A Facile Method for Regiospecific Hydroxylation of Resorcinol Diethers

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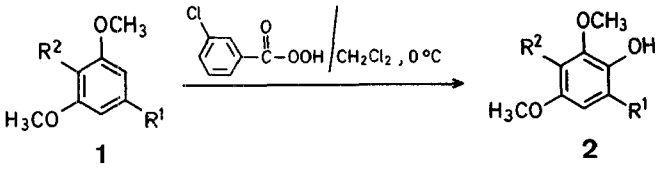
An early stage in the reaction of peroxyacids with alkyl aryl ethers appears to be hydroxylation, possibly by electrophilic attack. It has been postulated that, in most cases, the alkoxyphenols thus obtained are more reactive than the starting materials and are preferentially oxidized to the corresponding quinones[1,2,3].

We report now that 1,3-dimethoxybenzene **(1a)** and a number of its 5-alkyl derivatives **(1b–d)** as well as the ditetrahydropyran-2-yl diether of olivetol **(3)** and the 2-alkylolivetol diether **1e**, when oxidized with *m*-chloroperbenzoic acid in dichloromethane at 0°C give monohydroxylated products in good, preparatively useful yields (Table). The hydroxylation invariably takes place with regiospecificity, the product having the phenolic group *ortho* to one of the methoxy groups and *para*



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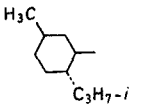
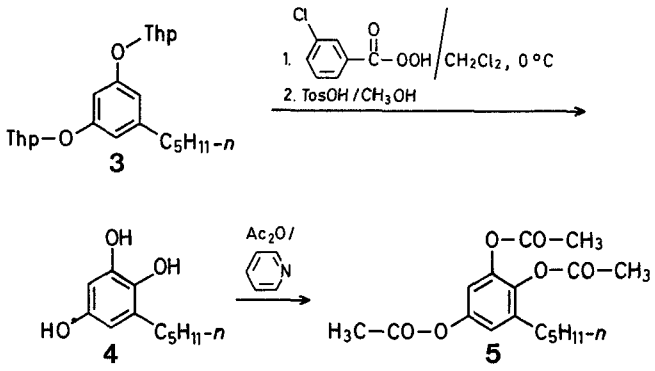
1,2	R^1	R^2
a	H	H
b	CH_3	H
c	n-C_5H_{11}	H
d	n-C_6H_{13}–C(CH_3)$_2$–	H
e	n-C_5H_{11}	

to the other, rather than *ortho* to both methoxyl groups. This is observed even in those cases where the C-4 position is considerably hindered by a branched alkyl side chain at the C-5 position. It is of interest to point out that, by contrast, while alkylations of 5-methylresorcinol take place mostly at the C-4 position, alkylations of 5-*n*-pentyl- or 5-(1,1-dimethylheptyl)-resorcinols take place preferentially at the C-2 position[4].

By the use of easily removable ether groupings, the above reaction can lead to the facile preparation of 1,2,4-trihydroxybenzene derivatives. Thus, oxidation of the ditetrahydropyran-2-yl diether **3** with *m*-chloroperbenzoic acid gave a hydroxylated diether which, without purification, was converted by acidic treatment into 1,2,4-trihydroxy-5-*n*-pentylbenzene **(4)**. The latter was isolated as the crystalline triacetate **5** in 55% overall yield.



The structures of the products were deduced from the analytical and spectroscopic data. We would like to point out that if symmetric hydroxylation products (i.e. 2,6-dimethoxyphenols) had been obtained, single peaks for the methoxy groups in the N.M.R. spectra, rather than the two peaks which actually appear, would have been observed.

Recently, a new hydroxylation procedure for phenol ethers using organocopper reagents was described[5]. In the few cases of 1,3-diethers presented, the hydroxylation took place exclusively at the C-2 position, i.e. *ortho* to both ether groupings. Hence, the organocopper reagent method and the one described now complement each other.

The starting compounds have been obtained commercially or according to known methods: **1a**[6], **1b**[6], **1c**[6], **1d**[7], **1e**[8], **3**[12].

Hydroxylation of Resorcinol Diethers 1a-e; General Procedure:
m-Chloroperbenzoic acid (2.2 mmol) is dissolved in dry dichloromethane (15 ml) and cooled to 0°C. The resorcinol diether (2 mmol) in dry dichloromethane (2 ml) is added dropwise, with stirring, under nitrogen. The reaction is followed by T.L.C. until completion (1–5 h). The reaction mixture is diluted with ether (30 ml), and the organic extract is washed successively with 5% sodium hydrogen sulfite solution (50 ml), 5% sodium hydrogen carbonate solution (50 ml), and brine (50 ml), and then dried with magnesium sulfate. After filtration and removal of the volatiles, the products are isolated on a medium pressure L.C. column (1000 mm × 10 mm) packed with Merck Kieselgel 60, 230–400 ASTM. Compounds **2b–e** are eluted with 1:99 diethyl ether/petroleum ether (b.p. 60–80°C); compound **2a** is eluted with 2:98 ethyl acetate/petroleum ether (b.p. 60–80°C); flow rate: 7 ml/min.

Conversion of 2,4-Dimethoxy-6-(1,1-dimethylheptyl)-phenol (2d) to 1,3-Dimethoxy-5-(1,1-dimethylheptyl)-benzene (1d):
In order to show that no rearrangement of the methoxy groups has taken place during the reaction, compound **2d** is converted back into the starting material **1d**. Compound **2d** (0.4 g, 1.4 mmol) is dissolved in dry carbon tetrachloride (5 ml), cooled to 0°C, and triethylamine (0.23 ml) and diethyl phosphite (0.21 ml) are added with stirring under an inert atmosphere. After stirring overnight, water (1 ml) is carefully added and the layers are separated. The organic layer is washed with 10% hydrochloric acid (10 ml), then with brine (10 ml), and dried with magnesium sulfate. The crude phosphate is reduced with lithium (0.1 g, 1.4 mmol) in liquid ammonia (10 ml) to furnish, after chromatography on Kieselgel (as above), eluting with 2:98 ethyl acetate/petroleum ether (b.p. 60–80°C), **1d**; overall yield: 80%.

A direct T.L.C. and N.M.R. comparison between compound **2d** and the isomeric 2,6-dimethoxy-4-(1,1-dimethylheptyl)-phenol[7] established their nonequivalency. The most obvious difference is in the chemical shifts of the protons of the methoxy groups: In the isomeric phenol, the six methoxy protons have an identical chemical shift ($\delta = 3.88$ ppm); in **2d**, two separate three proton peaks are observed (see Table).

1,2,4-Triacetoxy-6-*n*-pentylbenzene (5):
Compound **3** (1.4 g, 4 mmol) is oxidized according to the procedure described above for **1a–e**. The crude hydroxylated diether obtained is dissolved in methanol (20 ml) containing 3% *p*-toluenesulfonic acid. The mixture is stirred under nitrogen (1 h), diluted with water (20 ml), extracted with ether (20 ml), the extract is washed with a 10% solution of sodium hydrogen carbonate (20 ml), then with brine (20 ml), and dried with magnesium sulfate. Without further purification, the crude

Table. Regiospecific Hydroxylation of Resorcinol Diethers **1a–e**

Product	Yield [%]	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]	M.S. *m/e* (rel. int.)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
2a	60	26–27°[b]	25–27°[9]	154 (M^+, 100); 139 (80); 111 (47)	3.75 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 5.35 (s, 1H, OH); 6.3–6.9 (m, 3 H_{arom})
2b	55	105°[c] (pentane)	103–104°[9]	168 (M^+, 100); 153 (86); 125 (43)	2.24 (s, 3H, CH_3); 3.75 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 5.28 (s, 1H, OH); 6.31 (br. d, 2 H_{arom})
2c	55	47° (pentane)	$C_{13}H_{20}O_3$ (224.3)	224 (M^+, 100); 182 (23); 169 (90); 154 (63); 140 (48)	0.89 (t, 3H, J = 6.0 Hz, ω-CH_3); 1.42 [m, 6H, —$(CH_2)_3$—CH_3]; 2.63 (t, 2H, J = 6.6 Hz, CH_2—C_4H_9-*n*); 3.75 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 5.29 (s, 1H, OH); 6.3 (m, 2 H_{arom})
2d	82	oil	$C_{17}H_{28}O_3$ (280.4)	280 (M^+, 65); 196 (100); 182 (18); 181 (12); 168 (24)	0.80 (t, 3H, J = 5.8 Hz, ω-CH_3); 1.36 [s, 6H, $C(CH_3)_2$]; 3.76 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 5.50 (s, 1H, OH); 6.40 (s, 2 H_{arom}); 1.1–2.1 (10H)
2e[d]	70	oil	$C_{23}H_{38}O_3$ (362.6)	362 (M^+, 100); 277 (19); 237 (25); 224 (8)	0.85 (t, 3H, J = 5.8 Hz, ω-CH_3); 0.9–1.1 (m, 9H); 1.2–1.9 (m, 15H); 2.57 (t, 2H, J = 6.6 Hz); 2.9 (m, 1H); 3.72 (br. s, 6H, OCH_3); 5.34 (s, 1H, OH); 6.42 (s, 1 H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.3%, H ±0.2%.
[b] Benzoate m.p. 89°C (Lit.[10], m.p. 89°C).
[c] Acetate m.p. 53–54°C; for comparison: 1-acetoxy-2,6-dimethoxy-4-methylbenzene, Lit.[5], m.p. 71–72°C.
[d] $[\alpha]_D$: −76° (*c* 2.2, ethanol); U.V. (C_2H_5OH): $\lambda_{max}(\varepsilon)$ = 288 nm (4013).

triol **4** is acetylated with a 1:3 mixture of acetic anhydride/pyridine (25°C, 12 h) to give, after separation on medium pressure L.C., the triacetate **5**. The same chromatographic conditions as for **2a** are applied; yield: 55%; m.p. 74–75°C (pentane).

$C_{17}H_{22}O_6$	calc.	C 63.35	H 6.88
(322.4)	found	63.13	6.73

M.S.: *m/e* (rel. int.) = 322 (4, M^+); 280 (13); 238 (41); 196 (100).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.89$ (t, 3 H, $J = 5.7$ Hz, ω-CH_3); 1.38–1.67 (m, 6 H); 2.28 (s, 3 H, H_3C—CO); 2.30 (s, 3 H, H_3C—CO); 2.33 (s, 3 H, H_3C—CO); 2.85 (t, 2 H, $J = 6.5$ Hz, —CH_2—C_4H_9-*n*); 6.92 ppm (s, 2 H_{arom}).

Conversion of 5 to 1,2,4-Trihydroxy-6-*n*-pentylbenzene (4):

Compound **5** is further characterized by conversion to the triol **4**. Thus, **5** (322 mg, 1 mmol) is dissolved in methanol (10 ml) and excess sodium borohydride (0.5 g, 14.7 mmol) is added. After 15 min, T.L.C. analysis indicates absence of starting material. The mixture is diluted with water (5 ml) and extracted with ether (20 ml). After drying with magnesium sulfate and column chromatography as described in the general procedure, eluting with 30:70 ethyl acetate/petroleum ether (b.p. 60–80 °C), the triol **4** is obtained; yield: 90% and recrystallized from pentane; m.p. 94–95°C (Lit.[11], m.p. 70–75°C, reported for a degradation material from a natural product).

$C_{11}H_{16}O_3$	calc.	C 67.32	H 8.22
(196.2)	found	67.64	7.98

M.S.: *m/e* (rel. int.) = 196 (30, M^+); 140 (100).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.86$ (t, 3 H, $J = 5.6$ Hz, ω-CH_3); 1.37–1.63 (m, 6 H); 2.50 (t, 2 H, $J = 6.6$ Hz; CH_2—C_4H_9-*n*); 4.41, 4.49, 5.27 (3 br. s, 3 H, exchangeable with D_2O); 6.17, 6.23 ppm (2 d, 2 H_{arom}).

Conversion of 2c to 4:

The same material **4** is obtained from **2c** as follows: Compound **2c** (100 mg, 0.45 mmol) is dissolved in dry dichloromethane (10 ml) under nitrogen, and cooled to −70°C. Boron tribromide (3 equivalents) is added by a syringe dropwise. The mixture is allowed to come to room temperature overnight. The reaction mixture is diluted with water (10 ml) and extracted with ether (20 ml). The organic solvent is evaporated and the solid residue is recrystallized from pentane to give **4**; yield: 90%; identical (N.M.R., T.L.C., M.S., m.p.) with the material obtained on oxidation of **3** (see above). The triol **4** thus obtained is converted into **5** (yield: 95%), again identical to the material from the oxidation of **3**.

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