

PREPARATION OF 2- AND 4-ALKYLPHENOLS
BY REACTION OF 2- AND 4-HYDROXYBENZYL PHENYL SULFONES
WITH LITHIUM ALUMINIUM HYDRIDE*

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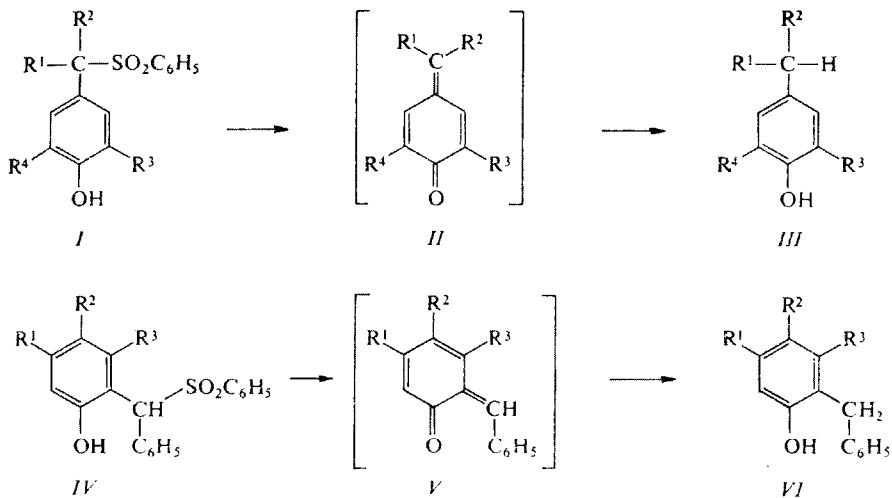
Several 2- and 4-alkylphenols have been prepared by reaction of 2- and 4-hydroxybenzyl phenyl sulfones with hydride reagents in aprotic solvents. In this two-step reaction, the *ortho* and *para* quinone methides have been shown as intermediates.

In connection with investigations on the oxidation of 4-alkylphenols, some difficulties were encountered in the preparation of 4-benzylphenols. Usual procedures¹ are based on the acid-catalysed reaction of benzyl chloride with the appropriate phenols. The expected product is obtained in a low yield only or is not formed at all when the aromatic ring is substituted in *ortho* and/or *para* position with respect to the phenolic hydroxyl by a group with electron-donating properties. Thus, *e.g.*, the reaction of 2-methoxy-4-propylphenol with 4-hydroxy-2-methoxybenzyl alcohol in dioxane-water-hydrogen chloride affords 5-(4-hydroxy-3-methoxybenzyl)-2-methoxy-4-propylphenol whereas the corresponding derivative of 6-benzylphenol could not be detected even on chromatography². Similarly, 3,4-dibenzyl-2,6-dimethylphenol is the only product of the reaction between 2,6-dimethylphenol and benzyl chloride in the presence of zinc chloride³. The 4-(or 2-)alkylphenols are sometimes alternatively prepared by reduction of the corresponding acylphenols; however, the severe deoxygenation conditions may result in the fission of alkoxy groups³.

In this paper, we wish to report a novel method for the preparation of 2- or 4-alkylphenols, based on the reaction of 2- or 4-hydroxybenzyl phenyl sulfones *I* or *IV* with lithium aluminium hydride in tetrahydrofuran. Such a reaction could be considered as a formal substitution of the phenylsulfonyl group by a hydrogen atom; the present reaction exhibits, however, a two-stage mechanism, very similar to that of the recently examined reaction of 4-hydroxybenzyl phenyl sulfones with sodium hydroxide^{4,5}. In the first stage, proton is abstracted from the phenolic hydroxyl by the hydride ion which acts as a strong base. This step is immediately followed by a shift of elect-

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rons resulting in elimination of the phenylsulfonyl anion. The thus-produced highly reactive 4-alkylidene-2,5-cyclohexadien-1-one (*II*) or 6-alkylidene-2,4-cyclohexadien-1-one (*V*) readily adds⁶ (by an 1,6- or 1,8-mechanism) a hydride ion with the formation of 4- or 2-alkylphenols *III* or *VI* (Scheme 1).

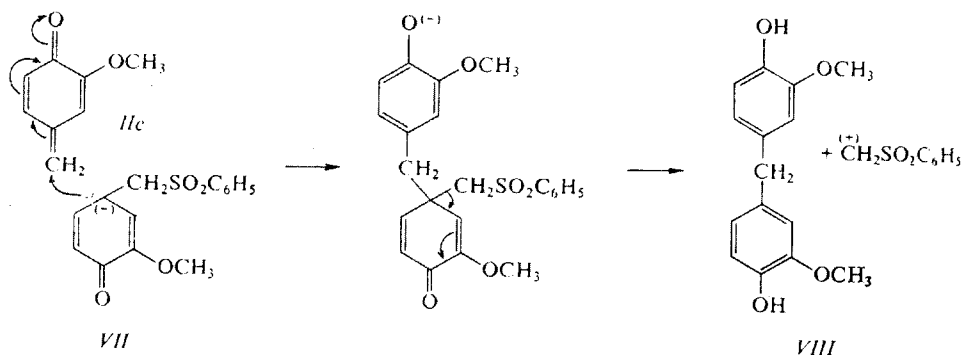


- Ia*, *IIIa*; $\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_5$
Ib, *IIIb*; $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{R}^4 = \text{CH}_3$
Ic, *IIIc*; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$, $\text{R}^4 = \text{OCH}_3$
Id, *IIIId*; $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{CH}_3$, $\text{R}^4 = \text{OCH}_3$
Ie, *IIIe*; $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{R}^4 = \text{OCH}_3$
If, *IIIIf*; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$, $\text{R}^3 = \text{R}^4 = \text{OCH}_3$
Ig, *IIIg*; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_5$, $\text{R}^3 = \text{R}^4 = \text{CH}_3$
Ih, *IIIh*; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_5$, $\text{R}^3 = \text{R}^4 = \text{OCH}_3$
Ii, *IIIi*; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_5$, $\text{R}^3 = \text{R}^4 = i\text{-C}_3\text{H}_7$
Ij, *IIIj*; $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{R}^4 = t\text{-C}_4\text{H}_9$
Ik, *IIIk*; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$, $\text{R}^3 = \text{R}^4 = t\text{-C}_4\text{H}_9$
Il, *IIIl*; $\text{R}^1 = \text{R}^2 = \text{CH}_3$, $\text{R}^3 = \text{R}^4 = t\text{-C}_4\text{H}_9$
Im, *IIIIm*; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_5$, $\text{R}^3 = \text{R}^4 = t\text{-C}_4\text{H}_9$
IVa, *VIa*; $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{CH}_3$
IVb, *VIb*; $\text{R}^1 = \text{R}^3 = \text{CH}_3$, $\text{R}^2 = \text{H}$

The rate of the C-S bond fission in sulfones *I* increases with the increasing number of alkyl groups on the CH_2 group of the benzyl moiety; thus, *e.g.*, the order of the relative rates in base-catalysed elimination of the phenylsulfonyl group from sulfones *Ij*, *Ik*, and *Il* corresponds to the ratio 1 : 35 : 6000. On the other hand, dependence of the addition rate of the hydride ion to the quinone methides *IIIj*, *IIIk*, and *IIIl* is quite opposite. The difference in rates of the two stages made possible the spectral proof of the quinone methides *IIIg*, *IIIh*, and *IIIIm* in the UV region. The lithium aluminium hydride reduction of most sulfones is fast enough at room temperature but

the sulfones *Ib-Ij* require a reflux temperature of the solvent and prolonged reaction time. Yields of the reduction are high and the obtained alkylphenols are chromatographically pure.

An unsatisfactory yield was obtained in the reduction of 4-hydroxy-3-methoxybenzyl phenyl sulfone (*Ic*). Moreover, the expected 2-methoxy-4-methylphenol (*IIIc*) was accompanied by an almost equal amount of bis(4-hydroxy-3-methoxyphenyl)methane (*VIII*). It may be assumed that the diarylmethane *VIII* is produced by a parallel reaction taking place under participation of the mesomeric phenoxide anion *VII* as nucleophile and the quinone methide *IIc* as alkylating agent (Scheme 2). This explanation is favoured by detection of phenyl methyl sulfide as the reduction product of the phenylsulfonylmethyl cation *IX*.



The above mechanism of the reduction of 4-hydroxybenzyl phenyl sulfones was confirmed by stoichiometric evidence. As shown by the titrimetric determination of lithium aluminium hydride during the reduction of the sulfone *Ih*, two hydride ions are required for the reduction, one of them being taken up instantaneously, the other one being consumed slowly. The eliminated benzenesulfinate anion was not reduced under the described reaction conditions.

The 2- and 4-hydroxybenzyl phenyl sulfones may also be hydrogenolysed by the action of some other hydride reagents soluble in aprotic solvents. Thus, *e.g.*, when kept in a benzenic solution of sodium bis(2-methoxyethoxy) aluminium hydride, the sulfone *Ii* is converted to the phenol *IIIi*. Similarly, the sulfone *IVa* was almost quantitatively reduced to the benzylphenol *VIa* with ethereal lithium borohydride.

EXPERIMENTAL

Melting points (uncorrected) were taken on a heated microscope stage (Kofler block). Analytical samples were dried at room temperature and 0.1 Torr for 8 h.

The hydroxybenzyl phenyl sulfones Ia—Im, IVa, and IVb were prepared from the corresponding alcohols and sodium benzenesulfinate in acetic acid⁷. For yields, melting points, and analyses of the sulfones see Table I.

TABLE I
Yields and Properties of Hydroxybenzyl Phenyl Sulfones Ia—Im, IVa, and IVb

Com- pound	Yield %	M.p. °C	Formula (m.w.)	Calculated / Found		
				% C	% H	% S
Ia	95	179—180	C ₁₉ H ₁₆ O ₃ S (312.4)	69.20	5.16	10.26
				69.00	5.30	10.40
Ib	93	146—148	C ₁₅ H ₁₆ O ₃ S (276.3)	65.19	5.83	11.60
				64.90	5.80	11.50
Ic	96	133—134	C ₁₄ H ₁₄ O ₄ S (278.3)	60.41	5.06	11.52
				60.55	5.15	11.40
Id	92	124—126	C ₁₅ H ₁₆ O ₃ S (276.3)	65.19	5.83	11.60
				65.35	5.69	11.62
Ie	95	134—135	C ₁₅ H ₁₆ O ₅ S (308.3)	58.42	5.23	10.39
				58.40	5.35	10.40
If	94	112—114	C ₁₆ H ₁₈ O ₅ S (322.4)	59.62	5.62	9.94
				59.35	5.50	10.00
Ig	90	192—193	C ₂₁ H ₂₀ O ₃ S (352.4)	71.56	5.72	9.09
				71.50	5.60	8.90
Ih	97	151—153	C ₂₁ H ₂₀ O ₅ S (384.4)	65.00	5.24	8.33
				65.25	5.32	8.30
Ii	96	136—137	C ₂₅ H ₂₈ O ₃ S (408.5)	73.49	6.90	7.84
				73.30	6.85	8.00
Ij	89	112—113	C ₂₁ H ₂₈ O ₃ S (360.5)	69.96	7.82	8.89
				68.80	7.89	9.05
Ik	91	134—136	C ₂₂ H ₃₀ O ₃ S (374.5)	70.54	8.07	8.56
				70.65	8.20	8.41
Il	90	155—156	C ₂₃ H ₃₂ O ₃ S (388.5)	71.09	8.30	8.25
				71.25	8.16	8.20
Im	85	172—173	C ₂₇ H ₃₂ O ₃ S (436.6)	74.27	7.38	7.34
				74.42	7.45	7.21
IVa	83	129—131	C ₂₀ H ₁₈ O ₃ S (338.4)	70.98	5.36	9.47
				71.22	5.43	9.47
IVb	86	110—112	C ₂₁ H ₂₀ O ₃ S (352.4)	71.56	5.72	9.09
				71.69	5.80	9.10

The lithium aluminium hydride reduction of 4-hydroxybenzyl phenyl sulfones I and IV. The appropriate sulfone (1 mmol) was added portionwise at room temperature with stirring to lithium aluminium hydride (5 mmol) in tetrahydrofuran (10 ml) under exclusion of atmospheric moisture. The content of the stirred mixture was periodically checked by thin-layer chromatography in 1 : 1 light petroleum-ether. When the reaction was complete (after about 1 h), the mixture was acidified with saturated aqueous citric acid, extracted with ether, the extract washed with saturated aqueous sodium hydrogen carbonate and water, dried, and processed as usual. In the case of sulfones *Id*–*If*, the hydrogenolysis was performed at the reflux temperature of the solvent for 2.5 h (*Id* and *If*) and for 15 h (*Ie*). Yields of the thus-prepared alkylphenols varied in the range of 91–98%; physical constants of products corresponded to the reported values.

Reduction of 4-hydroxy-3-methoxybenzyl phenyl sulfone (Ic). A mixture of the sulfone *Ic* (556 mg), lithium aluminium hydride (80 mg), and tetrahydrofuran (50 ml) was refluxed for 15 h, cooled down, acidified with saturated aqueous citric acid, the tetrahydrofuran evaporated, and the residue extracted with ether. The extract was processed as usual and the residue chromatographed on silica gel in light petroleum-ether (9 : 1 to 7 : 3) to afford 125 mg (45%) of 2-methoxy-4-methylphenol (*IIIc*), b.p. 219–220°C/760 Torr (reported⁸, b.p. 220–221°C/760 Torr), and 105 mg (40%) of bis(4-hydroxy-3-methoxyphenyl)methane (*VIII*), m.p. 108–109°C (reported⁹, 109–110°C).

The sodium bis(2-methoxyethoxy) aluminium hydride reduction of the sulfone Ii. The sulfone *Ii* (410 mg) in benzene (5 ml) was treated with a 80% solution of sodium bis(2-methoxyethoxy)aluminium hydride in benzene (0.5 ml) and the whole kept at 25°C for 1 h. Powdered sodium sulfate decahydrate (1.0 g) was then added and the stirring continued for 1 h. The salts were filtered off and the filtrate was evaporated. Crystallisation of the residue (255 mg) from pentane yielded the phenol *IIIi*, m.p. 35–36°C. For $C_{19}H_{24}O$ (268.4) calculated: 85.02% C, 9.01% H; found: 84.75% C, 9.20% H.

The lithium borohydride reduction of the sulfone IVa. A mixture of the sulfone *IVa* (675 mg), ether (3.0 ml), and 0.47M ethereal $LiBH_4$ (3.0 ml) was kept at room temperature for 12 h, acidified with 2M-HCl (1.5 ml), and processed as usual to afford 410 mg of the oily phenol *Vla*, b.p. 145–155°C/10 Torr. For $C_{14}H_{14}O$ (198.3) calculated: 84.79% C, 7.11% H; found: 85.06% C, 7.02% H.

Stoichiometry in the reduction of the sulfone Ih. A 0.05M solution of the sulfone *Ih* in tetrahydrofuran was added to a 0.1M solution of lithium aluminium hydride in tetrahydrofuran (10 ml). After 2 h at room temperature, the unreacted hydride was determined titrimetrically with 0.5M butanol in benzene¹⁰ (N-phenyl-4-aminoazobenzene as indicator¹¹). The following data were obtained:

Sulfone <i>Ih</i> , mmol	0.10	0.50	1.00
LiAlH ₄ uptake, mmol	0.04 ± 0.015	0.26 ± 0.01	0.49 ± 0.01

The titrated solutions were pooled, acidified with 2M-HCl (10 ml), diluted with water (100 ml), and processed as usual. Chromatography on silica gel in 4 : 1 light petroleum-ether yielded 720 mg of the phenol *IIIh*, m.p. 40–41°C (hexane). For $C_{15}H_{16}O_3$ (244.3) calculated: 73.74% C, 6.60% H; found: 73.65% C, 6.65% H.

Spectrophotometrical evidence of quinone methides IIg, III, and IIm. A 10^{-5} M solution of the appropriate sulfone (*Ig*, *II* or *Im*) in tetrahydrofuran was added to a 10^{-5} M solution (previously centrifuged for 20 min at 10000g to remove the small particles) of lithium aluminium hydride in tetrahydrofuran placed in a spectrophotometric cell and the 300–400 nm region was imme-

diately scanned. The observed maxima (348, 328, and 347 nm) in reduction of compounds *Ig*, *II*, and *Im* corresponded to the data of the appropriate authentic quinone methides *Ilg*, *III*, and *IIIm*.

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