SYNTHESIS AND ANTIINFLAMMATORY ACTION OF 4-(BENZOYLOXYMETHYLENE)PYRAZOLES

A. G. Makhsumov, U. B. Zakirov, M. A. Talipova, A. T. Nikbaev, and A. D. Dzhuraev

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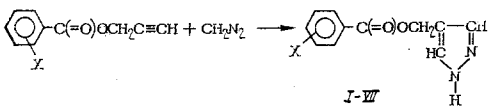
In view of the fact that a number of side effects and complications [1-3] accompany the primary action of many recognized antiinflammatory agents, the search for and study of new, more active antiinflammatory drugs of low toxicity remains one of the vital problems in modern pharmacology.

With this purpose in mind, we synthesized and tested seven compounds that are derivatives of 4-(benzoyloxymethylene)pyrazoles. They were produced by the cyclization of propargylic esters of aromatic acids with diazomethane. The reaction proceeded in a diethyl ether medium at room temperature in accordance with the following diagram:



I-VII

I: X = H; II: X = 2 = OCH_3; III: X = 4-Cl; IV: X = 2,4-Cl_2;
V: X = 3-J; VI: X = 3-NO_2; VII: X = 3,5-$(NO_2)_2$

The physicochemical characteristics of the synthesized compounds are given in Table 1.

The structure of the 4-(benzoyloxymethylene)pyrazoles was confirmed by infrared and PMR spectroscopy.

The IR spectrum of the 4-(benzoyloxymethylene)pyrazoles is characterized by the broad absorption band of the stretching vibrations of the NH group in the 3300 cm^{-1} region, and of the pyrazole C=N and C=C groups in the 1550-1540-cm^{-1} region, the carbonyl group at 1725-1730 cm^{-1}, and the phenyl ring at 1550-1600 cm^{-1}.

The protons of the —O—CH_2—group in the PMR spectra of all pyrazoles resonate in the region of 5.3-5.4 ppm. The protons of the aromatic ring resonate at 7.6-8.0 ppm, and the protons of the pyrazole ring appear at 6.65-7.9 ppm.

EXPERIMENTAL (CHEMICAL)

The infrared spectra were recorded on a UR-20 spectrophotometer as KBr pellets. The PMR spectra were recorded on a C-60-HL-type spectrometer. HMDS was the internal standard.

4-Methylenepyrazolyl-2,4-dichlorobenzoate (IV). A 2.29-g (0.01 mole) sample of the propargylic ester of 2,4-dichlorobenzoic acid was placed into an Erlenmeyer flask with a fitted stopper. Upon cooling on ice, 100 ml of a freshly distilled ether solution of diazomethane (from 2.2 g of nitrosomethylurea) was added to the mixture which was prepared at room temperature in darkness. After 48 h, the solvent with the excess diazomethane was removed

TABLE 1. Physicochemical Properties of 4-Methylenepyrazolyl-benzoates

Compound	Yield, %	mp., °C	Found, %				Calculated, %		
			C	H	N		C	H	N
I	44,0	59—60	65,31	4,86	13,74	$C_{11}H_{10}O_2N_2$	65,34	4,95	13,86
II	90,2	90—91	61,95	5,11	11,97	$C_{12}H_{12}O_3N_2$	62,06	5,17	12,06
III	83,3	103—105	55,68	3,72	11,78	$C_{11}H_9O_2N_2Cl$	55,81	3,80	11,83
IV	66,7	72—74	48,65	2,88	10,17	$C_{11}H_8O_2N_2Cl_2$	48,70	2,95	10,33
V	88,1	59—60	40,11	2,45	8,32	$C_{11}H_9O_2N_2I$	40,24	2,74	8,53
VI	98,2	80—82	53,28	3,51	16,88	$C_{11}H_9O_4N_3$	53,44	3,64	17,00
VII	97,5	83—85	45,16	2,55	19,07	$C_{11}H_8O_6N_4$	45,20	2,70	19,17

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TABLE 2. Effect of 4-(benzoyloxymethylene)pyrasoles and Amidopyrine on Formalin-Induced Inflammation

Compound	Dose, mg/kg	Average volume of rat paws, ml		Average increase in rat paw volume over initial		Antiinflammatory effect, %
		normal	3 h after formalin injection	ml	%	
I	50	0,79	1,35	0,56±0,034	70,8	17,4
	100	0,66	1,10	0,44±0,022	66,6	22,3
	200	0,73	1,22	0,49±0,023	67,1	21,8
II	50	0.81	1,44	0,63±0,034	77,7	9,4
	100	0,71	1,25	0,54±0,026	76,0	11,4
	200	0,67	1,2	0,53±0,032	79,1	7,8
III	50	0,76	1,32	0,56±0,028	73,6	14,2
	100	0,8	1,34	0,54±0,019	67,5	21,3
	200	0,68	1,15	0,47±0,018	69,1	19,4
IV	50	0,77	1,32	0,55±0,019	71,4	16,7
	100	0,69	1,12	0,43±0,022	52,3	27,4
	200	0,74	1,26	0,52±0,024	70,2	18,1
V	50	0,63	1,12	0,49±0,049	77,7	9,4
	100	0,81	1,35	0,54±0,018	66,6	22,3
	200	0,78	1,38	0,6±0,032	76,9	10,3
VI	50	0,59	1,06	0,47±0,049	79,6	7,2
	100	0,64	1,12	0,48±0,045	75,0	12,5
	200	0,67	1,18	0,52±0,039	76,1	11,3
VII	50	0,83	1,42	0,59±0,019	71	17,2
	100	0,84	1,41	0,57±0,012	67,8	20,9
	200	0,82	1,45	0,63±0,032	76,8	10,4
Amidopyrine	100	0,73	1,19	0,46±0,029	63,0	26,6

Note. Eight animals were tested in each trial.

under vacuum by a water aspirator, and the product was purified by column chromatography. The synthesized compound consisted of white crystals with a melting point 72-74°C. Yield was 1.6 g (66.7% of theoretical), R_f 0.37.

The remaining pyrazole derivatives were obtained in the same manner.

EXPERIMENTAL (BIOLOGICAL)

The synthesized pyrazole derivatives were tested for antiinflammatory activity (Table 2).

The compounds' action was examined on a model of formalin-induced inflammation. A 0.2-ml portion of a 1% formalin solution was subcutaneously injected into the talocrural joint. The volume of the experimental animal's paw was oncometrically measured three times at intervals of 3, 6, 24, 48, and 72 h prior to and after the formalin injection. A metallic probe was used to administer the test compounds in suspension form *per os*. Each compound was tested at no fewer than three dose levels. The compounds (2-5% solutions) were administered at a ratio of 0.1 ml per 100 g of body weight from 50 to 200 mg/kg.

The test substances and amidopyrine were administered in a specific pattern three times prior to the appearance of inflammation, i.e., at intervals of 48, 24 h, and 20 min prior to the formalin injection. The control animals were given an equivalent suspension of gum arabic in the same time pattern. Amidopyrine, which is chemically related to the test compounds and a recognized antiinflammatory preparation, was used as a basis for comparison. Amidopyrine was administered at a dose of 100 mg/kg since the literature data indicate that this is the dose at which amidopyrine has a pronounced antiinflammatory effect. The tests were conducted on 88 white rats ranging from 150-200 g in weight.

We found that all of the compounds possess antiinflammatory properties to one degree or another. The least active among these substances was 4-methylene pyrazolyl-m-nitrosobenzoate (VI). This preparation reduced the intensity of the inflammatory process by 14, 13.5, and 11.5% at doses of 50, 100, and 200 mg/kg, respectively. A somewhat stronger action was exhibited by 4-methylenepyrazolyl-2,4-dichlorobenzoate (IV) whose antiinflammatory action ranged between 16-17%. A more pronounced effect was exhibited by 4-methylene pyrazolyl-p-chlorobenzoate (III) and 4-methylene pyrazolyl-3,5-dinitrobenzoate (VII) whose antiimflammatory activity was 20-22.5%.

The strongest antiinflammatory properties were exhibited by 4-methylenepyrazolebenzoate (I) and 4-methylenepyrazole-o-methoxybenzoate (II). At their most effective doses they reduce the intensity of the inflammatory process by 26 to 28%, whereas amidopurine reduces that intensity by 26.6%.

A study of the chemical structure—antiinflammatory action relationship in a number of the examined compounds showed that a chlorine atom in the para position of the benzene ring and chlorine atoms in the 2,4-positions lead to a marked reduction in antiinflammatory activity. An even greater reduction in antiinflammatory activity results from the placement of the benzene ring's nitro group in the meta position, whereas an iodine atom in the meta position leads to a marked increase in antiinflammatory activity. Increased activity is also observed when the nitro group is in positions 3, 4, 5 of the benzene ring, and when a methoxy group is in the ortho position.

Thus, antiinflammatory activity is characteristic of the pyrazole benzoates. Some of them exceed the antiinflammatory action of amidopyrine.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4-ARYL (AND ARALKYL)IMINOBARBITURIC ACIDS

A. S. Zaks, S. B. Goncharenko, V. G. Voronin, E. A. Usachev, Yu. N. Portnov, Yu. M. Rabotnikov, and L. E. Pchelintseva

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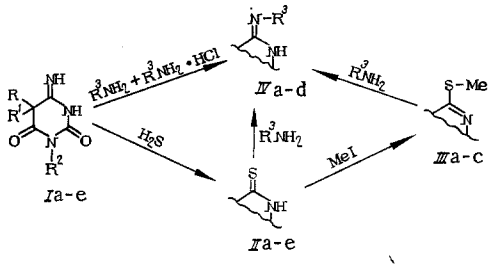
Barbituric acid derivatives, with their powerful hypnotic activity, are important synthetic drugs. Modification of the carbonyl groups in the trioxopyrimidine ring can give rise to compounds with new types of biological activity [8, 9]. For this reason, we have synthesized some 4-aryl(and aralkyl)iminobarbituric acids (IVa-w) by reacting 4-amino- (Ia-e), 4-thio- (IIa-e), or 4-methylthiobarbituric acids (IIIa-c) with aromatic and araliphatic amines, and examined their antiinflammatory and analgesic activity.

The intermediates IIa-e were obtained by reacting (Ia-e) with H_2S in solution in organic bases with heating [2], or in DMF at room temperature.

The IR spectra of IIa-e showed absorption at 3300-3080 cm^{-1} (NH stretching vibrations) and two bands in the region 1760-1670 cm^{-1} (C=O). Heating IIa-e with an excess of amine in the absence of a solvent at 160-180°C results in the formation of the imino-compounds IVa-e and IVr-v.



(Ia,e, IIa,e, IIa,c, IVa-k,v,w: R = R^1 = Et; Ic, IIc, IIIb, IVn-t: R = R^1 = Pr; Ib, IIb, IVl, m: R = Et, R^1 = Bu; Id, IId, IVu: R = R^1 = Bu; Ia-d, IIa-d, IIa,n, IVa-u: R^2 = H; Ie, IIe, IIIc, IVv,w: R^2 = Me; IVa,l,n,u,v: R^3 = Ph; IVb: R^3 = C_6H_4Me-m; IVc: R^3 = C_6H_4Me-p; IVd: R^3 = C_6H_4OMe-m; IVe,m,o: R^3 = C_6H_4OMe-p; IVf,q: R^3 = C_6H_4Cl-); IVg: R^3 = $PhCH_2$; IVh,r: R^3 = $C_6H_4NEt_2$-p; IVi: R^3 = $(CH_2)_2C_6H_4OH$-p; IVj: R^3 = 2-(indol-3-yl)ethyl; IVk,s: R^3 = $(CH_2)_2C_6H_4(OMe)_2$-3,4; (IVp,w: R^3 = C_6H_4Cl-m; IVt: R^3 = 3-pyridyl).

Branch of S. Ordzhonikidze All-Union Chemicopharmaceutical Scientific-Research Institute. Moscow Province. Perm Medical Institute.

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