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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XVII. THIOPHENE POLYENE ACIDS, ALDEHYDES, AND KETONES[1]

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In the course of our studies on the chemistry of heterocyclics, the synthesis of a series of polyene carbonyl compounds containing the thiophene nucleus has been accomplished by a variety of methods.

The polyene acids are most conveniently prepared by two methods which depend on the utilization of polyene aldehydes. These methods are the extension of Doebner's synthesis of sorbic acid, and the oxidation of the appropriate aldehyde with silver oxide. However, previous attempts (1) to prepare the higher thiophene polyenals invariably resulted in the formation of polymeric material.

In order to circumvent the necessity for preparing these aldehydes the synthesis of polyene acids containing the thiophene nucleus had to be developed by other means.

The method selected involves the use of vinylogs of a bromoacetic ester in the Reformatsky reaction. The potentialities of this reaction have been clearly demonstrated (2, 4). The bromovinylogs are conveniently prepared by the use of N-bromosuccinimide (3, 4).

The reaction of various thiophene carbonyl compounds with ethyl γ-bromocrotonate was carried out smoothly in the presence of zinc and a benzene-tetrahydrofuran solvent. The yields ranged from 30–35%. Although these figures were considerably lower than those reported for similar reactions (4), they compare favorably with those given by Jones, O'Sullivan and Whiting (5).

The esters were not distilled, since attempts indicated that decomposition had taken place. These substances were also unstable toward strong alkali, and were consequently saponified with 2% sodium hydroxide in methanol at room temperature. The attempt to isolate the α-vinyl acids, $CH_2=CHC(COOH)=CHR$ (5, 6) was not successful.

Fractional sublimation and crystallization failed to indicate two isomers. When a 10% solution of bromine in CCl_4 was added to the acids, the second equivalent was taken up very slowly. This is in accord with the known resistance of bromine addition to double bonds α,β to a carboxyl group. A Zerewitinoff determination was also negative. Consequently, it is believed that these acids possess a linear structure.

When methyl ω-bromosorbate was condensed with 2-thenaldehyde or β-2-

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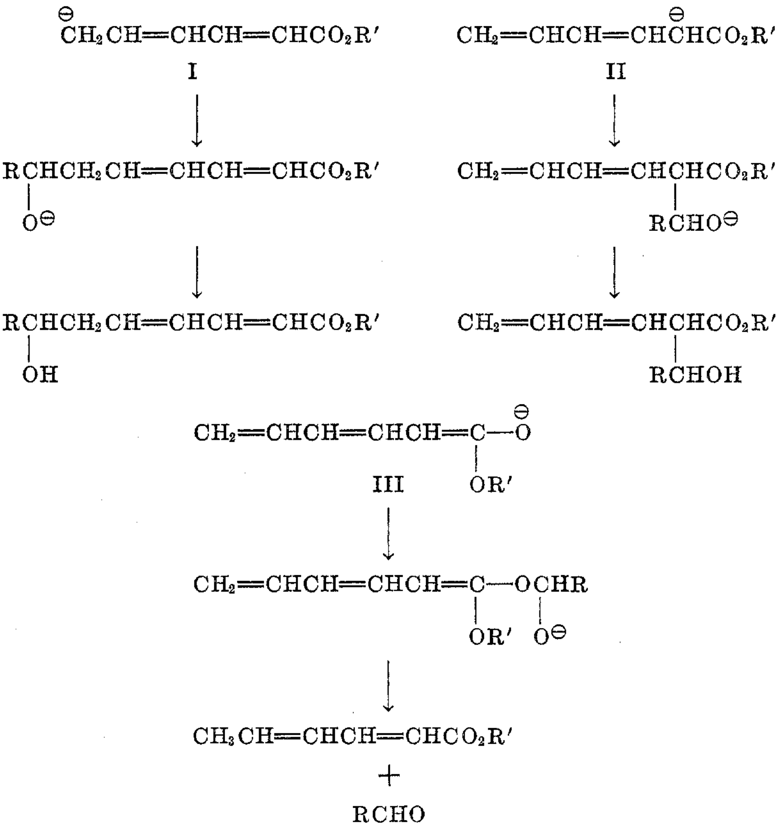
[1] This investigation was carried out under the aegis of the Office of Naval Research. The analyses were carried out by A. A. Sirotenko of this Department.

[2] Abridged from a part of the Dissertation submitted to the Graduate School of Fordham University, 1951, in partial fulfillment of the requirements of the Ph.D. degree. Present address: Monsanto Chemical Company, Dayton, Ohio.

thienylacrolein, the reaction appeared to proceed smoothly. However, after hydrolysis methyl sorbate and a large amount of the carbonyl compound were recovered. Similar results were observed by Jones (5) and Karrer (3). The expected condensation had apparently not taken place.

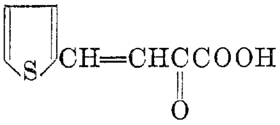
A plausible explanation (5) suggests that the anion of the complex can react with the aldehyde in several ways according to the major resonance structures.

FIGURE 1

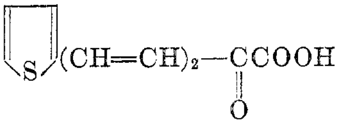


It is conceivable that structure III, resulting from a mesomeric shift of the electron pair, will be the most important contributor. The presence of the negative charge on the relatively electronegative oxygen atom leads to an increased contribution of this form to the resonance hybrid. Such a readily hydrolyzed intermediate would explain the dissolution of the metal and the formation of methyl sorbate among the final products.

A number of polyenic carbonyl compounds have been synthesized by base-catalyzed additions of nucleophilic reagents. Accordingly, pyruvic acid was condensed with 2-thenaldehyde and β-2-thienylacrolein in the presence of strong alkali. The yields of the α-keto-acids increased with an increase in molecular weight, owing to the diminishing tendency of the higher members to self-condense (7).



I



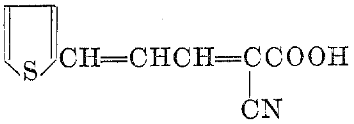
II

When the 6-(2-thienyl)-2-oxo-3,5-hexadiene-1-carboxylic acid (II) was treated with 30% hydrogen peroxide (8), evolution of carbon dioxide indicated oxidation of the carbonyl group. The precipitated acid was 5-(2-thienyl)-2,4-pentadiene-1-carboxylic acid.

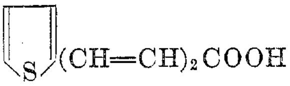
The α-ketoacid (I) obtained from 2-thenaldehyde and sodium pyruvate readily formed a solid anil (not isolated) when distilled with aniline (9). This compound was decomposed with mineral acid and then treated with semicarbazide hydrochloride and sodium acetate. The semicarbazone of β-2-thienylacrolein was isolated.

When β-2-thienylacrolein was condensed with ethyl cyanoacetate a very high yield of the condensation product (III) was obtained. It was observed (10) that Knoevenagel condensations with this ester gave excellent yields when acetates of bases, or acetamide in acetic acid were employed as catalysts. The optimum yields were obtained when the water formed during reaction was continuously removed by distillation.

The ester was saponified to give the cyanoacid, which was decarboxylated with copper in quinoline to give the nitrile. The crude nitrile was converted to 5-(2-thienyl)-2,4-pentadiene-1-carboxylic acid (IV) by alcoholic alkali. When attempts were made to hydrolyze the nitrile with mineral acid, no dienic acid was isolatable.

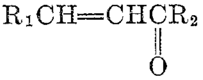


III



IV

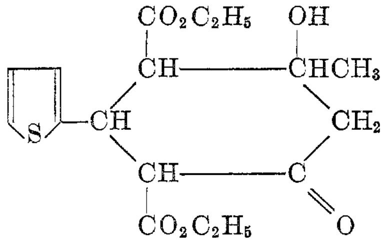
Acetone, acetophenone, acetoacetic ester, 2-acetothienones and benzaldehyde were reacted with various thiophene aldehydes under the catalytic influence of basic condensing agents.



$$R_1CH{=}CH\underset{\underset{O}{\|}}{C}R_2$$

V. $R_1 = C_4H_3S$; $R_2 = CH_3$
VI. $R_1 = C_4H_3S$; $R_2 = CH{=}CHC_4H_3S$
VII. $R_1 = C_4H_3S$; $R_2 = C_6H_5$
VIII. $R_1 = C_6H_5$; $R_2 = C_4H_3S$
IX. R_1 and $R_2 = C_4H_3S$

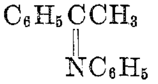
It was recently observed (15) that when 2-thenaldehyde and ethyl acetoacetate in equimolecular quantities were treated with a few drops of piperidine, the expected ethyl 2-thenalacetoacetic ester was not formed. Instead, the product isolated was shown to be ethyl 4-hydroxy-6-oxo-2,2′-thienyl-4-methylcyclohexane-1,3-dicarboxylate.



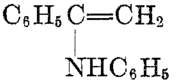
X

Independently, the preparation of the ethyl 2-thenalacetoacetate had been undertaken, using piperidine acetate as the catalyst. The acetoacetic ester was added dropwise to the catalyst and the aldehyde, but the compound isolated was apparently the same as reported.

It was desired to characterize these unsaturated ketones through the formation of Schiff bases. The great stability of Schiff bases as derived from purely aromatic aldehydes, is remarkable when compared with the condensation products of aromatic amines and aromatic ketones. It has been suggested (16) that the latter may exist in tautomeric forms as eneamines which are inclined to autoxidation and other subsequent reactions.



$$\mathrm{C_6H_5\underset{\substack{\| \\ NC_6H_5}}{C}CH_3}$$



$$\mathrm{C_6H_5\underset{\substack{| \\ NHC_6H_5}}{C}{=}CH_2}$$

The keto anils do not keep well even in sealed glass bottles. Reddelien (17), however, had developed a suitable method for the formation of keto anils which involved the use of the double salts of aromatic amines with zinc chloride as catalysts, instead of the usual means of splitting out water.

Hartough (18), on the other hand, had shown that 2-acylthiophenes condensed with aniline merely by refluxing a toluene solution of the ketone and aniline. Iodine was added to catalyze the addition. Zinc chloride could not be used as a catalyst, since insoluble complexes were formed.

It was rather surprising to note, therefore, that 2-thenalacetone and bis-2-thenalacetone did not undergo the expected condensation with aniline using iodine, zinc chloride or the aniline-zinc chloride double salt as a catalyst, as evidenced by the fact that no water collected in the Barrett trap. Although the reaction mixture was refluxed for four to six hours in toluene or xylene, the identification of the vacuum-distillate was unsuccessful.

But the fact that β-2-thienylacrolein did not form an anil under the same conditions was even more unusual, since cinnamaldehyde gave a bright yellow solid merely by mixing the two components. The possibility that a Michael type condensation can also occur with such conjugate unsaturated systems would indicate that further study is required to establish the feasibility of this type condensation.

The following thiophene acroleins are also reported.

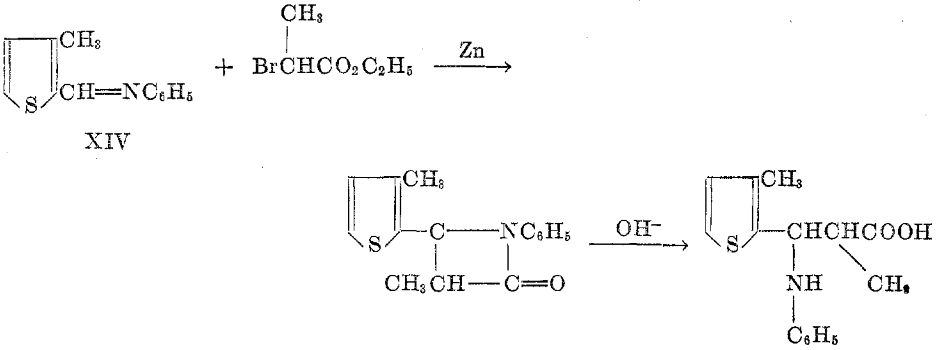
$$R_1CH{=}CR_2CHO$$

XI. R_1 = 3-methyl-2-thienyl; R_2 = H
XII. R_1 = 5-chloro-2-thienyl; R_2 = H
XIII. R_1 = 2-thienyl; R_2 = Cl

The aldehyde (XIII) decomposed rapidly on distillation. It was therefore converted to the semicarbazone for analytical purposes. When the semicarbazone was steam-distilled in the presence of oxalic acid, attempts to distill the resulting liquid again led to extensive charring and rapid decomposition.

Aldazines were prepared from several thiophene aldehydes.

The condensation of the anil of 3-methyl-2-thenaldehyde with ethyl α-bromopropionate in the presence of zinc followed the procedure of Gilman and Speeter (19). The 2-azetidinone did not undergo aldol condensations with either crotonaldehyde or acetophenone. The action of 2% alkali, even at 0–10°, was sufficient to hydrolyze the β-lactam to a substituted β-anilinopropionic acid.



XV XVI

This fact was in accord with qualitative data on the hydrolysis of 2-azetidonones. The ease of hydrolysis is apparently a function of the increasing size and number of substituents in the 3-position; with increased size and number hydrolysis becoming increasingly difficult (20).

The condensation of 1-chloro-1-nitroethane with 2-thenaldehyde or 2-acetothienone with zinc or magnesium was investigated. The reaction mixtures were refluxed for periods up to 18 hours in a variety of solvents without success.

The attempted Grignard reaction of 2-thenaldehyde with phenacyl bromide did not give the expected product. The reaction mixtures became deep blue to purple after one hour.

Following hydrolysis, only unreacted starting materials and varying amounts of acetophenone were isolated. This conversion of α-bromoketones to the corresponding unbrominated ketones by Grignard reagents was observed by many investigators (21, 22). The substitution of zinc for magnesium gave similar results, although the color change appeared only after two to five hours refluxing. No reaction was indicated before the color change had taken place.

In an attempt to prepare β-(2-thienyl)propionaldehyde by the reaction of acrolein with thiophene, the influence of several condensing agents was investigated. A procedure employing freshly prepared potassium ethoxide or sodium methoxide (23) was followed. Sulfur dioxide, which had been employed successfully with furan (24), was also studied. In each instance a resinous mixture was formed, from which no aldehyde could be isolated. The α-hydrogen atoms in the thiophene nucleus do not appear to be sufficiently activated to permit nucleophilic attack by these reagents.

EXPERIMENTAL

Materials. Crotonaldehyde was obtained from Carbide and Carbon Chemical Company, New York, N. Y. The 3-methylthiophene was kindly supplied by Socony-Vacuum Research Laboratories, Paulsboro, N. J., through the courtesy of Mr. Howard Hartough. A generous sample of chloroacetaldehyde (40%) was furnished by Dow Chemical Company, Midland, Mich.

The 2-thenaldehyde and 3-methyl-2-thenaldehyde were prepared according to the previously developed method. Sorbic acid was obtained in 40% yield by refluxing crotonaldehyde with malonic acid in pyridine solution according to the original direction. The methyl ester distilled at 90–92°/35 mm.; m.p. 11.1–11.5°.

Methyl ω-bromosorbate was prepared by the method of Karrer and Schwyzer (3). The yield was 18.4 g. (56.8%), b.p. 75–77°/1 mm.; m.p. 26.5°.

General conditions used for the Reformatsky Reactions. The aldehydes employed were freshly distilled before use. The bromo esters were generally used in *ca.* 0.3–0.5% excess over that required for reaction. The zinc, in excess of the theoretical quantity, was etched with dilute hydrochloric acid, washed successively with water, methanol and dry ether and covered with dry benzene, most of which was removed by distillation. The reactants dissolved in the appropriate dry solvent were added immediately to the warm zinc. The reactions usually commenced immediately under these anhydrous conditions. The remainder of the reactants were added at a rate sufficient to maintain gentle refluxing. Some external cooling was often necessary. If the reaction was difficult to start, the addition of *ca.* 100 mg. of mercuric chloride proved effective.

When the reactants had been added, the solution was refluxed for thirty minutes to complete the reaction. The solution was cooled and then decomposed with ice and 10% hydrochloric acid. The ester was isolated in ether in the usual way. The unchanged aldehyde was readily removed from the ester by distillation.

A solution of the crude ester and one gram of potassium hydroxide, dissolved in 50 cc. of 50% ethanol, was set aside at room temperature for forty-eight hours. After dilution with water and ether extraction acidification of the aqueous phase precipitated the acid. The acids were recrystallized from aqueous ethanol or benzene.

5-(2-Thienyl)-2,4-pentadiene-1-carboxylic acid (IV). A mixture of 2-thenaldehyde (22.0 g., 0.19 mole) and ethyl γ-bromocrotonate (40.0 g, slight excess) in 50 cc. of dry benzene was added to 15.0 g. of zinc. The reaction started readily, but soon ceased due to the separation of an insoluble complex. Tetrahydrofuran (20 cc.) was added, and the reaction recommenced on heating the mixture to gentle reflux. The acid (11.3 g., 33.0%) had the melting point 170–171°.

Anal. Calc'd for $C_9H_8O_2S$: C, 60.04; H, 4.44.
Found: C, 60.19; H, 4.53.

5-(5-Methyl-2-thienyl)-2,4-pentadiene-1-carboxylic acid. Ethyl γ-bromocrotonate (20.0 g.) and 12.0 g. (0.09 mole) of 5-methyl-2-thenaldehyde dissolved in 35 cc. of tetrahydrofuran and 35 cc. of dry benzene were added to 7.0 g. of zinc. The saponification of the crude ester yielded 5.2 g. (30.0%) of the acid, m.p. 135–136°.

Anal. Calc'd for $C_{10}H_{10}O_2S$: C, 61.90; H, 5.16.
Found: C, 62.08; H, 5.17.

5-(2-Thienyl)-2,4-hexadiene-1-carboxylic acid. A mixture of 2-acetothienone (16.0 g., 0.12 mole) and ethyl γ-bromocrotonate (30.0 g.) dissolved in 100 cc. of a 1:1 mixture of benzene and tetrahydrofuran was allowed to react with zinc (8.0 g.). The reaction was initiated by a trace of mercuric chloride. The acid resulting from saponification of the ester (4.3 g., 25%) had the melting point 173–174°.

Anal. Calc'd for $C_{10}H_{10}O_2S$: C, 61.90; H, 5.16.
Found: C, 61.74; H, 4.96.

7-(2-Thienyl)-2,4,6-heptatriene-1-carboxylic acid. β-2-Thienylacrolein (13.8 g., 0.1 mole) and ethyl γ-bromocrotonate (23.0 g.) dissolved in 50 cc. of dry benzene and 50 cc. of tetrahydrofuran were added slowly to 10.0 g. of zinc. A trace of mercuric chloride was also added. The reaction was completed by heating under reflux for one hour. The yield of acid was 8.2 g. (39.8%); m.p. 189–191°.

Anal. Calc'd for $C_{11}H_{10}O_2S$: C, 64.12; H, 4.85.
Found: C, 64.04; H, 5.15.

Condensation between β-2-thienylacrolein and methyl ω-bromosorbate. Methyl ω-bromosorbate (20.0 g., 0.1 mole) and β-2-thienylacrolein (13.8 g., 0.1 mole) dissolved in 70 cc. of a 1:1 mixture of benzene and tetrahydrofuran were caused to react with zinc (7.5 g.). A trace of mercuric chloride was added. The reaction proceeded slowly although the zinc went into solution. The mixture was refluxed for one hour after addition was complete. Distillation of the reaction mixture after hydrolysis yielded only methyl sorbate and β-2-thienylacrolein. A small amount of undistilled material remained. This was saponified, but no acid could be isolated.

Ethyl 2-cyano-5-(2-thienyl)-2,4-pentadiene-1-carboxylate (III). Ethyl cyanoacetate (9.0 g., 0.079 mole), β-2-thienylacrolein (15.0 g., 0.108 mole) and 5.0 g. (0.085 mole) of acetamide with 23 cc. of acetic acid was slowly distilled over four hours so that the temperature reached 105–115°; distillate collected, 32 cc. The crystalline residue was washed with two 50 cc.-portions of water. After three recrystallizations from methanol the golden-yellow crystals melted at 127.5–128°. Yield: 16.6 g. (90.0%).

Anal. Calc'd for $C_{12}H_{11}NOS$: C, 61.78; H, 4.75.
Found: C, 62.01; H, 4.78.

2-Cyano-5-(2-thienyl)-2,4-pentadiene-1-carboxylic acid. Barium hydroxide (17.1 g., 0.1 mole) was dissolved in 200 cc. of hot methanol. After the undissolved barium carbonate was filtered off, 3.5 g. (0.015 mole) of the above ester was added and the solution refluxed for one-half hour. The barium salt separated as a fine powder. This was washed with cold methanol and dried. The salt was then heated for 10 minutes with 2 *N* hydrochloric acid. The acid, after recrystallization from methanol, had the melting point 200.5–202°.

Anal. Calc'd for $C_{10}H_7NO_2S$: C, 58.47; H, 3.42.
Found: C, 58.26; H, 2.81.

The cyano acid obtained above (8.0 g., 0.039 mole), 40 cc. of freshly distilled quinoline, and 1.0 g. of copper powder were heated in an oil bath slowly to 175–180°. This temperature was maintained for twenty minutes. The mixture was cooled and decanted into dilute hydrochloric acid. The precipitated oil was extracted with ether and washed successively with dilute acid and water. The crude nitrile (*ca.* 2.0 g.) obtained after evaporation of the solvent was refluxed with 20% aqueous potassium hydroxide for two hours. The solution was cooled and acidified. The 5-(2-thienyl)-2,4-pentadiene-1-carboxylic acid was recrystallized from ethanol-water; yield 1.3 g. (25.0%); m.p. 169–170°.

The pentadienic acid was also obtained by refluxing 5.0 g. (0.0214 mole) of ethyl 2-cyano-5-(2-thienyl)pentadiene-2,4-dicarboxylate with 5.0 g. of potassium hydroxide, 25 cc. of H_2O and 25 cc. of ethanol for eighteen hours. After removal of the ethanol *in vacuo* and acidification the acid was recrystallized from ethanol. The mixed melting point with an analytical sample showed no depression; yield 2.2 g. (57.2%).

Anal. Calc'd for $C_9H_8O_2S$: C, 60.04; H, 4.44.
Found: C, 60.19; H, 4.53.

4-(2-Thienyl)-2-oxo-3-butene-1-carboxylic acid (I). Ten grams (10.0 g., 0.089 mole) of 2-thenaldehyde was added with continual shaking to an aqueous solution of sodium pyruvate (prepared by neutralizing 15.0 g. (0.17 mole) of pyruvic acid in 100 cc. of water held at 0–5°. The mixture was agitated on a shaking machine for three hours, then decomposed at 0° with a few cc. of 40% KOH. The mixture was allowed to stand 20–30 minutes, was then filtered, and washed with cold acetone and ether. Acidification with ice-cold HCl in the minimum amount of water yielded 5.2 g. (32.1%) of a yellow crystalline acid. After recrystallization from ethanol-water, it melted at 128–128.5°.

Anal. Calc'd for $C_8H_6O_3S$: C, 52.79; H, 3.29.
Found: C, 53.17; H, 3.23.

The acid (5.0 g., 0.027 mole) was mixed with a small excess of freshly distilled aniline and the solid aniline salt was heated; water and carbon dioxide were split out with foaming. The yellowish liquid was distilled immediately *in vacuo* to remove the unreacted materials. To the crude anil was added 15 cc. of 25% H_2SO_4 and the mixture was heated for 20 minutes on a steam-bath. It was extracted three times with ether and the extracts washed with sodium carbonate solution and water. The ether solution was evaporated and the residual oil taken up in ethanol. The ethanol solution was treated with semicarbazide hydrochloride and sodium acetate. The semicarbazone of β-2-thienylacrolein formed after warming 15 minutes on a steam-bath. Recrystallization from ethanol gave 1.9 g. (38.8%) of white needles, m.p. 218.5–219° (25).

6-(2-Thienyl)-2-oxo-3,5-hexadiene-1-carboxylic acid (II). β-2-Thienylacrolein (7.0 g., 0.0508 mole) was treated with 10.0 g. of an aqueous solution of sodium pyruvate as described above. On standing, a thick mass of lemon-yellow crystals formed. After acidification and recrystallization from ethanol-water the acid was obtained in 37.0% yield (3.9 g.); m.p. 107–108°.

Anal. Calc'd for $C_{10}H_8O_3S$: C, 57.67; H, 3.86.
Found: C, 57.80; H, 3.86.

The salt of the keto-acid (2.0 g., 0.009 mole) was dissolved in 40 cc. of water, the solution cooled in ice, and stirred during the addition of 4 cc. of 30% hydrogen peroxide. This solution became turbid as the evolution of carbon dioxide commenced. A precipitate formed. The stirring was continued as long as any gas was evolved. The solution was acidified and the acid was washed with water and dried *in vacuo*. The crude product weighed 1.2 g. (69.6%). Crystallized from benzene the 5-(2-thienyl)-2,4-pentadiene carboxylic acid had the m.p. 170–171°.

Ethyl 6-(2-thienyl)-1-oxy-2-oxo-2,5-hexadiene-1-carboxylate. Equimolecular amounts of 2-thenalacetone (9.0 g., 0.593 mole) and 8.7 g. (0.059 mole) of ethyl oxalate were added to a well-cooled solution of 8.0 g. of sodium in 60 cc. of ethanol. The mixture was allowed to stand 24 hours. A yellow mass of the salt precipitated, which was washed rapidly with ether and then dissolved in three volumes of water. The solution was carefully acidified with cold, dilute HCl. Recrystallized from ethanol, the ester melted at 126.5–127°; yield 10.5 g. (70.5%).

The ester gives a blood-red color with alcoholic ferric chloride. Dilute alkali decomposes the ester into 2-thenalacetone and sodium oxalate.

Anal. Calc'd for $C_{12}H_{12}O_4S$: C, 57.17; H, 4.76.
Found: C, 57.20; H, 4.50.

Ethyl 2,2'-thienyl-4-hydroxy-6-oxo-4-methylcyclohexane-1,3-dicarboxylate (X). Equimolar amounts of 2-thenaldehyde (5.0 g., 0.044 mole) and ethyl acetoacetate were mixed under strong cooling. One gram of piperidine acetate was added, and after cooling for one hour the mixture was allowed to stand at room temperature for 24 hours. The resulting solid was recrystallized from ether, white needles, m.p. 105–105.5°.

Anal. Calc'd for $C_{17}H_{19}O_6S$: C, 58.12; H, 5.46.
Found: C, 58.20; H, 5.50.

1,5-Bis-(2-thienyl)-1,4-pentadiene-3-one (VI). (a) A solution of 2-thenalacetone (20.0 g., 0.132 mole) and 19.0 g. (0.17 mole) of 2-thenaldehyde in 150 cc. of ethanol and 100 cc. of water was treated with 5.5 cc. of 1% sodium hydroxide and kept at 0° for several days. A yellow oil formed which solidified upon scratching. The product was neutralized with acetic acid and recrystallized from ethanol. Yield: 17.0 g. (52.5%); m.p. 113–114°.[3]

Anal. Calc'd for $C_{13}H_{10}OS_2$: C, 63.41; H, 4.06.

Found: C, 63.10; H, 4.27.

(b) The ketone was also prepared by adding dropwise to a solution of 2-thenaldehyde (24.0 g., 0.214 mole) and 9.0 g. of sodium hydroxide in 70% ethanol, 80.0 g. of 40% aqueous acetone. The temperature was held at 0–5° while stirring for 3 hours. The yield was 30.2 g. (57.5%). A mixed melting point showed no depression.

The 2,4-dinitrophenylhydrazone had m.p. 186.5–187°.

Anal. Calc'd for $C_{19}H_{14}N_4O_4S_2$: C, 53.53; H, 3.37.

Found: C, 53.21; H, 3.01.

1,3-Bis-(2-thienyl)-2-propene-1-one (IX). To a stirred solution of 3.0 g. of sodium hydroxide in 21 cc. of water and 13 cc. of ethanol was added 6.3 g. (0.05 mole) of 2-acetothienone and then 5.1 g. (0.045 mole) of 2-thenaldehyde. The mixture was maintained at 0–10° for 3 hours. After standing in an ice-box for 12 hours, the yellow solid was filtered, washed with ether and recrystallized from ethanol. The product weighed 5.9 g. (59.5%); m.p. 95–96°[4].

Anal. Calc'd for $C_{11}H_8OS_2$: C, 60.05; H, 3.63.

Found: C, 60.17; H, 3.65.

1-(2-Thienyl)-3-phenyl-2-propene-1-one (VIII). Benzaldehyde (4.8 g., 0.05 mole), 6.3 (0.05 mole) of 2-acetothienone and 3.0 g. of NaOH were reacted for 3 hours as described above. The ketone was obtained in 60% yield (6.4 g.); m.p. from ethanol 82–83°[5].

1-Phenyl-3-(2-thienyl)-2-propene-1-one (VII). The 2-thenaldehyde (5.1 g.), 0.045 mole) and acetophenone (6.0 g., 0.05 mole) were treated as described above. The yield was 5.8 g. (55%); m.p. 59–60°[6].

β-(3-Methyl-2-thienyl)acrolein (XI). To a stirred and well-cooled solution of 22.0 g. (0.175 mole) of 3-methyl-2-thenaldehyde and 5.0 g. of sodium hydroxide dissolved in 100 cc. of 70% ethanol, 40.0 g. of 40% aqueous acetaldehyde was added dropwise. Stirring was continued for 3 hours and the mixture was acidified, extracted with benzene and distilled. The yellow liquid had b.p. 133–136°/3 mm.; yield 10.4 g., (39.0%).

Anal. Calc'd for C_8H_8OS: C, 63.05; H, 5.26.

Found: C, 63.17; H, 5.42.

The *semicarbazone* had m.p. 203–204°.

Anal. Calc'd for $C_9H_{11}N_3OS$: C, 51.67; H, 5.27.

Found: C, 51.75; H, 5.30.

β-(5-Chloro-2-thienyl)acrolein (XII). The 5-chloro-2-thenaldehyde (30.0 g., 0.204 mole), and 40.0 g. of 40% aqueous acetaldehyde were reacted as described above. The acrolein was obtained in 42.1% yield (14.8 g.). The b.p. was 135–136°/3 mm., m.p. 35–36°.

Anal. Calc'd for C_7H_5ClOS: C, 48.74; H, 2.90.

Found: C, 48.83; H, 3.19.

The *semicarbazone* melted at 200–201°.

Anal. Calc'd for $C_8H_8ClN_3OS$: C, 41.84; H, 3.52.

Found: C, 42.08; H, 3.77.

α-Chloro-β-(2-thienyl)acrolein (XIII). The 2-thenaldehyde (24.0 g., 0.214 mole) and 80.0 g. (excess) of 40% aqueous chloroacetaldehyde were treated as described above. A portion of the crude acrolein (15.0 g., 42.2%) distilled at 131–139°/6 mm. with rapid decomposition. The semicarbazone had m.p. 238–239°.

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[3] Ref (11) gives 119–120°.

[4] Ref (13) gives 99°.

[5] Ref (13, 14) each give 82–83°.

[6] Ref (12) gives 59°.

Anal. Calc'd for $C_8H_8ClN_3OS$: C, 41.84; H, 3.52.
Found: C, 41.91; H, 3.37.

2-Thenaldehyde azine. The aldehyde (3.0 g., 0.0268 mole) was refluxed for several hours with 0.67 g. (0.0134 mole) of hydrazine hydrate in 15 cc. of ethanol. On cooling, yellow needles precipitated; from ethanol, the pale yellow needles melted at 157.5–158.5°[7].

Anal. Calc'd for $C_{10}H_8N_2S_2$: C, 54.55; H, 4.03.
Found: C, 54.65; H, 4.18.

β-(5-Chloro-2-thienyl)acrolein azine. Hydrazine hydrate (0.72 g., 0.0144 mole), and 5.0 g. (0.029 mole) of β-(5-chloro-2-thienyl)acrolein were refluxed in 15 cc. of ethanol. The azine had m.p. 155.5–156.5°.

Anal. Calc'd for $C_{14}H_{10}ClN_2S_2$: C, 49.27; H, 3.15.
Found: C, 49.17; H, 3.38.

β-(3-Methyl-2-thienyl)acrolein azine. An ethanol solution of 2.0 g. (0.0158 mole) of β-(3-methyl-2-thienyl)acrolein and 0.33 g. (0.0066 mole) of hydrazine hydrate gave yellow needles; m.p. 134.5–135.5°.

Anal. Calc'd for $C_{16}H_{16}N_2S_2$: C, 63.98; H, 5.36.
Found: C, 63.87; H, 5.42.

3-Methyl-2-thenalaniline (XIV). To 8.0 g. (0.22 mole) of 3-methyl-2-thenaldehyde, 24.0 g. (0.258 mole) of distilled aniline was added dropwise with stirring. The mixture was refluxed for fifteen minutes, then poured into absolute ethanol. The yield of crystalline anil was 38.1 g. (82.0%) m.p. 80–80.5°.

Anal. Calc'd for $C_{12}H_{11}NS$: C, 71.63; H, 5.52.
Found: C, 71.77; H, 5.35.

1-Phenyl-3-methyl-4-(3-methyl-2-thienyl)-2-azetidinone (XV). Thirty grams (0.14 mole) of the anil dissolved in 200 cc. of dry toluene was heated to boiling with 13.5 g. of zinc. A few cc. of ethyl α-bromopropionate was added to initiate the reaction. The remainder of the ester, 28.0 g. (slight excess), was added at a rate sufficient to maintain gentle reflux. The reaction was refluxed thirty minutes after addition was complete. The cooled mixture was hydrolyzed with cold ammonium hydroxide. The solvent was removed and the product crystallized from ethanol; yield 19.8 g. (55%), white plates melting at 112.5–113°.

Anal. Calc'd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.66.
Found: C, 69.89; H, 5.66.

α-Methyl-β-anilino-β-(3-methyl-2-thienyl)propionic acid (XVI). The azetidinone was cleaved by dilute aqueous potassium hydroxide at 0–5° to the acid; white needles from ethanol, m.p. 163–163.5°.

Anal. Calc'd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22.
Found: C, 65.43; H, 6.52.

SUMMARY

The preparation of a variety of thiophene polyene carbonyl compounds is reported.

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