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SYNTHESIS AND PSYCHOTROPIC ACTIVITY OF N-ARYLACETYLFORMAMIDOXIME HYDRAZONES

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The hydrazones are a group of compounds with high biological activity. They include compounds known to have antistaphylococcal, antiinfluenzal, antitubercular, and antitrypanosome activity [1-3]. Many hydrazones combine with iron to form complexes, enabling these compounds to be transported by iron in the body [4]. Some hydrazones have hypoglycemic activity [5].

We here described for the first time the psychotropic activity of some N-arylacetylformamidoxime hydrazones. Hydrazones (I-VII) were obtained by the reaction between N-arylacetylformamidoximes (VIII-XIV) and hydrazine hydrate in alcohol, either with heating or at room temperature

$$\underset{\text{VIII — XIV}}{CH_3COC(NOH)NHAr} \xrightarrow{N_2H_4\cdot H_2O} \underset{\text{I -- VII}}{CH_3C(NNH_2)C(NOH)NHAr}$$

I, VIII: Ar = p-$CH_3OC_6H_4$; II, IX: Ar = p-$C_2H_5OC_6H_4$; III, X: Ar = p-
= $(ClCH_2CH_2)_2NC_6H_4$; IV, XI: Ar = p-$(CH_3)_2NC_6H_4$; V, XII: Ar = p-ClC_6H_4;
VI, XIII: Ar = m-ClC_6H_4; VII, XIV: Ar = m-$CH_3C_6H_4$.

The synthesis of (I) and (II) has been described [6], together with that of the starting material (VIII-X) and (XII-XIV) [7, 8]; α-[p-(NN-dimethylamino)phenyleneamino]-α-isonitrosoacetone has been prepared for the first time.

Hydrazones (I-VIII) are colorless, crystalline solids which are insoluble in water, and which form hydrochlorides which disproportionate in water to give azines [6]. Of the new hydrazones (III-VII), only (III) was characterized as its hydrochloride. From its elemental

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TABLE 1. N-Arylacetylformamidoxime Hydrazones (III-VII)

Compound	Yield, %	Mp, °C	Found, %				Molecular formula	Calculated, %				IR spectrum, cm^{-1}		
			C	H	N	Cl		C	H	N	Cl	NH	C=N	N—OH
III	76,9	120	47,10	5,86	...	21,83	$C_{13}H_{10}Cl_2N_5O$	47,00	5,76	...	21,34	3395 3344	1630	923
IV	81,5	171	56,13	7,20	29,24	—	$C_{11}H_{17}N_5O$	56,15	7,28	29,77	—	3395 3370	1635	925
V	91,0	136	47,88	4,86	24,61	15,73	$C_9H_{11}N_4OCl$	47,69	4,89	24,72	15,64	3390 3375	1625	940
VI	91,0	121	47,65	4,88	...	15,80	$C_9H_{11}N_4OCl$	47,69	4,89	...	15,64	3380 3373	1630	958
VII	85,2	137	58,40	6,50	26,91	—	$C_{10}H_{14}N_4O$	58,23	6,84	27,20	—	3390 3375	1625	960

TABLE 2. Spectrum of Biological Activity of Hydrazones (I-VII)

Compound	LD_{50}, mg/kg	Dose of hydrazone, mg/kg	Reduction in rectal temperature after 30 min, °C	"Open field"		Duration of sombrevin sleep	"Hot plate"		
				number of occupied fields	number of apertures examined		background	30 min after administration of the hydrazone	30 min after administration of amidopyrine
I	400	50	—2,0*	48±7,7	16±2,8	3 min 33 sec ± 64 sec	7,1±0,62	6,9±0,74	21,6±1,4
II	200	50	—1,0*	67±4,5	21±5,3	4 min 34 sec ± 29 sec	7,6±0,86	7,9±0,99	21,1±1,6
III	160	50	—1,8*	45±8,9*	12±3,3	3 min 16 sec ± 37 sec	7,8±0,62	10,3±0,86	24,5±1,7
IV	375	50	—1,9*	59±6,1	15±2,5	4 min 16 sec ± 52 sec	6,1±0,50	10,3±0,86	20,1±2,8
V	300	50	—2,0*	73±12,4	23±4,7	3 min 2 sec ± 30 sec	7,9±1,11	11,7±0,62*	28,2±6,2
V	300	100	—2,8*	66,5±12,0	10,6±2,4*	11 min 9 sec ± 85* sec	—	—	—
V	300	150	—	—	—	15 min 55 sec ± 34* sec	—	—	—
VI	250	50	—1,5*	80±6,1	23±3,4	3 min 55 sec ± 27 sec	5,8±0,86	8,7±0,74	23,5±3,5
VII	300	50	—1,8*	67±7,1	15±1,9	2 min 27 sec ± 24 sec	7,2±0,74	12,0±1,11*	26,1±3,0
Control	—	—		70±7,1	21±2,7	3 min 0 c ± 21 sec	6,8±0,62	8,7±0,99	22,2±3,3

*Significantly different from the controls at $P < 0.05$.

analysis, this hydrochloride contained three moles of HCl per mole of the base. When this salt was dissolved in water, the azine (XV) separated

$$III \cdot 3HCl \xrightarrow{H^+} [CH_3C(=N)C(=NOH)NHC_6H_4N(CH_2CH_2Cl)_2\cdot p]_2.$$
XV

Compound (XV) was obtained directly from α-chloro-α-isonitrosoacetone azine [6] and NN-bis-(2-chloroethyl)-p-phenylenediamine. The antitumor activity of this compound has been described [9].

The IR spectra of (III-VII) displayed two absorption bands characteristic of NH (ν ∿ 3400-3350 cm^{-1}) in the hydrazone and amidoxime groups, and strong absorption for C=N (ν ∿1630 cm^{-1}) and N–OH (ν ∿ 960-925 cm^{-1}). Physicochemical data for (III-VII) are given in Table 1, and the results of the biological tests in Table 2.

EXPERIMENTAL CHEMISTRY

IR spectra were recorded on a UR-20 instrument (East Germany) in KBr disks. The PMR spectrum of a 10% solution of (III) in DMSO-d_6 was recorded on a ZKR-60 spectrometer, shifts given relative to tetramethylsilane.

α-[p-(NN-Dimethylamino)phenyleneamino]-α-isonitrosoacetone (XI). To a solution of 4.5 g (3.7 mmole) of α-chloro-α-isonitrosoacetone in ether was added with stirring and ice-water cooling a mixture of 3.74 g (3.7 mmole) of triethylamine and NN-dimethyl-p-phenylenediamine base, obtained from 8.7 g (3.7 mmole) of the hydrochloride, in ether. The mixture was stirred for 2-3 h, the solid filtered off, and ethereal HCl added to the filtrate. The hydrochloride of (XI) separated, and was isolated, washed with ether, dried, dissolved in water, and the solution basified with sodium carbonate solution. The free base which separated was filtered off and washed with water to give 4.9 g (60%) of a greenish-yellow crystalline powder, mp 93-94°C (from alcohol). Found, %: C 60.06; H 6.86; N 19.01. $C_{11}H_{15}N_3O_2$. Calculated, %: C 59.71; H 6.83; N 18.99.

Hydrochloride, obtained by treatment of the base with ethereal HCl, mp 192-193°C (from alcohol). Found, %: Cl 13.80. $C_{11}H_{15}N_3O_2 \cdot HCl$. Calculated, %: Cl 13.76.

Preparation of Hydrazones (IV-VII). To 7-10 mmole of the N-arylacetylformamidoxime (XI-XIV) in 2-5 ml of alcohol was added an approximately fourfold excess of 98% hydrazine hydrate. The mixture was boiled for 5-7 min, kept for 2-3 h at room temperature, an equal volume of water added, and left to crystallize. The solid was filtered off and crystallized from alcohol.

α-[p-NN-Bis-(α-chloroethyl)aminophenyleneamino]-isonitrosoacetone Hydrazone (III). To a suspension of 2.0 g (6.28 mmole) of α-[p-NN-bis-(2-chloroethyl)aminophenyleneamino]-α-isonitrosoacetone (X) [7] in about 30 ml of alcohol was added 25-30 mmole of 98% hydrazine hydrate, and the mixture was kept at room temperature. The solid gradually dissolved, and after 5-6 h crystals began to separate. An equal volume of water was added to the reaction mixture, which was cooled, and after 10-20 min the solid was filtered off and washed with water to give 1.6 g (76.9%) of (III), mp 120-122°C (from absolute alcohol). The product gradually turned yellow in the light. PMR spectrum, δ, ppm: 1.8 s, 3H(CH_3); 3.65, 8H($2CH_2CH_2Cl$); 6.35 s, 2H(NH_2); 6.57 4H(C_6H_4); 7.15 s, 1H(NH); 10.0 s, 1H(NOH).

The hydrochloride was obtained by treating a suspension of (III) in dry ether with an ethereal solution of HCl. Bright-yellow solid, reddening in air, mp 173-174°C (from absolute ethanol-ether), gave a depression in melting point on admixture with a sample of (V) hydrochloride. Found, %: Cl 39.63. $C_{13}H_{19}Cl_2N_5O_2 \cdot 3HCl$. Calculated, %: Cl 40.13.

α-[p-NN-Bis-2-(chloroethyl)aminophenyleneamino]-α-isonitrosoacetone Azine (XV). A. To a mixture of 0.59 g (2.5 mmole) of α-chloro-α-isonitrosoacetone azine [6] and 1.34 g (5 mmole) of NN-bis-(2-chloroethyl)-p-phenylenediamine hydrochloride in methanol was added dropwise with ice-water cooling a solution of 0.54 g (5 mmole) of Na_2CO_3 in water. Stirring was continued for 1 h at room temperature, and the solid was then filtered off, and the filtrate evaporated under water pump vacuum. The residue was mixed with water, filtered, and washed with water to give 1.41 g (89.9%) of the azine (XV). Green crystals, mp 155-156°C (decomp., from acetone).

B. (III) hydrochloride (0.09 g) was dissolved in approximately 1 ml of water. A green solid slowly began to separate, and after 3-4 h this was filtered off and washed with water to give 0.05 g (80%) of a compound, mp 153-154°C, identical with the azine (XV).

IR spectrum, ν, cm^{-1}: 3395 (NH); 1918 (C=N); 1525, 830 (C_6H_4); 945 (NOH); 745 (C—Cl). Found, %: C 49.32; H 5.68; Cl 22.66. $C_{26}H_{34}Cl_4N_8O_2$. Calculated, %: C 49.38; H 5.42; Cl 22.42.

The hydrochloride was obtained by treating an acetone solution of the base with ethereal HCl. mp 173-174°C (from alcohol—ether). Found, %: C 44.14; H 5.02; Cl 29.79. $C_{26}H_{34}Cl_4N_8O_2 \cdot HCl$. Calculated, %: C 44.27; H 5.14; Cl 30.16.

EXPERIMENTAL PHARMACOLOGY

The acute toxicities of hydrazones (I-VII) were determined by intraperitoneal administration to white mice. The LD_{50} values ranged from 160-400 mg/kg (Table 2). In sublethal doses, motor retardation of the animals was noted which occasionally preceded brief agitation, and in lethal doses, lateral positioning, increasing depression, and death after 20 min to several hours, as a result of cessation of respiration.

In a dose of 50 mg/kg (intraperitoneal), the compounds had no effect on the central coordinator mechanisms and the tonus of the striated musculature according to the rotating rod and taut horizontal wire tests. The rectal temperature of the mice was reduced by 1-2°C 30 min after administration of the hydrazones, but this had little effect on the activity of the mice as assessed by the "open field" test [10]. Apart from (III), the compounds in a dose of 50 mg/kg reduced neither the number of fields occupied (spontaneous motor activity) nor the number of apertures examined (orientational activity). However, administration of the hydrazone (V) in a dose of 100 mg/kg resulted in a significant reduction in the orientational activity of the animals without a corresponding reduction in the spontaneous motor activity (see Table 2).

Except for the hydrazone (II), the compounds did not appreciably affect the duration of narcosis induced by the intraperitoneal administration of sombrevin (250 mg/kg) [11], but increasing the dose of the hydrazone (V) to 100 and 150 mg/kg resulted in a clear potentiation of sombrevin sleep. In these doses, (V) also extended hexobarbital narcosis (60 mg/kg intraperitoneally) by factors of 2.3 and more than 3, respectively. The true nature of the potentiation is indicated by the renewal of the lateral position following further administration of the hydrazone immediately following arousal of the animal [12].

Anesthetizing effects in the hot plate test were shown only by (V) and (VII) (50 mg/kg), but like the remaining compounds they were without independent anesthetic activity and failed to potentiate the effects of amidopyrine (100 mg/kg) (see Table 2).

Subcutaneous administrations of amphetamine in doses of 7.5 and 10 mg/kg to grouped animals (the "group toxicity" test) [13] resulted in an increase in motor activity, rectal temperature, and finally the deaths of 50 and 100% of the mice, respectively. Previous administration of (V) prevented the development of amphetamine hyperthermia, but did not reduce the number of animals which died. Thus, 30 min after the administration of amphetamine in a dose of 7.5 mg/kg the rectal temperature was greater than normal by 2.1 ± 0.2°C, whereas when (V) was administered previously (50 mg/kg), this difference was reduced to 0.9 ± 0.3°C ($P < 0.05$). In this case, 50% of the animals died.

These results demonstrate the effects of the compounds on the central nervous system, which are apparent, however, only at high doses (33% of the LD_{50} and above). The ability of the hydrazone (V) to reduce rectal temperature, potentiate sombrevin and hexobarbital sleep, selectively reduce orientational activity, and prevent amphetamine hyperthermia indicates that this compound possesses tranquillizing properties [14].

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ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF ORGANOSILICON ETHERS, ESTERS, AND KETONES

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Organosilicon compounds have been observed to display many types of pharmacological (neurotropic, antiinflammatory, analgesic, etc.) activity [1-4]. Continuing work in this series, we have examined compounds synthesized in the Department of Organic Chemistry, Perm University, namely, esters of 2- and 3-trialkylsilyloxyacids (I-IX), α- and β-di- and trialkylsilyloxyketones (X-XV), 1,3-bis(tributylsilyloxy)pentane (XVI), ethyldibutylsilyl 4-ethyldibutylsilyloxypentanoate $CH_3CH[OSi(C_2H_5)(C_4H_9)_2]CH_2CH_2COOSi(C_2H_5)(C_4H_9)_2$ (XVII), dialkyl 1,1,5,5-tetraalkyl-substituted 2,4-dioxa-3,3-diethyl-3-silapentane-1,5-dicarboxylates (XVIII-XXV), and 3,7-dimethyl-3,7-dialkyl-4,6-dioxa-5,5-diethyl-5-sila-2,8-nonadiones (XXVI-XXIX).

Compounds (I-IX) were obtained by reacting equimolar amounts of the esters of 2- and 3-oxoacids with trialkylsilane [5]:

$$RCOXCOOAlk + HSiR'R_2'' \xrightarrow{Ni} RCH(OSiR'R_2'')XCOOAlk;$$

where , R, R′, R″, X Alk are I, C_4H_9, C_4H_9, C_4H_9, —, C_4H_9; II, C_4H_9, C_2H_5, C_2H_5 —, C_4H_9; III, C_4H_9, C_2H_5, C_4H_9, —, C_4H_9; IV, C_6H_{13}, C_2H_5, C_2H_5, —, C_4H_9; V, C_7H_{15}, C_2H_5, C_2H_5, —, C_2H_5; VI, CH_3, C_2H_5, C_4H_9, —, C_2H_5; VII, CH_3, C_3H_5, C_2H_5, $C(CH_3)_2$, CH_3; VIII, C_3H_7, C_2H_5, C_2H_5, $C(CH_3)_2$, C_2H_5; IX, C_3H_7, C_2H_5, C_2H_5, $C(CH_3)_2$, iso-(C_3H_7).

Compounds (X-XII) were prepared by reacting di- or trialkylsilanes with hydroxyketones [6]:

$$CH_3CR(OH)COCH_3 + HSiR'R_2'' \xrightarrow[-H_2]{Ni} CH_3CR(OSiR'R_2'')COCH_3$$

X — XII

where R, R′, R″ are X, C_7H_{15}, C_2H_5, C_4H_9; XI, C_2H_5, H, C_2H_5; XII, C_2H_5, C_2H_5, C_2H_5.

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