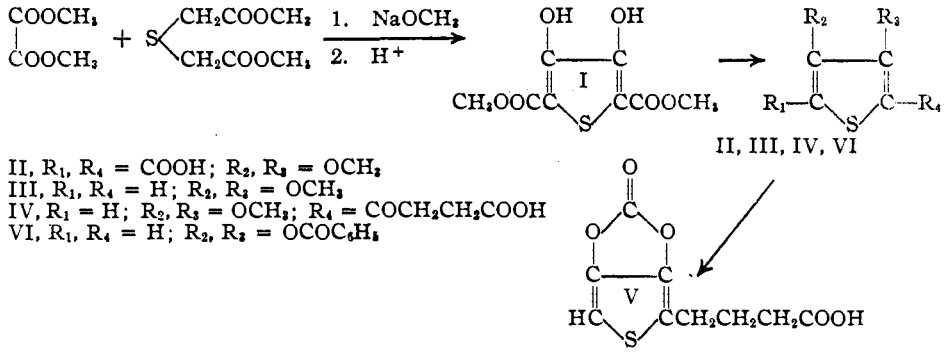
[CONTRIBUTION FROM THE STERLING CHEMICAL LABORATORY OF YALE UNIVERSITY]

Some Derivatives of 3,4-Dioxythiophene

BY EDWARD W. FAGER[1]

The work reported in this communication is the synthesis of some 3,4-dioxythiophenes in an attempt to obtain the compound represented by V. It was thought that such a compound might have interesting effects on the growth of organisms requiring biotin. Karrer[2] has reported the synthesis of some 3,4-dioxythiophenes of similar structure by an entirely different procedure. Because of the press of war research, the steps from compound IV to compound V have not been exhaustively studied. The work done so far indicates that they present considerable difficulty.

The proposed synthesis is



II, R_1, R_4 = COOH; R_2, R_3 = OCH_3
III, R_1, R_4 = H; R_2, R_3 = OCH_3
IV, R_1 = H; R_2, R_3 = OCH_3; R_4 = $COCH_2CH_2COOH$
VI, R_1, R_4 = H; R_2, R_3 = $OCOC_6H_5$

The condensation of diethyl oxalate and dimethyl thiodiglycollate by sodium methylate has been reported by Hinsberg[3] to give compound I. Following Hinsberg's directions the author obtained a material melting at 175–178° and giving an analysis intermediate between that calculated for the dimethyl ester and that for the diethyl ester. When dimethyl oxalate was used, this difficulty was removed and pure compound I was obtained in good yield.

Investigation of the methylation of compound I revealed that only very vigorous conditions led to reaction. It was found possible to proceed directly to compound II without the isolation and purification of intermediates. The decarboxylation of compound II proceeded smoothly when the copper–chromium oxide catalyst of Adkins[4] was used in quinoline. Demethylation of compound III was effected smoothly only through the use of anhydrous aluminum chloride. All attempts at the use of acids in various solvents led to extensive decomposition. The parent compound, 3,4-dioxythiophene, was not isolated due to its excessive instability toward oxygen. However, an alkaline solution of this compound, protected by nitrogen, reacted with benzoyl chloride to give the stable dibenzoate. The following methods were tried in extensive attempts to reduce compound IV: the Clemmensen reduction in various modifications,[5] sodium amalgam in both acidic and basic solutions and the Wolff–Kishner method. All methods tried resulted in the production of inorganic sulfide in quantity. In no case was any reduction product isolated.

Experimental

3,4-Dimethoxy-2,5-dicarboxythiophene (II).—A solution of 105 g. of sodium metal in one liter of absolute methanol was cooled to 5°. A solution of 267 g. of dimethyl thiodiglycollate and 267 g. of dimethyl oxalate in 750 cc. of absolute methanol was added dropwise to the stirred methylate solution. The temperature was kept below 30° by external cooling. The disodium salt of compound I precipitated as a pale yellow solid. Reaction was completed by warming the suspension to reflux for one hour. After cooling, the solid was filtered off and air dried. The powdered dry salt was heated for thirty minutes at 100° with 1134 g. of freshly distilled dimethyl sulfate. After removal of excess dimethyl sulfate, the solid was refluxed for thirty minutes with 750 cc. of 6 *N* sodium hydroxide. The product, isolated by acidification of the alkaline solution, weighed 205 g. This is 58.8% of the theoretical yield based on the weight of dimethyl thiodiglycollate used. This material was pure enough to be used directly for decarboxylation. Crystallization from water gave a white powder. It decomposed above 250° without melting.

Anal. Calcd. for $C_8H_8O_6S$: S, 13.79; neut. equiv., 116. Found: S, 13.75, 13.91; neut. equiv., 118, 117.

Dimethyl Ester of 3,4-Dioxy-2,5-dicarboxythiophene (I).—This compound was isolated by adding its disodium salt to dilute sulfuric acid. Crystallization from methanol gave a white solid; m. p. 180–180.5°.

Anal. Calcd. for $C_8H_8O_6S$: C, 41.40; H, 3.45; S, 13.79. Found: C, 41.39; H, 3.55; S, 13.76. This compound gives a deep green color with ferric chloride in aqueous ethanol.

3,4-Dimethoxythiophene (III).—A suspension of 16.5 g. of 3,4-dimethoxy-2,5-dicarboxythiophene (II) and 2 g. of copper–chromium oxide catalyst[4] in 50 cc. of quinoline was heated under nitrogen for thirty minutes in an oil-bath at 180°. The reaction mixture was cooled, diluted with

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(2) Karrer, *Helv. Chim. Acta*, **27**, 142, 237 (1944).

(3) Hinsberg, *Ber.*, **43**, 901 (1910).

(4) Adkins, Connor and Folkers, THIS JOURNAL, **54**, 1139 (1932).

(5) Fieser and Kennelly, *ibid.*, **57**, 1611 (1935); "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 155.

200 cc. of ether and filtered to remove the suspended catalyst. The ether solution was washed repeatedly with dilute hydrochloric acid, with dilute sodium hydroxide, and with water. Removal of ether left an oil which distilled at 108–115° under a pressure of 12 mm. The yield was 5.9 g., 58% of the theoretical. This material gave no color with ferric chloride in aqueous ethanol.

Dibenzoate of 3,4-Dioxythiophene (VI).—All operations were performed under an atmosphere of nitrogen to reduce oxidation of the intermediate 3,4-dioxythiophene. A solution of 0.8 g. of 3,4-dimethoxythiophene (III) in 5 cc. of dry benzene was heated for twenty minutes at 60° with 1.6 g. of anhydrous aluminum chloride. The resulting dark-colored suspension was poured onto ice and dilute hydrochloric acid. The acid solution was extracted with ether and the hydroxythiophene was extracted from the ether–benzene solution with sodium hydroxide. Treatment of the alkaline solution with a slight excess of benzoyl chloride gave VI. The dibenzoate was crystallized from dilute ethanol; m. p. 109.5–110°. This compound gives no color with aqueous ferric chloride.

Anal. Calcd. for $C_{18}H_{12}O_4S$: S, 9.88. Found: S, 9.94.

(3,4-Dimethoxy Thienoyl)-propionic Acid (IV).—A solution of 12.45 g. of 3,4-dimethoxythiophene (III) in 200 cc. of dry thiophene-free benzene was cooled to 5° under an atmosphere of nitrogen. A solution of 13 g. of CH_3OCO-CH_2CH_2COCl and 10.15 cc. of anhydrous stannic chloride in 75 cc. of dry thiophene-free benzene was added dropwise to the stirred solution of the thiophene. After one and one-half hour's stirring at 5°, the material was poured onto ice and dilute hydrochloric acid. The benzene layer was separated and the water layer was extracted several times with ether. After removal of the solvents, a small amount of volatile side product was removed by heating to 150° under a pressure of 1 mm. The resulting residue was refluxed with 20 cc. of 6 *N* sodium hydroxide. After the alkaline solution had been extracted with ether to remove a small amount of alkali-insoluble oil, it was added dropwise to 20 cc. of 6 *N* hydrochloric acid. The cream-colored precipitate weighed 10.67 g. This is 50.5% of the theoretical yield based on the weight of 3,4-dimethoxythiophene used. Crystallization from water gave white needles; m. p. 134.5–135.5°. This compound gives no color with ferric chloride in aqueous ethanol.

Anal. Calcd. for $C_{10}H_{12}O_5S$: C, 49.20; H, 4.92; S, 13.12; neut. equiv., 244. Found: C, 48.77; H, 4.71; S, 12.92; neut. equiv., 244, 246.

Summary

Some derivatives of 3,4-dioxythiophene have been prepared during investigation of methods of synthesis of compounds structurally related to biotin.

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Synthesis of *dl*-Methionine

BY J. E. LIVAK, E. C. BRITTON, J. C. VANDERWEELE AND M. F. MURRAY

The recently described syntheses of methionine by Booth, Burnop and Jones[1] and by Albertson and Tullar[2] suffer from the disadvantage of employing the strong vesicant β-chloroethylmethyl sulfide. The method of Hill and Robson,[3] employing α-amino-γ-butyrolactone, and the later modification reported by Snyder and co-workers,[4,5] are excellent laboratory procedures but possess certain operational disadvantages. It has now been found that the convenient synthesis of *dl*-methionine on a large scale can be realized by utilization of the readily available γ-butyrolactone.[6] Bromination of γ-butyrolactone gives α,γ-dibromobutyric acid which, on distillation or treatment with cold alkali, loses hydrogen bromide to give α-bromo-γ-butyrolactone in good yield. The chlorination of γ-butyrolactone was also studied but it was found that conversion of the α,γ-dichlorobutyric acid to γ-chlorobutyrolactone was not as convenient as through the brominated derivatives. Elaboration on the chemistry of these halogenated lactones and acids will be the subject of a separate paper. Amination of the α-bromo-γ-butyrolactone easily gives α-amino-γ-butyrolactone, from which compound the synthesis of methionine can be realized by three different procedures: (1) by the benzoylation method of Hill and Robson,[3] (2) by the diketopiperazine method of Snyder and co-workers[4] and (3) by the sequence of reactions shown.

Because of the unstable nature of α-amino-γ-butyrolactone (I), described by Fischer and Blumenthal[7] as a colorless sirup, it was not isolated in the present work but was converted to crystalline derivatives. The product obtained in the amination of α-bromo-γ-butyrolactone was either isolated as α-amino-γ-hydroxybutyric acid (II) or treated with aqueous hydrobromic acid solution to give α-amino-γ-butyrolactone hydrobromide. Conversion of the hydrobromide to 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine[4,7] was effected by treatment with potassium acetate in alcohol solution, removal of potassium bromide by filtration and heating of the filtrate under reflux to effect conversion of the α-amino-γ-butyrolactone to 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine. Other neutralization agents, including sodium acetate, sodium formate and sodium methylate were used, but the yields of the diketopiperazine were consistently lower than those obtained with potassium acetate. An attempt to prepare the diketopiperazine directly from α-amino-γ-hydroxybutyric acid proved unsuccessful.

(1) Booth, Burnop and Jones, *J. Chem. Soc.*, 666–667 (1944).
(2) Albertson and Tullar, THIS JOURNAL, **67**, 502 (1945).
(3) Hill and Robson, *Biochem. J.*, **30**, 248 (1936).
(4) Snyder, Andreen, Cannon and Peters, THIS JOURNAL, **64**, 2082 (1942).
(5) Snyder and Cannon, *ibid.*, **66**, 511 (1944).
(6) The γ-butyrolactone was obtained from the Cliffs Dow Chemical Company.
(7) Fischer and Blumenthal, *Ber.*, **40**, 11 (1907).