SYNTHESES BASED ON ALDEHYDES OF THE THIOPHENE SERIES

COMMUNICATION 2. SOME REACTIONS OF 2,5-THIOPHENEDICARBOXALDEHYDE MONOACETAL*

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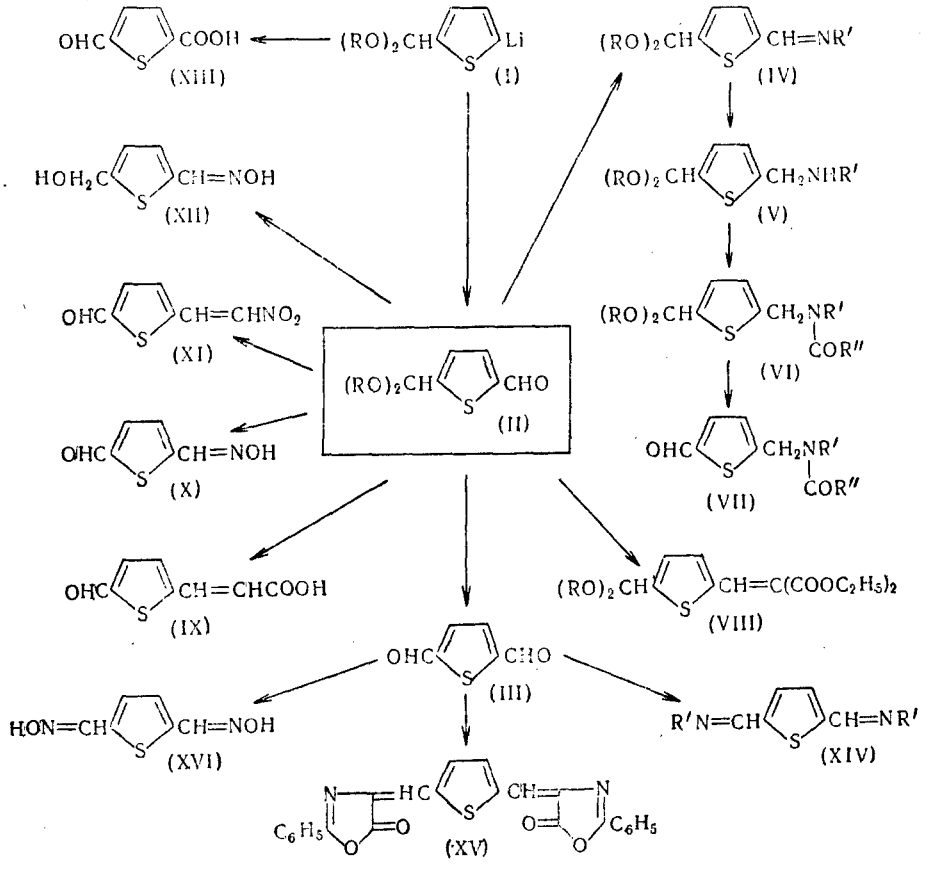
Previously, in collaboration with Fabrychnyi we [1] have shown that 2-thiophenecarboxaldehyde diethyl acetal is readily metalated by butyllithium and that from the organolithium compound then formed (I) (see reaction scheme) 2,5-thiophenedicarboxaladehyde mono[diethyl acetal] (II) may be prepared. This creates the interesting possibility of introducing a difference in reactivity between the two identical functions of the symmetrical 2,5-thiophenedicarboxaldehyde. As already stated [1], use may be made of this difference for the preparation in the pure state of products of the reaction of only one of the two aldehyde functions of 2,5-thiophenedicarboxaldehyde. The present paper is devoted mainly to a description of such reactions.



R = $-C_2H_5$; R' = n-C_6H_{13} ; cycloC_6H_{11} ; $-C_6H_5$; R'' = $-CH_3$; $-C_6H_5$.

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We must point out that the solution of such a problem starting from the symmetrical 2,5-thiophenedicarboxaldehyde would be rather complicated. Thus, we were unsuccessful in an attempt to prepare a monooxazolinone from this dialdehyde. Cooper and Nuttall [2] were unable to obtain the monooxime of 2,5-furandicarboxaldehyde, for in the treatment of one mole of the dialdehyde with one mole of the reagent the dioxime was formed. As will be seen from the reaction scheme, by working under conditions which excluded the possibility of the hydrolysis of the acetal grouping we were able to carry out a whole series of transformations of the free aldehyde group of the monoacetal (II). In particular, the Schiff bases (IV) are readily reduced with sodium borohydride into the corresponding amino acetals (V). These may be converted under the usual conditions into the N-acyl derivatives (VI), which on careful hydrolysis give the corresponding acylamino aldehydes (VII).

When the monoacetal (II) is heated with malonic ester in presence of a few drops of piperidine, then, as would be expected, only the aldehyde group reacts, which results in the formation of the unsymmetrical substituted thenylidenemalonic ester (VIII). From malonic acid, hydrolyamine, and nitromethane the monoacetal (II) gives, after hydrolysis, the compounds (IX), (X), and (XI), respectively. It is of course possible to pass from this acetal through the stage of the dialdehyde (III) to symmetrical bifunctional derivatives such as (XIV), (XV), and (XVI). By reducing (II) to the corresponding alcohol [1] we may pass, by virtue of the preservation of the acetal function, to the hydroxy aldehyde oxime (XII). Finally, by treatment with carbon dioxide the lithium compound (I) gives 5-formyl-2-thiophenecarboxylic acid (XIII).

In connection with the above we must point out that scarcely any study has been devoted to the action of organolithium compounds on acetals that do not contain another reaction center, e.g., 3-chloropropionaladehyde acetal [3]. Incidently, 2-thiophenecarboxaldehyde acetal may be regarded as an example of such a bifunctional compound in that it contains an extremely reactive α-position. On the other hand, we may point out that their are a number of facts that indicate a resemblance between organolithium and organomagnesium compounds [4, 5].

It was therefore of interest to study the behavior of the latter to 2-thiophenecarboxaldehyde acetal. The experiments showed that under conditions similar to those used in the synthesis of the monoacetal (II), i.e., in ether at room temperature, organomagnesium compounds are unable to metalate the free α-position of 2-thiophenecarboxaldehyde acetal. We should point out that at high temperature organomagnesium compounds are able to metalate some activated aromatic systems [6]. Organocalcium compounds are more active in this respect and metalate thiophene, even in ether [7].

The difference between organolithium and organomagnesium compounds is shown in their behavior toward the acetal grouping. If ether is removed from a mixture of the organomagnesium compound and 2-thiophenecarboxaldehyde acetal, a fairly vigorous process ensues which leads to the breakdown of the acetal grouping. Unfortunately, in this case the result of the reaction is less definite than in the case of benzaldehyde acetal [8]: a mixture is formed from which we were unable to isolate any individual compounds, including the original 2-thiophenecarboxaldehyde. The difference which we have found in this case between the behaviors of organolithium and organomagnesium compounds toward acetals is found also in their reactions with benzaldehyde acetal. Butyllithium reacts less vigorously with this than butylmagnesium bromide does, and the products usually observed in the reaction of organomagnesium compounds with benzaldehyde acetal (the ether and the hydrocarbon) are formed in very low yield.

In examining the cause of such different behaviors of such similar organometallic compounds toward the two acetals mentioned we may conclude that if the first stage of the reaction is coordination at the hetero atom, then in the case of 2-thiophenecarboxaldehyde and butyllithium coordination proceeds exclusively or predominantly at the ring sulfur atom [9]. The position may be different when organomagnesium compounds take part in the process. It is possible that in this case the coordination center is formed by oxygen atoms of the 2-thiophenecarboxaldehyde acetal. Such a point of view is in accord with the view that lithium has a lower affinity for oxygen than magnesium [10].

EXPERIMENTAL

5-Formyl-2-thiophenecarboxylic Acid (XIII). 52.0 g of 2-thiophenecarboxaldehyde mono[diethyl acetal] was added in a stream of nitrogen to a solution of 17.9 g of butyllithium in 500 ml of dry ether at −10°; the cooling bath was then removed, and the reaction mixture was kept for 2.5 h at room temperature. The dark-colored solution obtained was cooled to −40°, and excess of ground solid carbon dioxide was introduced into the flask. The product thickened, and on the next day it was treated with water. The ether layer was separated and washed with 1% potassium hydroxide solution; the washings were added to the main aqueous layer. The alkaline solution obtained was

filtered and acidified to Congo Red with concentrated hydrochloric acid. The precipitate that formed was filtered off and dried in air. On evaporation of the mother liquor a certain amount more of the same product was isolated. After recrystallization from water we obtained 26.2 g (60%) of red crystals, m.p. 165°. On treatment with charcoal and recrystallization we obtained white crystals of m.p. 166-167°. Found: C 46.25; 46.25; H 2.60; 2.72; S 20.63; 20.57%. $C_6H_4O_3S$. Calculated: C 46.15; H 2.56; S 20.55%.

5-[(Hexylamino)methyl]-2-thiophenecarboxaldehyde Diethyl Acetal (V, R' = n-C_6H_{13}). A mixture of 9.0 g of 2,5-thiophenedicarboxaldehyde monoacetal (II), 4.2 g of hexylamine, and 20 ml of alcohol was boiled for ten minutes, and then low-boiling substances were vacuum-distilled off from a water bath. We obtained 12.2 g of the Schiff base (IV) (R' = n-C_6H_{13}), and this was reduced without being distilled. For this purpose 1.4 g of sodium borohydride was added gradually with stirring at 20-30° to a solution of the base in 60 ml of anhydrous methanol. The mixture was stirred further for two hours and poured into 250 ml of water; the product that separated was extracted with ether. The extract was washed with water and dried with potassium carbonate. Ether was driven off, and we obtained 11.3 g (90%) of a yellowish liquid, n_D^{20} 1.4905. By vacuum distillation we isolated 9.9 g of product; b.p. 160-162° (3 mm); n_D^{20} 1.4905. Found: C 63.98; 63.98; H 9.65; 9.77; S 10.86; 10.70%. $C_{16}H_{29}NO_2S$. Calculated: C 64.17; H 9.75; S 10.72%.

5-[(N-Hexylacetamido)methyl]-2-thiophenecarboxaldehyde (VII, R' = n-C_6H_{13}, R" = CH_3). 30 ml of pyridine was added to a solution of 30 g of the amino acetal (V) (R' = n-C_6H_{13}) in 150 ml of benzene, and then 15.7 g of acetyl chloride was added gradually at 20-30°. The mixture was kept for 30 min at 60-70° and then decomposed with dilute hydrochloric acid. The benzene layer was washed several times with water and dried with magnesium sulfate. After the removal of solvent we isolated 21.4 g (80%) of a fraction having: b.p. 196-201° (2 mm); n_D^{20} 1.5410. After redistillation: b.p. 179-180° (2 mm); n_D^{20} 1.5410. Found: C 62.87; 63.08; H 8.06; 8.11; S 11.91; 12.01%. $C_{14}H_{21}NO_2S$. Calculated: C 62.87; H 7.93; S 12.00%. Semicarbazone, m.p. 193°. Found: N 16.75; 16.85%. $C_{15}H_{24}N_4O_2S$. Calculated: N 17.26%.

5-[(N-Cyclohexylbenzamido)methyl]-2-thiophenecarboxaldehyde (VIII, R' = cyclo-C_6H_{11}, R" = C_6H_5). 20.4 g of the Schiff base (IV) (R' = cyclo-C_6H_{11}), prepared in a similar way to the Schiff base described above, in 100 ml of anhydrous methanol was reduced by the addition of 3.7 g of sodium borohydride at 20-30°. The mixture was poured into water and treated as described above. Distillation gave 18.8 g of 5-[(cyclohexylamino)methyl]-2-thiophenecarboxaldehyde diethyl acetal (V, R' = cyclo-C_6H_{11}); b.p. 172-175° (3 mm); n_D^{20} 1.5110. To a suspension of 7.3 g of this amino acetal in 60 ml of 10% sodium hydroxide solution at 20° 4.2 g of benzoyl chloride was added with vigorous stirring. The oil that separated gradually solidified. After two hours it was dissolved in a mixture of ether and alcohol, and the solution was washed with water and dried with magnesium sulfate. After the removal of ether we obtained 8.0 g of a dark-red glassy substance. By distillation we isolated 4.5 g of the benzamido acetal (VI) (yield 47%). After treatment with alcoholic hydrochloric acid and crystallization from a mixture of benzene and heptane we obtained large crystals, m.p. 97-98°. Found: C 69.93; 69.69; H 6.67; 6.50; S 9.82; 9.78%. $C_{19}H_{21}NO_2S$. Calculated: C 69.68; H 6.47; S 9.80%.

5-[(N-Cyclohexylacetamido)methyl]-2-thiophenecarboxaldehyde Diethyl Acetal (VI, R' = cyclo-C_6H_{11}, R" = CH_3). A solution of 9.8 g of the amino acetal (V) (R' = cyclo-C_6H_{11}) in 20 ml of benzene was added to a stirred solution of 3.1 g of acetyl chloride in 15 ml of pyridine and 50 ml of benzene at 30-40°. The mixture was kept for two hours at 20° and 30 min at 50°, and was then treated with water. The organic layer was repeatedly washed with water and was dried with potassium carbonate. Benzene was removed, and we obtained 9.5 g of a viscous liquid. Distillation gave 6.8 g (60%) of the acetamido acetal (VI); b.p. 219-221° (3 mm); n_D^{20} 1.5240. Found: C 63.27; 63.18; H 8.70; 8.74; S 9.43; 9.49%. $C_{18}H_{29}NO_3S$. Calculated: C 63.68; H 8.60; S 9.45%. Semicarbazone, m.p. 161°. Found: N 17.44; 17.37%. $C_{15}H_{22}N_4O_2S$. Calculated: N 17.36%.

Diethyl (5-Formyl-2-thenylidene)malonate Diethyl Acetal (VIII). A mixture of 7.4 g of the monoacetal (II), 5.8 g of malonic ester, and eight drops of piperidine was heated for seven hours in a water bath, and then low-boiling substances were vacuum-distilled off. Distillation of the residue gave 9.11 g (74%) of a fraction having: b.p. 203-209° (3 mm); n_D^{20} 1.5310. After redistillation the substance had: b.p. 193-196° (2 mm); n_D^{20} 1.5380. Found: C 57.20; 57.28; H 6.88; 6.68; S 9.35; 9.33%. $C_{17}H_{24}O_6S$. Calculated: C 57.25; H 6.79; S 9.00%. Semicarbazone, m.p. 194-195°. Found: N 12.46; 12.64%. $C_{14}H_{15}N_5O_3S$. Calculated: N 12.45%.

5-Formyl-2-thiopheneacrylic Acid (IX). 1 ml of piperidine was added to a mixture of 13.7 g of the monoacetal (II), 6.9 g of malonic acid, and 35 ml of pyridine, and the mixture was heated in a water bath for two hours (until no more carbon dioxide came off).

The dark-colored solution was poured into water and acidified to Congo Red. The precipitate formed was filtered off, and the filtrate was extracted with ether. The solid residue remaining after the removal of ether was added to the precipitate on the filter, which had been recrystallized from water. We obtained 8.1 g (76%) of yellow crystals, m.p. 170°. After treatment with charcoal and crystallization from a mixture of benzene and alcohol it had m.p. 177°. Found: C 52.76; 52.69; H 3.39; 3.41; S 17.57; 17.43%. $C_8H_6O_3S$. Calculated: C 52.71; H 3.35; S 17.60%.

2-5-Thiophenedicarboxaldehyde Monooxime (X). 15.5 g of the monoacetal (II) was added to a solution of 4.9 g of hydroxylamine hydrochloride and a small excess of sodium carbonate in the least possible amount of water, and alcohol was added until a homogeneous solution was formed. The mixture was heated for four hours at the boil, and was then poured into water and acidified with hydrochloric acid. On cooling 9.2 g (84%) of the monooxime (X) was precipitated; m.p. 184-185° (from water). Found: N 8.92; 8.87. $C_6H_5NO_2S$. Calculated: N 9.02%.

5-(2-Nitrovinyl)-2-thiophenecarboxaldehyde (XI). A solution of sodium methoxide (from 0.9 g of sodium and 10 ml of methanol) was added to a stirred solution of 3.7 g of the monoacetal (II) and 1.1 g of nitromethane in 10 ml of methanol at −5°. The mixture was kept for 20 min at −5° and then for 30 min at 20-30°. The dark-colored solution formed was diluted with twice the volume of water and poured into 50 ml of 10% hydrochloric acid. The precipitate that separated was filtered off, washed with water, and dried. We obtained 2.68 g (85%) of product, m.p. 169°. After treatment with charcoal and recrystallization from benzene we obtained white needles, m.p. 172-173°. Found: C 46.27; 45.96; H 3.07; 3.05; S 17.30; 17.19; N 7.59; 7.42%. $C_7H_5NO_3S$. Calculated: C 45.91; H 2.72; S 17.52; N 7.64%.

5-(Hydroxymethyl)-2-thiophenecarboxaldehyde Oxime (XII). 2 ml of 10% hydrochloric acid was added to a solution of 8.5 g of 5-(hydroxymethyl)-1-thiophenecarboxaldehyde diethyl acetal [1] in 15 ml of alcohol, and the mixture was heated to the soil. The solution obtained was mixed with a solution of 2.8 g of hydroxylamine hydrochloride in water and neutralized with sodium carbonate. The mixture was boiled for two hours. On cooling, 4.0 g (77%) of white crystals, m.p. 117-118°, separated. After recrystallization from a mixture of alcohol and benzene they had m.p. 119-120°. Found: C 46.01; 46.13; H 4.35; 4.55; S 20.27; 20.22; N 8.75; 8.77%. $C_6H_7NO_2S$. Calculated: C 45.83; H 4.51; S 20.41; N 8.90%.

N,N'-(2,5-Thiophenediyldimethylidyne)bishexylamine (XIV). 6.1 g of hexylamine was added to a solution of 4.0 g of 2,5-thiophenedicarboxaldehyde (III) in 20 ml of alcohol; the mixture became warm. The mixture was boiled for 15 min, and then the low-boiling part was vacuum-distilled off. The residue was dried over phosphoric anhydride in a desiccator, and we obtained 8.8 g (99%) of yellow crystals, m.p. 50°. After recrystallization from dilute alcohol it had m.p. 50.5-51°. Found: N 9.08; 9.05; $C_{18}H_{30}N_2S$. Calculated: N 9.13%.

4,4'-(2,5-Thiophenediyldimethylidyne)bis[2-phenyl-2-oxazolin-5-one] (XV). 20 ml of acetic anhydride was added to a ground mixture of 2.8 g of 2,5-thiophenedicarboxaldehyde, 8.9 g of hippuric acid, and 8.8 g of fused sodium acetate, and the mixture was heated for two hours in a boiling water bath. The product was treated with 40 ml of alcohol, and the precipitate was filtered off, boiled with water, again filtered off, and dried. We obtained 6.9 g (82%) of dark-red crystals, m.p. 286-287°, raised to 288-289° by recrystallization from nitrobenzene. Found: C 67.86; 67.94; H 3.53; 3.53; S 7.59; 7.60%. $C_{24}H_{14}N_2O_4S$. Calculated: C 67.61; H 3.28; S 7.59%.

2,5-Thiophenedicarboxaldehyde Dioxime (XVI). This was prepared by boiling 2,5-thiophenedicarboxaldehyde (III) with two molecular proportions of hydroxylamine hydrochloride for 30 min. The reaction was carried out in an aqueous-alcoholic medium in presence of a small excess of potassium carbonate. The hot solution was acidified with hydrochloric acid to Congo Red and cooled. A crystalline precipitate formed, and was filtered off and dried; m.p. 193°, raised to 201° by recrystallization from alcohol. Found: C 42.47; 42.53; H 3.87; 3.69; S 18.56; 18.55%. $C_6H_6N_2O_2S$. Calculated: C 42.33; H 3.58; S 18.86%.

SUMMARY

The use of 2,5-thiophenedicarboxaldehyde monoacetal in synthesis makes it possible to prepare unsymmetrical bifunctional thiophene derivatives.

LITERATURE CITED

1. Ya. L. Gol'dfarb, B. N. Fabrichnyi, and V. I. Rogovik, Izv, AN SSSR. Otd. khim. n., 1963, 2172.
2. W. Cooper and W. Nuttall, J. Chem. Soc., 101, 1074 (1912).
3. G. Jones and H. D. Law, J. Chem. Soc., 1958, 3631.
4. K. A. Kocheskov and T. V. Talalaeva, Methods of Synthesis in the Field of the organometallic Compounds of Lithium, Sodium, Potassium Rubidium, and Cesium [in Russian], Vol. I, Parts 1-5, Moscow (1949).

5. S. Gronowitz and R. Hakanson, Arkiv for Kemi, 17, No. 6, 73 (1961).
6. H. Gilman and F. J. Web, J. Amer. Chem. Soc., 71, 4062 (1949).
7. D. Bruce-Smith and A. C. Skinner, J. Chem. Soc., 1963, 577.
8. A. E. Chichibabin and S. A. Elgazin, Zh. russk. fiz.-khim. obshch., 46, 39, 802 (1914).
9. H. Gilman, Organic Reactions [Russian translation], 8, IL, p. 335 (1956).
10. J. Mathieu and L. Allais, Principles of Organic Synthesis [Russian translation], Moscow, p. 338 (1963).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
