THE DIRECTION OF THE CHLOROMETHYLATION OF 2-ACETOTHIENONE AND 2-THIOPHENE ALDEHYDE

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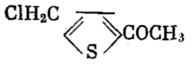
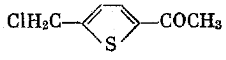
In a number of studies that we published earlier, it was shown that alkyl-2-thienyl ketones and 2-thiophene aldehyde in the form of complexes with aluminum chloride under the action of certain electrophilic agents are substituted almost exclusively in the 4-position of the thiophene ring [1]. The ratio of the isomers was determined for the products of bromination of 2-acetothienone [2] and 2-thiophene aldehyde [3], as well as the acetylation products of 2-acetothienone [4]. As for the isomeric composition of the products of chloromethylation of 2-acetothienone and 2-thiophene aldehyde, the data obtained earlier [3, 5] do not permit a sufficiently accurate judgment of the content of each of the isomers, since not the mixture formed directly, but products of its further conversion were subjected to investigation.

The purpose of this work was to determine the ratio of 4- and 5-substituted derivatives directly in the products of chloromethylation of 2-acetothienone and 2-thiophene aldehyde by monochloromethyl ether in the presence of an excess of anhydrous aluminum chloride* without a solvent, i.e., under the conditions described earlier [3, 5]. Having tested various stationary phases (polyethylene glycol, polyethylene glycol adipate, Apiezon, nitrile – silicone rubber), applied on Chromosorb W, we were unable to select the conditions of gas chromatographic separation of the mixtures of chloromethyl derivatives formed in this case. An attempt to use polarographic reduction for the analysis also did not lead to success. The problem was solved by NMR spectroscopy.

The NMR spectrum of the product of chloromethylation of 2-acetothienone (Fig. 1) contains intense signals with δ 2.43 (CH_3CO group), 4.55 (CH_2Cl group), 7.63 and 7.70 ppm (protons of the thiophene ring); in addition, a weak signal with δ 4.73 ppm appears. The presence of two unsplit signals in a weak field is evidence that the basic component of the mixture is 4-chloromethyl-2-acetothienone (I), in which spin – spin interaction of the protons in the 3- and 5-positions of the ring does not appear. The weak signal (4.73 ppm) can be assigned to a small admixture of 5-chloromethyl-2-acetothienone (II)


(I)


(II)

since the proximity of the electrophilic sulfur atom should lead to a shift of the signal of the protons of the CH_2 groups in the weak field direction in comparison with the isomer I (cf. [6]).

To confirm such an interpretation, we took the NMR spectrum of a sample of chloromethyl-2-acetothienone, produced by the action of paraform and hydrogen chloride in chloroform [7], which the authors considered as individual 5-chloromethyl-2-acetothienone (II). However, on the basis of the data of [8, 9], it may be assumed that this sample contains a more or less substantial impurity of compound (I). The spectrum of this product (Fig. 2) contains signals with δ 2.43, 4.55, 4.71 ppm and a group of signals in a

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*Just as in [3, 5], technical aluminum chloride containing ~90% of the basic substance was used; in converting to 100% $AlCl_3$, we used 2.2 moles of aluminum chloride per mole of the carbonyl compound.

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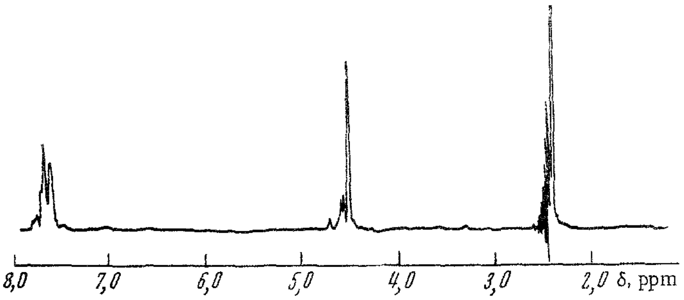


Fig. 1. NMR spectrum of the products of chloromethylation of 2-acetothienone by monochloroethyl ether in the presence of excess $AlCl_3$.

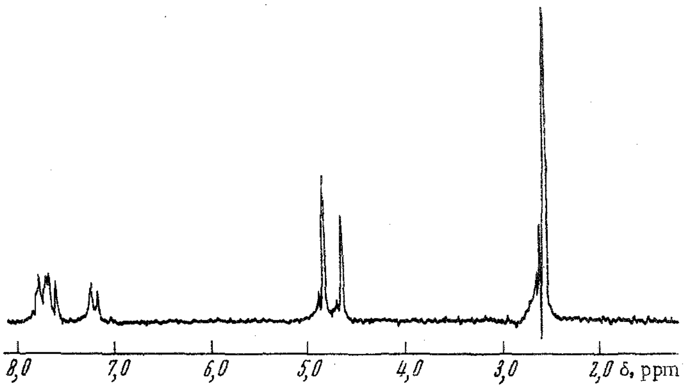
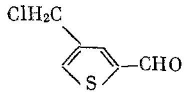


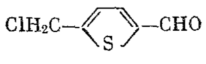
Fig. 2. NMR spectrum of the products of chloromethylation of 2-acetothienone by the action of paraform and HCl in chloroform.

weak field (7.0-7.6 ppm). If the assignment of the signals cited above is correct, then the spectrum depicted in Fig. 2 should belong to a mixture of the isomers II and I in a ratio close to equimolar. For a definitive elucidation of this question, we synthesized the individual compounds (I) and (II) by independent pathways. The NMR spectra of standard samples I and II, cited in Figs. 3 and 4, entirely confirmed the interpretation that we gave above and permit an evaluation of the composition of the mixtures of interest to us. Caclulation according to the areas of the signals for the products of chloromethylation of 2-acetothienone in the presence of 2.2 M aluminum chloride (according to [5]) leads to the conclusion that the content of 4-chloromethyl-2-acetothienone (I) in it is ~98%, and that of 5-chloromethyl-2-acetothienone (II) ~2%. On the other hand, the sample obtained according to the method of [7] by the action of paraform and hydrogen chloride on 2-acetothienone in chloroform, contained ~43% (I) and ~57% (II).*

Judging by the NMR spectrum (Fig. 5), the isomer with the chloromethyl group in the 4-position (III) also comprises the bulk (~93%) of the products of chloromethylation of 2-thiophene aldehyde in the presence of 2.2 M aluminum chloride (according to [3])



(III)



(IV)

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*The data cited on the composition of the mixtures agree with the IR spectra and the results of gas – liquid chromatography on a capillary glass column 40 m long, 0.45 mm in diameter, 190°, phase nitrile – silicone rubber NSKT-33.

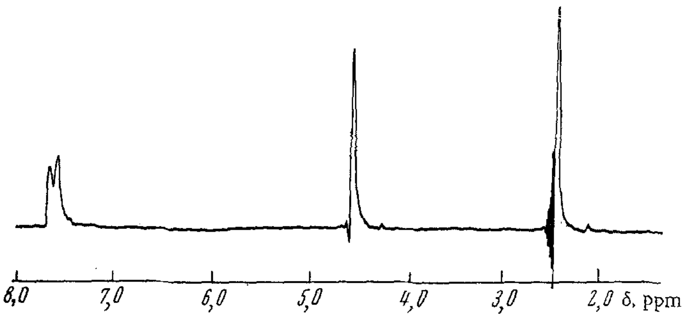


Fig. 3. NMR spectrum of 4-chloromethyl-2-acetothienone (I).

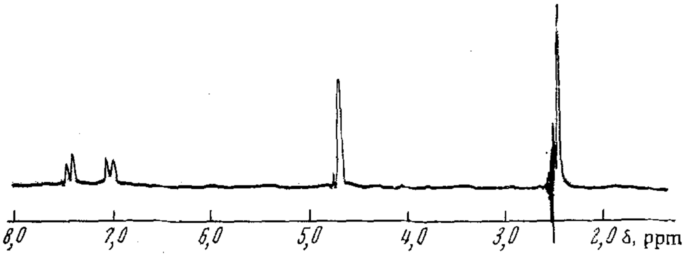
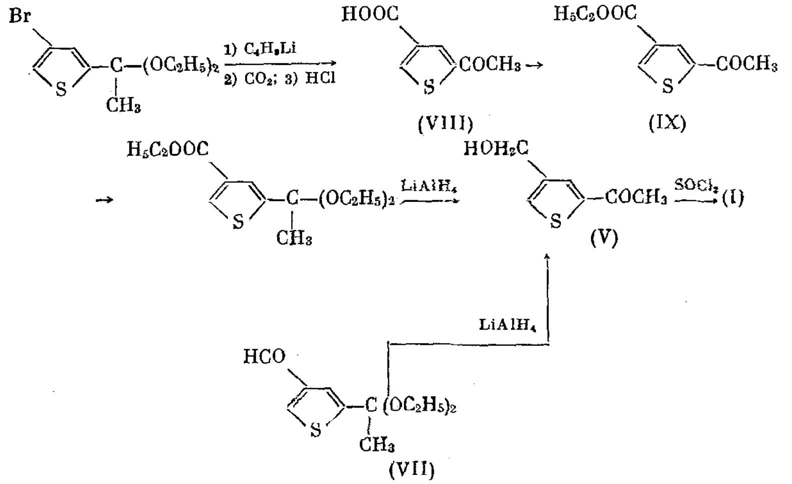
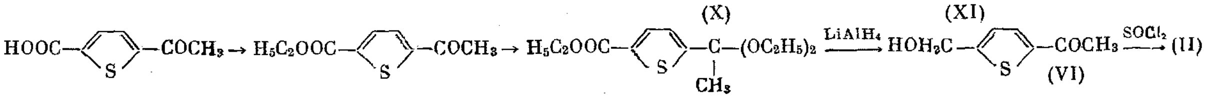


Fig. 4. NMR spectrum of 5-chloromethyl-2-acetothienone (II).

Standard samples of 4- and 5-chloromethyl-2-acetothienones (I) and (II) were produced by the action of thionyl chloride on 4- and 5-hydroxymethyl-2-acetothienone (V) and (VI). 4-Hydroxymethyl-2-acetothienone (V) was produced in two ways: from the diethylketal of 4-formyl-2-acetothienone (VII) [10] and according to a scheme similar to that described for the synthesis of p-chloromethylacetophenone [11]



We synthesized 5-chloromethyl-2-acetothienone (II) on the basis of 5-acetyl-2-thiophenecarboxylic acid (X), produced according to the well-known method [12]



Attempts to produce the isomer II by shorter pathways (acetylation of 2-thenyl chloride and 2-thenyl acetate, the action of hydrogen chloride, thionyl chloride or acetyl chloride on 5-methoxymethyl-2-acetothienone) proved unsuccessful. The individuality of samples I and II was confirmed by the NMR spectra (see Figs. 3 and 4) and the IR spectra.

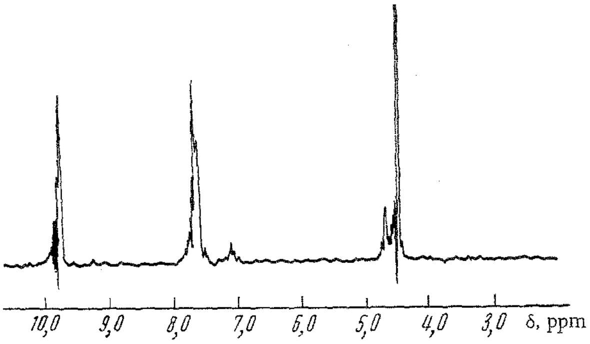


Fig. 5. NMR spectrum of the product of chloromethylation of 2-thiophene aldehyde by monochloromethyl ether in the presence of excess $AlCl_3$.

The data that we obtained show that when carbonyl compounds of the thiophene series are bound in a complex with aluminum chloride, chloromethylation, analogously to a number of reactions of electrophilic substitution, proceeds almost exclusively in the 4-position of the thiophene ring. On the contrary, in the chloromethylation of 2-acetothienone according to the method of Lukes, Yanda, and Kefurt [7], substitution proceeds nonselectively, similarly to the chloromethylation of 2-propionylthiophene [8]. It is also important to note that a sample produced by chloromethylation of 2-acetothienone by formalin and hydrochloric acid under the conditions described in [7] contains only ~20% of a mixture of chloromethyl derivatives, while the bulk of the product is comprised of substances that we did not identify.

EXPERIMENTAL

The NMR spectra were taken in CCl_4 on an N-60 spectrometer with a working frequency of 60 MHz, using hexamethyldisiloxane as an internal standard. The IR spectra were taken on a UR-20 spectrophotometer for solutions in CCl_4 with a concentration of 2-3% by weight. The spectra contained bands characteristic of the conjugated $C = O$ group (1675 cm^{-1} for I and 1670 cm^{-1} for II), $C = C$ bond (1550 and 1538 cm^{-1}, respectively), $C - Cl$ bonds (715 and 720 cm^{-1}), as well as the deformational vibrations of the CH_2 and CH_3 groups (1430, 1460, and 1360 cm^{-1} for I and 1460 and 1360 cm^{-1} for II).

Chloromethylation of 2-Acetothienone in the Presence of Excess Aluminum Chloride (cf. [5]). To 32 g anhydrous aluminum chloride, placed in a flask with a reflux condenser, thermometer, dropping funnel, and effective mixer, 12.6 g 2-acetothienone was added at a temperature no higher than 40-45°. Over a period of 1 h, 10 g of monochloromethyl ether was added to the complex obtained, cooled to 2-5°. The reaction mixture was mixed for 4 h at 5° and left for 15 h at 20°. The dense black mass formed was poured out onto ice, extracted with ether, the extract washed with water, with a solution of $NaHCO_3$, again with water, and dried over $MgSO_4$. After the solvent was distilled off, the residue was redistilled under vacuum. The following fractions were isolated: I) bp 36-40° (0.2 mm); 2.4 g; n_D^{20} 1.5670 – initial 2-acetothienone, 19% recovery; II) bp 96-98° (0.2 mm); 7.09 g; mp 17.5-22° – mixture of 4-(I) and 5-chloromethyl-2-acetothienone (II), yield 41% of the initial 2-acetothienone and 47% of the reacted 2-acetothienone, content of I (according to NMR data) ~98%. Recrystallization from petroleum ether yielded a sample with mp 22-23.5°. Found: 48.57; 48.64; H 4.29; 4.19; Cl 20.38; 20.19; S 18.45; 18.24%. C_7H_7ClOS. Calculated: C 48.13; H 4.04; Cl 20.31; S 18.36%.

A phthalimide derivative with mp 132-132.5° (from alcohol) was obtained from fraction II. Found: C 63.26; 63.06; H 4.02; 3.99; N 4.98; 4.98; S 11.36; 11.12%. $C_{15}H_{11}NO_3S$. Calculated: C 63.14; H 3.89; N 4.91; S 11.24%.

Chloromethylation of 2-Acetothienone by the Action of Paraform and HCl in the Presence of $ZnCl_2$ (cf. [7]). Hydrogen chloride was passed into a mixture of 12.6 g 2-acetothienone, 4.5 g paraform, and 3.4 g zinc chloride in 50 ml dry chloroform with mixing for 3 h at 30°, after which the reaction mixture was decomposed with 100 ml of cold water and extracted with chloroform. The extract was washed with water, with a solution of $NaHCO_3$, with water, and dried over $MgSO_4$. After the solvent was distilled off, the residue was redistilled. The following fractions were isolated: I) bp 45-47° (0.25 mm); 7.5 g; n_D^{20} 1.5664 – initial 2-acetothienone, recovery 60%; II) bp 97-99° (0.25 mm); 3 g; n_D^{20} 1.5820 – mixture of I and II in a ratio of ~1 : 1.3, yield 43% of the reacted 2-acetothienone and 17% of the 2-acetothienone taken in the reaction. Found: C 48.30; H 4.05; Cl 19.75; S 17.86%. C_7H_7ClOS. Calculated: C 48.13; H 4.04; Cl 20.31; S 18.36%.

Chloromethylation of 2-Thiophene Aldehyde in the Presence of Excess Aluminum Chloride (cf. [3]). To the complex obtained from 16.6 g anhydrous $AlCl_3$ and 5.6 g 2-thiophene aldehyde, we added 4.8 g monochloromethyl ether with vigorous mixing at a temperature of 40°. The mass was mixed at 60-70° for 4 h, after which it was poured out onto ice and extracted with ether. The extract was washed with water, with a solution of $NaHCO_3$, and dried over $MgSO_4$. The residue was redistilled after the ether was distilled off. We isolated 1.4 g (25% recovery) of the initial 2-thiophene aldehyde, bp 32-36° (0.5 mm); n_D^{20} 1.5962, and 2.2 g (28% of the amount taken and 37% of the 2-thiophene aldehyde used) of a mixture of 4-(III) and 5-chloromethyl-2-thiophene aldehyde (IV), containing, according to the NMR data, ~93% (III); bp 94-95° (0.5 mm); n_D^{20} 1.6062. Found: C 45.38; 45.35; H 3.25; 3.21; Cl 21.95; 21.74; S 19.83; 19.67%. C_6H_5ClOS. Calculated: C 44.86; H 3.14; Cl 22.09; S 19.97%.

Ethyl Ester of 5-Acetyl-2-thiophene Carboxylic Acid (XI). A solution of 3.4 g (X), produced according to [12] (mp 203-204°), in 40 ml abs. alcohol in the presence of 0.3 ml conc. H_2SO_4 was boiled for 46 h. The excess alcohol was distilled off, the residue dissolved in ether, washed with water, with a saturated solution of Na_2CO_3, again with water, and dried over $MgSO_4$. After the solvent was distilled off, the ethyl ester of 5-acetyl-2-thiophene carboxylic acid (XI), yield 2.9 g (74%) mp 53.5-54.5° (from hexane), was obtained in the residue. According to the data of [13]: mp 49-51°. Found: C 54.56; 54.79; H 4.94; 5.16; S 16.28; 16.15%. $C_9H_{10}O_3S$. Calculated: C 54.52; H 5.04; S 16.18%.

5-Hydroxymethyl-2-acetothienone (VI). A solution of 2.5 g (XI) in 5 ml abs. alcohol and 5 ml orthoformic ester was boiled for 7 h in the presence of two drops of conc. hydrochloric acid. After cooling the mixture was neutralized with an alcohol solution of sodium ethylate and filtered off. The residue was redistilled after the alcohol was distilled off. The yield of the diethylketal (XI) was 2.7 g (80%), bp 124-125° (0.7 mm); n_D^{20} 1.4960. Calculated: C 58.05; 57.79; H 7.55; 7.87; S 11.46; 11.67%. $C_{13}H_{20}O_4S$. Calculated: C 57.33; H 7.40; S 11.77%. The ketal obtained in 30 ml of abs. ether was added without additional purification to a suspension of 0.5 g $LiAlH_4$ in 20 ml abs. ether with mixing at a temperature of 0-2°. Then the mixture was mixed for 1.5 h at ~20°. The excess $LiAlH_4$ was decomposed by adding 1.5 ml of water at 6-8°. The precipitate formed was filtered off and repeatedly boiled with ether. The combined ether extracts were dried over $MgSO_4$. After the solvent was distilled off, 5-hydroxymethyl-2-acetothienone (VI) was obtained in the residue, yield 1.39 g (89%), mp 39-40.5° (from hexane). Found: C 53.45; 53.32; H 5.03; 5.00; S 20.39; 20.34%. $C_7H_8O_2S$. Calculated: C 53.83; H 5.16; S 20.53%.

5-Chloromethyl-2-acetothienone (II). A solution of 1 g (VI) and 1 g thionyl chloride in 20 ml abs. benzene was gradually heated to 80°, until the evolution of gas ceased. After the benzene was distilled off, the residue was redistilled. We isolated 0.7 g (62.5%) 5-chloromethyl-2-acetothienone (II), bp 110-112° (0.25 mm); mp 30-31° (from petroleum ether). Found: C 48-54; 48.30; H 4.21; 4.24; Cl 20.40; 20.24; S 18.46; 18.29%. C_7H_7ClOS. Calculated: C 48.13; H 4.04; Cl 20.31; S 18.36%. According to the data of [9]: mp 33-34°. Phthalimide derivative, mp 164-165° (from alcohol). According to the data of [9]: mp 162-163°. Found: C 63.05; 63.27; H 3.83; 4.06; N 5.48; 5.18; S 11.10; 11.09%. $C_{15}H_{11}NO_3S$. Calculated: C 63.14; H 3.89; N 4.91; S 11.24%.

5-Acetyl-3-thiophenecarboxylic Acid (VIII). To 5.5 g n-butyllithium in 100 ml abs. ether in a stream of nitrogen at a temperature no higher than –70°, 23.8 g of the diethylketal of 4-bromo-2-acetothienone [10] in 30 ml abs. ether was added with mixing over a period of 30 min. Then the solution was mixed for 5 min, after which it was poured out onto dry ice in ether. After treatment analogous to the production of the acid (X) [12], we obtained 9.45 g (yield 65%) of 5-acetyl-3-thiophenecarboxylic acid (VIII), mp 200-201°. A mixed sample with the acid synthesized in our laboratory by A. P. Yakubov by oxidation of 4-formyl-2-acetothienone with silver oxide gives no depression of the melting point. A mixture of the acid (VIII) and (X) melts at 170-175°.

Ethyl Ester of 5-Acetyl-3-thiophenecarboxylic Acid (IX). This was synthesized analogously to (XI) from 6 g of 5-acetyl-3-thiophenecarboxylic acid, 60 ml abs. ethanol, and 0.5 ml conc. H_2SO_4. Yield of (IX) 6.35 g (91%), mp 69-70° (from hexane). Found: C 54.56; 54.79; H 4.94; 5.16; S 16.28; 16.15%. $C_9H_{10}O_3S$. Calculated: C 54.52; H 5.04; S 16.18%.

4-Hydroxymethyl-2-acetothienone (V). From the reaction products of 1.2 g $LiAlH_4$ and 6.1 g of the diethylketal of the ethyl ester of 4-acetyl-2-thiophenecarboxylic acid [obtained with a yield of 75%, bp 98-100° (0.2 mm)] in 45 ml abs. ether, was isolated 3.28 g (yield 92%) (V), mp 43-44.5° (from hexane). Found: C 53.95; 53.87; H 5.29; 5.38; S 20.29%. $C_7H_8O_2S$. Calculated: C 53.83; H 5.16; S 20.53%.

(V) was also produced in the reduction of 3 g of the diethylketal of 4-formyl-2-acetothienone [10] with 0.45 g $LiAlH_4$ in abs. ether. Yield 1.4 g (68%), mp 42-43.5° (from hexane). A mixture with a sample obtained according to the first method has mp 42.5-44.5°.

4-Chloromethyl-2-acetothienone (I) was produced from 1.5 g 4-hydroxymethyl-2-acetothienone (V) by the action of 1.5 g thionyl chloride in 30 ml abs. benzene analogously to the synthesis of (II). Yield of (I) 1.04 g (62%); bp 98-102° (0.25 mm); mp 21-23° (from petroleum ether). Found: C 48.42; 48.41; H 4.04; 4.24; Cl 20.15; 19.99; S 18.25; 18.06%. C_7H_7ClOS. Calculated: C 48.13; H 4.04; Cl 20.31; S 18.36%.

Phthalimide derivative, mp 139.5-140.5° (from alcohol). Found: C 63.14; 63.07; H 4.06; 4.07; N 4.62; 4.72; S 11.29; 11.04%. $C_{15}H_{11}NO_3S$. Calculated: C 63.14; H 3.89; N 4.91; S 11.24%.

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CONCLUSIONS

1. The chloromethylation of 2-acetothienone and 2-thiophene aldehyde by monochloromethyl ether in the presence of 2.2 M anhydrous aluminum chloride without a solvent is directed almost exclusively in the 4-position of the thiophene ring: the products of chloromethylation contain ~98 and 93% 4-chloromethyl derivatives, respectively.

2. The product of chloromethylation of 2-acetothienone by paraform and HCl in chloroform, described in the literature as 5-chloromethyl-2-acetothienone, is actually an almost equimolar mixture of the 4- and 5-chloromethyl derivatives.

3. Samples of individual 4- and 5-chloromethyl-2-acetothienones were synthesized, and their NMR and IR spectra were studied.

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