TABLE 3. Antiinflammatory and Analgesic Activity of 1-(Quinoxal-2-on-3-yl)-1-phenylazoacetophenones

Compound	Antiinflammatory action (increase of rat paw volume, %)		Analgesic action (reflex time, sec)
	after 3 h	after 6 h	
I	78	74	17,6±1,5
II	81	65	20,1±1,2
III	79	87	17,1±1,8
IV	100	125	—
Control			
Formalin	148	79	—
Phenylbutazone	55	44	—
2% starch paste	—	—	13,1±1,1
Amidopyrine	—	—	27,6±1,3

β-Phenylazobenzoylpyruvic Acid Methyl Ester (IX). An aqueous solution of benzene diazonium chloride, obtained from aniline (1.74 g) and sodium nitrite (1.36 g), was added dropwise with constant stirring at 0-10° to a solution of (V) (4 g) in methyl alcohol (150 ml). Sodium acetate (3 g) was added and 1 h later the solid was filtered off. Compound IX (4.7 g) was obtained. Compounds X, XI, and XII were obtained similarly.

1-(Quinoxal-2-on-3-yl)-1-phenylazoacetophenone (I). A solution of XII (0.35 g) in diethyl ether (20 ml) was poured into a solution of IX in diethyl ether (70 ml). After 12 h the solid was filtered off. Compound I (1.1 g) was obtained. Compounds II, III, and IV were obtained similarly.

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α-PHENYL-β-HEXAMETHYLENIMINO 4-SUBSTITUTED PROPIOPHENONES AND THEIR ANTIINFLAMMATORY ACTIVITY

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It is known that the biological activity of β-aminoketones depends on the structure of the amino fragment of the molecule [1]. We have synthesized α-phenyl-β-hexamethylenimino 4-substituted propiophenones (I) with the aim of investigating this dependence on antiinflammatory activity.

Synthesis of I was achieved by the condensation of substituted phenyl benzyl ketones (II) with paraformaldehyde and hexamethylenimine in a medium of absolute ethanol or dioxan

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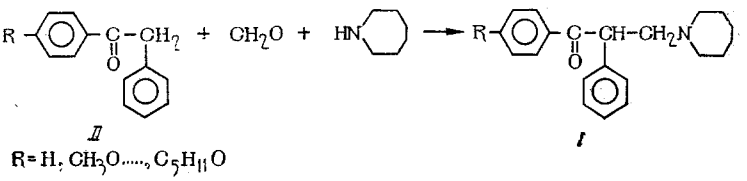
TABLE 1. α-Phenyl-β-hexamethylenimino 4-Substituted Propiophenones (I)

R	Yield, %	Melting point, °C	R_f	Found, %			Empirical formula
				C	H	N	
H	61,9	62—3	0,27	81,89	7,89	4,68	$C_{21}H_{25}NO$
CH_3O	74,2	75—6	0,26	79,09	7,86	4,57	$C_{22}H_{27}NO_2$
C_2H_5O	65,2	71—2	0,26	78,50	8,54	4,31	$C_{23}H_{29}NO_2$
C_3H_7O	69,1	68—9	0,30	79,06	9,10	3,65	$C_{24}H_{31}NO_2$
C_4H_9O	65,6	48—9	0,38	79,30	9,06	4,03	$C_{25}H_{33}NO_2$
$C_5H_{11}O$	75,0	—	0,35	79,08	9,04	3,52	$C_{26}H_{35}NO_2$

R	Calculated, %			Hydrochloride			Methiodide		
	C	H	N	melting point, °C	found, % Cl	calculated, % Cl	melting point, °C	found, % I	calculated, % I
H	82,24	8,41	4,28	110—1	9,38	9,65	206—7	26,92	27,42
CH_3O	78,33	8,30	4,15	129—30	9,41	9,49	199—200	26,58	26,51
C_2H_5O	78,65	8,31	3,98	140—2	8,83	9,15	174—6	24,96	25,43
C_3H_7O	78,86	8,48	3,83	133—6	8,90	9,08	150—2	25,30	25,02
C_4H_9O	78,91	8,73	3,67	130—2	7,90	8,53	138—9	23,50	23,71
$C_5H_{11}O$	79,16	8,93	3,54	134—5	8,50	8,23	159—61	22,99	23,67

according to the following scheme:



II

R = H, CH_3O, ..., $C_5H_{11}O$

I

It was established that the reaction proceeds better at a higher pH in dioxane. Thus, on conducting the reaction at pH 8.0-9.0, heating for 4-6 h provided a yield of aminoketone of 60-80% while at pH 1.0-2.0 the yield of aminoketone reached 30-35% with the same heating time (Table 1).

The aminoketones I were crystalline substances. Hydrochlorides and methiodides were obtained for the study of their biological properties. The homogeneity of compounds I was determined by gas–liquid chromatography (GLC) and by thin-layer chromatography (TLC).

A bathochromic shift of the absorption maximum (R = H, λ = 221 nm; R = AlkO, λ = 242-243 nm) was observed in the UV-absorption spectra of I hydrochlorides. An absorption band for the carbonyl group (1680 cm^{-1}) was observed in the IR spectra.

EXPERIMENTAL

Pharmacology

The antiinflammatory activity of the obtained compounds was studied on the acute inflammation model of rat paw on administration of 1% carrageenan (0.1 ml). The inflammatory edema of the paw in percent was determined by measuring the distance between the rear and underside parts in arbitrary units. Measurement was carried out before administering the preparation and 3 h after applying carrageenan. The antipyretic properties of preparations were studied on the model of fever caused by milk.

Milk (1 ml) was administered intravenously to rats. Substances were introduced at the time of maximum temperature increase 3 h later. The change in temperature was recorded 1.5 h after giving the preparations. A 5% solution of carboxymethylcellulose was administered to control animals.

Toxicity of compounds was determined in experiments on mice. Each compound was tested at five to six doses (three to four mice for each dose). The initial dose for therapy was taken at one sixth to one eighth the dose (MTD). Preparations were given intraperitoneally

TABLE 2. Antiinflammatory and Antipyretic Activity of Methiodides and Hydrochlorides of α-Phenyl-β-hexamethylenimino 4-Substituted Propiophenones

R	MTD, mg/kg	Fall in temperature, deg (dose 25 mg/kg)	Change in carrageenan edema, % control	
			25 mg/kg	10 μg/kg
		Methiodides		
	170	1,1±0,46 (<0,01)	80 (<0,25)	137,7
CH_3O	170	1,73±0,37 (<0,001)	127	102
C_2H_5O	180	2,0±0,14 (<0,001)	94	110
C_3H_7O	150	1,7±0,45 (<0,001)	57 (0,02)	96
C_4H_9O	180	1,4±0,18 (<0,001)	50 (0,05)	129
$C_5H_{11}O$	180	1,8±0,46 (<0,001)	75 (0,01)	80,4 (0,05)
		Hydrochlorides		
H	200	No fall	123	—
CH_3O	120	Ditto	200	137,7
C_2H_5O	150	"	111,6	102
C_3H_7O	300	"	107,5	—
C_4H_9O	200	"	116	129
$C_5H_{11}O$*	300	"	87	—
Control	—	0,18±0,07	100	100

Note. P value is given in parentheses.
*At a dose of 50 mg/kg preparations had no action on fever caused by milk or on carrageenan edema.

in 0.3 ml 5% carboxymethylcellulose solution.

A comparative study of the antiinflammatory and antipyretic properties of the methiodic and hydrochloride derivatives of α-phenyl-β-hexamethylenimino 4-substituted propiophenones showed that all the methiodides possessed antipyretic properties. Of them the propoxy, butoxy, and amyloxy derivatives suppressed inflammatory edema at a dose of 25 mg/kg. The hydrochlorides of the same compounds did not disclose antiinflammatory or antipyretic action (Table 2).

Chemistry

Analysis by GLC was carried out on a Khrom-4 chromatograph with a flame ionization detector. Stationary phase was polyethylene glycol (PEG) 6% applied to chromaton (0.2-0.25 mm) and treated with 1% potassium hydroxide solution. Column operating temperature was 160-180°C, length 1.2 m, diameter 3 mm; carrier gas (nitrogen) supply rate was 30-40 ml/min, sensitivity was 1:50.

TLC was carried out on silica gel layers bound with gypsum in the solvent system butanol—ethanol—acetic acid—water (8:2:1:3). Visualization was with iodine vapor.

Melting points were determined on a Boétius micro hot stage.

IR spectra were taken on a UR-20 spectrophotometer in Nujol mulls.

4-Substituted Phenyl Benzyl Ketones. These compounds were obtained by the method described in the literature [2].

α-Phenyl-β-hexamethylenimino 4-Substituted Propiophenones. A mixture of II (0.1 mole), paraformaldehyde (4.15 g: 0.15 mole), and hexamethylenimine (14.85 g: 0.15 mole) in absolute ethanol was boiled for 6-7 h. After distilling off the solvent diluted (1:1) hydrochloric acid was added to the residue to pH 1.0. The mixture was twice extracted with ether. A solution (100 ml) of 40% sodium hydroxide was added to the aqueous layer. The aminoketone was either filtered off and recrystallized from a 1:1 mixture of ethyl acetate—ligroin or was extracted with ether and the extract dried over anhydrous sodium sulfate. After distill-

ing off the ether the residue was reconverted into the hydrochloride. Constants are given in Table 1.

Methiodides of α-Phenyl-β-hexamethylenimino 4-Substituted Propiophenones. A mixture of an ether solution of α-phenyl-β-hexamethylenimino 4-substituted propiophenone (0.01 mole) and methyl iodide (0.01 mole) was kept at room temperature for 24 h. The solid which separated was filtered off and washed with absolute ether (see Table 1).

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IMIDAZOLES.

XII. SYNTHESIS OF SUBSTITUTED BENZYLTHIOALKYLIMIDAZOLINES

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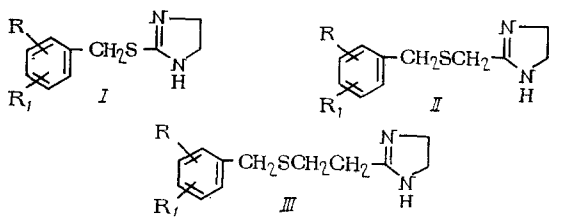
In order to test them for hypotensive properties, we have previously obtained 2-benzylimidazolines substituted with halogen, alkoxy, and nitrogroups in the benzyl radical [1, 2].

This paper describes the preparation and examination of imidazolines (I-III) in which the aryl substituent and the heterocycle are separated by carbon and sulfur atoms, which according to the literature [3-7] often results in modification of the active compounds.



*Deceased.

TABLE 1. Substituted Benzylthioalkylimidazolines

Compound	R	R_1	Yield, %	Melting point, deg	Found, %		Molecular formula	Calculated %		Hydrochloride, mp, deg
					N	S		N	S	
Ia*	4-C_3H_7O	H	89,0	99—100	11,21	12,50	$C_{13}H_{18}N_2OS$	11,19	12,81	115—6
Ib*	4-CH_3O	3-CH_3O	88,2	106—7	10,87	12,43	$C_{12}H_{16}N_2O_2S$	11,10	12,71	192—3
Ic	4-CH_3O	3-Cl	86,6	108—9	10,78	12,20	$C_{11}H_{13}ClN_2OS$	10,91	12,49	226—8
Id*	4-C_3H_7O	3-Cl	87,2	70—1	10,01	10,98	$C_{13}H_{17}ClN_2OS$	9,84	11,26	152—3
Ie*	4-CH_3O	3-Br	89,7	124—5	9,44	10,39	$C_{11}H_{13}BrN_2OS$	9,30	10,64	231—2
If*	4-C_3H_7O	3-Br	86,8	83—4	8,82	9,85	$C_{13}H_{17}BrN_2OS$	8,51	9,74	165—6
Ig	2-CH_3O	5-Br	90,0	133—4	9,32	10,51	$C_{11}H_{13}BrN_2OS$	9,30	10,64	235—6
Ih	2-C_2H_5O	5-Br	85,1	108—10	8,81	9,85	$C_{12}H_{15}BrN_2OS$	8,89	10,17	220—1
Ii	2-C_3H_7O	5-Br	87,8	103—4	8,23	9,50	$C_{13}H_{17}BrN_2OS$	8,51	9,74	174—5

*Biological activity examined.

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