Benzodifurans. I. The Synthesis of Benzo[1,2-*b*:5,4-*b*']difuran and Some Methyl Analogs (1)

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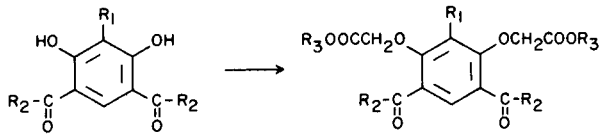
The first parent benzodifuran (XVI) and three di- and trimethylated derivatives have been synthesized and screened for erythemal activity (negative response). Two benzodifurans were prepared from resorcinol and 2-methylresorcinol by acetylation, Fries rearrangement, alkylation of the resulting 4,6-diacetylresorcinols with ethyl bromoacetate, saponification, and then cyclization of the (4,6-diacetyl-1,3-phenylenedioxy)diacetic acids. Another was prepared from the Claisen rearrangement product of 1,3-bis(allyloxy)-2-methylbenzene by acetylation, bromination, and cyclization. Ozonolysis of the Claisen rearrangement product gave additional support to the formulation of *o*-hydroxyphenylacetaldehydes as cyclic hemiacetals. The parent benzodifuran was synthesized from 5-formyl-6-hydroxybenzofuran, which was prepared in two steps from 5-bromo-6-methoxybenzofuran. Alkylation of the former with ethyl bromoacetate, saponification, and cyclization furnished benzo[1,2-*b*:5,4-*b*']difuran. The ultraviolet and nuclear magnetic resonance spectra of the four benzodifurans are compared.

The potent dermal photosensitizing activity of furo[3,2-*g*]coumarins (psoralens) (3) raises the possibility of similar activity in structurally related compounds. However, during the late 1950's several structure-activity studies supported the conclusion that this type of activity is limited to psoralens (3-4). Therefore, it was exciting and surprising to learn that a very crude sample of 2,6,8-trimethylbenzo[1,2-*b*:5,4-*b*']difuran (IX) prepared in our laboratories elicited a "quite active" erythemal response when screened on depilated albino guinea-pigs (5). That response stimulated the work reported in this article. Described below are syntheses of three methyl-substituted benzo[1,2-*b*:5,4-*b*']difurans (the benzodifuran ring system most similar to that of psoralen) as well as the synthesis of the unsubstituted (or parent) compound. This is the first report of any parent benzodifuran. When the pure benzodifurans were subjected to erythemal screening, the response was negative (6).

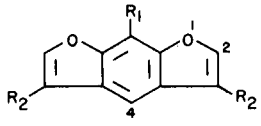
Syntheses of linear benzodifurans must overcome unfavorable directive effects whether resorcinol derivatives or 6-hydroxybenzofurans are used as intermediates. For example, resorcinol diacetate when treated with aluminum chloride (Fries reaction) gave a mixture of 2,4-diacetyl- and 4,6-diacetylresorcinol (Ia). In our hands separation by steam distillation (7) gave the 4,6-isomer in only 15% yield.

Repetition of the work of Algar, Barry, and Tworney (8) by alkylation of 4,6-diacetylresorcinol with ethyl bromoacetate, saponification of the resulting ester IIa, and then decarboxylative cyclization according to Rössing (9) gave 3,5-dimethylbenzo[1,2-*b*:5,4-*b*']difuran (IIIa) (10). Although we obtained a yield of 74% in the final step



Ia. $R_1 = H, R_2 = CH_3$
b. $R_1 = R_2 = CH_3$
c. $R_1 = CH_3, R_2 = H$

IIa. $R_1 = H, R_2 = CH_3, R_3 = C_2H_5$
b. $R_1 = R_2 = CH_3, R_3 = C_2H_5$
c. $R_1 = R_2 = CH_3, R_3 = H$
d. $R_1 = CH_3, R_2 = H, R_3 = C_2H_5$

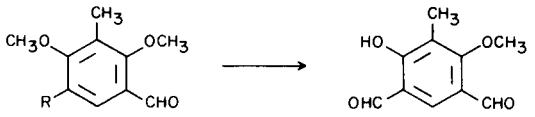


IIIa. $R_1 = H, R_2 = CH_3$
b. $R_1 = R_2 = CH_3$
c. $R_1 = CH_3, R_2 = H$

instead of the reported 38% (8), the overall yield from resorcinol was only 6.5% due to the low yield in the Fries rearrangement step.

To overcome that problem, 2-methylresorcinol was converted into its diacetate (11), which underwent the Fries rearrangement to give 4,6-diacetyl-2-methylresorcinol (Ib) in 58% yield. Alkylation and then saponification of the resulting ester IIb followed by cyclization gave the new benzodifuran IIIb in 8.6% overall yield from 2-methylresorcinol. This value is deceptively low since the alkylation and then saponification sequence was not investigated thoroughly and proceeded in only 27% overall yield.

We also investigated an approach to the synthesis of the 8-methylbenzodifuran (IIIc). 4,6-Dihydroxy-5-methylisophthalaldehyde (Ic) was prepared by the method used by Geissman and coworkers for the 5-ethyl derivative (12). 2,4-Dihydroxy-3-methylbenzaldehyde (13) was methylated, and the dimethyl ether (IVa) was chloromethylated. Conversion of the chloromethyl derivative IVb into the corresponding carbinol and then oxidation with nitric acid gave the isophthalaldehyde IVc, which was demethylated with 24% hydrobromic acid in a sealed tube at 130° to give the dibasic phenol Ic. Demethylation of IVc in refluxing 24% hydrobromic acid furnished the partially demethylated compound V. Alkylation of Ic with ethyl bromoacetate furnished the ester IId as a sharp-melting, white solid, which on attempted saponification gave in low yield a yellow solid which could not be characterized.



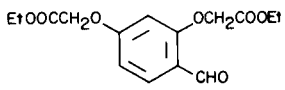
V

IVa. R = H
b. R = CH_2Cl
c. R = CHO

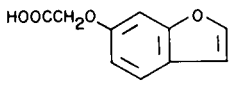
Ic

To investigate the recalcitrant saponification, 2,4-dihydroxybenzaldehyde was converted into the ester VI. Attempted saponification of this ester followed by crystallization of the crude product from 1% hydrochloric acid gave in greater than theoretical yield a tan solid which contained sodium. This report is similar to that of Carter and Lawrence who alkylated catechol with ethyl bromoacetate and then obtained upon saponification an acid that contained potassium (14). Their substance also "was not easily decomposed by boiling hydrochloric acid."

The crude, sodium-containing acid obtained from the ester VI was cyclized with decarboxylation in acetic acid-acetic anhydride (15) to give the benzofuran VII in 86% overall yield from the ester VI. Therefore, even though the esters VI and IId could not be saponified smoothly, the crude, metal-containing saponification products appear to be suitable for use in the final step of this scheme.

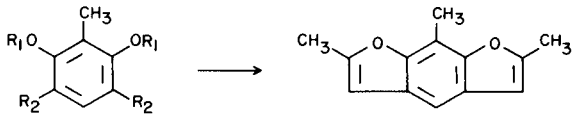


VI



VII

In a related scheme 2-methylresorcinol was converted into the diallyl ether VIIIa, which underwent the Claisen rearrangement to give 4,6-diallyl-2-methylresorcinol (VIIIb). Acetylation and bromination gave the tetrabromide VIIId, which was cyclized according to Kaufman (16) with sodium ethoxide in ethanol to yield a crude sample of the new benzodifuran IX. It was this sample that gave the positive erythemal response referred to earlier. Upon repeating the reaction sequence on a larger scale, extensive purification yielded only 3% of the benzodifuran.



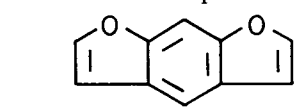
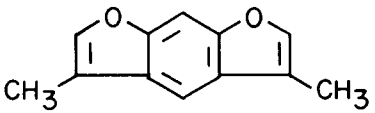
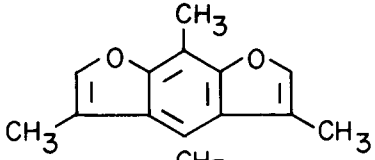
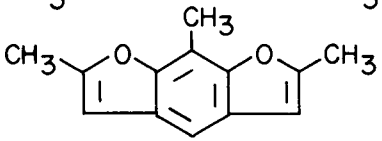
VIIIa. R_1 = allyl, R_2 = H
b. R_1 = H, R_2 = allyl
c. $R_1 = COCH_3$, R_2 = allyl
d. $R_1 = COCH_3$, $R_2 = CH_2CHBrCH_2Br$

IX

The Claisen rearrangement product VIIIb was utilized in a second approach to the synthesis of the 8-methylbenzodifuran IIIc. Aneja, Mukerjee, and Seshadri (17) in a new benzofuran synthesis subjected *o*-allylphenols to ozonolysis and then treated the ozonolysis products with 85% phosphoric acid to obtain benzofuran derivatives. They described the latter step as "cyclodehydration" of *o*-hydroxyphenylacetaldehydes. This scheme has been used for the synthesis of a furocoumarin from 5-allyl-6-hydroxy-4-methylcoumarin (18). Since the infrared spectrum (Nujol mull) of the ozonolysis product of the coumarin gave no evidence of an aldehyde function (no aldehyde C-H absorption in the region 2695-2730 cm^{-1} and no carbonyl other than the coumarin lactone carbonyl at 1700 cm^{-1}), the ozonolysis product was formulated as a cyclic hemiacetal rather than an *o*-hydroxyphenylacetaldehyde (18).

TABLE I

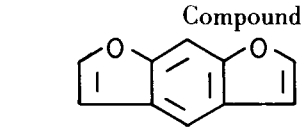
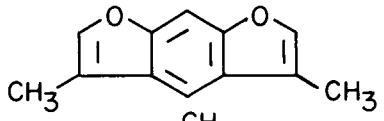
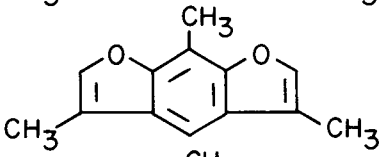
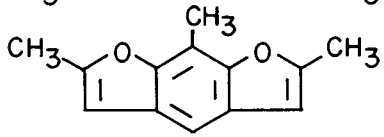
Benzodifuran Ultraviolet Spectral Data (a)

Compound	λ max (log ε) (mμ) (ethanol)							
	*ca.*252(sh)(3.72)	260(3.89)	269(3.93)	282(3.52)	287(3.68)	293(3.83)	299(3.86)	305(3.93)
	*ca.*256(sh)(3.41)	267(3.85)	276(3.89)	283(3.46)	289(3.74)	295(3.87)	301(3.87)	308(3.92)
	*ca.*256(sh)(3.74)	266(3.97)	275(4.02)	—	287(3.69)	293(3.81)	299(3.78)	306(3.86)
	*ca.*251(sh)(3.81)	260(4.01)	269(3.98)	*ca.*283(sh)(3.43)	289(3.64)	294(3.84)	300(3.85)	306(3.98)

(a) sh = shoulder.

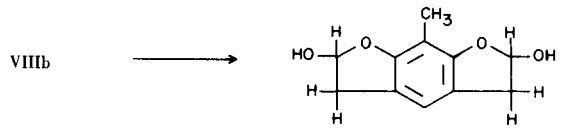
TABLE II

Benzodifuran Nuclear Magnetic Resonance Spectral Data (a)

Compound	Solvent	C2-*H* and C6-*H*	C3-*H* and C5-*H*	C4-*H*	C8-*H*	furan methyl groups	C8-CH_3
	$CDCl_3$	2.40 τ d, J = 2.5 Hz	3.24 τ quartet, $J_{2,3}$ = 2.5 Hz $J_{3,8}$ = 1 Hz	2.33 τ s	2.37 τ d, J = 1 Hz	—	—
	CCl_4	2.65	—	2.57	2.57	7.72 (s)	—
	CCl_4	2.65	—	2.77	—	7.72 (s)	7.37 (s)
	CCl_4	—	3.73	2.84	—	7.52 (s)	7.38 (s)

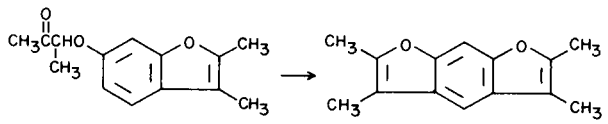
(a) All the peaks in the spectrum determined in $CDCl_3$ are sharp and clearly defined. Since the peaks representing aromatic and vinyl protons in the spectra determined in CCl_4 are broad and poorly defined, no attempt has been made to identify them as singlets, doublets, *etc.*

This conclusion is reinforced by the infrared spectrum [3430, 2720, 2680 (OH); 1625, 1590 (C=C); 1250, 1185, 1090, 1030 (C-O); and 860, 795, and 725 cm^{-1} (phenyl substitution)] of the ozonolysis product X of the *o*-allylphenol VIIIb, which contains no coumarin lactone carbonyl and, therefore, gives even clearer evidence of the absence of an aldehyde function, at least in the solid state (Nujol mull). When the ozonolysis product X was treated with 85% phosphoric acid according to the procedure of Aneja and coworkers (17), a highly insoluble solid was obtained that failed to give the sulfuric acid color test described (8) for the benzodifuran IIIa.



X

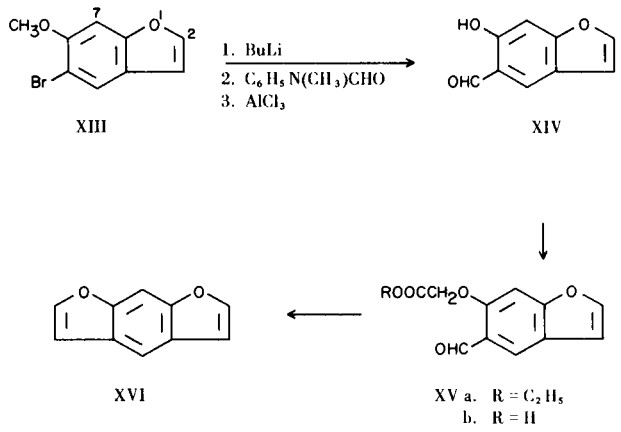
Another possible approach to benzo[1,2-*b*:5,4-*b'*]difurans is through 6-hydroxybenzofurans. Again, the directive effects are unfavorable. For example, 6-hydroxybenzofuran is formylated in the 2-position (19a-b). When the 2-position is blocked, electrophilic substitution occurs predominantly at carbon 7 (20). Thus, cyclization of the ketone XI with phosphorus oxychloride gave a mixture of the linear benzodifuran XII and its angular isomer, 2,3,7,8-tetramethylbenzo[1,2-*b*:3,4-*b'*]-difuran (21).



XI XII

A synthesis free of isomer separation problems of benzo[1,2-*b*:5,4-*b'*]difurans unsubstituted in the 8-position depends on the availability of a 5-acyl-6-hydroxybenzofuran. We recently reported an unambiguous synthesis of the key intermediate 5-formyl-6-hydroxybenzofuran (XIV) in 29% overall yield from 2,4-dihydroxybenzaldehyde *via* halide XIII (19b). Metal-halogen interchange, formylation of the resulting aryllithium intermediate, and ether cleavage gave the benzofuran XIV.

Alkylation of XIV with ethyl bromoacetate and then saponification of the resulting ester XVa followed by decarboxylative cyclization in acetic acid-acetic anhydride (15) furnished benzo[1,2-*b*:5,4-*b'*]difuran (XVI) itself in 44% overall yield from XIV.



XIII XIV

XV a. R = C_2H_5
b. R = H XVI

The similar and highly characteristic ultraviolet spectra of four linear benzodifurans are summarized in Table I. The nuclear magnetic resonance spectrum (Table II) of the parent compound shows long-range coupling of 1 Hz between the protons on carbons 3 and 5 with the proton on carbon 8. Coupling across similar 6-atom systems has been observed previously (18, 22).

EXPERIMENTAL

Melting points (capillary) below 225° are corrected. Infrared, ultraviolet, and (in some cases) nuclear magnetic resonance spectra of most of the compounds described below are on file. Photocopies will be supplied on request (2a). (See text of article for ultraviolet and nmr spectral data of the benzodifurans.) In nmr descriptions, s = singlet, d = doublet.

4,6-Diacetyl-2-methylresorcinol (Ib).

A mixture of 24.8 g. (0.200 mole) of commercial 2-methylresorcinol, 120 ml. (1.2 mole) of acetic anhydride, and 2 g. of anhydrous powdered sodium acetate were heated under reflux for 8 hours, poured into 1 l. of ice water, stirred for 1 hour, and extracted with ether. The ether layer was extracted with ice cold aqueous sodium bicarbonate until the extracts remained basic. The ether was then dried and evaporated (reduced pressure) to give 34.4 g. (83%) of 2-methylresorcinol diacetate as a pale yellow oil that was pure enough for use in the next step. Crystallization of a small sample from petroleum ether (b.p. 30-60°) gave long, thick needles, m.p. 42-44° [lit. (11) m.p. 42-44°].

Aluminum chloride (6.72 g., 0.050 mole) was added in small portions to a cooled, stirred solution of 5.0 g. (0.024 mole) of 2-methylresorcinol diacetate in 10 ml. of redistilled nitrobenzene, and the mixture was heated at 67° (oil bath temperature) for 4 hours. The resulting hard cake was stored in a freezer chest overnight and then diluted with ice chips and dilute hydrochloric acid. Removal of nitrobenzene by steam distillation and chloroform extraction of the crude 4,6-diacetyl-2-methylresorcinol, which had crystallized as needles in the still pot, furnished 3.84 g. (77%) of a cream-colored solid, m.p. 125-132°. Crystallization from ethanol gave 2.90 g. (58%) of long, white needles, m.p. 139-142°.

Recrystallization of a small sample from ethanol for analysis did not change the m.p.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.53; H, 5.93.

4,6-Dihydroxy-5-methylisophthaldehyde (Ic).

A mixture of 500 mg. (2.40 mmoles) of the isophthalaldehyde IVc and 5 ml. of 24% hydrobromic acid was sealed in a Pyrex tube and heated for 15 hours at 130°. The reaction mixture then was extracted with chloroform, and the chloroform solution was dried (sodium sulfate) and evaporated. Sublimation of the resulting brown, sticky residue at 130° (0.05 mm.) afforded 356 mg. of crude, white 4,6-dihydroxy-5-methylisophthalaldehyde, which after two crystallizations from ethanol gave 173 mg. (40%) of colorless, interlaced needles, m.p. 185-185.5°; NMR (acetone) 0.16 (s, 2, C*H*O) and 1.82 τ (s, 1, C2-*H*). The mother liquors gave 183 mg. of crude, solid material that required further demethylation.

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48; OCH_3, 0.00. Found: C, 60.10; H, 4.27; OCH_3, 0.00.

Diethyl (4,6-Diacetyl-2-methyl-1,3-phenylenedioxy)diacetate (IIb).

A mixture of 18.89 g. (0.0908 mole) of 4,6-diacetyl-2-methylresorcinol, 31.1 g. (0.187 mole) of ethyl bromoacetate, 27.0 g. (0.195 mole) of anhydrous potassium carbonate, and 275 ml. of acetone was stirred under reflux for 23 hours. Most of the solvent was removed, and the residue was diluted with water and extracted with chloroform. Repeated extraction of the organic phase with ice cold aqueous sodium hydroxide and then evaporation of the chloroform (reduced pressure) gave 25.31 g. (73%) of the ester IIb as an amber oil which crystallized upon standing and was used in the next step without further purification. A small portion of the crude ester was treated with boiling hexane, and the hot hexane was decanted from insoluble oily impurities. When the hexane cooled, the pure ester IIb precipitated as an amorphous white solid, m.p. 67-67.5°.

Anal. Calcd. for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 59.93; H, 6.05.

(4,6-Diacetyl-2-methyl-1,3-phenylenedioxy)diacetic Acid (IIc).

A mixture of 3.80 g. (10 mmoles) of the crude ester IIb, 3 g. of potassium hydroxide pellets, 70 ml. of ethanol, and 100 ml. of water was heated under reflux for 40 minutes and then acidified. After a seed crystal was formed by prolonged scratching of the flask walls, the acid slowly precipitated. Crystallization of the collected precipitate from ethanol gave 1.23 g. (38%) of the acid IIc as a light yellow powder, m.p. 198.5-200° (dec.). A small sample was recrystallized from ethanol for analysis, m.p. 200.5-202.5° (dec.).

Anal. Calcd. for $C_{15}H_{16}O_8$: C, 55.55; H, 4.97. Found: C, 55.65; H, 4.99.

Diethyl (2-Methyl-4,6-diformyl-1,3-phenylenedioxy)diacetate (IId).

Alkylation of 676 mg. of 4,6-dihydroxy-5-methylisophthalaldehyde (Ic) with ethyl bromoacetate under the conditions described for the alkylation of 4,6-diacetylresorcinol (8) furnished the crude ester IId, which after two crystallizations from ethanol gave 539 mg. (41%) of a white solid, m.p. 109.5-111°. Recrystallization of a small sample for analysis raised the m.p. to 111-111.5°.

Anal. Calcd. for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 58.09; H, 5.74.

Attempted Saponification of Diethyl (2-Methyl-4,6-diformyl-1,3-phenylenedioxy)diacetate (IId).

The ester IId was refluxed for 1 hour with equal volumes of 1*N* aqueous sodium hydroxide and ethanol, diluted with water, and acidified. This gave a very crude yellow solid that after treatment with boiling water and decolorizing carbon melted at 139-177° and represented 15% of the mass of product expected from the reaction.

3,5-Dimethylbenzo[1,2-*b*;5,4-*b*′]difuran (IIIa).

Alkylation of 4.52 g. of 4,6-diacetylresorcinol (Ia) (23) with ethyl bromoacetate according to Algar, Barry, and Tworney (8) furnished diethyl (4,6-diacetyl-1,3-phenylenedioxy)diacetate (IIa) as white, glistening platelets from ethanol, 6.26 g. (74%), m.p. 129-131.5° [lit. (8) m.p. 130-131°, 61%)]. Saponification of 6.19 g. of this diester gave 5.22 g. (100%) of the corresponding diacid, m.p. 271° (dec.) [lit. (8) m.p. 264-266°]. A stirred mixture of 3.00 g. (9.70 mmoles) of this diacid, 18 g. of anhydrous sodium acetate, and 70 ml. of acetic anhydride was heated under reflux for 1 hour, poured into 0.6 l. of ice water, and refrigerated overnight. The resulting crystalline solid was collected and recrystallized from ethanol to give 1.33 g. (74%) of the benzodifuran IIIa as off-white prisms, m.p. 105.5-107.5° [lit. (8) m.p. 107-108° (39%)].

3,5,8-Trimethylbenzo[1,2-*b*:5,4-*b*′]difuran (IIIb).

A mixture of 3.24 g. (0.010 mole) of the diacid IIb, 19 g. of anhydrous sodium acetate, and 120 ml. of acetic anhydride was stirred under reflux for 1 hour and then poured into 0.8 l. of ice water, stirred for 5 minutes, and extracted with ether. The ether solution was washed with cold 1% aqueous sodium hydroxide until the washes were basic, and then the ether was dried and evaporated (reduced pressure) to leave a black oil that solidified upon standing. Chromatography of the solid on Alcoa F-20 alumina (elution with 1:4 benzene-petroleum ether) furnished the benzodifuran as a colorless solid, which after crystallization from ethanol was obtained as white prisms, m.p. 76-76.5°, 1.15 g. (57%).

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.87; H, 6.10.

2,4-Dimethoxy-3-methylbenzaldehyde (IVa).

A solution of 147 g. (2.25 moles) of 85% potassium hydroxide pellets in 0.9 l. of water was added dropwise along with 174 ml. (1.87 moles) of dimethyl sulfate from two calibrated dropping funnels to a stirred, refluxing solution of 11.4 g. (0.075 mole) of 2,4-dihydroxy-3-methylbenzaldehyde (13) in 75 ml. of methanol. Both additions took 1.5 hours. After an additional 20-minute reflux period the solution was cooled, acidified, and then boiled for 30 minutes to remove methanol. The solution was cooled, and the precipitated dark solid was extracted into ether. After being washed with dilute aqueous sodium hydroxide, dried, and evaporated, the ether solution yielded the product as a dark yellow solid, which after crystallization from petroleum ether (b.p. 30-60°) gave 7.90 g. (59%) of light yellow needles, m.p. 53.5-54°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.15; H, 6.68.

5-Chloromethyl-2,4-dimethoxy-3-methylbenzaldehyde (IVb).

2,4-Dimethoxy-3-methylbenzaldehyde (IVa) (6.86 g.) was chloromethylated by the procedure of Geissman and coworkers 12). Crystallization of the crude product from hexane gave 6.29 g. (72%) of the chloromethyl compound IVb as hard, white prisms, m.p. 76-78°. Recrystallization of a small sample for analysis raised the m.p. to 77-78.5°.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 57.77; H, 5.73; Cl, 15.50. Found: C, 57.96; H, 5.66; Cl, 15.30.

4,6-Dimethoxy-5-methylisophthalaldehyde (IVc).

Conversion of 5.62 g. of the chloromethyl compound IVb into the isophthalaldehyde IVc according to the procedure of Geissman and coworkers (12) and crystallization of the crude product from ethanol gave 2.92 g. (55%) of colorless, interlaced needles, m.p. 123-124.5°; NMR (acetone) 0.01 (s, 2, C*HO*), 1.85 (s, 1, C2-*H*), and 5.98 τ (s, 6, OCH_3).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.35; H, 5.66.

4-Hydroxy-6-methoxy-5-methylisophthalaldehyde (V).

When 4,6-dimethoxy-5-methylisophthalaldehyde (IVc) was refluxed in 24% hydrobromic acid according to the procedure of Geissman and coworkers (12) and the crude product was dissolved in hot benzene-hexane (1:4) and allowed to cool slowly, 4-hydroxy-6-methoxy-5-methylisophthalaldehyde (V) crystallized as white needles. When the solution cooled to near room temperature, the completely demethylated product Ic crystallized as a white, granular solid. Collection of the needles before the granular solid started to appear and treatment of the needles similarly a second time afforded partially demethylated material in 11% yield as tiny white needles, m.p. 124.5-125.5°; NMR (acetone) 0.06 (s, 1, Cl-C*HO*), 0.28 (s, 1, C3-C*HO*), 1.82 (s, 1, C2-*H*), and 5.99 τ (s, 3, OCH_3).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.90; H, 5.11.

Diethyl (4-Formyl-1,3-phenylenedioxy)diacetate (VI).

2,4-Dihydroxybenzaldehyde (1.38 g.) was alkylated with ethyl bromoacetate under the conditions described for the alkylation of 4,6-diacetylresorcinol (8). Crystallization of the crude product from ethanol furnished the ester VI as a colorless solid, m.p. 101-101.5°, 1.10 g. (36%).

Anal. Calcd. for $C_{15}H_{18}O_7$: C, 58.06; H, 5.84. Found: C, 58.00; H, 5.97.

Attempted Saponification of Diethyl (4-Formyl-1,3-phenylenedioxy)diacetate (VI).

A mixture of 884, mg. (2.85 mmoles) of the ester VI, 8.6 ml. (8.6 mmoles) of 1*N* aqueous sodium hydroxide, and 8.6 ml. of ethanol was stirred under reflux for 1 hour and then poured into ice water and strongly acidified. Crystallization of the crude product from 1% hydrochloric acid furnished 1.31 g. (> 100%) of a light tan solid which held water tenaciously and contained sodium (residue after ignition). This material was used in the next step without further purification.

[3,4-*b*]Furophenoxyacetic Acid (VII).

A mixture of the light tan solid described above that had been obtained from 884 mg. (2.85 mmoles) of the ester VI, 2.6 g. of anhydrous sodium acetate, 4.5 ml. of acetic anhydride, and 9 ml. of acetic acid was refluxed for 4 hours. Then an additional 4.5 ml. of acetic anhydride was added, and the mixture was refluxed for 6 hours, poured into water, acidified strongly, and extracted with ether. The gummy product thus isolated was heated on a steam bath with dilute aqueous sodium hydroxide in ethanol to cleave any mixed anhydride present. The product after reisolation by acidification and ether extraction was digested with 25 ml. of hot benzene. Filtration and evaporation of the benzene solution and then crystallization of the off-white, solid residue from benzene with decolorizing carbon gave 473 mg. (86% overall yield from the ester VI) of the acid VII, m.p. 141-142.5°. Recrystallization of this material for analysis from ethanol-water furnished stout, off-white needles, m.p. 142-143°.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.44; H, 4.36.

1,3-Bis(allyloxy)-2-methylbenzene (VIIIa).

A mixture of 24.8 g. (0.2 mole) of 2-methylresorcinol, 138 g. (1 mole) of anhydrous potassium carbonate, and 173 ml. (2 moles) of allyl bromide was stirred under reflux in 1 l. of acetone for 28 hours. The solvent was removed at 100° (20 mm.), and the residue was extracted with ether. The ether solution was washed with aqueous sodium hydroxide, dried, and evaporated (reduced pressure) to leave the crude ether VIIIa, which distilled at 84-94° (0.15 mm.) as a clear, pale green oil, 40.6 g. (100%).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.20; H, 7.93.

4,6-Diallyl-2-methylresorcinol (VIIIb).

1,3-Bis(allyloxy)-2-methylbenzene (VIIIa) (23.4 g.) was refluxed for 3 hours under a nitrogen atmosphere in 40 ml. of *N,N*-diethylaniline. The solution was cooled, poured onto 200 g. of cracked ice, and acidified with concentrated hydrochloric acid. After saturation of the aqueous phase with sodium chloride, the mixture was extracted with ether, and the ether solution was dried and evaporated. The residual oil was distilled on a Nester and Faust 18-inch semimicro spinning band column at 86° (0.038 mm.) to give 16.1 g. (69%) of 4,6-diallyl-2-methylresorcinol as a colorless oil that crystallized upon standing. This white, crystalline solid darkens even at 0°. After one week at room temperature the material is dark brown or purple. Although the crude white solid was sufficiently pure for use in the next step, it could be sublimed at 46° (0.06 mm.) or crystallized from hexane to give a white, string-like solid, m.p. 54.5-55°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 75.92; H, 7.86.

4,6-Diallyl-2-methylresorcinol Diacetate (VIIIc).

The diacetate, a pale yellow, viscous oil, b.p. 166.5° (no range) (0.05 mm.), was formed in 88% yield by the conditions employed for the preparation of 2-methylresorcinol diacetate. [See directions for the preparation of 4,6-diacetyl-2-methylresorcinol (Ib).]

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99; Found: C, 70.82; H, 6.89.

4,6-Bis(2,3-dibromopropyl)-2-methylresorcinol Diacetate (VIIId).

Bromine (11.2 g., 0.07 mole) dissolved in *ca.* 20 ml. of chloroform was added at such a rate as to insure instantaneous decolorization of the bromine to a solution of 10.0 g. (0.035 mole) of the diacetate VIIIc in 50 ml. of chloroform maintained at a temperature of 10-15°. The purple residue obtained by evaporation of the solvent at 30° (20 mm.) was crystallized from ethanol to give 15.4 g. (72%) of the tetrabromide VIIId as colorless needles of m.p. 129.5-132.5°.

Anal. Calcd. for $C_{17}H_{20}Br_4O_4$: C, 33.58; H, 3.31. Found: C, 33.95; H, 3.41.

2,6,8-Trimethylbenzo[1,2-*b*:5,4-*b*′]difuran (IX).

The tetrabromide VIIId (9.12 g., 0.015 mole) was added under nitrogen to a hot, stirred solution of 4.50 g. (0.15 mole) of sodium in 150 ml. of magnesium-dried ethanol (24). After being refluxed for 1.75 hours, the solution was poured into a mixture of 600 g. each of cracked ice and 3.5% hydrochloric acid, and the resulting oily precipitate was extracted with ether. The ether solution was washed with dilute aqueous sodium hydroxide, dried, and evaporated to leave an amber oil that was chromatographed on *ca.* 50 g.

of Alcoa F-20 alumina (elution with petroleum ether). Evaporation of the solvent furnished 0.88 g. of a cloudy oil that crystallized in part upon standing overnight. This oil was rechromatographed on a 1.2-cm. diameter column of *ca.* 40 g. of Woelm activity grade 1 basic alumina. The eluent was collected in 25-ml. portions and then evaporated. Those fractions that crystallized spontaneously were combined and crystallized twice from ethanol-water to give 93 mg. (3.1%) of the benzodifuran IX as colorless, rectangular prisms, m.p. 91.5-92°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.81; H, 6.11.

2,6-Dihydroxy-8-methyl-2,3,5,6-tetrahydrobenzo[1,2-*b*:5,4-*b*']-difuran (X).

Ozone (70.3 mmoles) was passed through a cooled (ice-salt bath) solution of 7.70 g. (37.75 mmoles) of 4,6-diallyl-2-methylresorcinol (VIIIb) in 200 ml. of ethyl acetate. The solution was shaken with hydrogen at room temperature in the presence of 0.77 g. of 5% palladium on charcoal until rapid uptake ceased. Removal of the catalyst by filtration and concentration of the filtrate to dryness gave a brown residue that was converted to 2.70 g. of a yellow solid by trituration with *ca.* 40 ml. of ether. Recrystallization from methyl ethyl ketone gave 1.91 g. (24%) of light yellow crystals, m.p. 177.5-181°. An additional recrystallization did not raise the melting point but gave nearly colorless crystals, a few of which dissolved in 5% aqueous sodium hydroxide to give a solution that turned deep blue on standing for a few minutes. Ultraviolet, λ max (95% ethanol) 226 (log ε 3.85) and 286 mμ (log ε 4.53). Infrared, see text of article.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.36; H, 5.44.

Attempted Dehydration of the Hemiacetal (X).

A mixture of 13.0 g. of the dihydroxytetrahydrobenzodifuran X and 500 cc. of 85% phosphoric acid was heated on a steam bath for 20 minutes and poured into *ca.* 2 l. of ice water. Filtration gave a solid that was washed with 5% aqueous sodium hydroxide followed by water and then was found to be too insoluble in a wide variety of organic solvents for recrystallization. A small sample added to concentrated sulfuric acid failed to yield the cherry red color characteristic of the benzodifuran IIIa (8).

Ethyl (5-Formyl-6-benzofuranyloxy)acetate (XVa).

A mixture of 1.00 g. (6.17 mmoles) of 5-formyl-6-hydroxybenzofuran (19b), 1.12 g. (8.11 mmoles) of anhydrous granular potassium carbonate, 1.28 g. (7.67 mmoles) of ethyl bromoacetate, and 40 ml. of acetone that had been freshly distilled over phosphorus pentoxide was stirred under reflux for 2 hours and then concentrated until most of the solvent was gone. The remaining solvent and residue were dissolved in water and ether. The ether layer was washed with 5% sodium hydroxide, dried (magnesium sulfate), and evaporated to leave the crude ester XVa, which was washed thoroughly with 50 ml. of petroleum ether to remove unreacted ethyl bromoacetate. This left 1.39 g. (91%) of a pale yellow solid, m.p. 93.5-95.5°. Crystallization of a small sample from carbon tetrachloride gave fine, white needles, m.p. 94.5-95.5°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.95; H, 4.91.

(5-Formyl-6-benzofuranyloxy)acetic Acid (XVb).

(a) A mixture of 0.248 g. (1.00 mole) of the ethyl ester XVa, 5.0 ml. (5.0 mmoles) of 1*N* sodium hydroxide, and 5 ml. of ethanol was heated under reflux for 1 hour, and the resulting orange solution was worked up to furnish 0.206 g. (94%) of the acid XVb as a yellow powder, m.p. 191-203° (dec.). Crystallization of this material twice from acetic acid-1,2-dichloroethane with very poor recovery gave a brown, amorphous analytical sample, m.p. 204.5-206.5° (dec.).

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.81; H, 3.88.

In a subsequent saponification, recrystallization of the acid XVb from aqueous 1,4-dioxane with 34% recovery gave an orange, amorphous material, m.p. 215-217° (dec.).

(b) A mixture of 0.300 g. (1.21 mmoles) of the ethyl ester XVa and 15 ml. of 10% sulfuric acid was stirred under a reflux condenser at 100° (oil bath temperature) for 1.5 hours and then was refrigerated overnight. A tan solid was collected, washed with water, and dried (vacuum desiccator), yield 0.254 g. (95%), m.p. 210-212° (dec.). Recrystallization of this material from glacial acetic acid gave 0.155 g. (58%) of an amorphous orange solid, m.p. 212-214° (dec.).

Benzo[1,2-*b*:5,4-*b*']difuran (XVI).

A mixture of 0.110 g. (0.500 mmole) of the (5-formyl-6-benzofuranyloxy)acetic acid (XVb) that had been crystallized from glacial acetic acid, 0.180 g. (2.20 mmoles) of anhydrous powdered sodium acetate, and 1.0 ml. each of acetic acid and acetic anhydride (15) was heated under reflux for 5 hours and then poured into 10 ml. of water and stirred until decomposition of the acetic anhydride was complete. The reaction mixture was extracted with ether, and the ether layer was thoroughly extracted with base, dried (magnesium sulfate), and concentrated to dryness to leave 0.083 g. (104%) of the crude benzodifuran XVI, m.p. 55-58.5°. Sublimation of this material at 50° (water aspirator pressure) furnished 0.066 g. (83%) of long, white needles, m.p. 62° (no range). Crystallization from methanol of a small sample for analysis gave long, white needles, m.p. 62.5° (no range).

Anal. Calcd. for $C_{10}H_6O_2$: C, 75.94; H, 3.82. Found: C, 75.86; H, 4.08.

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