ANTIINFLAMMATORY ACTIVITY OF SOME PYRAZOLE DERIVATIVES

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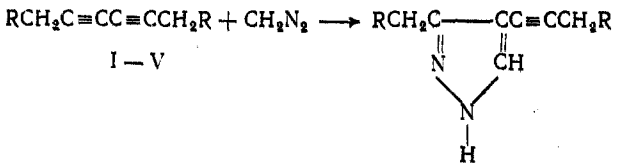
Antiinflammatory preparations are widely used in the modern clinic, as pathogenetic agents in the treatment of many illnesses and pathological processes, alone or more frequently in combination with other drugs. However many of the known antiinflammatory agents cause a range of side phenomena and complications in addition to the main effect. Consequently the search for and study of new more active antiinflammatory agents of low toxicity is one of the urgent problems of contemporary science.

It seemed of interest to us to synthesize new pyrazole derivatives and to study their antiinflammatory activity.

All compounds were obtained on the basis of the cyclization reaction of symmetrical diacetylenic esters of benzoic acid with diazomethane which was carried out at room temperature in a medium of sulfuric acid according to the scheme.



I—V

R = 4-chlorobenzoyloxy (I), 2-chlorobenzoyloxy (II), 2,4-dichlorobenzoyloxy (III), 2-iodobenzoyloxy (IV), 3-iodobenzoyloxy (V).

Physicochemical characteristics are given in Table 1.

The homogeneity of the obtained compounds was checked by TLC on Al_2O_3 of activity grade II. Structure was demonstrated by data of IR spectra and elemental analysis.

In the IR spectrum in the frequency range 3400-3300 cm^{-1} absorption bands were observed corresponding to the stretching vibrations of the NH group of the pyrazole ring, vibrations of the pyrazole ring itself were observed in the 1540-1520 cm^{-1} region.

The synthesized pyrazole derivatives were checked for toxicity and antiinflammatory properties (Table 2).

Toxicity was studied in 150 white mice of both sexes of weight 18-23 g. Preparations were administered at 1-10% in oil solutions subcutaneously. Preparations were tested in not less than six animals at each dose. The volume of introduced solution did not exceed 1 ml.

The value of the mean lethal dose (LD_{50}) was determined by the method of Litchfield and Wilcoxon at $p = 0.05$. It was established that the synthesized compounds were of low toxicity. Even at doses of 1500 mg/kg they did not cause death of animals. Experiments on the study of antiinflammatory activity were carried out on 250 white rats of both sexes of weight 120-200 g. Inflammation was caused by formalin. Substances were administered subcutaneously as an oil solution 1 h before formalin.

The activity of a preparation was compared with that of the widely known preparation amidopyrine. Determination was carried out by an oncometric method 3, 6, and 24 h after administration of formalin.

Results of a study of antiinflammatory activity are given in Table 2. It is evident from Table 2 that the synthesized compounds display antiinflammatory activity to a varying degree. The most marked activity was detected for the compound 3-(o-iodobenzoyloxymethyl)-4-(o-iodobenzoyloxy propyn-1-yl)pyrazole. At a dose of 100 mg/kg it reduced inflammation by 35.3% while amidopyrine at the same dose gave only 29.2 % reduction.

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TABLE 1. Physicochemical Characteristics of Pyrazole Derivatives

Compound	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated N, %
I	83,2	62—63	6,57 6,51	$C_{21}H_{14}O_4N_2Cl_2$	6,52
II	81,5	Oily	6,56 6,50	$C_{21}H_{14}O_4N_2Cl_2$	6,52
III	89,3	101—102	5,73 5,68	$C_{21}H_{12}O_4N_2Cl_2$	5,71
IV	92,3	34—45	4,60 4,56	$C_{21}H_{14}O_4N_2I_2$	4,57
V	89,4	Oily	4,59 4,51	$C_{21}H_{14}O_4N_2I_2$	4,57

TABLE 2. Antiinflammatory Activity and Toxicity of Pyrazole Derivatives

Compound	LD_{50} with confidence limits	Antiinflammatory activity, % dose, mg/kg		
		25	50	100
I	Administration of compound at doses up to 1500 mg/kg did not cause death of animals	14,2	20,3	24,2
II	Same	16,2	24,2	28,6
III	» »	12,3	16,6	28,3
IV	» »	30,2	34,2	35,3
V	» »	20,2	22,4	26,3
Amidopyrine	250 (221,2—282,5)	—	—	29,2

Consequently the synthesized new pyrazole derivatives possess low toxicity and a comparatively high antiinflammatory activity.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on UR-20 spectrometer (DDR) in KBr disks.

3(-(p-Chlorobenzoyloxymethyl)-4-(p-chlorobenzoyloxypropyn-1-yl)pyrazole (I). The initial diacetylenic ester[1,6-bis(p-chlorobenzoyloxy)hexa-2,4-diyne] (1.5 g) was placed in a flat-bottomed conical flask and then a freshly prepared solution of diazomethane (0.92 g: 0.02 g-mole) in ether (25 ml) was added gradually. The reaction mixture was stored in the dark at room temperature. Depending on the decoloration of the yellow color of the solution fresh portions of diazomethane were added until stability of the yellow color. After this the solvent was evaporated off and the product purified by TLC on Al_2O_3. After this the solvent was evaporated off and the product purified by TLC on Al_2O_3. The obtained product was a white crystalline substance. Yield was 1.24 g (83.2% theory), mp 62-63°C.

Under analogous conditions 3-(o-chlorobenzoyloxymethyl)-4-(o-chlorobenzoyloxypropyn-1-yl) pyrazole (II), 3-(2,4-dichlorobenzoyloxymethyl)-4-(2,4-dichlorobenzoyloxypropynyl)pyrazole (III), 3-(o-iodobenzoyloxymethyl)-4-(o-iodobenzoyloxypropyn-1-yl)pyrazole (IV), and 3-(m-benzoyloxymethyl)-4-(m-iodobenzoyloxypropynyl) pyrazole (V) were obtained.