[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION OF SHARP AND DOHME, INC.]

Some Amino Alkyl Phenols[1]

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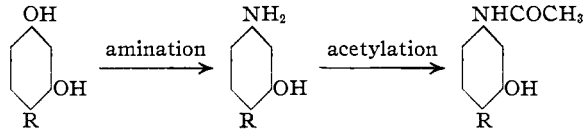
It is reported that the introduction of an amino group into the 3-position of 4-hydroxybenzoic esters reduces the antibacterial activity of these esters by about 75%.[3] It now appears that a similar effect is produced when an amino group is introduced into the aromatic nucleus of an otherwise highly active alkylphenol. *o-n*-Hexylphenol has a phenol coefficient of above 100 toward *Staphylococcus aureus* when tested by the F. D. A. method, whereas 2-*n*-hexyl-4-aminophenol is less than 10 under similar conditions. A corresponding reduction in activity is shown by the homologs of *o*-hexylphenol.[4]

The compounds were prepared from the alkylresorcinols[5] by reaction with ammonia under pressure in the presence of bisulfite at elevated temperatures, by an adaptation of the procedure for the conversion of resorcinol into *m*-aminophenol.[6] Since evidence from various sources indicates that the hydroxyl ortho to the alkyl group in the less reactive,[7] it is presumed that the para hydroxyl is replaced and that the products are 2-alkyl-5-amino-phenols. These aminated alkylphenols are obtained in yields of 70–80%, as crystalline solids, and on treatment with acetic anhydride are converted into monoacetyl derivatives.

The data for six members of the homologous series are summarized in Table I.



It is possible to carry out the amination with less than 1 g. of material and, since the products obtained have sharp melting points, the reaction may be employed for the qualitative identification of the individual alkylresorcinols, with additional confirmation available in the respective monoacetyl derivatives.

Amination.—A typical experiment is carried out as follows: a mixture of 19.3 g. of hexylresorcinol, 5.4 g. of ammonium chloride, 10.4 g. of sodium bisulfite and 25 ml. of concd. ammonium hydroxide is placed in an open Pyrex tube of appropriate size; the tube and its contents is placed in a steel bomb and heated at 240–250° for about four hours. After cooling, the 2-hexyl-5-aminophenol, obtained as a glistening crystalline solid, is removed from the reaction mixture by filtration and, on drying, weighs 14–15 g. It is further purified by forcing from a toluene solution by the addition of heptane; m. p. 127.3–127.6°.

Acetylation.—A typical reaction is carried out as follows. One gram of the purified amine is dissolved in 1 ml. of acetic anhydride; the solution is heated for several minutes over a luminous flame to boiling and after five minutes is poured into cold water. The oil which first forms gradually crystallizes, and after drying is recrystallized from toluene.

By substituting any other alkylresorcinol for hexylresorcinol in the procedure just described, the corresponding aminoalkylphenol may be prepared.

TABLE I

AMINATED ALKYL RESORCINOLS AND ACETYL DERIVATIVES

Intermediate alkyl resorcinol	Amino derivative M. p., °C.	Formula	% N Calcd.	% N Found[a]		Mono-acetyl derivative M. p., °C.	Formula	% N Calcd.	% N Found[a]	
n-Propyl	109.0–110.0	$C_9H_{13}ON$	9.27	9.18	8.99	Liquid				
n-Butyl	132.3–133.0	$C_{10}H_{15}ON$	8.49	8.28	8.46	142–143				
n-Amyl	122.0–123.0	$C_{11}H_{17}ON$	7.78	7.79	7.82	147–147.5				
n-Hexyl	127.3–127.6	$C_{12}H_{19}ON$	7.26	7.18	7.16	130.1–130.3	$C_{14}H_{21}O_2N$	5.96	5.81	5.78
n-Heptyl	130.5–130.9	$C_{13}H_{21}ON$	6.76	6.95	6.78	141.2–141.8	$C_{15}H_{23}O_2N$	5.62	5.84	5.64
n-Octyl	129.5–130.3	$C_{14}H_{23}ON$	6.34	6.34	6.39	130.1–130.5	$C_{16}H_{25}I_2N$	5.32	5.21	5.36

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(1) Presented at the Kansas City Meeting, American Chemical Society, April, 1936.

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(3) Sabalitschka and Triedge, *Arch. Pharm.*, **272**, 383 (1934).

(4) The bacteriological tests were made by W. A. Feirer and S. R. Pence, to whom the authors are indebted.

(5) Dohme, Cox and Miller, THIS JOURNAL, **48**, 1688 (1926).

(6) Ikuta, *Am. Chem. J.*, **15**, 39 (1893); German Patents 44,792, 49,060 and 117,471.

(7) *Cf.* Twiss, THIS JOURNAL, **48**, 2206 (1926).

Summary

Alkyl resorcinols may be converted in good yields into the corresponding, definitely crystalline amino alkyl phenols. These, on acetylation, yield crystalline mono-acetyl derivatives. The products possess negligible or no germicidal properties.

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