue gave 2.88 g (47%) of methyl 5-bromo-2-thienyl sulfide with bp 112-116° C (17 mm) and n_D^{20} 1.6330 (bp 113-116° C (18 mm), n_D^{20} 1.6325 [20]).

Methyl 4,5-Dibromo-2-thienyl Sulfide. This compound was similarly obtained in 17% yield from methyl 4-bromo-2-thienyl sulfide [19] and had bp 117-120° C (2 mm). The sample obtained contained ~ 20% of impurities, which were identified by GLC as the 4- and 3-monobromo products and the 3,5- and (presumably) 4,5-dibromo derivatives of methyl 2-thienyl sulfide.

Methyl 3,5-dibromo-2-thienyl Sulfide. A solution of 5.5 ml (0.1 mole) of bromine in 150 ml of chloroform was added dropwise to a solution of 6.5 g (0.05 mole) of methyl 2-thienyl sulfide in 15 ml of chloroform at −10° C. The mixture was stirred at 20° C for 2 h and poured over crushed ice. The organic layer was separated and washed with water, 5% $Na_2S_2O_3$ solution, and water, dried with $MgSO_4$, and evaporated. The residue was distilled to give 11.1 g (77%) of pure (according to GLC) methyl 3,5-dibromo-2-thienyl sulfide with bp 120-125°C (5 mm), n_D^{20} 1.6644, and d_4^{20} 1.9862. Found: C 20.4; 20.5; H 1.3; 1.2; Br 55.1; 55.3; S 22.1; 22.2%. $C_5H_4Br_2S_2$. Calculated: C 20.8; H 1.4; Br 55.5; S 22.3%. PMR spectrum (in CCl_4): CH_3S singlet at δ 2.42 ppm and 3-H singlet at 6.91 ppm.

Nitration of Dimethyl(2-thienyl)sulfonium Salts. A 3.75-g (0.018 mole) sample of dimethyl(2-thienyl)-sulfonium nitrate [1] was added gradually to a mixture of 9 ml of H_2SO_4 and 8 ml of concentrated HNO_3 (sp. gr. 1.49) at 18-20°C. The resulting solution was stirred at the same temperature for 30 min and was then heated at 60°C for 5 h. The mixture was poured over ice, and the resulting precipitate was removed by filtration, washed with ether, and vacuum-dried over paraffin and P_2O_5 to give 0.31 g (7%) of dimethyl(nitro-2-thienyl)sulfonium nitrate with mp 146°C (from methanol). Found: N 11.6; 11.6%. $C_6H_8N_2O_5S_2$. Calculated N 11.1%. A small amount of perchloric acid was added to the filtrate, and the resulting precipitate was removed by filtration and dried to give 0.41 g (8%) of dimethyl(nitro-2-thienyl)sulfonium perchlorate with mp ~200°C. An analytic sample had mp 208-210°C (from methanol). Found: N 5.1; 5.0%. $C_6H_8ClNO_6S_2$. Calculated: N 4.8%.

Nitration of 12.6 g (0.05 mole) of dimethyl(2-thienyl)sulfonium perchlorate under similar conditions gave 11.1 g (77% based on the crude product) of dimethyl(4- and 5-nitro-2-thienyl)sulfonium perchlorates with mp 168-170°C. A sample recrystallized from methanol (mp 208-210°C) did not depress the melting point of a sample obtained from dimethyl(2-thienyl)sulfonium nitrate (see above). The crude product of the nitration of dimethyl(2-thienyl)sulfonium perchlorate (10 g) was refluxed with 3.5 ml of pyridine in 60 ml of water for 7 h, and the mixture was then extracted with ether. Evaporation of the ether gave ~6 g of residue, which contained methyl 4- and 5-nitro-2-thienyl sulfides in a ratio of ~3:2 (according to PMR spectroscopy and GLC). Chromatography of 3 g of the mixture on Al_2O_3 with elution by hexane–ether (1:1) gave 1.16 g of methyl 4-nitro-2-thienyl sulfide (0.67 g with mp 21-22°C and 0.49 g with mp 17-20°C) and 1.05 g of methyl 5-nitro-2-thienyl sulfide with mp 52-56°C. An analytical sample of methyl 4-nitro-2-thienyl sulfide had mp 21-22°C (sublimed at ~100°C and 20 mm). Found: C 34.3; 34.5; H 2.9; 2.9; N 7.8; 7.8; S 36.4; 36.1%. $C_5H_5NO_2S_2$. Calculated: C 34.3; H 2.9; N 8.0; S 36.6%. Vacuum sublimation and crystallization from hexane of methyl 5-nitro-2-thienyl sulfide gave a product with mp 56.5-57.5°C. Found: C 34.3; 34.2; H 3.0; 2.9; S 36.4; 36.5%. $C_5H_5NO_2S_2$. Calculated: C 34.3; H 2.9; S 36.6%.

Nitration of Methyl 2-Thienyl Sulfide. A cooled mixture of 3 ml of fuming nitric acid and 10 ml of acetic anhydride was added dropwise in the course of 2 h to a cooled (to −70°C) solution of 8.8 g (0.067 mole) of methyl 2-thienyl sulfide in 13 ml of acetic anhydride. The resulting solution was stirred for another 20 min at −60°C and was then poured over ice. The nitration product was extracted with ether, and the extract was washed with 5% sodium carbonate solution and water, dried with $MgSO_4$, and evaporated to give 3.8 g of a dark, viscous residue, from which 0.4 g of a dirty-yellow precipitate with mp 38-58°C was isolated by refluxing with hexane. Found: N 8.1; 8.3%. $C_5H_5NO_2S_2$. Calculated: N 8.0%. Chromatography on Al_2O_3 with elution with hexane–ether (9:1) gave the 5-nitro and 3-nitro derivatives. Methyl 5-nitro-2-thienyl sulfide (0.17 g) had mp 57-57.5°C and did not depress the melting point of the sample described above, which was obtained from the products of the nitration of the sulfonium salt. Found: N 8.1; 8.2%. $C_5H_5NO_2S_2$. Calculated N 8.0%. Methyl 3-nitro-2-thienyl sulfide (0.13 g) had mp 81-82°C, in agreement with the values in [15, 19] (see the general section).

Attempts to Synthesize Methyl 4-Nitro-2-thienyl Sulfide. The nitration of 1.1 g of dimethyl(5-bromo-2-thienyl)sulfonium nitrate [1] under the conditions described for salt I gave 1.03 g (73%) of dimethyl(5-bromo-4-nitro-2-thienyl)sulfonium perchlorate with mp 162-163°C. Found: C 19.2; 19.4; H 1.7; 1.8; Br 21.6; 21.5; Cl 9.6; 9.5; S 17.3; 17.2%. $C_6H_7BrClNO_6S_2$. Calculated: C 19.5; H 1.9; Br 21.7; Cl 9.6; S 17.4%. Decomposition of 1 g of this perchlorate on the acetate-form ÉDÉ-10p resin (see [1]) gave 0.96 g (97%) of methyl 5-bromo-4-nitro-2-thienyl sulfide with mp 35-36°C (eluted with ether and petroleum ether). Found: C 24.0; H 2.1; Br 31.5; S 25.3%. $C_5H_4BrNO_2S_2$. Calculated C 23.6; H 1.6; Br 31.5; S 25.2%. A solution of 0.8 g (0.003 mole) of methyl 5-bromo-4-nitro-2-thienyl sulfide in 20 ml of propionic acid was refluxed for 15 min with 0.64 g (0.01 g-atom) of copper powder. The residue (0.5 g) obtained after removal of the propionic acid by vacuum distillation was washed with water and recrystallized from aqueous ethanol to give 0.01 g of an oily substance, which was shown by GLC to be identical to methyl 4-nitro-2-thienyl sulfide formed by demethylation of a mixture of the products of nitration of dimethyl(2-thienyl)sulfonium salts.

Methyl 3,5-dibromo-2-thienyl sulfoxide with mp 45-50°C was obtained in 36% yield from methyl 3,5-dibromo-2-thienyl sulfide by the action of HNO_3 in acetic anhydride under the conditions described above, except that stirring was carried out at −50°C, after which the mixture was allowed to stand for 2 h with simultaneous raising of the temperature to −10°C. An analytical sample had mp 55-56°C (from hexane).

Found: C 19.9; 20.2; H 1.2; 1.5; Br 52.7; 52.9; S 21.1; 21.2%. $C_5H_4Br_2OS_2$. Calculated: C 19.7; H 1.3; Br 52.5; S 21.1%. PMR spectrum (in CCl_4): CH_3 singlet at 2.83 and 4-H singlet at 6.99 ppm.

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