1,2,6-Trimethyl-4-(2-nitrophenyl)-3,5-bis(ethoxycarbonyl)pyridinium Perchlorate (IIIh). This compound had mp 158-159°C (from isopropyl alcohol). PMR spectrum (d_6-DMSO): 0.75 (t, 6H) and 3.90 (q, 4H, 3- and 5-OCH_2CH_3); 2.78 (s, 6H, 2- and 6-CH_3); 4.09 (s, 3H, 1-CH_3), 7.08-7.29 (m, 1H), 7.63-7.86 (m, 2H), and 8.13-8.35 ppm (m, 1H, C_6H_4).

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SYNTHESIS OF 5-HYDROXY- AND 5-ACYLHYDRAZINOPYRAZOLIDINES BY THE REACTION OF β-SUBSTITUTED HYDRAZIDES WITH α,β-UNSATURATED ALDEHYDES AND THEIR BIOLOGICAL ACTIVITY

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The reaction of β-substituted hydrazides with alkenals (acrolein, methacrolein, crotonaldehyde, and cinnamaldehyde) serves as a method for the synthesis of the corresponding 1-acyl-5-hydroxypyrazolidines and, in a number of cases, 1-acyl-5-acylhydrazinopyrazolidines. Some of the 1-acyl-5-hydroxypyrazolidines obtained have antiphlogistic activity.

It is known [1, 2] that 1,2-dimethyl- and 1-methyl-2-phenylhydrazines usually form 3-pyrazolines upon reaction with α,β-unsaturated carbonyl compounds. In individual cases Jacquier and co-workers [3, 4] have observed the formation of hydroxypyrazolidines — cyclic semihydrazinals.

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TABLE 1. 5-Hydroxy- (I-XXI) and 5-(β-Acylphenylhydrazino)pyrazolidines (XX-XXVI)

Compound	R¹	R²	R³	R⁴	mp, °C or bp, °C (mm)	PMR spectrum, δ, ppm (multiplicity, J, Hz)								Yield, %
						R¹	R²	R³(R⁴)	3-H	4-H	5-H	OH(NH)	solvent	
I	Me	*t*-Bu	H	H	58—60[a]	2,00 (s)	1,10 (s)	—	1,8—3,4 (m)		5,79 (dd, 5,0; 7,0)	5,18 (br.s)	CCl_4	89
II	Me	CH_2Ph	H	H	79—80[a]	1,95 (s)	3,96 (s); 7,3—7,5 (m)	—	2,1—3,4 (m)		5,92 (dd, 4,5; 5,5)	4,75 (br.s)	$CDCl_3$	90
III	Et	Ph	H	H	220—222[b]	1,00 (t, 7,0); 2,45 (q, 7,0)	7,0—7,5 (m)	—	3,3—3,6 (m)	2,2—2,7 (m)	6,7—6,9 (m)	5,30 (d, 4,0)	$CDCl_3$	17
IV	OEt	*i*-Pr	H	H	—[c]	1,22 (t, 7,0); 3,9—4,4 (m, AB part of an ABX_3 system)	1,00 (d, 6); 2,8—3,6 (m)	—	—[d]	2,0—2,3 (m)	5,77 (dd, 4,5; 6,0)	4,90 (br.s)	$CDCl_3$	75
V	CH_2Ph	*i*-Pr	H	H	78—80[a]	3,97; 3,43 AB system, 13,5); 7,0—7,3 (m)	1,06 (d, 6,0); 1,09 (d, 6,0); 3,14 (m, 6,0)	—	2,1—2,6 (m)	1,9—2,1 (m)	5,74 (dd, 5,5; 6,5)	4,93 (br.s)	CCl_4	80
VI	CH_2Ph	Ph	H	H	117[e]	4,00 (s); 7,0—7,3 (m)		—	3,3—3,7 (m)	2,0—2,2 (m)	5,7—5,9 (m)	4,85 (br.s)	$CDCl_3$	37
VII	Ph	*i*-Pr	H	H	96—97[a]	7,1—8,0 (m)	0,78 (d, 7,0); 0,92 (d, 7,0); 2,0—3,6 (m)	—	2,0—3,6 (m)		5,94 (dd, 4,0; 6,0)	4,62 (br.s)	CCl_4	88
VIII	Ph	CH_2Ph	H	H	[10]									
IX	H	*i*-Pr	Me	H	[8][f]									
X	H	*t*-Bu	Me	H	70[f]	8,08 (s)	1,08 (s)	0,90 (d, 6,0)	3,53 (ddq, 2,0; 6,0; 6,0)	1,93 (ddd, 2,0; 7,5); 2,17 (ddd, 6,0; 5,7); J_{gem}=13,5	5,73 (dd 5,7; 7,5)	4,68 (br.s)	CCl_4	75
XI	Me	Et	Me	H	118—119 (0,7)	2,03 (s)	0,95 (t, 7,0); 2,83 (AB part of an ABX_3 system)	0,90 (d, 6,5)	3,35 (ddq, 1,8; 6,5; 6,5)	1,7—1,9 (m); 2,1—2,3 (m)	5,84 (dd, 4,5; 7,0)	not localized	CCl_4	76
XII	Me	Pr	Me	H	94—95 (0,08)	2,00 (s)	0,98 (t, 7,0); 1,65 (m); 2,88 (t, 7,0)	0,90 (d, 6,5)	3,50 (ddq, 1,5; 6,5; 6,5)	2,0—2,4 (m); 1,7—2,0 (m)	5,85 (dd, 5,0; 7,0)	5,60 (br.s)	CCl_4	70

XIII	Me	*i*-Pr	Me	H	79,5—80,5[d]	2,00 (c)	0,88 (d, 6,0); 1,04 (d, 6,0); 3,15 (sept., 6,0)	1,06 (d, 7,0)	3,48 (ddq., 1,2; 6,5; 7,0)	1,7—2,0 (m); 2,0—2,4 (m)	5,85 (dd, 4,5; 7,0)	5,16 (br.s)	CCl_4	86
XIV	Me	Ph	Me	H	108[a]	1,95 (s)	6,8—7,3 (m)	1,24 (d, 7,0)	4,00 (m, 4,0; 7,0)	2,0—2,4 (m)	6,07 (m, 3,0; 6,0)	5,40 (d, 3,0)	$CDCl_3$	60
XV	Et	Ph	Me	H	103[g]	1,05 (t, 7,0); 2,20 (kB, 7,0)	7,0—7,3 (m)	1,30 (d, 7,0)	4,00 (ddq, 2,0; 7,0; 7,0)	2,2—2,8 (m)	6,10 (m, 3,0; 6,0)	5,20 (d, 3,0)	$CDCl_3$	21
XVI	Ph	*i*-Pr	Me	H	87—89[a]	7,0—7,2 (m); 7,5—8,0 (m)	0,70 (d, 6,0); 1,13 (d, 6,0); 3,00 (m, 6,0)	0,92 (d, 6,5)	3,55 (ddq., 1,5; 6,5; 6,5)	1,96 (ddd, 1,5; 6,5); 2,21 (ddq, 4,5; 6,5); Jgem = 13.5	5,96 (dd., 4,5; 6,5)	5,05 (br.s.)	CCl_4	92
XVII	Ph	CH_2Ph	Me	H	126—127[a]	6,9—7,7 (m)	4,18 (c)	0,98 (d, 7,0)	3,50 (ddq., 1,5; 7,0; 7,0)	1,80 (m, 1,5; 6,0); 2,55 (m) 7,0; 5,5)	6,42 (add, 4,0; 5,5; 6,0)	5,09 (d, 4,0)	C_6D_6	83
XVIII	CH_2Ph	*i*-Pr	Me	H	62—63[a]	3,52; 3.95 (AB system 14,5); 7,08 (m)	0,98 (d, 7,0); 1,12 (d, 7,0); 3,08 (d, 7,0)	0,85 (d, 6,5)	3,44 (ddq., 1,5; 7,0; 6,5)	1,6—1,9 (m); 2,0—2,5 (m)	5,82 (dd., 4,5; 7,0)	5,24 (br.s)	CCl_4	72
XIX	H	*i*-Pr	H	Me	49—51[e]	8,21 (d, 1,0)	0,98 (d, 7,0); 1,01 (d, 7,0); 3,09 (m, 7,0)	1,00 (d, 7,0)	3,20 (m 6,0); Jgem = 12,0	2,50 (m 6,0; 7,0; 8,0)	5,35 (d, 8,0)	5,20 (br.s)	CCl_4	84
XX	Ph	CH_2Ph	H	Me	104—105[a]	6,9—7,8 (m)	3,95 (s)	1,08 (d, 7,0)	2,5—3,3 (m)		5,42 (m 3,0; 6,0)	5,20 (d, 3,0)	d_6-DMSO	65
XXI	Me	Ph	Ph	H	229—230[a]	2,05 (s)	6,9—7,6 (m)		3,6—4,0 (m)	2,2—2,8 (m)	6,1—6,3 (m)	5,70 (d, 4,0)	$CDCl_3$	28
XXII	Me	Ph	H	H	183—186[b]	1,20 (s); 2,90 (s)	7,1—8,0 (m)	—	3,7—4,0 (m)	2,2—2,5 (m)	6,9—7,1 (m)	5,50 (br.s)	$CDCl_3$	41
XXIII	Me	Ph	Me	H	169[a]	1,53 (s); 2,15 (s)	6,9—7,7 (m)	1,46 (d, 6,0)	4,1—4,4 (m)	2,1—2,3 (m); 2,5—2,7 (m)	6,6—7,0 (m)	5,87 (br.s); 6,36 (br.s)	$CDCl_3$	38
XXIV	Et	Ph	Me	H	198b	2,05 (s); 2,15 (s)	7,0—7,6 (m)		5,0—5,3 (m)	2,6—2,8 (m); 3,0—3,3 (m)	6,8—7,2 (m)	5,90 (br.s); 6,40 (br.s)	$CDCl_3$	20
XXV	Et	Ph	H	H	144[a]	1,00 (t, 7,0); 2,40 (q, 7,0)	6,8—7,4 (m)	—	3,5—3,7 (m)	2,2—2,4 (m); 2,6—2,7 (m)	6,5—6,7 (m)	5,15 (br.s); 5,90 (br.s)	$CDCl_3$	20
XXVI	Et	Ph	Me	H	114—115[h]	1,00 (t, 7,0); 2,15 (q, 7,0)	6,9—7,4 (m)	1,47 (d, 6,0)	4,0—4,2 (m, 7,0)	2,2—2,4 (m); 2,7—2,9 (m)	6,7—6,9 (m)	5,85 (br.s); 6,20 (br.s)	$CDCl_3$	18

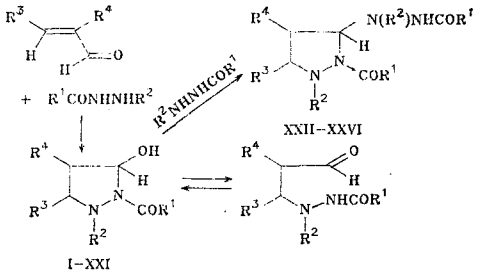
[a] From benzene with hexane.
[b] From benzene.
[c] Isolated by chromatography with a column packed with Al_2O_3 by elution with ether.
[d] Overlapping of the 3-H and $CH(CH_3)_2$ signals
[e] From a mixture of chloroform with hexane.
[f] From hexane.
[g] From a mixture of ether with hexane.
[h] From a mixture of propanol with ether.

On the other hand, 3-hydroxypyrazolidines were the principal transformation products in the reaction of cyclic hydrazides of dicarboxylic acids (diethylmalonic, succinic, maleic, and phthalic acids) with unsaturated aldehydes; they underwent dehydration to the corresponding 3-pyrazolines only under severe conditions [5]. The same cyclic hydrazides reacted with methyl vinyl ketone to give only products of addition to the C=C bond, viz., β-hydrazido ketones [5, 6]. Compounds of the same type are formed in the condensation of methyl vinyl ketone with hydrazobenzene and with β-alkyl(aryl)hydrazides [7].

In addition to this, we have found that the corresponding 5-hydroxypyrazolidine is formed in the condensation of 1-formyl-2-isopropylhydrazine with acetaldehyde [8]. The structure of this compound corresponds formally to the product of addition of the starting hydrazide to crotonaldehyde. A more profound transformation was observed in the reaction of acetaldehyde and crotonaldehyde with hydrazobenzene, as a result of which a substance in which the OH group of the hydroxypyrazolidine is replaced by a hydrazobenzene residue is formed [9]. We have recently found that 1-benzoyl-2-benzylhydrazine reacts virtually quantitatively with acrolein to give the corresponding 5-hydroxypyrazolidine, which in polar media exists in equilibrium with the open β-hydrazido aldehyde form [10].

It follows from the material set forth above that the condensation of α,β-unsaturated aldehydes with hydrazides requires a systematic study. In the present research we studied the reaction of β-alkyl(aryl)hydrazides with acrolein, methacrolein, crotonaldehyde, and cinnamaldehyde.

We found that this transformation is a convenient method for the preparation of the corresponding 1-acyl-5-hydroxypyrazolidines (I-XXI, Table 1). Brief heating of the reagents (with or without a solvent) is the optimal condition for their synthesis. In the case of 1-formyl-2-isopropylhydrazine it was shown that the corresponding 5-hydroxypyrazolidine IX is also formed in the reaction of the hydrazide with acetaldehyde and acetaldol, although in lower yields.



The nature of the substituents in the alkylhydrazides has little effect on the course of the reaction, whereas substitution in the aldehyde, particularly at the carbon atom in the α position, leads to a substantial increase in the reaction time and a decrease in the yield of the final product.

The reactions with phenylhydrazides present a more complicated situation. Thus, in addition to the corresponding 5-hydroxy derivatives, 5-(1-phenyl-2-acylhydrazino)pyrazolidines (XXII-XXVI, Table 1) are formed in the reaction of 1-acetyl- and 1-propionyl-2-phenylhydrazines with crotonaldehyde or cinnamaldehyde, as well as with acrolein in the case of 1-phenyl-2-propionylhydrazine. The use of methylene chloride and aromatic hydrocarbons as the solvent and an increase in the reaction time and temperature lead to an increase in the yields of the hydrazino derivatives. However, in the case of the reactions of hydrazobenzene with acrolein and crotonaldehyde only the corresponding 5-hydrazinopyrazolidines (XXVII and XXVIII, see the experimental section) are formed. Let us additionally point out that the product of condensation of hydrazobenzene with crotonaldehyde (XXVIII) is identical to the compound previously obtained in [9]. The formation of hydrazino derivatives from phenylhydrazides is evidently explained by the same reasons as in the case of hydrazobenzene [9]. The reactivities of phenylhydrazides also depend to a considerable degree on the nature of the acyl residue and are determined by both electronic and steric factors. Thus the yield of the corresponding 5-hydroxypyrazolidine VI in the reaction of acrolein with phenylacetic acid phenylhydrazide is substantially lower than usual; a 5-hydrazino derivative of pyrazolidine is not formed in this case. 1-Pivalyl-2-phenyl-2-hydroxypyrazolidine is not formed in the reaction of pivalic acid phenylhydrazide; a product of symmetrization of the hydrazide, viz., 1,2-dipivalylphenylhydrazine (XXIX, see the experimental section), was isolated in only low yield.

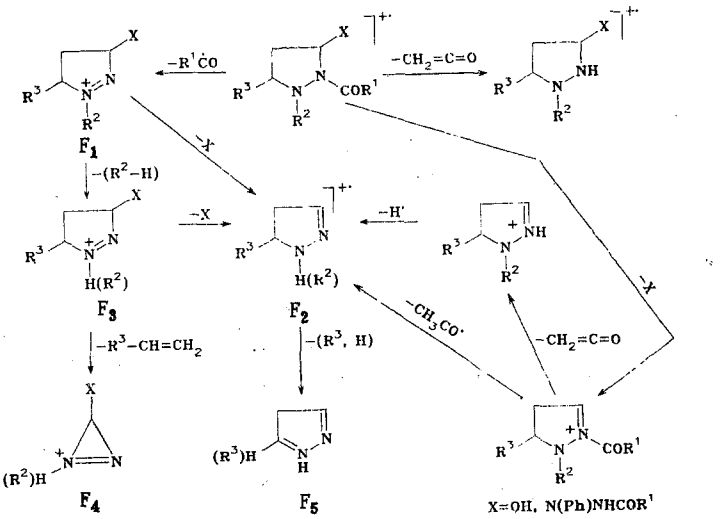
TABLE 2. ^{13}C NMR Spectra of Solutions of II, IV, VII, XIII, XIV, XIX, and XX in $CDCl_3$

Compound	Chemical shifts, ppm				
	C=O	$C_{(5)}$	$C_{(3)}$	$C_{(4)}$	other signals
II	171,7	81,2	51,4	32,2	136,9, 129,3, 128,1, 127,4 (Ar); 61,7 ($CH_2C_6H_5$), 20,8 (CH_3)
IV	155,8	82,6	61,1	32,7	54,6 [$CH(CH_3)_2$], 48,6 (OCH_2), 19,9 [$CH(CH_3)_2$], 13,9 (CH_3CH_2O)
VII	168,8	82,9	48,9	32,8	135—127,4 (Ar), 55,2 [$CH(CH_3)_2$], 21,3, 20,5 [$CH(CH_3)_2$]
XIII	173,3	80,4	56,4[a]	38,7	54,8 [$CH(CH_3)_2$][a], 21,1, 19,9, 20,1 ([$CH(CH_3)_2$], 3-CH_3), 20,4 (CH_3C=O)
XIV	173,9	81,1	63,5	39,8	151,4, 130,0, 122,3, 117,0 (Ar), 20,7 (CH_3C=O), 20,1 (3-CH_3)
XIX	163,6	85,8	57,4[a]	40,2	54,5 [$CH(CH_3)_2$][a], 20,7, 20,6 [$CH(CH_3)_2$], 14,7 (4-CH_3)
XX	167,6	88,7	61,7[a]	39,2	137,5, 129,4, 128,6, 127,7, 127,2, 126,5 (Ar), 57,4[a] ($CH_2C_6H_5$), 14,5 (4-CH_3)

[a]There is no strict assignment of the $C_{(3)}$ and $CH(CH_3)_2$ signals in the spectra of XIII and XIX and of the $C_{(3)}$ and $CH_2C_6H_5$ signals in the spectrum of XX.

It is noteworthy that, in contrast to 1-benzoyl-2-benzyl-5-hydroxypyrazolidine (VIII) [10], in all of the remaining cases we did not detect ring-chain tautomerism even when we used polar solvents (acetone, methanol, and DMSO) in the recording of the ^1H and ^{13}C NMR spectra of these compounds. In this respect, the products of condensation of hydrazides with unsaturated carbonyl compounds behave like o-acylbenzamide derivatives [11], which exist in the cyclic form when an aldehyde group is present and in the linear form in the case of ketone derivatives. In other words, the ring-chain equilibrium in the case under consideration is shifted so strongly to favor the cyclic tautomer that the linear isomer is not detected.

The cyclic structure of the compounds obtained* is confirmed by data from the IR spectra, in which absorption of an OH group at 3270-3440 cm^{-1} is absent. Magnetic nonequivalence of the prochiral substituents attached to the nitrogen atoms, which is due to the presence of an enantiotopic center, viz., the $C_{(5)}$ atom, is observed in the PMR spectra (Table 1). In a number of cases the signal of the OH group of the 5-hydroxypyrazolidines is a doublet (J = 3-4 Hz) due to coupling with the 5-H proton, which resonates at significantly stronger field (∿5-6 ppm) than one might have expected for the "aldehyde" proton of the linear isomer. As expected, the signal of the $C_{(5)}$ atom in the ^{13}C NMR spectra (Table 2) lies at ∿80 ppm.



*The peculiarities of their three-dimensional structures will be the subject of a separate publication.

TABLE 3. Mass Spectra of II, IX, XIII, XIV, and XXIII

Compound	m/z values (relative intensities in percent of the maximum peak)
II	220 (18,4), 178 (28,7), 177 (100,0), 162 (19,5), 161 (18,4), 133 (48,3), 132 (21,8), 129 (19,5), 107 (44,8), 105 (25,3), 92 (63,2), 91 (93,1), 87 (93,1), 77 (19,5), 65 (69,0), 60 (36,0)
IX	172 (25,0), 157 (18,1), 144 (5,6), 143 (59,3), 127 (8,2), 115 (10,6), 111 (13,2), 101 (100,0), 99 (8,9), 98 (17,2), 87 (27,0), 85 (27,0), 84 (15,7), 83 (12,1), 71 (15,0), 69 (19,1)
XIII	186 (8,9), 144 (10,1), 143 (72,9), 129 (11,1), 126 (1,3), 111 (12,0), 101 (100,0), 99 (9,9), 87 (4,1), 85 (9,2), 84 (8,7), 83 (12,7), 69 (7,1), 59 (10,7), 56 (13,5)
XIV	220 (84,0), 178 (86,7), 177 (100,0), 163 (78,3), 161 (24,0), 160 (58,0), 145 (42,0), 136 (39,1), 135 (82,3), 118 (78,4), 117 (78,0), 93 (36,1), 92 (62,0), 91 (40,1)
XXIII	203 (16,1), 161 (100,0), 160 (33,2), 150 (5,0), 145 (15,9), 119 (4,0), 118 (18,3), 108 (4,0), 107 (5,1), 104 (6,5), 97 (4,0), 91 (6,1), 77 (78,4)

The mass-spectral fragmentation (see the scheme and Table 3) of the compounds obtained depends substantially on the nature of the substituents in the 2 and 5 positions of the pyrazolidine ring and is determined primarily by the presence of an acyl residue at the $N_{(1)}$ atom. Thus in the case of 5-hydroxypyrazolidines the molecular ion initially always loses an acyl residue, as a result of which an F_1 ion is formed.* This ion subsequently loses either a hydroxy group (the principal fragmentation pathway when R^2 = Ph) or the olefin corresponding to substituent R^2 with hydrogen transfer to the nitrogen atom (R^2 = Alk) with the formation of F_2 and F_3 ions; the F_3 ion gives the maximum peak in the spectrum in this case. The elimination of an OH group from the F_3 ion leads to the F_2 ion. The F_3 ion also eliminates a molecule of olefin (destruction of the ring at the 1—5 and 2—3 bonds) to give the F_4 ion. This fragmentation is of low intensity in the case of the 2-alkyl derivatives but becomes extremely substantial in the case of 2-phenyl-substituted 5-hydroxypyrazolidines. The F_2 ion loses a substituent from the 3 position (R^3 or H) to give an intense isopyrazolium ion (F_5).

In contrast to 5-hydroxypyrazolidines, the 5-hydrazino-substituted derivatives do not give molecular-ion peaks in their mass spectra. The peak of the ion corresponding to the loss of a hydrazine substituent, which subsequently eliminates an acyl residue to give the F_2 ion, which has maximum intensity, has the maximum mass in the spectra. The mass spectrum of XXIII is presented as a typical example in Table 3; the character of the fragmentation of the remaining compounds is extremely similar.

In connection with the fact that many derivatives of pyrazolone and pyrazolidine have antiphlogistic activity [12, 13] (the preparations amidopyrine, antipyrine, analgin, butadion, etc.), it seemed of interest to study some of the compounds obtained (V, X, XIV, XXIII, and XXIV) in this respect as compared with the most active preparation of this group, viz., butadion, which is widely used in medical practice. It is known that undesirable side effects develop when the latter is used, and the search for more active and less toxic preparations with this type of activity is therefore timely. Despite the closeness of the chemical structures of the substances, it was found that their toxicities differ. The least toxic compound was 1-acetyl-2-phenyl-3-methyl-5-(1-phenyl-2-acetylhydrazino)pyrazolidine (XXIII), the LD_{50} of which is higher by a factor of four than that of butadion, and the most toxic compound was hydroxypyrazolidine X (LD_{50} = 70 mg/kg, i.e., lower by a factor of 3.5 than that of the control compound). The toxicities of the remaining compounds are close to the toxicity of the control compound. The products of condensation of 1-acetyl-2-phenylhydrazine with crotonaldehyde, viz., XIV and XXIII, which have a favorable effect on both the exudative and proliferative phases of the inflammatory process, display the highest antiphlogistic activity, which is close to the activity of butadion. The other compounds either do not have antiphlogistic activity or have less activity than butadion.

The detection among the synthesized compounds of substances that have pronounced antiphlogistic activity and low toxicity creates prerequisites for further research in this direction.

*The M — 17 ion is always present in the spectra; however, its intensity is low.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene were recorded with a UR-20 spectrometer. The PMR spectra were recorded with XL-100 and Tesla BS-497 spectrometers (100 MHz) with hexamethyldisiloxane as the internal standard; the ^{13}C NMR spectra were recorded with a CFT-20 spectrometer (20 MHz). The mass spectra were obtained with a CH-6 spectrometer with direct introduction of the substances into the ion source at 30-70°C and an ionizing voltage of 70 eV. The course of the reactions and the purity of the compounds were monitored by thin layer chromatography (TLC) on Silufol UV-254 plates in a benzene–ethyl acetate system (2:3) and on activity II aluminum oxide in chloroform–methanol (50:1) and petroleum ether–ether (5:2) systems.

The starting hydrazides were obtained by the methods in [8, 14-16]. The aldehydes were distilled immediately prior to the reaction.

The constants, yields, and physicochemical characteristics of the compounds obtained are presented in Tables 1-3.

1-Acyl-5-hydroxypyrazolidines (I, II, IV-XXI). A 10-20 mmole sample of the alkenal was added to 10 mmole of the corresponding hydrazide in 20 ml of the solvent (ether, methylene chloride, or benzene)* while maintaining the temperature at no higher than 20°C. The course of the reaction was monitored by TLC, and, when necessary, the reaction mixture was refluxed until complete conversion of the starting hydrazide was realized. The 2-phenyl-5-hydroxypyrazolidines were obtained by refluxing a mixture of the starting substances (in the case of acrolein) or by heating to 70°C (in the case of crotonaldehyde) for 1 h. The volatile components were evaporated *in vacuo*, and the residual mass was distilled or recrystallized from a suitable solvent. If the residue did not crystallize immediately, 10-20 ml of ether was added, and the mixture was cooled with dry ice.

1-Acyl-5-acylhydrazinopyrazolidines (XXII-XXIV, XXVI). A mixture of 10 mmole of phenylhydrazide, 20-30 mmole of the unsaturated aldehyde, and 10 ml of the solvent (benzene in the case of XXII, XXIII, and XXVI; toluene in the case of XXIV) was refluxed (for 5 h in the case of XXII and XXIII, for 10 h in the case of XXIv, and for 40 h in the case of XXIV, XXVI), during which the course of the reaction was monitored by TLC. The solvent and excess aldehyde were evaporated *in vacuo*, 10 ml of ether was added to the residue, and the mixture was cooled with dry ice. The precipitate was purified by recrystallization.

1-Propionyl-2-phenyl-5-hydroxypyrazolidine (III) and 1-Propionyl-2-phenyl-5-(1-phenyl-2-propionylhydrazino)pyrazolidine (XXV). A mixture of 2 g (12 mmole) of 1-phenyl-2-propionylhydrazine and 0.9 ml (15 mmole) of acrolein in 20 ml of methylene chloride was refluxed for 15 h, after which the solvent was removed by distillation, and 20 ml of ether was added. The precipitated III was separated, and hexane was added to the mother liquor until it became slightly turbid. Cooling with dry ice yielded XXV.

1,2-Diphenyl-3-(1,2-diphenylhydrazino)pyrazolidine (XXVII). A mixture of 4.6 g (25 mmole) of hydrazobenzene and 2.1 ml (35 mmole) of acrolein was heated at 50°C for 1 h until it became completely homogeneous, after which it was cooled, and the solidified mass was recrystallized from a mixture of benzene with hexane to give 4.6 g (91%) of a product with mp 168-169°C. PMR spectrum ($CDCl_3$): 6.1-7.6 (20H, m, Ar), 5.68 (1H, dd, 3-H, J_{34} = 6.0, $J_{34'}$ = 6.5 Hz), 5.25 (1H, s, NH), 3.5-4.0 (2H, m, 5-H), and 2.4-2.6 ppm (2H, m, 4-H). Found: C 80.1; H 6.5; N 13.7%. $C_{27}H_{16}N_4$. Calculated: C 79.8; H 6.4; N 13.8%.

1,2-Diphenyl-3-(1,2-diphenylhydrazino)-5-methylpyrazolidine (XXVIII). The reaction of 4.6 g (25 mmole) of hydrazobenzene and 2.8 g (40 mmole) of crotonaldehyde under the same conditions gave 4.4 g (84%) of XXVIII with mp 145-146°C (benzene–hexane). PMR spectrum ($CDCl_3$): 6.1-7.4 (20H, m, Ar), 5.72 (1H, dd, 3-H, J_{34} = 2.6, $J_{34'}$ = 5.0 Hz), 5.17 (1H, s, NH), 4.20 (1H, dq, 5-H, J_{45} = J_{5-CH_3} = 7 Hz), 2.60 (1H, ddd, 4-H, J_{34} = 2.6, J_{45} = 7.0, J_{gem} = 14.0 Hz), 2.15 (1H, ddd, 4-H, J_{34} = 5.0, J_{45} = 7.0, J_{gem} = 14.0 Hz), and 1.31 ppm (3H, d, 5-CH_3, J = 7.0 Hz). According to the data in [9], this compound had mp 151°C.

1,2-Dipivalyl-1-phenylhydrazine (XXIX). A solution of 0.96 g (5 mmole) of 1-phenyl-2-pivalylhydrazine and 0.7 ml (12.5 mmole) of acrolein in 10 ml of benzene was heated on a

*In the preparation of I, VII, X, XIV, XIX, and XX the starting reagents were mixed without addition of a solvent. Substance XXI was obtained by refluxing in toluene for 1 h.

water bath for 30 min, after which the benzene was evaporated, 10 ml of ether was added to the residue, and the precipitate was removed by filtration to give 0.3 g (38%) of a product with mp 150°C (from benzene). IR spectrum: 3310 (NH); 1650, 1700 cm^{-1} (C=O). Mass spectrum (m/z, relative intensity, %): M^+ 276 (33), 219 (3), 216 (2), 193 (60), 192 (100), 177 (1), 119 (15), 107 (50), 100 (22). Found: C 69.8; H 8.6; N 10.0%. $C_{16}H_{24}N_2O_2$. Calculated: C 69.5; H 8.8; N 10.1%.

The antiphlogistic activity was evaluated by means of methods that make it possible to evaluate the activity of the compounds in the exudative and proliferative phases of the inflammatory reaction. The methods of thermal edema of the paws of animals and "cotton granuloma" with determination of the effect of the compounds on the exudation and proliferation processes was used [17].

The Kerber method was used to determine the toxicities of the compounds and calculate the LD_{50} values. White mice with masses of 18-22 g and white rats with masses of 180-220 g were used as the test animals. The preparations were administered intramuscularly in doses ranging from 10 to 100 mg/kg of mass of the animal. Untreated animals to which oil had been administered (in the experiments the investigated water-insoluble compounds were administered in the form of oil solutions) served as controls.

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