

cc, per hour and at a temperature of 345°. The dehydration was quantitative. The olefins were separated from the water, dried over sodium sulfate and distilled over metallic sodium. The position of the double bond in the dehydrated *t*-alkylcyclopentanol is being studied.

***t*-Butylcyclopentene.**—Boiling point by Cottrell<sup>4</sup> method, 139.6° at 760 mm.,  $dT/dP$  (770 to 730 mm.) = 0.048°/mm.,  $d^{20}_{vac}$  0.8021;  $d^{40}_{vac}$  0.7861;  $n^{20}_D$  1.4421;  $n^{20}_{H\beta}$  1.4486;  $n^{20}_{H\alpha}$  1.4397;  $\Delta^{20}$  (dispersion) 88.8;  $\delta^{20}$  (specific dispersion) 110.7. *Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>: C, 87.08; H, 12.92. Found: C, 87.35; H, 12.90.

***t*-Amylcyclopentene.**—B. p. 163–165° at 743 mm.,  $d^{20}_{vac}$  0.8256;  $n^{20}_D$  1.4554;  $n^{20}_{H\beta}$  1.4618;  $n^{20}_{H\alpha}$  1.4527;  $\Delta^{20}$  90.8;  $\delta^{20}$  110.0. *Anal.* Calcd. for C<sub>10</sub>H<sub>18</sub>: C, 86.86; H, 13.14. Found: C, 86.72; H, 13.27.

VI. ***t*-Alkylcyclopentane.**—This hydrocarbon was prepared by hydrogenating at 60° *t*-alkylcyclopentene in the presence of 10% by weight of nickel catalyst and 100 atmospheres of hydrogen. The hydrogenation proceeded to completion, for the final product was stable toward a nitrating mixture composed of 2 volumes of concentrated sulfuric acid and 1 volume of concentrated nitric acid.

***t*-Butylcyclopentane**, m. p. -96 ± 0.2°, boiling point by Cottrell method 145.2° at 760 mm.,  $dT/dP$  (770–730 mm.) = 0.052°/mm.,  $d^{20}_{vac}$  0.7911;  $d^{40}_{vac}$  0.7753;  $n^{20}_D$

(4) Cottrell, *This Journal*, **41**, 721 (1929); Braun and Hicks-Braun, *Bur. Standards J. Research*, **6**, 871 (1931).

1.4341;  $n^{20}_{H\beta}$  1.4396;  $n^{20}_{H\alpha}$  1.4320;  $\Delta^{20}$  76.4;  $\delta^{20}$  96.6. *Anal.* Calcd. for C<sub>9</sub>H<sub>18</sub>: C, 85.63; H, 14.37. Found: C, 85.75; H, 14.49.

***t*-Amylcyclopentane.**—Boiling point by Cottrell method 173.9° at 760 mm.,  $dT/dP$  (770–730 mm.) = 0.054°/mm.,  $d^{20}_{vac}$  0.8071;  $d^{40}_{vac}$  0.7923;  $n^{20}_D$  1.4457;  $n^{20}_{H\beta}$  1.4511;  $n^{20}_{H\alpha}$  1.4433;  $\Delta^{20}$  78.0;  $\delta^{20}$  96.6. *Anal.* Calcd. for C<sub>10</sub>H<sub>20</sub>: C, 85.63; H, 14.37. Found: C, 85.63; H, 14.25.

**Acknowledgment.**—The authors wish to express their thanks to Mr. M. Savoyias for the assistance he rendered, to Mr. R. W. Moehl for the analyses and to Mr. R. C. Wackler for the refractometric measurements.

### Summary

Synthesis of *t*-butyl- and *t*-amylcyclopentane from *p*-*t*-butyl- and *p*-*t*-amylphenols is described.

The following compounds and their derivatives were synthesized for the first time: 4-*t*-amylcyclohexanol,  $\beta$ -*t*-butyl- and  $\beta$ -*t*-amyladipic acid, 3-*t*-butyl- and 3-*t*-amylcyclopentanone, 3-*t*-butyl- and 3-*t*-amylcyclopentanol, *t*-butyl- and *t*-amylcyclopentene, *t*-butyl- and *t*-amylcyclopentane.

RIVERSIDE, ILLINOIS

RECEIVED JULY 19, 1939

[CONTRIBUTION No. 174 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

## Utilization of Alkoxy Ketones in the Synthesis of Quinolines by the Pfitzinger Reaction

BY LOY B. CROSS<sup>1,2</sup> WITH HENRY R. HENZE

Although the utilization of simple aldehydes and ketones in the synthesis of quinoline acids has received considerable attention, but little effort has been made to use bifunctional carbonyl compounds in this manner. Indeed, Henze<sup>3</sup> has reported the initial investigation in which keto ethers were employed in the Pfitzinger reaction, namely, the preparation of four 3-aryloxy-4-quinaldinecarboxylic acids from the appropriate aryloxyacetones.

Our study of the utilization of keto ethers in the Pfitzinger reaction has been extended to include alkoxy ketones and the condensation of ethoxyacetone and ethoxymethyl ethyl ketone with isatin to produce the corresponding 2-alkyl-3-ethoxycinchoninic acids. However, no evidence has been obtained of the formation of any of the isomeric 2-ethoxyalkylcinchoninic

acids.<sup>4</sup> The substituted cinchoninic acids are readily decarboxylated by heating at the temperature of their melting points to form 2-alkyl-3-ethoxyquinolines. Also, these 3-alkoxycinchoninic acids are cleaved at the ether linkage by heating with concentrated hydrochloric acid under pressure. The cinchoninic acids and the 2-alkyl-3-ethoxyquinolines are both extremely resistant to reduction by means of hydriodic acid and red phosphorus and no hydrogenation of the pyridine nucleus was observed. However, 2-ethyl-3-hydroxyquinoline was converted, by means of the reducing action of tin and hydrochloric acid, into 2-ethyl-1,2,3,4-tetrahydroquinoline. An attempt was made to form the phthalone of 3-ethoxyquinaldinic acid by heating with phthalic anhydride. Although the temperature employed was approxi-

(1) From the Ph.D. dissertation of Loy B. Cross, June, 1938.

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(3) Calaway with Henze, *This Journal*, **61**, 1355 (1939).

(4) Methyl ethyl ketone reacts with isatin in alkaline solution to form both 2,3-dimethylcinchoninic acid [Pfitzinger, *J. prakt. Chem.*, **56**, 283 (1897)] and 2-ethylcinchoninic acid [von Braun, Gmelin and Schultheiss, *Ber.*, **56**, 1344 (1923)].

mately fifty degrees below that of the melting point of the quinoline acid, the product of the reaction proved to be the phthalone of 3-hydroxyquinaldine. The latter was obtained also by phthalonation of 3-hydroxyquinaldine.

### Experimental

**Preparation of Alkoxy Ketones.**—Ethoxyacetone was prepared in 65% yield by interaction of 0.9 mole of ethoxyacetone nitrile (76.5 g.) and the Grignard reagent produced from one gram atom of magnesium and 1.1 moles of methyl iodide; b. p. 34–36° (corr.) (28 mm.);  $n_D^{20}$  1.4000;  $d_4^{20}$  0.9117; *MR* calcd., 26.94; *MR* found, 27.16.

**Ethoxymethyl ethyl ketone** was prepared in the same manner in 51% yield; b. p. 53–54° (corr.) (24–25 mm.);  $n_D^{20}$  1.4065;  $d_4^{20}$  0.9064; *MR* calcd., 31.56; *MR* found, 31.52.

**Preparation of 3-Ethoxycinchoninic Acids.**—Forty-six grams of isatin (0.313 mole) was dissolved in 200 g. of 33% potassium hydroxide solution, 32 g. of ethoxyacetone (0.314 mole) was added and the mixture was heated under a reflux condenser for twenty-four hours on a steam-bath. The mixture was diluted with water to about 750 cc., decolorized with Norite, cooled with ice, and acidified with a slight excess of acetic acid. The solid which separated was filtered, washed and dried; weight 32 g. (44% yield). After recrystallization from hot water, 3-ethoxy-4-quinaldinecarboxylic acid melts at 243° (corr.) with decomposition.

*Anal.* Calcd. for  $C_{13}H_{13}NO_3$ : C, 67.50; H, 5.67; N, 6.05; neut. equiv., 231.2. Found: C, 67.35; H, 5.67; N, 6.24; neut. equiv., 227.9.

From 60.0 g. of isatin (0.408 mole), dissolved in 300 g. of 33% potassium hydroxide solution, and 52 g. of ethoxymethyl ethyl ketone under the same conditions was obtained 93 g. (92% yield) of crude 2-ethyl-3-ethoxycinchoninic acid melting at 168–177°. After recrystallization from hot water, colorless needles were obtained melting at 199–201° (corr.) with decomposition.

*Anal.* Calcd. for  $C_{14}H_{15}NO_3$ : C, 68.5; H, 6.17; N, 5.71; neut. equiv., 245.3. Found: C, 68.22; H, 6.32; N, 5.69; neut. equiv., 244.8.

In preparing 2-ethyl-3-ethoxy-6-methylcinchoninic acid, 15 g. of 33% potassium hydroxide solution was used to dissolve 3.28 g. of 5-methylisatin (0.0223 mole) and, after adding 2.6 g. of ethoxymethyl ethyl ketone, the mixture was heated for ten hours under reflux on a steam-bath. The yield of crude product was 3.25 g. (56% of the theoretical). Purification was achieved by solution in 0.3 *N* sodium hydroxide, decolorization with Norite and reprecipitation with 0.3 *N* hydrochloric acid. Thus was obtained 2.25 g. (39% yield) of acid melting at 222° (corr.) with decomposition.

*Anal.* Calcd. for  $C_{15}H_{17}NO_3$ : C, 69.47; H, 6.55; N, 5.40; neut. equiv., 259.3. Found: C, 69.26; H, 6.55; N, 5.41; neut. equiv., 258.7.

**Decarboxylation of 3-Ethoxy-2-alkylcinchoninic Acids.**—Thirty grams of 3-ethoxy-4-quinaldinecarboxylic acid (0.13 mole) was heated in a 125-cc. Claisen distilling flask at 250°. The solid melted and then carbon dioxide was

evolved. After heating for thirty minutes, the residual liquid was distilled at 140–141° (corr.) (2–3 mm.); the colorless material, weighing 14.5 g. (59% yield), solidified in the receiver. This product, 3-ethoxyquinaldine,<sup>5</sup> melts at 68–69° (corr.).

*Anal.* Calcd. for  $C_{12}H_{13}NO$ : C, 76.97; H, 7.00; N, 7.49. Found: C, 76.62; H, 6.94; N, 7.21.

In a similar manner, 2-ethyl-3-ethoxyquinoline was obtained by heating 7 g. of 2-ethyl-3-ethoxycinchoninic acid (0.0286 mole) at 210° which gave a colorless liquid, distilling at 138–140° (corr.) (3–4 mm.) and solidifying in the receiver. The yield of solid melting at 58.5° (corr.) was 2.7 g., corresponding to 47% of the theoretical.

*Anal.* Calcd. for  $C_{13}H_{15}NO$ : C, 77.61; H, 7.51; N, 6.97. Found: C, 77.74; H, 7.60; N, 6.98.

**Cleavage of 3-Ethoxy-4-quinaldinecarboxylic Acid with Concd. Hydrochloric Acid.**—Two grams of 3-ethoxy-4-quinaldinecarboxylic acid was heated with concd. hydrochloric acid in a sealed tube for two hours at 150°. The cooled reaction mixture was neutralized with sodium hydroxide, producing a chrome-yellow precipitate which was purified by solution in alkali and reprecipitation with acid, producing 1.25 g. of material melting at 242–244° (corr.) with decomposition. The product was shown to be 3-hydroxy-4-quinaldinecarboxylic acid.<sup>6</sup>

*Anal.* Calcd. for  $C_{11}H_9NO_3$ : C, 65.03; H, 4.52; N, 6.89. Found: C, 65.75; H, 4.67; N, 6.82.

**Cleavage of 2-Alkyl-3-ethoxyquinolines with Concd. Hydrochloric Acid.**—Eleven and one-half grams of 3-ethoxyquinaldine and 50 cc. of concd. hydrochloric acid were heated together in a sealed tube for three hours at 180°. The reaction mixture was diluted with a little water and the acid was neutralized with sodium hydroxide. The white solid which separated was filtered, dissolved in dilute alkali and reprecipitated with acid; after drying at 110° the product weighed 8 g. (81.5% yield). When heated, 3-hydroxyquinaldine darkens at about 250° and melts at 260° (corr.).<sup>7</sup>

*Anal.* Calcd. for  $C_{10}H_9NO$ : C, 75.49; H, 5.66; N, 8.80. Found: C, 75.50; H, 5.73; N, 8.68.

In a similar manner, 1 g. of 2-ethyl-3-ethoxyquinoline was heated with 10 cc. of concd. hydrochloric acid in a sealed tube for five hours at 200°. Upon dilution of the reaction mixture with a little water a white crystalline solid separated. The latter was dissolved in alkali and reprecipitated by addition of acetic acid. The yield of 2-ethyl-3-hydroxyquinoline, of melting point 206–208° (corr.) with decomposition, thus obtained was 0.8 g. (93% of the theoretical).

*Anal.* Calcd. for  $C_{11}H_{11}NO$ : C, 76.26; H, 6.41; N, 8.09. Found: C, 75.57; H, 6.57; N, 8.22.

(5) Koenigs and Stockhausen, *Ber.*, **35**, 2556 (1902), report its preparation by the interaction of ethyl iodide and an alcoholic potassium hydroxide solution of 3-hydroxyquinaldine and its m. p. 69–70° (corr.).

(6) The synthesis of this compound, from isatic acid and halogenated acetone, has been reported recently [French patent 784,365, July 22, 1935, through *C. A.*, **30**, 111 (1936)] but no data concerning physical properties were recorded.

(7) Koenigs and Stockhausen, ref. 5, report that 3-hydroxyquinaldine, prepared by condensation of *o*-aminobenzaldehyde and chloroacetone in dilute aqueous sodium hydroxide solution, darkens at 240° (corr.) and melts at 260° (corr.).

**Action of Hydriodic Acid and Red Phosphorus on 3-Ethoxyquinolines.**—Two grams of 3-ethoxyquinaldine, 1.7 g. of red phosphorus and 20 cc. of hydriodic acid (sp. gr. 1.7) were heated together under reflux for seven days at 150°. The phosphorus was removed from the hot mixture by filtration through asbestos and the filtrate subjected to steam distillation to remove most of the hydrogen iodide. The residual solution was made basic with sodium hydroxide, cooled, extracted with ether, and the ether extract dried over sodium sulfate. The aqueous layer was acidified with acetic acid, causing a white solid to separate. The precipitate was filtered, washed with water and dried yielding material melting at 251–256°. The melting point of a mixture with an authentic sample of 3-hydroxyquinaldine was 253–257°.

*Anal.* Calcd. for  $C_{10}H_9NO$ : N, 8.80. Found: N, 8.68.

The ether extract was concentrated on a steam-bath, diluted with alcohol and treated with an alcoholic solution of picric acid. The solution was warmed, diluted with water to faint turbidity and cooled in ice. The bright yellow, crystalline precipitate was recrystallized from dilute alcohol; m. p. 192–194° (corr.).<sup>8</sup>

*Anal.* Calcd. for  $C_{16}H_{12}N_4O_7$ : N, 15.05. Found: N, 14.92.

In a similar manner, 6.6 g. of 2-ethyl-3-ethoxyquinoline, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) were heated together under reflux, but for only twenty-four hours at 140–150°. After removal of the unreacted phosphorus, there separated 3 g. of a cream colored solid which contained iodine and melted at 193–198° (corr.). The melting point of a mixture with an authentic sample of the hydroiodide of 2-ethyl-3-ethoxyquinoline was 190–197° (corr.).

The filtrate from the hydroiodide yielded 1 g. of a white solid melting at 206–208° (corr.). Mixed with known 2-ethyl-3-hydroxyquinoline the melting point was 206–208° (corr.).

**Attempted Reduction of 2-Ethyl-3-ethoxycinchoninic Acid with Hydriodic Acid and Red Phosphorus.**—A mixture of 8.1 g. of 2-ethyl-3-ethoxycinchoninic acid, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) was heated under reflux at 125° for twenty-four hours. The hot reaction mixture was filtered from phosphorus and cooled, when 2 g. of a chrome-yellow solid separated. After solution in alkali and reprecipitation with acid the product melted at 208–209° (corr.) with decomposition. Additional material was obtained from the filtrate, giving a total yield of 4.5 g., corresponding to 63.5% of the theoretical, of 2-ethyl-3-hydroxycinchoninic acid.

*Anal.* Calcd. for  $C_{12}H_{11}NO_8$ : C, 66.33; H, 5.11; N, 6.45; neut. equiv., 217.2. Found: C, 66.26; H, 5.28; N, 6.67; neut. equiv., 207.6.

In a second attempt at reduction the mixture was refluxed at 140–150° for forty-eight hours with additions of hydriodic acid from time to time until a total volume of 50 cc. of acid had been added. A small amount of the hydroiodide of 2-ethyl-3-ethoxyquinoline, m. p. 190–197°, was obtained, but the chief product of the reaction was the bright yellow, crystalline 2-ethyl-3-hydroxycinchoninic acid.

(8) Pictet and Bunzl, *Ber.*, **22**, 1847 (1889), record that the picrate of quinaldine melts at 191° (corr.).

*Anal.* Calcd. for  $C_{12}H_{11}NO \cdot HI$ : I, 38.57. Found: I, 39.09.

**Phthalonation of Quinaldine Derivatives.**—An intimate mixture of 1 g. of 3-hydroxyquinaldine and 1 g. of phthalic anhydride was heated for three hours at 200°. The cooled reaction mixture was dissolved in concd. sulfuric acid and the solution poured over ice. The brown solid which formed was purified by crystallization from glacial acetic acid. The phthalone of 3-hydroxyquinaldine is a dark orange colored solid melting at 264–266° (corr.) with decomposition.

Likewise, an intimate mixture of 23 g. of 3-ethoxy-4-quinaldinecarboxylic acid (0.1 mole) and 15 g. of phthalic anhydride (0.1 mole) was heated for five hours at 200°. After recrystallization from glacial acetic acid, the reaction product melted at 264.5–265.5° (corr.) with decomposition. A mixture of this material with the phthalone of 3-hydroxyquinaldine melted at 264–265° (corr.) with decomposition. The yield of phthalone from the carboxylic acid was 10 g., or 34%.

*Anal.* Calcd. for  $C_{18}H_{11}NO_8$ : C, 74.73; H, 3.83; N, 4.84; mol. wt., 289.3. Found: C, 74.88; H, 4.30; N, 5.00; mol. wt. (Rast), 298.6.

**Reduction of 2-Ethyl-3-hydroxyquinoline.**—The reduction of this compound was accomplished in the same manner as that utilized by Reher<sup>9</sup> for the reduction of 2-ethylquinoline. After 23 g. of 2-ethyl-3-ethoxyquinoline (0.15 mole) had been heated with 125 cc. of concd. hydrochloric acid in a sealed tube for five hours at 175°, the solution was diluted with 150 cc. of concd. acid and treated with 77 g. of granulated tin (0.65 gram atom); the mixture was warmed intermittently on a steam-bath until all of the tin had dissolved. Then the solution was saturated with hydrogen sulfide, made basic with sodium hydroxide and subjected to steam distillation. A colorless oil in the distillate was extracted with ether, dried over sodium sulfate and the extract distilled *in vacuo*. The product, 2-ethyl-1,2,3,4-tetrahydroquinoline,<sup>10</sup> a colorless liquid boiling at 125–127° (corr.) (7 mm.), weighed 5 g. (21% yield);  $n_D^{20}$  1.5652;  $d_4^{20}$  1.0178; *MR* calcd., 51.89; *MR* found, 51.54.

*Anal.* Calcd. for  $C_{11}H_{15}N$ : C, 81.94; H, 9.38; N, 8.69. Found: C, 81.22; H, 9.33; N, 8.70.

A picrate was formed by the interaction of 2.5 g. of the reduction product and 3.5 g. of picric acid dissolved in 150 cc. of 75% alcohol. Five grams of bright yellow picrate was obtained (83% yield). After recrystallization from 95% alcohol, there was recovered 3.5 g. of the purified picrate of 2-ethyl-1,2,3,4-tetrahydroquinoline melting at 143–145° (corr.).

*Anal.* Calcd. for  $C_{17}H_{18}N_4O_7$ : N, 14.35. Found: N, 14.34.

## Summary

1. Pfitzinger's method has been extended to include the utilization of alkoxy ketones in the initial synthesis of three examples of a new type of substituted cinchoninic acid. The structure of

(9) Reher, *Ber.*, **19**, 2998 (1886).

(10) Reher, *ref.* 9, reported b. p. 259–263°.

one of these acids has been elucidated through a study of its degradation products.

2. 3-Ethoxycinchonic acids and 3-ethoxyquinolines resist reduction by means of concd. hydriodic acid and red phosphorus, but the

ether linkage is cleaved by this treatment.

3. Both 3-ethoxy-4-quinolinecarboxylic acid and 3-hydroxyquinaldine on phthalonation yield the same phthalone.

AUSTIN, TEXAS

RECEIVED AUGUST 14, 1939

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 200]

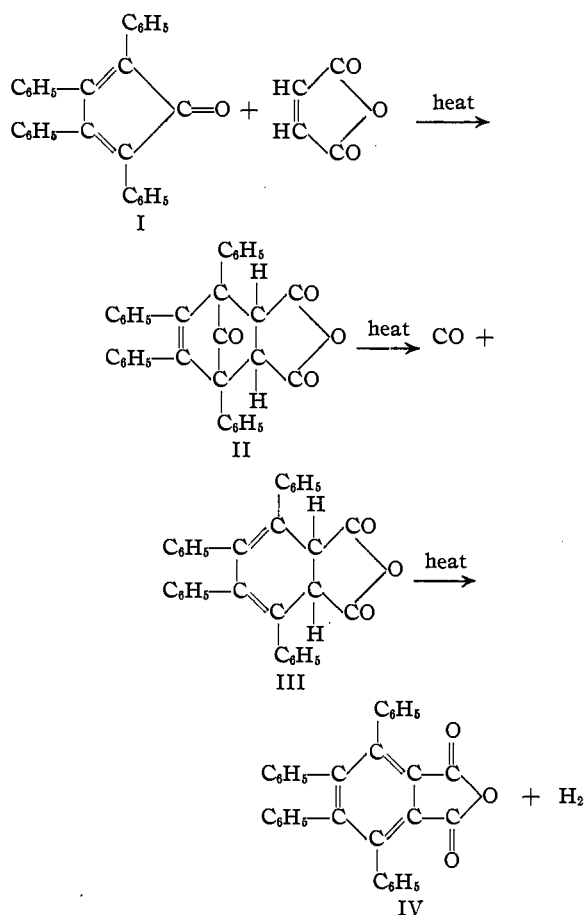
## The Reaction of a Thiophene Derivative with Maleic Anhydride

BY DANIEL B. CLAPP<sup>1</sup>

It has been shown by Dilthey and his collaborators<sup>2</sup> that diene syntheses may be carried out readily between various highly arylated cyclopentadienones and maleic anhydride or other ethylenic or acetylenic derivatives. A typical example is the reaction of 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone) (I) with maleic anhydride.<sup>2a</sup> The initial product of this reaction is 3,6-endocarbonyl-3,4,5,6-tetraphenyl-1,2-dihydrophthalic anhydride (II) which on heating successively loses carbon monoxide and hydrogen yielding tetraphenylphthalic anhydride (IV).

In the hope that the same product might be obtained in starting with the sulfur analog of tetracyclone, an attempt was made to bring about a reaction between tetraphenylthiophene (thionessal) and maleic anhydride. By analogy, if an adduct were formed, it might be expected to lose hydrogen sulfide. However, several attempts to carry out this reaction gave completely negative results.

Since it is well known that furan and many of its derivatives will take part readily in diene syntheses, undoubtedly attempts have been made to carry out such syntheses with corresponding thiophene derivatives. However, in a recent review of the Diels-Alder reaction<sup>3</sup> it is stated that no case of a thiophene derivative undergoing this reaction has been recorded. It is evident that the 1,4-conjugate system in thiophene compounds is less active than that present in furan derivatives, the former class being more aromatic in character and resembling benzene derivatives, none of which have been shown to undergo a Diels-Alder reaction. It may be noted that



Schomaker and Pauling<sup>4</sup> recently have shown that electron diffraction results, resonance energies, and other considerations indicate a greater degree of resonance stabilization for thiophene than for furan.

It is possible that the introduction of certain substituents into the thiophene nucleus might so activate the 1,4-system that a diene synthesis could occur. In the case of hydrindene, fixation

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(2) (a) *Ber.*, **66**, 1627 (1933); (b) *ibid.*, **67**, 495, 1959, 2004 (1934); (c) *ibid.*, **68**, 1159 (1935); (d) *ibid.*, **71**, 974 (1938).

(3) Delaby, *Bull. soc. chim.*, [5] **4**, 765 (1937).

(4) Schomaker and Pauling, *THIS JOURNAL*, **61**, 1769 (1939).