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-acetothiophene 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-acetothiophene (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-acetothiophene (VII) from 2-acetothiophene through 4-chloromethyl- (I) and 4-acetoxymethyl-2-acetothiophene (V) in three steps, whereas in [4, 6] the same compound was obtained through 4-bromo-2-acetothiophene 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-acetothiophene (XIV) by reduction of chloromethylated I is extremely convenient, since the preparation of this ketone from 3-methylthiophene is complicated by the formation


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of a mixture of acylation products in each of the free \( \alpha \) positions, and the major component in this mixture is the isomeric \( 3\text{-}methyl-2\text{-}acetothienone \) [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 1.46 g of the quaternary salt. A solution of 0.4 g (1.3 mmole) of the salt in 10 ml of 50% \( \text{CH}_3\text{COOH} \) was refluxed for 2 h, after which it was extracted with ether. The extract was washed successively with water, \( \text{Na}_2\text{CO}_3 \) solution, and water and dried with \( \text{MgSO}_4 \). 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% \( \text{CH}_3\text{COOH} \). Found: C 72.7; H 5.3%. \( \text{C}_9\text{H}_8\text{O}_2 \). Calculated: C 73.0; H 5.4%. The dioxime had mp 124.5-126° (from 20% alcohol). Found: C 60.9; H 5.6%. \( \text{C}_9\text{H}_{10}\text{N}_2\text{O}_2 \). 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 \( \text{CH}_3\text{COOH} \) 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 \( \text{MgSO}_4 \). Removal of the ether gave 1.8 g (76%) of 4-acetoxymethyl-2-acetothienone with bp 128-129° (0.5 mm) and \( n_D^\circ 1.5433 \). Found: C 54.4; H 5.0; S 16.1%. \( \text{C}_9\text{H}_{10}\text{O}_3\text{S} \). 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 \( \text{CH}_3\text{COOH} \) 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%. \( \text{C}_8\text{H}_8\text{O}_3\text{S} \). 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 \( \text{NH}_4\text{Cl} \) 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 \( \text{NaCl} \) 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 \( \text{CH}_2\text{Cl}_2 \) 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-Acetyltiophene-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 \( \text{H}_2\text{SO}_4 \)) 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 \( \text{MgSO}_4 \). Removal of the solvent by distillation gave 0.52 g (96.5%) of 5-acetyltiophene-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