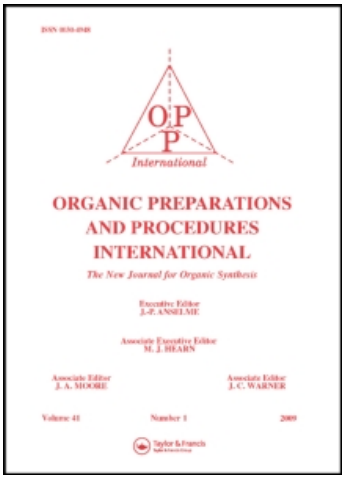

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C-ALKYLATION OF PHENOLS BY 2-HYDROXYBENZYLAMINE DERIVATIVES

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C-ALKYLATION OF PHENOLS BY 2-HYDROXYBENZYLAMINE DERIVATIVES

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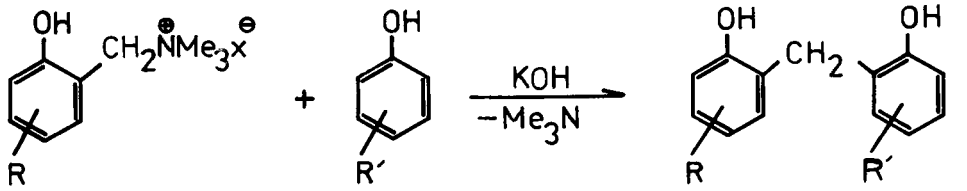
The introduction of a 2-hydroxybenzyl moiety into the ortho position of p-substituted phenols leads to the biologically active, unsymmetrically substituted derivatives of 2,2'-dihydroxydiphenylmethane (I). These compounds have previously been obtained by the reaction of p-substituted phenols with benzyl halides,[1,2] albeit in low yields. Since derivatives of 2,2'-dihydroxydiphenylmethane possess antimicrobial and antiparasitical properties, a new and simpler synthesis was developed and we now report that good yields of I can be obtained by the reaction of the corresponding benzylammonium salt (II) with p-substituted phenols in an aqueous alcoholic solution at pH > 9 (Table I). The reaction of 2-hydroxy-5-chlorobenzyltrimethylammonium bromide, iodide and sulfate with p-cresol in different solvent systems is reported in Table II.



II I

Derivatives of I could be obtained by utilizing N,N-dimethylbenzylamines as the alkylating agent, however in these cases lower yields were observed.

EXPERIMENTAL

Preparation of 2,2-Dihydroxydiphenylmethanes (I). General Procedure.- A mixture of the quaternary salts (II) in ethanol or water, an equimolar amount of the phenol and a 10% excess of KOH were heated under reflux until a significant decrease in the rate of evolution of trimethylamine was observed (20-50 hrs). When ethanol was used as the solvent, it was evap-

Table I. 2,2'-Dihydroxydiphenylmethanes (I).

R	R'	Yield (%)	mp. (°C)	Elemental Analysis Calcd C	Found C	Calcd H	Found H	Calcd Cl	Found Cl
5-CH_3	5-Cl	80[a,c]	146-147	67.65	67.59	5.23	5.16	14.28	14.36
5-Cl	5-t-Bu	83[a]	178-179	70.22	70.35	6.54	6.47	12.22	12.31
5-Cl	5-Cl	71[b]	173-174[d]						
5-Cl	5-Br	75[a]	155-157[a]	49.76	49.71	3.19	3.07	36.84[f]	36.99
5-Cl	4-CH_3-5-Cl	71[b,c]	172-174[d]						
4-CH_3-5-Cl	5-Cl	60[b,c]	177-177.5[d]						
4-CH_3-5-Cl	4,6-Dimethyl-5-chloro	97[c]	164-165[c]	61.74	61.86	5.14	5.21	22.83	22.59
3,5-Dichloro	5-CH_3	72[b]	179-181[c]	59.36	59.21	4.24	4.14	25.09	25.08
5-NO_2	5-CH_3	83[d]	172-175[e]						

a) Crystallization of sodium salt. b) Crystallization from water.
c) Crystallization from CCl_4. d) See ref. 1. e) See ref. 3.
f) % Cl and Br.

orated and the residue was dissolved in a small amount of water. The aqueous solution was acidified with 10% HCl to pH ∿ 1 and the unreacted phenol was steam distilled. The residue was extracted with ether, washed with 10% HCl and the product was reextracted with 5% NaOH. The alkaline solution was heated with charcoal, filtered and acidified with carbon dioxide. The isolated products II were purified by crystallization from a suitable solvent or from water as their sodium salt. This method was used for alkylation of p-cresol with 2-hydroxy-5-chlorobenzyltrimethylammonium salts in various solvents (Table I).

Several compounds of type I were obtained from the ammonium methyl hydrogen sulphates (II, $X^- = CH_3SO_4^-$) and the appropriate phenols in aqueous medium (Table II).

Table II. Alkylation of p-Cresol with 2-hydroxy-5-chlorobenzyltrimethylammonium salts (II).

X	Br	I	I	I	I	CH_3SO_4	CH_3SO_4
Solvent	BuOH	EtOH	BuOH	EtOH/H_2O 4:1	H_2O	BuOH	H_2O
Yield %*	79	61	76	81	80	80	83

*2,2'-dihydroxy-5-methyl-5'-chlorodiphenylmethane, mp. 146-147° (H_2O,CCl_4).

The compounds synthesized were identical with those described in the literature. Acceptable elemental analysis results and NMR spectra were obtained for the new compounds.

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