[CONTRIBUTION FROM THE CHEMICAL CENTRAL RESEARCH INSTITUTE OF THE HUNGARIAN ACADEMY OF SCIENCES]

Synthesis and Investigation of Organic Fluorine Compounds. XXIII.* Preparation of Aromatic Fluorinated Esters as Local Anesthetics

GEORGE A. OLÁH, ATTILA E. PAVLÁTH, JUDITH A. OLÁH, AND FRANCIS HERR

Received April 30, 1956

A number of new fluorobenzoic and fluorophenylacetic acid esters have been prepared. The effect of these compounds as local anesthetics is similar to or greater than that of procaine; at the same time they do not cause tissue irritation.

Fosdick and coworkers[1-4] have been interested in the synthesis and pharmacological properties of fluorine compounds related to procaine (β-diethylaminoethyl *p*-aminobenzoate) for use in producing anesthesia. Several alkylaminoalkyl esters of *p*-fluorobenzoic acid were prepared. The anesthetic efficiency of these compounds was equal to, or slightly greater than, that of procaine and all possessed a low toxicity. Unfortunately tissue irritation was so pronounced that they could not be used for clinical work.

It appeared interesting therefore to examine some aminoalkyl esters of different aromatic fluorocarboxylic acids, in the hope of finding good local anesthetics without tissue-irritating properties.

In the present work some alkylaminoethyl esters of the isomeric fluorobenzoic and fluorophenylacetic acids have been investigated.

The hydrochlorides of the *o*-, *m*- and *p*-fluorobenzoic acid β-dimethylamino-, β-diethylamino-, β-piperidino-, and β-morpholino-ethyl esters were prepared. Among these compounds the dimethylamino and diethylaminoethyl esters of *p*-fluorobenzoic acid had already been reported. These compounds have proved in our experiments, in contrast to Fosdick's data, less active than procaine itself. The ten newly synthesized derivatives behave similarly. Among the esters of fluorobenzoic acids, the *m*-fluorobenzoic acid β-dimethylaminoethyl ester showed the greatest activity. Among the new derivatives the β-piperidinoethyl esters are of special interest, since with these compounds no tissue irritation could be observed.

The new fluorophenylacetic acid alkylaminoethyl esters now prepared have much more suitable properties. Löfgren and Lundquist[5] have described the local anesthetic activity of phenylacetic acid diethylaminoethyl ester hydrochloride. A similar effect for other phenylacetic acid derivatives has not yet been reported. The local anesthetic activity of *o*-, *m*- and *p*-fluorophenylacetic acid dimethylamino-, diethylamino-, and β-piperidinoethyl ester hydrochlorides is not far different from that of procaine itself. The effect of *o*-fluorophenylacetic acid β-piperidinoethyl ester is two times greater than that of procaine. The toxicities of these derivatives were found generally half as great as that of procaine. These compounds do not show tissue irritation in concentrations up to 2%, which is four times the therapeutical concentration.

The physical data, yields, analyses, and pharmacological data of the fluorobenzoic and fluorophenylacetic acid alkylaminoethyl esters prepared in this work are listed in Table I.

The local anesthetic activities of the compounds were examined by the method of Herr and coworkers[6] by determining the concentration of a 0.1 mole ester solution which caused anesthesia.

The isomeric fluorophenylacetic acids, of which *p*-fluorophenylacetic acid was already known,[7,8] were obtained from the corresponding fluorobenzyl bromides by the hydrolysis of the intermediate nitriles. The fluorophenylacetyl chlorides not described in the literature were prepared from the corresponding fluorophenylacetic acids by refluxing with thionyl chloride.

The fluorobenzoic acid, and the corresponding fluorophenylacetic acid alkylaminoethyl ester hydrochlorides were synthesized from the corresponding acid chlorides by reaction with amino alcohols in benzene solution.

EXPERIMENTAL

The *o- and m-fluorobenzoic acids* were prepared by the method of Fosdick and Campaigne[1] for the synthesis of *p*-fluorobenzoic acid (from the Grignard derivative of the fluorobromobenzene by carbonation).

The *o-, m- and p-fluorobenzoyl chlorides* were obtained according to the procedures of Meyer and Hub,[9] and Cohen,[10] and Holleman and Slothouwer.[11]

* Paper XXII: G. A. Oláh, S. J. Kuhn, and G. Kovacs-Bruckner, *J. Org. Chem.* **22**, 979 (1957).

(1) L. S. Fosdick and E. E. Campaigne, *J. Am. Chem. Soc.*, **63**, 974 (1941).

(2) L. S. Fosdick and H. I. Barnes, *J. Am. Chem. Soc.*, **67**, 335 (1945).

(3) L. S. Fosdick and A. F. Dodds, *J. Am. Chem. Soc.*, **65**, 2305 (1943).

(4) L. S. Fosdick and R. Q. Blackwell, *J. Am. Chem. Soc.*, **66**, 1165 (1944).

(5) N. Löfgren and B. Lundquist, *Svensk. Kem. Tidskr.*, **58**, 206 (1946) [*Chem. Abstr.*, **43**, 1022 (1949)].

(6) F. Herr, *Arch. Exp. Path.*, **217**, 207 (1952).

(7) J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1466 (1934).

(8) G. Oláh, A. Pavláth, and S. Kuhn, *Acta Chim. Acad. Sci. Hung.*, **7**, 85 (1955).

(9) Meyer and Hub, *Monatsch.*, **31**, 934 (1910).

(10) Cohen, *J. Chem. Soc.*, **99**, 1063 (1911).

(11) Holleman and Slothouwer, *Zentrall.*, **I**, 91 (1911).

TABLE I

PROPERTIES, ANALYSES, AND PHARMACOLOGICAL DATA OF FLUORINE COMPOUNDS RELATED TO PROCAINE

Ethyl Ester Hydrochloride	M.P., °C.	Yield, %	N Calcd.	N Found	C Calcd.	C Found	Effective Concentration, %	Toxicity, mg./kg.
o-Fluorobenzoic acid β-dimethylamino-	92	83	6.66	6.51	16.62	16.71		800
o-Fluorobenzoic acid β-diethylamino-	102	77	5.89	5.88	14.69	14.62	2	800
o-Fluorobenzoic acid β-piperidino-	104	70	5.60	5.79	13.96	13.80	2	800
o-Fluorobenzoic acid β-morpholino	102	76	5.56	5.61	13.88	13.76		800
m-Fluorobenzoic acid β-dimethylamino-	111	69	6.66	6.38	16.62	16.54	1	800
m-Fluorobenzoic acid β-diethylamino-	98	72	5.89	5.99	14.69	14.60	2	600
m-Fluorobenzoic acid β-piperidino-	100	70	5.60	5.76	13.96	13.88	2	500
m-Fluorobenzoic acid β-morpholino-	90	80	5.56	5.55	13.88	13.80		800
p-Fluorobenzoic acid β-dimethylamino[a]	107	74	6.66	6.71	16.62	16.52	2	500
p-Fluorobenzoic acid β-diethylamino-[a]	126	76	5.89	6.05	14.69	14.60	2	600
p-Fluorobenzoic acid β-piperidino	98	71	5.60	5.59	13.96	13.88	2	500
p-Fluorobenzoic acid β-morpholino-	90	81	5.56	5.40	13.88	13.71		800
o-Fluorophenylacetic acid β-dimethylamino-	108	69	6.31	6.48	15.71	15.52		800
o-Fluorophenylacetic acid β-diethylamino-	101	70	5.59	5.66	13.99	13.92	0.5	800
o-Fluorophenylacetic acid β-piperidino-	110	83	5.34	5.39	13.23	13.12	0.25	800
m-Fluorophenylacetic acid β-dimethylamino-	62	76	6.31	6.56	15.71	15.66		800
m-Fluorophenylacetic acid β-diethylamino-	67	80	5.59	5.51	13.99	13.84	0.5	800
m-Fluorophenylacetic acid β-piperidino-	106	68	5.34	5.30	13.23	13.23	0.5	800
p-Fluorophenylacetic acid β-dimethylamino	103	73	6.31	6.42	15.71	15.64		800
p-Fluorophenylacetic acid β-diethylamino-	71	89	5.59	5.70	13.99	13.90	1	800
p-Fluorophenylacetic acid β-piperidino-	100	83	5.34	5.48	13.23	13.06	1	800
Procaine							0.3–0.4	450

[a] Previously described by Fosdick and Campaigne, Footnote 1.

o-, m- and p-Fluorobenzyl bromide. Into a solution of 0.4 mole of fluorotoluene in 60 ml. of dry benzene was dropped 18 ml. (0.35 mole) of bromine over a period of 4 hr. under refluxing and ultraviolet irradiation. After completion of the reaction the product was purified by fractional distillation.

	B.P., °C.	Yield, %	Br Calcd.	Br Found
o-Fluorobenzyl bromide	195–202	71		42.51
m-Fluorobenzyl bromide	196–200	75	42.32	42.44
p-Fluorobenzyl bromide	195–202	82		42.49

o-, m- and p-Fluorobenzyl cyanide. A solution of 37 g. (0.2 mole) of fluorobenzyl bromide in 40 ml. of ethanol was dropped, over a period of 3 hr., into a solution of 10 g. of sodium cyanide in 15 ml. of water, contained in a three-neck, round-bottom flask, under maintenance of efficient stirring and heating on a water bath. The reaction mixture was refluxed for 4 hr. following the addition of the fluorobenzyl bromide. The cooled mixture was filtered from the inorganic salts and washed with a little alcohol. The alcohol was removed from the filtrate by distillation, and the residue was again filtered and washed with saturated aqueous sodium chloride solution. After drying, the organic layer was fractionated.

	B.P., °C.	Yield, %	N Calcd.	N Found
o-Fluorobenzyl cyanide	230–235	85		10.31
m-Fluorobenzyl cyanide	229–230	82	10.37	10.46
p-Fluorobenzyl cyanide	228–230	90		10.40

o-, m- and p-Fluorophenylacetic acid. Fluorobenzyl cyanide (27 g., 0.2 mole) was heated with 90 g. of aqueous sulfuric acid (diluted 3:2) until an exothermic reaction started. When the mixture began to boil, external heating was discontinued. After the cessation of boiling the solution was further heated for 2–3 min. The fluorophenylacetic acid which precipitated on cooling was filtered and recrystallized from chloroform.

	M.P., °C.	Yield, %	C Calcd.	C Found	H Calcd.	H Found	F Calcd.	F Found
o-Fluorophenylacetic acid	59	82		62.39		4.71		12.17
m-Fluorophenylacetic acid	38	87	62.33	62.21	4.54	4.58	12.33	12.20
p-Fluorophenylacetic acid	85	79		62.46		4.41		12.48

o-, m- and p-Fluorophenylacetyl chloride. To 23 g. (0.15 mole) of fluorophenylacetic acid in a round-bottom flask fitted with a reflux condenser was added 50 ml. of thionyl chloride. The ensuing exothermic reaction was allowed to go to completion. After removal of the excess thionyl chloride the product was fractionated.

	B.P., °C.	Yield, %	Cl Calcd.	Cl Found
o-Fluorophenylacetyl chloride	203–204	70		20.52
m-Fluorophenylacetyl chloride	201–202	72	20.58	20.46
p-Fluorophenylacetyl chloride	202–204	85		20.49

Reaction of fluorobenzoyl and fluorophenylacetyl chlorides with alkylaminoethanols. The amino alcohol (0.015 mole) was dissolved in 50 ml. of dry benzene and the solution was cooled with ice water. To this solution was added 0.015 mole of acyl chloride under efficient stirring. The white ester hydrochloride precipitated. After standing 1 hr. the reaction mixture was filtered and the precipitate was washed with a little benzene, recrystallized from ether-alcohol, and dried *in vacuo* (the products are strongly hygroscopic).

The properties of the compounds are listed in Table I.

BUDAPEST, HUNGARY

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

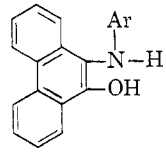
Studies of Quinoid Structures. I. Action of Arylmagnesium Halides on Phenanthrenequinonimine

WILLIAM IBRAHIM AWAD AND ABDEL REHIM ABDEL RAOUF

Received June 18, 1956

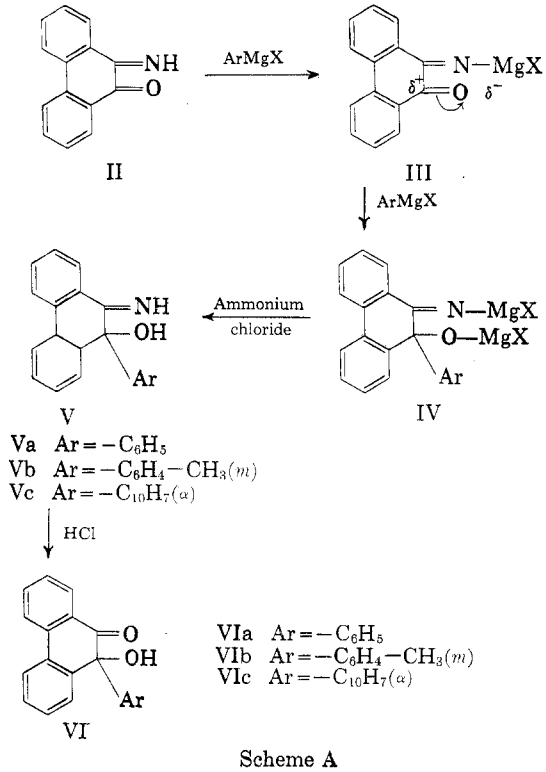
Arylmagnesium halides react with phenanthrenequinonimine by 1,2-addition and not by 1,4-addition as described by Mustafa and Kamel.[1] The constitution of the Grignard products is discussed.

Mustafa and Kamel[1] stated that arylmagnesium halides react with phenanthrenequinonimine by 1,4-addition yielding 10-arylamino-9-phenanthrol (I). The main line of evidence was the identity of their product (from phenylmagnesium bromide and phenanthrenequinonimine) with the 10-phenylamino-9-phenanthrol obtained by Schmidt and Lumpp[2] from aniline and 9,10-dihydroxyphenanthrene. They claimed that a mixture melting point experiment gave no depression and hence structure I was assigned.



I
Ia Ar = $-C_6H_5$
Ib Ar = $-C_6H_4$-$CH_3(m)$
Ic Ar = $-C_{10}H_7(\alpha)$

In contrast to Mustafa and Kamel,[1] we found that the Grignard product (Va) gave a depression in melting point with Schmidt's compound (Ia). Also, the compounds gave different colors with concentrated sulfuric acid (Schmidt's compound, after purification, was orange-brown; the Grignard compound was green.) The benzoyl derivatives of the compounds gave different colors with concentrated sulfuric acid and a depression was noted in the mixture melting point.



Scheme A

(1) Mustafa and Kamel, *J. Am. Chem. Soc.*, **76**, 124 (1954).

(2) Schmidt and Lumpp, *Ber.*, **43**, 787 (1910).