[CONTRIBUTION FROM THE INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

Cyclic Sulfones. IV.[1,2,3] Alkylation of 2,5-Diphenyl-3,4-dihydroxythiophene-1-dioxide with Methyl and Ethyl Iodide. An Extension of a Method for the Alkylation of Benzyl Sulfone

BY C. G. OVERBERGER AND JOHN M. HOYT

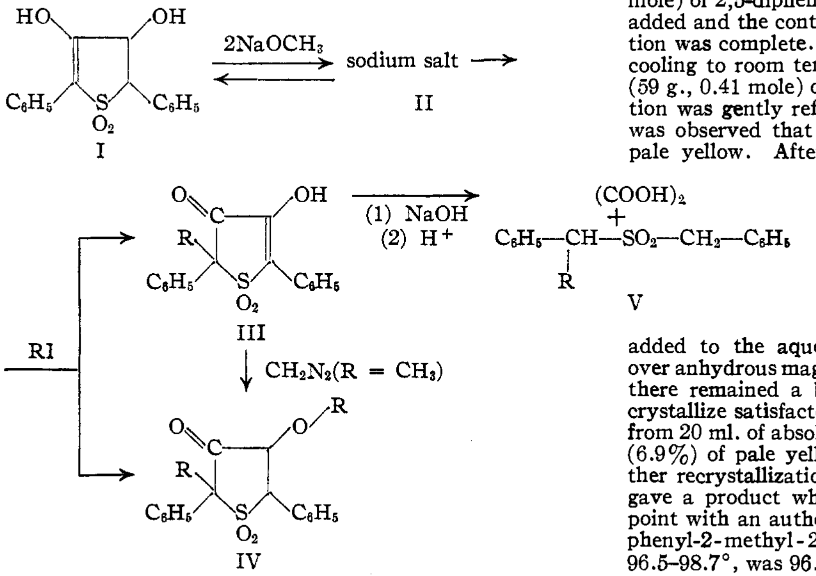
The reaction of methyl iodide with the sodium salt of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide gave largely 4-hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide, the structure of which was established and a small amount of 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide, which was previously characterized. The reaction with ethyl iodide gave analogous products.

A previous paper[2] reported the preparation and proof of structure of 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide by reaction of methyl sulfate with the sodium salt of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide. This paper reports the reaction of methyl iodide with the same sodium salt, and subsequent isolation and proof of structure of two products III and IV, 4-hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide and 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide, respectively. The ethyl analogs of III and IV are likewise described.

The reaction of III with base is an extension of the previously reported procedure[3] for the preparation of methylated diarylmethyl sulfones. The benzyl-α-phenylpropyl sulfone hydrolysis product from the ethyl analog of III has likewise been characterized.

Discussion

The reaction is indicated schematically.



When two equivalents of base were added to I and the product reacted with methyl iodide, two products resulted, 4-hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide (III, $R = CH_3$, 88%; $R = C_2H_5$, 75.6%) and 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide (IV, $R = CH_3$, 6.9%; $R = C_2H_5$, 9.0%).

The structure of III ($R = CH_3$) was demonstrated by formation of an acetate, a quinoxaline and conversion with alcoholic base to oxalic acid and benzyl-α-phenylethyl sulfone (V) in high yield (94.2%). A mixed melting point of this sulfone with an authentic sample[3] was not depressed. Reaction of III with diazomethane gave IV in 98% yield.

Reaction of III, $R = C_2H_5$, with alcoholic base gave benzyl-α-phenylpropyl sulfone in 96.4% yield. The structure of IV ($R = CH_3$) has previously been demonstrated.[3]

Experimental[4]

Methylation of the Sodium Salt of 2,5-Diphenyl-3,4-dihydroxythiophene-1-dioxide with Methyl Iodide. (A) 4-Methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide.—In a 250-ml. one-necked, round-bottomed flask fitted with an efficient reflux-condenser, was placed 60 ml. of methanol and 1.95 g. (0.085 g. atom) of freshly-cut sodium. When all the sodium had dissolved, 12.0 g. (0.04 mole) of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide was added and the contents of the flask were refluxed until solution was complete. To the resulting orange solution, after cooling to room temperature, there was then added 26 ml. (59 g., 0.41 mole) of redistilled methyl iodide, and the solution was gently refluxed for four hours. In this period, it was observed that the orange color eventually faded to a pale yellow. After standing overnight, the solution was concentrated to a volume of 25 ml. at reduced pressure. The residue was transferred to a separatory funnel with ether and 200 ml. of water. The layers were separated, and the aqueous layer was extracted with ether. The combined ether layers were washed with water and the water washings were added to the aqueous layer. The ether layer was dried over anhydrous magnesium sulfate. On removal of the ether there remained a brown, gummy material which did not crystallize satisfactorily. Recrystallization of this material from 20 ml. of absolute ethanol with charcoal yielded 0.91 g. (6.9%) of pale yellow needles, m.p. 91–97°. Several further recrystallizations from absolute ethanol with charcoal gave a product which melted at 96.7–99°, mixed melting point with an authentic sample of 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide,[3] m.p. 96.5–98.7°, was 96.5–98.8°.

(B) **4-Hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide.**—The yellow aqueous layer was acidified with 1:1 hydrochloric acid solution. The colorless, sticky precipitate which appeared was extracted with ether and the ether layer was dried with anhydrous magnesium sulfate. The solvent was carefully removed and the product dried to a constant weight in a vacuum desiccator, 11.0 g. (88%), m.p. 120–121°. Several recrystallizations from benzene–petroleum ether (60–68°) gave shining, white flakes which, after careful and thorough drying at room temperature, were analytically pure, m.p. 121–122°.

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[1] This is the fourth in a series of papers describing the chemistry of substituted thiophene dioxides.

[2] For the third paper in this series, see C. G. Overberger and John M. Hoyt, THIS JOURNAL, 73, 3305 (1951).

[3] A portion of this work was supported by a contract from the Office of Naval Research.

[4] All melting points are corrected unless otherwise noted.

Anal.[5] Calcd. for $C_{17}H_{14}SO_4$: C, 64.95; H, 4.49. Found: C, 65.25; H, 4.62.

Derivatives of 4-Hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide (A) Acetate.—The acetate was prepared according to the method of Shriner and Fuson.[6] From 1.0 g. (0.0033 mole) of 4-hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide, 0.5 g. of anhydrous sodium acetate, and 5 ml. of acetic anhydride, was obtained 1.0 g. (88%) of a pale yellow powder, m.p. 148.3–150.1°. A number of recrystallizations from benzene–petroleum ether (60–68°) yielded an analytical sample of fine, white needles, m.p. 149.1–150.3°.

Anal. Calcd. for $C_{19}H_{16}O_5S$: C, 64.03; H, 4.53. Found: C, 64.10; H, 4.44.

(B) **Quinoxaline.**—The quinoxaline was prepared according to the method of Hickinbottom.[7] From 0.5 g. (0.0016 mole) of 4-hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide and 0.18 g. (0.0017 mole) of recrystallized *o*-phenylenediamine in 5 ml. of methanol, was obtained, after refluxing for two hours, a dark brown solution. On standing several days this solution deposited a yellow powder. A number of additional crops were obtained by concentrating the filtrate. The total yield was 0.19 g. (29%), m.p. 206–207° uncor. An analytical sample was prepared by recrystallizing the crude material several times from methanol, m.p. 206–208° uncor. The quinoxaline melted, but the resulting yellow liquid quickly blackened and eventually decomposed about 5° above the melting point. The characteristic quinoxaline color test with concentrated sulfuric acid was obtained with this compound, the color observed being dark red.

Anal. Calcd. for $C_{23}H_{18}O_2SN_2$: N, 7.25. Found: N, 7.46.

The Reaction of 4-Hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide with Diazomethane.—In a 250-ml. erlenmeyer flask was placed 2.0 g. (0.0064 mole) of 4-hydroxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide in 40 ml. of ether. To the solution cooled in an ice-bath was added diazomethane in ether solution, prepared from 2.4 g. of nitrosomethylurea.[8]

After standing three hours the solvent was removed by distillation from a water-bath in a good hood. The yellow, viscous residue was induced to crystallize by the addition of 1–2 ml. of absolute ethanol and scratching with a glass rod. Upon drying this crystalline product in a vacuum desiccator, there remained 2.04 g. (98%) of a pale yellow powder, m.p. 83.5–88°. Two recrystallizations from absolute ethanol yielded pale, yellow needles, m.p. 97.7–99°. These crystals gave a mixed melting point of 96.8–99° with an authentic sample of 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide,[3] which melted at 96.5–98.7°.

Alkylation of 2,5-Diphenyl-3,4-dihydroxythiophene-1-dioxide with Ethyl Iodide.—The alkylation with ethyl iodide was carried out in a manner similar to that described for the alkylation with methyl iodide. From 6.00 g. (0.02 mole) of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide and sodium methoxide from 0.97 g. (0.042 g. atom) of freshly-cut sodium and 30 ml. of methanol there was obtained, on treatment with 31.2 g. (0.2 mole) of redistilled ethyl iodide, 1.48 g. of crude 4-ethoxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide, and 5.02 g. (76.5%) of crude 4-hydroxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide, m.p. 140.5–143°.

4-Ethoxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide.—Recrystallization of 1.48 g. of the crude diethylated derivative from ethanol with Norite gave 0.64 g. (9%) of product, m.p. 92–96°. Additional recrystallizations with Norite gave colorless needles which turned yellow on standing, m.p. 95–96°.

Anal. Calcd. for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66. Found: C, 67.81; H, 5.65.

4-Hydroxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide.—Several recrystallizations of the crude product described above from benzene yielded a white powder, m.p. 142.6–143.2°.

Anal. Calcd. for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91. Found: C, 66.02; H, 5.11.

Conversion of 4-Hydroxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide to Benzyl-α-phenylethyl Sulfone.—The decomposition of 4-hydroxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide was carried out in the manner already described for 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide.[3] The time required for the discharge of color in refluxing alcoholic sodium hydroxide solution was 40 minutes. The amount of benzyl-α-phenylethyl sulfone isolated was 2.45 g. (94.2%), m.p. 92.6–94.6°. After recrystallization from ethanol the product melted at 100–101°, mixed m.p. with an authentic sample of benzyl-α-phenylethyl sulfone[3] 100.1–101.3°.

By continuous extraction for three days with ether it was possible to isolate a sample of oxalic acid which afforded a di-*p*-toluidide, m.p. 266.5–268° uncor., mixed m.p. with an authentic sample, 266.5–268° uncor.

The total oxalic acid formed was 0.838 g. (93.2%), determined by titration with standard permanganate.

Conversion of 4-Hydroxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide to Benzyl-α-phenylpropyl Sulfone.—The alkaline decomposition was carried out as described above for the decomposition of the methyl analog. From 1.64 g. (0.005 mole) of 4-hydroxy-3-keto-2,5-diphenyl-2-ethyl-2,3-dihydrothiophene-1-dioxide in 50 ml. of 1 *M* solution of sodium hydroxide in 95% ethanol was obtained 1.32 g. (96.4%) of a white solid, m.p. 86–88°. Recrystallization from ethanol yielded an analytical sample, white needles, m.p. 87.5–88.9°.

Anal. Calcd. for $C_{10}H_{18}O_2S$: C, 70.04; H, 6.61. Found: C, 69.95; H, 6.44.

BROOKLYN, N. Y. RECEIVED FEBRUARY 26, 1951

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[5] Analyses by Drs. Weiler and Strauss, Oxford, England.

[6] Shriner and Fuson, "Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 165.

[7] Hickinbottom, "Reactions of Organic Compounds," 2nd edition, Longmans, Green and Co., London, 1948, p. 325.

[8] Arndt, "Organic Syntheses," Coll. Vol. II, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.