Reaction of glyoxal at the ortho position of phenols. Synthesis of 5*a*,10*b*-dihydrobenzofuro[2,3-*b*]benzofurans and 2-(3-benzofuranyl)phenols

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The acid-catalyzed reaction of glyoxal at the ortho position of phenols has been shown to yield, as initial products, substituted 5*a*,10*b*-dihydrobenzofuro[2,3-*b*]benzofurans, such structures being indicated by the nuclear magnetic resonance spectra, and confirmed in several cases by synthesis via an unambiguous route. At higher temperatures in acidic media, and in the absence of glyoxal, these initial products were converted into the corresponding 2-(3-benzofuranyl)phenols. When glyoxal was present in acidic media, the 2-(3-benzofuranyl)phenols reacted further to give unidentified products of appreciably higher molecular weight.

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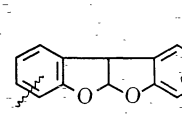
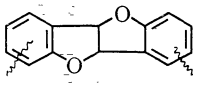
It has been reported by different investigators that the acid-catalyzed reaction of glyoxal at the ortho position of phenols gives products having the acetal type of structure I (1) or the ether type of structure II (2). The reaction of glyoxal with β-naphthol was reported by Dischendorfer (1) to give a compound assigned acetal structure III, based on the fusion of the compound with potassium hydroxide at 220°, which yielded 1,1-methylenebis(2-naphthol). On the other hand, the reaction of glyoxal with *p*-cresol was reported by Rosenthal and Zaionchkovsky (2) to give a product assigned ether structure IV rather than the alternate acetal structure V. The structural assignment in this case was based on the fact that their product was identical with that obtained by the bimolecular reduction of 2-hydroxy-4-methylbenzaldehyde, which had been assigned structure IV by Anselimo (3). Stevens and Dobbs (4) reported that the reaction of glyoxal with 2-*t*-butyl-4-methylphenol yielded a product possessing either structure VI or structure VII, but they did not attempt to distinguish between these two possibilities. A recent article reviewing previous work (but not that of Dischendorfer) stated that the reaction of glyoxal at the ortho position of phenols gave products having the ether type of structure II (5).

Since we were interested in the utilization of products having the acetal type of structure I as intermediates for the synthesis of 2-(3-benzofuranyl)phenols (6), we examined the 100 Mc.p.s. nuclear magnetic resonance (n.m.r.) spectra of these condensation products of glyoxal and phenols obtained by previous authors. Acetals VIII and IX



I



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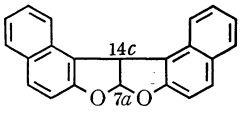
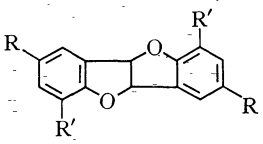
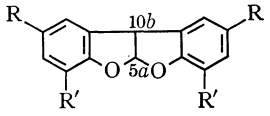


III



IV R = CH_3, R′ = H
VI R = CH_3, R′ = $C(CH_3)_3$



V R = CH_3, R′ = H
VII R = CH_3, R′ = $C(CH_3)_3$
VIII R = Cl, R′ = H
IX R = R′ = Cl

were prepared by the unambiguous method of Riemschneider and his associates (7), and the n.m.r. spectra of these acetals were used for comparison with those of the three compounds whose structures were in question. In all cases the n.m.r. spectra indicated that the compounds had the acetal structure, i.e. III, V, and VII were the correct structures. The spectra of all these compounds (III, V, VII, VIII, and IX) showed a doublet (J = 6–7 c.p.s.) in the region δ 4.8–5.4 p.p.m. assigned to the hydrogen on the diarylmethyl carbon (C-10*b* in V, VII, VIII, and IX; C-14*c* in III), and a doublet (J = 6–7 c.p.s.) in the region δ 6.8–7.0 p.p.m. assigned to the hydrogen on the acetal carbon (C-5*a* in V, VII, VIII, and IX; C-7*a* in III).[1] In some of these compounds (V, VII, and VIII) bands arising from the aromatic protons partially overlapped the doublet assigned to the hydrogen on the acetal carbon. It was found that, by running the n.m.r. spectra in acetone or in an acetone-d_6–deuteriochloroform mixture, the acetal hydrogen doublet was shifted downfield relative to the bands attributed to the aromatic protons, and that overlapping was removed (cf. Fig. 1). While this work was in progress, Thyagarajan *et al.* (8) published the 60 Mc.p.s. n.m.r. spectrum of the glyoxal–*p*-cresol reaction product and concluded from their spectrum that the acetal structure V was the correct one. However, on the basis of the 100 Mc.p.s. spectra obtained in the present investigation, we consider their interpretation of the 60-Mc.p.s. spectrum to be incorrect; they assigned the two signals at δ 4.8 and 4.9 p.p.m. to the hydrogens on C-5*a* and C-10*b* (i.e. each signal represented one hydrogen), and failed to detect anything except aromatic protons in the δ 6.6–7.1 p.p.m. region. The 100 Mc.p.s. spectra of the present investigation leave little doubt that the signals at δ 4.8 and 4.9 p.p.m. represent a doublet assignable to the hydrogen on C-10*b*, and that the hydrogen on C-5*a* is represented by a doublet at δ 6.8 p.p.m.

The structure of VII was confirmed by synthesis via the unambiguous method of Riemschneider (7); 2-*t*-butyl-4-methylphenol was condensed with dichloroacetaldehyde diethyl acetal to yield α,α-bis(3-*t*-butyl-2-hydroxy-5-methylphenyl)-β,β-dichloroethane, which, on treatment with potassium hydroxide in methanol at room temperature, gave acetal VII, identical with the product obtained by the condensation of glyoxal with 2-*t*-butyl-4-methylphenol. Similarly, condensation of *p*-cresol with dichloroacetaldehyde diethyl acetal gave α,α-bis(2-hydroxy-5-methylphenyl)-β,β-dichloroethane, which, when treated with potassium hydroxide in methanol, gave acetal V in a good yield. Acetal V obtained by this method was identical with the glyoxal–*p*-cresol reaction product.

It was also found that the condensation of glyoxal with *p*-chlorophenol gave acetal VIII, identical with acetal VIII prepared by the unambiguous method of Riemschneider and his associates (7).

The condensations of glyoxal with these phenols were carried out under strongly acidic conditions, but at sufficiently low temperatures and (or) a sufficiently high initial concentration of the phenol that the acetal, as it formed, was insoluble in the reaction medium and did not appear to undergo further reaction. However, it was already known that acetals possessing structure I were readily converted into the corresponding 2-(3-benzofuranyl)phenols by refluxing them in acetic acid containing hydrochloric acid (1) or by heating them in 10% aqueous sulfuric acid (6). In agreement with previous results, it was found that the treatment of acetal V with refluxing acetic acid containing sulfuric acid readily effected conversion of the acetal into 2-(5-methyl-3-benzofuranyl)-4-methylphenol (X). Analysis of the crude product

[1]A referee has suggested the use of the spin-decoupling technique to confirm the assignments of the signals attributed to the hydrogen on the diarylmethyl carbon and to the hydrogen on the acetal carbon. Double-resonance experiments, using frequency-swept spin decoupling, and deuteriochloroform as solvent, were therefore carried out on acetals III and V. In both cases irradiation at the resonance frequency of the doublet assigned to the hydrogen on the diarylmethyl carbon (C-14*c* in III, C-10*b* in V) caused the doublet assigned to the hydrogen on the acetal carbon (C-7*a* in III, C-5*a* in V) to collapse to a singlet.

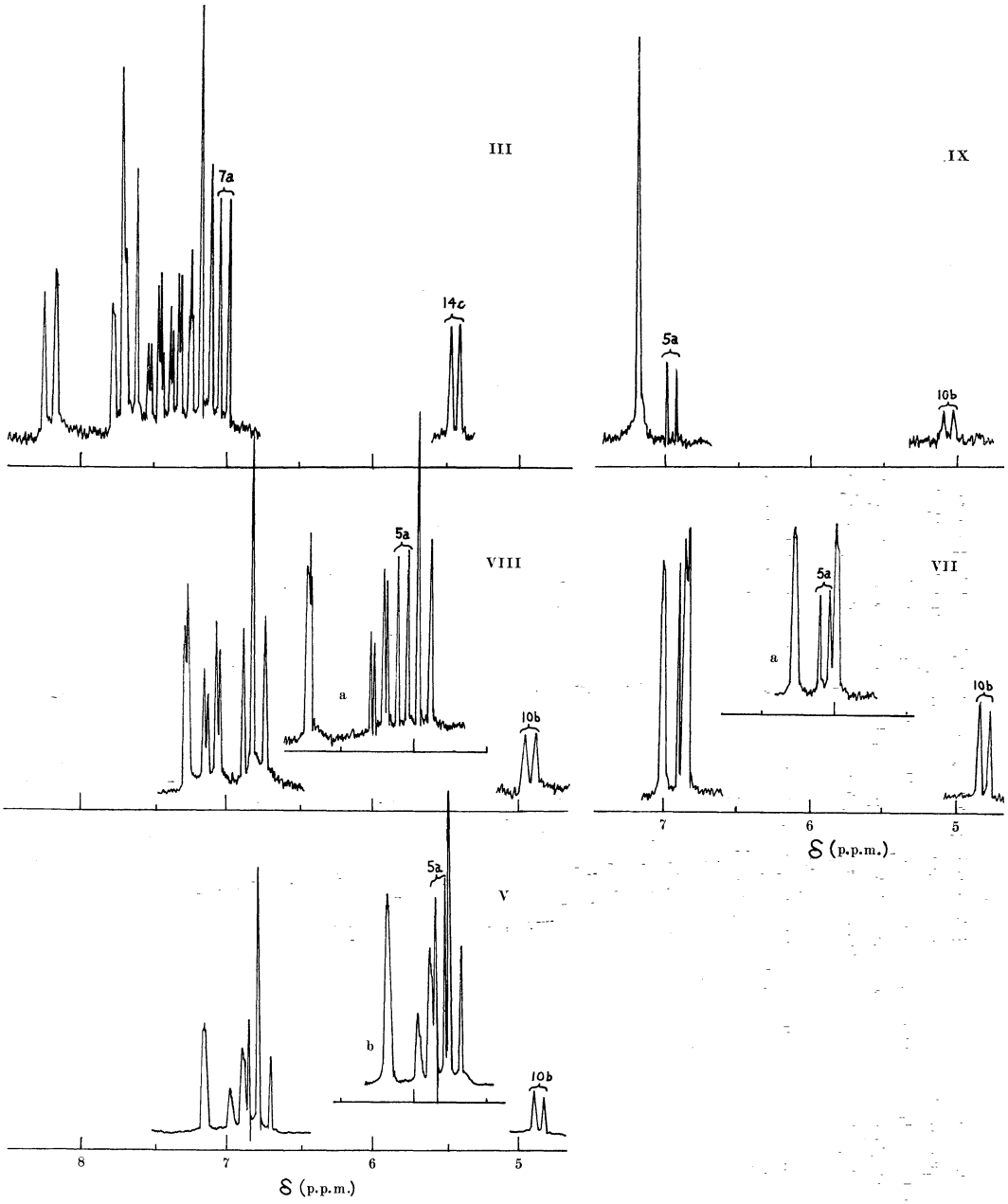
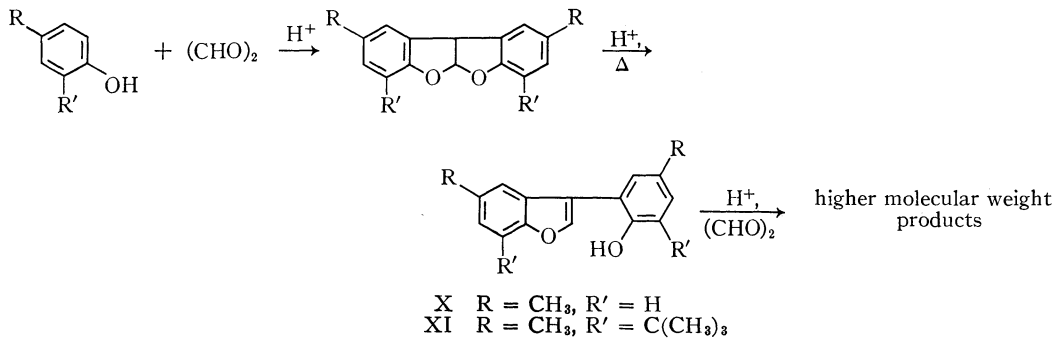


FIG. 1. Partial n.m.r. spectra at 100 Mc.p.s. of acetals III, V, VII, VIII, and IX. The insert spectra indicate the effect of determining the spectra in (*a*) acetone and (*b*) 12% acetone-d_6 in deuteriochloroform.

from this reaction by gas–liquid chromatography (g.l.c.) indicated the presence of about 5% of an impurity with a longer retention time than X. The infrared spectrum of the crude product showed a weak peak at 1 760 cm^{-1}, suggesting that the impurity might be the acetate of X. Further evidence that the impurity might be the acetate of X was obtained by saponification of the crude product, which resulted in the



X R = CH_3, R′ = H
XI R = CH_3, R′ = $C(CH_3)_3$

REACTION SCHEME 1. Reactions of *p*-cresol and 2-*t*-butyl-4-methylphenol with glyoxal in the presence of sulfuric acid.

disappearance of the peak in the infrared spectrum at 1 760 cm^{-1}, and also in the disappearance of the impurity peak in the gas–liquid chromatogram. The saponification product showed only one peak (X) on g.l.c. analysis.

Since acetal V could thus be converted into benzofuranyl phenol X, it was conjectured that the direct condensation of *p*-cresol with glyoxal in refluxing acetic acid containing sulfuric acid should yield benzofuranyl phenol X. Attempts to effect this reaction were not successful until it was observed that both benzofuranyl phenols X and XI reacted with glyoxal at room temperature to yield further condensation products of higher molecular weight (whose structures have not yet been investigated). Thus it was necessary to ensure that all the glyoxal had been consumed in the formation of the acetal before further conversion of the acetal into the benzofuranyl phenol was attempted. This could be effected by carrying out the condensation of 2 moles of the phenol with 1 mole of glyoxal at room temperature to yield the acetal, and then heating the reaction mixture containing the acetal to reflux to effect conversion into the benzofuranyl phenol. In this manner both benzofuranyl phenols X and XI were obtained directly from the corresponding phenols and glyoxal. These reactions are summarized in Reaction Scheme 1.

Although these results showed that 2-(3-benzofuranyl)phenols could be synthesized from the appropriate phenol and glyoxal, other experiments indicated that a better method of synthesis of the benzofuranyl phenols was to react the appropriate acetal of the type of structure I with potassium hydroxide in hot methanolic dimethyl sulfoxide. This method resulted in higher yields and purer products in the two cases investigated, both benzofuranyl phenols X and XI being obtained in an excellent yield from the corresponding acetals. Reactions of similar acetals with base to yield the corresponding benzofuranyl phenols have already been observed (1, 6).

EXPERIMENTAL

The infrared spectra were recorded as Nujol mulls or thin films (neat). The ultraviolet spectra were measured in methanol. The 100 Mc.p.s. n.m.r. spectra were measured in deuteriochloroform, acetone, or acetone-d_6–deuteriochloroform mixtures, either with tetramethylsilane as internal standard or, for the spectra recorded in acetone, corrected to refer to tetramethylsilane as $\delta = 0$ p.p.m. The melting points are uncorrected.

For the g.l.c. analyses, a 4 ft × ¼ in. column containing 2% SE-30 on Chromosorb P was used, with flame-ionization detection. The column was operated at 180° and 35 ml of helium/min for analysis of products containing acetal V and benzofuranyl phenol X. The column was operated at 205° and 45 ml of helium/min for analysis of products containing acetal VII and benzofuranyl phenol XI.

Synthesis of Acetals Having Structure I by Reaction of the Appropriate Phenol with Glyoxal

The following standard procedure gave reasonable yields of acetals III, V, and VII. In the case of acetal VIII it was necessary to reduce the amount of solvent (acetic acid) employed before the acetal could be isolated, albeit in only a moderate yield.

A mixture of the phenol (0.10 mole) and glyoxal (0.05 mole of a 40% aqueous solution) was dissolved in acetic acid (100 ml). Concentrated sulfuric acid

(20 ml) was added drop by drop, with stirring, the temperature of the reaction mixture being kept between 25 and 30°. During the addition of the sulfuric acid (15–35 min) the acetal began to precipitate from solution. The mixture was then stirred at room temperature until the total time of addition and stirring was 1 h. The reaction mixture was then poured into water (500 ml), and the product was removed by filtration and washed with water. The crude product was slurried with dilute sodium hydroxide, removed by filtration, washed with water, and dried. (In one experiment, in which all of the acid had not been removed from the crude acetal, subsequent drying at 100° resulted in extensive decomposition.)

Details concerning the synthesis of each individual acetal are given under the appropriate title in the following part of the Experimental.

Synthesis of Acetal III by Reaction of β-Naphthol with Glyoxal

The standard procedure was employed. The crude product, m.p. 170–210°, 15.3 g, was recrystallized from acetic acid to give 12.2 g (79%) of acetal III, m.p. 227–233°. Further recrystallizations from acetic acid gave acetal III, m.p. 236.5–238° (reported m.p. 235° (1)).

Synthesis of Acetal V (5a,10b-Dihydro-2,9-dimethylbenzofuro[2,3-b]benzofuran)

By Ring Closure of α,α-Bis(2-hydroxy-5-methylphenyl)-β,β-dichloroethane

Crude α,α-bis(2-hydroxy-5-methylphenyl)-β,β-dichloroethane, m.p. 70–80° (0.55 g), was dissolved in methanol (2 ml). To this solution was added potassium hydroxide (0.5 g) dissolved in methanol (5 ml). The reaction mixture was stirred at 20° for 1.25 h. The resultant precipitate was removed by filtration and washed with methanol and water to yield 0.36 g (87%) of acetal V, m.p. 193–193°. The product was recrystallized from ethanol to give long colorless blades, m.p. 195.5–196°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.23; H, 5.89.

By Reaction of p-Cresol with Glyoxal

The standard procedure was employed. The crude product, m.p. 150–180°, 8.1 g, was recrystallized from ethanol to give 6.3 g (53%) of acetal V, m.p. 194–194.5° (reported m.p. 192–194° (2)). The mixture melting point with authentic acetal V of m.p. 195.5–196° was 195–195.5°.

Synthesis of Acetal VII (4,7-Di-t-butyl-5a,10b-dihydro-2,9-dimethylbenzofuro[2,3-b]benzofuran)

By Ring Closure of α,α-Bis(3-t-butyl-2-hydroxy-5-methylphenyl)-β,β-dichloroethane

The α,α-bis(3-*t*-butyl-2-hydroxy-5-methylphenyl)-β,β-dichloroethane (3.61 g) was dissolved in methanol (21 ml). To this solution (in a nitrogen atmosphere) was added potassium hydroxide (3.5 g) in methanol (30 ml), with stirring and sufficient cooling to keep the reaction mixture temperature below 25°. The reaction mixture was stirred at room temperature for 1 h. The resultant precipitate was removed by filtration, washed with methanol and water, and dried to yield 1.74 g (58%) of acetal V, m.p. 185–193°. Two recrystallizations from hexane gave colorless crystals, m.p. 194–195°.

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 81.93; H, 8.53.

By Reaction of 2-t-Butyl-4-methylphenol with Glyoxal

The standard procedure was employed. The crude product, m.p. 175–185°, 14.5 g, was recrystallized from ethanol–acetone (3:1 v/v) (seeding with authentic acetal VII) to give 10.9 g (62%) of acetal VII, m.p. 190.5–194° (reported m.p. 190.5–191.5° (4)). The mixture melting point with authentic acetal VII of m.p. 194–195° was 190.5–193°.

Synthesis of Acetal VIII by Reaction of p-Chlorophenol with Glyoxal

The standard procedure was employed, except that only 20 ml of acetic acid (rather than 100 ml) was used as the solvent. The crude product was recrystallized from acetic acid to give 3.5 g (25%) of acetal VIII, m.p. 234–236°. The mixture melting point with authentic acetal VIII of m.p. 232–235°, prepared by the method of Riemschneider (7), was 232–234.5°.

Synthesis of α,α-Bis(2-hydroxy-5-methylphenyl)-β,β-dichloroethane

A solution of *p*-cresol (10.8 g, 0.10 mole) in tetrahydrothiophene 1,1-dioxide (100 ml) was stirred at 0–5° while sulfuric acid (15 ml), and dichloroacetaldehyde diethyl acetal (9.0 g, 0.05 mole) in tetrahydrothiophene 1,1-dioxide (10 ml), were added at the same time from separate dropping funnels. After the addition was completed (50 min), the reaction solution was stirred at 0–5° for a further 1 h, and then at room temperature overnight. The brown solution was poured into water (500 ml) to give a waxy solid, which was removed by filtration and washed with water.

This waxy solid (m.p. ~70–80°) was dissolved in benzene–ether and the solution washed many times with water. After the mixture was dried over sodium sulfate, film evaporation left a gummy solid smelling strongly of tetrahydrothiophene 1,1-dioxide. The gummy solid was heated on the steam bath (*in vacuo*) to give a solid material which was dissolved in carbon tetrachloride. The carbon tetrachloride solution was washed four times with water, dried over sodium sulfate, and film evaporated to leave 11.4 g of product, m.p. 125–135°. Two recrystallizations from benzene–hexane gave 6.9 g (45%) of crystalline α,α-bis(2-hydroxy-5-methylphenyl)-β,β-dichloroethane, m.p. 141–142°. Analytically pure material from a similar experiment had m.p. 141.5–142.5°.

Anal. Calcd. for $C_{16}H_{16}Cl_2O_2$: C, 61.75; H, 5.18. Found: C, 62.08; H, 5.30.

Synthesis of α,α-Bis(3-t-butyl-2-hydroxy-5-methylphenyl)-β,β-dichloroethane

A mixture of 2-*t*-butyl-4-methylphenol (6.6 g, 0.04 mole) and dichloroacetaldehyde diethyl acetal (3.6 g, 0.02 mole) was warmed to effect solution, and then cooled to 15°; sulfuric acid (5 ml) was added drop by drop, with stirring, the temperature of the

reaction mixture being kept below 25°. After the addition of the sulfuric acid was completed (30 min), the reaction mixture was stirred for a further 15 min at room temperature. The mixture of solid and supernatant liquid was distributed between benzene and water. The benzene layer was washed five times with water, dried over sodium sulfate, and film evaporated to give a crude, partially crystalline product. Four recrystallizations from hexane gave 1.0 g of product, m.p. 177–185°. The n.m.r. spectrum had peaks at δ 1.40 (18H, singlet), 2.25 (6H, singlet), 5.16 (1H, doublet, J = 10 c.p.s.), 5.82 (2H, singlet, peak disappeared after exchange with D_2O), 6.50 (1H, doublet, J = 10 c.p.s.), and 6.95 p.p.m. (4H, singlet), assigned, respectively, to the *t*-butyl protons, the methyl protons, the proton on the diarylmethyl carbon, the hydroxyl protons, the proton on the dichloromethyl carbon, and the protons on the benzene rings.

Anal. Calcd. for $C_{24}H_{32}O_2Cl_2$: C, 68.10; H, 7.62. Found: C, 68.13; H, 7.56.

Synthesis of 2-(5-Methyl-3-benzofuranyl)-4-methylphenol (X)

By Reaction of Acetal V with Potassium Hydroxide in Methanolic Dimethyl Sulfoxide

Acetal V (5.2 g) was dissolved in dimethyl sulfoxide (50 ml). A solution of potassium hydroxide (5 g) in methanol (50 ml) and dimethyl sulfoxide (75 ml) was added, under nitrogen, and the solution warmed (no refluxing) on the steam bath for 1 h. After the solution was left overnight at room temperature, it was poured into water (500 ml) containing concentrated hydrochloric acid (7.5 ml). The mixture was extracted with benzene, and the benzene extract was washed with water, dried over sodium sulfate, and film evaporated to yield 5.0 g of a brown oil. Distillation gave 4.1 g of a yellow viscous oil, b.p. 163–165° at 1.8 mm. Analysis by g.l.c. indicated 27% of acetal V and 73% of benzofuranyl phenol X.

The total distillate was reacted again with potassium hydroxide in methanolic dimethyl sulfoxide, the mixture being heated this time with an oil bath to ensure that it refluxed for 1 h. Isolation of the product as before gave 3.9 g of an oil, which was shown by g.l.c. analysis to contain only benzofuranyl phenol X, and no acetal V. Distillation gave 2.9 g (56%) of benzofuranyl phenol X as a yellow viscous oil, b.p. 169–171° at 1.3 mm, n_D^{25} 1.6194. For analysis, the distilled material was evaporated and condensed in a sublimation apparatus at 120° and 1.3 mm to yield X as a pale-yellow oil, n_D^{25} 1.6192, λ_{max} 291 (ϵ 7 700), 283 (ϵ 6 700), and 251 mμ (ϵ 11 200). The n.m.r. spectrum showed peaks at δ 2.30 (3H, singlet), 2.40 (3H, singlet), 5.00 (1H, singlet, peak disappeared after exchange with D_2O), 6.82–7.44 (6H, multiplet), and 7.68 p.p.m. (1H, singlet), assigned, respectively, to the protons of the two methyl groups on the benzene rings, the hydroxyl proton, the protons on the benzene rings, and the proton on the α-carbon of the furan ring.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.54; H, 5.85.

The 3,5-dinitrobenzoate, prepared by reaction with 3,5-dinitrobenzoyl chloride in pyridine, had m.p. 181.5–182° (crystallized from ethanol).

Anal. Calcd. for $C_{23}H_{16}N_2O_7$: C, 63.89; H, 3.73. Found: C, 64.20; H, 3.76.

(The reaction of acetal V with methanolic dimethyl sulfoxide containing potassium hydroxide was repeated, this time ensuring that the reaction solution was refluxed (with stirring) for 2.75 h. Isolation of the product as before gave 90% (distilled product) of benzofuranyl phenol X, shown by g.l.c. analysis to be free of other material.)

By Reaction of Acetal V in Refluxing Acetic Acid Containing Sulfuric Acid

Acetal V (1.17 g) was heated for 30 min in refluxing acetic acid (30 ml) containing sulfuric acid (0.5 ml) and water (2.0 ml). The pale-yellow solution was cooled and poured into water, and the mixture was extracted with ether. The ether extract was washed with water, dilute potassium carbonate, and water, and then dried over sodium sulfate. Film evaporation yielded 0.92 g of a pale-green oil; its infrared spectrum was very similar to that of 2-(5-methyl-3-benzofuranyl)-4-methylphenol (X), except for the addition of a weak peak at 1 760 cm^{-1}. Analysis by g.l.c. indicated 95% of benzofuranyl phenol X and 5% of an impurity with a retention time of 1.33 relative to X, but no acetal V.

The crude product (0.72 g) was dissolved in ethanol (10 ml). Sodium hydroxide (0.95 g) in water (2 ml) was added, and the solution was refluxed (under nitrogen) for 1.5 h. The solution was then cooled and poured into water (100 ml) containing concentrated hydrochloric acid (2.5 ml), and the mixture was extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and film evaporated, and the residue was dissolved in benzene and again film evaporated to yield 0.64 g of a brown oil. The infrared spectrum of this brown oil was identical with that of the analytically pure benzofuranyl phenol X prepared by the first described method. Analysis by g.l.c. indicated the presence of only one component (X).

A sample was evaporated and condensed in a sublimation apparatus at 130° and 0.7 mm to give a viscous yellow oil, n_D^{25} 1.6198 (found for analytically pure X: n_D^{25} 1.6192).

By Reaction of Glyoxal with p-Cresol

A mixture of *p*-cresol (10.8 g, 0.10 mole) and glyoxal (7.25 g of a 40% aqueous solution, 0.05 mole) was dissolved in acetic acid (30 ml) and water (10 ml). Sulfuric acid (10 ml) was added drop by drop, with stirring, the temperature of the reaction mixture being kept at 20–30°. After the mixture was stirred for 30 min at 30°, a further 10 ml of sulfuric acid was added and the mixture stirred for another 30 min. The resultant slurry of acetal V was heated to 70°, an additional 40 ml of acetic acid added, and the reaction mixture heated to 110–120° and stirred at that temperature for 15 min. The dark-brown solution was cooled, poured into water (500 ml), and extracted with benzene. The benzene solution was washed with water, dilute potassium car-

bonate, and again water, dried over sodium sulfate, and film evaporated to yield 11.0 g of a viscous brown oil.

A 9.0 g portion of this oil was distilled to yield 5.8 g of distillate, b.p. 142–150° at 0.5 mm. The infrared spectrum of the distillate was very similar to that of the benzofuranyl phenol prepared by the first described method, but, in addition, showed weak-intensity peaks at 1 840 and 1 755 cm^{-1}.

The total distillate was dissolved in ethanol (30 ml), sodium hydroxide (5 g) in water (10 ml) added, and the solution refluxed (under nitrogen) for 2 h. The solution was cooled, poured into water (300 ml) containing concentrated hydrochloric acid (11 ml), and extracted with benzene. The benzene extract was washed three times with water, dried over sodium sulfate, and film evaporated to leave 5.0 g of a viscous orange oil. A 4.2 g portion was distilled to yield 3.4 g of a pale-yellow, viscous oil, b.p. 140–144° at 0.1 mm, n_D^{25} 1.6239. The infrared spectrum was identical with that of the analytically pure X prepared by the first described route. Analysis by g.l.c. indicated 98% of benzofuranyl phenol X and 2% of acetal V, but no other peaks. The overall yield of benzofuranyl phenol X by this method was calculated to be 44%.

Reaction of Benzofuranyl Phenol X with Glyoxal in the Presence of Sulfuric Acid

A mixture of benzofuranyl phenol X (2.12 g, 0.0089 mole) and glyoxal (0.65 g of a 40% aqueous solution, 0.0045 mole) was dissolved in acetic acid (12 ml), and a solution of sulfuric acid (2 ml) in acetic acid (2 ml) was added drop by drop, with stirring, the temperature of the reaction solution being kept at 20–25°. The solution was then stirred at room temperature for 45 min, during which a gum precipitated.

The entire mixture was poured into water (100 ml), and the resultant, greenish-yellow solid was removed by filtration, washed with water, resuspended (with stirring) in water, separated by filtration, and dried to yield 1.91 g of a pale yellow green solid, m.p. ~130–140°. The infrared spectrum of the product showed many differences from that of the benzofuranyl phenol X, but hydroxyl absorption (band at 3 420 cm^{-1}) remained. The ultraviolet spectrum had λ_{max} 292, 284, 280 (sh), and 267 mμ.

The crude product was washed with sodium carbonate solution and water, dried, dissolved in chloroform, and filtered to remove a trace of insoluble material. The chloroform solution was film evaporated to leave an orange resin which was dissolved in acetic acid. The acetic acid solution was poured into water to yield a pale-yellow precipitate, which was removed by filtration, washed with carbonate solution and water, and dried. The amorphous solid thus obtained had m.p. ~130–140° and a molecular weight (osmometric in acetone) of 524.

Synthesis of 2-t-Butyl-6-(7-t-butyl-5-methyl-3-benzofuranyl)-4-methylphenol (XI)

By Reaction of Acetal VII with Potassium Hydroxide in Methanolic Dimethyl Sulfoxide

Acetal VII (1.1 g) was suspended in dimethyl sulfoxide (10 ml), and potassium hydroxide (1 g) in methanol (10 ml) and dimethyl sulfoxide (10 ml) was added all at once. The mixture was heated on the steam bath (in a nitrogen atmosphere) for 4 h, during which the acetal dissolved and the solution turned yellow. The solution was then cooled and poured into water (100 ml) containing concentrated hydrochloric acid (1.5 ml). The precipitate which formed was removed by filtration, washed with water, and dried to yield 1.0 g (91%) of benzofuranyl phenol XI, m.p. 30–50°. Analysis by g.l.c. indicated the presence of no remaining acetal in the product and only a trace of other contaminants (<1%).

A sample was distilled to yield a colorless glass, b.p. 110–120° at 0.4 mm, which was sublimed at 110° and 0.03 mm to yield colorless glassy benzofuranyl phenol XI, m.p. 45–50°, λ_{max} 291 (ε 6 700), 283 (ε 6 000), and 248 (sh) mμ (ε 10 500). The n.m.r. spectrum showed peaks at δ 1.44 (9H, singlet), 1.51 (9H, singlet), 2.29 (3H, singlet), 2.38 (3H, singlet), 5.27 (1H, singlet, peak disappeared after exchange with D_2O), 6.97–7.13 (4H, multiplet), and 7.69 p.p.m. (1H, singlet), assigned, respectively, to the protons of the *t*-butyl groups on the benzene rings, the protons of the methyl groups on the benzene rings, the hydroxyl proton, the protons on the benzene rings, and the proton on the α-carbon of the furan ring.

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 82.03; H, 8.41.

The 3,5-dinitrobenzoate, prepared by reaction with 3,5-dinitrobenzoyl chloride in pyridine, had m.p. 202–204° (crystallized from ethanol).

Anal. Calcd. for $C_{31}H_{32}N_2O_7$: C, 68.37; H, 5.92. Found: C, 68.19; H, 6.03.

By Reaction of 2-t-Butyl-4-methylphenol with Glyoxal

A mixture of 2-*t*-butyl-4-methylphenol (1.64 g, 0.01 mole) and glyoxal (0.73 g of a 40% aqueous solution, 0.005 mole) was dissolved in acetic acid (7 ml), and sulfuric acid (1 ml) in acetic acid (3 ml) was added drop by drop, with stirring, the temperature of the reaction mixture being kept below 30°. Stirring was continued at room temperature for 15 min, a further 20 ml of acetic acid added, and the mixture then refluxed for 30 min. The resultant, dark-red solution was cooled, poured into water (200 ml), partially neutralized with potassium carbonate, and extracted with benzene. The benzene extract was washed several times with water, dried over sodium sulfate, and film evaporated to leave 1.9 g of a partially crystalline product.

The crude product was stirred with methanol (10 ml), and the insoluble material was removed by filtration and washed with methanol. The combined filtrates were film evaporated to leave 1.1 g of a viscous oil. Chromatography of this oil on 40 g of silica gel, with hexane as eluent (50 ml fractions), gave, in the second and third fractions, 0.51 g of a pale-yellow gum. Analysis by g.l.c. indicated 94% of benzofuranyl phenol XI, 5% of acetal VII, and 1% of other unidentified peaks. This was equivalent to an overall yield of benzofuranyl phenol XI of 27%.

The 3,5-dinitrobenzoate of the chromatographed material had m.p. 202.5–203.5°, mixture m.p. 200–203° with authentic 3,5-dinitrobenzoate of XI.

Reaction of Benzofuranyl Phenol XI with Glyoxal in the Presence of Sulfuric Acid

A mixture of benzofuranyl phenol XI (0.062 g, 1.77 mmoles) and glyoxal (0.020 g of a 40% aqueous solution, 1.41 mmoles) was dissolved in acetic acid (3.7 ml). Sulfuric acid (0.1 ml) in acetic acid (1 ml) was added drop by drop, with stirring, the temperature of the reaction solution being kept at 20–25°. The solution was stirred at room temperature for 30 min, and then at 80° for 30 min.

The resultant, dark-red solution was cooled and poured into water (50 ml) to give a precipitate, which was removed by filtration, washed with water, and dried to give 0.051 g of a grey powder, m.p. ~90–100°. The infrared spectrum still showed hydroxyl absorption (bands at 3 520 and 3 550 cm^{-1}). The ultraviolet spectrum had λ_{max} 291, 283, and 253 (sh) $m\mu$. The molecular weight (osmometric in acetone) was **712.**

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