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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XII.[1] PREPARATION OF ACETYLENIC DERIVATIVES OF THIOPHENE

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The chemistry of compounds containing acetylenic linkages has been the subject of intensive investigation during the past fifteen years. Among the many developments in this field of organic chemistry, the synthesis of heterocyclic compounds containing a carbon-carbon triple bond in the side chain has, however, received little more than passing mention (1–5).

As an extension of the investigations on the chemistry of heterocyclic compounds conducted in this laboratory, the synthesis of 2-thienylacetylene and other thiophene compounds containing the acetylenic linkage has been undertaken. The present paper is limited to the methods for the creation of the triple bond. Investigations dealing with the multitude of reactions in which the acetylenic linkage takes part are in progress and will be reported later.

Two fundamental methods are available for the preparation of mono- and di-substituted acetylenes (6), namely, dehydrohalogenation and synthesis from organometallic derivatives of acetylenes. 2-Thienylacetylene and β-2-thienylpropiolic acid were obtained *via* the first method.

Dehydrohalogenation produces acetylenic compounds from *vic*-dihalides of olefins, or, alternately, by the closely related method involving elimination of two molecules of a hydrogen halide from a *gem*-dihalide. Both alcoholic and molten potassium hydroxide were used to effect this reaction.

The *vic*-dihalide (III) was readily prepared by the bromination of β-2-thienylacrylic acid (I). It was necessary to excercise careful control over the reaction conditions since hydrogen bromide was eliminated during the reaction, indicating that bromination of the thiophene nucleus may have occurred. This side-reaction was avoided by dissolving the acrylic acid in hot carbon tetrachloride and adding the bromine in several portions with shaking.

When the *vic*-dibromide was treated with 10% aqueous potassium hydroxide, carbon dioxide was rapidly evolved and an oily layer separated. This was shown to be the monobrominated 2-thienylethylene (VI). Upon dropwise addition of the substituted ethylene onto molten potassium hydroxide at 200–225°, 2-thienylacetylene (X) was formed. This compound gave an immediate and characteristic precipitate with ammoniacal silver nitrate and cuprous chloride.

The *gem*-dihalide (VIII) was prepared by the action of phosphorus pentachloride on 2-acetothienone (7, 8). The monochloro-2-thienylethylene (VII) was

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[1] For paper No. XI of this series see Crowe and Nord, *J. Org. Chem.*, **15**, 1177 (1950). Presented before the Division of Organic Chemistry, American Chemical Society, Chicago, Ill., September 1950. This investigation was carried out under the auspices of the Office of Naval Research.

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also obtained during the reaction. The reaction must be carried out in a solvent above 50°. When the synthesis was attempted without a solvent, little or no reaction was observed below this temperature, while extensive polymerization occurred above it. Phosphorus pentachloride was covered with benzene and an equivalent amount of the ketone was added. When the vigorous reaction subsided, the reaction mixture was heated for two hours. The crude mixture of chlorinated products, which does not need to be separated into its component fractions, was then added dropwise to the molten alkali.

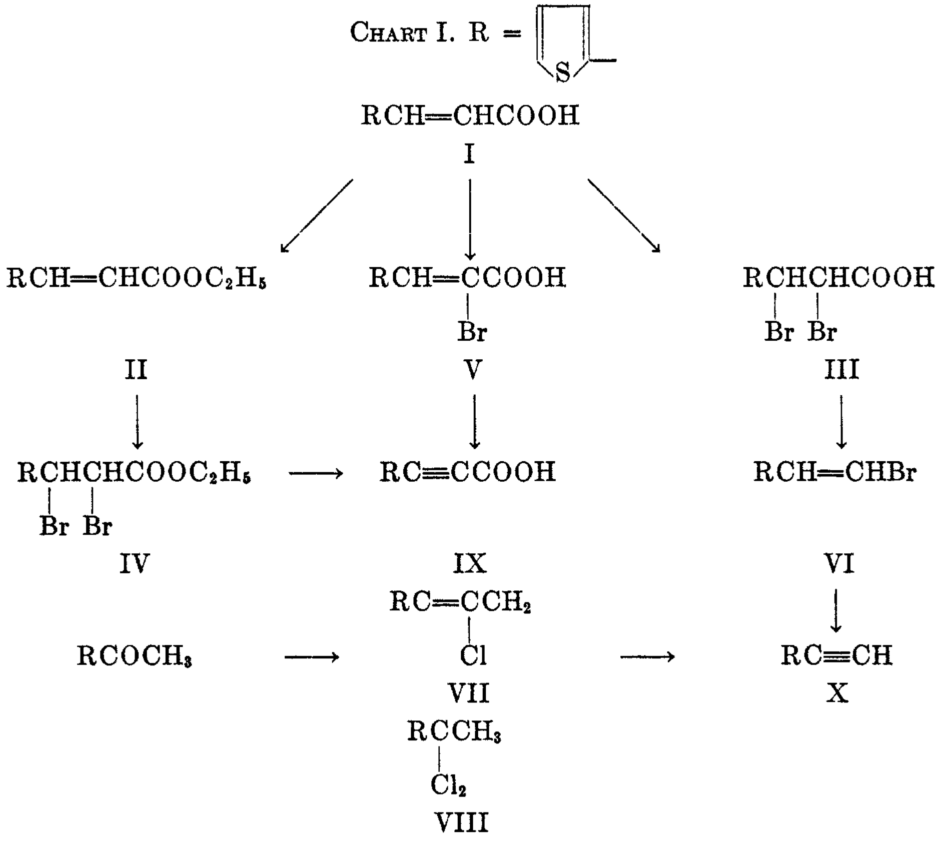
CHART I. R =

The yield of 2-thienylacetylene by either method was 20–25% . The reactions are summarized in Chart I.

The β-2-thienylpropiolic acid was also synthesized. The β-2-thienylacrylic acid dibromide (III) was readily converted to a β-2-thienylbromoacrylic acid (V) in boiling glacial acetic acid. When the acid (V) was treated with alcoholic potassium hydroxide β-2-thienylpropiolic acid was obtained in 50% yield. The reaction was accompanied by some decarboxylation which was minimized by keeping the temperature as low as possible during acidification of the alkaline reaction mixture.

It was also found that the dibromide of ethyl β-2-thienylacrylate (IV) gave lower yields of the propiolic acid upon treatment with alkali than did the dibromide of the acid (III).

The Reformatsky reaction was utilized to synthesize the thiophene acetylenic carbinols, 1-(2-thienyl)-3-butyn-1-ol (XI) and 1-(2-thienyl)-1-hexen-5-yn-3-ol (XII) from 2-thenaldehyde and β-2-thienylacrolein respectively.

This novel reaction (9, 10), in which propargyl bromide is substituted for the usual α-halogen ester, gave high yields (40–60%), especially when tetrahydrofuran was employed as the solvent. The propargyl bromide, obtained from propargyl alcohol by reaction with phosphorus tribromide and pyridine, was freshly prepared before each reaction.

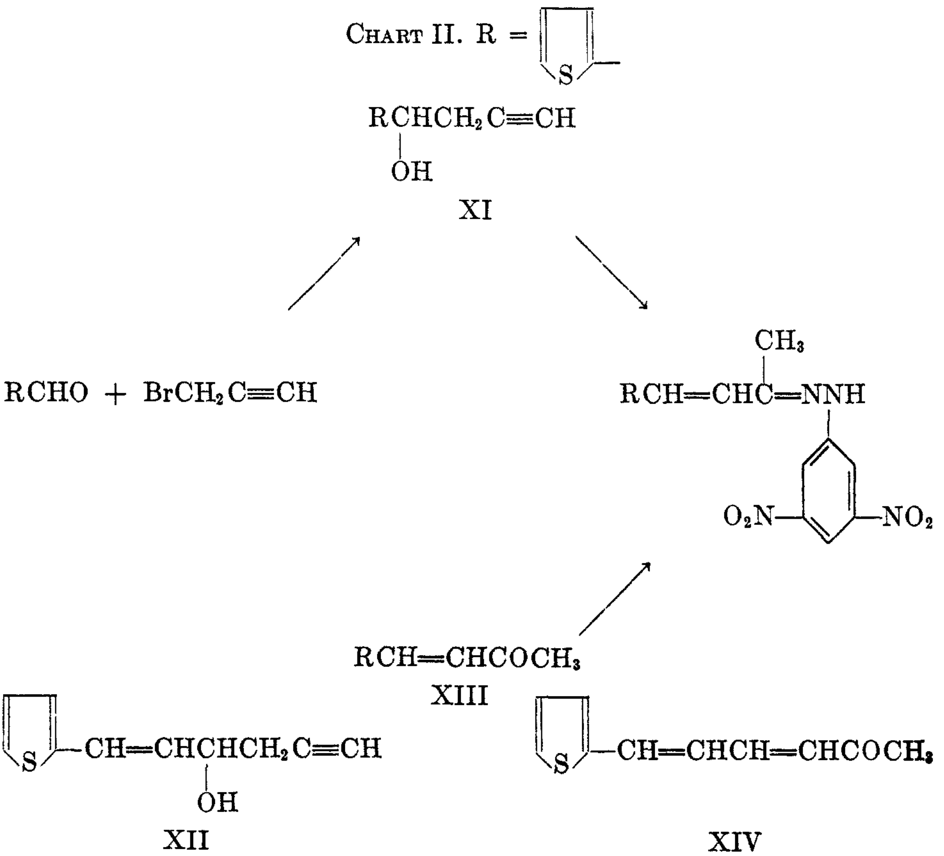

CHART II. R =

When the carbinols were treated with a methanolic solution of 2,4-dinitrophenylhydrazine sulfate, ketonic derivatives were obtained. These were probably formed by a dehydration-hydration mechanism which was induced by the sulfuric acid.

The compounds 4-(2-thienyl)-3-buten-2-one (XIII) and 6-(2-thienyl)-3,5-hexadien-2-one (XIV) were prepared from 2-thenaldehyde and β-2-thienylacrolein on treatment with acetone and dilute alkali.

The 2,4-dinitrophenylhydrazones obtained from these ketones did not depress the melting points when mixed with the 2-4-dinitrophenylhydrazones obtained from the respective carbinols.

EXPERIMENTAL[3]

β-2-Thienylacrylic acid dibromide (III). To 15.4 g. (0.10 mole) of β-2-thienylacrylic acid (11, 12) dissolved in 200 ml. of hot carbon tetrachloride was added, in 2–3 portions with shaking, 16 ml. of a solution of 16 g. (0.10 mole) of bromine in carbon tetrachloride. The bromine color disappeared gradually and the product began to separate from the solution in 10–15 minutes. No evolution of hydrogen bromide was observed. The mixture was poured into a large dish and the solvent evaporated spontaneously. The resulting crystals weighed 30.7 g. (97.5%). The product evolves hydrogen bromide easily, especially on heating. After recrystallization from carbon tetrachloride, a substance was obtained which softened at 135–140° and melted with decomposition at 185–186°, corresponding to the melting point of the β-2-thienylbromoacrylic acid.

Anal. Calc'd for $C_7H_6Br_2O_2S$: C, 26.76; H, 1.91.
Found: C, 26.11; H, 1.82.

When kept in a bottle for a week, the product softened at 100–125° and melted with decomposition at 165–175°. The product obtained by heating a portion of this material on a steam-bath melted at 170–180° without appreciable softening. A sample heated at 130° in a test tube until no more hydrogen bromide was given up was almost carbonized. When a portion of the product was refluxed for five hours in carbon tetrachloride, it softened at 135–140° and melted at 170–177°.

β-2-Thienylbromoacrylic acid (V). An acetic acid solution of compound III was refluxed for 30 minutes and recrystallized to give a product melting at 185–188°.

Anal. Calc'd for $C_7H_5BrO_2S$: C, 36.05; H, 2.14; Br, 34.33.
Found: C, 36.30; H, 2.34; Br, 33.96.

The same product was obtained by adding dropwise a solution of bromine (1 mole) in carbon tetrachloride to a refluxing solution of β-2-thienylacrylic acid (1 mole). The addition required 30 minutes. After recrystallization from carbon tetrachloride and acetic acid a sample melted at 185–188°.

5-Chloro-β-(2-thienyl)bromoacrylic acid (V). In a three-necked round-bottom flask equipped with a stirrer, a reflux condenser, and a dropping-funnel was placed 4.71 g. (0.025 mole) of 5-chloro-β-(2-thienyl)acrylic acid (11, 12) in 20 ml. of glacial acetic acid. The mixture was refluxed and a solution of 4 g. of bromine in 4 ml. of carbon tetrachloride was added dropwise. This required 30 minutes, during which time the mixture was continually stirred. Crystals separated when approximately three-quarters of the bromine solution had been added. Refluxing was continued for 15 minutes after the addition was complete. The 5-chloro-β-(2-thienyl)bromoacrylic acid was dried in air. Yield of the crude product, 5.2 g., m.p. 200–223°. After recrystallization from alcohol the melting point was 226-228°.

Anal. Calc'd for $C_7H_3BrClO_2S$: C, 31.40; H, 1.49.
Found: C, 31.72; H, 1.69.

5-Bromo-β-(2-thienyl)bromoacrylic acid (Vb). When 4.62 g. (0.03 mole) of β-2-thienylacrylic acid (I) in 20 ml. of glacial acetic acid was treated as described above with 9.6 g. of bromine in 9.6 ml. of carbon tetrachloride, 7.8 g. of 5-bromo-β-(2-thienyl)bromoacrylic acid, m.p. 225–230°, was obtained. After recrystallization from glacial acetic acid, the melting point was 234–235°.

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[3] The compound 2-acetothienone was obtained through the courtesy of Dr. N. B. Sommer of the Jefferson Chemical Company. The tetrahydrofuran was kindly furnished by the Electrochemicals Division, E. I. du Pont de Nemours & Company, Wilmington, Del. The analyses recorded in this paper were carried out by A. A. Sirotenko of this department.

Anal. Calc'd for $C_7H_4Br_2O_2S$: C, 26.89; H, 1.27; Br, 51.28.
Found: C, 27.19; H, 1.30; Br, 51.66.

α(ω)-Bromo-(2-thienyl)ethylene (VI). To 31.4 g. (0.1 mole) of β-2-thienylacrylic acid dibromide (III) was added with shaking 200 ml. of a 10% potassium hydroxide solution. There was a rapid evolution of carbon dioxide and an oily layer separated. With occasional shaking, the mixture was left at room temperature for one hour. The oil was separated and the aqueous portion was extracted with ether. The oil and ether extracts were combined and dried over calcium chloride. The ether was then removed and the product was distilled under reduced pressure at 77–78°/4 mm. The yield was 11 g. (58.2%); b.p.$_2$ 65–67°, n_D^{20} 1.6386.

Anal. Calc'd for C_6H_5BrS: C, 38.09; H, 2.64.
Found: C, 38.00; H, 2.42.

The alkaline aqueous solution was acidified and extracted with ether, but gave only a tarry product.

2-Thienylacetylene (X). The method of the preparation of phenylacetylene (13, 14) was used. Potassium hydroxide (10 g.) was heated to 200° in an oil-bath. The bromo compound (VI) (7 g.) was dropped slowly on to the melted alkali and the temperature raised very slowly to 240°. A mixture of water, 2-thienylacetylene, and unreacted starting material was distilled. A foul-smelling oil (4.5 g.) was separated and dried over calcium chloride. Upon distillation, 1 g. of 2-thienylacetylene, b.p.$_{3.5}$ 31–33° was obtained; n_D^{20} 1.5884.

Anal. Calc'd for C_6H_4S: C, 66.66; H, 3.70.
Found: C, 66.37; H, 3.75.

An alcoholic solution of 2-thienylacetylene gave with ammoniacal silver nitrate solution a yellow precipitate which turned white on shaking; and with ammoniacal cuprous chloride solution a yellow-green precipitate was formed.

2-(1,1-Dichloroethyl)thiophene (VIII) (15, 16). Phosphorus pentachloride 165 g. (0.79 mole) was covered with 100 ml. of dry benzene in a 500-ml. apparatus (similar to that used for Va). The 2-acetothienone (75 g., 0.595 mole) was then added and the stirrer started. Within 5–10 minutes a vigorous reaction began with rapid evolution of hydrogen chloride; the temperature rose to 50–55°. In 10–15 minutes the reaction had subsided and the temperature began to fall. The mixture was then heated on the steam-bath to 60–70°. At the end of two hours all the pentachloride had reacted. The light brown solution was cooled and poured carefully with stirring into a mixture of 500 g. of ice and 150 ml. of ether. The ether layer was separated and treated with water until the water layer was absolutely clear. The ether extract was dried over sodium sulfate and rectified. Two cuts, 15 g., b.p.$_3$ 50–63° and 26 g., b.p.$_3$ 79–82°, were obtained. During the distillation these products colored rapidly, especially the first fraction. It is believed that the first fraction is the monochlorinated 2-thienylethylene (VII), and that the second fraction is the dichlorinated product (VIII), but the fractions did not analyze correctly.

The mixture of the two products was saponified in the same manner as VI to give 20–22% of 2-thienylacetylene.

Ethyl β-2-thienylacrylate (II) (11, 12). A mixture of 20 g. of β-2-thienylacrylic acid, 130 ml. of absolute alcohol, and 5 ml. of concentrated sulfuric acid was refluxed for 7–8 hours. The mixture was cooled, poured on to ice, extracted with ether, washed with water, dried and distilled; b.p.$_5$ 120–122°, b.p.$_8$ 128–129°; b.p.$_{23}$ 155–157°. Yield: 29 g. (81%).

Ethyl α,β-dibromo-2-thienylpropionate (IV) (16). In the usual apparatus (see preparation Va above) was placed 17.5 g. (0.096 mole) of β-2-thienylacrylic ester (II) dissolved in 10 ml. of carbon tetrachloride. The flask was cooled by ice, and 15.4 g. (0.096 mole) of bromine in 15.4 ml. of carbon tetrachloride was added dropwise with stirring over a 20-minute period. No hydrogen bromide was evolved. After stirring 30 minutes more, the solution was poured into a large dish and evaporated *in vacuo*. The residue was recrystallized from petroleum ether (b.p. 70–80°) and dried in air; m.p. 68–70°; yield 16 g. (59%).

Anal. Calc'd for $C_9H_{10}BrO_2S$: C, 31.57; H, 2.92.
Found: C, 31.81; H, 2.81.

β-2-Thienylpropiolic acid (IX). Potassium hydroxide (80%, 14 g.) was dissolved in 60 ml. of alcohol by refluxing on a steam-bath. To the alkaline solution, cooled to 40–50°, was added 15.5 g. (0.45 mole) of the dibromo ester (IV). The mixture was refluxed for 6 hours on a steam-bath. The reaction mixture was cooled and the salt separated. The filtrate was made neutral to litmus with conc'd hydrochloric acid and the salt again separated. The filtrate was distilled on a steam-bath (the vapor reached 80–85°). The residue was cooled, treated with water and ice, and acidified with conc'd hydrochloric acid. The acid was filtered, washed with water, and dissolved in 5% sodium carbonate. The solution was then refluxed for 30 minutes in the presence of Norit. The mixture was filtered, cooled, and acidified. The precipitated acid was dried in air. Yield: 2 g. (30%). Recrystallized from carbon tetrachloride, the acid melted at 130–131°.

Anal. Calc'd for $C_9H_8O_2S$: C, 55.26; H, 2.63.
Found: C, 55.12; H, 2.75.

The saponification of β-2-thienylbromoacrylic acid (V), under four hours reflux, gave the same product in 50% yield.

5-Chloro-β-(2-thienyl)propiolic acid (IXa). 5-Chloro-β-(2-thienyl)bromoacrylic acid (3.5 g.) (Va) was refluxed as described above for only 90 minutes. The yield of crude product was 40–45%. Recrystallized from carbon tetrachloride, 5-chloro-β-(2-thienyl)propiolic acid melted at 118–120°.

Anal. Calc'd for $C_7H_3ClO_2S$: C, 45.04; H, 1.60.
Found: C, 45.25; H, 1.89.

5-Bromo-β-(2-thienyl)propiolic acid (IXb). 5-Bromo-β-(2-thienyl)bromoacrylic acid (7.8 g.) was treated as described above. The 5-bromo-β-(2-thienyl)propiolic acid melted at 125–126°; yield: 35–40%.

Anal. Calc'd for $C_7H_3BrO_2S$: C, 36.36; H, 1.29.
Found: C, 36.67; H, 1.58.

β-2-Thienylacrolein. Sodium hydroxide (10 g.) was added to 60 ml. of ethyl alcohol and 120 ml. of water, and then 45 g. (0.40 mole) of freshly distilled 2-thenaldehyde (17) was added within 15 minutes. To this mixture, 100 g. of a 40% solution of acetaldehyde in water was added at 0° over 3½ hours with vigorous stirring. The mixture was held at this temperature and stirred an additional one-quarter hour. Following neutralization with ice-cold acetic acid, the mixture was extracted with benzene, washed with water, and dried. Distillation yielded 30 g. (54%); b.p.$_{1}$ 85–90° (18); b.p.$_{4}$ 105–108°; n_D^{20} 1.6638 (18); melting point of the semicarbazone, 218–219°.

Propargyl bromide (19). Phosphorus tribromide (slight excess) and a drop of pyridine were slowly added dropwise to a mixture of 35 g. (0.625 mole) of propargyl alcohol and *ca.* 15 mole-% of pyridine with occasional shaking. The mixture was kept at −10 to 0° in a flask protected from moisture. The product was distilled immediately; b.p. 82–85°.

1-(2-Thienyl)-3-butyn-1-ol (XI). In the usual 500-ml. apparatus (see preparation Va), 14 g. of freshly etched zinc was covered with 50 ml. of dry benzene. The mixture was heated to boiling and 10 ml. was distilled off. This removed any moisture as a benzene-water azeotrope. A few ml. of the reactants [24 g. (0.21 mole) of 2-thenaldehyde and a slight excess of propargyl bromide in 40 cc. of dry tetrahydrofuran] was added immediately to the warm mixture. When the reaction commenced, the remainder of the reactants was added at a rate sufficient to maintain gentle reflux. After the addition was complete, the reaction mixture was refluxed for 30 minutes. After cooling, the mixture was hydrolyzed with cold acetic acid, washed with sodium carbonate solution, and dried. Yield: 16.0 g. (59.3%); b.p.$_{3}$ 98–100.5°; n_D^{20} 1.5235.

Anal. Calc'd for C_8H_3OS: C, 63.17; H, 5.25.
Found: C, 62.96; H, 5.00.

One-half gram (0.5 g.) of the carbinol was added to a methanolic solution of 2,4-dinitrophenylhydrazine sulfate and set aside for one hour. Recrystallization from ethyl acetate yielded the 2,4-dinitrophenylhydrazone of 4-(2-thienyl)-3-buten-2-one, m.p. 215–218°.

1-(2-Thienyl)-1-hexen-5-yn-3-ol (XII). β-2-Thienylacrolein (10 g. 0.072 mole), a slight excess of propargyl bromide, and 8 g. of zinc were treated as described above. Yield: 5.2 g.

(41%); b.p.$_3$ 129–132°; n_D^{20} 1.5968; m.p. of the 2,4-dinitrophenylhydrazone of 6-(2-thienyl)-3,5-hexadien-2-one, 223–224°.

Anal. Calc'd for $C_{10}H_{10}OS$: C, 67.45; H, 5.62.
Found: C, 67.20; H, 5.42.

4-(2-Thienyl)-3-buten-2-one (XIII). (20, 21, 22) In a 250 ml. round-bottom flask equipped with a stirrer were mixed 43 g. (0.74 mole) of acetone, 31 g. (0.277 mole) of 2-thenaldehyde, and 30 ml. of water. To this mixture, 10 ml. of 10% aqueous sodium hydroxide was slowly added from a dropping-funnel. The solution was stirred and cooled to 20–25°. The addition required 30 minutes. The mixture was then stirred for 2½ hours. At the end of this time, cold dilute hydrochloric acid was added until the mixture was acid to litmus and the mixture was extracted with benzene. The benzene was removed on a steam-bath, and the residue distilled *in vacuo*. The material which distilled at 112–114°/3 mm. solidified to a crystalline mass on standing. Yield, 24 g. (64%); m.p. 34–35°.

Anal. Calc'd for C_8H_8OS: C, 63.20; H, 5.79.
Found: C, 63.04, H, 5.70.

Melting point of the semicarbazone, 176.5–177.5°.

Anal. Calc'd for $C_9H_{11}N_3OS$: C, 57.72; H, 5.27.
Found: C, 57.50; H, 5.07.

Melting point of the 2,4-dinitrophenylhydrazone, 214–215°.

Anal. Calc'd for $C_{14}H_{12}N_4O_4S$: C, 50.61; H, 3.61.
Found: C, 50.36; H, 3.42.

6-(2-Thienyl)-3,5-hexadien-2-one (XIV). β-2-Thienylacrolein (10 g., 0.072 mole), 28 g. of acetone (0.20 mole), and 10 ml. of water were treated as described above. Yield: 7.6 g. (59%); b.p.$_2$ 119–121°; m.p. 53–54°.

Anal. Calc'd for $C_{10}H_{10}OS$: C, 67.45; H, 5.62.
Found: C, 67.19; H, 5.50.

Melting point of semicarbazone, 188–188.5°.

Anal. Calc'd for $C_{11}H_{13}N_3OS$: C, 58.28; H, 5.54.
Found: C, 56.34; H, 5.34.

Melting point of 2,4-dinitrophenylhydrazone, 222–225°.

Anal. Calc'd for $C_{16}H_{14}N_4OS$: C, 53.69; H, 3.91.
Found: C, 54.03; H, 3.63.

SUMMARY

Studies on the chemistry of heterocyclics have been extended to the preparation of acetylenic derivatives of thiophene.

2-Thienylacetylene has been prepared by the dehydrohalogenation of *vic*- and *gem*-thiophene dihalides. β-2-Thienylpropiolic acid has also been synthesized. Two thiophene acetylenic carbinols were prepared by means of the Reformatsky reaction with propargyl bromide.

β-2-Thienylacrolein, 4-(2-thienyl)-3-buten-2-one, and 6-(2-thienyl)-3,5-hexadien-2-one have been synthesized by Claisen-Schmidt reactions.

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