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).

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[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% over-all 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).

was equal to or greater than procaine. However, with the exception of the diethylaminoethyl ester, all of the compounds gave evidence of considerable irritation. Rabbits' eyes showed inflammation, and wheals became nacrotic. These symptoms contraindicated clinical use.

## Experimental

***p*-Fluorobenzoic Acid.**—One and one-half moles (262.5 g., b. p. 149–152°) of fluorobromobenzene was caused to react with 36 g. of magnesium in about 400 cc. of dry ether. The reaction, catalyzed by a crystal of iodine, proceeded vigorously to completion. The Grignard reagent was poured onto 400 g. of dry ice (theor. 68 g.) with stirring and a dark glassy tar formed. After standing for one-half hour, 1000 g. of ice and 100 g. of concentrated hydrochloric acid were added slowly with stirring. After the vigorous reaction had subsided, the *p*-fluorobenzoic acid formed a mushy white layer with the ether. The acid was obtained as a white amorphous solid; yield, 86 g., 41%, m. p. 182°.

In a second method to one mole of fluorobenzene, b. p. 83–85°, in 300 cc. of carbon disulfide, 300 g. (2.25 moles) of aluminum chloride was added, and the mixture was gently refluxed while 0.9 mole (90 g.) of redistilled acetic anhydride was added dropwise. The refluxing and vigorous stirring were continued for two hours more. The excess carbon disulfide was removed by distillation and the residual oil was poured over 190 g. of sulfuric acid and 1000 g. of ice. The pink oil which formed was separated, the water layer was extracted with ether, and the combined oil and ether extracts were dried over calcium chloride. After removal of the ether, the residual oil was distilled at reduced pressure. A clear violet oil was collected between 87–90° at 17 mm. The yield of fluoroacetophenone was oxidized with sodium dichromate in acid solution. The yield was 80% based on fluoroacetophenone or 44% based on fluorobenzene.

**Alkamine Ester Hydrochlorides.**—The alkamine ester hydrochlorides were prepared according to the method of Kamm[5] using equimolar quantities of the appropriate alcohol and *p*-fluorobenzoyl chloride.

**Free Bases.**—A weighed quantity of the hydrochloride was dissolved in water. If any color was present the mixture was clarified with "Norit" and the free base precipitated with concentrated ammonium hydroxide. The solution was thrice extracted with ether and the combined ether extracts dried over anhydrous calcium chloride. The ether was evaporated leaving a clear yellow oil. Pure samples were obtained by distillation under reduced pressure.

**Alkamine Ester Borates.**—A weighed quantity of free base was dissolved in dry acetone and placed in a soxhlet extraction apparatus. An excess of boric acid crystals was placed in the extraction thimble and extracted by refluxing the acetone solution until crystals started to precipitate from the hot acetone. The solution was then placed in an ice box. Finely divided white crystals precipitated and were removed by filtration. The borates decomposed on heating. The physical constants and analytical data appear in the table.

TABLE I

| Compound[a] | Yield, % | M. p. or b. p., °C. | N Analyses, % Calcd. | Found |
|---|---|---|---|---|
| Diethylaminoethyl | 69 | 136–137 (7 mm.) | 5.85 | 5.78 |
| Hydrochloride | 48 | 124–126 | 5.09 | 5.20 |
| Borate | 52 | [b] | 3.06 | 3.08 |
| Dipropylaminoethyl | 69 | 149–150 (7 mm.) | 5.20 | 5.18 |
| Hydrochloride | 58 | 115–117 | 4.62 | 4.68 |
| Borate | 52 | [b] | 2.87 | 2.82 |
| Dibutylaminoethyl | 88 | 168–169 (7 mm.) | 4.75 | 4.70 |
| Hydrochloride | 64 | 115–116 | 4.25 | 4.20 |
| Borate | 71 | [b] | 2.72 | 2.6 |
| Diethylaminopropyl | 75 | 148–149 (7 mm.) | 5.53 | 5.46 |
| Hydrochloride | 63 | 122–124 | 4.85 | 4.72 |
| Borate | 77 | [b] | 2.50 | 2.56 |
| Dipropylaminopropyl | 90 | 161–161.5 (7 mm.) | 4.98 | 4.90 |
| Hydrochloride | 83 | 124–126 | 4.40 | 4.31 |
| Borate | 72 | [b] | 2.57 | 2.58 |
| Dibutylaminopropyl | 65 | 175.5–177 (6 mm.) | 4.54 | 4.48 |
| Hydrochloride | 67 | 100 | 4.05 | 3.92 |
| Borate | 48 | [b] | 2.42 | 2.36 |

[a] All compounds are *p*-fluorobenzoates. [b] Decomposed.

## Summary

1. Two methods for the preparation of *p*-fluorobenzoic acid are described.

2. Six alkamine esters of *p*-fluorobenzoic acid have been prepared, and the hydrochlorides and borates described.

3. These compounds are efficient anesthetics of low toxicity, but they possess irritating qualities which contraindicate their clinical use.

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