SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF UNSYMMETRICAL DIARYLHYDRAZIDES

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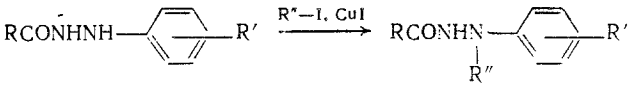
Some acyl derivatives of the hydrazines, particularly of arylhydrazines, possess significant antiinflammatory activity [4]. The N,N-diaryl-N'-acylhydrazines – intermediates in the synthesis of N-aryl-2-aminoindoles by the Kost reaction [5] – proved to be practically unstudied in this regard.

The present work is the continuation of investigations into the study of the properties and conversions of N,N-diaryl-N'-acylhydrazines containing an electron-acceptor substituent.

We previously [2] described in a brief communication a fairly simple and practicable method for the isolation of the N,N-diaryl-N'-acylhydrazines by the arylation of the corresponding N-aryl-N'-acylhydrazines by aryl halides in the presence of copper (Cu^+) iodide and a base.

The given communication is devoted to the further study of this reaction as well as the investigation of the antiinflammatory activity of the derivatives of diarylhydrazines obtained.

The N,N-diaryl-N'-acylhydrazines (IIa-t), containing different substituents both in the aromatic ring and in the acyl residue, served as the objects of the investigation. It was of interest to examine the influence of the substitution in the aryl nucleus of the aryl halides on the activity of the halogen atoms in the arylation reaction of the acylhydrazines. The character of the base also plays an important role since it was established [2] that the arylation reaction does not proceed in its absence.



IIa-t

The selection of the N-aryl-N'-acylhydrazines (Ia-t) for the study, namely those with an electron-acceptor substituent in the aromatic nucleus, was dictated by the circumstance that the unsubstituted N-phenyl-N'-acylhydrazines or the compounds containing an electron-donating substituent decompose in the reaction conditions with the formation of the symmetrical N,N-diaryl-N'-acylhydrazines [2]. Thus, when cuprous iodide is added to the solution of propionyl-N-phenylhydrazide and sodium ethoxide, the release of nitrogen and the formation of a brown precipitate is observed. After the corresponding treatment of the reaction mass, N,N-diphenyl-N'-propionylhydrazine, which is identical to the known sample according to its physicochemical properties, was isolated with the yield of about 50%.

An analogous conversion is observed in the Gatterman–Tafel reaction [8] where the decomposition of N-aryl-N'-acylhydrazines proceeds in the presence of copper salts with the formation of nitrogen and the phenyl radical, which further adds to the aniline nitrogen atom with the formation of the N,N-diaryl-N'-acylhydrazine.

N-Aryl-N'-acylhydrazines containing the nitro group as the electron-acceptor substituent were utilized in the course of further investigations. The reaction proceeds under the conditions described earlier [2] with a good yield. The confirmation of the fact that the arylation proceeds at the aniline nitrogen atom is the absence of the high-frequency NH absorption band, which corresponds to the aniline group [4], in the IR spectrum, as well as the presence

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TABLE 1. N,N-Diaryl-N'-acylhydrazines (IIa-t)

Compound	R	R'	R"	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
					C	H	N		C	H	N	
IIa	C_2H_5	p-NO_2	C_6H_5	178—9	63,23	5,24	14,58	$C_{15}H_{15}N_3O_3$	63,15	5,30	14,73	95,6
IIb	C_2H_5	p-NO_2	$C_6H_4CH_3$-p	203—4	64,57	5,72	13,99	$C_{16}H_{17}N_3O_3$	64,20	5,73	14,04	81,8
IIc	C_2H_5	p-NO_2	$C_6H_4NH_2$-p	154—6	60,28	5,59	17,86	$C_{15}H_{16}N_4O_3$	59,99	5,37	18,66	50
IId	C_2H_5	p-NO_2	$C_6H_4NO_2$-p	162—6	54,59	4,37	16,23	$C_{15}H_{14}N_4O_5$	54,55	4,27	16,96	54
IIe	C_2H_5	p-NO_2	$C_6H_4OCH_3$-p	198—9	60,87	5,46	13,36	$C_{16}H_{17}N_3O_4$	60,94	5,44	13,33	96,8
IIf	C_2H_5	p-NO_2	$C_6H_4NH_2$-o	173—4	63,15	5,36	14,10	$C_{15}H_{16}N_4O_3$	63,15	5,30	14,73	72
IIg	C_2H_5	m-NO_2	C_6H_5	108—9	62,62	5,10	14,64	$C_{15}H_{15}N_3O_3$	63,15	5,30	14,73	74,5
IIh	C_2H_5	m-NO_2	$C_6H_4CH_3$-p	119—20	63,76	6,10	13,28	$C_{16}H_{17}N_3O_3$	64,20	5,73	14,04	55,6
IIi	C_2H_5	m-NO_2	$C_6H_4OCH_3$-p	117—8	61,13	5,62	12,65	$C_{16}H_{17}N_3O_4$	60,94	5,44	13,33	66,3
IIj	C_2H_5	o-NO_2	C_6H_5	149—51	62,58	5,34	14,84	$C_{15}H_{15}N_3O_3$	63,15	5,30	14,73	52,9
IIk	C_2H_5	o-NO_2	$C_6H_4CH_3$-p	107—8	63,24	5,76	13,91	$C_{16}H_{17}N_3O_3$	64,20	5,73	14,04	66,8
IIl	C_2H_5	o-NO_2	$C_6H_4OCH_3$-p	118—9	60,98	5,91	13,10	$C_{16}H_{17}N_3O_3$	60,94	5,44	13,33	50
IIm	$CH_2C_6H_5$	p-NO_2	C_6H_5	196—7	69,40	5,17	11,90	$C_{20}H_{17}N_3O_3$	69,15	4,93	12,10	98
IIn	$CH_2C_6H_5$	p-NO_2	$C_6H_4CH_3$-p	184—5	69,30	5,15	12,12	$C_{21}H_{19}N_3O_3$	69,79	5,30	11,63	95,2
IIo	$CH_2C_6H_5$	p-NO_2	$C_6H_4OCH_3$-p	202—6	66,51	5,25	12,04	$C_{21}H_{19}N_3O_3$	66,83	5,07	11,3	83,3
IIp	$CH_2C_6H_5$	p-NO_2	$C_6H_4NH_2$-p	208—9	66,15	4,86	14,83	$C_{20}H_{18}N_4O_3$	66,29	5,01	15,46	95,2
IIq	C_5H_{11}	p-NO_2	C_6H_5	149,5—150,6	66,09	6,54	12,35	$C_{18}H_{21}N_3O_3$	66,04	6,47	12,84	89,9
IIr	C_5H_{11}	p-NO_2	$C_6H_4OCH_3$-p	161—2	66,75	7,02	12,30	$C_{19}H_{23}N_3O_3$	66,84	6,79	12,31	94
IIs	C_5H_{11}	p-NO_2	$C_6H_4OCH_3$-p	119—20	64,00	6,76	10,51	$C_{19}H_{23}N_3O_4$	63,85	6,49	11,76	99,8
IIt	C_5H_{11}	p-NO_2	$C_6H_4NH_2$-p	220—1	63,20	6,79	16,25	$C_{18}H_{22}N_4O_3$	63,14	6,48	16,36	96

TABLE 2. N,N-Diaryl-N'-acylhydrazines (IIa-t) and Their Antiinflammatory Properties

Compound	LD_{50}, mg/kg	Dose, mg/kg, ip	Inhibition of inflammation, %	
			after 3 h	after 5 h
IIa	890	90	1	23
IIb	>1000	100	48*	50*
IIc	>1000	100	75*	56*
IId	>1000	100	22	31*
IIe	>1000	100	21	31*
IIf	1000	100	10	10
IIg	—	—	—	—
IIh	—	—	—	—
IIi	>1000	100	20	26
IIj	—	—	—	—
IIk	—	—	—	—
IIl	>1000	100	31	12
IIm	1000	100	34	36
IIn	>1000	100	25	18
IIo	>1000	100	33*	41*
IIp	>1000	100	47*	37*
IIq	>1000	100	45*	41*
IIr	>1000	100	34*	31*
IIs	>1000	100	28	17
IIt	>1000	100	3	2

*Reliable difference from the control at $p \leq 0.05$.

in the mass spectrum of the fragmentation peak with the breaking of the N—N bond and the formation of the diarylamine residue. The signal of the proton of the aniline nitrogen atom is absent from the PMR spectrum of compound (IIa).

It was established that the rate of the reaction changes insignificantly depending on the position of the nitro group in the aromatic ring. Thus, the rate of reaction decreases by approximately twofold in the arylation of the hydrazides (Ij-l) containing a nitro group in the ortho position. This testifies to the fact that the reaction does not proceed by the mechanism of nucleophilic substitution.

With the object of studying the influence of the volume and size of the acyl residue, we synthesized hydrazides with different substituents; the reaction rate and the yield of the products also change insignificantly when they are arylated.

The aryl iodides are the best arylating agents. It is also possible to utilize the aryl bromides, but the reaction time increases by approximately threefold in this case. The introduction of different substituents into the aromatic ring of the aryl halide does not show significant influence on the process of the arylation.

As was previously noted [2], the reaction only proceeds in the presence of a base, whereby its nature plays a large role. The optimal conditions are obtained when a 5-10% excess of sodium ethoxide is utilized. The reaction proceeds in 3-3.5 h with the yield of the order of 70%. The hydrazides (IIa-t) are obtained under these conditions (Table 1). The hydroxides and carbonates of alkali metals may also be utilized as the base.

EXPERIMENTAL (CHEMICAL)

The IR spectra were taken on a "Perkin-Elmer 577" spectrophotometer using suspensions in mineral oil. The PMR spectra were recorded on a "Tesla BS-467" instrument in $(CD_3)_2SO$. The mass spectra were obtained on an MX-1303 instrument with the system for the direct input of the sample to the ion source at the ionizing voltage of 70 eV. The monitoring of the course of the reaction and the purity of the compounds obtained was carried out using TLC on plates of Silufol UV-254 in the 2:1 system of benzene-acetone.

N-(p-Nitrophenyl)-N'-propionylhydrazine. To the intensively stirred mixture of 3.1 g (0.02 mole) of p-nitrophenylhydrazine and 60 ml of benzene at 20-25°C are added dropwise 2.8 ml (0.022 mole) of propionic anhydride; the mixture is stirred until the disappearance of the

initial p-nitrophenylhydrazine according to the TLC (the 10:1 mixture of benzene–i-PrOH). At the end of the reaction, the residue is filtered off, washed with hexane, and recrystallized from i-PrOH. The yield of N-(p-nitrophenyl)-N'-propionylhydrazine is 5 g (86.7%); it has the mp 205-206°C. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3340, 3270 (NH), 1665 (C=O), 1605 (C=C), and 1510 (NO_2). Found, %: C 52.15, H 5.00, and N 19.63. $C_9H_{11}N_3O_3$. Calculated, %: C 51.67, H 5.30, and N 20.09.

N-(p-Nitrophenyl)-N'-phenylacetylhydrazine. This compound is obtained analogously by the reaction of p-nitrophenylhydrazine with phenylacetyl chloride and the equimolar amount of Et_3N. The yield is 67%, and the mp is 200-202°C. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3360, 3250 (NH), 1660 (C=O), 1605 (C=C), and 1510 (NO_2). Found, %: C 62.00, H 4.91, and N 15.41. $C_{14}H_{13}N_3O_3$. Calculated, %: C 61.97, H 4.83, and N 15.49.

N-(p-Nitrophenyl)-N'-hexanoylhydrazine. This compound is obtained analogously by the reaction of p-nitrophenylhydrazine with caproic anhydride. The yield is 85%, and the mp is 153-154°C. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3350, 3260 (NH), 1650 (C=O), 1600 (C=C), and 1520 (NO_2). Found, %: C 58.38, H 7.15, and N 17.30. $C_{12}H_{17}N_3O_3$. Calculated, %: C 57.30, H 6.82, and N 16.72.

N-(m-Nitrophenyl)-N'-propionylhydrazine. To the intensively stirred suspension of 7.7 g (0.04 mole) of m-nitrophenylhydrazine hydrochloride, 150 ml of benzene, and 5 g (0.05 mole) of Et_3N at 20-22°C are added, dropwise, 6.5 ml (0.05 mole) of propionic anhydride; the mixture is stirred until the disappearance of the initial m-nitrophenylhydrazine according to the TLC (the 3:1 mixture of benzene–acetone). The reaction mass is concentrated in vacuo; the residue is triturated in petroleum ether (3 by 50 ml), after which the viscous mass is dissolved in 100 ml of the 5:1 mixture of benzene–$CHCl_3$ and purified by boiling it with silica gel L 40/100. The residue is filtered off and washed with 3 by 15 ml of the benzene–$CHCl_3$ mixture. The filtrate is concentrated in vacuo, and the residue is recrystallized from benzene. The yield of N-(m-nitrophenyl)-N'-propionylhydrazine is 6.2 g (73%), and the mp is 131-132°C (from benzene). The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3360, 3305 (NH), 1665 (C=O), 1600 (C=C), and 1520 (NO_2). Found, %: C 52.29, H 5.10, and N 19.21. $C_9H_{11}N_3O_3$. Calculated, %: C 51.67, H 5.30, and N 20.09.

N-(o-Nitrophenyl)-N'-propionylhydrazine. This compound is obtained by an analogous method. The yield is 76.6%, and the mp is 104.5-106.5°C. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3370, 3240 (NH), 1665 (C=O), 1605 (C=C), and 1525 (NO_2). Found, %: C 51.68, H 5.57, and N 20.18. $C_9H_{11}N_3O_3$. Calculated, %: C 51.67, H 5.30, and N 20.09.

Reaction of N-Phenyl-N'-propionylhydrazine with Cuprous Iodide in the Presence of Sodium Ethoxide. To the solution of sodium ethoxide (0.58 g of sodium and 30 ml of ethanol) are added 4.14 g (0.0252 mole) of N-phenyl-N'-propionylhydrazine. The solution is then evaporated to dryness; the oily residue is treated with 50 ml of abs. benzene prior to the evaporation. Further, 60 ml of DMF are added, and the mixture is heated up to 35°C prior to the addition of 4.8 g (0.0252 mole) of cuprous iodide. The mixture is held at the temperature of 70-80°C. The release of nitrogen and the formation of a fine amorphous residue are observed according to the extent of the reaction. After the disappearance of the initial hydrazide according to the TLC, the reaction mixture is concentrated in vacuo. The residue is dissolved in $CHCl_3$, and the residue is filtered off. The filtrate is chromatographed on a column 50 by 80 cm with silica gel L 40/100, eluting it with $CHCl_3$.

The N,N-diphenyl-N'-propionylhydrazine was isolated in 31% yield together with other decomposition products; it was identical with a known sample, obtained from diphenylhydrazine and propionic anhydride [7], according to its physicochemical properties.

Synthesis of the N,N-Diaryl-N'-acylhydrazines (IIa-t) (General Method). To the solution of 0.012 mole of sodium ethoxide in 30 ml of abs. ethanol are added 0.012 mole of the corresponding N-aryl-N'-acylhydrazine, 0.0125 mole of the aryl iodide, and 0.0024 mole of cuprous iodide. The mixture is boiled for 3 h until the disappearance of the initial hydrazide according to the TLC (the 2:1 mixture of benzene–acetone). To the reaction mass is added 0.017 mole of AcOH, and the mixture is concentrated in vacuo. The residue is diluted with 100 ml of $CHCl_3$, and the mixture is stirred prior to the addition of 2 ml of water and 20 g of silica gel L 40/100. The suspension is stirred for 0.5 h at room temperature; the residue is filtered off and washed with $CHCl_3$ (3 by 20 ml). The filtrate is evaporated in vacuo, and the residue is triturated in hexane. The yield and the properties of the N,N-diaryl-N'-acylhydrazines (IIa-t) are presented in Table 1.

EXPERIMENTAL (PHARMACOLOGY)

The acute toxicity of the compounds was studied on white mice using the ip injection and the determination of the LD_{50} according to [6].

All compounds give the picture of spasm in mice in the first 5-10 min after the injection into the abdominal cavity; this testifies to the irritating action. The substances studied have low toxicity (Table 2): the LD_{50} values of the majority of them are greater than 1000 mg/kg. In the maximum doses tested, they all induce restraint and a decrease in the tone of the skeletal musculature in the mice, with the maintainance of the reaction to pain. The onset of death occurs at 8-10 h after the injection of the substances.

The antiinflammatory activity was determined using the modified model of agar inflammation produced by the subplantar application of 0.15 ml of 0.15% Difco agar to the hind feet of rats [3]. The substances were injected ip 1 h before the experiment at the dose of 100 mg/kg, comprising less than 0.1 LD_{50}. The inhibition of the inflammation (in %) was calculated from the formula

$$\frac{C-E}{C}\cdot 100,$$

where the result of the control is indicated by C, and the result of the experiment is indicated by E.

As can be seen from Table 2, the compounds (IIb, c, o, p, q, r) showed marked antiinflammatory activity in the course of the entire observation period, whereas the compounds (IId, e) only showed distinct action at the late stage of inflammation (at 5 h after the application of the agar). The decrease of the dose to 25 mg/kg led to the loss of the activity of all the substances indicated.

Since there are common groupings at R" in the compounds (IIa-f) and (IIm-t), an attempt was made to show the dependence between the structure and the antiinflammatory activity of the substances indicated. It was shown that the antiinflammatory effect does not appear in the case of the compounds type (IIa) (R" = Ph), but an exception is the compound (IIq). The p-substituents Me (IIb, r), NH_2 (IIc, p), and OMe (IIe, o) give a reliable increase in the antiinflammatory activity of the compounds; exceptions are (IIn, t, s). The introduction of the NH_2 group at the o-position of the phenyl ring (IIf) leads to the loss of activity.

The analgesic action using the test of mechanical pain stimulation as well as the state of the coordination mechanisms and the tone of the skeletal muscles according to the "stationary horizontal rod" test [1] were investigated in the mice at the doses of 100 mg/kg.

Under these conditions, it was shown that not one of the compounds investigated shows anesthetizing action and influences the central mechanisms of the coordination of movements.

LITERATURE CITED

1. V. V. Gatsura, Methods of the Primary Pharmacological Investigation of Biologically Active Substances [in Russian], Moscow (1974), p. 143.
2. V. P. Zhestkov, V. G. Voronin, and Yu. N. Portnov, Zh. Org. Khim., 22, No. 7, 1560-1561 (1986).
3. A. S. Zaks and M. L. Suslina, Farmakol. Toksikol., No. 3, 308-310 (1975).
4. V. É. Kolla and I. S. Berdinskii, The Pharmacology and Chemistry of Hydrazine Derivatives [in Russian], Ioshkar-Ola (1976), p. 264.
5. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, Dokl. Akad. Nauk SSSR, 200, 342-345 (1971).
6. V. B. Prozorovskii, M. P. Prozorovskaya, and V. M. Demchenko, Farmakol. Toksikol., No. 4, 497-502 (1978).
7. C. Gattermann and L. Jonson, Ber. Dtsch. Chem. Ges., 25, 1075-1081 (1892).
8. J. Houben-Weyl, Methoden der Organischen Chemie, Vol. 10/2, No. 2, Berlin (1967), pp. 232-233.