THE COMPOSITION OF MIXTURES OF PRODUCTS OF THE CHLOROMETHYLATION OF 2-ACETOTHIENONE IN THE PRESENCE OF AN EXCESS OF ALUMINUM CHLORIDE AND THE SYNTHESIS OF 4- AND 5-FORMYL AND 4- AND 5-HYDROXYMETHYL-2-ACETOTHIENONES

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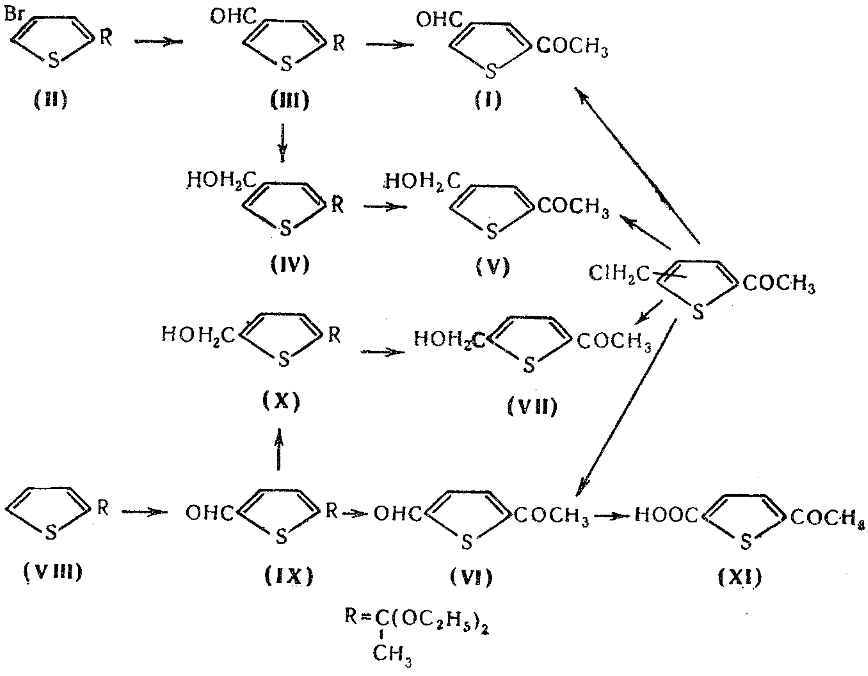
Translated from Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk,
No. 12, pp. 2238-2240, December, 1960
Original article submitted May 5, 1960

In an earlier communication dealing with the chrolomethylation of acetophenone and 2-acetothienone in the presence of an excess of aluminum chloride [1], it was shown that the firat of these two substances forms m-(chloromethyl)-acetophenone and the second a mixture of 4- and 5-(chloromethyl)-2-acetothienones. The approximate ratio of the isomers was estimated by us on the basis of the quantities of methylglutaric and adipic acids which formed from the chloromethylacetothienones after the latter had undergone a 4-stage conversion. Because data on the composition of the mixture in question could be used to interpret the characteristics of the chloromethylation process carried out under the conditions described by us, it appeared of interest to establish more precisely the content of each of the isomers. To do this, the mixture of chloromethylacetothienones was converted by a one-stage process into a mixture of ketoaldehydes, and the quantity of individual components in the latter mixture was determined polarographically. To determine the initial constants of the ketoaldehydes, it was necessary to have them in a pure state. For this purpose, a synthesis of the 4- and 5-formyl-2-acetothienones was undertaken. 4-Formyl-2-acetothienone (I) was synthesized from the diethylketal of 4-bromo-2-acetothienone (II) [2, 3]. From the latter, by using a method proposed by Gronovitz [4], the diethylketal of 4-formyl-2-acetothienone (III) was obtained. Hydrolysis of the diethylketal yielded the ketoaldehyde (I). Furthermore, (III) was reduced with $NaBH_4$ [5] to the diethylketal of 4-(hydroxymethyl)-2-acetothienone (IV), which on hydrolysis gave 4-(hydroxymethyl-2-acetothienone (V). The preparation of 5-formyl-2-acetothienone (VI) and 5-(hydroxymethyl)-2-acetothienone (VII) was carried



out analogously from the diethylketal of 2-acetothienone (VIII) over the diethylketals of 5-formyl-2-acetothienone (IX) [6] and 5-(hydroxymethyl)-2-acetothienone (X).

Comparison of the physical constants of a benzoate obtained from the mixture of hydroxymethyl compounds derived from the chloromethylation products with those of the benzoates of the isomeric alcohols (VII) and (V) showed that this benzoate is a derivative of a ketoalcohol having the constitution (V). A benzoate corresponding to (VII) could not be isolated from the mixture.

A polarographic analysis of the mixture of formyl derivatives prepared by the Sommelet reaction from the chloromethyl derivatives and of the isomer that were synthesized showed that the mixture which had not been purified and consisted to 85% of aldehydes contained 69% of the 4-isomer and 16% of the 5-isomer, which corresponds to a ratio of 4.3 : 1. Study of UV-spectra demonstrated that the ketoaldehydes isolated by us from the mixture of products of the Sommelet reaction was identical with the 4-isomer (I). An isomer of the structure (VI) could not be isolated from the mixture. The structure of (VI) was confirmed by oxidation to 5-acetylthiophene-2-carboxylic acid (XI). The constants of the acid obtained, as had already been shown on a former occasion of our laboratory [7], do not correspond to those reported for this acid by Hartough and Kosak [8].

EXPERIMENTAL

Diethylketal of 4-bromo-2-acetothienone (II). To 20.5 g of 4-bromo-2-acetothienone [2] in 15 ml, of absolute alcohol 22 g of orthoformic ester and 2 drops of concentrated HCl were added. After 20 hr the mixture was neutralized with an alcoholic solution of sodium ethylate and filtered. On evaporation of the alcohol the residue was distilled in vacuum. At 118-125° (8 mm) 24.7 g of product (II) went over and were collected (yield 88.8%). Repeated distillation of this ketal, as well as of the other ketals described below, resulted in partial splitting off of alcohol, so that the index of refraction was changed. For the same reason, values for C and H that were too high were obtained.

Diethylketal of 4-formyl-acetothienone (III). To 40 ml of an ether solution of butyl lithium containing 2.9 g of C_4H_9Li and brought down to a temperature of minus 70°, a cooled to minus 70° solution of 9.7 g of II in 20 ml of absolute ether was added while a stream of nitrogen was passed through. The solution obtained in this manner was added 5 min later under cooling with ice to 4.4 g of $HCON(CH_3)_2$ in 5 ml of absolute ether. The suspension which was formed agitated for 2 hr. On the following day it was poured on ice and extracted with ether. The ether extract was washed and dried over $CaCl_2$. The yield of III was 5.2 g (66%); b. pt. 128-134° (5 mm).

4-Formyl-2-acetothienone (I). A mixture of 1 g of III, 3 ml of CH_3OH, and 1 ml of concentrated HCl was heated to boiling and poured into water. The substance I which precipitated was filtered off; b.p. 86-86.5 after two recrystallizations from aqueous alcohol, yield 0.7 g. (98%) . λ_{max} (in alcohol) 240 mμ (ε 29,100). Found: C 54.59; 54.80; H 3.76; 3.95; S 20.62; 20.80%. $C_7H_6O_2S$. Calculated: C 54.53; H 3.92; S 20.79%.

4-Hydroxymethyl-2-acetothienone (V). To 5 g of III in 40 ml of CH_3OH at 8-15° a solution of 0.42 g of $NaBH_4$ in 8 ml of water containing 1 drop of a 40% solution of NaOH was added dropwise druing 8 min. The pH of the solution was brought to 6 with glacial CH_3COOH and 5 min later to 3 with H_2SO_4. Water was added and the mixture extracted with ether; after the ether had been distilled off, the residue (3.5 g) was dissolved in 8 ml of CH_3OH and hydrolized similarly to III. The mixture was poured into water and extracted with ether; the ether extracts were dried over $MgSO_4$. After the ether had been distilled off, 1.5 g of an oil (yield (43.5%) remained. This oil decomposed during distillation in vacuum. The benzoate (from alcohol) had a m.p. of 76-76.5°. Found: C 64.02; 64.34; H 4.60; 4.62; S 12.30; 12.39%. $C_{14}H_{12}O_3S$. Calculated %: C 64.60; H 4.65; C 12.32%. The benzoate obtained from the mixture of alcohols derived from the chloromethylation products [1] melted at 76-76.5° and gave no melting point depression when mixed with the benzoate from V. Found: C 64.12; 64.37; H 4.77; 4.44; S 12.23, 12.34%. $C_{14}H_{12}O_3S$. Calculated: C 64.60; H 4.65; S 12.32%.

Diethylketal of 2-acetothienone (VIII). VIII was prepared similarly to II from 25.6 g of 2-acetothienone. Yield 21.6 g (54.1%); b.p. 85-89° (9-11 mm).

Diethylketal of 5-formyl-2-acetothienone (IX). To 38 ml of an ether solution of butyl lithium (2.75 g of C_4H_9Li) 8.6 g of VIII in 40 ml of absolute ether were added within 20 min. The mixture was cooled with ice and salt and nitrogen was passed through it during the reaction. After 30 min the mixture was poured into a solution of 4.7 g of $HCON(CH_3)_2$ dissolved in 30 ml of absolute ether and worked up as described in the case of III. Yield 4.7 g (47.6%); b.p. 129-137°(5 mm).

5-Formyl-2-acetothienone (VI). VI was prepared similarly to I by hydrolyzing the ketal. Yield 74.1%; m.p. 104-105° (from a hexane-benzene mixture); λ_{max} (in alcohol) 292 mμ; (ε 11,500). Found: C 54.64; 54.83; H 4.01; 3.96; S 20.57; 20.56%. $C_7H_6O_2S$. Calculated: C 54.53; H 3.92; S 20.79%.

5-Hydroxymethyl-2-acetothienone (VII). By reacting 3.5 g of IX with 0.3 g of $NaBH_4$, VII was prepared similarly to V. Yield 1.6 g (65.8%); m.p. of the benzoate (from alcohol) 92-92.5°. Found: C 64.85; 64.97; H 4.64; 4 81; S 12.26; 12.37%. $C_{14}H_{12}O_3S$. Calculated: C 64.60; H 4.65, S 12.32%.

5-Acetyl-2-thiophenecarboxylic acid (XI). To a suspension of Ag_2O prepared from 1.6 g of $AgNO_3$ and 0.76 g, of NaOH and containing 7 ml of water 0.7 g of VI were added within 10 min; the mixture was shaken for 30 min. Working up of the mixture yielded XI with a m.p. of 205.5-206° (from water), which did not give a melting point depression in a mixed sample with XI prepared from ethyl-(5-acetyl-2-tenyl) sulfone [7].

Sommelet reaction of mixture of 4- and 5-(chloromethyl)-2-acetothienones. A mixture of hexamethylenetetramine salts was obtained from 6.9 g of the mixture of chloromethyl derivatives [1] and 5.5 g of hexamethylenetetramine in 12 ml of CCl_3H; yield 11.5 g (93%). Five grams of the salts, 20 ml of CH_3COOH, and 30 ml of water were boiled for 30 min. The mixture was extracted with ether; the ether extract was neutralized with soda and evaporated. The residue consisted of 0.8 g of a mixture of ketoaldehydes (yield 31%, m.p. 56-74°), which was subjected to spectral and polarographic analysis. λ_{max} (in alcohol) 240 mμ (ε 17,000); 285 mμ (ε 6600). After fourfold crystallization from aqueous alcohol, a product was isolated which had a m.p. of 86-87° and did not give a melting point depression in a mixed sample with I. λ_{max} (in alcohol) 240 mμ (ε 26800). Found: C 54.72; 54.62; H 3.97; 3.83; S 20.77; 20.60%. $C_7H_6O_2S$. Calculated: C 54.53; H 3.92; S 20.79%. From the products contained in the mother liquors no substance melting above 86° could be isolated.

SUMMARY

1. Starting from the diethylketals of 2-acetothienone and 4-bromo-2-acetothienone, 5-formyl-2-acetothienone and 4-formyl-2-acetothienone were synthesized.

2. It was established on the basis of data obtained by polarographic analysis that in the mixture of ketoaldehydes obtained from the chloromethyl derivatives of 2-acetothienone, the 4- and 5-isomers were present in a ratio of 4.3 : 1.

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