SYNTHESIS AND PHYSIOLOGICAL PROPERTIES OF N-PHENYLANTHRANILIC ACIDS WITH FLUORINE-CONTAINING SUBSTITUENTS

E. S. Endel'man, V. S. Danilenko, F. P. Trinus, P. A. Yufa, A. G. Fadeicheva, I. I. Muravov, Yu. A. Fialkov, and L. M. Yagupol'skii

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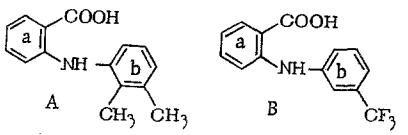
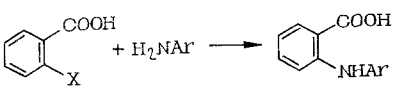
Compounds have been recently discovered among the substituted N-phenylanthranilic acids which possess antiphlogistic, analgesic, and antipyretic activity. N-(2,3-Dimethylphenyl)anthranilic acid (A), "Mefanamic acid" or Ponstan, and N-(3-trifluoromethylphenyl)anthranilic acid (B), "fluorfenamic acid," have found use in medicine [1-3].



N-Phenylanthranilic acid derivatives containing fluorine atoms in the ortho, meta, and para positions of ring (b) have also been described, and their physiological activity was investigated [4].

In our search for new effective antiphlogistic compounds, we synthesized a number of N-phenylanthranilic acid derivatives containing the following fluorinated groups: CF_3, $OCHF_2$, $SCHF_2$, OCF_3, SCF_3, SO_2CHF_2, and SO_2CF_3 in various positions on ring (b) and which have not been described in the literature; the physiological properties of the compounds obtained were also investigated.

The Ullmann reaction, the arylation of substituted anilines with o-halobenzoic acids in the presence of potassium carbonate and copper powder as the catalyst, is principally employed to synthesize the N-phenylanthranilic acid derivatives. The following compounds (I-XIII) (Table 1) were synthesized by this method:



Compounds VII and XI-XIII were prepared from o-chlorobenzoic acid. o-Bromobenzoic acid was used in the synthesis of compounds I-VI, VIII, and IX; and o-iodobenzoic acid was used for substance X.

As is evident from the data given in Table 1, the yields of the N-phenylanthranilic acid derivatives obtained by arylating substituted anilines depend to a great extent on the basicity of the amine used. Thus, the yields of the corresponding N-phenylanthranilic acids (I, IV, IX and X) amount to 6-12% in all during the reaction of halobenzoic acids with aniline derivatives containing electron-acceptor substituents. When anilines with $OCHF_2$ and OCF_3 groups are used, the highest yields of condensation products (VI and XIII) are observed for the more basic para derivatives.

In order to synthesize the compounds containing the $SCHF_2$ and SO_2CHF_2 groups in ring (b) (compounds XIV-XIX), it proved to be more expedient to choose another variant of the Ullmann reaction, the arylation

Kiev Scientific-Research Institute of Pharmacology and Toxicology, Ministry of Public Health of the Ukrainian SSR; Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 7, No. 12, pp. 15-19, December, 1973. Original article submitted August 10, 1972.

TABLE 1. Fluorinated N-Phenylanthranilic Acid Obtained by the Arylation of Substituted Anilines with o-Halobenzoic Acids

Compound	Ar	Meth. of obt. subs. aniline	Yield, %	mp, deg	Found F, %	Empirical formula	Calculated F, %
I	2,5-$(CF_3)C_6H_3$	[8]	12,0	203—204	32,38; 32,68	$C_{15}H_9F_6NO_2$	32,67
II	3,5-$(CF_3)_2C_6H_3$	[8]	29,0	200—201	32,58; 32,45	$C_{15}H_9F_6NO_2$	32,67
III	2-Cl-5-$CF_3C_6H_3$	[9]	27,5	179—180	18,25; 18,38	$C_{14}H_9ClF_3NO_2$	18,06
IV	4-Cl-6-$CF_3C_6H_3$	[10]	10,5	203—204	18,18; 18,25	$C_{14}H_9ClF_3NO_2$	18,06
V	3-$CF_3OC_6H_4$	[11]	33,0	110—112	18,56; 18,66	$C_{14}H_{10}F_3NO_3$	19,19
VI	4-$CF_3OC_6H_4$	[12]	56,0	175—176,5	19,19; 19,22	$C_{14}H_{10}F_3NO_3$	19,19
VII	3-$CF_3SC_6H_4$	[13]	24,0	115—117	18,49; 18,58	$C_{14}H_{10}F_3NO_2S$	18,21
VIII	4-$CF_3SC_6H_4$	[14]	38,0	132—133	18,12; 18,36	$C_{14}H_{10}F_3NO_2S$	18,21
IX	4-$CF_3SO_2C_6H_4$	[15]	6,0	199—200	16,28; 16,38	$C_{14}H_{10}F_3NO_4S$	16,52
X	2-CH_3-5-$CF_3SO_2C_6H_3$	[16]	12,0	200—202	15,48; 15,58	$C_{15}H_{12}F_3NO_4S$	15,88
XI	2-$CHF_2OC_6H_4$	[17]	30,5	139—140	13,41; 13,60	$C_{14}H_{11}F_2NO_3$	13,62
XII	3-$CHF_2OC_6H_4$	[17]	18,5	129—130	13,29; 13,36	$C_{14}H_{11}F_2NO_3$	13,62
XIII	4-$CHF_2OC_6H_4$	[17]	48,0	151—153	13,30; 13,39	$C_{14}H_{11}F_2NO_3$	13,62

Note. Compounds I, V, VI, and VII were crystallized from petroleum ether; II, III, IV, and X-XIII from aqueous alcohol; VIII from alcohol; and IX from a mixture of benzene and petroleum ether.

TABLE 2. Fluoro Derivatives of N-Phenylanthranilic Acid Obtained by Arylating Anthranilic Acid with Substituted Bromobenzenes

Compound	Ar	Reaction conditions: bath temperature, deg	Reaction conditions: duration of reaction, h	Yield, %	mp, deg	Found F, %	Empirical formula	Calculated F, %
XIV	2-$CHF_2SC_6H_4$	135	2	17,0	149—150	12,70; 12,81	$C_{14}H_{11}F_2NO_2S$	12,88
XV	3-$CHF_2SC_6H_4$	180	1,5	37,0	114—115	12,43; 12,47	$C_{14}H_{11}F_2NO_2S$	12,88
XVI	4-$CHF_2SC_6H_4$	175	4	46,0	123—124	12,38; 12,67	$C_{14}H_{11}F_2NO_2S$	12,88
XVII	2-$CHF_2SO_2C_6H_4$	135	2	24,5	206—207	11,72; 11,75	$C_{14}H_{11}F_2NO_4S$	11,62
XVIII	3-$CHF_2SO_2C_6H_4$	135	2	21,5	162—163	11,31; 11,40	$C_{14}H_{11}F_2NO_4S$	11,62
XIX	4-$CHF_2SO_2C_6H_4$	145	1,5	28,5	188—189	11,40; 11,56	$C_{14}H_{11}F_2NO_4S$	11,62

TABLE 3. Bromo Derivatives of Difluoromethylmercaptobenzene

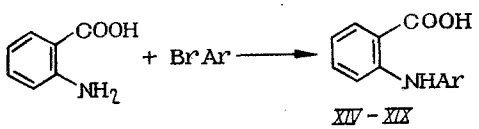
Derivative	Reaction conditions: reagents: sodium hydroxide, g	reagents: water, ml	reagents: dioxane, ml	duration of passage, h	Yield, %	bp, deg	n_D^{20}	d_{20}^{20}	Found, F, %	Empirical formula	Calculated F, %
ortho*	9,5	60	60	2	61,5	75—90 (3 mm)	1,556	—	—	—	—
meta	15,5	45	45	3	65,0	90—92 (5 mm)	1,555	1,608	15,69; 15,90	$C_7H_5BrF_2S$	15,90
para	14,5	45	45	3	55,0	93—95 (5mm)	1,557	1,6931	16,12; 16,29	$C_7H_5BrF_2S$	15,90

*The technical product was recovered for the reactions involving arylation and oxidation to the sulfone.

TABLE 4. Bromo Derivatives of Phenyldifluoromethyl Sulfone

Derivative	Yield, %	mp, deg	Found F, %	Empirical formula	Calculated F, %
ortho	97,0	46—47	14,32; 14,13	$C_7H_5BrF_2O_2S$	14,03
meta	98,5	60—71	13,90; 13,86	$C_7H_5BrF_2O_2S$	14,03
para	84,5	68—69	14,19; 14,04	$C_7H_5BrF_2O_2S$	14,03

of anthranilic acid by the appropriate bromobenzene derivatives (Table 2):



XIV - XIX

The bromobenzene derivatives needed for this reaction (Tables 3, 4) were obtained by the following scheme:

$$BrC_6H_4SH \xrightarrow[NaOH]{CHClF_2} BrC_6H_4SCHF_2 \xrightarrow{H_2O_2} BrC_6H_4SO_2CHF_2.$$

The corresponding sulfone (XIX) was obtained by oxidizing compound XVI containing the difluoromethylmercapto group with hydrogen peroxide.

As a result of this, 19 new N-phenylanthranilic acid derivatives with various fluorine-containing substituents were synthesized.

It was established during the pharmacological investigation of the compounds obtained that these substances possess an average toxicity. Their LD_{50} for mice when injected intraperitoneally is found to be in the range 140-300 mg/kg. The presence of fluorinated substituents regardless of their nature somewhat increases the toxicity of the substances as compared to unsubstituted N-phenylanthranilic acid. The introduction of a second CF_3 group into the meta position of ring (b) (compound II) increases the toxicity relative to compound B; the chlorine-containing analogs of the latter (compounds III and IV) differ little in their toxicity from it. The compounds containing strong electron-acceptor substitutents, the SO_2CF_3 and SO_2CHF_2 groups (IX, X and XVII-XIX), are less toxic than the substance whose molecule contains the OCF_3 (V and VI), SCF_3 (VII and VIII), and also the $OCHF_2$ (XI-XIII) substituents.

The antiphlogistic activity of all of the compounds we synthesized, which was investigated for various types of edemas, does not exceed that for compound A which served as a standard. Since the compounds containing the SO_2CF_3 and SO_2CHF_2 groups (IX, X and XVII-XIX) proved to be the least toxic, we investigated their antiphlogistic activity in relation to formalin and trypsin edemas in more detail. It was thereby established that the antiphlogistic activity of these compounds decreases in the transition from the ortho to the meta to the para substituted compounds (XVII > XVIII > XIX).

Because the substances investigated possessed the ability to inhibit trypsin edema, we decided to examine their antiprotease activity. The inhibiting activity of the compounds relative to the named enzyme was investigated for this in in vitro and in vivo experiments. It was established that the quantity of trypsin which leads to the loss of the animals as a result of the slow intravenous infusion of the enzyme, is noticeably decreased compared to the control when the compounds were preliminarily intraperitoneally injected at a dose of 10% of the LD_{50}. It was found that all the compounds are two-three orders of magnitude more effective trypsin inhibitors than unsubstituted N-phenylanthranilic acid in the in vitro experiments with the following different substrates: trypsin–casein (by Kunitz's method [5]) and N-benzoyl-DL-arginyl-p-nitroanilide (by Erlanger's method [6]), and the substances with the OCF_3 (V and VI) and SCF_3 (VII and VIII) groups exceed compounds A and B in this regard. It should be mentioned that the effect of a structural factor on the antiprotease activity of the compounds clearly appears in this series of experiments. The para substituted compounds, of all the compounds with the various substituents, are the most active ones independent of the nature of the latter. The inhibiting effect of the substances in relation to the type of fluorinated radical present in ring (b) increases in the following order: CHF_2O (XI-XIII) < CHF_2SO_2 (XVII-XIX) < CF_3O (V, VI) < CF_3S (VII, VIII).

Thus, the data from the biological experiments showed that the N-phenylanthranilic acid derivatives with fluorine-containing substituents that we synthesized yield somewhat to mefenamic acid (A) and fluorfenamic acid (B) in their antiphlogistic activity and exceed them in their antiprotease activity.

EXPERIMENTAL

Arylation of Anilines with o-Chlorobenzoic Acid (Compounds VII, XI-XIII). To a mixture of 7.8 g (0.05 mole) of o-chlorobenzoic acid, 3.58 g (0.025 mole) of anhydrous potassium carbonate, and 0.8 g (0.0125 g-atom) of copper powder in 40 ml of anhydrous isoamyl alcohol was added with intensive agitation a solution of 0.05 mole of the appropriate aniline in 10 ml of isoamyl alcohol. The reaction mixture was boiled for 4 h, cooled, and brought to pH 8-8.5 by adding 6-7 ml of 10% sodium hydroxide, agitated for 10 min, and the amine which did not react and isoamyl alcohol was stream distilled off. The remainder was filtered

free of sludge, which was washed with hot water. The solution of the sodium N-arylanthranilate was treated with carbon and acidified with dilute hydrochloric acid. The product was filtered off, washed with cold water and 3-4 ml of cold methanol, and crystallized.

Arylation of Anilines with o-Bromo- and o-Iodobenzoic Acids (Compounds I-VI and VIII-X). The reaction was carried out under the same conditions with the same molar ratios of the components as above. Anhydrous dimethylformamide was used as the solvent during the synthesis of compounds I, IX, and X. The unreacted difficult-to-steam-distill starting amines used in the synthesis of IX and X were removed from the condensation product by filtering alkaline solutions of the sodium salts of acids IX and X. The filtered solution was acidified and the free acid was extracted with ether (IX) or filtered off (X).

The Arylation of Anthranilic Acid with Bromobenzene Derivatives (Compounds XIV-XIX). A mixture of 13.7 g (0.1 mole) of anthranilic acid, 6.9 g (0.05 mole) of anhydrous potassium carbonate, 1.6 g (0.025 g-atom) of copper powder (in order to synthesize compounds XVII-XIX, 0.08 g-atom of copper was used), and 0.1 mole of the appropriate bromobenzene derivative in 85 ml of anhydrous isoamyl alcohol was heated while being intensively agitated on an oil bath. After cooling, 5% sodium hydroxide was added to the mixture to pH 8-8.5, and the solvent and unreactive bromo derivative were steam distilled off. The remainder in the flask was cooled, filtered free of sludge, the solution was acidified in the cold with dilute hydrochloric acid, and the product was filtered off.

During the synthesis of the compounds containing the $SCHF_2$ group (compounds XIV-XVI), the substance was extracted with boiling heptane, freed of the sediment insoluble in the heptane, evaporated to dryness, and crystallized from aqueous alcohol. In order to purify substances XVII-XIX, the dried product was crystallized from aqueous alcohol without extracting it with heptane.

Difluoromethylmercaptobromobenzenes. A stream of difluorochloromethane (Freon 22) was passed with agitation through a mixture of 9.5 g of o-, m-, or p-bromothiophenol [7] and an aqueous dioxane–sodium hydroxide solution at 60°C for several hours and was cooled. The reaction mixture was diluted with water, filtered free of the mineral salt residue and the product was extracted from the filtrate with ether. The ether extract was washed with water, dried, the ether was distilled off, and the remainder was vacuum distilled.

Difluoromethylsulfonylbromobenzenes. A mixture of 2.4 g of the appropriate difluoromethylmercaptobromobenzene and 4 ml of 30% hydrogen peroxide in 6 ml of glacial acetic acid was boiled for 2 h and poured onto ice. The precipitated product was filtered off, washed with water, and crystallized from aqueous alcohol.

N-(4-Difluoromethylsulfonylphenyl)anthranilic Acid (XIX). A mixture of 1.5 g of N-(4-difluoromethylmercaptophenyl)anthranilic acid (XVI) and 5 ml of 30% hydrogen peroxide in 10 ml of glacial acetic acid was boiled for 2 h and poured into water. The precipitate was filtered off. The yield was 0.5 g (30%), mp 184-187°C (from aqueous alcohol). The compound did not give a melting point depression when mixed with the substance obtained by the Ullmann reaction.

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