hydrogen, but its derivatives all had the expected composition.

The **diacetate** was prepared by refluxing the diphenol with acetic anhydride in pyridine. The product was obtained as white plates from acetic acid, m. p. 234°.

Anal.[8] Calcd. for $C_{30}H_{22}O_4$: C, 80.72; H, 4.93. Found: C, 80.79; H, 4.79.

The **dipropionate** was prepared by refluxing the diphenol for two hours with propionyl chloride. The hot mixture was poured on ice, the product collected and recrystallized from acetic acid as fine plate-like white crystals, m. p. 185–186°.

Anal. Calcd. for $C_{32}H_{26}O_4$: C, 81.01; H, 5.48. Found: C, 80.81; H, 5.79.

The dipropionate was saponified by refluxing with 10% alcoholic potassium hydroxide solution which, upon acidification, gave the diphenol, m. p. 296–298°. This gave no depression of melting point when mixed with the original sample.

9,10-bis-(*p*-Methoxyphenyl)-phenanthrene (V).—(a) By cyclization of the glycol (III): 1,2-bis-(*p*-methoxyphenyl)-1-(2-biphenyl)-glycol (III) was prepared from 40.8 g. of anisoin as previously described. This glycol was cyclized as described under the preparation of 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene (IV) except that 34% hydrobromic acid was used instead of the 41% acid. The product, purified by repeated crystallization from acetic acid, was obtained as a mat of very fine white needles, m. p. 256°; yield 1.3 g. (2%).

(b) From the diphenol: a sample of 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene was dissolved in 10% sodium hydroxide solution and treated with an excess of methyl sulfate. The white solid formed was collected and recrystallized from acetic acid, m. p. 256–258°, and gave no depression of melting point when mixed with a sample prepared from the glycol as described above.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 86.15; H, 5.64. Found: C, 86.27; H, 5.79.

The dimethyl ether was refluxed for twenty-four hours with a mixture of hydriodic and acetic acids and the product recrystallized from alcohol, m. p. 296–298°. This was shown to be identical with 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene by means of a mixed melting point determination. Essentially the same result was obtained if the ether was refluxed for forty-eight hours with a mixture of acetic and 42% hydrobromic acids.

(8) Analyses by T. S. Ma.

Summary

By aromatic cyclodehydration of suitable 2-biphenyl glycols, 9,10-diphenyl- and 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene have been prepared.

DURHAM, N. C. RECEIVED AUGUST 30, 1943

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

The Synthesis of Some Alkyl and Dialkylaminoalkyl Esters of 3-Amino-4-fluorobenzoic Acid

BY L. S. FOSDICK AND A. F. DODDS[1a]

In 1941, some alkamine esters of *p*-fluorobenzoic acid were prepared[1b] and the pharmacological properties studied.[2] It was found that these compounds produced anesthesia both when injected and when applied topically to mucous membrane. The anesthetic efficiency when injected was equal to or slightly greater than that of procaine hydrochloride. The toxicity of the procaine analog was one-third that of procaine. The toxicity of other members of the series was also very low. All of the compounds produced some tissue irritation, and all of them, with the exception of the procaine analog, produced definite tissue necrosis.

In view of the low toxicities and relatively high anesthetic efficiencies of these compounds, it was thought interesting to continue the investigation. It seemed to us that the introduction of both an amino and a fluoro group on the benzene ring might lower the toxicity. It was hoped that the resultant compounds would not be irritating to tissue. This paper deals with the esters of 3-amino-4-fluorobenzoic acid. The other isomers are in the process of synthesis.

As fluorobenzoic acid was not readily available, it was prepared by oxidizing *p*-fluorotoluene. The *p*-fluorotoluene was prepared by the method of Schiemann[3] and was oxidized to *p*-fluorobenzoic acid with potassium permanganate by the method of Slothouwer.[4] It was then nitrated with fuming nitric acid by the method of Rouche[5] and converted to the acid chloride by refluxing with thionyl chloride. The fluoro nitro esters were prepared by refluxing the acid chloride with the appropriate alcohol. Finally, the nitro group was reduced with hydrogen, using platinum oxide as the catalyst.

The toxicity of the dialkylaminoalkyl 3-amino-4-fluorobenzoate hydrochlorides was determined by subcutaneous injection in white mice, and the anesthetic efficiency was estimated by the method of Schmitz.[6] All of the salts were potent topical anesthetics, with the exception of the dimethylaminoethyl ester hydrochloride. A 2% solution of the other members of the series varied from one-half the effectiveness to equal that of a 1% solution of cocaine hydrochloride. The diethylaminoethyl ester hydrochloride was three-fourths as effective as cocaine.

The toxicities of the compounds tested were

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

(1b) Fosdick and Campaigne, THIS JOURNAL, **63**, 974 (1941).

(2) Campaigne, Starke, Fosdick and Dragstedt, *J. Pharm. Exptl. Ther.*, **71**, 59 (1941).

(3) Balz and Schiemann, *Ber.*, **60**, 1186 (1927).

(4) Slothouwer, *Rec. trav. chim.*, **33**, 324 (1914).

(5) Rouche, *Bull. Sci. Acad. Roy. Belg.*, **7**, 534 (1921).

(6) Schmitz and Loevenhart, *J. Pharmacol.*, **24**, 159 (1924).

from one-third to equal that of procaine hydrochloride. The toxicity of the diethylaminoethyl ester hydrochloride was about one-half that of procaine hydrochloride.

All of the solutions were yellow in color and decomposed on standing. They all produced more irritation than procaine but less than that of the *p*-fluorobenzoates. If it were not for these undesirable characteristics, the compounds would merit clinical study.

Experimental

3-Nitro-4-fluorobenzoyl Chloride.—One-half mole, 87 g., of 3-nitro-4-fluorobenzoic acid was refluxed gently for three hours with an excess (120 cc.) of thionyl chloride. The excess thionyl chloride was removed by distillation. The acid chloride was obtained as a yellow oil that distilled at 140–150° (6–7 mm.). After distillation the acid chloride solidified to a white solid after standing in an ice box. This compound had previously been prepared and described as a liquid (b. p. 210°, 130 mm.) by Rouche.[5] The solid, m. p. 23.5–25°, was obtained in yields of 74–86%. *Anal.* Calcd. for $C_7H_3O_3NFCl$: Cl, 17.42. Found: Cl, 17.49, 17.10.

Alkyl Ester Hydrochlorides of 3-Nitro-4-fluorobenzoic Acid.—The alkyl esters were prepared by refluxing 3-nitro-4-fluorobenzoyl chloride with an excess of the appropriate alcohol for thirty minutes. The esters were then precipitated by the addition of ice-water. The solid esters were recrystallized from dilute alcohol, while the liquid compounds were distilled at reduced pressure.

Dialkylaminoalkyl Ester Hydrochlorides of 3-Nitro-4-fluorobenzoic Acid.—The alkamine ester hydrochlorides were prepared according to the method of Kamm[7] using equimolecular quantities of the appropriate alcohol and 3-nitro-4-fluorobenzoyl chloride. All of the compounds, with the exception of the dibutylaminoethyl and the dibutylaminopropyl ester hydrochlorides separated as solids. The two exceptions solidified after cooling overnight in an icebox. The hydrochlorides were recrystallized from ether alcohol mixtures. Attempts were made to prepare and characterize the free bases. These compounds readily separated from water solutions of the salts upon the addition of ammonium hydroxide. They were all unstable liquids, that decomposed on standing and could not be distilled *in vacuo*. For this reason only the salts were characterized.

TABLE I

ESTERS OF 3-NITRO-4-FLUOROBENZOIC ACID

Ester	Yield, %	Melting point, °C.	Analyses, % Calcd.	Found
Methyl	69	60–61	7.04 N	6.88
Ethyl	74	47–48[a]		
n-Propyl	76	147–157 (4 mm.)	6.17 N	5.99
n-Butyl	93	190–200 (35 mm.)	5.81 N	5.68
Dimethylaminoethyl·HCl	98	168–169	12.11 Cl	12.16
Diethylaminoethyl·HCl	84	142–143	11.06 Cl	11.08
Diethylaminopropyl·HCl	84	145–147	10.59 Cl	10.54
Dipropylaminoethyl·HCl	74	123–124	10.17 Cl	10.10
Dipropylaminopropyl·HCl	93	140–141	9.77 Cl	9.77
Dibutylaminoethyl·HCl	67	80–82	9.41 Cl	9.40
Dibutylaminopropyl·HCl	78	83–84	7.17 N	7.01

[a] Given as 45.3° by Rouche, ref. 5.

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

Alkyl Esters of 3-Amino-4-fluorobenzoic Acid.—These compounds were prepared by the reduction of the corresponding nitro esters with hydrogen, using a platinum oxide catalyst according to the method of Adams.[8] No difficulty was experienced in purifying the esters, although they were all rather unstable and rapidly discolored on standing.

Dialkylaminoalkyl Esters of 3-Amino-4-fluorobenzoic Acid and their Hydrochlorides.—These compounds were also prepared by the reduction of the corresponding nitro compounds according to the method of Adams.[8]

After the reduction, the catalyst was removed by filtration, the solution dried over anhydrous sodium sulfate and then poured into dry ether. The hydrochloride separated as a gummy mass, which usually solidified on standing. The hydrochloride was dissolved in water and boiled with "norite." After removing the "norite" the free base was liberated with ammonium hydroxide. The free base was taken up in ether, dried with anhydrous sodium sulfate, and the hydrochloride precipitated with dry hydrogen chloride. It was sometimes necessary to repeat this process several times in order to get the salts sufficiently pure for analysis. All of the esters and salts were extremely unstable and discolored rapidly on standing. This probably explains the extremely small yields on most of the alkamine ester hydrochlorides. Attempts to make crystalline sulfates and borates were unsuccessful. The physical constants and analytical data appear in the tables.

TABLE II

ESTERS OF 3-AMINO-4-FLUOROBENZOIC ACID

Ester	Yield, %	Melting point, °C.	Analyses, % Calcd.	Found
Methyl	82	123–126	8.28 N	8.12
Ethyl	78	120–128 (3 mm.)[a]	7.65 N 140–145 (5 mm.)[a]	7.52
n-Propyl	68	24–26	7.10 N	6.96
n-Butyl	81	155–160[b]	6.63 N	6.55
Dimethylaminoethyl·HCl	20	170–172	13.50 Cl	13.34
Diethylaminoethyl·HCl	12	138–140	12.20 Cl	12.03
Diethylaminopropyl·HCl	10	138–142	11.63 Cl	11.52
Dipropylaminoethyl·HCl	5	119–120	11.12 Cl	11.31
Dipropylaminopropyl·HCl	5	145–148	10.65 Cl	10.75
Dibutylaminoethyl	70	[c]	9.03 N	8.79
Dibutylaminopropyl·HCl	5	136–138	7.76 N	7.59

[a] Boiling point. [b] With decomposition. [c] Could not be vacuum distilled without decomposition.

Summary

1. Several alkyl and dialkylaminoalkyl esters of 3-nitro-4-fluoro and 3-amino-4-fluorobenzoic acid have been synthesized and characterized.

2. The anesthetic efficiency and toxicity of the 3-amino-4-fluoro esters were studied and the compounds were found to be of low toxicity and high anesthetic efficiency. All of the compounds studied were far too unstable to be of clinical importance.

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(8) Adams, Voorhees and Shriner, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 452.