was refluxed an additional 2 hours on the steam-bath then decomposed with cold dilute sulfuric acid. The acid solution was extracted with ether, the extracts dried and evaporated and the residue distilled. Compounds 61 and 62 (Table III) were prepared by this procedure. Substitution of phenylacetylene by *n*-butylacetylene afforded compound 60 (Table III).

Acetylenic Glycols.—To a solution of 0.6 mole of ethylmagnesium bromide in 500 ml. of anhydrous ether there was added dropwise 0.3 mole of the ethinyl carbinol in 100 ml. of anhydrous benzene. The mixture was refluxed with stirring for 3 hours, cooled in an ice-bath and 0.3 mole of the appropriate aldehyde or ketone in 50 ml. of anhydrous ether added dropwise with vigorous stirring. Stirring was continued for an additional 6 hours at 5–10° and the mixture kept overnight at room temperature. The Grignard complex was decomposed with dilute sulfuric acid and extracted with ether. The residue of the ethereal extract was purified by distillation or recrystallization. Compounds 63, 64, 65, 66 and 67 of Table III were prepared by this procedure.

Ethyl β-(1-Hydroxy-1-cyclohexyl)-propiolate (No. 49).—A solution of 40 g. of β-(1-hydroxycyclohexyl)-propiolic acid[21] in 200 ml. of anhydrous ethanol containing 1% concentrated sulfuric acid was refluxed 16 hours. After neutralization with aqueous potassium carbonate, the reaction mixture was extracted with ether, the ethereal solution dried and the residue distilled; yield 70%, b.p. 135.5–140° (2.5 mm.), $n^{27}D$ 1.4889. *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.09; H, 8.42.

1,2-Bis-(1-hydroxycyclohexyl)-acetylene (No. 50).—Ethination of cyclohexanone in ether in the presence of powdered potassium hydroxide[22] afforded a 90% yield of product, m.p. 103–104°,[5] after recrystallization from carbon tetrachloride.

γ-Ethinyl-γ-valerolactone (No. 51).—To a solution of 1 mole of sodium acetylide in 1 liter of liquid ammonia there was added over a period of 2 hours a solution of 58 g. (0.5 mole) of levulinic acid in 100 ml. of anhydrous ether. The reaction mixture was worked up as described under the ethination procedures. After evaporation of the ammonia, the residue was acidified and the aqueous solution saturated with salt and extracted with ether in a continuous extractor for 10 hours. The ether extract was dried, evaporated and the residue distilled; yield 46 g. (74%), b.p. 93–94° (5 mm.), $n^{23}D$ 1.4550. *Anal.* Calcd. for $C_7H_8O_2$: C, 67.76; H, 6.49. Found: C, 68.00; H, 6.83.

(21) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 503 (1946).

(22) A. Babayan, *Bull. Armenian Branch Acad. Sci. U.S.S.R.*, 121 (1941); *C. A.*, **40**, 3394 (1946).

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

The Synthesis and Properties of the 5-Phenyl-2- and 3-thiophene-ols[1]

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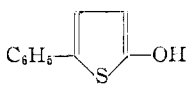
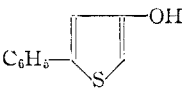
5-Phenyl-2-thiophene-ol has been synthesized by the oxidation of 2-phenyl-5-thienyl Grignard reagent or the corresponding lithium derivative, and by cyclization of β-benzoylpropionic acid. The chemical reactions of this thiophene-ol and of the 3-ol isomer demonstrate that these compounds exist in both keto and enol forms. The spectral data indicate that the enol structures predominate in alcohol solution and the keto tautomers in chloroform solution.

This paper is concerned with the synthesis and properties of 5-phenyl-2-thiophene-ol and 5-phenyl-3-thiophene-ol (I, II).



I



II

II was synthesized by the method of Friedländer and Kielbasinski[3]; a number of modifications are noted in the Experimental section.

The preparation of I was effected both by oxidation of the corresponding organometallic compound and by sulfuration and cyclization of β-benzoylpropionic acid (III). Dehydrogenation of 2-(1-cyclohexenyl)-thiophene[4] (IV) with chloranil[5] produced 2-phenylthiophene (V) in 79% yield. Both N-bromosuccinimide and bromine brominated V in the 5-position in comparable yields, and the derived Grignard reagent was oxidized in the presence of isopropyl- or cyclohexylmagnesium bromide.[6,7] Together with a 30% yield of I, there was obtained a small amount of 5,5′-diphenyl-2,2′-dithienyl (VI). The oxidation is very sensitive to slight changes in conditions; in some runs the quantity of I isolated was negligible, continued oxidation to bis-(β-mercaptostyryl)-maleic acid di-γ-lactone (VII) having taken place.

The formation of VI occurs primarily in the oxidation step rather than by a Fittig-type reaction between Grignard reagent and halide during the preparation of the organometallic, since when one-half of a solution of phenylthienyl Grignard reagent was oxidized we obtained VI in 10% yield, whereas carbonation of the remainder of the solution gave 2-phenylthiophene-5-carboxylic acid in 61% yield without any isolable VI. Numerous examples of the formation of coupled products R–R during the oxidation of organometallics RM are recorded in the literature.

We were also able to oxidize the lithium derivative of V in the presence of excess cyclohexylmagnesium bromide to I in 30% yield. In our second synthesis III was smoothly converted to I in pyridine–chloroform solution in 22% yield.[8] This one-step synthesis of I from readily available materials may be formulated as involving thiation of the car-

(1) Presented in part before the Division of Organic Chemistry at the 121st Meeting of the American Chemical Society, Buffalo, N. Y., March, 1952.

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(3) P. Friedländer and S. Kielbasinski, *Ber.*, **45**, 3389 (1912).

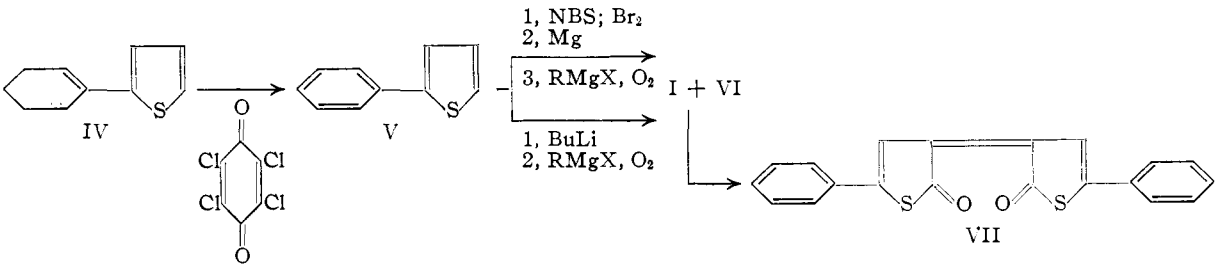
(4) (a) L. F. Fieser and J. Szmuszkovicz, THIS JOURNAL, **70**, 3352 (1948); (b) J. Szmuszkovicz and E. Modest, *ibid.*, **72**, 571 (1950).

(5) R. T. Arnold and C. J. Collins, *ibid.*, **61**, 1407 (1939).

(6) (a) C. D. Hurd and K. L. Kreuz, *ibid.*, **72**, 5543 (1950); (b) C. D. Hurd and H. J. Anderson, *ibid.*, **75**, 5124 (1953).

(7) M. S. Kharasch and W. B. Reynolds, *ibid.*, **65**, 501 (1943).

(8) *Cf.* E. Klingsberg and D. Papa, *ibid.*, **73**, 4988 (1951).



bonyl group, cyclization, loss of a proton, and a final tautomerization to the phenylthiophene-ol.

The reported conversion of III to V in 10–20% yield by heating with phosphorus pentasulfide in the *absence* of solvents or in inert media[9] could not be duplicated by Mitra, Chakrabarty and Mitra[10] nor by us, although the reaction was run under a variety of conditions.[11] The syntheses of I and V were also essayed by other routes. Mitra and co-workers[10,12] devised a method for the preparation of thienyl ethers wherein keto acids were treated with hydrogen sulfide and hydrogen chloride; this did not give satisfactory results in our hands, and appears to proceed well only in the case of γ-oxo esters bearing substituents (particularly carbethoxyl) in the β-position. Whereas Elks and Hey[13] isolated diphenyl in 37% yield after refluxing 1-phenyl-3,3-dimethyltriazene with benzene in acidic media, we could not isolate V from the analogous reaction with thiophene. The mechanistically similar coupling reactions between thiophene and diazohydroxides[14] or N-nitrosoacetylamines[15] give phenylthiophenes in low yield. Finally, when 1-phenyl-1-butene was heated with sulfur, or added dropwise thereto,[16] yields of V of the order of 4% were obtained.

Solutions of I and II in basic solvents (amines, alcohols) are readily oxidized to tars and to VII and the isomeric 5,5′-diphenyl $\Delta^{2,2'}$(3H,3′H)-bithiophene-3,3′-dione (VIII), respectively, by atmospheric and dissolved oxygen, the destruction of I proceeding much more rapidly than that of II. Solutions of I in less basic solvents[17] acquire the bluish-purple color characteristic of VII instantly but, since I can be recovered almost quantitatively after 18 hours, the amount of oxidized material responsible for the color must be very small. In the solid state, a layer of indigoid dimer forms on the surface of I and II and protects the remainder of the compound. VIII had previously been obtained by the oxidation of II with potassium ferricyanide[5] and this indigoid type structure has been derived from other substituted thiophene-ols.[18] The ready oxidation of I and II may be accounted for by assuming that it proceeds by a series of one-electron transfers[19] which produce resonance-stabilized intermediates.

Chemical and physical evidence indicates that I and II exist in both keto and enol forms. This is in accordance with the situation obtaining with other hydroxythiophenes.[6,18] We have confirmed the earlier observation[3] that II is nitrosated by nitrous acid, condenses with aldehydes in the presence of base, is converted to the methyl ether by dimethyl sulfate, and forms a tribromo derivative when treated with bromine.[20] I undergoes aldol condensation, is converted to the methyl ether by dimethyl sulfate (the ether could not be prepared through the Williamson synthesis or by the use of diazomethane),[21] and can be readily acetylated; attempts to isolate a nitrosation product were unsuccessful. Both I and II gave positive ferric chloride tests which were obscured by precipitation of the indigoid dimers. Formation of VII was a troublesome side-reaction encountered generally in transformations of I.

Hurd and Kreuz[6] observed a marked shift of the maximum toward longer wave lengths in the ultraviolet spectrum of 2-thiophene-ol as compared to that of the methyl ether, and attributed it to the thiolactone structure. The spectra of II and of its methyl ether in alcoholic solution (Fig. 1) are almost identical, and indicate that II exists very largely in the enol form in this solvent; the same coincidence of the wave length maxima obtains in the case of I and its methyl ether (Fig. 2), although the values of the two molecular extinction coefficients are somewhat different. This discrepancy is due, at least in part, to the partial oxidation of I to VII during the determination of the spectrum; the appearance of the purple color characteristic of dilute solutions of the indigo was noted even when the measurements were made with a Cary spectrophotometer operating at full speed. The difference in the positions of tautomeric equilibrium of the unsubstituted 2-thiophene-ol system and its phenyl derivatives is ascribed to the stabilization of the enol structures in the latter owing to the contributions of quinonoid resonance forms involving the phenyl group which cannot be written for the keto tautomer. Comparison of the absorption curve of V with that of I and II and their re-

(9) (a) W. Kues and C. Paal, *Ber.*, **19**, 3141 (1886); (b) A. Chraszczewska, *Roczniki Chem.*, **5**, 1, 33 (1925).

(10) S. Mitra, N. K. Chakrabarty and S. K. Mitra, *J. Chem. Soc.*, 1116 (1939).

(11) Reactions of this type seem to become progressively poorer as the volatility of the product decreases and its distillation from the reaction mixture as formed becomes more difficult.

(12) N. Chakrabarty and S. K. Mitra, *J. Chem. Soc.*, 1385 (1940).

(13) J. Elks and D. Hey, *ibid.*, 441 (1943).

(14) M. Gomberg and W. Bachmann, THIS JOURNAL, **46**, 2339 (1924).

(15) E. Bamberger, *Ber.*, **30**, 366 (1897).

(16) M. G. Voronkov and A. C. Brown, *J. Gen. Chem.* (*U.S.S.R.*), **19**, (81) 1356 (1949); *cf.* A. W. Horton, *J. Org. Chem.*, **14**, 761 (1949).

(17) (a) W. Gordy and S. C. Stanford, *J. Chem. Phys.*, **9**, 204 (1941); (b) W. Gordy, *ibid.*, **9**, 215 (1941).

(18) W. Steinkopf and A. Thormann, *Ann.*, **540**, 1 (1939).

(19) L. Michaelis, *Trans. Electrochem. Soc.*, **71**, 107 (1937); *cf.* also L. Michaelis and E. S. Fetcher, THIS JOURNAL, **59**, 1246 (1937); R. B. Woodward and R. H. Eastman, *ibid.*, **68**, 2229 (1946).

(20) Friedländer and Kielbasinski (ref. 3) assigned to this halogenated compound the 2,2,4-tribromo structure on the basis of inconclusive evidence.

(21) Attempts to prepare the allyl and cinnamyl ethers of I and II *via* the Williamson method also failed.

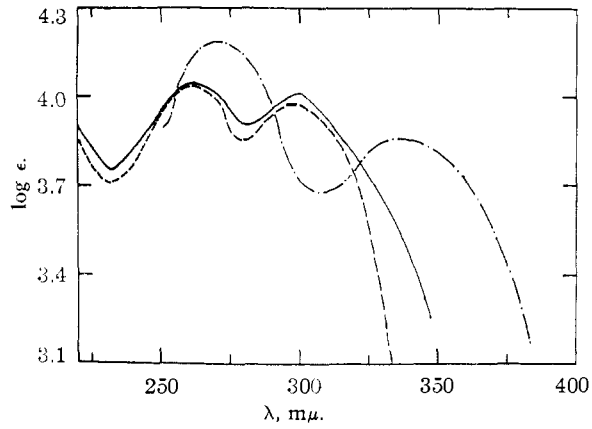


Fig. 1.—Ultraviolet absorption spectra: II in ethanol, —; II in chloroform, -·-·; 3-methoxy-5-phenylthiophene in ethanol, - - -. Curves determined with Beckman quartz spectrophotometer.

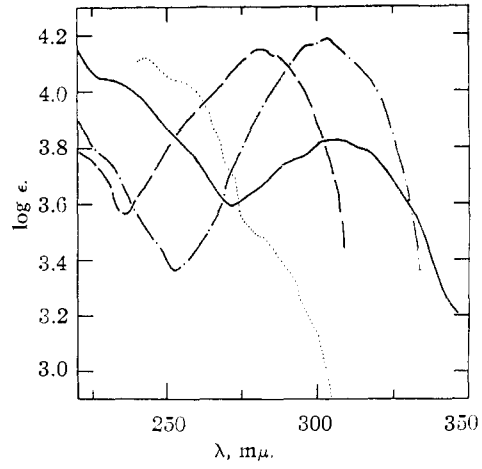


Fig. 2.—Ultraviolet absorption spectra: I in ethanol, —; in chloroform, ...; 2-methoxy-5-phenylthiophene in methanol, -·-·; V in ethanol, - - -. Spectra of I taken with Cary spectrophotometer.

spective methyl ethers in alcohol solution shows that the expected bathochromic effect of the substituents is operative.

In chloroform solution the maxima of II (Fig. 1) are shifted toward longer wave lengths, suggesting that the position of tautomeric equilibrium is affected by the nature of the solvent. The infrared spectrum in chloroform solution shows no absorption in the hydroxyl range and strong absorption in the carbonyl region at 5.90 μ. In chloroform solution I also absorbs in the carbonyl region of the infrared and not in the hydroxyl region. The ultraviolet spectrum (Fig. 2) is quite different from that determined in ethanol; the change in the shape of the curve and the shift of the maximum to shorter wave lengths are consistent with the lesser degree of conjugation present in the keto form of I as compared with its enol structure or the keto tautomer of II.

The spectrum of I in isoöctane has the same shape as that in chloroform with the maximum shifted 6 mμ to shorter wave lengths. This decrease in enol content of the thiophene-ols as the polarity of the solvent decreases would be anticipated on the basis of the expected greater solubility of the enol structure in polar solvents, and the dependence of the equilibrium constant on the ratio of the solubilities of the two tautomers in a given solvent.[22]

Experimental[23]

3-Phenyl-1,2-dithia-3-cyclopentene-5-one.—Synthesized[3] in 47% yield; m.p. from methanol 116.0–116.8°. Extraction of the sulfur–ethyl cinnamate reaction product with acetone followed by ethanol resulted in higher yields than did the original procedure, and obviated the somewhat unpleasant series of boiling acetic acid extractions.

***cis*-4-Keto-6-phenyl-3,7-dithia-5-nonenedioic Acid.**—To a solution of 25 g. of chloroacetic acid in 1.5 l. of water at 0° (the low temperature minimizes hydrolysis) was added an equimolar quantity of sodium carbonate. A solution of 170 g. of cyclic disulfide in 484 g. of molten sodium sulfide nonahydrate was added to the ice-cold sodium chloroacetate solution immediately after the latter's preparation. Unreacted disulfide was precipitated during the addition and was collected by filtration. The filtrate was acidified with 1:1 hydrochloric acid (congo red) and the resultant oil crystallized after standing for 3 days. The procedure was repeated with two 165-g. portions of disulfide and with the recovered disulfide which precipitated from these three runs; the weight of combined product was 450 g. (56% based on 500 g. of disulfide), m.p. 155–156°; a sample recrystallized from acetic acid as colorless needles, m.p. 156.5–157.0°.

5-Phenyl-3-thiophene-ol Acetate.—A mixture of 200 g. of the nonenedioic acid and 200 g. of anhydrous sodium acetate was heated in 600 ml. of acetic anhydride for 4 hours on a water-bath. Most of the excess acetic anhydride was removed and 3 l. of ice and water was added. After standing overnight, the dark brown precipitate was filtered, washed with water, and extracted repeatedly with 200-ml. portions of petroleum ether (90–120°) at room temperature until no more material was being extracted. The combined extracts yielded 112 g. (90%) of faintly yellow material melting at 72–75°.

5-Phenyl-3-thiophene-ol (II).—A mixture of 5 g. of 3-acetoxy-5-phenylthiophene in 200 ml. of ethanol and 10 ml. of 10% sodium hydroxide solution was warmed for several minutes until the addition of a drop of it to water no longer produced turbidity. Ice-water was added to the reaction mixture and it was acidified with dilute hydrochloric acid. A pink precipitate formed on standing and was recrystallized from petroleum ether (40–60°) to yield 2.4 g. (59%) of pale yellow II, m.p. 78°.

2-(1-Cyclohexenyl)-thiophene (IV).—(a) Prepared by the method of Fieser and Szmuszkovicz[4] in 80% yield; b.p. 107–108° (7 mm.)[24]; (b) 117.8 g. (1.2 moles) of cyclohexanone in 200 ml. of ether was added rapidly to a stirred ethereal solution of 2-lithiothiophene, prepared from 101 g. of thiophene,[25] cooled in a Dry Ice–acetone-bath. After standing overnight at room temperature, the reaction mixture was again cooled, and was hydrolyzed with cold hydrochloric acid. The organic layer was washed with water, dried, and fractionated to give 94.2 g. (43%) of IV boiling at 117–120° (5 mm.) and 43 g. of unreacted thiophene.

2-Phenylthiophene (V).—In a typical run, a mixture of 120 g. of chloranil, 41 g. of IV and 150 ml. of benzene was refluxed for 24 hours. The product was filtered, and the filtrate was extracted with 50-ml. portions of 12% sodium hydroxide solution until the extracts were colorless. The benzene solution was washed with 100 ml. of water, dried and distilled. We obtained 29.5 g. (74%) of V, b.p. 109–110° (4 mm.), m.p. 35–36°. A sample was recrystallized from aqueous methanol; colorless plates, m.p. 37.0–37.5°. No marked variation in yield was observed with reaction times as short as 8 hours; the maximum yield in any run

(22) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 607 ff.

(23) Microanalyses were performed by Clark Microanalytical Laboratories, Urbana, Ill.; Microanalytical Laboratory, University of Pittsburgh, Pittsburgh, Pa.; Schwarzkopf Microanalytical Laboratory, Middle Village, N. Y.; W. Manser, Zürich.

(24) We wish to thank Dr. C. A. Hochwalt and the Monsanto Chemical Co. for a gift of thiophene.

(25) H. Gilman and D. A. Shirley, THIS JOURNAL, 71, 1870 (1949).

was 87%. On standing at room temperature the material gradually decomposed; it can be safely stored in stoppered bottles in the refrigerator.

2-Bromo-5-phenylthiophene.—(a) A solution of 45 g. of V, 49.5 g. of N-bromosuccinimide and 1 g. of benzoyl peroxide in 230 ml. of carbon tetrachloride was refluxed for 7.5 hours. The cooled mixture was filtered, the succinimide residue washed with solvent, and the filtrate extracted five times with 50-ml. portions of 10% sodium hydroxide solution and then twice with water. Removal of the carbon tetrachloride from the dried solution, and recrystallization of the resultant residue from aqueous methanol, yielded 56.5 g. (85%) of colorless platelets, m.p. 84.0–84.5°; recrystallization from ether raised the m.p. to 85.0–86.0°. The best yield obtained was 88%. (b) A solution of 83 g. of bromine in 500 ml. of carbon tetrachloride was added dropwise to a refluxing solution of 83 g. of V in 500 ml. of carbon tetrachloride. After 12 hours at room temperature the mixture was washed with sodium bicarbonate solution, dried over calcium chloride, and distilled. A 90% yield (114 g.) of pale yellow material melting at about 56° was obtained; recrystallization from methanol gave 105 g. (85%) of bromide, m.p. 85–86°, lit. m.p. 85–86°.[26]

5-Phenyl-2-thiophene-ol (I).—(a) The Grignard reagent was prepared from 23.9 g. of 2-bromo-5-phenylthiophene, 6.5 g. of magnesium and 18.5 g. of isopropyl bromide in 200 ml. of ether. An additional 10 g. of isopropyl bromide in 30 ml. of ether was added, the solution was refluxed for an hour, and oxygen was passed into the flask (closed system) which had been cooled in an ice–salt-bath, at such a rate that the temperature remained below 7.5°. During the course of one hour, 0.1 mole of oxygen was admitted to the reaction mixture; completion of the reaction was evidenced by an increase in pressure in the system. The flask was stoppered, stored overnight in an ice–salt mixture, and poured into a Dry Ice–dilute sulfuric acid mixture; some hydrogen sulfide was evolved during the hydrolysis, and a yellow solid separated. Benzene was added to the organic layer, the latter was extracted with three 50-ml. portions of cold 12% sodium hydroxide solution, and the dried solvent was then distilled. The residue was combined with the yellow solid previously obtained and recrystallized from benzene to yield 0.51 g. of V as yellow plates melting at 241–242°, reported m.p. 237°.[26] The alkaline extracts were acidified and extracted with ether, and the ethereal solution was extracted three times with sodium bicarbonate solution to remove 5-phenyl-2-thiophenecarboxylic acid; 0.57 g. of this compound, m.p. 186–187°, was obtained after clarification of its sodium salt with charcoal and recrystallization of the free acid from 50% aqueous acetic acid.[27] The ethereal solution was dried over Drierite in the cold under nitrogen and then freed of solvent. The residue was taken up in cold methanol, precipitation was effected by the addition of water, and the colorless crystals were collected by filtration in a dry-box filled with nitrogen; 5.40 g. (30%) of colorless plates, m.p. 81.5–81.8°.

Anal. Calcd. for $C_{10}H_8OS$: C, 68.2; H, 4.5. Found: C, 67.9; H, 4.6.

The thiophene-ol turned steel-gray on standing; it could be repurified conveniently by vacuum sublimation. It produced a dermatitis on the hands of two of the authors.

(b) To the solution of 2-phenyl-5-lithiothiophene prepared by adding 23.8 g. of V to 0.23 mole of *n*-butyllithium and 185 ml. of ether[28] was added 0.4 mole of an ether solution of cyclohexylmagnesium bromide (nitrogen). The solution was cooled in a Dry Ice–acetone-bath and oxygen was bubbled in at such a rate that the temperature did not rise above −20°. When the absorption of oxygen had ceased, the flask was stoppered and allowed to stand in a refrigerator for 18 hours. The product was filtered, and the filtrate was acidified with 60 ml. of cold hydrochloric acid, washed with 100 ml. of ice-water, and extracted with five 100-ml. portions of 12% sodium hydroxide solution. The alkaline extracts were washed thrice with 100 ml. of 1:1 ether–benzene and then acidified with 30 ml. of cold hydrochloric acid. The precipitate was quickly taken up in ether from which 7.8 g. (30%) of I was obtained, m.p. 81.2–81.6°.

When allylmagnesium bromide was substituted for the cyclohexyl Grignard reagent, the yield of I was 5%; *n*-butyllithium gave no I and 18% of V, m.p. 230.0–231.5°.

Determination of the Coupling Step during the Formation of I.—The Grignard reagent from 6.0 g. of 2-bromo-5-phenylthiophene and 5.0 g. of cyclohexyl bromide was divided into halves. One part was poured over Dry Ice; the other half was oxygenated. The carbonation reaction product was hydrolyzed with cold, dilute hydrochloric acid and extracted with sodium carbonate solution. After acidification and recrystallization from ether, 1.3 g. (61%) of 2-phenylthiophene-5-carboxylic acid was obtained. No coupled product could be isolated. The oxidized aliquot was worked up as outlined previously and yielded 0.2 g. (10%) of VI and 0.06 g. of VII.

I from III.—A solution of 46.7 g. of phosphorus pentasulfide in 275 g. of hot pyridine was added to a solution of 35.6 g. of III in 100 g. of pyridine and 400 ml. of chloroform through which nitrogen was being bubbled, and the mixture was refluxed for 80 minutes. A mixture of 466 ml. of hydrochloric acid and ice was added, the aqueous layer was decanted and extracted with five 300-ml. portions of chloroform, and the combined extracts and organic phase were extracted repeatedly with 6% sodium hydroxide solution. The alkaline extracts were cooled in Dry Ice and acidified with cold hydrochloric acid, and the precipitate was collected. Recrystallization (nitrogen atmosphere) from ether and from petroleum ether (equal parts of 40–60° and 70–90° ligroin) gave 7.85 g. (22%) of I, m.p. 80–81°.

Unless oxygen is rigorously excluded from the reaction mixture, VII is the principal, or sole, product obtained.

3-Methoxy-5-phenylthiophene.—Three milliliters of dimethyl sulfate was added dropwise over a period of one hour to a stirred solution of 5 g. of II and 1.6 g. of potassium hydroxide in 20 ml. of water maintained at 0° and in a nitrogen atmosphere. The solution was then refluxed for 20 minutes, the aqueous phase was separated and extracted twice with ether, and the combined organic material was dried over Drierite. Distillation gave 3.15 g. (60%) of methyl ether, b.p. 128–134° (3 mm.). A sample for analysis was redistilled twice, b.p. 141–142° (3 mm.). The ether tends to discolor on standing.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.5; H, 5.3; S, 16.8. Found: C, 69.9; H, 5.5; S, 16.8.

2-Phenyl-4-benzal-5-keto-3,4-dihydrothiophene.—To a solution of 0.85 g. of I, 0.70 g. of benzaldehyde and 25 ml. of methanol was added hydrochloric acid dropwise until a faint turbidity was observed. The mixture was allowed to stand at room temperature for 3 hours, the solvent was removed, and the orange residue, after recrystallization from petroleum ether, melted at 64.5–65.0°.

Anal. Calcd. for $C_{17}H_{12}OS$: C, 77.0; H, 4.6. Found: C, 77.0; H, 4.8.

5-Phenyl-2-thiophene-ol Acetate.[29]—(a) A mixture of 1 g. of I, 6 ml. of acetic anhydride, 1 g. of zinc dust, and 2 drops of benzyltrimethylammonium hydroxide[30] was refluxed until the colored material disappeared. Three drops of acetic acid was added, the mixture was filtered into a flask containing 1 ml. of boiling acetic acid, and water was added dropwise to hydrolyze the acetic anhydride. The cooled solution was extracted with ether, dried, decolorized with Darco, and concentrated until crystallization occurred. A 77% yield (0.95 g.) of crude ester, m.p. 45–51°, was obtained. Vacuum sublimation produced colorless needles, m.p. 55–57°.

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.0; H, 4.6; S, 14.7. Found: C, 66.2; H, 4.7; S, 14.4.

2-Methoxy-5-phenylthiophene.—To a stirred solution at 0° of 8.8 g. of I and 2.1 g. of sodium hydroxide in 50 ml. of water was added 6.3 g. of dimethyl sulfate. The reaction mixture, which was under nitrogen, was allowed to stand at room temperature for 24 hours and was then extracted with ether. The ethereal solution was washed twice with 20-ml. portions of 12% sodium hydroxide and then with water, dried, clarified with Darco, and distilled. After three

(26) W. Steinkopf, H. Petersdorff and R. Gording, *Ann.*, **527**, 272 (1937).

(27) M.p. reported as 184–185° by W. Steinkopf and R. Gording, *Biochem. Z.*, **292**, 368 (1937).

(28) The position at which metalation occurred was determined by treating IV with phenyllithium and carbonating the solution; a 75% yield of 5-phenylthiophene-2-carboxylic acid was obtained.

(29) *Cf.* L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 399.

(30) We wish to thank the Rohm and Haas Co. for a gift of this material.

vacuum distillations, 3.7 g. (39%) of a pale yellow liquid, b.p. 135–136° (1 mm.), was obtained, $n^{25}D$ 1.6308.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.5; H, 5.3; S, 16.8. Found: C, 69.6; H, 5.5; S, 16.0.

Intractable tars resulted when compound I was treated with diazomethane solution. Etherification procedures wherein the lithium salt of I was treated with methyl iodide or dimethyl sulfate, or where the sodium salt was treated with methyl iodide, were unsuccessful.

The Reaction of Sulfur with Phenylbutene.—(a) To 500 g. of stirred molten sulfur was added dropwise 63 g. of 1-phenyl-1-butene, b.p. 67–69° (5 mm.).[31] The reaction vessel was maintained at a pressure of 270–330 mm., and 56 g. of an orange distillate was collected. Fractionation of this product yielded 39 g. of unreacted olefin, b.p. 45–48° (2 mm.); 1.75 g. of material of b.p. 48–80° (2 mm.); and a dark brown residue. Recrystallization of the second fraction from 85% ethanol produced 1.24 g. (1.6%) of V as colorless needles, m.p. 35–38°. (b) A mixture of 101 g. of 1-phenyl-1-butene and 70.5 g. of sulfur was heated at 195–200° for 13 hours. By distillation, 9.9 g. of a fraction boiling at 80–120° (3 mm.) was secured along with 14.3 g. of recovered olefin, b.p. 96–98° (2 mm.), m.p. 36–38°.

Attempted Nitrosation of I.—(a) Addition of a solution of I and sodium nitrite in aqueous ethanol to cold, dilute hydrochloric acid produced VII and a trace of yellow solid, m.p. 196–198°. (b) Addition of a solution of I and sodium nitrite in aqueous base to cold hydrochloric acid gave a dark-colored base-insoluble solid. (c) Nitrogen oxides and I gave intractable oils and VII. (d) Isoamyl nitrite was dropped into a solution of I in ether through which hydrogen chloride was bubbling. VII and tars were isolated.

The Conversion of I to VII by Atmospheric Oxygen.—In each case 10 ml. of solvent was added to 100 mg. of I in a 25-ml. erlenmeyer flask which was then loosely stoppered with cotton. The solvents were reagent grade or were purified prior to use, except for petroleum ether (40–60°) which was a practical grade and chloroform which was U.S.P. and contained a small amount of alcohol. Observations were made after 0.25, 3.5 and 18 hours. The benzene, carbon tetrachloride, carbon disulfide and petroleum ether solutions were purple when made up and showed no further change on standing for 18 hours. The dioxane, ether and chloroform solutions had acquired a reddish tinge when observed at the end of 3.5 hours, and were redder at the end of 18 hours; no precipitation was observed, and almost all of I could be recovered as such. The solution in absolute ethanol had deposited a slight precipitate at 3.5 hours and the solute had completely precipitated as VII at 18 hours. The 95% ethanol and methanol solutions contained small precipitates at the end of 0.25 hour, and precipitation was complete at 18 hours. (In the three preceding cases, the supernatant liquid was colorless at 18 hours.) A heavy precipitate was deposited almost immediately from pyridine solutions. A carbon disulfide solution of I is markedly dichroic: red by reflected light, purple by transmitted light. VII crystallized from dioxane as dark green needles, m.p. 304–305°. VII dissolves in concentrated sulfuric acid to form a brilliant green solution; dilute or concentrated solutions of alkalies readily decompose VII.

Anal. Calcd. for $C_{20}H_{12}O_2S_2$: C, 69.0; H, 3.4; S, 18.4. Found: C, 68.5; H, 3.3; S, 18.4.

Solutions in morpholine or piperidine gradually deposit colorless crystals which are sulfur-free. The product from morpholine melts at 103–104° dec.

Anal. Found: C, 49.5; H, 8.0.

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Pyridazine Derivatives. III.[1,2] Some 3,6-Disubstituted Pyridazines Having Neuromuscular Blocking Activity

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A series of pyridazines bearing basic substituents in positions 3 and 6, having the general structure I, was prepared for investigation as potential neuromuscular blocking agents. Several of the compounds reported, especially those having a three-carbon chain as A and A′ (in structure I), showed good potency with few side-effects.

Agents which selectively block neuromuscular transmission have found clinical use in conjunction with relatively light anesthesia during a variety of operations.[3] The pharmacology and chemistry of this group of drugs have been the subject of much investigation, as indicated in a number of reviews.[4–9] It has been shown that the activity of such compounds is closely associated with the presence of (at least) two quaternary groups situated about 15 Å. apart. There are two principal modes for depressing the activity of skeletal muscle; those producing competitive blocking resemble *d*-tubocurarine, and those which cause depolarization at the neuromuscular junction are similar to decamethonium salts. It was of interest to determine whether the bis-quaternary salts of certain 3,6-disubstituted pyridazines would have value as neuromuscular blocking agents without the side-effects resulting from lack of selectivity of action, as an influence on preganglionic autonomic transmission. A number of pyridazines having the general structure I was synthesized and salts (quaternary ammonium and acid-addition salts) prepared therefrom. Several representatives had high levels of neuromuscular blocking activity, with the

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