

## Synthesis of Some Benzodipyrones, Potential Photochemical DNA Crosslinking Agents

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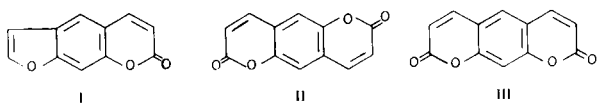
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Certain substituted coumarins, especially the furocoumarin psoralen (I) and its derivatives, are potent carcinogenic agents and bacterial mutagenic agents (1). Their mode of action has been attributed to an ultraviolet photoactivation, followed by [2 + 2] addition of the double bonds to the double bonds of the pyrimidine bases of the DNA molecules of the organism in question (2). Since the psoralens contain two reactive double bonds, it is postulated that they could undergo double addition to form cross-linked DNA adducts (3). Recent evidence with a mutated bacterial strain of *Bacillus subtilis* is in accord with this postulate (3).

Since molecular orbital calculations suggest that the  $\pi-\pi^*$  triplet of the coumarin ring in the psoralens is the reacting species (3,4), compound II (2*H*,7*H*-benzo[1,2-*b*:4,5-*b'*]dipyran-2,7-dione) and compound III (2*H*,8*H*-benzo[1,2-*b*:4,5-*b'*]dipyran-2,8-dione) were chosen to further test this postulate. Compound II has the coumarin double bonds in an ideal geometrical relationship to span successive coils of a DNA molecule, as judged by model building, whereas III does not have such favorable geometry.

We report here the synthesis of the benzodipyrene (II), as well as give details of an improvement of the recorded synthesis (5) of the isomer III. Photochemical and microbiological studies on the compounds are being reported elsewhere (3).



The benzodipyrene III was obtained by improvements in the reported synthetic sequence (5). Direct condensation between resorcinol and two equivalents of ethyl acrylate in the presence of hydrogen chloride and aluminum chloride gave the corresponding tetrahydro derivative of III in 10% yield. Dehydrogenation with palladium in refluxing diphenylether then gave III, as reported (5).

For the synthesis of the benzodipyrene II, a longer reaction sequence was necessary, since attempted condensation between hydroquinone and ethyl acrylate was unsuccessful. Chloroformylation of hydroquinone di-

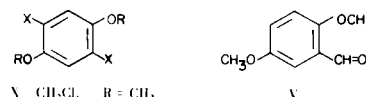
methyl ether gave the 2,5 isomer IVa, as reported (6). This compound was converted into the corresponding diacetate, IVb, with sodium acetate in refluxing acetic acid. Saponification then gave the dialcohol IVc (86% overall yield for the three steps). This was smoothly oxidized with chromic acid (Jones reagent) to the known (7) dialdehyde IVd (70%).

The reported direct conversion of the dichloride IVa to the dialdehyde IVd *via* a Sommelet reaction (7) could not be duplicated. Only a tiny amount of the highly fluorescent dialdehyde IVb could be detected within the first few minutes of the reaction and it was destroyed rapidly under the reaction conditions.

An attempt to generate the dialdehyde IVd directly from hydroquinone dimethyl ether and dichloromethyl methyl ether in the presence of titanium tetrachloride (8) gave the monoformylated product V instead. Only tiny traces of IVd could be detected when the reaction was carried out under forcing conditions.

The methyl ether protecting groups of IVd were removed with HBr in refluxing acetic acid as reported (9) to give IVe in 65% yield. The phenol aldehyde IVe underwent a double Perkin condensation when heated with sodium acetate in acetic anhydride at 190° in a sealed tube, to yield the benzodipyrene II, in 55% yield.

When the Perkin condensation was carried out under the usual conditions, in refluxing acetic anhydride, a quantitative yield of the hexaacetate IVf was obtained instead of II. Heating IVf in the sealed tube to 190° with excess sodium acetate and acetic anhydride converted it into II. Early speculation that such *ortho*-acetates may be transient intermediates in the Perkin condensation have been disproved (10). In the present case, the compound IVf is probably a side product, which is formed reversibly under the reaction conditions, rather than a true intermediate.



- IVa X = CH<sub>2</sub>Cl, R = CH<sub>3</sub>  
 b X = CH<sub>2</sub>OAc, R = CH<sub>3</sub>  
 c X = CH<sub>2</sub>OH, R = CH<sub>3</sub>  
 d X = CH=O, R = CH<sub>3</sub>  
 e X = CH=O, R = H  
 f X = CH(OAc), R = Ac

## EXPERIMENTAL

2*H*,8*H*-Benzo[1,2-*b*:4,5-*b'*]dipyran-2,8-dione (III).

A stream of hydrogen chloride gas was bubbled through a solution of 55 g. (0.50 mole) of resorcinol and 116.4 g. (1.16 mole) of ethyl acrylate in 250 ml. of anhydrous ether while 140 g. (1.05 mole) of aluminum chloride was added in portions over 1.5 hours. Then the ether was distilled off and the reaction mixture heated to 150° for 3 hours. The orange mixture bubbled vigorously and then set to a solid. This was pulverized and added to excess cold hydrochloric acid, then extracted with ether, which was dried over magnesium sulfate and the ether removed to give 120 g. of viscous oil. Vacuum distillation gave, after a forerun of ethyl 3-chloropropionate, a material, b.p. 200-210°, which solidified in the condenser. This was crystallized from 95% ethanol to give 10.75 g. (0.050 mole, 10%), m.p. 224-225° (lit. (5) 224-225°). Dehydrogenation of this material with Pd/C in refluxing diphenyl ether for 24 hours as described (5) gave 7.3 g. of the dipyrone (III), which was purified by crystallization from 95% ethanol and vacuum sublimation twice, m.p. 348-351°, (lit. (5) m.p. 328-330 dec.).

## 2,5-Dichloromethyl-1,4-dimethoxybenzene (IVa).

This compound was prepared in 78% yield by the method of Wood and Gibson; (6) m.p. 167-167.5.

## 2,5-Diacetoxymethyl-1,4-dimethoxybenzene (IVb).

A mixture of 2.35 g. (10 mmoles) of IVa and 3.08 g. (37 mmoles) of anhydrous sodium acetate in 15 ml. of glacial acetic acid was refluxed 10 hours and the acetic acid removed at the aspirator. The resulting solid was collected and washed well with water, then crystallized from methanol, yield 2.35 g. (8.4 mmoles, 84%), m.p. 116-118°; nmr (deuteriochloroform): singlets at  $\delta$  2.15 (6H), 3.85 (6H), 5.15 (4H), 6.90 (2H); ir ( $\nu$  potassium bromide): 2960, 1730, 1525, 1475, 1425, 1325, 1240, 1020  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{18}\text{O}_6$ : C, 59.57; H, 6.43. Found: C, 59.35; H, 6.42.

## 2,5-Dihydroxymethyl-1,4-dimethoxybenzene (IVc).

A stirred solution of 2.35 g. (8.4 mmoles) of the diacetate IVb in 50 ml. of methanol and 10 ml. of 10% sodium hydroxide was refluxed for 0.5 hour, then poured into ice water. The resulting solid was crystallized from water to give 1.34 g. (6.8 mmoles, 81%) of IVc, m.p. 164-165°; nmr (DMSO- $d_6$ ): 3.65 (6H, singlet), 4.40 (4H, doublet), 4.90 (2H, triplet), 6.95 (2H, singlet); ir ( $\nu$  potassium bromide): 3300-3150, 2950, 1510, 1460, 1410, 1200, 1020, 860  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{10}\text{H}_{14}\text{O}_4$ : C, 60.59; H, 7.12. Found: C, 60.13; H, 7.16.

In a large scale run, without purifying intermediates, 69.1 g. (0.50 mole) of hydroquinone dimethylether was converted into 85.0 g. (0.43 mole, 86%) of the dialcohol IVc.

## 2,5-Dimethoxyterephthaldehyde (IVd).

A stirred solution of 26.1 g. (132 mmoles) of dialcohol IVc in 500 ml. of acetone was cooled in an ice bath and 65 ml. of 8 *N* chromic acid (Jones reagent) was added dropwise over 0.5 hour. The resulting mixture was diluted with 500 ml. of water and the yellow solid collected, yield 18.0 g. (93 mmoles, 70%), m.p. 205-209° (lit. (7) m.p. 207°); nmr (deuteriochloroform): singlets at  $\delta$  3.98 (6H), 7.54 (2H), and 10.65 (2H). The compound gives a brilliant green fluorescence under uv light.

## 2,5-Dihydroxyterephthaldehyde (IVe).

This compound was produced as described (9), with the modification that the total black reaction product was extracted overnight with refluxing benzene in a Soxhlet apparatus to isolate the product, m.p. 258-260°, 65% yield (lit. (9) 262°, 35% yield). The compound gives a brilliant purple color in base; nmr (DMSO- $d_6$ ): singlets at  $\delta$  7.35 (2H) and 10.40 (2H).

## 2,5-Dimethoxybenzaldehyde (V).

To a solution of 1.06 g. (7.65 mmoles) of hydroquinone dimethyl ether and 2.69 g. (23 mmoles) of dichloromethyl methyl ether in 30 ml. of methylene chloride under nitrogen was added 5.78 g. (30 mmoles) of titanium tetrachloride. The dark red mixture was refluxed 48 hours. Water was then added and the solution washed with dilute sodium bicarbonate and then water, dried, and the solvent removed to give a solid residue which gave a major blue fluorescent spot by tlc for V and a very minor green one for IVd. Crystallization from ethanol gave 0.59 g. (3.55 mmoles, 46%) of V, m.p. 50-52° (lit. (11) m.p. 51°); nmr (deuteriochloroform):  $\delta$  3.83 (3H, singlet), 7.04 (1H, singlet), 7.11 (1H, doublet,  $J = 3$ ), 7.38 (1H, doublet,  $J = 3$ ), 10.50 (1H, singlet).

Anal. Calcd. for  $\text{C}_9\text{H}_{10}\text{O}_3$ : C, 65.05; H, 6.07. Found: C, 64.92; H, 6.13.

The use of several equivalents of the reagent in various solvents or neat at elevated temperatures gave either compound V or tar, with only traces of IVd being detected by thin layer chromatography. Likewise, use of hydroquinone under these conditions gave only tars, no IVe being formed.

## 2,5-Diacetyxyterephthaldehyde, Orthoacetate (IVf).

A solution of 0.20 g. (1.03 mmoles) of the phenol dialdehyde IVe in 2 ml. of acetic anhydride containing 0.5 g. of sodium acetate was refluxed for 1 hour, then the mixture poured into water and stirred for 10 minutes. Then the hexaacetate was recovered by filtration (0.26 g., 0.57 mmole, 55%) and recrystallized from acetone-ether, m.p. 203-205°. The compound gave back IVe on base hydrolysis and had nmr (deuteriochloroform): singlets at  $\delta$  2.10 (12H), 2.37 (6H), 7.49 (2H), 7.94 (2H); Mass spectrum:  $m/e$  352 (P -  $\text{Ac}_2\text{O}$ ), 250 (Base, P - 2 acetic anhydride); 208, 160.

Anal. Calcd. for  $\text{C}_{20}\text{H}_{22}\text{O}_{12}$ : C, 49.59; H, 4.49. Found: C, 49.49; H, 4.53.

2*H*,7*H*-Benzo[1,2-*b*:4,5-*b'*]dipyran-2,7-dione (II).

An intimate mixture of 1.00 g. (5.15 mmoles) of the phenol dialdehyde IVe and 1.0 g. of anhydrous sodium acetate was added to 3.5 ml. of acetic acid in a 30 cm., 10 mm diameter pyrex tube, which was sealed and heated inside a pipe to 190° for 24 hours. The tube was then cooled in liquid nitrogen and broken. The black residue was stirred with aqueous sodium bicarbonate, filtered, and sublimed at 0.1 mm to give 0.70 g. (3.25 mmoles, 63%) of the benzodipyrone II, which was further purified by crystallization from DMSO, (sublimes above 380°). It was too insoluble in any solvent to obtain an nmr spectrum: ir ( $\nu$  potassium bromide): 3070, 1720, 1610, 1500, 1430, 1320, 1270, 1200, 1100, 890, 840  $\text{cm}^{-1}$ ; Mass spectrum:  $m/e$  214 (P, base), 186 (P-CO), 158 (P-2CO).

Anal. Calcd. for  $\text{C}_{12}\text{H}_6\text{O}_4$ : C, 67.30; H, 2.82. Found: C, 67.19; H, 2.97.

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