ANTIINFLAMMATORY ACTIVITY OF 3,4-DISUBSTITUTED PYRAZOLES

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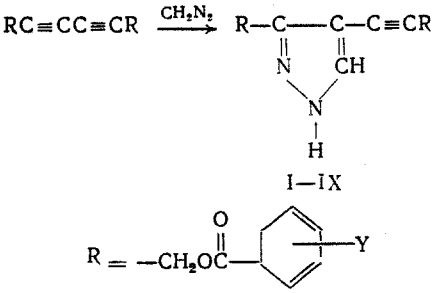
Inflammation plays a key role in the development and course of many diseases. Antiinflammatory agents are used in the prevention and treatment of inflammation; such preparations include derivatives of pyrazole, salicylic acid, indole, anthranilic acid, propionic acid, corticosteroids, and others. In particular, pyrazole derivatives are widely used, even though, as with other compounds which act similarly, they do not completely fulfil the requirements of such a drug, and often cause undesirable side effects; for example, complications of the cardiovascular, digestive, circulatory, and other systems have been reported [1, 2]. Consequently, the search for new highly effective and nontoxic antiinflammatory agents is one of the current problems of contemporary science.

Continuing our study of biologically active pyrazole derivatives, we have synthesized 9 new derivatives in the hope of finding new antiinflammatory agents. These compounds were obtained by the cyclocondensation of symmetrical diacetylene esters using diazomethane.



I: Y = H; II: Y = Br-2; III: Y = Br-4; IV: Y = NO_2-2; V: Y = NO_2-4; VI: Y = $(NO_2)_2$-3,5; VII: Y = OMe-2; VIII: Y = OMe-3; IX: Y = OMe-4.

The physicochemical constants of compounds I-IX are given in Table 1.

Individual compounds were checked by TLC on grade II Al_2O_3. The structures were confirmed by IR spectroscopy and elemental analysis.

The IR spectrum contains peaks at 3400-3300 cm^{-1} corresponding to the stretching vibrations of the NH group of the pyrazole ring, vibrations which in pyrazole itself absorb at 1540-1520 cm^{-1}.

TABLE 1. Physicochemical Constants for Pyrazole Derivatives I-IX.

Compound	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated N, %
I	88,9	43—4	7,62	$C_{21}H_{16}O_4N_2$	7,7
II	89,2	91—3	5,39	$C_{21}H_{14}O_4N_2Br_2$	5,40
III	90,5	98—100	5,41	$C_{21}H_{14}O_4N_2Br_2$	5,40
IV	90,3	58—60	12,42	$C_{21}H_{14}O_8N_4$	12,44
V	92,3	68—70	12,41	$C_{21}H_{14}O_8N_4$	12,44
VI	94,1	80—2	15,54	$C_{21}H_{12}O_{12}N_6$	15,56
VII	80,9	48—50	6,54	$C_{23}H_{20}O_6N_2$	6,57
VIII	89,3	61—2	6,55	$C_{23}H_{20}O_6N_2$	6,57
IX	91,5	73—4	6,55	$C_{23}H_{20}O_6N_2$	6,57

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TABLE 2. Antiinflammatory Activity (in %) of the Pyrazole Derivatives I-IX

Compound	Dose, mg/kg	
	100	200
I	33	20
II	8	7
III	87	26
IV	45	3
V	35	30,3
VI	27	30
VII	15	20
VIII	10	—
IX	69	13
Amidopyrine	28	...

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a UR-20 (GDR) spectrometer (KBr pellets).

3-(Benzoyloxymethyl)-4-(benzoyloxypropyl-1)pyrazole (I). To 1 g of bis(benzoyloxymethyl)diacetylene was gradually added 0.92 g of a freshly prepared solution of diazomethane in 25 ml of ethyl ether. The reaction mixture was kept in the dark at room temperature. Further portions of diazomethane solution were added until the solution had a stable yellow color. The solvent was then distilled off, and the product purified by TLC on Al_2O_3. Compound I was obtained as a yellow crystalline material, yield 88.9%, mp 43-44°C.

The remaining pyrazole derivatives were obtained by the same method.

EXPERIMENTAL (BIOLOGICAL)

The toxicity and antiinflammatory action of the pyrazole derivatives synthesized were examined (Table 2).

The activity of the compounds was studied on models of inflammation produced by injecting formalin (0.2 ml of 1% solution) under the aponeurosis of the joint of the lower part of the limb. The paw size of the experimental animals was measured oncometrically at 3, 6, 24, 48, and 72 hours after the formalin injection. Suspensions of the test compounds were given orally with a metal probe. Each compound was tested with at least 3 dosages; 2-5% solutions of the preparation were given based on 0.1 ml/100 g weight, in doses of between 100 and 200 mg/kg.

The test substances and amidopyrine were administered as described above, 3 times prior to the appearance of the inflammation, i.e. at 48, at 24 h, and at 30 min prior to the administration of the formalin. Control animals received an equivalent volume of distilled water and gum arabic suspension according to the same scheme. A known anti-inflammatory agent, amidopyrine, chemically similar to the test compounds was used for comparison: it was given at a dosage of 100 mg/kg, since, according to the literature at this dose it exhibits an appreciable antiinflammatory effect. The investigation was carried out using white rats weighing 150-200 g.

It was established that all the compounds possessed some anti-inflammatory activity; this was particularly noticeable 3 hours after injection of formalin.

Appreciable antiinflammatory activity was exhibited by compounds IX and IV; doses of 100 mg/kg of these compounds suppressed the development of edema by 69 and 45% respectively. Compound III was the most effective, and was 4 times as active as amidopyrine.

Least effective were compounds II, VII, and VIII, all of which were less active than amidopyrine. Of the compounds studied, compounds I, V, and VI were of intermediate activity, and were equal to, or slightly better than amidopyrine.

A comparative study showed that there is a relationship between the antiinflammatory activity of the pyrazole derivatives and their chemical structure. Thus, for example, compounds III and IX, which have a bromine or methoxy group in the para-position of the aromatic ring, had the highest activity. Compounds IV and V having a nitro-group in the ortho- or

para-position were less active. Compounds with a bromine in the ortho-position (II) or a methoxy-group in the meta-position (VIII) had lower antiinflammatory activity.

Thus, for this series of pyrazole derivatives, the relationship between antiinflammatory activity and chemical structure could be used for a directed synthesis of improved preparations with similar activity.

Toxicity was studied on white mice of both sexes weighing 18-23 g. The substances were injected subcutaneously as 1-10% oil solutions. All preparations were tested on at least 6 animals for each dosage. The volume of the injected solution did not exceed 1 ml.

Values of the mean lethal dose (LD_{50}) were determined by the method of Litchfied and Wilcoxon ($P = 0.05$). The compounds synthesized were found to have low toxicity: even in doses of 1500 mg/kg, the animals were not killed. The toxicity of amidopyrine is 250 (221.2-282.5) mg/kg.

Thus, the new pyrazole deirvatives that we synthesized exhibited low toxity and comparatively high antiinflammatory activity.

LITERATURE CITED

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