Tolyl Ethers of Choline[1]

The tolyl ethers of choline were prepared by a modification of the method used by Renshaw and Armstrong for the preparation of other aryl ethers.[3]

β-Cresoxy-ethyl Bromides.—One mole of the appropriate cresol and 2 moles of ethylene dibromide were suspended in water, stirred and heated to boiling. One mole of sodium hydroxide in 50% solution was added slowly and refluxing was continued for two hours. The lower oily layer was separated, washed free of alkali, dried and fractionated. The products so obtained are described in Table I.

TABLE I

β-CRESOXY-ETHYL BROMIDES

Compound	B. p., °C. (18 mm.)	Formula	Bromine, % Calcd.	Bromine, % Found	
Ortho	142.0–142.5	$C_9H_{11}OBr$	37.19	37.10	37.12
Meta	146.5–147.0	$C_9H_{11}OBr$	37.19	37.18	37.15
Para	136.0–138.0	$C_9H_{11}OBr$	37.19	37.00	37.19

Cresoxy-ethyl-trialkylammonium Bromides.—One mole of cresoxyethyl bromide in toluene solution and 1.2 moles of trimethylamine were mixed in a pressure bottle and heated to 40° for seventy-two hours. The precipitated solid was filtered and crystallized. The triethyl homologs were prepared similarly except that the time required for complete reaction was about one month at 60°. The products obtained are described in Table II.

TABLE II

CRESOXY-ETHYL-TRIALKYLAMMONIUM BROMIDES

$CH_3C_6H_4OCH_2CH_2NR_3^+Br^-$

R		M. p., °C.	Formula	Bromine, % Calcd.	Bromine, % Found	
CH_3	Ortho[a]	157.5	$C_{12}H_{20}NOBr$	29.20	29.30	29.19
	Meta[a]	145.4	$C_{12}H_{20}NOBr$	29.20	29.09	29.10
	Para[c]	144.0	$C_{12}H_{20}NOBr$	29.20	29.01	29.20
C_2H_5	Ortho[b]	152.0–152.5	$C_{15}H_{26}NOBr$	25.30	25.50	25.41
	Meta[b]	136.4	$C_{15}H_{26}NOBr$	25.30	25.31	25.40
	Para[d]	134.5	$C_{15}H_{26}NOBr$	25.30	25.23	25.41

[a] Purified by precipitation from ethyl acetate solution with amyl acetate. [b] Crystallized from acetone-ethyl acetate mixture. [c] Crystallized from acetone. [d] Crystallized from acetone–amyl acetate mixture.

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(1) These compounds were prepared by A. R. Goldfarb[2] under the direction of the late Professor R. R. Renshaw.

(2) Present address Lawrence, Richard, Bruce, Inc., Stamford, Connecticut.

(3) Renshaw and Armstrong, *J. Biol. Chem.*, **103**, 187 (1933).

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RECEIVED JUNE 9, 1941

Aryl and Alkyl Ethers of β-Methylcholine[1]

The syntheses of the intermediates and final products are reported.

1-Dialkylamino-propanol-2.—Dimethylamine from 50 g. of dimethylamine hydrochloride was passed through a mixture of 54 g. of propylene oxide and 50 cc. of methanol at 60°, under a reflux condenser. The addition of dimethylamine was regulated to last three hours. The mixture was fractionated twice through a fractionating column; 53 g. (70%) of product was obtained, b. p. 124.5–126.0° at 758 mm.

Anal. Calcd. for $C_5H_{13}ON$: N, 13.58. Found: N, 13.48, 13.52.

The diethyl homolog was prepared by a modification of the method described by Callsen and Hahl[3] in which methanol was used instead of water. In this case the yields were consistently 10% higher than those reported by Callsen and Hahl and obtained by this author using water; 72 g. of diethylamine was mixed with 59 g. of propylene oxide under reflux. No reaction occurred until the catalyst, 20 cc. of methanol, was added. After about five minutes, a strongly exothermic reaction set in, causing the reaction mixture to boil. After one hour the reflux subsided and the mixture was refluxed for one hour longer. The reaction product was fractionated twice, yielding 115 g. of product which boiled at 62.5–63.5° at 22 mm.

Anal. Calcd. for $C_7H_{17}ON$: N, 10.61. Found: N, 10.65, 10.70.

2-Chloropropyl-1-dialkylammonium Chlorides.—One-half mole of dialkylamino-propanol-2 in 100 cc. of dry chloroform was added slowly to a well-stirred solution of 60 cc. of thionyl chloride in 500 cc. of dry chloroform, cooled to −5 to 0°. The addition required two hours and the mixture was allowed to stand for two hours longer in the freezing mixture. At no time in this interval was the temperature of the reaction mixture permitted to rise above 0°. The chloroform was distilled off at a low temperature, alcohol was added and the alcohol was distilled *in vacuo* on a water-bath. The addition and distillation of alcohol was repeated until the distillate was free of the odor of sulfur dioxide. The solid was crystallized twice from an ethanol-ethyl acetate mixture. Yields consistently higher than 70% were obtained.

Anal. Calcd. for $C_5H_{13}NCl_2$: Cl, 22.44. Found: Cl, 22.48, 22.56. Calcd. for $C_7H_{17}NCl_2$: Cl, 19.05. Found: Cl, 19.18, 19.00.

Reaction of β-Chloropropyl-dialkylammonium Chlorides with Sodium Alcoholates and Arylates.—The β-chloropropyl-dialkylammonium chloride (one mole) was dissolved in the alcohol corresponding to the ether which was to be formed. A solution of 2.2 atoms of sodium metal, dissolved in the same alcohol, was added to the solution with stirring. The reaction mixture was heated on a water-bath for twenty-four hours and then filtered. The filtrate was fractionated through a one-foot column. The aryl ethers were prepared in the same manner, using anhydrous methyl alcohol as solvent, and the required phenol.

It was found necessary that the solvents be absolutely anhydrous, since small amounts of water hydrolyze the chloro compound rapidly. Average yields of 40–50% were obtained and the properties of the free amines are given in Table I. The amines were not analyzed but were converted directly to the quaternary ammonium salts.

Ethers of β-Methylcholine Iodide.—β-Aryloxy and β-alkoxy-propyl-dimethyl amines were treated with excess

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(1) These compounds were prepared by A. R. Goldfarb[2] under the direction of the late Professor R. R. Renshaw.

(2) Present address: Lawrence, Richard, Bruce, Inc., Stamford, Connecticut.

(3) German Patent 430,960.