THE SYNTHESIS AND SOME REACTIONS OF THIOPHENE SULFIDES

XVIII. The Synthesis and Reactions of 5-Alkylthio-4-chloromethyl-2-alkylthiophenes*

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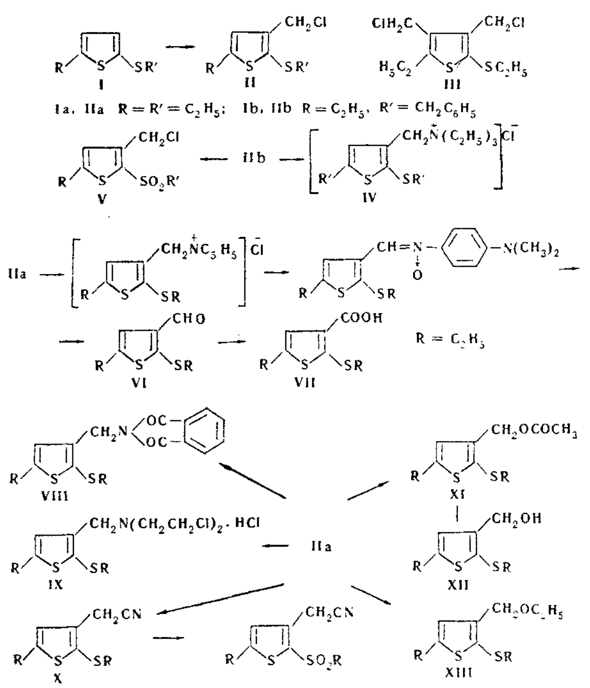
Chloromethyl ether reacts with alkyl 5-alkyl-2-thienyl sulfides to introduce the chloromethyl group in the 3-position of the thiophene ring. From 5-ethylthio-4-chloromethyl-2-ethylthiophene are prepared derivatives of ethyl 5-ethyl-2-thienyl sulfide with various functional groups in the 3-position.

The chloromethylated alkyl 2-thienyl sulfides are of interest as starting materials for the synthesis of disubstituted thiophenes bearing, in addition to the alkylthio group, another functional group. No similar compounds have previously been described. An attempt was made in 1954 to obtain compounds of this type by the chloromethylation of methyl 2-thienyl sulfide with formaldehyde and HCl, but no pure reaction products were obtained [1]. We have found no reference in the literature to the chloromethylation of alkyl 5-alkyl-2-thienyl sulfides. Meanwhile, during the course of our work on sulfides of the thiophene series, the need arose to investigate this problem. It was found that alkyl 5-alkyl-2-thienyl sulfides (I) readily undergo chloromethylation with chloromethyl ether at room temperature, or on brief warming to 35–40° C in acetic acid, as is the case with 2,5-dimethylthiophene [2]. 5-Alkylthio-4-chloromethyl-2-alkylthiophenes (II) are formed in 70% yield together with, in the case of **Ia**, some 3,4-bischloromethylated compound III. 5-Ethylthio-4-chloromethyl-2-ethylthiophene is a colorless, mobile liquid which distills readily in vacuo, while 5-benzylthio-4-chloromethyl-2-ethylthiophene is less stable, decomposing on distillation in vacuo, and was characterized as the crystalline triethylammonium chloride IV and sulfone V. We failed to obtain the phthalimido derivative in a crystalline state.

The entry of the first chloromethyl group into the position ortho to the alkylthio group was confirmed by conversion of the chloromethyl derivative **IIa** into the previously described aldehyde VI [3] by Kröhnke's method [4,5] or by treatment with dimethyl sulfoxide [6]. From the aldehyde VI were prepared the known 2,4-dinitrophenylhydrazone [3] and acid VII [7].

The chloromethyl derivative **IIa** was utilized for the synthesis of alkyl 5-alkyl-2-thienyl sulfides with various functional groups in the 3-position, since these were of interest for the preparation of new complexing agents of the thiophene series. Known methods were used to prepare the phthalimido derivative VIII, the tertiary amine IX, the nitrile X, and the acetoxy-, hydroxy- and ethoxy-derivatives XI, XII, and XIII, the preparation of which will be described in later communications.



The chloromethylation of ethyl 2-thienyl sulfide (XIV) with a free α-position in the thiophene ring is very complex. The reaction products are undistillable, uncrystallizable mixtures of chloromethyl derivatives from which no pure compounds were obtained. Oxidation with hydrogen peroxide or potassium permanganate similarly did not throw any light on the composition of the mixture. However, reaction with potassium phthalimide gave a pure bisphthalimido-derivative, which in its composition and molecular weight agreed with 5,5'-bisethylthio-4,4'-bisphthalimidomethyl-2,2'-dithienylmethane (XV); reaction with sodium ethoxide also afforded the dithienylmethane derivative XVI. The structures of XV and XVI were not specifically established, but it may be assumed that linkage occurs in the α-position of the thiophene ring as in the case of 2-ethylthiophene [8], and that substitution by the chloromethyl group occurs at the carbon atom adjacent to the alkylthio group:

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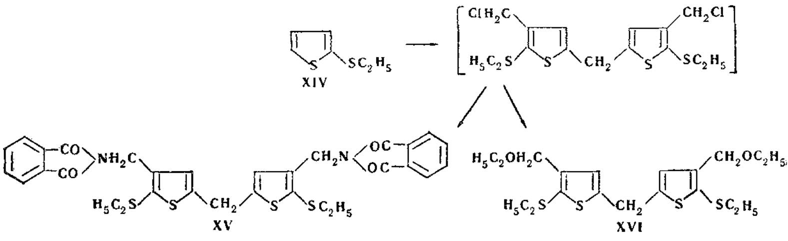
*For part XVII, see [11].



XIV

XV

XVI

EXPERIMENTAL

5-Ethylthio-4-chloromethyl-2-ethylthiophene (IIa). To a solution of 30 g (0.17 mole) of 5-ethylthio-2-ethylthiophene (Ia) in 90 ml of glacial acetic acid was added, with stirring at +10° C, 21 g (0.26 mole) of chloromethyl ether. The mixture was stirred for 30 min at room temperature and 30 min at 35–40° C. On the following day the mixture was poured onto ice, the organic layer separated, the aqueous layer extracted with benzene, the benzene solution washed with water and dried over $CaCl_2$. The residue after removal of the benzene was distilled in vacuo to give 26.7 g (69.3%) of IIa, bp 120–122.5° C (3 mm). n_D^{20} 1.5694. Found, %: C 49.02, 49.04; H 5.84, 5.82. Calculated for $C_9H_{13}ClS_2$, %: C 48.96; H 5.93.

There was also isolated 2.8 g of 5-ethylthio-3, 4-bischloromethyl-2-ethylthiophene (III), which distilled with decomposition at 160–180° C (3 mm). Use of a 10% excess of chloromethyl ether reduced the yield of monochloromethylated product to 60%, and some of the bis-chloromethylated derivative was still obtained.

5-Ethylthio-4-phthalimidomethyl-2-ethylthiophene (VIII). A solution of 5.8 g (0.026 mole) of the chloromethyl derivative IIa in 50 ml of N, N-dimethylformamide and 4.9 g (0.026 mole) of potassium phthalimide was heated on a boiling water bath for 2 hr. The precipitate was filtered off, and the filtrate diluted with chloroform and water. The aqueous layer was separated and extracted with chloroform, and the chloroform layer washed with water, 10% NaOH, and water, and dried over $MgSO_4$. The residue after removal of the solvent was recrystallized from ethanol to give 6 g (68.5%) of VIII, mp 63–64.5° C. Found, %: C 61.21; H 5.05; S 19.11. Calculated for $C_{17}H_{17}NO_2S_2$, %: C 61.42; H 5.15; S 19.29.

5-Ethylthio-3, 4-bisphthalimidomethyl-2-ethylthiophene was obtained as described above, from 5-ethylthio-3, 4-bischloromethyl-2-ethylthiophene, and recrystallized from ethyl acetate, mp 198.5° C. Found, %: C 63.46, 63.57; H 4.76, 4.66; S 12.85, 12.90. Calculated for $C_{26}H_{24}N_2O_4S_2$, %: C 63.39; H 4.91; S 13.02.

5-Benzylthio-4-chloromethyl-2-ethylthiophene (IIb) was obtained similarly to IIa in 55% yield from 20.7 g (0.089 mole) of 5-benzylthio-2-ethylthiophene [3], 9 g (0.11 mole) of chloromethyl ether and 60 ml of glacial acetic acid. The chloromethyl compound distilled with decomposition at 182–184° C (3 mm), n_D^{20} 1.6050.

Triethyl(2-benzylthio-5-ethyl-3-thienyl)ammonium chloride (IV). One—(about 0.04 mole) of IIb was heated for several minutes with 0.5 ml of triethylamine. The mixture crystallized on cooling. The solid was filtered off, washed with ether, and reprecipitated from absolute ethanol with dry ether to give 1.2 g (98%) of colorless, hygroscopic crystals, mp 159.5–161° C (decomp., in a sealed capillary), which deliquesced in air but kept well in a closed vessel. Found, %: C 62.35, 62.57; H 8.02, 8.09; Cl 8.97, 8.86; S 16.24, 16.02. Calculated for $C_{20}H_{30}ClNS_2$, %: C 62.55; H 7.87; Cl 9.23; S 16.70.

4-Chloromethyl-5-benzylsulfonyl-2-ethylthiophene (V). A mixture of 2 g (about 0.007 mole) of compound IIb, 1.8 ml of 30% hydrogen peroxide, and 15 ml of glacial acetic acid was warmed to 35° C to obtain a homogeneous solution, and kept for three days at room temperature. The oil that was precipitated by water was extracted with ether and the ether solution washed with $NaHCO_3$ solution and water, giving 1.7 g of a colorless crystalline material, which after recrystallization from ethanol melted at 54.5–55.5° C. Found, %: C 53.46, 53.47; H 4.83, 4.73; Cl 11.10, 11.22; S 20.27, 20.05. Calculated for $C_{14}H_{15}ClO_2S_2$, %: C 53.41; H 4.80; Cl 11.26; S 20.37.

2-Ethylthio-5-ethyl-3-thiophenealdehyde (VI). A). A mixture of 2.7 g (0.012 mole) of IIa, 1.3 ml of dry pyridine and 1.3 ml of absolute ethanol was boiled on the water bath for 30 min. The pyridinium salt, which was precipitated as an oil by addition of dry ether, was twice washed with ether, and mixed with 1.7 g (0.011 mole) of p-nitrosodimethylaniline and 33 ml of ethanol. To the solution was added at +10° C a solution of 0.5 g (0.013 mole) of NaOH in 12 ml of water, and the resulting reddish-brown mixture stirred for 1 hr at +10° C, followed by 1 hr at about 20° C. After addition of 50 ml of water, the dark-colored oil which was precipitated was washed with water and treated with 33 ml of 2 N HCl. The mixture was extracted thoroughly with benzene, the benzene solution washed with water and dried over $MgSO_4$. The aldehyde distilled at 127–128° C (4 mm); n_D^{20} 1.5880. Lit. [3]; bp 118–119° C (2 mm); n_D^{20} 1.5889. The 2, 4-dinitrophenylhydrazone of VI melted at 150–151.5° C (from ethyl acetate), undepressed on admixture with a sample obtained previously [3]. Found, %: C 47.31; H 4.36; S 16.77. Calculated for $C_{15}H_{16}N_4O_4S_2$, %: C 47.35; H 4.24; S 16.85.

B). A 7.7-g (0.035 mole) quantity of IIa in 20 ml of dimethyl sulfoxide and 2.9 g (0.035 mole) of sodium bicarbonate were heated for 7 hr at 100° C. The dark solution was poured into water and the oil extracted with ether. The extract was washed with water, dried over $MgSO_4$, and distilled to give 4.7 g (64%) of the aldehyde VI, bp 134–138° C (4 mm); n_D^{20} 1.5880. 2, 4-Dinitrophenylhydrazone of VI, recrystallized from ethyl acetate, melted at 151–152° C, and gave no depression of mp on admixture with a sample of the hydrazone obtained previously [3].

2-Ethylthio-5-ethyl-3-thiophenecarboxylic acid (VII) was obtained by the oxidation of the aldehyde VI with freshly precipitated silver oxide [9], mp 126.5–128° C (from 50% ethanol). Found, %: C 49.97; H 5.62; S 29.34. Calculated for $C_9H_{12}Cl_2S_2$, %: C 49.97; H 5.59; S 29.65. A mixed mp with a sample of the acid obtained by oxidation of 2-ethylthio-5-ethyl-3-acetothienone [7] gave no depression.

5-Ethylthio-4-di-(β-chloroethyl)aminomethyl-2-ethylthiophene (hydrochloride) (IX). A solution of 4 g (0.018 mole) of IIa in chloroform (5 ml) was added to 5 g (0.035) mole of β, β'-dichlorodiethylamine [10] in 20 ml of a mixture of benzene and chloroform. The mixture was boiled for 12 hr, the precipitated β, β'-dichlorodiethylamine hydrochloride filtered off, and to the filtrate was added 20 ml of methanolic HCl of concentration 0.635 g/ml. The solvents were removed in vacuo, the oily residue treated with dry ether and the residue filtered off and dried in vacuo to give 3.1 g (47%) of IX hydrochloride, mp 81–85° C, raised by twice reprecipitating from ethanol with dry ether to 92.5–94° C. Found, %: C 42.75, 42.51; H 6.18, 6.34; N 4.02, 4.03. Calculated for $C_{13}H_{21}Cl_2NS_2 \cdot HCl$, %: C 43.03; H 6.11; N 3.86.

5-Ethylthio-4-cyanomethyl-2-ethylthiophene (X). To a solution of 3.5 g (0.071 mole) of sodium cyanide in 8 ml of water and 8 ml of dimethylformamide was added gradually 18.3 g (0.083 mole) of IIa in 20 ml of dimethylformamide. The mixture was heated at 80° C for 4 hr, kept overnight, diluted with 50 ml of water and extracted thoroughly with ether. The ether extract was washed with water, dried over $MgSO_4$ and distilled to give 14.5 g of the nitrile X, bp 130–131° C (4 mm). It was purified chromatographically on Al_2O_3 using benzene as eluent, n_D^{20} 1.5628. Found, %: C 56.84, 56.76; H 6.25, 6.14; S 30.40, 30.60. Calculated for $C_{10}H_{13}NS_2$, %: C 56.80; H 6.20; S 30.33.

5-Ethylsulfonyl-4-cyanomethyl-2-ethylthiophene was obtained in 83% yield by oxidation of the nitrile **X** with 30% hydrogen peroxide in glacial acetic acid for 2 hr at 100° C as colorless needles, which melted after recrystallization from 50% ethanol and from pentane at 67.5–68° C. Found, %: C 49.32, 49.10; H 5.40, 5.45; S 26.33, 26.13; Calculated for $C_{10}H_{13}NO_2S_2$, %: C 49.36; H 5.38; S 26.46.

5-Ethylthio-4-acetoxymethyl-2-ethylthiophene (XI). A mixture of 10.3 g (0.047 mole) of **IIa**, 4 g (0.049 mole) of fused sodium acetate and 35 ml of glacial acetic acid was heated with stirring at 60° C for 5 hr. The precipitate was filtered off, the solvent distilled off, water added to the residue and extracted thoroughly with ether. The ether extract was dried and distilled to give 9.1 g of the acetoxy-compound **XI** (79%), bp 135–136° C (4 mm); d_4^{20} 1.1241; n_D^{20} 1.5415. Found, %: C 53.83, 53.70; H 6.49, 6.48; S 26.33, 26.29; MR_D 68.36. Calculated for $C_{11}H_{16}O_2S_2$, %: C 54.06; H 6.60; S 26.24; MR_D 68.10.

5-Ethylthio-4-hydroxymethyl-2-ethylthiophene (XII). To a solution of sodium ethoxide, prepared from 0.36 g (0.016 g-atom) of sodium in 60 ml of absolute ethanol, was added 15.3 g (0.063 mole) of the acetoxy compound **XI**, and the solution kept at room temperature for 60 hr. The small amount of solid was filtered off, the solvent removed, and NH_4Cl and absolute ethanol added to the residue. The solid which separated was filtered off, the ethanol removed, the residue treated with water, extracted thoroughly with benzene, the benzene solution washed with water, dried over $MgSO_4$ and distilled to give 9.4 g of the hydroxymethyl derivative **XII**, in 73.5% yield, bp 134° C (4 mm); d_4^{20} 1.1377; n_D^{20} 1.5712. Found, %: C 53.74, 53.69; H 6.88, 6.76; S 31.42, 31.48; MR_D 58.45. Calculated for $C_9H_{14}OS_2$, %: C 53.42; H 6.97; S 31.69; MR_D 58.16.

5-Ethylthio-4-ethoxymethyl-2-ethylthiophene (XIII). To a solution of sodium ethoxide, obtained from 2.5 g (0.11 g-atom) of sodium and 100 ml of absolute ethanol, was added at 60° C 18 g (0.082 mole) of **IIa**, and the solution heated at this temperature for 7.5 hr. After this time, chloride ion was absent from the solution. The NaCl was filtered off and washed with ethanol. The alcoholic solution was evaporated and the residue washed with water and extracted thoroughly with benzene. The benzene solution was dried and evaporated to give 17.2 g (93%) of **XIII**, bp 115–116° C (5 mm); d_4^{20} 1.0529; n_D^{20} 1.5362. Found, %: C 57.20, 56.95; H 8.03, 7.82; S 27.95, 27.99; MR_D 67.25. Calculated for $C_{11}H_{18}OS_2$, %: C 57.34; H 7.87; S 27.90; MR_D 67.52.

Chloromethylation of ethyl 2-thienyl sulfide. To a solution of 14.4 g (0.1 mole) of ethyl 2-thienyl sulfide in 40 ml of glacial acetic acid was added at 10° C 16.1 g (0.2 mole) of chloromethyl ether. After stirring at 20° C for 1.5 hr, a dark oil separated from the solution (the temperature rising to 32° C). The mixture was heated for 1.5 hr at 30–35° C, then poured onto ice. The oil was separated and the aqueous layer was extracted thoroughly with benzene. The extract and the organic layer were washed with water, 10% sodium bicarbonate solution and water, and dried over $CaCl_2$. Removal of the benzene left a dark, viscous oil which decomposed on distillation in vacuo. The oil (3 g) in 40 ml of dimethylformamide and 2.8 g of potassium phthalimide were stirred for 2 hr at 90° C, the precipitate filtered off, and the filtrate treated with 20 ml of water. The turbid solution was extracted thoroughly with chloroform and the extract washed with water, 10% sodium hydroxide solution, and water, and dried over $MgSO_4$. Removal of the chloroform left 4 g of a viscous brown oil which was treated with hot ethanol, cooled, and triturated with ethanol and ether to give a colorless powder. There was obtained 1 g of 5,5'-bisethylthio-4,4'-bis-(phthalimidomethyl)-2,2'-dithienylmethane (**XV**), which after recrystallization from acetone and ethyl acetate with charcoal, melted at 152–153.5° C. Found, %: C 60.17, 60.29; H 4.21, 4.25; S 20.62, 20.54; N 4.59, 4.50; M 597.8. Calculated for $C_{31}H_{26}N_2O_4S_4$, %: C 60.20; H 4.24; S 20.74; N 4.53, M 618.4. The molecular weight was determined ebullioscopically in benzene.

5,5'-Bisethylthio-4,4'-bisethoxymethyl-2,2'-dithienylmethane (XVI). A 17 g quantity of the crude mixture of chloromethyl derivatives of ethyl 2-thienyl sulfide (see above) was heated with stirring with a solution of sodium ethoxide (obtained from 3 g (0.13 g-atom) of sodium and 130 ml of absolute ethanol) for 5.5 hr at 60° C. The precipitate was filtered off and washed with ethanol. The alcoholic filtrate was evaporated, the residue diluted with water, and extracted thoroughly with ether. The ether solution was washed with 5% NaOH and water, dried and evaporated. The residue (6.4 g) was distilled in vacuo to give fraction 1), bp 120–140° C (2 mm), n_D^{20} 1.5327, weight 0.75 g, and fraction 2), bp 246–250° C (2 mm), n_D^{20} 1.5800, weight 3.8 g. Fraction 2) after two redistillations gave the dithienylmethane **XVI**, bp 190° C (0.1 mm), n_D^{20} 1.5802. Found, %: C 55.05, 54.94; H 6.56, 6.55; S 30.99, 30.75. Calculated for $C_{19}H_{28}O_2S_4$, %: C 54.77; H 6.77; S 30.78. We were unable to obtain a crystalline sulfone from this oil.

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