SYNTHESIS AND STUDY OF THE BIOLOGICAL PROPERTIES OF FLUORINATED DERIVATIVES OF 1-PHENYL-3-METHYLPYRAZOL-5-ONE. ANALOGS OF ANTIPYRINE WITH HETEROATOMIC FLUORINE-CONTAINING SUBSTITUENTS

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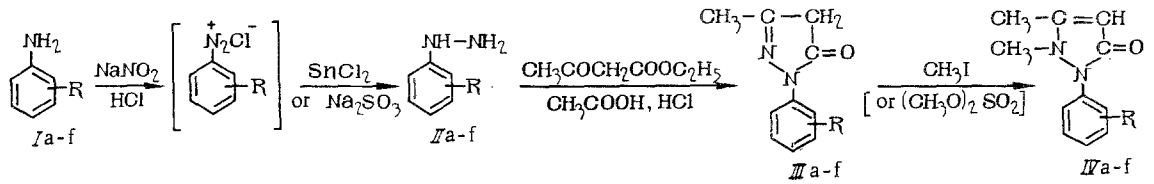
We have previously described the synthesis and pharmacological properties of fluorine-containing N-phenylanthranilic acids obtained by the Ullman condensation of ortho halobenzoic acids and aniline derivatives with fluorine-containing substituents such as $OCHF_2$, $SCHF_2$, and SO_2CHF_2 [1].

Continuing the search for new antiinflammatory preparations made from available anilines substituted with fluorinated substituents of various electronic nature, we undertook the synthesis and study of the physiological properties of fluorinated analogs of antipyrine (IVa-f). Compounds of similar type are little known and have not been studied.

The preparations investigated were obtained according to the scheme:



a: R = 3-$OCHF_2$; b: R = 4-$OCHF_2$; c: R = 3-$SCHF_2$; d: R = 4-$SCHF_2$;
e: R = 3-SO_2CHF_2; f: R = 4-SO_2CHF_2

The derivatives of phenylhydrazine (IIa-e) (Table 1) were obtained by reduction with stannous chloride in hydrochloric acid of diazonium salts obtained from the appropriate substituted aniline (Ia-f). In the synthesis of hydrazine (IIf) described in the literature previously [2] sodium sulfite was used for reduction.

Phenylhydrazines (IIa-d) were liquids decomposing on distillation even under high vacuum. They were nearly all made and used further in the synthesis of the corresponding pyrazolones as their hydrochlorides. It was not possible to obtain the hydrochloride of compound IIc crystalline. It was identified as the benzoyl derivative and picrate and was put into the condensation without purification.

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TABLE 1. Phenylhydrazine Derivatives (IIa-f)

Compound	Yield, %	Melting point, °C*	Found, %	Empirical formula	Calc., %
IIa	57,2	167—8 (dec.)†	Cl 17,08, 17,11	$C_7H_9ClF_2N_2O$	Cl 16,86
IIb	47,6	188—9 (dec.)†	Cl 16,81, 16,90 F 18,67, 18,68	$C_7H_9ClF_2N_2O$	Cl 16,86 F 18,05
IIc	78,4‡	—	—	—	—
Benzyl derivative of IIc					
IIc picrate	—	146—7	F 13,20, 13,37	$C_{14}H_{12}FN_5OS$	F 12,93
IId	—	147—8 (dec.)†	N 16,73, 16,83	$C_{13}H_{11}F_3N_5O_7S$	N 16,68
	66,2	163—4 (dec.)†	Cl 15,78, 15,95 F 16,02, 16,23	$C_7H_9ClF_2N_2S$	Cl 15,67 F 16,80
IIe	59,2	93—4	F 17,38, 17,43	$C_7H_8F_2N_2O_2S$	F 17,12
IIf	32,7	73—4 [2]	—	—	—

*Compounds IIa and IId were crystallized from ethanol; IIb from methanol; derivatives of IIc from aqueous ethanol; IIe and IIf from a benzene–heptane mixture.

†Melting points and analytical data are given for hydrochlorides in which form these substances were isolated.

‡The yield indicated is for the unpurified product.

TABLE 2. Derivatives of 1-Phenyl-3-methylpyrazol-5-one (III)

Compound	Yield, %	Melting point, °C*	Found F, %	Empirical formula	Calculated F, %
IIIa	60,3	86—7	15,57, 15,77	$C_{11}H_{10}F_2N_2O_2$	15,82
IIIb	35,5	119—20	15,97, 16,19	$C_{11}H_{10}F_2N_2O_2$	15,82
IIIc	21,5	95—7	14,79, 14,90	$C_{11}H_{10}F_2N_2OS$	11,85
IIId	69,5	137—8	14,67, 14,90	$C_{11}H_{10}F_2N_2OS$	14,85
IIIe	60,0	143—5	12,92, 13,17	$C_{11}H_{10}F_2N_2O_3S$	13,17
IIIf	73,0	182—3	12,75, 12,95	$C_{11}H_{10}F_2N_2O_3S$	13,17

*Compounds IIIa, b, and e were crystallized from aqueous ethanol; IIIc from a mixture of benzene and heptane; IIIf from ethanol.

TABLE 3. Derivatives of Antipyrine (IV)

Compound	Yield, %	Melting point, °C*	Found F, %	Empirical formula	Calculated F, %
IVa	31,5	64—6	14,89, 15,09	$C_{12}H_{12}F_2N_2O_2$	14,96
IVb	45,0	105—7	14,91, 15,04	$C_{12}H_{12}F_2N_2O_2$	14,96
IVc	28,7	95—6	15,10, 15,32	$C_{12}H_{12}F_2N_2OS$	14,08
IVd	42,6	132—3	14,32, 14,43	$C_{12}H_{12}F_2N_2OS$	14,08
IVe	33,0	119—20	12,72, 12,90	$C_{12}H_{12}F_2N_2O_3S$	12,58
IVf	50,0	158—9	12,44, 12,60	$C_{12}H_{12}F_2N_2O_3S$	12,58

*Compound IVa was crystallized from a mixture of benzene–heptane; IVb, d, and e from heptane; IVc and f from aqueous ethanol.

Derivatives of 1-phenyl-3-methylpyrazol-5-one (III) (Table 2) were obtained by the usual route by condensing the appropriate phenylhydrazines (IIa-f) with acetoacetic ester. Methylation of them was effected by heating with methyl iodide in methanol in sealed ampuls. The most weakly basic pyrazolone (IIIf) containing a strongly electron-accepting substituent, viz., the SO_2CHF_2 group in the para position of the benzene ring, was successfully methylated only by heating with dimethyl sulfate. The synthesized derivatives of antipyrine are given in Table 3.

Bands were present in the IR spectra of the obtained pyrazolone derivatives (UR-20 instrument, potassium bromide disks) in the 800-900 cm^{-1} region which were of medium intensity and were assigned to the deformation vibration of CF bonds. Absorption bands were observed in the 1210-1230 cm^{-1} region in the spectra of preparations containing the difluoromethoxy group $OCHF_2$ corresponding to the ether bond. Bands at 1680-1690 cm^{-1} were observed in the spectra of antipyrines and pyrazolones which were characteristic for the stretching vibrations of C=O bonds. A broad intense band was also present at 2600-3000 cm^{-1} in the spectrum of substance IIIf indicating the presence of an OH group. Hence the conclusion may be drawn that the introduction of an electron accepting substituent (the SO_2CHF_2 group) into the para position of the benzene ring significantly increased the content of enol form in the corresponding phenylmethylpyrazolone derivative. The vibration of the C–H bonds of the methyl groups appeared in the 2900-3100 cm^{-1} region in these preparations, where they were superimposed on the absorption of hydroxyl. For compounds containing the SO_2CHF_2 group there were characteristic intense absorption bands in the 1160-1170 region and at 1350 cm^{-1}, which were assigned to the stretching vibrations of the SO_2 fragment.

EXPERIMENTAL

Pharmacology

The acute toxicity of compounds was investigated in experiments on mice of 18-24 g total body weight. Substances were injected intraperitoneally, observations were carried out for 3 days. The LD_{50} values were calculated by the method of Litchfield and Wilkinson as modified by Roth [3].

On treating mice with fluorine derivatives of antipyrine a reduction in the activity of animals was observed with labored breathing. At doses in the LD_{50}-LD_{100} range, atonia set in which was replaced by convulsions of mixed type in the terminal period. Death of mice occurred in the period from 5 min to 26 h after injection of compounds. As is seen from Table 4 the toxicity of fluorinated analogs of antipyrine had practically no dependence on the position and nature of the fluorine containing substituent and was higher than for unsubstituted antipyrine.

Antiinflammatory action was investigated on the "formalin" and "trypsin" edema models of the rear paw of rats; 0.1 ml 0.25% trypsin solution of 0.1 ml 2% formalin solution was administered under the aponeurosis. The effect was calculated 1, 2, 3, and 4 h after intraperitoneal injection of compounds IVa, b, d-f in provisionally therapeutic doses equal to 10% LD_{50}.

The antiedema action was recorded by a volumetric method [4]. The paw volume was expressed in linear units (cm) corresponding to the volume of mercury displaced by the paw. For convenience of calculation the volume of displaced mercury was expressed in relative units (1 unit = 1 cm) of the movement of an air bubble in a capillary of 1 mm diameter. The effect was calculated from the formula:

$$\frac{Y_c - Y_o}{Y_c} \cdot 100\%,$$

where Y_c is the increase in raw paw volume in controls; Y_o is the increase in raw paw volume after injection of the preparation. Measurement of paw volume was carried out before and 1, 2, 3, and 4 h after injection of the phlogogenic substances.

As it turned out the antiinflammatory action of preparations was expressed to an insignificant degree and did not exceed the action of unsubstituted antipyrine and amidopyrine (see Table 4).

Chemistry

Phenylhydrazine Derivatives (IIa-f) (see Table 1). Compounds (IIa-e). A mixture of the appropriate aniline derivative (Ia-e) (0.1 mole) [1] and 36% hydrochloric acid (50 ml) was diazotized at –4° with a solution of sodium nitrite (7 g) in water (20 ml). A mixture of $SnCl_2 \cdot 2H_2O$ (60 g) and 36% hydrochloric acid (60 ml) was poured into the filtered diazo solution with vigorous stirring. The thick reaction mass was stirred at 0° for 1 hour, then

TABLE 4. Toxicity and Antiedema Action of Fluorine Derivatives of Antipyrine

Compound	LD_{50}, mg/kg	Inhibition of edema, % (M ± m)							
		formalin edema				trypsin edema			
		1 h	2 h	3 h	4 h	1 h	2 h	3 h	4 h
Antipyrine	1150 (982,4—1345,5)	5,9÷0,3	7±1,4	9,3±1,6	8,3±1,2	11,2±1,6	24,4±3,3	32,2±1,4	35±1,9
Amidopyrine	280 (241—325)	26±3,2	26±3,4	28±2,7	20±1,9	9,2±1,6	19±3,3	27±2,2	32±1,9
IVa	410 (350—470)	17±2,1	16±1,9	8,8±1,1	10±1,1	15±4,1	17,5±1	16±1,4	10±2,1
IVb	385 (310—420)	8,8±0,6	15,5±3,4	12,4±0,9	12±2,1	7±0,5	16,6±0,9	14±2	8,8±1,2
IVc	442 (390,5—500)	20,4±3,2	17±4,2	18,3±2,4	9,9±2,1	11,1±2,5	24±3,6	29±4,2	28,9±1
IVd	424 (373—500,3)	8,5±0,5	13,3±1,7	14±3,1	12,3±0,8	7,7±0,8	10,6±0,9	11,1±1,1	20±2,2
IVe	413 (350—490)	0	20±3,5	15±2,3	10,1±1	16,6±1,5	16,1±4,4	17±2,1	17,7±0,8

40% sodium hydroxide solution (400 ml) was added gradually at the same temperature. The hydrazine was extracted with ether; the ether extract was washed with water, and dried with sodium sulfate. The ether solution was evaporated to small volume. Hydrazine derivatives (IIa, b, d) were isolated as hydrochlorides by passing dry hydrogen chloride through the solution.

Compound (IIf). 4-Difluoromethylsulfonylaniline (If) (20 g) was diazotized as described above and stirred at −8° for 2 h. 4,4'-Bis(difluoromethylsulfonyl)azobenzene (about 6 g) of mp 214-216° (ethanol) was filtered off. Found, %: F 18.80; 18.87; N 7.19; 7.20. $C_{14}H_{10}F_4N_2O_4S_2$. Calculated, %: F 18.55, N 6.83. The filtrate was poured with vigorous stirring at 0° during 15 min into a solution of sodium sulfite (30 g) and sodium hydroxide (2.6 g) in water (60 ml). After 5 min 36% hydrochloric acid (100 ml) was added and the mixture stored for 12 h. The precipitated crystals of hydrazine sulfonate were filtered off, stirred with 36% hydrochloric acid (30 ml), and heated on a water bath for 20 min. The mix was cooled, the mixture of the hydrazine hydrochloride and sodium chloride was filtered off, treated with warm ethanol, filtered, and the filtrate evaporated. The yield of hydrochloride was 12.5 g (50%). It was dissolved in water, the solution was made alkaline with 40% sodium hydroxide, the precipitated base extracted with benzene, the extract washed with water, dried with sodium sulfate, and the solvent evaporated off.

Derivatives of 1-Phenyl-3-methylpyrazol-5-one (IIIa-f) (see Table 2). Compounds (IIIa-e). A mixture of the appropriate hydrazine hydrochloride (IIa, b, d) or base (IIc, e) (0.025 mole), acetoacetic ester (0.025 mole), acetic acid (5 ml) [when using bases 36% hydrochloric acid (2 ml) was also added], water (25 ml), and sufficient ethanol for homogenization was stirred at 30-40° for 1 h, at 105-110° for 4-5 h, left overnight, and then diluted with water. Compounds IIIa, b, d, and e were separated, washed with water, dried, and purified from oily contaminants by crystallization from heptane or a benzene–heptane mixture. Pyrazolone (IIIc) was extracted with ether, washed with water, 1% sodium hydroxide, and water, and dried with sodium sulfate. After removal of ether the residue was dissolved in 50% ethanol and boiled with carbon. The filtrate was diluted with a large quantity of water, left for several days, and the precipitated crystals separated.

Compound (IIIf). Hydrazine (IIf) (2.2 g), acetoacetic ester (1.3 g), and glacial acetic acid (5 ml) were stirred at 110-115° for 5 h. After 12 h the precipitated product was filtered off and washed with water.

Derivatives of Antipyrine (IVa-f) (see Table 3). Compounds (IVa-e). A solution of the appropriate pyrazolone (III) (0.02 mole) in methanol (20 ml) containing methyl iodide (0.024 mole) was heated in a sealed ampul at 110-115° for 15 h, the solvent distilled off, water (15 ml), 40% sodium hydroxide (4 ml), and benzene (50 ml) were added to the residue and the mixture was stirred at 45-50° for 15 min. The benzene layer was separated, washed with water, 5% sodium hydrosulfite, 5% NaOH, and with water, and dried over sodium sulfate. After removal of benzene the residue gradually crystallized.

Compound (IVf). Pyrazolone (IIIf) (1.7 g) was added to dimethyl sulfate (0.8 g) at 90° with stirring. The mixture was maintained at 165-170° for 5 h, water (3 ml) was added, and the mixture maintained at 105° for 3 h. Sodium hydroxide (40%; 3 ml) was introduced and the mixture stirred at 90° for 5 min. The oil which separated crystallized gradually on cooling.

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LITERATURE CITED

1. E. E. Éndel'man, V. C. Danilenko, F. P. Trinus, et al., Khim. Farm. Zh., No. 12, 15 (1973).
2. A. de Cat, R. van Poucke, R. Pollet, et al., Bull. Soc. Chim. Belg., 74, 270 (1965).
3. Litchfield and Wilkinson, cited by M. L. Belen'kii, in: Elements of the Quantitative Assessment of Pharmacological Effects [in Russian], Leningrad (1963), pp. 81-106.
4. N. A. Mokhort and T. K. Ryabukha, Patol. Fiziol., No. 2, 101 (1971).