2. "Solid phosphoric acid" will catalyze the following reactions: between ethanol and methanol to form ethyl methyl ether; between diethyl and dimethyl ethers to form ethyl methyl ether; between benzyl and methyl alcohols to form benzyl methyl ether.

EVANSTON, ILLINOIS,
AND RIVERSIDE, ILLINOIS RECEIVED NOVEMBER 7, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MIAMI UNIVERSITY]

Reactions of Monoalkylanilines with β,β'-Dichlorodiethyl Ether: 4-Phenylmorpholine

BY H. C. BRILL, C. N. WEBB AND H. S. HALBEDEL[1]

A study of the reaction of β,β'-dichlorodiethyl ether with methyl, ethyl, *n*-butyl and isoamylanilines was undertaken in the expectation of preparing phenylalkylaminoethyl-β-chloroethyl ether and using it in further reactions in the preparation of other compounds that might possess local anesthetic properties.

In their investigation of the preparation of divinyl ether by treatment of β,β'-dichloro and of β,β'-diiodo-diethyl ether with various bases, Ruigh and Major[2] found the dichloro to be unreactive with dimethylaniline but that the diiodo yielded the diiodide of *bis*-β,β'-phenyldimethylaminoethyl. The dichloro ether produced no identifiable products when heated with quinoline. Apparently tertiary bases of this nature do not split out hydrogen chloride or hydrogen iodide.

No such trouble was anticipated with the secondary amines which we contemplated using. Nevertheless, in actuality a reaction of quite another type took place.

Dichlorodiethyl ether was refluxed with the above-mentioned monoalkyl anilines. Two-tenths of a mole each of the ethyl- and methylanilines and 0.06 and 0.1 mole of the *n*-butyl and isoamylanilines were taken, respectively. Equal molar quantities of the amines were taken in each case and the time of heating varied between two and four hours. The boiling points of all the mixtures rose to approximately 225°, although with the two higher alkyl anilines a temporary drop in temperature occurred prior to the distillation of the volatile liquid. Hydrogen chloride was evolved in all cases. With methyl- and ethylaniline gases (3 liters) were given off insoluble in water, heavier than air, with a sweetish odor, and burning with a green flame yielding hydrogen chloride. The gas obtained from the ethylaniline, tested by the method of Demer and Dysinger,[3] gave no indication of ethylene. With *n*-butyl- and isoamylanilines, low-boiling liquids were produced in amounts of 1.1 and 4 g. These were distilled off in the middle of the refluxing period and after purification by redistillation boiled at 77–77.5 and 98–102° and had refractive indices ($n^{20}\text{D}$) of 1.4027 and ($n^{18}\text{D}$) 1.4110, respectively. *n*-Butyl chloride and isoamyl chloride have boiling points of 78 and 99.7°, and refractive indices ($n^{20}\text{D}$) of 1.4015 and ($n^{18}\text{D}$) 1.4112, respectively. It is evident that the gases are methyl and ethyl chlorides, and the volatile liquids *n*-butyl and isoamyl chlorides, respectively.

The original reaction mixtures on cooling gave a mixture of oil (unchanged reactants) and crystals. The oil was removed by a porous plate and the crystals purified by recrystallization from 50% alcohol using boneblack. A yield of about 15 g. was obtained from the methyl and ethyl anilines and 3 g. and 1 g., respectively, from the *n*-butyl and isoamylanilines.

A molecular weight determination was made on the product of the ethylaniline, with the following results.

Mol. wt., subs. 0.2725 g., benzene 19.06 g. Δt 0.420°. Found: mol. wt.:, 162; mol. wt., 4, phenylmorpholine, 163.

Mixed melting point determinations on the four solid products with known 4-phenylmorpholine prepared by the method of Cretcher, Koch and Pittenger[4] showed that they all were 4-phenylmorpholine.

Attempts to run this reaction with ethylaniline in the presence of 10% aqueous sodium hydroxide or in toluene solution were unsuccessful.

While no intermediate products have been

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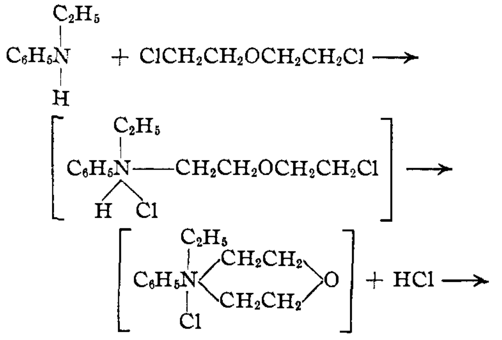
(1) Abstract of a thesis submitted in partial fulfillment of the requirements for a degree of Master of Arts.

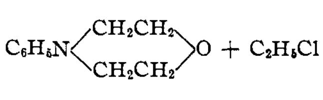
(2) Ruigh and Major, THIS JOURNAL, 53, 2662 (1931).

(3) Demer and Dysinger, *ibid.*, 61, 750 (1939).

(4) Cretcher, Koch and Pittenger, *ibid.*, 47, 1174 (1925).

isolated, it is possible that the 4-phenylmorpholine may result from a series of reactions somewhat related to those occurring in the Hofmann exhaustive methylation of amines:





Summary

1. Reactions of mono-alkylanilines with β,β'-dichlorodiethyl ether gave in all cases 4-phenylmorpholine, hydrogen chloride and the appropriate alkyl halide.

2. No olefin was identified in the reaction products.

3. Methyl- and ethylanilines gave approximately the same yields, *n*-butyl- and isoamylanilines smaller yields of 4-phenylmorpholine.

Oxford, Ohio Received September 12, 1940

[Contribution from the Noyes Chemical Laboratory, University of Illinois]

The Reductive Alkylation of Hindered Aromatic Primary Amines

By William S. Emerson, F. W. Neumann and T. P. Moundres

Reductive alkylation of aromatic primary amines[1] with aldehydes is not feasible in acidic media since the reactants form polymers under these conditions. However, it seemed probable that success could be achieved with amines in which the active positions (2, 4 and 6) were blocked. In fact, it had already been shown that 2,4,6-tribromoaniline could be methylated in 77% yield with formaldehyde and formic acid.[2]

In the present work the alkylation of mesidine and 2,4,6-tribromoaniline with carbonyl compounds was studied. Using formic acid as the reducing agent, N,N-dimethylmesidine was obtained readily from mesidine and formaldehyde. With either of the amines and acetaldehyde or propionaldehyde, tars were formed, while the reaction of these amines with acetone or isobutyraldehyde was slower than that with formic acid itself, so that the substituted formanilide was the sole product.

In the case of 2,4,6-tribromoaniline, when zinc and hydrochloric acid was substituted for formic acid as the reducing agent, bromine was removed from the benzene ring.[3] On the other hand, mesidine was alkylated smoothly with this reagent. Formaldehyde yielded N,N-dimethylmesidine in 70% yield, while acetone, isobutyraldehyde and isovaleraldehyde gave the corresponding secondary amines in 18 to 94% yield. Also using this procedure 31% of N-isopropylaniline was obtained from aniline and acetone, although with isobutyraldehyde aniline yielded a tar.

When nitromesitylene was used in place of mesidine with formaldehyde and isovaleraldehyde, N,N-dimethylmesidine and N-isoamylmesidine were obtained directly in 68 and 61% yields, respectively.

Experimental

General Procedure for Formic Acid Alkylations.—The amine, the aldehyde or ketone and 85% formic acid were mixed in a 200-cc. round-bottomed flask and boiled under reflux for from two to seven hours. Ten cubic centimeters of concentrated hydrochloric acid was added and the excess formic acid was distilled at reduced pressure. The product precipitated when the residue was made basic with aqueous sodium hydroxide.

N,N-Dimethylmesidine was isolated in the crude state by steam distilling the alkaline reaction mixture obtained by the above procedure from 10.8 g. (0.08 mole) of mesidine, 15 g. (0.20 mole) of 40% aqueous formaldehyde and 120 g. (2.22 moles) of formic acid. After it had been removed from the distillate by ether extraction and the ether evaporated, the product distilled at 214–220°; $n^{20}\text{D}$ 1.5111. The yield of 9.5 g. (73%) was identified as the picrate, m. p. 181–182° (182°).[4]

Other Attempted Alkylations of Mesidine.—When acetone was used in place of formaldehyde, formesidide precipitated as soon as the reaction mixture was neu-

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[1] Emerson and Walters, This Journal, **60**, 2023 (1938); Emerson and Robb, *ibid.*, **61**, 3145 (1939).

[2] Clarke, Gillespie and Weisshaus, *ibid.*, **55**, 4571 (1933).

[3] Emerson, Dorf and Deutschman, *ibid.*, **62**, 2159 (1940).

[4] Hey, *J. Chem. Soc.*, 1581 (1931).