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THE PROBLEM OF SYNTHESIZING 5-PROPIONYL-2-THIOPHENE ALDEHYDE

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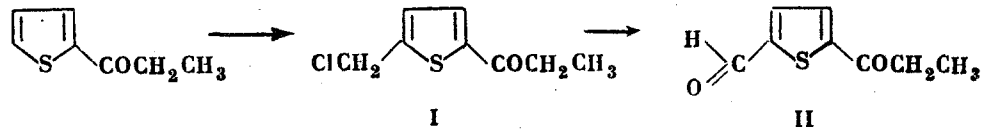
5-Propionyl-2-thiophene aldehyde, mp 101-101.5°, is synthesized by two routes, from 2-propiothienone, and from 2-thiophene aldehyde, and its structure is confirmed by oxidation to 5-propionyl-2-thiophene carboxylic acid and thiophene-2,5-dicarboxylic acid. The fact that 2-acetals and 2-ketals of the thiophene series are metallated only at position 5 in the ring by n-butyllithium is confirmed. Attempts to synthesize 5-propionyl-2-thiophene aldehyde by a method given by Janda and Dvorak [1, 2] were unsuccessful.

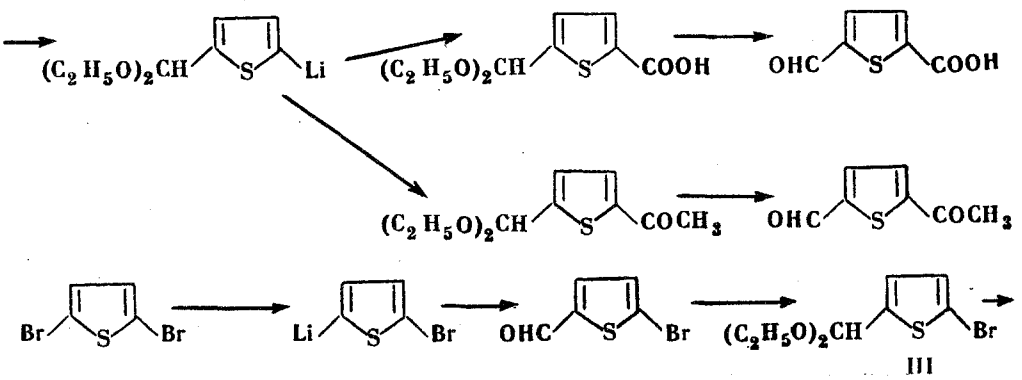
In 1962 Janda and Dvorak published a paper [1], in which they claimed to have synthesized 5-propionyl-2-thiophene aldehyde II by chloromethylating 2-propiothienone and then oxidizing the 5-chloromethyl-2-propiothienone I with lead nitrate, or by the Sommelet reaction. In a patent [2] on preparing II, these authors state that it has antibiotic activity, similar to the action of 5-formyl-2-propionylthiophene (junipal) isolated from the fungi Daedelea juniperina Murr.



I II

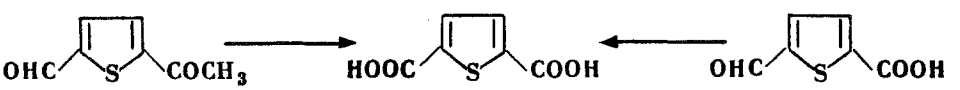
When the paper was carefully considered, it appeared noteworthy that their 5-propionyl-2-thiophene aldehyde [1, 2] was stated to be a low-boiling liquid (76°/0.9 mm). Among other things, its nearest homolog, 5-acetyl-2-thiophene aldehyde, is a crystalline substance mp 106° [3]. Another doubtful point was that the authors considered that chloromethylation of 2-propiothienone involved nuclear substitution only, though there was a second reaction center in the form of an exocyclic methylene group activated by a carbonyl group [4].

In connection with the publication of these results of the Czech authors [1, 2], it became necessary to confirm that the compound mp 106° previously obtained by the present authors by metallating and formylating 2-acetothienone diethylketal, was 5-acetyl-2-thiophene aldehyde [3], and for this purpose it was synthesized thus:



III

Metallation of the bromoaldehyde acetal followed by the action of CO_2 gives a good yield of 5-formyl-2-thiophene carboxylic acid, previously prepared by the present authors by carbonating the product of metallating 2-thiophene aldehyde acetal [5]. Since the lithium replaces an atom of halogen in these reactions, and not an atom of hydrogen, there is no doubt about the course of the reaction. The 5-acetyl-2-thiophene aldehyde and 5-formyl-2-thiophene carboxylic acid thus prepared gave undepressed mixed melting points with the compounds previously obtained [3, 5]. Oxidation provided further proof of the structures of these compounds synthesized, the product in both cases being thiophene-2,5-dicarboxylic acid, identified as its dimethyl ester:

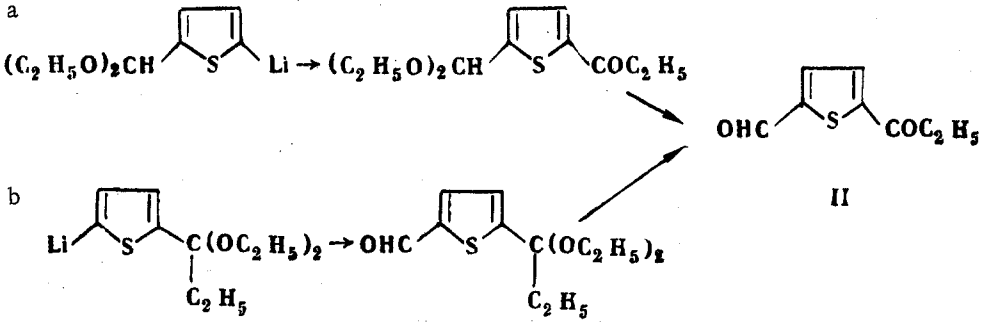


Consequently the syntheses carried out provide proof of the fact, previously established [3, 5], that 2-acetals and 2-ketals of the thiophene series metallate at position 5.

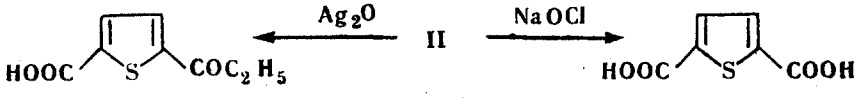
Convinced that their results were correct, the present authors attempted to synthesize 5-propionyl-2-thiophene aldehyde (II) by the method of Janda and Dvorak [1, 2]. Actually chloromethylation of 2-propiothienone in the presence of zinc chloride* gave a substance whose analytical data were those of a monochloromethyl derivative. Oxidation of it with nitric acid under the conditions given by the Czech authors [1] gave a mixture of products containing organic acids, chloropicrin, and sulfuric acid formed by rupture of the thiophene ring. The yield of sulfuric acid calculated on the chloromethyl derivative was 20%, and this alone casts doubt on Janda and Dvorak's claim that dimethyl thiophene-2, 5-dicarboxylate was formed in 87% yield. Treatment with diazomethane of the organic acid isolated by the present authors gave a 25% yield, based on the chloromethyl derivative, of a substance melting over a wide range, 107-130°, and whose elementary analysis was that of a dimethyl thiophene dicarboxylate. As its melting point was altered by repeated crystallization, it can be assumed to be a mixture, and not an individual compound.

Attempts to oxidize the above chloromethyl derivative with lead nitrate, or by the Sommelet method also failed to give a satisfactory result, and 5-propionyl-2-thiophene aldehyde could not be prepared by those methods.

The latter compound was conceivably of interest and it was decided to prepare it by treating 5-lithium-2-thiophene aldehyde diethylacetal with propionic anhydride (method a). The resultant substance was a crystalline compound mp 101°. To prove that it was 5-propionyl-2-thiophene aldehyde it was synthesized by an independent method from 5-lithium-2-propiothienone diethylketal (method b):



Oxidation experiments provided conclusive proof of the structure of II. A high yield of thiophene-2, 5-dicarboxylic acid was obtained by oxidizing both functional groups with sodium hypochlorite solution. 5-Propionyl-2-thiophene carboxylic acid was obtained by the action of moist silver oxide in the presence of an equivalent amount of sodium carbonate:



It may be mentioned here that silver oxide oxidation in the presence of sodium hydroxide gives an acidic product without a definite melting point and only partly soluble in hot water. The water-insoluble portion was a resin which softened on heating. It would appear that formation of these polymeric substances involves first oxidation of 5-propionyl-2-thiophene aldehyde followed by intermolecular condensation under the action of alkali. The benzene analog of II, p-acetylbenzaldehyde, undergoes a similar condensation [6].

The fact, previously described, that thiophene derivatives metallate exclusively in the nucleus, and here further confirmed, for acetals and ketals, independent of the way in which II is prepared, and also the elementary analysis, molecular weight, and composition of products of oxidation show that the compound with mp 101°, is 5-propionyl-2-thiophenealdehyde. The physical constants of compound II given by the Czech authors [1, 2] are wrong.

The 5-propionyl-2-thiophene aldehyde prepared by the present authors has been tested for antibacterial activity, and test results showed that its antibacterial activities towards Staph. aureus 209 p and Dipl. pneumoniae were very low and of no interest from the practical point of view.

Experimental

5-Bromo-2-thiophene aldehyde was prepared, by the method previously described [7], from 2, 5-dibromothiophene, via 5-bromo-2-thienyllithium.

*The paper's statement that the chloromethylation catalyst is stannic chloride is an obvious error.

5-Bromo-2-thiophene aldehyde diethylacetal [3] was prepared by refluxing (1 hr) 8.9 g bromoaldehyde and 10.5 ml ethyl orthoformate in 15 ml absolute alcohol containing 3 drops of alcoholic hydrogen chloride; yield 10.9 g (about 100%), bp 137-142° (23 mm), n_D^{20} 1.5289.

5-Acetyl-2-thiophene aldehyde (III). 19 ml of an ethereal solution of n-butyllithium (2.5 g n—C_4H_9Li) was added dropwise to a solution of 10 g 5-bromo-2-thiophene aldehyde diethylacetal in 50 ml dry ether, in a current of nitrogen, and at −50°. After 15 min the resultant pale yellow solution was added to a solution of 5.7 g freshly distilled acetic anhydride in 50 ml dry ether maintained at −60°. The resultant suspension was stirred while being allowed to warm slowly up to room temperature. The darkish reaction products were poured into ice water, and made acid to congo red with acetic acid. The ether solution was washed with water, soda solution, then water again, and finally dried over calcium chloride. After distilling off the ether the residue was distilled in a vacuum. The fraction bp 123-124.5° (3 mm) was dissolved in twice its volume of methanol, a like volume of hydrochloric acid was added, the whole heated to boiling, and poured into water. The resultant precipitate was filtered off and twice recrystallized from dilute alcohol. 0.3 g II was obtained, mp 104.2-105.2°. Mixed mp of the product with 5-acetyl-2-thiophene aldehyde synthesized by a method previously described by the present authors [3], was undepressed.

Oxidation of 5-acetyl-2-thiophene aldehyde. 4 g 5-acetyl-2-thiophene aldehyde [3] was added in a few portions to a solution of sodium hypochlorite (from 21 g sodium hydroxide and 15.2 g chlorine) heated to 58°. After adding the first portions of the substance, the temperature was raised to 68° and maintained there by the rate of addition of the aldehydoketone. At the end of the addition the solution was allowed to cool to 30° with stirring. Excess hypochlorite was destroyed by adding sodium bisulfite solution. The initial aldehydoketone was extracted from the solution with ether (0.74 g recovered). The aqueous solution was made acid to Congo Red with hydrochloric acid, and precipitate (2.2 g) filtered off, and the filtrate extracted with ether. A further 0.5 g thiophene-2,5-dicarboxylic acid was obtained from the extract. Yield 74%, calculated on the reacted 5-acetyl-2-thiophene aldehyde.

Dimethyl thiophene-2,5-dicarboxylate. 0.86 g thiophene-2,5-dicarboxylic acid in 100 ml dry ether, was treated with an ethereal solution of diazomethane (from 3 g nitrosomethylurea). Yield of dimethyl ester 0.9 g (90.5%), mp 144.5-146.5°. After two recrystallizations from 60% alcohol, the product had mp 149-150°, mixed mp with authentic dimethyl thiophene-2,5-dicarboxylate undepressed. The literature gives [8] mp 148.5-149.5°.

5-Formyl-2-thiophene carboxylic acid. A solution of 8.7 g 5-bromo-2-thiophene aldehyde diethylacetal in 50 ml dry ether was added, in a current of nitrogen, to a solution of 2.5 g n-butyllithium in 80 ml dry ether held at −70°. The mixture was stirred for 1 hr at −70°, then excess powdered solid CO_2 added, the whole heated to boiling, and 50 ml aqueous sodium hydroxide solution added. The aqueous layer was heated for 20 min on a steam bath, made acid to Congo Red with hydrochloric acid, and the acid which was precipitated filtered off, yield 4.4 g (85%), mp 168-169° after two recrystallizations from water. The literature gives [9] mp 171-172°. Neutralization equivalent, found: 157.2, 155.0. Calculated for $C_6H_4O_3S$: 156.2.

Oxidation of 5-formyl-2-thiophene carboxylic acid. A solution of 2.5 g 5-formyl-2-thiophene carboxylic acid was added in a number of portions to a suspension of silver oxide (prepared from 5.4 g silver nitrate in 12 ml water plus 2.6 g sodium hydroxide in 12 ml water). The resultant suspension was shaken for 30 min, then heated to 60°. The precipitate was filtered off, and the filtrate made acid to Congo Red. Yield of thiophene-2,5-dicarboxylic acid 2.3 g (83.8%).

Dimethyl thiophene-2,5-dicarboxylate. This was prepared by treating an ethereal suspension of the acid with an ether solution of diazomethane. Two recrystallizations from ether gave a 50% yield, mp 146.5-147.5° (from n-heptane). Mixed mp with an authentic specimen of the ester undepressed. Found: C 47.72, 47.74; H 3.83, 3.83; S 16.14, 15.96%. Calculated for $C_8H_8O_4S$: C 47.99; H 4.02; S 16.01%.

5-Propionyl-2-thiophene aldehyde (II).

a) From 5-lithium-2-thiophene aldehyde diethylacetal. An ethereal solution of 5-lithium-2-thiophene aldehyde diethylacetal [5] (from 16.8 g 2-thiophene aldehyde diethylacetal and 5.8 g n-butyllithium) was dropped into a solution of 14.3 g propionic anhydride in 100 ml ether cooled to −60°. Next day water was added, the ethereal solution washed with water and dried over potash. Distillation gave 3.8 g II, bp approximately 140° (2 mm), mp 96-97°. Recrystallized from heptane it had mp 101-101.5°. Found: C 57.35, 57.38; H 4.68, 4.69; S 19.20, 19.37%. Calculated for $C_8H_8O_2S$: C 57.10; H 4.81; S 19.08%.

b) From 5-lithium-2-propiothienone diethylketal. 2-Propiothienone diethylketal was prepared by heating 2-propiothienone with ethyl orthoformate in the presence of ethanolic hydrogen chloride (catalyst). Diethylketal yield 76%, bp 102-104° (13 mm), n_D^{20} 1.4850. 12 g dimethylformamide in 50 ml ether was dropped into an ether solution of 5-lithium-2-propiothienone diethylketal (from 16.2 g 2-thienone diethylketal and 5.4 g n-butyllithium) held at −60°. Next day water was added to the resultant suspension, the ether layer separated off, washed with water, and dried over potash. Distillation gave 14.1 g 5-propionyl-2-thiophene aldehyde diethylketal bp 150-155° (13 mm), n_D^{20} 1.5129. Saponifica-

tion of the ketal (by heating with an aqueous alcoholic hydrogen chloride) gave 8.5 g (66%) II, mp 93°. After recrystallization from heptane it had mp 101-101.5°, mixed mp with a specimen obtained by method a) above, undepressed. Molecular weight (cryoscopic in benzene), found: 167.1, 175.0. Calculated for $C_8H_8O_2S$: 168.3.

Treatment of a solution of 5-propionyl-2-thiophene aldehyde with excess of 2, 4-dinitrophenylhydrazine in alcoholic hydrogen chloride gave the mono-2, 4-dinitrophenylhydrazone, mp 247° (from dimethylformamide). Found: N 15.94, 16.12%. Calculated for $C_{14}H_{12}N_4O_5S$: N 16.08%.

Oxidation of 5-propionyl-2-thiophene aldehyde.

a) By moist silver oxide. A precipitate of silver oxide (from 1.6 g silver nitrate and 0.75 g sodium hydroxide) was washed with water till it was no longer alkaline to phenophthalein, then suspended in water, 0.3 g soda added, followed by a saturated alcohol solution of 0.7 g 5-propionyl-2-thiophene aldehyde. The contents of the flask were shaken for 1 hr at room temperature, then heated at 40-50° for 15 min. The precipitate was twice filtered off and washed with water. The filtrate was extracted with ether, the aqueous layer made acid to Congo Red with hydrochloric acid, and then extracted three times with ether. The extracts were bulked and dried over calcium chloride, and the ether then distilled off, to give a residue of 0.7 g (96.8%) 5-propionyl-2-thiophene carboxylic acid, which after three recrystallizations from water had mp 184-185°. Found: C 51.96, 51.87; H 4.34, 4.31; S 17.68, 17.53% mol. wt. (neutralization equivalent) 186, 184. Calculated for $C_8H_8O_3S$: C 52.17; H 4.37; S 17.41%; mol. wt. 184.2.

When the ether was distilled off from the ether extract of the neutral reaction products, a few drops of oily material remained.

b) Sodium hypochlorite. The oxidation was similar to that of 5-acetyl-2-thiophene aldehyde. 4 g 5-propionyl-2-thiophene aldehyde gave 3.1 g (88.7%) thiophene-2, 5-dicarboxylic acid.

Neutralization equivalent: Found: 86.1, 85.9%. Calculated for $C_6H_4O_4S$: 86.1%.

Dimethyl thiophene-2, 5-dicarboxylate. 0.86 g thiophene-2, 5-dicarboxylic acid obtained in the previous experiment was esterified in the way described above, and the yield of dimethyl ester was approximately 100%. After two recrystallizations from 60% alcohol it had mp 149-150°, mixed mp with an authentic specimen of dimethyl thiophene-2, 5-dicarboxylate undepressed. Found: C 48.14, 48.12; H 4.14, 4.21; S 15.94, 15.86%. Calculated for $C_8H_8O_4S$: C 47.99; H 4.02; S 16.01%.

Chloromethylation of 2-propiothienone (see [1]). A stream of dry hydrogen chloride was passed for 3 hr through a mixture of 33.6 g 2-propiothienone (prepared by treating thiophene with propionyl chloride in the presence of stannic chloride), 11.0 g paraformaldehyde, and 8.4 g anhydrous zinc chloride in 126 ml dry chloroform, maintained at 25-30°. The resultant solution was poured into 160 ml water, the organic layer separated off, and the aqueous layer extracted with chloroform. The extract was bulked with the organic layer, and the whole washed with water, then dried over calcium chloride. The chloroform was distilled off, and the residue distilled under vacuum, three cuts being taken: 1st bp 70-125° (3 mm), 2nd 125-135° (3 mm), n_D^{20} 1.5715; 3rd bp 135-143° (3 mm). Fractions 2 and 3 were bulked and redistilled, to give 10.7 g substance bp 115-118° (1 mm) n_D^{20} 1.5730, whose analysis corresponded to the monochloromethyl derivative of 2-propiothienone. Found: C 50.79, 50.73; H 5.19, 4.92%. Calculated for C_8H_9ClOS: C 50.92; H 4.81%.

Attempt to prepare 5-propionyl-2-thiophene aldehyde by oxidizing the chloromethyl derivative of 2-propiothienone with lead nitrate. 19.4 g powdered lead nitrate was added to 11.9 g chloromethyl-2-propiothienone (n_D^{20} 1.5730). The mixture was stirred and heated for 15 min on a steam bath (when it darkened). Then 85 ml water was added, and the whole refluxed for 2 hr. The volatile reaction products were steam distilled off, the distillate extracted with ether, and the extract dried over magnesium sulfate. After removing the ether all that remained was a few drops of oil with a very sharp odor. So it did not prove possible to prepare 5-propionyl-2-thiophene aldehyde by this method.

Attempt to prepare 5-propionyl-2-thiophene aldehyde from the chloromethyl derivative by the Sommelet reaction. 11.3 g urotropine and 80 ml chloroform were added to 9.7 g chloromethyl-2-propiothienone, and the whole refluxed for 2 hr. At first a solution was formed, and then a precipitate separated. After cooling the mixture was extracted with water (a few times, 400 ml in all). The yellow chloroform layer was rejected, and the aqueous one treated with active carbon and refluxed for 1 hr. Drops of dark oil, which could not be steam distilled, separated. Insoluble in ether, they were extracted with chloroform, the extract dried over magnesium sulfate, and the solvent then distilled off. When an attempt was made to distill the residue in a vacuum (4 mm), marked decomposition, accompanied by gas evolution, set in. Hence 5-propionyl-2-thiophene aldehyde could not be prepared by the Sommelet reaction.

Nitric acid oxidation of the chloromethyl derivative of 2-propiothienone. 77 ml dilute nitric acid (d 1.30) was added to 7.7 g chloromethyl-2-propiothienone, and the mixture refluxed for 3 hr (nitrogen oxides evolved), to give a transparent yellow solution containing drops of heavy oil, and having an odor of chloropicrin. Cooling with ice gave a precipitate which was filtered off and washed with water, mass 1.62 g. The usual treatment with diazomethane gave 1.75 g substance mp 96-140°, which after recrystallization from dilute methanol had mp 107-130°. Despite its having

such a wide melting range, the analytical results corresponded to dimethyl thiophene dicarboxylate, so that apparently it was a mixture of isomers. Found: C 47.55, 47.05; H 3.78, 3.76%. Calculated for $C_8H_8O_4S$: C 47.99; H 4.02%.

When a solution of barium chloride was added to the mother liquor (after isolating the thiophene dicarboxylic acid) a precipitate of barium sulfate (1.84 g) was obtained. Theoretically 7.7 g chloromethyl-2-propiothienone could give 9.3 g barium sulfate, so that approximately 19.5% of the starting chloromethyl-2-propiothienone was oxidized to sulfuric acid.

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