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C-ALKYLATION OF PHENOLS BY 2-HYDROXYBENZYLAMINE DERIVATIVES

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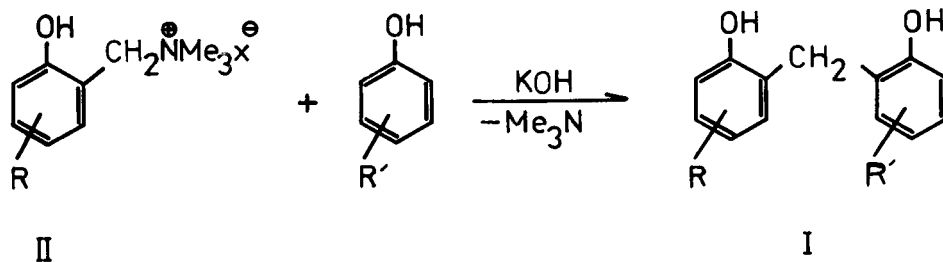
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C-ALKYLATION OF PHENOLS BY 2-HYDROXYBENZYLAMINE DERIVATIVES

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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 anti-parasitidal 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-chlorobenzyl-trimethylammonium bromide, iodide and sulfate with p-cresol in different solvent systems is reported in Table II.



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	Found	
				C	H	Cl
5-CH ₃	5-Cl	80 ^{a,c}	146-147	67.65	5.23	14.28
				67.59	5.16	14.36
5-Cl	5-t-Bu	83 ^a	178-179	70.22	6.54	12.22
				70.35	6.47	12.31
5-Cl	5-Cl	71 ^b	173-174 ^d			
5-Cl	5-Br	75 ^a	155-157 ^a	49.76	3.19	36.84 ^f
				49.71	3.07	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	5.14	22.83
				61.86	5.21	22.59
3,5-Dichloro	5-CH ₃	72 ^b	179-181 ^c	59.36	4.24	25.09
				59.21	4.14	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 CCl₄. d) See ref. 1. e) See ref. 3.
 f) % Cl and Br.

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orated and the residue was dissolved in a small amount of water. The aqueous solution was acidified with 10% HCl to pH \sim 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-chlorobenzyl-trimethylammonium salts (II).

X	Br	I	I	I	I	CH ₃ SO ₄	CH ₃ SO ₄
Solvent	BuOH	EtOH	BuOH	EtOH/H ₂ O 4:1	H ₂ O	BuOH	H ₂ O
Yield %*	79	61	76	81	80	80	83

*2,2'-dihydroxy-5-methyl-5'-chlorodiphenylmethane, mp. 146-147° (H₂O, CCl₄).

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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