

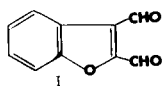
The Synthesis of 2,3-Diformylbenzo[*b*]furan and Certain 7,9-Disubstituted-8*H*-cyclohepta[*b*]benzo[*d*]furan-8-ones

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As a part of a program designed to expand the chemistry of benzofuran, it became necessary to synthesize 2,3-diformylbenzo[*b*]furan (I).



Different methods have been used for the preparation of adjacent diformyl-heterocyclic compounds. Formylation of dilithium salts (1-3), reduction of adjacent dicyanitrile with diisobutylaluminum hydride (4-6), and reduction of dithioesters with raney nickel (7) have been often employed. Recently, oxidation of diol with silver carbonate was used in the preparation of 1-methyl-3,4-diformylpyrrole (8). This method seemed to be a convenient route and was tried for the synthesis of the

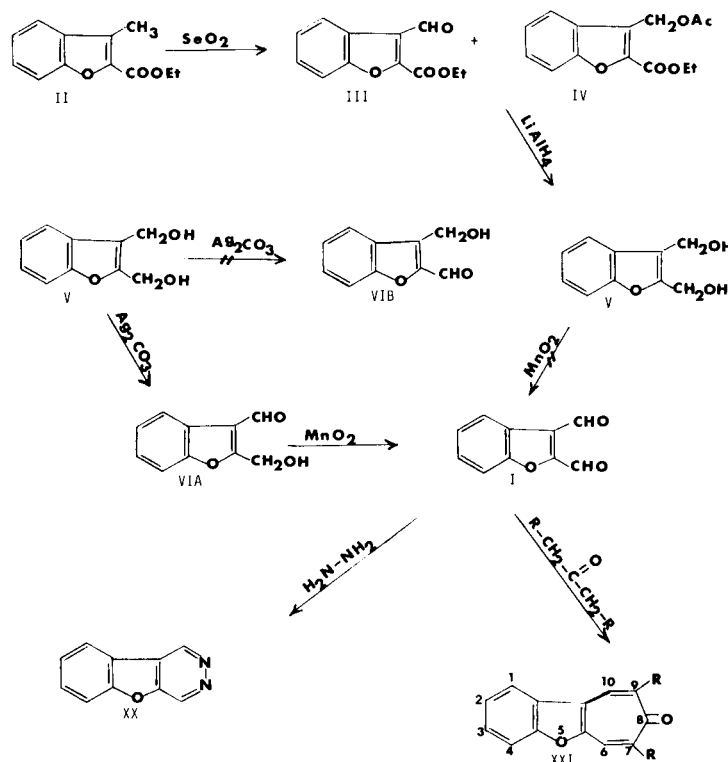
desired compound I.

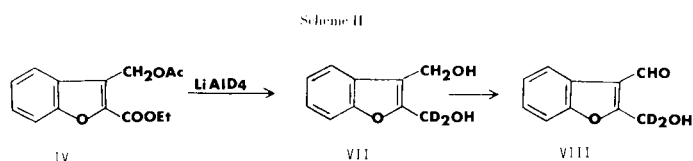
Synthesis of the starting diol, 2,3-dihydroxymethylbenzo[*b*]furan (V), was easily achieved from the readily available ethyl 3-methylcoumarilate (II) (9).

Selenium dioxide oxidation of ethyl 3-methylcoumarilate in acetic acid afforded a mixture of compounds III (10) and IV. Lithium aluminum hydride reduction of the mixture gave 2,3-dihydroxymethylbenzo[*b*]furan (V) in high yield.

Silver carbonate oxidation of compound V did not give the desired compound I. In this reaction only one of the hydroxyl groups was oxidized. The product could be either 2-hydroxymethyl-3-formylbenzo[*b*]furan (VIA) or its isomer, 3-hydroxymethyl-2-formylbenzo[*b*]furan (VIB) (Scheme I).

Scheme I





As a means of determining the site of oxidation, compound IV was reduced with lithium aluminium deuteride, and the product VII was oxidized with silver carbonate (Scheme II). The nmr spectrum of the product showed the presence of an aldehyde proton, and electron impact confirmed the retention of two deuterium atoms, in conformity with compound VIII. It is therefore concluded that silver carbonate oxidizes only the hydroxymethyl at position 3.

An obvious alternative method for the preparation of compound I would be the oxidation of the diol V with manganese dioxide. However, manganese dioxide oxidation of compound V under different conditions did not give

the desired compound I. In all cases either the starting diol or polymer were isolated.

Finally, manganese dioxide oxidation of VIA in chloroform yielded compound I in moderate yield (Scheme I).

The availability of compound I and its deuterium analogue IX, which could be readily obtained from silver carbonate oxidation of compound VIII, permitted the study of the electron impact of this compound. The fragmentation pattern of the latter is shown in Scheme III.

The fragmentation pattern shown above was similar to 2-formylbenzo[*b*]furan reported previously (11).

Finally, reaction of I with hydrazine and ketones were studied (Scheme 1). Treatment of I with hydrazine in ethanol gave benzofuro[2,3-*d*]pyridazine (XX) in high yield. This compound has recently been prepared by another method (12).

Condensation of I with diethyl ketone in alkaline medium afforded a new condensed ring system, 7,9-dimethyl-8*H*-cyclohepta[*b*]benzo[*d*]furan-8-one (XXI, R = CH<sub>3</sub>).

Heating of I with equimolar acetonedicarboxylic acid dimethylester in benzene, in the presence of piperidine, did not give the desired compound XXI (R = COOCH<sub>3</sub>). However, using equimolar of piperidine acetate instead of piperidine yielded XXI (R = COOCH<sub>3</sub>) in moderate yield.

## EXPERIMENTAL

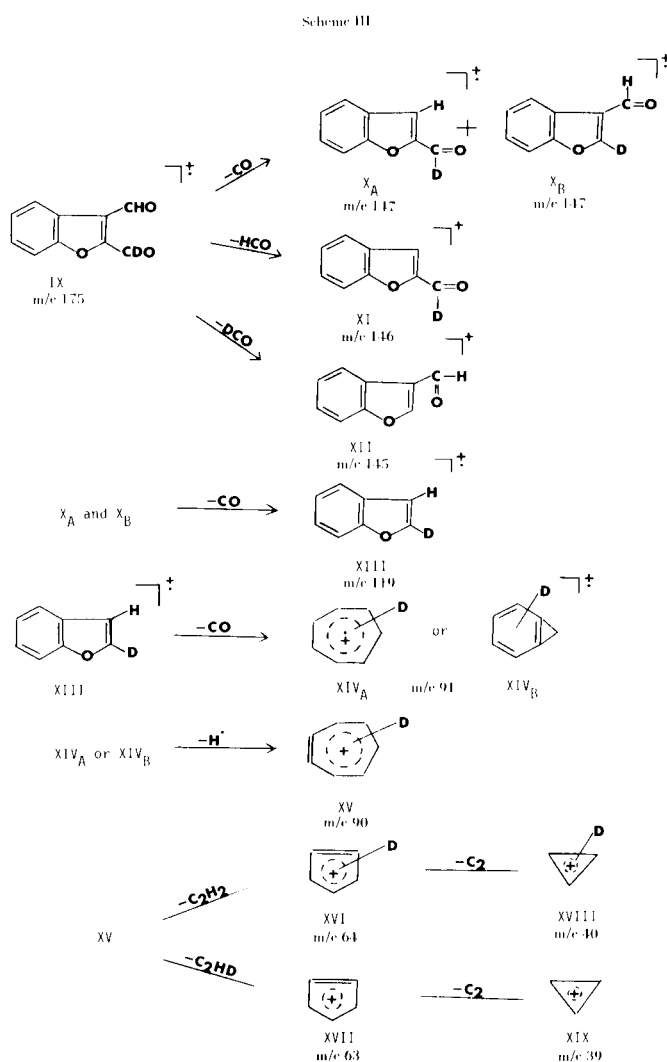
Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Perkin-Elmer Model 137 spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer and chemical shifts ( $\delta$ ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT CH-5 spectrometer at 70 ev.

Reaction of Selenium Dioxide with Ethyl 3-Methylcoumarilate (II).

A mixture of 204 mg. (1 mmole) of II and 123 mg. (1.1 mmole) of selenium dioxide in 5 ml. acetic acid was stirred and refluxed for 72 hours. The reaction mixture was filtered and evaporated to dryness. The crude product was chromatographed (tlc, silica gel, dichloromethane). The least polar fraction was crystallized from ether to give 65 mg. (30%) of compound III, m.p. 91-92° [lit. (10), m.p. 113°]; ir (chloroform): 2900 (aldehyde C-H), 1725 (ester) and 1672 cm<sup>-1</sup> (aldehyde); nmr (deuteriochloroform): 10.20 (s, 1H, HCO), 8.33 (m, 1H, H<sub>4</sub>), 7.27 (m, 3H, aromatic), 4.52 (q, 2H, OCH<sub>2</sub>) and 1.50 (t, 3H, CH<sub>3</sub>); m/e: 218, 200, 199, 173, 162, 146, 145, 144, 118, 117, 116, 105, 101, 89, 63 and 39.

Anal. Calcd. for C<sub>12</sub>H<sub>10</sub>O<sub>4</sub>: C, 66.06; H, 4.59. Found: C, 66.24; H, 4.55.

The more polar fraction was crystallized from petroleum ether to give 160 mg. (61%) of compound IV, m.p. 48-49°; ir (potassium bromide): 1735 and 1690 cm<sup>-1</sup> (ester); nmr (deuteriochloroform): 7.93-7.30 (m, 4H, aromatic), 5.70 (s, 2H, CH<sub>2</sub>O), 4.53 (q, 2H, OCH<sub>2</sub>), 2.10 (s, 3H, COCH<sub>3</sub>) and 1.45 (t, 3H, CH<sub>3</sub>); m/e 262.



*Anal.* Calcd. for  $C_{14}H_{14}O_5$ : C, 64.12; H, 5.34. Found: C, 64.25; H, 5.41.

#### 2,3-Dihydroxymethylbenzo[*b*]furan (V).

A mixture of II (20.4 g., 0.1 mole) and selenium dioxide (12.32 g., 0.11 mole) in 100 ml. acetic acid was stirred and refluxed for 72 hours. The reaction mixture was filtered and evaporated to dryness. The residue was dissolved in 150 ml. of dry ether. To the solution was added lithium aluminium hydride (5.7 g., 0.15 mole). The stirring was continued for one hour. The mixture was decomposed with saturated sodium sulfate solution and filtered. The solvent was evaporated and the residue was crystallized from ethyl acetate to give V (14.3 g., 80%), m.p. 129-130°; nmr (deuteriochloroform): 7.70-7.10 (m, 4H, aromatic), 4.78 (s, 2H,  $CH_2O$  at position 3), 4.71 (s, 2H,  $CH_2O$  at position 2) and 4.17 (broad band, 2H, OH); *m/e* 178.

*Anal.* Calcd. for  $C_{10}H_{10}O_3$ : C, 67.42; H, 5.62. Found: C, 67.65; H, 5.45.

Compound VII was prepared from IV and lithium aluminium deuteride in ether in 90% yield, m.p. 127-128°; nmr (deuteriochloroform): 7.80-7.10 (m, 4H, aromatic), 4.78 (s, 2H,  $CH_2O$  at position 3) and 4.17 (broad band, 2H, OH); *m/e*: 180.

#### 2-Hydroxymethyl-3-formylbenzo[*b*]furan (VIA).

A mixture of V (178 mg., 1 mmole) and silver carbonate (3 g.) (13) in 20 ml. ethyl acetate was stirred and refluxed for 20 hours. The mixture was filtered and evaporated. The residue was crystallized from ethyl acetate to give VIA (150 mg., 85%), m.p. 124-125°; *ir* (chloroform): 2870 (aldehyde CH) and 1700  $cm^{-1}$  (CO); nmr (deuteriochloroform): 10.30 (s, 1H, CHO), 8.13-7.97 (m, 1H, aromatic), 7.50-7.23 (m, 3H, aromatic), 5.03 (s, 2H,  $CH_2O$ ) and 3.28 (broad s, 1H, OH); *m/e*: 176.

*Anal.* Calcd. for  $C_{10}H_8O_3$ : C, 68.18; H, 4.55. Found: C, 68.02; H, 4.69.

Compound VIII was prepared from VII and silver carbonate similar to VIA, m.p. 123-124° (ethyl acetate); *ir* (chloroform): 2870 (aldehyde CH) and 1680  $cm^{-1}$  (CO); nmr (deuteriochloroform): 10.33 (s, 1H, CHO), 8.13-7.97 (m, 1H, aromatic), 7.50-7.23 (m, 3H, aromatic) and 3.22 (broad s, 1H, OH).

#### 2,3-Diformylbenzo[*b*]furan (I).

A mixture of VIA (352 mg., 2 mmoles) and manganese dioxide (1.5 g.) in 20 ml. of chloroform was stirred for 4 hours. The reaction mixture was filtered and evaporated to dryness. The *tlc* of the residue (silica gel, chloroform-methanol; 97:3) gave 209 mg. (60%) of compound I m.p. 143° (chloroform-carbon tetrachloride); *ir* (chloroform): 2860 (aldehyde CH), 1698 and 1682  $cm^{-1}$  (CO); nmr (deuteriochloroform): 10.80 (s, 1H, CHO at position 3), 10.66 (s, 1H, CHO at position 2), 8.33-8.10 (m, 1H, aromatic) and 7.67-7.23 (m, 3H, aromatic); *m/e* (%): 174 (M, 75), 146 (38), 145 (46), 118 (50), 90 (100), 89 (92), 63 (54), 62 (33) and 39 (33).

*Anal.* Calcd. for  $C_{10}H_6O_3$ : C, 68.97; H, 3.45. Found: C, 68.79; H, 3.36.

Compound IX was prepared from VIII and manganese dioxide similarly, m.p. 141-142°; *ir* (chloroform): 2825 (aldehyde CH) and 1670  $cm^{-1}$  (CO); nmr (deuteriochloroform): 10.78 (s, 1H, CHO at position 3), 8.45-8.20 (m, 1H, aromatic), and 7.70-7.33 (m, 3H, aromatic); *m/e* (%): 175 (M, 97), 147 (43), 146 (24), 145 (38), 119 (43), 91 (100), 90 (76), 64 (30), 63 (35), 40 (6) and 39 (22).

#### Benzo[*f*]uro[2,3-*d*]pyridazine (XX).

A solution of I (174 mg., 1 mmole) and hydrazine hydrate

(50 mg., 1 mmole) in 4 ml. of methanol was stirred for 2 hours. The solvent was evaporated and the residue was crystallized from ethyl acetate to give XX (94%), m.p. 147-148° [lit. (12) m.p. 143°].

#### 7,9-Dimethyl-8*H*-cyclohepta[*b*]benzo[*d*]furan-8-one (XXI, R = $CH_3$ ).

To a solution of I (87 mg., 0.5 mmole) and diethylketone (43 mg., 0.5 mmole) in 10 ml. methanol was added a solution of 60 mg. of sodium hydroxide in 1 ml. of water. After stirring for 24 hours, the mixture was acidified with dilute hydrochloric acid and extracted with chloroform. The organic layer was dried over sodium sulfate and evaporated. The residue was purified by *tlc*, using chloroform-methanol (95:5) as eluting solvent. The product was crystallized from ether to give 30 mg., of XXI (R =  $CH_3$ , 27%), m.p. 108-109°, nmr (deuteriochloroform): 7.77 (s, 1H,  $H_{10}$  or 6), 7.70 (s, 1H,  $H_6$ , or 10), 7.57-7.20 (m, 4H, aromatic) and 2.33 (s, 6H,  $CH_3$ ); *m/e*: 224.

*Anal.* Calcd. for  $C_{15}H_{12}O_2$ : C, 80.36; H, 5.36. Found: C, 80.22; H, 5.45.

#### 7,9-Dicarbomethoxy-8*H*-cyclohepta[*b*]benzo[*d*]furan-8-one (XXI, R = $COOCH_3$ ).

A solution of I (87 mg., 0.5 mmole), acetone dicarboxylic acid dimethyl ester (87 mg., 0.5 mmole) and 73 mg. of piperidine acetate in 10 ml. of benzene was refluxed for 4 hours. The mixture was cooled, poured in ice-water, acidified with hydrochloric acid and extracted with chloroform. The organic layer was dried over sodium sulfate and evaporated. The residue was crystallized from benzene to give 94 mg. (60%) of XXI (R =  $COOCH_3$ ), m.p. 158-159°; *ir* (chloroform): 1720  $cm^{-1}$  (ester); nmr (deuteriochloroform): 8.40 (s, 1H,  $H_6$  or 10), 8.23 (s, 1H,  $H_{10}$  or 6), 8.0-7.40 (m, 4H, aromatic) and 3.93 (s, 6H,  $OCH_3$ ); *m/e*: 312.

*Anal.* Calcd. for  $C_{17}H_{12}O_6$ : C, 65.38; H, 3.85. Found: C, 65.53; H, 3.98.

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