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ARTICLE *in* PHARMACEUTICAL CHEMISTRY JOURNAL · JUNE 2006

Impact Factor: 0.45 · DOI: 10.1007/s11094-006-0130-7

SYNTHESIS, ANALGESIC AND ANTIPYRETIC ACTIVITY OF 2-(ANTIPYRIN-4-YL)HYDRAZONES OF 1,2,3-TRIKETONES AND THEIR DERIVATIVES

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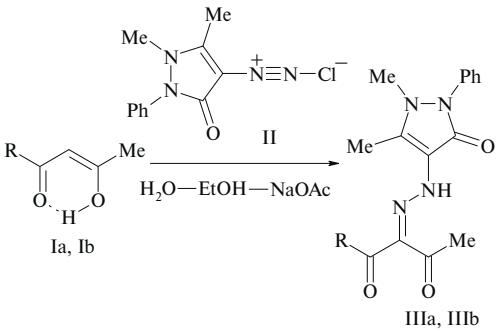
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 40, No. 7, pp. 27 – 29, July, 2006.

Original article submitted November 18, 2004.

1,2,3-Triketone 2-(antipyrin-4-yl)hydrazones were synthesized via the azo-coupling reactions of 1,3-diketones with 2-(antipyrin-4-yl)diazonium chloride. The fluoroalkyl-containing hetarylhydrazone enters into cyclocondensation with hydrazines at the 1,3-dicarbonyl fragment to yield 3-tetrafluoroethyl derivatives of pyrazole. It was found that 1,2,3-triketone 2-(antipyrin-4-yl)hydrazones and N-(2-hydroxyethyl)-substituted pyrazole exhibit analgesic activity comparable with that of their structural analog analgin (metamizole sodium), but do not possess antipyretic properties. In contrast, N-phenyl-substituted pyrazole did not exhibit analgesic properties but produced a certain antipyretic effect four hours after pyrogenic administration. Fluoroalkyl-containing compounds are less toxic substances than nonfluorinated 2-(antipyrin-4-yl)hydrazone and analgin.

As is known, the widely used analgesic and antipyretic drugs are rather toxic substances [1]. We attempted to modify the antipyrine structure so as to obtain new low-toxicity compounds possessing analgesic and antipyretic properties.

Using the azo-coupling reactions of 1,3-diketones (Ia and Ib) with 2-(antipyrin-4-yl)diazonium chloride (II) in the presence of sodium acetate, we obtained the corresponding 1,2,3-triketone 2-(antipyrin-4-yl)hydrazones (IIIa and IIIb). The proposed structures of these products were confirmed by the data of elemental analyses and the results of IR and ^{1}H NMR spectroscopic measurements. Indeed, the presence of characteristic absorption bands due to carbonyl groups (at 1660 – 1680 cm^{-1}) and a weak band due to the stretching vibrations of amino groups of the hydrazone fragment (at 3300 – 3470 cm^{-1}) in the IR spectra, as well as the absence of signals from methane protons in the ^{1}H NMR spectra, showed evidence for a hydrazone-diketone tautomer structure of the synthesized compounds.



I, III: R = Me (a), H(CF$_2$)$_2$ (b).

5,5,6,6-Tetrafluorohexane-2,4-dione-3-(antipyrin-4-yl)-hydrazone IIIb enters into cyclocondensation with α-N,N-dinucleophiles (2-hydroxyethylhydrazine, phenylhydrazine) at the 1,3-dicarbonyl fragment on boiling in ethanol to yield 3-tetrafluoroethyl derivatives of pyrazole (IV, V). The chemical shifts of the signals from protons in C-methyl groups (2.54 – 2.63 ppm) in the ^{1}H NMR spectra and the signals from α-CF$_2$ in tetrafluoroethyl substituents in the ^{19}F NMR spectra showed that pyrazoles possess a 3-R^f-regioisomer structure [2, 3]. According to the data of IR and ^{1}H NMR spectroscopy, the (1-phenyl)-substituted pyrazole V com-

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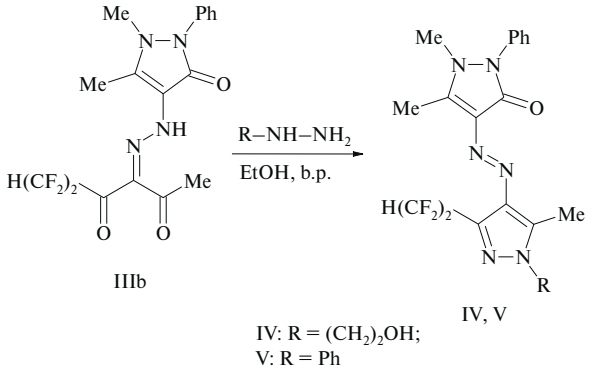
prises a mixture of *cis* and *trans* azo-isomers in a 9 : 1 ratio, while the 1-(2-hydroxyethyl)-containing pyrazole IV exists in the form of a pure *trans* azo-isomer.



IIIb

IV, V

IV: R = $(CH_2)_2OH$;
V: R = Ph

The synthesized compounds III – V appeared as crystalline substances of a yellow color, insoluble in water, well soluble in DMSO, and sparingly soluble in ethanol.

EXPERIMENTAL CHEMICAL PART

The course of reactions was monitored and the purity of the target product was checked by TLC on Sorbfil plates, which were eluted in chloroform and developed by exposure to UV radiation. The melting points were determined using a Boetius heating stage (Germany). The IR spectra in the 400 – 4000 cm^{-1} wavenumber range were recorded with a Perkin-Elmer Spectrum-One FTIR spectrophotometer (UK). The ^1H and ^{19}F NMR spectra were measured on a Bruker DRX-400 spectrometer (Germany) operating at a working frequency of ~400 and 376 MHz, respectively. The chemical shifts were determined relative to $SiMe_4$ and C_6F_6 used as the internal standards.

The initial 1,3-diketones were synthesized using the Claisen condensation reaction [4]. The data of elemental analyses agree with the results of calculations using empirical formulas.

General method for the synthesis of 1,2,3-triketone 2-(antipyrin-4-yl)hydrazones (IIIa, IIIb). To 4-aminoantipyrine (2.03 g, 10 mmole) in a two-neck flask equipped with a stirrer and a dropping funnel was added a hydrochloric acid solution (prepared from 3 ml of concentrated HCl and 10 ml water). To this mixture was gradually added dropwise with intense stirring and cooling to 0°C a solution of sodium nitrite (0.7 g, 10 mmole) in 3 ml water. The thus obtained 2-(antipyrin-4-yl)diazonium chloride solution was added dropwise with cooling (10°C) to a mixture of sodium acetate (4.55 g, 55 mmole) solution in 8 ml water and 1,3-diketone (10 mmole) solution in ethanol (31 ml). At the end of this procedure, the target hydrazone crystals begin to precipitate. The precipitated crystals were separated by filtration, recrystallized from ethanol, and dried under vacuum.

Pentane-2,3,4-trione-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)hydrazone (IIIa). Compound IIIa was obtained with a yield of 1.63 g (52 %); m.p., 165 – 166°C; $C_{16}H_{18}N_4O_3$.

IR spectrum (ν_{max}, cm^{-1}): 3470, 1595 (NH), 1670 (C=O), 1620 (C=N), 1530, 1490 (C=C); ^1H NMR spectrum in DMSO-d_6 (δ, ppm): 2.33 (s, 3H, C(=O)Me), 2.56 (s, 3H, C(=O)Me), 3.16 (s, 3H, NMe), 7.34 – 7.52 (m, 5H, Ph), 14.42 (s, 1H, NH).

5,5,6,6-Tetrafluorohexane-2,3,4-trione-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)hydrazone (IIIb). Compound IIIb was obtained with a yield of 2.28 g (57 %); m.p., 130 – 132°C; $C_{17}H_{16}F_4N_4O_3$.

IR spectrum (ν_{max}, cm^{-1}): 3300, 1600 (NH), 1680, 1660 (C=O), 1620 (C=N), 1525, 1500 (C=C), 1100 – 1140 (C–F); ^1H NMR spectrum in $CDCl_3$ (δ, ppm): 2.49 (s, 3H, C(=O)Me), 2.59 (s, 3H, C=C–Me), 3.20 (s, 3H, NMe), 6.74 (tt, 1H, J_1 53 Hz, J_2 6 Hz, $H(CF_2)_2$), 7.36 – 7.52 (m, 5H, Ph), 15.40 (s, 1H, NH); ^{19}F NMR spectrum in $CDCl_3$ (δ, ppm): 24.04 (dt, 2F, J_1 53 Hz, J_2 8 Hz, $HC\underline{F}_2CF_2$), 41.10 (m, 2F, $HCF_2C\underline{F}_2$).

General method for the synthesis of pyrazoles IV and V. To a solution of 5,5,6,6-tetrafluorohexane-2,4-dione-3-(anti-

TABLE 1. Acute toxicity and Analgesic Activity of 1,2,3-Triketone-2-(antipyrin-4-yl)hydrazones and Their Derivatives in Mice

Compound	LD_{50}, mg/kg	PASS prognosis		Analgesic activity		
		Pa	Pi	Dose, mg/kg	Number of convulsions	Percentage decrease in number of convulsions
IIIa	1030 (880 – 1180)	0.963	0.005	54	8.50 ± 2.43*	64
IIIb	> 2000	0.912	0.006	69	4.83 ± 2.47*	79
Analgin	1630 (1400 – 1900)	0.993	0.003	55	7.83 ± 1.56*	67
Control	–	–	–	–	23.50 ± 2.13	–
IV	> 2000	0.899	0.006	76	8.50 ± 2.70*	72
V	> 2000	0.943	0.005	82	24.83 ± 4.60	20
Control	–	–	–	–	30.83 ± 6.10	–

* Differences reliable for $p < 0.05$ relative to control.

TABLE 2. Antipyretic Activity of 1,2,3-Triketone-2-(antipyrin-4-yl)hydrazones and Their Derivatives in Rats

Compound	PASS prognosis		Antipyretic effect (body temperature, °C) at various times after pyrogenic injection			
	Pa	Pi	Dose, mg/kg	3 h	4 h	5 h
IIIa	0.932	0.002	98	37.41 ± 0.22	37.50 ± 0.17	37.93 ± 0.36
IIIb	0.883	0.003	124	37.70 ± 0.23	37.80 ± 0.35	38.42 ± 0.14*
Analgin	0.980	0.001	100	36.86 ± 0.09*	36.24 ± 0.19*	36.94 ± 0.30
Control	–	–	–	37.83 ± 0.16	37.45 ± 0.25	37.32 ± 0.34
IV	0.839	0.004	137	36.22 ± 0.43	37.93 ± 0.22	38.42 ± 0.40
V	0.883	0.003	147	37.22 ± 0.23	37.03 ± 0.22	37.99 ± 0.33*
Control	–	–	–	36.92 ± 0.33	37.57 ± 0.39	39.08 ± 0.07

* Differences reliable for $p < 0.05$ relative to control.

pyrin-4-yl)hydrazone (1.2 g, 3 mmole) in 30 ml of ethanol was added 3 mmole of the corresponding α-N,N-dinucleophile (2-hydroxyethylhydrazine, phenylhydrazine) and the reaction mass was boiled for 4 h. The precipitate was separated by filtration, recrystallized from ethanol, and dried under vacuum.

4-[1-(2-Hydroxyethyl)-5-methyl-3-tetrafluoroethylpyrazole-4-ylazo]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (IV). Compound IV was obtained with a yield of 0.91 g (76 %); m.p., 143 – 145°C; $C_{19}H_{20}F_4N_6O_2$.

IR spectrum (ν_{max}, cm^{-1}): 3340 (OH), 1645 (C=O), 1590, 1540, 1495 (OC), 1413 (N=N *trans*-isomer), 1090 – 1130 (C–F); ^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 2.57 (s, 3H, C=C–Me), 2.60 (s, 3H, OC–Me), 3.36 (s, 3H, NMe), 3.76 (q, 2H, J 5.2 Hz, CH_2-$\underline{CH}_2$-OH), 4.21 (t, 2H, J 5.2 Hz, $C\underline{H}_2$-CH_2-OH), 5.00 (t, 1H, J 5.2 Hz, CH_2-CH_2-O$\underline{H}$), 7.30 (tt, 1H, J_1 53 Hz, J_2 6 Hz, $H(CF_2)_2$), 7.38 – 7.58 (m, 5H, Ph); ^{19}F NMR spectrum in DMSO-d_6 (δ, ppm): 23.73 (dt, 2F, J_1 53 Hz, J_2 10 Hz, $HC\underline{F}_2CF_2$), 48.42 (m, 2F, $HCF_2C\underline{F}_2$).

4-(3-Tetrafluoroethyl-5-methyl-1-phenylpyrazole-4-ylazo)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (V). Compound V was obtained with a yield of 0.74 g (62 %); m.p., 202 – 204°C; $C_{23}H_{20}F_4N_6O$.

IR spectrum (ν_{max}, cm^{-1}): 1665 (C=O), 1595, 1565, 1500 (C=C), 1545 (N=N *cis*-isomer), 1410 (N=N *trans*-isomer), 1100 – 1200 (C–F); ^{1}H NMR spectrum in $CDCl_3$, N=N *cis*/*trans* ~ 22 : 3 mixture (δ, ppm): N=N *cis*-isomer, 2.54 (s, 3H, C=C–Me), 2.63 (s, 3H, C=C–Me), 3.33 (s, 3H, NMe), 7.34 – 7.52 (m, 10H, 2Ph), 7.66 (tt, 1H, J_1 52.5 Hz, J_2 6 Hz, $H(CF_2)_2$); N=N *trans*-isomer, 2.60 (s, 3H, C=C–Me), 2.62 (s, 3H, C=C–Me), 3.32 (s, 3H, NMe), 7.34 – 7.52 (m, 10H, 2Ph); 7.66 (tt, 1H, J_1 52.5 Hz, J_2 6 Hz, $H(CF_2)_2$); ^{19}F NMR spectrum in $CDCl_3$, N=N *cis*/*trans* ~ 22 : 3 mixture (δ, ppm): N=N *cis*-isomer 22.66 (m, 2F, $HC\underline{F}_2CF_2$), 53.44 (m, 2F, $HCF_2C\underline{F}_2$); N=N *trans*-isomer, 23.50 (dt, 2F, J_1 52.5 Hz, J_2 9.8 Hz, $HC\underline{F}_2CF_2$), 46.04 (m, 2F, $HCF_2C\underline{F}_2$).

EXPERIMENTAL BIOLOGICAL PART

The acute toxicity of the synthesized compounds (in terms of half-lethal dose, LD_{50}) was determined by the conventional method [5] using intraperitoneal injections in a group of male and female white mice weighing 16 – 22 g.

The analgesic activity was studied in a group of male and female white mongrel mice weighing 16 – 22 g, which were subjected to the conventional test for acetate-induced convulsions [6]. The convulsions were induced by injections of a 0.75 % aqueous acetic acid solution (0.25 ml per 10 g animal body weight) and counted for a 10-min period of time. The synthesized compounds were administered perorally in doses (with a coefficient taking into account the molecular weight) corresponding to that of the reference drug analgin (50 mg/kg) as suspensions in a 2% starch jelly 1 h before irritant injection. The analgesic effect was evaluated by the change in the number of convulsions relative to that in the control group, where the animals received an equivalent volume of pure 2% starch jelly.

The antipyretic properties were studied in a group of male white mongrel rats weighing 180 – 240 g with a model fever induced by the intravenous injections of pyrogenal (500 MTD per kilogram body weight). The synthesized compounds were introduced by intraperitoneal injections in doses (with a coefficient taking into account the molecular weight) corresponding to that of the reference drug analgin (100 mg/kg) on the background of the maximum temperature increase (2 h after pyrogenal injection). The dynamics of temperature variations was thermometrically monitored in the rectum [8] over 3 h and compared to that in the control group, where the animals were injected with an equivalent volume of pure 2% starch jelly.

Each test was performed in a group of six animals. The experimental results were statistically processed in terms of the Student *t*-criterion [9] and the observed changes were considered as reliable for $p \le 0.05$.

The biological activity was also evaluated using a computer program package for the prediction of activity spectra of substances (PASS, Ver. 1.511) [10] in terms of the proba-

bility of the presence (Pa) or absence (Pi) of a certain type of action for a compound possessing a definite structure (see Tables 1 and 2).

It was established that 1,2,3-triketone 2-(antipyrin-4-yl)hydrazones (IIIa and IIIb) and N-(2-hydroxyethyl)-substituted pyrazole (IV) exhibit analgesic activity comparable with that of analgin, but do not possess antipyretic properties. In contrast, N-phenyl-substituted pyrazole (V) did not exhibit analgesic properties but produced certain antipyretic action two hour after administration (four hours after pyrogenal injection, see Tables 1 and 2). Fluoroalkyl-containing compounds (IIIb, IV, V) exhibit lower acute toxicity than nonfluorinated 2-(antipyrin-4-yl)- hydrazone and the reference drug analgin (Table 1).

ACKNOWLEDGMENTS

This study was supported by the Russian Foundation for Basic Research (project Nos. 03–03–33118 and 03–03–06471) and the Presidential Program of Support for Leading Scientific Schools in Russia (project no. NSh-1766.2003.3).

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