Synthesis of 2(3*H*)Benzofuranones from Glyoxal and Phenols

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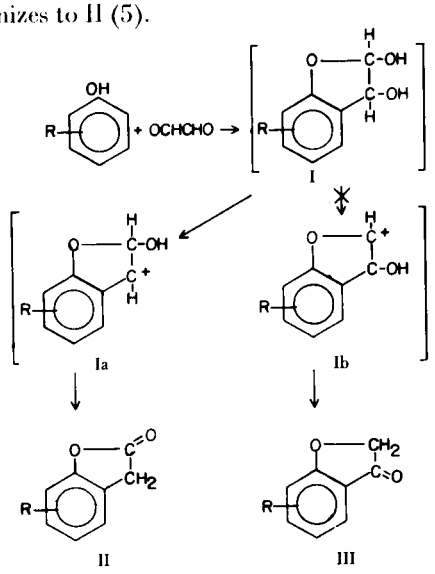
It has been reported that the acid-catalyzed reaction of glyoxal at the *ortho* position of phenols gives resins (1) or substituted 5a,10b-dihydrobenzofuro[2,3-*b*]benzofurans (2,3). Generally, this reaction is carried out at room temperature using large amounts of acid catalyst; however, higher temperatures have also been used (4).

We wish to report that 2(3*H*)benzofuranones (II) and not the benzofurans are readily obtained when the reaction of glyoxal with phenols is carried out at high temperatures in the presence of a relatively small amount of acid catalyst. Also, 3(2*H*)benzofuranones (III) are not formed even though III should be more stable than II, based on resonance theory. This reaction can be explained through the formation of a non-isolable 2,3-dihydroxy-2,3-dihydrobenzofuran (I) which, in the rate-determining step, is dehydroxylated to Ia and not Ib (Ia is more stable than Ib based on resonance theory). Compound Ia rapidly loses a proton to give the aromatic 2-hydroxybenzofuran which ketonizes to II (5).

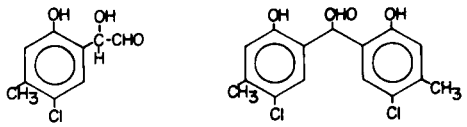


The reaction is conveniently run in refluxing acetic acid with hydrochloric acid or *p*-toluenesulfonic acid as the catalyst. Since 2(3*H*)benzofuranones have previously been prepared by multistep reactions (5), where applicable this reaction represents a very convenient route to 2(3*H*)benzofuranones. Excellent yields are obtained when undesired condensation reactions at *ortho* and *para* positions of the phenolic compound are prevented by substitution (1,6). Thus, 2,4-dialkylphenols give 90% yields of products. Even where polymer forming condensation reactions occur, as in the case of phenol, 4,4′-isopropylidinediphenol, and the like, the formation of 2(3*H*)benzofuranones are detected by the presence of a lactone band at about 1800 cm^{-1} in the infrared spectrum. However, no attempt was made to isolate these products.

Electron withdrawing substituents retard the reaction. No lactone is detected using 2,4-dichlorophenol. 4-Chloro-3-methylphenol gives a relatively poor yield of 5-chloro-4-methyl-2(3*H*)benzofuranone. Interestingly, none of the thermodynamically favored 6-chloro-5-methyl-2(3*H*)benzofuranone forms. A similarity to the Jacobsen reaction (7) is noted.

On the other hand, the acetal from glyoxal and 4-chloro-3-methylphenol is exclusively the thermodynamically favored product 4,7-dichloro-3,8-dimethyl-5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran (2,3). These facts allow us to propose the following reaction mechanisms for the formation of acetals and of benzofuranones.

Acetals are formed by the attack of the large protonated glyoxal carbonium ion at the least hindered *ortho* position of the phenol to give intermediate IV. Intermediate IV gives the benzyl carbonium ion which reacts with another phenol to give V and then the acetal. This mechanism is consistent with the formation of 5a,10b-dihydrobenzofuro[2,3-*b*]-benzofurans rather than their isomeric 4b,9b-dihydrobenzofuro[3,2-*b*]benzofuran ethers (3). The ethers would form if the carbonyl group of IV reacts with another phenol.



On the other hand, benzofuranones are formed by the attack of protonated glyoxal at the phenolic oxygen to give a hemiacetal VI. Hemiacetal VI cyclizes to II. Compound

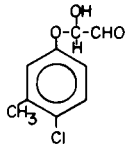
Table I

2(3*H*)Benzofuranones

2(3*H*)Benzofuranone	% Yield	M.P.	Molecular Formula	Analyses
4,7-Di-*t*-butyl-5-hydroxy 2(3*H*)benzofuranone	90	209-211	$C_{14}H_{22}O_2$	Calcd.: C, 75.63; H, 9.97. Found: C, 75.84; H, 9.66.
5-Methyl-7-*t*-butyl-2(3*H*)benzofuranone	90	179-180	$C_{13}H_{16}O_2$	Calcd.: C, 76.44; H, 7.90. Found: C, 76.88; H, 7.91.
4,7-Di-*t*-butylnaphtho-[2,1-*b*]furan-2(1*H*)one	60	186-188	$C_{20}H_{24}O_2$	Calcd.: C, 81.04; H, 8.16. Found: C, 81.23; H, 8.29.
4-*t*-Butyl-6,7,8,9-tetrahydro-naphtho[2,1-*b*]furan-2(1*H*)one	81	168-170	$C_{16}H_{20}O_2$	Calcd.: C, 78.65; H, 8.25. Found: C, 79.08; H, 8.23.
5-Chloro-4-methylbenzofuran-2(3*H*)one	30	132-133	$C_8H_7ClO_2$	Calcd.: C, 59.19; H, 3.86. Found: C, 59.02; H, 3.96.
5,7-Di-*t*-pentyl-2(3*H*)-benzofuranone	95	57-58	$C_{18}H_{26}O_2$	Calcd.: C, 78.22; H, 9.48. Found: C, 78.52; H, 9.50.
5,7-Dimethyl-2(3*H*)-benzofuranone	60	125-127	$C_{10}H_{10}O_2$	Calcd.: C, 74.05; H, 6.22. Found: C, 74.21; H, 6.28.

IIa forms and gives the benzofuranone rather than the acetal by the favored intramolecular reaction. It was proven that IIa does not give the acetal by running the reaction in a fourfold excess of the phenol. Under these reaction conditions only benzofuranone forms. The fact that IIa gives only benzofuranone and no acetal is further support for the proposed mechanism for acetal formation.

Benzofuranones that have been prepared from phenols, hydroquinones, and naphthols are given in Table I.



VI

EXPERIMENTAL

The melting points were determined in capillary tubes in an electrically heated, stirred oil bath and are uncorrected. The ir spectra (Fluorolube mulls) were recorded on a Perkin-Elmer 467 spectrometer and elemental analyses were obtained on a Hewlett Packard CHN-Analyzer Model 185. Pmr spectra were recorded on a Varian A-60 spectrometer with TMS as an internal reference using 10% solutions in deuteriochloroform. The starting phenols and hydroquinone were purchased from Aldrich or Eastman Chemical Companies. The naphthols are reported in the literature (8).

Typical Reaction of Glyoxal with a Phenol.

2-*t*-Butyl-*p*-cresol (33 g., 0.2 mole), 15 g. (0.1 mole) of 40% aqueous glyoxal, and 2 ml. of 38% aqueous hydrochloric acid were dissolved in 150 ml. of glacial acetic acid. The reaction mixture was stirred and refluxed at about 106° for 16 hours, 200 ml. of water was added and the solid collected by filtration to give 38 g. of product (90% yield). The product was recrystallized from glacial acetic acid to give a solid with a melting point of 179-180°. The ir spectrum contained a characteristic strong lactone band at 1800 cm^{-1}. The pmr spectrum was consistent with the structural assignment of 5-methyl-7-*t*-butyl-2(3*H*)benzofuranone: δ 1.38 (s, 9H, CH_3), 2.33 (s, 3H, $PhCH_3$), 3.63 (s, 2H, $-CH_2-$), 6.95 (s, 1H, Ar-H), and 7.04 (s, 1H, Ar-H). The product reacts as a typical lactone. It forms a water soluble sodium salt of the phenylacetic acid on treatment with sodium hydroxide solution which regenerates the lactone on acidification. Compounds given in Table I were made in a similar manner.

5-Chloro-4-methyl-2(3*H*)benzofuranone.

Made according to the above procedure. A VPC showed a 60:40 mixture of starting phenol and lactone product. The product distilled at 110-120°/0.5 and was recrystallized from a benzene-ethanol mixture, m.p. 132-133°; Pmr spectrum: $\delta^A = 7.27$ ppm, $\delta^B = 6.84$, $J_{AB} = 8.8$ (2 aromatic protons), 3.65 (s, 2H, $-CH_2-$), and 2.28 (s, 3H, CH_3). Elemental analysis in Table I.

4,7-Dichloro-3,8-dimethyl-5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran.

4-Chloro-3-methylphenol (43 g., 0.3 mole), 44 g. (0.3 mole) of 40% aqueous glyoxal, and 200 ml. of glacial acetic acid were stirred and maintained at 30° while 50 ml. of concentrated sulfuric acid is slowly added (about 1 hour). The mixture was stirred and heated to 50° for 1 hour more. The mixture was poured into water, filtered, washed with water, and dried to give 35 g. of product, m.p. 254-256° from THF; pmr spectrum: δ, 7.72 (s, 1H, Ar-H), 7.07, 6.96 (d, 1H, J = 6.6 Hz, -OCHO-), 6.91 (s, 1H, Ar-H), 5.21, 5.10 (d, 1H, J = 6.6 Hz, C-H), and 2.25 (s, 6H, $-CH_3$).

Anal. Calcd. for $C_{16}H_{12}Cl_2O_2$: C, 62.56; H, 3.94. Found: C, 62.31; H, 3.97.

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