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

Some Derivatives of Acetanilide[1a]

BY L. S. FOSDICK AND G. W. RAPP[1b]

In 1936, Sanna,[1c] in an attempt to solubilize some of the insoluble anesthetics, prepared ethyl *p* - (dimethylaminoacetylamino) - benzoate, *p* - $(CH_3)_2NCOCH_2NHC_6H_4COOC_2H_5$, and the corresponding diethylamino compound. It was found that the substituted anesthesine was an anesthetic, but not superior to those already in use.

Later, in 1937, Erdtman and Lofgren,[2] investigating a large number of anesthetic type compounds, synthesized α-diethylaminoacetanilide and found that its anesthetic efficiency was comparable with the substituted anesthesine, thus showing that the anesthesia produced with these particular compounds was not a function of the ester groups.

In 1938, Ahmed[3] prepared α-diethylamino-*o*-aminoacetanilide as an intermediate in the synthesis of 2-diethylaminomethylbenzimidazole, and the latter was found to have vasopressor activity. Insofar as it may be desirable to have local anesthetics possessing vasoconstrictor properties, it was thought by us that the synthesis of the α-dialkylamino ortho, meta and para-aminoacetanilides might yield compounds of this type.

The α-chloracetanilide and the ortho, meta and para nitro derivatives have been previously reported.[4,5,6] The α - diethylaminoacetanilide, (2) α-diethylamino - *o* - nitroacetanilide, and α-diethylamino-*o*-aminoacetanilide, (3) have also been described.

The substituted acetanilides were prepared from Eastman Kodak Company ortho, meta and para nitroaniline. The various nitroanilines were treated with chloroacetyl chloride to produce the α-chloroacetanilides. These were then treated with a dialkylamine to produce the α-dialkylamino ortho, meta or para nitroacetanilide. The nitro group was then reduced with hydrogen, using a platinum oxide catalyst.

It was found that the substituted acetanilides did possess anesthetic activity. However, it was found, contrary to expectation, that the compounds of larger molecular weight possessed less anesthetic activity than did the lighter members of the series. Furthermore, the presence of the amino group in the ring produced compounds with less anesthetic efficiency than when no groups were present on the ring.

Preliminary studies on the toxicity of these compounds were made by subcutaneous injection in white mice. It was found that all of the compounds were extremely toxic. The toxicity was high in comparison to that of the unsubstituted acetanilide. The M.L.D. of all of the compounds varied from 300 to 400 mg./kg., in contrast to 800 mg./kg. for acetanilide.

The compounds with the amino group in the ring produced no vasoconstriction, but perhaps slight vasodilation. The nitro compounds in no case produced local anesthesia, but did possess slight vasopressor properties.

Experimental

The α-Chloroacetanilides.—Two-tenths of a mole of aniline or of nitroaniline was dissolved in 100 ml. of acetone, and 0.1 mole of chloroacetyl chloride was added dropwise, with agitation. The mixture was refluxed for one hour, cooled, and poured into cold water. The product usually separated as an oil which soon crystallized. The α-chloroacetylanilide and the nitro derivatives were recrystallized from dilute alcohol.

The α-Dialkylaminoacetanilides.—Two-tenths mole of the appropriate dialkylamine was added to 0.1 mole of α-chloroacetanilide, dissolved in 75 ml. of acetone, and refluxed for two hours. The dialkylamine hydrochloride was filtered off, and the filtrate was poured into 500 ml. of cold water, whereupon the desired product separated. The product was isolated and distilled under reduced pressure.

The α-Dialkylaminonitroacetanilides.—The α-dialkylaminonitroacetanilides were prepared in the same manner as the unsubstituted varieties, with the exception that the appropriate nitroaniline was used in place of aniline. It should be noted that the free base in many cases is an unstable liquid. In all of these cases a solid crystalline dihydrochloride was formed. In some of the cases the unstable liquids were purified by washing and reprecipitation procedures so that an analysis could be made. In other cases this procedure was omitted.

The hydrochlorides of the above compounds were prepared by adding a saturated solution of hydrogen chloride gas in ether to an ether solution of the free base. In most cases the hydrochlorides separated as sticky gums which solidified on standing in the icebox. These hydrochlorides were purified by dissolving in ethyl alcohol, boiling with "norite," and precipitating with ether.

α-Dialkyl *o*-, *m*- and *p*-Aminoacetanilides.—The amino compounds were prepared by the reduction of the nitro group with Adams platinum oxide catalyst, using 40 to 50 lb. pressure.[7] The platinum catalyst was removed by filtration, the excess alcohol evaporated, and the products purified by recrystallization from dilute alcohol. The hydrochlorides were prepared as described for the nitro compounds. The physical characteristics and yields are in the tables.

(1a) This work was carried out under a grant from the Abbott Foundation for Medical Research.

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

(1c) Sanna, *Ann. Chim. Applicata*, **25**, 638 (1936).

(2) Erdtman and Lofgren, *Svensk Kem. Tid.*, **49**, 163 (1937).

(3) Ahmed, Narang and Ray, *J. Indian Chem. Soc.*, **15**, 152 (1938).

(4) Meyer, *Ber.*, **8**, 1152 (1875).

(5) Votoček and Burda, *ibid.*, **48**, 1003 (1915).

(6) Abderhalden, von Ehrenvall, Schwab and Zumstein, *Fermentforschung*, **13**, 408 (1932).

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

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.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 2, 1943

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

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

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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).