

## Studies on the Furan Series

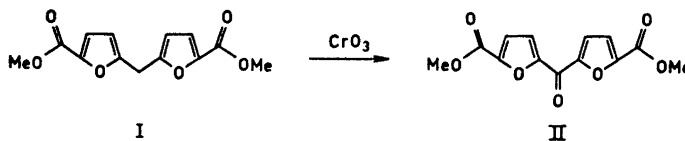
## Part II. Oxidation of Bis(5-methoxycarbonyl-2-furyl)methane

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Bis(5-methoxycarbonyl-2-furyl)methane, having electron withdrawing substituents in the furan rings, can easily be oxidized to the corresponding ketone. The reaction on methyl 2-furoate with carbon tetrachloride in the presence of  $\text{AlCl}_3$  did not give the expected ketone, but tris(5-methoxycarbonyl-2-furyl)carbinol (III). Some reactions of 2,2'-difurylketone derivatives are described.

A previous paper<sup>1</sup> describes the condensation of methyl 2-furoate with Atrioxane in concentrated sulphuric acid, which gives bis(5-methoxycarbonyl-2-furyl)methane (I). The methylene group in compound I has properties similar to those of the corresponding group in diphenylmethane. Compound I is smoothly oxidized with  $\text{CrO}_3$  in refluxing glacial acetic acid to bis(5-methoxycarbonyl-2-furyl)ketone (II) in 62 % yield (Scheme 1).



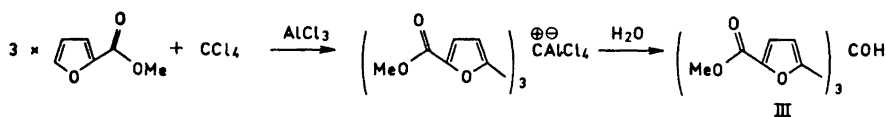
Scheme 1.

The electron withdrawing methoxycarbonyl groups in the furan rings stabilize compound II to withstand the strong oxidation conditions.

An attempt to synthesize compound II *via* the reaction of methyl 2-furoate with  $\text{CCl}_4$  in the presence of  $\text{AlCl}_3$  (analogous to the preparation of benzophenone from benzene and  $\text{CCl}_4/\text{AlCl}_3$ ) gave no II. However, another compound was obtained, which had  $\nu$  3340  $\text{cm}^{-1}$  in the IR spectrum due to a hydroxyl group. This could not be acetylated, but silylation with  $\text{Me}_3\text{SiCl}$  produced a trimethylsilyl ether. According to the mass spectrum the molecular weight of the hydroxyl product was 404. The formula tris(5-methoxycarbonyl-

2-furyl)carbinol (III) was indicated for this compound by the spectra and elemental analyses.

The fact that the reaction (Scheme 2) gave only III but no II is explained by the great reactivity of the furfuryl chloride intermediate. Kirner<sup>2</sup> has mentioned that furfuryl chloride is 1500 times more reactive than benzyl chloride. While the reaction of benzene and  $\text{CCl}_4/\text{AlCl}_3$  stops at the stage of the diphenyldichloromethane/ $\text{AlCl}_3$  complex (which is hydrolyzed to benzophenone), the analogous complex (now reactive) from the furanoid compound and  $\text{CCl}_4/\text{AlCl}_3$  reacts once more with a molecule of methyl 2-furoate to give the trifurylchloromethane/ $\text{AlCl}_3$  complex (Scheme 2).



Compound III, like the triarylcarbinols, forms a bright red halochromic salt with strong acids (e.g. conc.  $\text{H}_2\text{SO}_4$ ). Ramanathan and Levine<sup>3</sup> have mentioned that difurylcarbinols and related compounds are quite sensitive to oxygen, and when exposed to air are oxidized to black resins. The stability of III towards air and conc.  $\text{H}_2\text{SO}_4$  is due to the electron-withdrawing ester groups in the three furan rings.

*Some reactions of bis(5-methoxycarbonyl-2-furyl)ketone.* II is hydrolyzed with KOH in methanol into bis(5-carboxy-2-furyl)ketone (IV), m.p.  $> 310^\circ\text{C}$ . The dicarboxylic acid IV can be decarboxylated with copper in quinoline at  $150-160^\circ\text{C}$  to 2,2'-difurylketone (V). Reichstein *et al.*<sup>4</sup> have previously prepared V by the Grignard reaction of 2-bromofuran and 2-cyanofuran. Boyle *et al.*<sup>5</sup> and Michael and Hörnfeldt<sup>6</sup> have treated 2-furyllithium with gaseous carbon dioxide and dimethylcarbamoyl chloride, respectively, to give V.

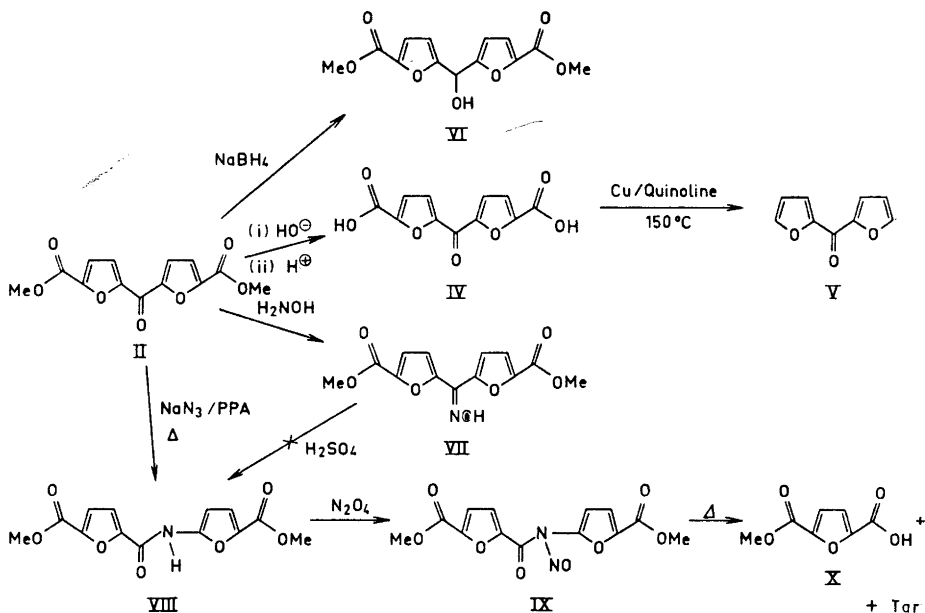
The reduction of II with  $\text{NaBH}_4$  gave bis(5-methoxycarbonyl-2-furyl)carbinol (VI) in quantitative yield.

The ketone group of II is to some extent sterically hindered, because no phenylhydrazine adduct was formed.

Baeyer-Villiger conditions<sup>7</sup> (40% peracetic acid) failed to affect II.

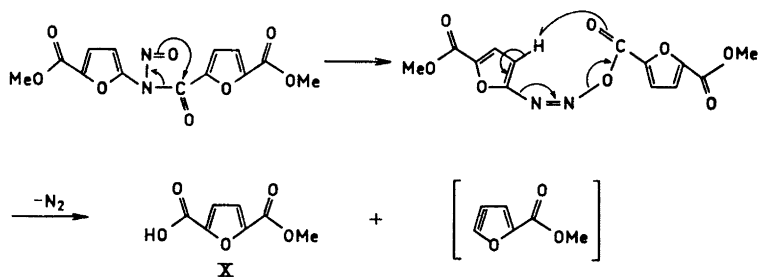
However, oxime (VII) was formed after 65 h refluxing in dried dioxane. The Beckmann rearrangement of the oxime VII was attempted by the methods of Hill and Chortyk<sup>8</sup> and Emmons<sup>9</sup> (or concentrated sulphuric acid at  $80^\circ\text{C}$ ) but no reaction took place. When the temperature of the conc.  $\text{H}_2\text{SO}_4$  was  $100-110^\circ\text{C}$ , sulphonation of the furan rings probably occurred because the compound became water soluble.

In contrast to the failure of the Baeyer-Villiger reaction and the Beckmann rearrangement, the Schmidt reaction was successful. When II was treated with sodium azide in polyphosphoric acid,<sup>10,11</sup> the compound formed was, according to the spectra and elemental analyses, *N*-(5-methoxycarbonyl-2-furyl)-5-methoxycarbonyl-2-furamide (VIII). Because the ketone II is symmetrical, only one rearrangement product resulted.



Scheme 3. Some reactions of bis(5-methoxycarbonyl-2-furyl)ketone.

White<sup>12</sup> has mentioned that when *N*-alkylamide, under cooling, is treated with nitrogen tetroxide, the result is a labile *N*-alkyl-*N*-nitrosoamide which can be rearranged by heating to an ester or an alkene. When VIII was treated at  $-70^\circ\text{C}$  with  $\text{N}_2\text{O}_4$  and after that refluxed in  $\text{CCl}_4$ , 2,5-furandicarboxylic acid monomethyl ester (X) was produced. According to the mechanism proposed by White,<sup>12</sup> the formation of compound X can be visualized as given in Scheme 4.



Scheme 4.

## EXPERIMENTAL

The spectra were determined on the following instruments: NMR spectra on a Varian A60, UV spectra on a Beckman DK-2, IR spectra on a Perkin-Elmer 125, and mass spectra on a Perkin-Elmer 270B. Elemental analyses were carried out on an F&M 185 CHN-analyzer. All melting points are uncorrected.

The preparation of the starting material bis(5-methoxycarbonyl-2-furyl)methane (I) is described in the previous paper.<sup>1</sup>

*Bis(5-methoxycarbonyl-2-furyl)ketone (II)*. 2.60 g of I and 5.20 g of  $K_2Cr_2O_7$  were refluxed in 70 ml of glacial acetic acid for 5 h. The mixture was cooled and poured into 400 ml of cold water. The precipitate formed was filtered, washed first with dilute HCl, bicarbonate solution and after that with ethyl acetate. The recrystallization of the greyish material was performed in water-acetic acid mixture. Yield 1.70 g (62 %); m.p. 205–206°C;  $\lambda_{max}$  313 ( $\epsilon$  26 000), 322 ( $\epsilon$  25 800) nm;  $\nu_{max}$  3160, 2960, 1720, 1630  $cm^{-1}$ ;  $\tau$  (in  $CF_3COOH$ ) 2.37 (2H d 3.5 cps), 2.74 (2H d 3.5 cps), 6.18 (6H s). (Found: C 56.09; H 3.56. Calc. for  $C_{13}H_{10}O_7$ : C 56.12; H 3.62.)

*Tris(5-methoxycarbonyl-2-furyl)carbinol (III)*. 5.00 g of methyl 2-furoate and 10.00 g of  $AlCl_3$  were refluxed in 100 ml of  $CCl_4$  for half an hour. The reaction mixture was poured into ice water, which was extracted with two portions (75 ml) of ethyl acetate. The ester layer was separated, dried with  $MgSO_4$  and evaporated. The brown, viscous residue was purified by silica gel column chromatography (elution with  $EtOAc-CHCl_3$  1:1). The recrystallization was carried out in a mixture of petrol ether and chloroform. Yield 1.30 g (25 %); m.p. 147°C;  $\lambda_{max}$  260 ( $\epsilon$  26 700) nm;  $\nu_{max}$  3340, 3130, 2950, 1730, 1005  $cm^{-1}$ ;  $\tau$  (in acetone) 2.78 (3H d 3.5 cps), 3.43 (3H d 3.5 cps), 3.28 (1H s dis. with  $D_2O$ ), 6.18 (9H s); *m/e* 404 (26 %), 387 (100 %), 373 (12 %), 345 (37 %). (Found: C 56.53; H 3.75. Calc. for  $C_{19}H_{16}O_{10}$ : C 56.44; H 3.99.) Acetylation of III did not succeed. Silylation of III was carried out with trimethylchlorosilane in triethylamine. The NMR spectrum of the silylether:  $\tau$  2.92 (3H d 3.5 cps), 3.58 (3H d 3.5 cps), 6.19 (9H s), 9.98 (9H s).

*Bis(5-carboxy-2-furyl)ketone (IV)*. 10.00 g of II was kept with 8.00 g of KOH in 150 ml of water-methanol (1:10) for 12 h at room temperature. The mixture was acidified with dilute HCl. The precipitate formed was separated, washed with water and dried. Yield 7.80 g (97 %); m.p. > 310°C;  $\nu_{max}$  3400–2500 (broad)  $cm^{-1}$ .

*2,2'-Difurylketone (V)*. 2.00 g of IV and 0.50 g of finely powdered copper in 30 ml of quinoline were stirred at 150–160°C for 2 h. After cooling, 100 ml of ethyl acetate was added and quinoline was washed off with dilute HCl. The organic layer was then washed with water, dried with  $MgSO_4$  and evaporated. The residue (almost black, viscous oil) was purified in a silica gel column (elution with chloroform). Yield 1.10 g (95 %); m.p. 32°C (recryst. from petrol ether). Reichstein *et al.*<sup>4</sup> give the melting point as 33–34°C.  $\nu_{max}$  3134, 1630, 1500, 870  $cm^{-1}$ ;  $\tau$  2.34 (2H d 1.5 cps), 2.54 (2H d 3.5 cps), 3.45 (2H dd 1.5 and 3.5 cps).

*Bis(5-methoxycarbonyl-2-furyl)carbinol (VI)*. 2.00 g of II and 0.40 g of  $NaBH_4$  were refluxed in 40 ml of  $CHCl_3$  for 4 h. The mixture was washed with water, dried with  $MgSO_4$  and evaporated. The residue was recrystallized from a mixture of petrol ether and  $CHCl_3$ . Yield 2.00 g (99 %); m.p. 144°C;  $\nu_{max}$  3578, 3125, 2960, 1725;  $\tau$  (in  $CDCl_3$ ) 2.87 (2H d 3.5 cps), 3.52 (2H d 3.5 cps), 4.08 (1H s), 4.11 (1H s dis. with  $D_2O$ ), 6.12 (6H s). (Found: C 55.45; H 4.41. Calc. for  $C_{13}H_{12}O_7$ : C 55.72; H 4.32.)

*Bis(5-methoxycarbonyl-2-furyl)ketone oxime (VII)*. 1.50 g of II, 5 ml of dried pyridine, and 1.50 g of  $NH_2OH \cdot HCl$  were refluxed in dried dioxane for 65 h. The mixture was poured into water. The precipitate formed was washed with water and recrystallized from ethanol. Yield 1.40 g (89 %); m.p. 216°C;  $\lambda_{max}$  286 ( $\epsilon$  35 200) nm;  $\nu_{max}$  3360, 3160, 2960, 1730, 1690, 990  $cm^{-1}$ ;  $\tau$  (in  $CF_3COOH$ ) 2.11 (2H d 3.5 cps), 2.48 (2H d 3.5 cps), 5.90 (6H s). (Found: C 53.11; H 3.87; N 4.56. Calc. for  $C_{13}H_{11}NO_7$ : C 53.24; H 3.78; N 4.78.)

*N-(5-Methoxycarbonyl-2-furyl)-5-methoxycarbonyl-2-furamide (VIII)*. 1.00 g of II was heated in PPA at 75°C. 0.30 g of  $NaN_3$  was added gradually. After 3 h the mixture was poured into water, which was extracted twice with 50 ml of  $EtOAc$ . The organic layer was washed with water, dried with  $MgSO_4$  and evaporated. The brownish residue was purified in a silica gel column (elution with  $CHCl_3-EtOAc$  1:1). Yield 0.65 g (62 %); m.p. 223°C (recryst. from ethanol);  $\lambda_{max}$  262 ( $\epsilon$  31 500), 311 ( $\epsilon$  33 100) nm;  $\nu_{max}$  3300, 3150, 2950, 1720, 1675, 1540, 1520  $cm^{-1}$ ;  $\tau$  (in acetone) 2.73 (2H d 3.5 cps), 3.28 (2H d

3.5 cps), 6.01 (3H s), 6.08 (3H s). (Found: C 53.18; H 3.65; N 4.77. Calc. for  $C_{13}H_{11}O_7$ : C 53.24; H 3.78; N 4.78.)

*N-Nitroso-N-(5-methoxycarbonyl-2-furyl)-5-methoxycarbonyl-2-furamide (IX) and 2,5-furandicarboxylic acid monomethylester (X)*. 0.30 g of VII in 40 ml of EtOAc was treated with 3 ml of liquid  $N_2O_4$  at  $-70^\circ C$ . The mixture was stirred and its temperature rose to  $20^\circ C$  during 2 h. Water was added; the organic layer was dried with  $MgSO_4$  and evaporated. The residue (the labile *N*-nitroso compound IX) was not purified, but dissolved in 50 ml of  $CCl_4$  and refluxed for 12 h.  $CCl_4$  was evaporated and the black residue was purified in a silica gel column (elution EtOAc–AcOH 10 : 1). Yield 0.12 g (82 %) of X; m.p.  $198^\circ C$  (recryst. from hot water). Ref. 13 gives the m.p. as  $201^\circ C$ .  $\nu_{max}$  3200–2500, 1720, 1690  $cm^{-1}$ ;  $\tau$  (in  $CF_3COOH$ ) 2.58 (1H d 4 cps), 2.62 (1H d 4 cps), 5.95 (3H s). The color reaction with isatine<sup>13</sup> to confirm 2,5-furandicarboxylic acid gave positive result when hydrolyzed X was used.

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