SYNTHESIS OF SOME 2,4-DISUBSTITUTED DERIVATIVES OF THE THIOPHENE SERIES FROM 4-CHLOROMETHYL-2-ACETOTHIENONE AND 4-CHLOROMETHYL-2-FORMYLTHIOPHENE

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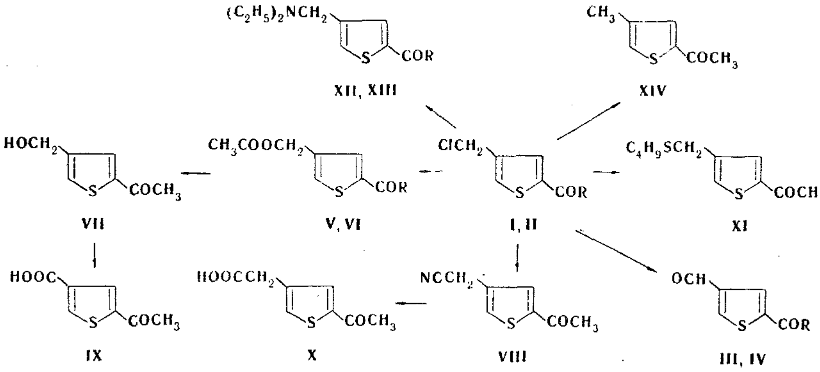
Some difficult-to-obtain 2,4-disubstituted compounds of the thiophene series were synthesized starting from 4-chloromethyl-2-acetothienone and 4-chloromethyl-2-formylthiophene.

The use of complexes of α-carbonyl compounds of the thiophene series with aluminum chloride in electrophilic substitution reactions opens up broad possibilities for the synthesis of difficult-to-obtain 2,4-disubstituted thiophenes (see the review in [1]). We have recently [2] shown the possibility (in contrast to what was described in [3-5]) of the preparation of individual 4-chloromethyl-2-acetothienone (I) and 4-chloromethyl-2-formylthiophene (II) by chloromethylation of the corresponding carbonyl compounds, if α,-α'-bischloromethyl ether rather than the monochloromethyl ether is used as the chloromethylating agent in the presence of aluminum chloride. Thanks to this procedure, conditions are set up for the extension of the number of possible transformations of I and II by the action of nucleophilic agents; this makes it possible to obtain previously difficult-to-obtain compounds by a simpler route. Thus we synthesized 4-hydroxymethyl-2-acetothienone (VII) from 2-acetothienone through 4-chloromethyl- (I) and 4-acetoxymethyl-2-acetothienone (V) in three steps, whereas in [4, 6] the same compound was obtained through 4-bromo-2-acetothienone and its ketal in four steps by one method and in six steps by another.

Starting from I and II, for the first time we obtained some difunctional compounds containing, in addition to acetyl or formyl groups, nitrile (VIII), carboxyl (IX, X), alkylmercapto (XI), and dialkylamino (XII, XIII) groups. In addition to compounds of the thiophene series, we obtained m-formylacetophenone (XV) from m-chloromethylacetophenone by means of the Sommelet reaction.

The synthesis of 4-methyl-2-acetothienone (XIV) by reduction of chloromethylated I is extremely convenient, since the preparation of this ketone from 3-methylthiophene is complicated by the formation



I, III, V, XII R=CH_3; II, IV, VI, XIII R=H

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of a mixture of acylation products in each of the free α positions, and the major component in this mixture is the isomeric 3-methyl-2-acetothienone [7] rather than XIV.

EXPERIMENTAL

4-Formyl-2-acetothienone (III). A mixture of 0.9 g (5 mmole) of 4-chloromethyl-2-acetothienone and 0.7 g (5 mmole) of hexamethylenetetramine in 3 ml of chloroform was refluxed for 45 min to give 1.45 g of the quaternary salt. A solution of 0.4 g (1.3 mmole) of the salt in 10 ml of 50% CH_3COOH was refluxed for 2 h, after which it was extracted with ether. The extract was washed successively with water, Na_2CO_3 solution, and water and dried with $MgSO_4$. The ether was removed by distillation to give 0.08 g (40%) of keto aldehyde III with mp 86.5-87.5°. No melting-point depression was observed for a mixture of this product with a sample (mp 86-86.5°) obtained previously in [6].

2,4-Diformylthiophene (IV). Refluxing of a mixture of 1.6 g (0.01 mole) of 4-chloromethyl-2-formylthiophene and 1.4 g (0.01 mole) of hexamethylenetetramine in 4 ml of chloroform gave 2.5 g of a salt, which was converted as described above to give 0.72 g (51%) 2,4-diformylthiophene (IV) with mp 80-81° (benzene–hexane) (mp 78.8-79.5° [4]).

m-Formylacetophenone (XV). Refluxing of 5 g (0.03 mole) of m-(chloromethyl)acetophenone [3] with 4.2 g (0.03 mole) of hexamethylenetetramine in 10 ml of chloroform gave 7.8 g of a salt, from 7 g of which 0.85 g (19.4%) of m-formylacetophenone (XV) with mp 49.5-51° (from hexane) was obtained as a result of refluxing for 30 min in 70 ml of 50% CH_3COOH. Found: C 72.7; H 5.3%. $C_9H_8O_2$. Calculated: C 73.0; H 5.4%. The dioxime had mp 124.5-126° (from 20% alcohol). Found: C 60.9; H 5.6%. $C_9H_{10}N_2O_2$. Calculated: C 60.7; H 5.6%.

4-Acetoxymethyl-2-acetothienone (V) (see [3]). A mixture of 2.2 g (8 mmole) of 4-chloromethyl-2-acetothienone, 1.25 g (15 mmole) of anhydrous sodium acetate, and 5 ml of glacial CH_3COOH was refluxed with stirring for 5 h and allowed to stand at 20° for 15 h. The acetic acid was removed by vacuum distillation, and the residue was treated with water. The mixture was extracted with ether, and the extract was washed successively with water, sodium carbonate solution, and water and dried with $MgSO_4$. Removal of the ether gave 1.8 g (76%) of 4-acetoxymethyl-2-acetothienone with bp 128-129° (0.5 mm) and n_D^{20} 1.5433. Found: C 54.4; H 5.0; S 16.1%. $C_9H_{10}O_3S$. Calculated: C 54.5; H 5.1; S 16.1%.

4-Acetoxymethyl-2-formylthiophene (VI). A mixture of 3.6 g (22 mmole) of 4-chloromethyl-2-formylthiophene, 2 g (24 mmole) of anhydrous sodium acetate, and 9 ml of glacial CH_3COOH was refluxed with stirring for 14 h and allowed to stand at 20° for 15 h. The mixture was worked up as described above to give 1.9 g (46%) of VI with mp 35.5-36.5° (from hexane). Found: C 52.1; H 4.4; S 17.5%. $C_8H_8O_3S$. Calculated: C 52.2; H 4.4; S 17.4%.

4-Hydroxymethyl-2-acetothienone (VII) (see [3]). A 3-g (15 mmole) sample of 4-acetoxymethyl-2-acetothienone was added to a solution of sodium ethoxide, obtained from 18 ml of absolute alcohol and 0.08 g (3.5 mg-atom) of Na, and the mixture was allowed to stand at 20° for 48 h. The alcohol and resulting ethyl acetate were removed by vacuum distillation, and 0.1 g of NH_4Cl and 3 ml of absolute alcohol were added to the residue. The mixture was shaken for a few minutes until the odor of ammonia vanished, after which the precipitated NaCl was removed by filtration and washed with alcohol, and the filtrates were evaporated to give 2 g (85%) of a residue with mp 34-39°. Reprecipitation with petroleum ether from CH_2Cl_2 gave a product with mp 43-44.5°. No melting-point depression was observed for a mixture of this product with the 4-hydroxymethyl-2-acetothienone obtained previously in [5]. A mixture with 5-hydroxymethyl-2-acetothienone [5] melted at room temperature.

5-Acetylthiophene-3-carboxylic Acid (IX). A total of 8 ml of the Jones reagent [8] (39 g of chromic anhydride in 117 ml of water and 30 ml of concentrated H_2SO_4) was added with stirring at 10-12° to a solution of 0.5 g (3 mmole) of 4-hydroxymethyl-2-acetothienone in 10 ml of acetone, during which the mixture became red. Stirring was continued for another 1.5 h at room temperature, after which the solution was poured into ice water. The aqueous mixture was extracted with ether, and the extract was dried with $MgSO_4$. Removal of the solvent by distillation gave 0.52 g (96.5%) of 5-acetylthiophene-3-carboxylic acid with mp 199-200°. No melting-point depression was observed for a mixture of this product with a sample previously obtained in [5] (mp 200-201°).

4-Cyanomethyl-2-acetothienone (VIII). A solution of 3.9 g (22 mmole) of 4-chloromethyl-2-acetothienone and 1.65 g (25 mmole) of KCN in 4 ml of acetone and 4 ml of water was held at 70° for 20 h, after which it was poured into water. The aqueous mixture was extracted with benzene, and the extract was dried with $MgSO_4$. The solvent was removed, and the residue was sublimed at 110-120° (3 mm) to give 2.65 g (71%) of keto nitrile VIII with mp 43-44.5° (from hexane). Found: C 58.1; H 4.3; S 19.2%. C_8H_7NOS. Calculated: C 58.2; H 4.3; S 19.4%.

5-Acetyl-3-thienylacetic Acid (X). A solution of 0.5 g (3 mmole) of 4-cyanomethyl-2-acetothienone (VIII) in 5 ml of concentrated HCl was held at room temperature for 12 days, after which it was diluted with water and extracted with ether. The ether solution was washed with a saturated solution of K_2CO_3, and the extract was acidified with concentrated HCl. The acidic mixture was extracted with ether, and the extract was dried with $MgSO_4$. The ether was removed by distillation to give 0.24 g (45%) of keto acid X with mp 110-111.5° (sublimed at 115-120° and 4 mm). Found: C 52.0; H 4.5; S 17.5%. $C_8H_8O_3S$. Calculated: C 52.2; H 4.4; S 17.4%.

4-Butylmercaptomethyl-2-acetothienone (XI). A solution of 3.5 g (20 mmole) of 4-chloromethyl-2-acetothienone in 40 ml of absolute benzene was added with stirring at 6-8° in the course of 1 h to a solution of sodium butylmercaptide, obtained from 2.25 g (25 mmole) of butylmercaptan and 0.55 g (25 mg-atom) of sodium in 30 ml of absolute methanol, during which NaCl precipitated. Stirring was continued for another hour, after which the mixture was allowed to stand at 20° for 16 h and then refluxed for 2 h. The benzene and methanol were removed by distillation, water was added to the residue, and the mixture was extracted with ether. The extract was dried with $MgSO_4$ and evaporated to give 3 g (78.8%) of 4-butylmercaptomethyl-2-acetothienone with bp 194-195° (2 mm) and n_D^{20} 1.5651. Found: C 58.0; H 7.1; S 28.4%. $C_{11}H_{16}OS_2$. Calculated: C 57.8; H 7.1; S 28.1%.

4-Diethylaminomethyl-2-acetothienone (XII). A mixture of 1.5 g (9 mmole) of 4-chloromethyl-2-acetothienone, 4 g of diethylamine (55 mmole), and 0.8 g (6 mmole) of powdered potassium carbonate was heated, after termination of the exothermic reaction that developed on mixing, at 50-55° for 6 h with stirring, after which it was allowed to stand at 20° for 16 h. It was then poured into cold water, and the aqueous mixture was extracted with benzene. The extract was washed with dilute (1:10) HCl, and the acid extract was extracted with benzene. The aqueous layer was saturated with potassium carbonate and extracted with benzene, and the extract was dried with potassium carbonate. Distillation of the extract gave 1.4 g (77%) of amide XII with bp 132-133° (0.3 mm) and n_D^{20} 1.5349. Found: C 62.8; H 8.4; N 7.2%. $C_{11}H_{17}NOS$. Calculated: C 62.5; H 8.1; N 6.6%.

4-Diethylaminomethyl-2-formylthiophene (XIII). This compound was obtained as above from 1.6 g (10 mmole) of 4-chloromethyl-2-formylthiophene, 3.7 g (50 mmole) of diethylamine, and 0.97 g (7 mmole) of potassium carbonate, except that stirring at 50-55° was continued for 12 h. The yield of XIII with bp 108-109° (0.8 mm) and n_D^{20} 1.5440 was 1.5 g (76.5%). Found: C 61.4; H 7.5; N 7.2; S 16.3%. $C_{10}H_{15}NOS$. Calculated: C 60.9; H 7.7; N 7.1; S 16.3%.

4-Methyl-2-acetothienone (XIV). A suspension of 3.25 g (19 mmole) of 4-chloromethyl-2-acetothienone and 1.5 g (23 mg-atom) of zinc dust in 20 ml of dioxane and 8 ml of water was stirred and refluxed for 15 h, after which 100 ml of chloroform was added, and the precipitate was removed by filtration. The organic layer was separated, washed with water, and dried with $MgSO_4$. Distillation of the organic layer gave 1.6 g (61.5%) of 4-methyl-2-acetothienone with bp 75-77° (1.6 mm) and n_D^{20} 1.5596. Found: C 60.1; H 5.9; S 22.7%. C_7H_8OS. Calculated: C 60.0; H 5.8; S 22.9%.

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