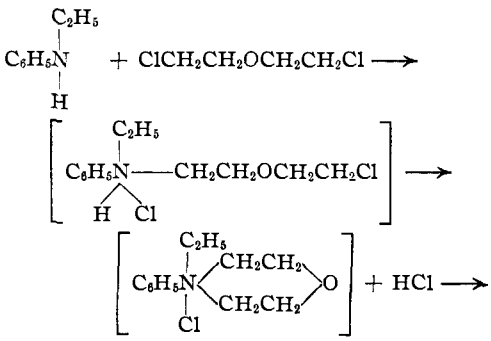
isolated, it is possible that the 4-phenylmorpholine may result from a series of reactions somewhat related to those occurring in the Hofmann exhaustive methylation of amines:



$$C_6H_5N(CH_2CH_2)_2O + C_2H_5Cl$$

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.

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[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°; $n^{20}D$ 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-

(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).

tralized. After one crystallization from aqueous alcohol it melted at 178–179° (177°).[5] The yield was 55%. In addition, 11% of unchanged mesidine was recovered, but no alkylation products could be detected. With acetaldehyde as the alkylating agent only a black polymer was obtained.

Attempted Alkylations of 2,4,6-Tribromoaniline.—Several alkylations were attempted using 2,4,6-tribromoaniline instead of mesidine. With acetone and with isobutyraldehyde, 2,4,6-tribromoformanilide, m. p. 217–219° (221.5°)[6] was obtained in 77 and 92% yields, respectively. In the former case 6% of the unchanged primary amine was also recovered. Attempted alkylations with acetaldehyde and propionaldehyde yielded polymers as the sole products.

General Procedure for Amalgamated Zinc and Hydrochloric Acid Alkylations.—The apparatus consisted of a one-liter three-necked flask equipped with a reflux condenser, dropping funnel and mechanical stirrer. In it was placed the amine, the aldehyde or ketone, amalgamated zinc[7] and glacial acetic acid. This mixture was refluxed over an electric hot plate for about twenty-four hours, the concentrated hydrochloric acid being added during the first five hours. Afterwards it was diluted with water and sodium hydroxide added until zinc salts started to precipitate. The product was then extracted with benzene.

N,N-Dimethylmesidine was obtained by this procedure from 10.1 g. (0.075 mole) of mesidine, 17 g. (0.23 mole) of 40% aqueous formaldehyde, 100 g. (1.53 mole) of amalgamated zinc, 100 cc. of glacial acetic acid and 200 cc. (2.50 moles) of concentrated hydrochloric acid. This product boiled at 210–221°; $n^{20}D$ 1.5119; d^{20}_{20} 0.9074; $M^{20}D$ calcd. 54.9; $M^{20}D$ found 54.3; yield 8.5 g. (70%). It was identified as the picrate, m. p. 181–182° (182°).[4]

The hydrochloride was also prepared, m. p. 155–156° (dec.).

Anal. Calcd. for $C_{11}H_{18}NCl$: Cl, 17.8. Found: Cl, 17.6.

When nitromesitylene was used in place of mesidine, the general procedure was modified in that the 50 cc. of glacial acetic acid covering 100 g. (1.53 moles) of amalgamated zinc was heated to boiling and a mixture of 150 cc. of glacial acetic acid, 12 g. (0.073 mole) of nitromesitylene, 27.5 g. (0.37 mole) of 40% aqueous formaldehyde and 50 cc. (0.63 mole) of concentrated hydrochloric acid was added over a one hour period. One hundred and fifty cubic centimeters (1.88 moles) of concentrated hydrochloric acid was added during the next one and one quarter hours and refluxing was continued for twenty hours more. The reaction mixture was worked up in the usual way to obtain 8.0 g. (68%) of N,N-dimethylmesidine, $n^{20}D$ 1.5113.

It was identified as the picrate, m. p. 181–182° (182°).[4]

N-Isobutylmesidine was the sole product from 10 g. (0.074 mole) of mesidine, 15.9 g. (0.22 mole) of isobutyraldehyde, 100 g. (1.53 moles) of amalgamated zinc, 100 cc. of glacial acetic acid and 200 cc. (2.50 moles) of concentrated hydrochloric acid. It boiled at 267–277°; $n^{20}D$ 1.5070; d^{20}_{20} 0.8986; $M^{20}D$ calcd. 63.3; $M^{20}D$ found, 63.3; yield 12.9 g. (91%). The acetyl derivative melted at 71.5–72.5° after four crystallizations from aqueous methyl alcohol.

Anal. Calcd. for $C_{15}H_{23}ON$: N, 6.01; Found: N, 6.07.

The hydrochloride melted at 148–150° (dec.).

Anal. Calcd. for $C_{13}H_{22}NCl$: Cl, 15.6. Found: Cl, 15.5, 15.4.

N-Isoamylmesidine was likewise the sole product from 7.0 g. (0.052 mole) of mesidine, 11.0 g. (0.128 mole) of isovaleraldehyde, 50 g. (0.77 mole) of amalgamated zinc, 150 cc. of glacial acetic acid and 100 cc. (1.25 moles) of concentrated hydrochloric acid. It distilled at 155–165° (20 mm.); $n^{20}D$ 1.5020; d^{20}_{20} 0.897; $M^{20}D$ calcd. 68.0; $M^{20}D$ found 67.6; yield 10.0 g. (94%).

The benzoyl derivative melted at 92–93° after three crystallizations from petroleum ether and one from aqueous alcohol.

Anal. Calcd. for $C_{21}H_{27}ON$: N, 4.53. Found: N, 4.71.

Treatment of the amine with dry hydrogen chloride in anhydrous ether yielded an oil.

When 8.5 g. (0.051 mole) of nitromesitylene was used in place of mesidine with 11.0 g. (0.128 mole) of isovaleraldehyde, 150 g. (2.30 moles) of amalgamated zinc, 150 cc. of glacial acetic acid and 200 cc. (2.50 mole) of concentrated hydrochloric acid under the same conditions as were used for the preparation of N,N-dimethylmesidine from nitromesitylene, 6.5 g. (61%) of N-isoamylmesidine, $n^{20}D$ 1.5035 was obtained.

N-Isopropylmesidine was obtained from 10 g. (0.074 mole) of mesidine, 17 g. (0.29 mole) of acetone, 75 g. (1.15 moles) of amalgamated zinc, 150 cc. of glacial acetic acid and 150 cc. (1.87 moles) of concentrated hydrochloric acid. The 7.5 g. of crude product boiled at 114–123° (17 mm.). Separation from unreacted mesidine was effected by refluxing the crude product for one hour with 40 cc. of acetic anhydride. After pouring in water, extracting with ether, washing the ether solution with sodium carbonate and evaporating the ether, acetmesidide crystallized when the mixture was cooled in the presence of ethyl acetate; yield 5.75 g. (44% recovery); m. p. 213–215° (216–217°).[8] The oil obtained from the filtrate boiled at 118–123° (3 mm.); yield 3.0 g. (18%) of N-isopropylacetmesidide.

Anal. Calcd. for $C_{14}H_{21}ON$: N, 6.40. Found: N, 6.44

N-Isopropylaniline was obtained from 9.7 g. (0.104 moles) of aniline, 15.8 (0.27 mole) of acetone, 100 g. (1.53 moles) of amalgamated zinc and 200 cc. of glacial acetic acid. In this case the reaction mixture was allowed to stand ten hours before it was heated and 200 cc. (2.50 moles) of concentrated hydrochloric acid added. The crude product weighing 4.6 g. contained aniline as well as N-isopropylaniline.

In order to remove the aniline, 1.9 g. of the product was shaken with benzenesulfonyl chloride and alkali. In this way 0.22 g. of N-phenylbenzenesulfonamide, m. p. 110–111° (110°)[9] was obtained. It represented 0.21 g. (2.2% recovery) of unreacted aniline in the total crude product.

The residual oil was treated with benzoyl chloride and

(5) Limpach, *Ber.*, **21**, 640 (1888).

(6) Chattaway and Orton, *ibid.*, **32**, 3473 (1899).

(7) Prepared by the method of Martin, THIS JOURNAL, **58**, 1438 (1936).

(8) Ladenburg, *Ann.*, **179**, 163 (1875).

(9) Chiozza, *ibid.*, **91**, 102 (1854).

alkali, giving N-isopropyl-benzanilide, m. p. 61–64° (63–65°).[10] By difference the yield of isopropylaniline was 4.4 g. (31%). Using this same procedure aniline and isobutyraldehyde yielded a tar as the sole product.

Summary

Amalgamated zinc and hydrochloric acid has been found to be an excellent reagent for the reductive alkylation of mesidine. From the corresponding aldehydes and ketones in glacial acetic acid solution N,N-dimethyl-, N-isopropyl-, N-isobutyl- and N-isoamylmesidine have been prepared in 18 to 94% yield by this means.

(10) Emerson and Uraneck, THIS JOURNAL, **63**, 749 (1941).

URBANA, ILLINOIS RECEIVED JANUARY 22, 1941

[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Alkamine Esters of *p*-Fluorobenzoic Acid and Their Salts[1]

BY L. S. FOSDICK AND E. E. CAMPAIGNE

Recently a number of compounds resembling physiologically active substances, but having fluorine substituted for hydroxyl groups, have been prepared. Schiemann and Winkelmüller[2] prepared 4-fluorophenylalanine, the analog of tyrosine, and fluorine-substituted beta-phenylethylamines similar to tyramine. Hansen[3] prepared 3-fluoro-4-hydroxy-ω-aminoacetophenone, an analog of adrenalone, and found it to be active, but a weaker vasopressor than adrenalone.

The alkamine esters of *p*-hydroxybenzoic acid and the *p*-alkoxybenzoic acids were prepared by Rohmann and Scheurle.[4] They found that the esters of *p*-hydroxybenzoic acid were good local anesthetics, but quite toxic. By changing the free hydroxyl group to various ethereal radicals they decreased anesthetic efficiency as well as toxicity.

In view of the above facts, the influence of fluorine on the anesthetic efficiency and toxicity of alkamine esters of benzoic acid seemed interesting. These esters were readily prepared by the method of Kamm,[5] using the amino alcohol and the acid chloride in the following reaction

$$FC_6H_4COCl + HOC_nH_{2n}NR_2 \longrightarrow FC_6H_4COOC_nH_{2n}NR_2\cdot HCl$$

Fluorobenzoic acid was originally prepared by oxidation of fluorotoluene. More recently, it was prepared from *p*-aminoethyl benzoate.[6] Two new methods were tried, and compared to the oxidation of *p*-fluorotoluene. These methods were: 1, reaction of *p*-fluorophenylmagnesium bromide with carbon dioxide followed by acid hydrolysis, and 2, reaction of fluorobenzene with acetic anhydride in the presence of anhydrous aluminum chloride to give *p*-fluoroacetophenone, and the oxidation of this compound to give *p*-fluorobenzoic acid. The acid chloride was readily prepared, using thionyl chloride and the dry acid. The various fluorine compounds were prepared by the method of Schiemann.[7]

In preparing fluorobenzoic acid from fluorotoluene, an average of three runs gave 16% overall yield, based on the starting compound, *p*-toluidine. Use of the Grignard reagent with *p*-fluorobromobenzene gave an over-all yield of 16%, based on bromoaniline. The Friedel–Crafts reaction with fluorobenzene and acetic anhydride gave, for an average of three runs, an over-all yield of 20%, based on aniline. The last method is the most efficient of the three.

The formula of the borate of procaine is given in "New and Non-official Remedies" as $NH_2C_6H_4COOC_2H_4N(C_2H_5)_2\cdot 5HBO_2$. The formulas of the borates made were calculated empirically from the nitrogen analyses, and found to check nicely for $5HBO_2$ in compounds 1, 2, and 3, but $6HBO_2$ corresponded more closely to the found nitrogen in compounds 5 and 6, as did $7HBO_2$ in compound 4. This may be due to the increased length of the carbon chain between the acid and the nitrogen, which increases the basicity of compounds of this type.[8]

The anesthetic efficiency and toxicity of the hydrochlorides have been investigated and reported elsewhere. It was found that the toxicity of these compounds was less than that of procaine in white mice, and that the anesthetic efficiency

(1) Abstract of a thesis submitted to the faculty of the Graduate School of Northwestern University by E. E. Campaigne in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

(2) Schiemann and Winkelmüller, *Ber.*, **65B**, 1435 (1932).

(3) Hansen, THIS JOURNAL, **59**, 280 (1937).

(4) *Arch. Pharm.*, **274**, 110 (1931).

(5) Kamm, THIS JOURNAL, **42**, 1030 (1920).

(6) Schiemann, "Organic Syntheses," Vol. XIII, 1933, p. 52.

(7) Schiemann, *Ber.*, **60B**, 1186 (1927).

(8) Vliet and Adams, THIS JOURNAL, **48**, 2158 (1926).