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

The Synthesis of Some Alkyl and Dialkylaminoalkyl Esters of 2-Nitro-5-fluorobenzoic Acid and 2-Amino-5-fluorobenzoic Acid

BY L. S. FOSDICK AND R. Q. BLACKWELL

Recently it was found[1] that certain alkamine esters of *p*-fluoro- and of 3-amino-4-fluorobenzoic acid produce excellent anesthesia, both by injection and by topical application to mucous membrane. Although some of them are less toxic than procaine, they cause local tissue irritation and are unstable in solution.

In view of the many favorable properties of these esters, it appeared desirable to prepare some of the same series in which the amino and fluoro groups occupied other relative points on the benzene ring; and a number of alkyl and alkamine esters of 2-amino-5-fluorobenzoic acid have therefore been prepared. For this purpose *m*-fluorotoluene[2] was oxidized to *m*-fluorobenzoic acid,[3,4] which with thionyl chloride yielded the corresponding acid chloride. This, on treatment with the required alkamine and subsequent reduction of the nitro ester, gave the required alkamine 2-amino-5-fluorobenzoic ester.

The compounds reported here all produced highly colored solutions which were relatively unstable. Profound anesthesia was produced both topically and upon injection, the topical anesthesia lasting in some cases as long as twenty-four hours. All compounds caused considerable local irritation and, in some cases, tissue necrosis. When applied topically to the cornea of a rabbit's eye, tissue damage was sometimes observed. It was not determined whether this damage was due to the long anesthesia produced or to the irritating properties of the drug. The toxicity of the procaine analog was slightly greater than that of procaine.

TABLE I

ESTERS OF 2-NITRO-5-FLUOROBENZOIC ACID

Ester	Yield, %	Melting point, °C.	Analyses, % Calcd.	Found
Methyl	71	36.5– 37.0	N, 7.04	6.96
Ethyl	80	43.5– 44.0	N, 6.57	6.78
n-Propyl	89	127 –128 at 3 mm.[a]	N, 6.17	6.06
n-Butyl	88	152 at 7 mm.[a]	N, 5.81	5.84
Dimethylaminoethyl·HCl	89	154 –155	Cl, 12.11	12.22
Diethylaminoethyl·HCl	80	147.5–148.3	Cl, 11.06	11.22
Diethylaminopropyl·HCl	88	137.5–138.2	Cl, 10.59	10.66
Di-*n*-propylaminoethyl·HCl	93	131.0–131.5	Cl, 10.17	10.25
Di-*n*-propylaminopropyl·HCl	86	122.0–122.5	Cl, 9.77	9.81
Di-*n*-butylaminoethyl·HCl	84	74.5– 75.5	Cl, 9.41	9.45
Di-*n*-butylaminopropyl·HCl	77	98.3– 99.3	Cl, 9.07	9.21

[a] Boiling point.

TABLE II

ESTERS OF 2-AMINO-5-FLUOROBENZOIC ACID

Ester	Yield, %	Melting point, °C.	N Analyses, % Calcd.	Found
Methyl	80	105° at 2 mm.[a]	8.28	8.23
Ethyl	82	110° at 2 mm.[a]	7.65	7.66
n-Propyl	78	116° at 2 mm.[a]	7.10	6.94
n-Butyl	80	130° at 2 mm.[a]	6.63	6.64
Dimethylaminoethyl·HCl	93	175°[b]	10.67	11.14
Diethylaminoethyl·HCl	95	125°[b]	9.63	9.70
Diethylaminopropyl·HCl	90	133–134°[b]	9.13	8.61
Di-*n*-propylaminoethyl·HCl	94	165°[b]	8.79	8.40
Di-*n*-propylaminopropyl·HCl	90	145°[b]	8.57	8.30
Di-*n*-butylaminoethyl·HCl	86	125°[b]	8.07	8.02
Di-*n*-butylaminopropyl·HCl	83	107–108°[b]	7.76	7.32

[a] Boiling point. [b] Compound becomes colored below its melting point, but shows a sharp melting point.

Experimental Procedures

2-Nitro-5-fluorobenzoyl Chloride.—A mixture of 20 g. of 2-nitro-5-fluorobenzoic acid was refluxed on a steam-bath for three hours with 30 cc. of thionyl chloride. The excess thionyl chloride was distilled off and three successive 50-cc. portions of anhydrous benzene were boiled from the mixture. The residue was then heated on a steam-bath for an hour at 20 mm. to remove the last trace of the thionyl chloride. The acid chloride was then distilled under reduced pressure; b. p. 130–140° (6–7 mm. pressure); yield, 75–90%. Since no reference to 2-nitro-5-fluoro-

(1) Fosdick and Dodds, THIS JOURNAL, **65**, 2305 (1943).
(2) Balz and Schiemann, *Ber.*, **60**, 1186 (1927).
(3) Ohman, THIS JOURNAL, **16**, 533 (1894).
(4) Slothouwer, *Rec. trav. chim.*, **33**, 324 (1914).

benzoyl chloride has been found in the literature, the compound was analyzed. One-gram samples were hydrolyzed in an aqueous sodium hydroxide solution, acidified with nitric acid and the chloride precipitated as silver chloride which was weighed in a tared Jena crucible.

Anal. Calcd. for $C_7H_3O_3NFCl$: Cl, 17.42. Found: Cl, 17.32, 17.34.

Alkyl Esters of 2-Nitro-5-fluorobenzoic Acid.—2-Nitro-5-fluorobenzoyl chloride was refluxed in an excess of the appropriate alcohol for thirty minutes. The addition of water to the reaction mixture caused precipitation of the esters. The liquid esters were distilled under reduced pressure; the solid esters were recrystallized from dilute alcohol.

Dialkylaminoalkyl Ester Hydrochlorides of 2-Nitro-5-fluorobenzoic Acid.—The acid chloride was dissolved in anhydrous benzene and an equimolecular quantity of the appropriate alkylamino alcohol, also dissolved in anhydrous benzene, was added. In most instances the alkamine ester hydrochloride separated out immediately. The reaction mixture was refluxed for one hour. The dimethylaminoethyl and diethylaminoethyl ester hydrochlorides precipitated as solids at once; the diethylaminopropyl ester hydrochloride separated as an oily layer heavier than benzene but solidified upon refluxing; the di-*n*-propylaminoethyl and di-*n*-propylaminopropyl ester hydrochlorides separated as oily layers heavier than benzene which crystallized when the reaction mixtures were cooled in an ice–salt bath. The di-*n*-butylaminoethyl ester hydrochloride appeared to be completely soluble in the benzene since no layer separated; when the mixture was cooled, the ester crystallized out. The di-*n*-butylaminopropyl ester hydrochloride separated out as an oily layer lighter than benzene and crystallized when the reaction mixture was cooled in an ice–salt bath. The products were filtered off and washed with anhydrous ether; recrystallization was carried out by dissolving the products in a minimum of anhydrous ethanol and precipitating them from the cooled ethanol solution with anhydrous ether.

Alkyl Esters of 2-Amino-5-fluorobenzoic Acid.—These compounds were prepared by the reduction of the corresponding nitro esters with hydrogen, using a platinum oxide catalyst prepared according to the method of Adams.[5] No difficulty was experienced in purifying these esters.

The Dialkylaminoalkyl Esters of 2-Amino-5-fluorobenzoic Acid.—These compounds were also prepared by the reduction of the corresponding nitro esters. After the reduction, the catalyst was removed by filtration and the solution dried over anhydrous sodium sulfate. The anhydrous alcohol solution was then poured into anhydrous ether and the hydrochlorides separated as an amorphous mass which crystallized upon standing.

Summary

Several alkyl and alkamine esters of 2-nitro-5-fluorobenzoic acid and 2-amino-5-fluorobenzoic acid have been prepared. All of the esters of 2-amino-5-fluorobenzoic acid possess anesthetic properties. The toxicity of the procaine analog was slightly higher than that of procaine. All of the anesthetic esters were quite unstable and formed highly colored solutions. The compounds possess no practical value as anesthetics.

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

CHICAGO, ILLINOIS RECEIVED MARCH 17, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Catalytic Hydrogenation of Pyridinols, Quinolinols and their Esters

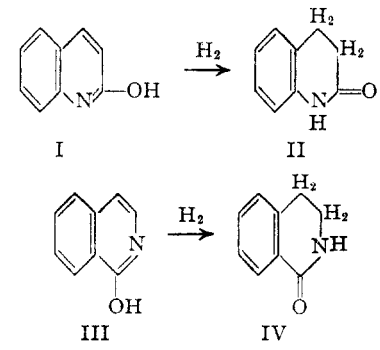
BY CHESTER J. CAVALLITO AND THEODORE H. HASKELL

In the continuation of some work on the preparation of phenolic acid esters described in a recent publication,[1] the attempt was made to prepare pyridinyl and quinolinyl esters of phenolic acids. The method consisted of treating the pyridinol or quinolinol with the benzyloxyaroyl chloride, followed by catalytic hydrogenolysis of the benzyl group. Instead of obtaining the corresponding pyridinyl or quinolinyl hydroxybenzoate, in several hydrogenations entirely unexpected reactions occurred, which varied with the position of the hydroxyl group on the pyridine or quinoline ring. In order to determine the types of hydrogenation which could take place, the isomeric pyridinols, quinolinols and certain of their esters were investigated.

Hydrogenation was carried out in a dioxane or ethanol solution of the compound at 25 and 55° with a palladium sponge catalyst[2] and with from one to three atmospheres of hydrogen super pressure in a modified[3] Parr low pressure hydrogenator. An Adams platinum or Raney nickel catalyst was ineffective in catalyzing these reactions under the conditions employed.

(1) Cavallito and Buck, THIS JOURNAL, **65**, 2140 (1943).
(2) Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 123 (1921).
(3) Buck and Jenkins, THIS JOURNAL, **51**, 2163 (1929).

Under the conditions of these experiments, 2-pyridinol yielded α-piperidone, whereas 3- and 4-pyridinols did not reduce. The 2-quinolinol (I) and 1-isoquinolinol (III) gave the 3,4-dihydroquinolones (II and IV) but the 3-, 5-, 6-, 7- and 8-



quinolinols yielded the corresponding 1,2,3,4-tetrahydroquinolinols. 4-Quinolinol, 2-methyl-4-quinolinol and 4-methyl-2-quinolinol did not reduce.

Under the conditions of reduction, naphthalene did not hydrogenate, and pyridine showed some hydrogen uptake; however, most of the starting material was recovered. Quinoline hydrogenated