ing about 0.02 g. of sodium hydrosulfite was added. The resulting solutions from ten such runs were combined, and adjusted to pH 12 with 50% sodium hydroxide. The mixture was extracted four times with 350-ml. portions of ether to remove nonphenolic materials (about 20–30% of the starting material was recovered). The aqueous phase was adjusted to pH 8.5 with ammonium chloride and extracted four times with 350-ml. portions of a 3:1 mixture of chloroform and isopropyl alcohol. Evaporation of the extract gave 8 g. of residue, which was fractionated by chromatography on 400 g. of Florisil to give 2.5 g. of crude product. Solvents used in the chromatographic separation were 2000 ml. of 75% (by volume) benzene–25% isopropyl alcohol, followed by 2200 ml. of 97% methanol–2% water–1% concentrated (28–30%) ammonium hydroxide. The crude products from four separations were combined and recrystallized twice from ethanol-water (the solid was dissolved in hot alcohol treated with Darco G-60 and water added until crystallization began) to give 5 g. of material, m.p. 198–201°. Three successive crystallizations from acetone gave a product with a constant specific rotation and melting point; yield, 2.8 g. (3.7% conversion, or about 5% after allowing for recovered starting material), m.p. 208.5–210.5°, $[\alpha]_D^{25}$ −117° (c 1.02, 95% USP ethanol).[7] Values previously reported[1] were $[\alpha]_D^{21}$ −140° (c 1.0), m.p. 196–198°.

6-Methylenedihydrodesoxycodeine (II). A sample of I was methylated with diazomethane in ether-methanol solution. The infrared absorption spectrum was identical to that of II prepared directly by the Wittig reaction,[1] $[\alpha]_D^{21}$ −124° (c 0.73, 95% USP ethanol), lit. $[\alpha]_D^{21}$ −123°.

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(7) The discrepancy in physical constants has been discovered independently by Prof. Henry Rapoport who reported in a private communication the values m.p. 207–209, $[\alpha]_D^{22}$ −115° (c, 0.9, ethanol).

Nitration of 1,1,1-Trichloro-2,2-bis(2-thienyl)ethane[1]

PRICE TRUITT

Received July 3, 1961

In the course of studying the physiological properties of compounds containing the nitro group, it was decided to prepare 1,1,1-trichloro-2,2-bis(5-nitro-2-thienyl)ethane (II) *via* the nitration of 1,1,1-trichloro-2,2-bis(2-thienyl)ethane (I). The nitration was carried out with a mixture of acetic acid, acetic anhydride, nitric acid, and 1,1,1-trichloro-2,2-bis(2-thienyl)ethane in a manner similar to that used for the nitration of thiophene.[2] When the temperature was carefully controlled and not allowed to rise above 10°, the expected product II was obtained as a white, crystalline material, m.p. 110–110.5°.

When the nitration temperature was allowed to rise to 20–30° a yellow oil was obtained. This oil crystalized readily when stirred with ethyl acetate and gave bright yellow crystals of III, m.p. 130–131°, which was subsequently identified as 1,1-dichloro-2,2-bis(5-nitro-2-thienyl)ethylene. Analysis of III indicated the composition $C_{10}H_4Cl_2N_2O_4S_2$. Attempts to convert II to III with alcoholic potassium hydroxide gave a tar; however, II was converted to III in excellent yield by heating an acetone solution of II with potassium permanganate. This procedure was used by Lorenz[3] to convert 1,1,1-trichloro-2,2-bis(4-nitrophenyl)ethane to 1,1-dichloro-2,2-bis(4-nitrophenyl)ethylene. 1,1,1-Trichloro-2,2-bis(2-thienyl)ethane (I) was not changed by refluxing in acetone with potassium permanganate for thirty-six hours.

Oxidation of III with chromic oxide in acetic acid gave a good yield of bis(5-nitro-2-thienyl)-ketone (IV), m.p. 152–154°. The 2,4-dinitrophenylhydrazone of IV melted at 222–223°.

The spectra of II and III showed strong bands in the region 1500 cm.$^{-1}$, 1335 cm.$^{-1}$ and 1495 cm.$^{-1}$, 1330 cm.$^{-1}$, respectively. These bands are indicative of the nitro groups. The ketone (IV) gave a carbonyl frequency of 1632 cm.$^{-1}$ and nitro frequencies of 1510 cm.$^{-1}$ and 1332 cm.$^{-1}$

EXPERIMENTAL

Nitration of 1,1,1-trichloro-2,2-bis(2-thienyl)ethane. Procedure A. A solution of 29.8 g. (0.1 mole) of 1,1,1-trichloro-2,2-bis(2-thienyl)ethane[4] in 75 ml. of acetic anhydride was cooled and added dropwise to a well stirred, cold solution of 11 ml. of nitric acid (90%) in 50 ml. of acetic acid. The temperature was kept below 10° during the addition. The reaction mixture was then stirred for 1 hr., poured over ice, and the oil washed several times with water. The gummy product was recrystallized from ethyl acetate and alcohol. Fourteen grams of white crystals of 1,1,1-trichloro-2,2-bis-(5-nitro-2-thienyl)ethane (II) were obtained, m.p. 110–110.5°.

Anal. Calcd. for $C_{10}H_5Cl_3N_2O_4S_2$: Cl, 27.44; N, 7.23. Found: Cl, 27.13; N, 7.25.

Procedure B. The same nitration was carried out except the temperature was maintained at 20–30° during the reaction and the reaction mass allowed to stand overnight. The product was isolated as above, and the yellow oil was stirred with a small amount of ethyl acetate. A yellow solid soon formed. This solid was dissolved in ethyl acetate, charcoaled, and cooled. The yellow crystals (24 g.) were removed and recrystallized twice from ethyl acetate to give 13 g. of 1,1-dichloro-2,2-bis(5-nitro-2-thienyl)ethane, (III), m.p. 130–131°.

Anal. Calcd. for $C_{10}H_4Cl_2N_2O_4S_2$: Cl, 20.10; N, 7.98. Found: Cl, 20.80; N, 7.64.

Conversion of 1,1,1-trichloro-2,2-bis(5-nitro-2-thienyl)-ethane (II) *to 1,1-dichloro-2,2-bis(5-nitro-2-thienyl)ethylene* (III). A mixture of 1.25 g. of II, 30 ml. of acetone, and 1 g. of potassium permanganate was refluxed for 1 hr., filtered, and the acetone allowed to evaporate. Recrystallization of the yellow solid from ethyl acetate gave 0.6 g. of III, m.p. 130–131°. The infrared spectra of this compound was identical with the yellow compound obtained by nitration of I *via* Procedure B.

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(1) This work was supported in part by a grant (CY-3908) from The National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, Bethesda, Md.

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(3) W. Lorenz, *Chem. Ber.*, **81**, 422 (1948).

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Oxidation of 1,1-dichloro-2,2-bis(5-nitro-2-thienyl)ethylene (III). A mixture of 3.51 g. (0.01 mole) of III and 50 ml. of acetic acid was heated to reflux, and a solution of 3 g. of chromic oxide in 10 ml. of water was added over a period of 10 min. The solution was refluxed for 6 hr. The hot solution was diluted with 20 ml. of water and allowed to cool slowly. The pale yellow crystals of bis(5-nitro-2-thienyl) ketone (IV) were removed, washed with water, and recrystallized from acetic acid to give 1.2 g. of pale yellow needles, m.p. 152–154°.

Anal. Calcd. for $C_9H_4N_2O_5S_2$: N, 9.85; S, 22.56. Found: N, 9.91; S, 22.99.

The 2, 4-dinitrophenylhydrazone of the ketone(IV) was prepared in the usual manner, m.p. 222–223°.

Anal. Calcd. for $C_{15}H_8N_6O_8S_2$: N, 18.10. Found: N, 18.32.

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Mannich Reaction with Hydroxycoumarins[1]

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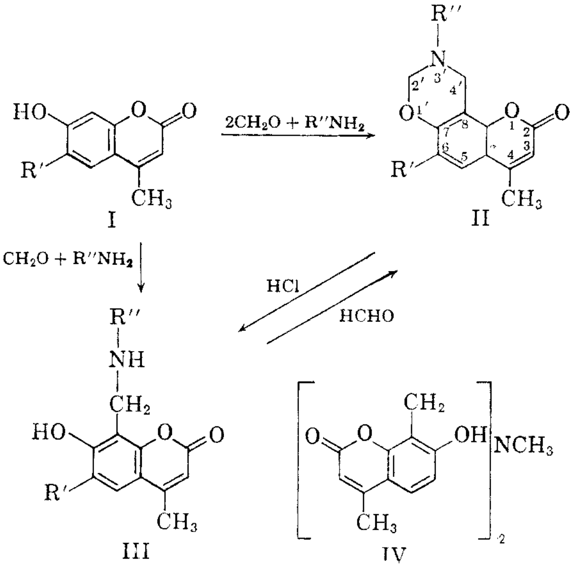
Received August 4, 1961

Although a considerable effort has gone into the condensation of phenols and naphthols with formaldehyde and amines,[3] there appears to have been only a single publication[4] dealing with the use of a hydroxycoumarin as the reactive nucleus in this reaction. Since Robertson and Link confined their study to 4-hydroxycoumarins which have the hydroxyl group in the heterocyclic ring, it seemed of interest to investigate the behavior of hydroxycoumarins having the hydroxyl group attached to the benzenoid ring. The present communication describes the reaction of formaldehyde and primary amines with 7-hydroxy-, 6-hydroxy-, and 5-hydroxy-coumarin derivatives. From 7-hydroxy-4-methylcoumarin derivatives (I), by reaction with benzylamine or aniline, it was possible to obtain either 7,8-(3′-substituted-4′-dihydro)-*m*-oxazino-4-methylcoumarins (II) or 7-hydroxy-8-substituted aminomethyl-4-methylcoumarins (III), depending upon whether two equivalents or only one equivalent of formaldehyde was used. The oxazino derivatives (II) could be formed by addition of formaldehyde to the simple Mannich reaction products (III), and hydrolysis of the oxazino derivatives yielded the Mannich-type products.



(R′, R″, see Table I)

Under all experimental conditions tried the major product obtained from 7-hydroxy-4-methylcoumarin with methylamine was the secondary amine IV.

In all cases it was assumed that, as in formylation,[5] the Claisen rearrangement,[6] and the Fries shift[7] with 7-hydroxy-4-methylcoumarin, the new substituent would appear at position 8. In one case (III, $R'' = C_6H_5CH_2$) it was shown that position 6 was not occupied, for it was proved that the bromination product was the 3,6-dibromo derivative. Under the usual Mannich conditions 7-methoxy- and 6-hydroxy-4-methylcoumarins do not react, while 5-hydroxy-4,7-dimethylcoumarins appeared to give only complex products with formaldehyde and aniline or methylamine. Under the proper conditions benzylamine afforded what is believed to be 5,6-(3′-benzyl-4-dihydro)-*m*-oxazino-4 7-dimethylcoumarin.[8,9] On the basis of the present study 7-hydroxycoumarins seem more suited for the Mannich reaction than do the 5- or 6-hydroxy analogs.

EXPERIMENTAL[10]

General methods for the synthesis of benzo-α-pyroneoxazines. Procedure A. A solution of 1.2 g. (0.4 mole) of paraformaldehyde in 5 ml. of absolute ethanol containing 0.015 g. of potassium hydroxide was prepared by gentle warming.

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[1] Abstracted from the thesis presented by the author in fulfillment of the requirements for the Ph.D. degree at the University of Bombay.

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[10] Melting points were taken in open capillary tubes and are uncorrected.