873. *The Synthesis of Benzofurans.*

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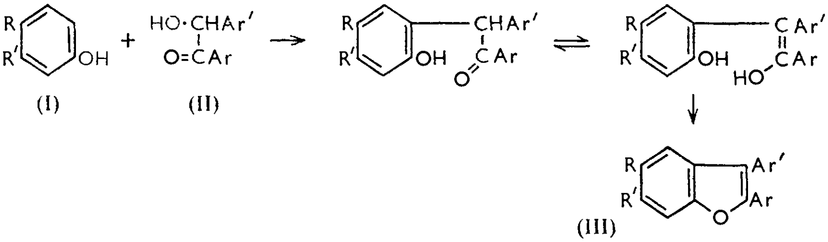
A general synthesis of 3-alkoxyphenylbenzofurans from alkoxybenzoins and phenols has been developed. Variation of the proportions of reactants enables benzo-di- and -tri-furans to be prepared. The structure of the products follows from the mode of synthesis and their ultraviolet spectra.

Knowledge of the reaction of *p*-methoxybenzyl alcohols with phenols[1] has led to consideration of subsequent condensation of the phenolic hydroxyl group with a second (enolic) hydroxyl group in the alcohol to yield ethers. Thus a compound such as anisoin (II; Ar = Ar′ = *p*-MeO·C_6H_4) would be expected to condense with resorcinol (I; R = H, R′ = OH) to yield a substituted 2 : 3-diphenylbenzofuran (III). Because of the activating groups this reaction should proceed under less vigorous conditions than the condensation[2] of benzoin with phenols in presence of 73% sulphuric acid at 120—160°, and thus enable alkoxybenzofurans to be synthesised in good yield.



p-Anisoin when boiled under reflux for one hour with an excess of resorcinol and 8% hydrogen chloride in aqueous dioxan has yielded, after methylation, 83% of 6-methoxy-2 : 3-di-*p*-methoxyphenylbenzofuran (III; R = H, R′ = OMe, Ar = Ar′ = *p*-MeO·C_6H_4). It is necessary to use dioxan which is free from peroxides, in order to avoid oxidation of the benzoins to benzils and consequent reduction in yields. Ethanol is not a useful solvent because, in the presence of hydrogen chloride, it reacts with benzoins to yield ethyl ethers.[3]

The method has proved to be a general one for the preparation of substituted benzofurans (see Table). With phenol itself the furan synthesis occurs only to the

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[1] Brown, Cummings, and Somerfield, *J.*, 1957, 3757.

[2] Japp and Meldrum, *J.*, 1899, **75**, 1035.

[3] Irvine and McNicoll, *J.*, 1908, **93**, 1601.

extent of 4%, to yield 2 : 3-di-*p*-methoxyphenylbenzofuran (III; R = R′ = H, Ar = Ar′ = *p*-MeO·C_6H_4), because benzyl alcohols condense preferentially with a position *para* to a phenolic hydroxyl group.[1] When the *para*-position is blocked, as with *p*-cresol, the yield of benzofuran is increased. With resorcinol it is possible to omit the methylation and isolate a 6-hydroxybenzofuran (*e.g.*, III; R = H, R′ = OH, Ar = Ar′ = *p*-MeO·C_6H_4), and, with β-naphthol, naphthofurans (IV) are obtained. There is no doubt that other phenols could be used with equal success, but this has not been pursued further in the present work.

Benzoin does not react under the described conditions, but the introduction of a methoxyl group *ortho* or *para* to the alcoholic group leads to easy formation of the benzofuran; for example, from 4′-methoxybenzoin (II; Ar = Ph, Ar′ = *p*-MeO·C_6H_4). The isomer, 4-methoxybenzoin (II; Ar = *p*-MeO·C_6H_4, Ar′ = Ph), with β-naphthol, readily yields the same naphthofuran (IV; Ar = C_6H_5, Ar′ = *p*-MeO·C_6H_4) (mixed melting point and infrared comparison), indicating that, with this benzoin, enolisation occurs before reaction. Comparison of the ultraviolet spectra of the benzofurans (*e.g.*, $\lambda_{max.}$ 203, 248, 318 mμ, ε 46,770, 23,710, 26,920 for III; R = H, R′ = OMe, Ar = Ar′ = *p*-MeO·C_6H_4) with that ($\lambda_{max.}$ 233, 318 mμ, ε 21,630, 25,700) of 6-methoxy-2 : 3-diphenylbenzofuran (III; R = H, R′ = OMe, Ar = Ar′ = Ph), prepared by a proved method,[2] confirms the structures deduced from their mechanism of formation.

Benzofurans (III), *naphtho*[2, 1-b]*furans* (IV), *benzo*[1, 2-b, 5, 4-b′]*difurans* (V), *and the benzotrifuran* (VII).

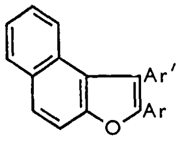
No.	Type	R	R′	Ar	Ar′	Yield (%)
1	(III)	H	MeO	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	83
2	(III)	H	HO	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	65
3	(III)	H	H	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	4
4	(III)	Me	H	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	39
5	(III)	H	MeO	*o*-MeO·C_6H_4	*o*-MeO·C_6H_4	54
6	(III)	H	MeO	Ph	*p*-MeO·C_6H_4	24
7	(III)	H	MeO	3 : 4-$CH_2O_2{>}C_6H_3$	3 : 4-$CH_2O_2{>}C_6H_3$	38
8	(IV)	—	—	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	93
9	(IV)	—	—	*o*-MeO·C_6H_4	*o*-MeO·C_6H_4	47
10	(IV)	—	—	Ph	*p*-MeO·C_6H_4	58[a], 68[b]
11	(IV)	—	—	3 : 4-$CH_2O_2{>}C_6H_3$	3 : 4-$CH_2O_2{>}C_6H_3$	76
12	(V)	H	—	*p*-MeO·C_6H_4	—	47
13	(V)	Me	—	*p*-MeO·C_6H_4	—	52
14	(VI)	Me	—	*p*-MeO·C_6H_4	—	25
15	(VII)	—	—	*p*-MeO·C_6H_4	—	25

No.	Crystal form	Solvent.*	M. p.	Formula	Found (%)		Required (%)	
					C	H	C	H
1	Needles	Pet[c]	91—92°	$C_{23}H_{20}O_4$	76·8	5·5	76·7	5·55
2	,,	Pet[d]	136—137	$C_{22}H_{18}O_4$	76·1	5·1	76·3	5·2
3	Prisms	Pet[d]	147—148	$C_{22}H_{18}O_3$	79·65	5·55	80·0	5·45
4	Needles	EtOH	122—123	$C_{23}H_{20}O_3$	80·0	6·0	80·2	5·8
5	Prisms	Aq. MeOH	47—49	$C_{23}H_{20}O_4$	76·85	5·8	76·7	5·55
6	Needles	Pet[e]	131—132	$C_{22}H_{18}O_3$	80·3	5·7	80·0	5·45
7	,,	Pet[d]	193—194	$C_{23}H_{16}O_6$	70·7	4·3	71·1	4·1
8	,,	Pet[e]	116—117	$C_{26}H_{20}O_3$	82·1	5·3	82·1	5·3
9	,,	,,	125—126	$C_{26}H_{20}O_3$	82·15	5·0	82·1	5·3
10	Prisms	,,	133—135	$C_{25}H_{18}O_2$	85·9	5·2	85·7	5·1
11	Plates	EtOAc–$COMe_2$	168—169	$C_{26}H_{16}O_5$	76·8	4·05	76·5	3·9
12	Needles	EtOAc–MeOH	221—223	$C_{38}H_{30}O_6$	78·2	5·2	78·35	5·15
13	Prisms	,,	230—231	$C_{39}H_{32}O_6$	78·3	5·4	78·5	5·4
14	,,	Pet[e]	202—203	$C_{39}H_{32}O_6$	78·1	5·6	78·5	5·4
15	Needles	C_6H_6–Pet	340 (dec.)	$C_{54}H_{42}O_9$	77·5	5·0	77·7	5·05

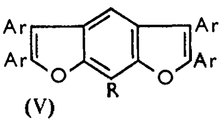
* Pet = light petroleum.

[a] From 4′-methoxybenzoin. [b] From 4-methoxybenzoin. [c] B. p. 40—45°. [d] B. p. 65—70°. [e] B. p. 80—100°.

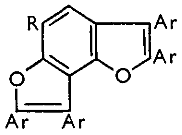
The use of two mols. of anisoin with one mol. of a resorcinol has enabled benzodifurans (V) to be prepared. These are known to be "linear" compounds from the following considerations. The reaction of anisoin with 2-methylresorcinol must give a "linear" difuran (V; R = Me, Ar = p-MeO·C_6H_4). Conversely, with 4-methylresorcinol an "angular" difuran (VI; R = Me, Ar = p-MeO·C_6H_4) is the only one which can be formed. Comparison of the ultraviolet spectra of compounds (V; R = H, Ar = p-MeO·C_6H_4), (V; R = Me, Ar = p-MeO·C_6H_4), and (VI; R = Me, Ar = p-MeO·C_6H_4) leaves no doubt that the reaction with resorcinol itself leads to the "linear" isomer. This is confirmed by the close similarity between the spectrum of our compound (V; R = H, Ar = p-MeO·C_6H_4) and that of the difuran (V; R = H, Ar = Ph) obtained by Japp and Meldrum; [2] the "linear" structure of the latter compound is known from the oxidative degradation carried out by Dischendorfer.[4] The use of phloroglucinol with excess of anisoin yields the trifuran (VII; Ar = p-MeO·C_6H_4) which resembles the "angular" difuran in its ultraviolet spectrum.



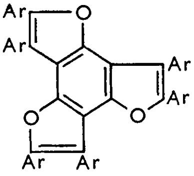
(IV)



(V)



(VI)



(VII)

All the benzofurans prepared exhibit a blue-violet fluorescence in solution, and the "linear" difurans are characterised by a particularly marked fluorescence in the solid state in ordinary light.

EXPERIMENTAL

The light petroleum was of b. p. 40—60° unless otherwise stated. Alumina was Spence Grade O deactivated with 10% acetic acid (10 ml. per 100 g. of alumina). The dioxan was freed from peroxides in the usual way and redistilled from stannous chloride immediately before use.

Monobenzofurans.—The substituted benzoin (1·0 g.), a phenol (3·0 g.), dioxan (30 ml.), and concentrated hydrochloric acid (10 ml.) were mixed and boiled for 1—2 hr. The mixture was poured into water (100 ml.), and the resulting oil taken up in ether.

When monohydric phenols were used this ethereal solution was washed with aqueous sodium hydroxide and water to remove unchanged phenol and other alkali-soluble material, and evaporated. The residue was dissolved in light petroleum–benzene and put on a column of alumina. Elution with light petroleum or light petroleum–benzene yielded the solid benzofuran which was further purified by recrystallisation.

When resorcinol was used the ethereal solution was washed with water and twice with 8% aqueous sodium hydroxide (50 ml.), and the alkaline solution gradually treated with dimethyl sulphate (4 ml.), methylation being completed at 100° for 30 min. The crude product was isolated by using ether and purified on alumina.

For the isolation of 6-hydroxy-2 : 3-di-p-methoxyphenylbenzofuran the ethereal solution was washed with water and extracted twice with 8% aqueous sodium hydroxide (50 ml.). The alkaline solution was decolorised by charcoal and acidified, and the crude hydroxybenzofuran isolated in ether. Successive recrystallisation from light petroleum–benzene and from light petroleum (b. p. 60—70°) yielded the pure compound.

Benzodifurans.—Anisoin (1·5 g.), the resorcinol (0·35 g.), dioxan (30 ml.), and concentrated hydrochloric acid (10 ml.) were mixed and boiled for 3 hr. The mixture was poured into water (100 ml.), and the alkali-insoluble *benzofuran* isolated and purified on alumina.

2 : 3 : 5 : 6 : 8 : 9-*Hexa*-p-*methoxyphenylbenzo*[1, 2-*b*, 3, 4-*b*′, 5, 6-*b*″]*trifuran* (*Ring Index No.* 2235) (VII; Ar = p-MeO·C_6H_4).—Anisoin (2·0 g.), phloroglucinol (0·35 g.), dioxan (50 ml.), and concentrated hydrochloric acid (10 ml.) were mixed and boiled for 6 hr. The crystalline deposit (0·5 g.) was separated and recrystallised several times from benzene containing a little light petroleum, to give the *benzotrifuran* as colourless needles, m. p. 340° (decomp.). The compound decomposes in light.

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[4] Dischendorfer, *Monatsh.*, 1933, **62**, 270.

6-*Methoxy*-2 : 3-*diphenylbenzofuran* (III; R = H, R′ = OMe, Ar = Ar′ = Ph).—6-Hydroxy-2 : 3-diphenylbenzofuran [2] was methylated in the usual way. The *product* was purified on alumina and recrystallised from light petroleum (b. p. 60—70°) as prisms, m. p. 123° (Found: C, 84·3; H, 5·7. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·35%).

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