ACETANILIDES

Compound	Melting point or boiling point, °C.	Yield, %	Analyses, % Calcd.	Found
α-Dipropylamino	B. p. 145–146 (1.5 mm.)	90	12.01 N	12.00
-hydrochloride	M. p. 184–186	95	13.59 Cl	13.49
α-Dibutylamino	B. p. 155–156 (1 mm.)	92	10.68 N	10.62
-hydrochloride	M. p. 101–102	89	11.89 Cl	11.85
α-Dipropylamino-*o*-nitro	M. p. 48.5–50	82	15.16 N	15.06
-hydrochloride	M. p. 114–115	83	11.32 Cl	11.34
α-Dibutylamino-*o*-nitro	[a]	76	13.68 N	13.43
-hydrochloride	M. p. 132–133	92	10.62 Cl	10.57
α-Dipropylamino-*o*-amino	[a]	78	17.00 N	16.85
-dihydrochloride	M. p. 182–183	88	22.65 Cl	22.71
α-Dibutylamino-*o*-amino	[a]	82	15.17 N	15.03
-dihydrochloride	M. p. 178–180	89	20.85 Cl	20.91
α-Diethylamino-*m*-nitro	[a]	73	16.73 N	16.44
-hydrochloride	M. p. 195–197	82	12.33 Cl	12.10
α-Dipropylamino-*m*-nitro	[a]	..	...	...
-hydrochloride	M. p. 147–149	73	11.32 Cl	11.16
α-Dibutylamino-*m*-nitro	[a]	83	13.68 N	13.52
-hydrochloride	M. p. 131–132	93	10.62 Cl	10.55
α-Diethylamino-*m*-amino	[a]	..	...	...
-dihydrochloride	M. p. 231–234	77	24.49 Cl	24.28
α-Dipropylamino-*m*-amino	Oil[a]	..	...	...
-dihydrochloride	M. p. 180–182	93	22.65 Cl	22.56
α-Dibutylamino-*m*-amino	Oil[a]	..	...	...
-dihydrochloride	M. p. 172–174	83	20.85 Cl	20.65
α-Diethylamino-*p*-nitro	M. p. 44–46	89	16.73 N	16.70
α-Dipropylamino-*p*-nitro	M. p. 46–48	85	15.16 N	15.06
α-Dibutylamino-*p*-nitro	M. p. 75–76	92	13.68 N	13.77
α-Diethylamino-*p*-amino	Oil[a]	76	19.00 N	18.95
-dihydrochloride	M. p. 235–240	83	24.49 Cl	24.38
α-Dipropylamino-*p*-amino	Oil[a]	..	...	...
-dihydrochloride	M. p. 269–273	92	22.65 Cl	22.72
α-Dibutylamino-*p*-amino	M. p. 43–45	85	15.17 N	15.18

[a] Viscous liquid that could not be distilled at 1 mm. without decomposition.

Summary

Various α-dialkylamino ortho, meta and para nitro and amino acetanilides have been prepared and characterized. The nitro compounds were found to have slight vasopressor activity, and the amino substituted compounds were found to possess slight anesthetic activity. All of the compounds studied were extremely toxic.

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

Synthesis of Bis-(Dialkylaminoalkyl) Esters of 4-Fluoroisophthalic Acid

BY L. S. FOSDICK AND J. C. CALANDRA

In 1941, some dialkylaminoalkyl esters of 4-methoxyisophthalic acid were synthesized[1] in an attempt to obtain compounds with local anesthetic activity. It was reasoned that if certain compounds having one carbonyl group conjugated with double bonds[2] produced the most effective anesthetics, two such groups conjugated with double bonds in the same molecule might be even more effective. The methoxyisophthalates were anesthetics of about the same potency as procaine, and slightly less toxic.

Insofar as the dialkylaminoalkyl esters of *p*-fluorobenzoic acid[3] possessed topical anesthetic activity, it was thought that the fluoroisophthalates might also possess this property.

This paper deals with the synthesis of some bis-(dialkylaminoalkyl) esters of 4-fluoroisophthalic acid. The bis-(dialkylaminoalkyl) esters of 4-aminoisophthalic acid also have been prepared by the authors and will be presented in another paper.

All of the esters in the series were prepared as follows: 4-amino-1,3-dimethylbenzene was con-

(1) Fosdick and Fancher, THIS JOURNAL, **63**, 1277 (1941).

(2) Shriner and Keyser, *ibid.*, **60**, 286 (1938).

(3) Fosdick and Campaigne, *ibid.*, **63**, 974 (1941).

verted to 4-fluoro-1,3-dimethylbenzene by Schiemann's method.[4] This was next oxidized to the acid with neutral permanganate which was subsequently converted to the acid chloride with thionyl chloride. The alkamine esters were obtained by the reaction of the acid chloride with the appropriate amino alcohol. The dihydrochloride salts of this series possessed no topical anesthetic activity, although the free bases did possess this property. The toxicities varied from one-half to one-eighth that of procaine hydrochloride. In general they followed the usual trend, the toxicity increasing with increase in length of the side chain.

Experimental

4-Fluoroisophthalic Acids.—To a 15-g. portion of 4-fluoro-*m*-xylene in a three-liter, three-neck flask fitted with mechanical stirrer and water condenser, on a heated steam-bath, a saturated solution containing 80 g. of potassium permanganate in water was added over a period of several hours. After oxidation was completed, the manganese dioxide was removed by filtration and the filtrate acidified with dilute hydrochloric acid. The 4-fluoroisophthalic acid precipitated as a white fluffy powder. This was dissolved in alkali and reprecipitated in order to purify it; yield, 70%. Neutralization equivalent: 92; theoretical, 92; melting point, 282–286°.

4-Fluoroisophthalyl Chloride.—A 10 g. portion of 4-fluoroisophthalic acid was treated with 60 cc. of thionyl chloride. The mixture was gently refluxed on a steam-bath until all of the acid went into solution. The excess thionyl chloride was removed by distillation. The acid chloride, a heavy colorless liquid, distilled at 100–103° at 2 mm. pressure; yield, 93%.

Anal. Calcd. for $C_8H_3O_2Cl_2F$: Cl, 32.09. Found: Cl, 31.92, 31.53.

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

TABLE I

DIHYDROCHLORIDES OF ESTERS OF 4-FLUOROISOPHTHALIC ACID (4)F—C_6H_3^{COOR(1)}_{COOR(3)}·2HCl

R	Yield, %	Melting point, °C.	Nitrogen, % Calcd.	Found
Bis-(β-diethylaminoethyl)	82	181	6.30	6.20
Bis-(β-dipropylaminoethyl)	88	195	5.60	5.48
Bis-(β-dibutylaminoethyl)	79	165	4.94	5.00
Bis-(γ-diethylaminopropyl)	70	155	5.78	5.68
Bis-(γ-dipropylaminopropyl)	63	110	5.17	5.05
Bis-(γ-dibutylaminopropyl)	70	193	4.69	4.55

Bis-(dialkylaminoalkyl)-4-fluoroisophthalates.—These compounds were prepared according to the method of Kamm,[5] wherein the acid chloride was allowed to react with the calculated amount of the appropriate amino alcohol, using anhydrous benzene as the solvent. In the case of the higher alkamine esters, it was necessary to reflux the mixture for about thirty minutes to complete the reaction, but the lower members reacted almost immediately. After refluxing, the mixtures were cooled and the dihydrochlorides of the esters separated. All of the esters crystallized nicely from the reaction mixture. They were purified by recrystallization from alcohol–ether mixtures.

The yields and analytical data are in the accompanying table.

Summary

4-Fluoroisophthalic acid, 4-fluoroisophthalyl chloride, and six dialkylaminoalkyl esters of 4-fluoroisophthalic acid were prepared and their properties investigated. The hydrochlorides of this series possess no topical anesthetic effect, but the free bases are topical anesthetics. These compounds are less toxic than procaine.

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

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Cinchona Alkaloids in Pneumonia. XII. Derivatives of 6'-Aminoapocinchonidine

BY A. G. RENFREW, W. W. CARLSON AND L. H. CRETCHER

A new type of cinchona derivative, in which an alkylamino- group replaces the phenolic hydroxyl of apocupreine, has been prepared by the use of the Bucherer reaction.[1,2] This study of cinchona derivatives containing an additional basic component was undertaken in view of the recognized importance of the basic nucleus in compounds which show antimalarial action. Findlay[3] remarks that "any reduction in the basic character of cinchona alkaloids or other synthetic antimalarial drugs" is associated with a reduction or total disappearance of activity. Buttle, *et al.*,[4] make a similar statement after testing a number of modified cinchonas in bird malaria. In a somewhat different application Glen, *et al.*,[5] prepared a series of quinolyl-(acridyl)- ethenes and found that an amino group in position-6 in the quinoline ring seemed to confer trypanocidal power in tests against *T. brucei*.

It was realized that attempts to enhance pharmacological action by multiplication of the active groupings within a molecule frequently lead actually to less effective compounds. As will be observed from examination of the results of biological studies, the new 6'-hydroxyethylaminoapocinchonidine (II) showed relatively low mouse

(1) Woroshtzow and Kogan, *Ber.*, **65**, 142 (1932); Roger Adams, "Organic Reactions," J. Wiley and Sons, Inc., New York, N. Y.

(2) A similar application of this reaction has been reported by L. Ach in the preparation of 6'-aminohydrocinchonine and 6'-aminohydrocinchonidine; German Patent 720,160; *C. A.*, **37**, 2020 (1943).

(3) Findlay, "Recent Advances in Chemotherapy," The Blakiston Co., Philadelphia, Pa., p. 115.

(4) Buttle, Henry, Solomon, Trevan and Gibbs, *Biochem. J.*, **32**, 47 (1938).

(5) Glen, Southerland and Wilson, *J. Chem. Soc.*, 654 (1938).