PREPARATION OF DERIVATIVES OF 1,2-DIHYDRO- AND 1,2,3,6-TETRAHYDRO-PYRAZINONES FROM ACYLATED 1,2-HYDROXYLAMINO KETONES

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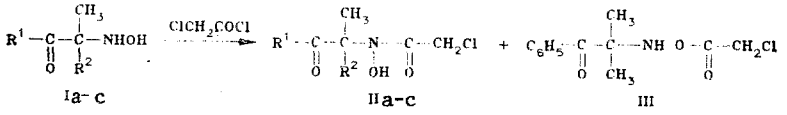
N-(2-Oxoalkyl)-2-chloroacetohydroxamic acids were obtained by acylation of 1,2-hydroxylamino ketones with chloroacetyl chloride. Their reaction with urotropin and sodium azide gives urotropinium salts and acetoxyhydroxamic acid azides. 1-Hydroxy-2-oxo-1,2,3,6-tetrahydropyrazines were obtained by treating N-(2-oxoalkyl)-2-chloroacetohydroxyamic acids with ammonia, and also by reacting the urotropinium salts and azides of acetohydroxamic acids with hydrochloric acid and triphenylphosphine, respectively. The reaction of N-(1-methyl-2-oxo-2-phenylethyl)-2-chloroacetohydroxamic acid with urotropin in an acid medium leads to the formation of 6-methyl-2-oxo-5-phenyl-1,2-dihydropyrazine.

Acylation of 1,2-hydroxylaminooximes with a hydroxylamino group attached to a tertiary carbon atom by α-haloacid chlorides leads to N- and O-acylation products at the hydroxylamino group, while treatment with bases of the N-acylation products — N-(2-hydroximinoalkyl)-2-haloalkanohydroxamic acids — depending on conditions, leads to 1-hydroxy-2-oxo-1,2,3,6- or 1-hydroxy-2-oxo-1,2,5,6-tetrahydropyrazine 4-oxides [1]. In the present work, we examined the acylation of 1,2-hydroxylamino ketones Ia-c with the hydroxylamino group attached to tertiary (Ia, b) and secondary (Ic) carbon atoms, in order to obtain the N-acylation products — N-(2-oxoalkyl)-2-chloroacetohydroxamic acids II — followed by their transformation into pyrazinone derivatives which do not contain an N-oxide group. The pyrazine derivatives containing a hydroxamic acid fragment attract attention of research workers due to the biological activity of compounds in this series [2].

Acylation of 1,2-hydroxylamino ketones Ia-c by chloroacetyl chloride in THF leads to N-(2-oxoalkyl)-2-chloroacetohydroxamic acids IIa-c, in yields of 38-47%. During the acylation of Ib, as well as IIb, 2-methyl-1-phenyl-2-chloroacetoxyamino-1-propanone (III), a product of O-acylation of the hydroxylamino group, was also isolated in a yield of 40%. In the IR spectra of hydroxamic acids IIa-c, absorption bands are observed in the 1630-1655 and 1680-1730 cm^{-1} regions (Table 1), corresponding to the stretching vibrations of the C=O bond of the hydroxamic and ketonic groups, respectively. In the IR spectrum of the O-acylation product III (Table 1), besides the stretching vibration band of the conjugated C=O bond at 1690 cm^{-1}, a band at 1770 cm^{-1} is also observed, corresponding to the stretching vibrations of the C=O bond of the the chloroacetoxyamino group (cf. [1]).



Ia-c IIa-c III

I, II a $R^1=R^2=CH_3$; b $R^1=C_6H_5$, $R^2=CH_3$; c $R^1=C_6H_5$, $R^2=H$

Several methods are known for the cyclization of 2-haloacylamino ketone derivatives including those using the substitution reaction of the chlorine atom by the amino- [3, 4], azido- [5, 6], and hexamethyleneamino groups [7, 8]. During treatment of solutions of compounds IIa, b in dioxane by an aqueous alcoholic solution of ammonia under the conditions of [4], 1-hydroxy-2-oxo-1,2,3,6-tetrahydropyrazines (IVa,b) were obtained in yields of 8 and 17%, respectively. Under similar conditions, chloroacetamide was obtained from IIc in a yield of 60%.

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TABLE 1. Spectral Characteristics of Compounds II-VI, VIII

Compound	IR spectrum, cm^{-1} (in KBr)	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, ppm (J, Hz)*				
			R^1	R^2	CH_3	CH_2	OH
IIa	1635, 1655, 1730 (C=O)	—	2,02 s	1,34, s		4,37, s	9,23, s
IIb	1630, 1680 (C=O)	244 (4,12)	7,3—7,6; 7,9—8,2, m	1,51, s		4,22, s	9,57, s
IIc	1630, 1650, 1700 (C=O)	244 (4,09)	7,5—7,7; 7,9—8,1, m	6,14, q (7,5)	1,57, d (7,5)	4,37, s	
III	(B CCl_4) 1690, 1770 (C=O)	246 (4,17)	7,2—7,6; 7,8—8,2, m	1,44, s		3,89, s	
IVa	1680 (C=O)	—	2,07, t (1,5)	1,51, s		4,19, s (1,5)	
IVb	1660 (C=O)	235 p (3,60)	7,39, s	1,42, s		4,44, s	9,71, bs
Va†	1660, 1730 (C=O)	—	2,23, s	1,40, s		4,09, s	
Vb†	1660, 1685 (C=O)	242 (4,00)	7,4—7,7; 7,9—8,1, m	1,63, s		3,92, s	
VI	1700 (C=O)	257 (4,42) 342 (4,04)	7,31, s		2,25, s	7,77, s‡	
VIIIa	1620, 1645, 1725 (C=O), 2120, 2150 (N_3)	—	1,98, s	1,24, s		4,02, s	
VIIIb	1630, 1695 (C=O), 2130 (N_3)	245 (4,17)	7,3—7,5; 7,8—8,0, m	1,44, s		3,97, s	10,34, s

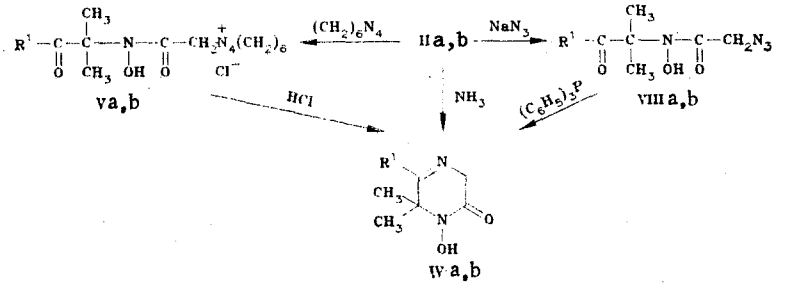
*The PMR spectra of IVb, VI, VIIIa,b were recorded in $(CD_3)_2SO$, IIa,b in $(CD_3)_2CO$, IIc in $CDCl_3$, Va,b in D_2O, III in CCl_4, IVa in CD_3OD.

†In the PMR spectrum, the signals of the urotropinium fragment for Va are observed at: 4.65 (6H, s, CH_2), 5.37 ppm (6H, s, CH_2); for Vb, 4.49 (6H, br. s, CH_2), 4.95 ppm (6H, s, CH_2)

‡A methine proton signal.

Data on the IR, UV, and PMR spectra of IVa,b derivatives (Table 1) are in agreement with the structure of 1-hydroxy-2-oxo-1,2,3,6-tetrahydropyrazines. Thus, for example, in the PMR spectrum, the spin-spin interaction (J = 1.5 Hz) between the methyl group protons in position 5 and methylene protons in position 3 of the heterocyclic ring in IVa is possible only for the cyclic structure.

Because of the low yields of pyrazines IVa,b, which is possibly due to a cleavage of the hydroxy-amide bond in compounds IIa,b during their treatment with ammonia, urotropin was used as the aminating agent (cf. [7-9]). The reaction of compounds IIa,b with urotropin in acetonitrile leads to urotropinium salts Va,b, which are readily soluble in water and polar organic solvents. Treatment of salts Va,b with an alcoholic solution of hydrochloric acid gives IVa,b in yields of 10 and 71%, respectively.



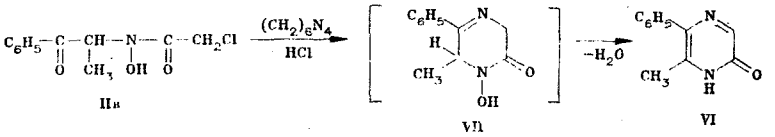
A urotropinium salt could not be obtained from compound IIc under the conditions described above. At the same time, heating IIc with urotropin in the presence of hydrochloric acid leads to 6-methyl-2-oxo-5-phenyl-1,2-dihydropyrazine (VI) [10]. The reaction probably proceeds with the formation of an intermediate tetrahydropyrazinone VII, whose dehydration under the reaction conditions leads to VI. (Formula, following page, below table.)

The formation of pyrazinones IVa,b could be expected from 2-azidoacetohydroxamic acids VIIIa,b (cf. [5, 6]), which were obtained by the reaction of IIa,b with sodium azide in DMFA.

TABLE 2. Characteristics of Synthesized Compounds II-VI, VIII

Compound	mp,* °C	Found, %				Empirical formula	Calculated, %			
		C	H	Cl	N		C	H	Cl	N
IIa	136—137	43,6	6,4	19,0	7,2	$C_7H_{12}ClNO_3$	43,4	6,3	18,3	7,2
IIb	145—147	56,4	5,7	14,0	5,4	$C_{12}H_{14}ClNO_3$	56,4	5,5	13,9	5,5
IIc	110—112	54,9	4,9	14,6	5,7	$C_{11}H_{12}ClNO_3$	54,7	5,0	14,7	5,8
III	Oil	56,2	5,5	14,2	5,3	$C_{12}H_{14}ClNO_3$	56,4	5,5	13,9	5,5
IVa	130—132	54,0	7,8	—	17,7	$C_7H_{12}N_2O_2$	53,8	7,7	—	17,9
IVb	156—158	66,5	6,5	—	12,8	$C_{12}H_{14}N_2O_2$	66,0	6,5	—	12,8
Vc	190—192 (dec)	46,2	7,4	11,2	21,2	$C_{13}H_{24}ClN_5O_3$	46,8	7,3	10,6	21,0
Va	162—164 (dec)	54,1	6,7	8,6	17,2	$C_{18}H_{26}ClN_5O_3$	54,6	6,6	9,0	17,7
VI	252—254	71,5	5,4	—	15,1	$C_{11}H_{10}N_2O$	71,0	5,4	—	15,1
VIIIa	109—111	41,5	5,8	—	28,0	$C_7H_{12}N_4O_3$	42,0	6,0	—	28,0
VIIIb	122—124	55,0	5,4	—	21,4	$C_{12}H_{14}N_4O_3$	55,0	5,4	—	21,4

*Compounds IIa from alcohol, IIb,c, IVa,b, VIIIa,b from ethyl acetate, VI from methanol, Va,b reprecipitated from alcohol by ether.



Treatment of compounds VIIIa,b with triphenylphosphine in THF leads to IVa,b in yields of 79 and 53%, respectively.

EXPERIMENTAL

The IR spectra were run on a UR-20 spectrophotometer and the UV spectra on a Specord UV-vis spectrometer in alcohol. The PMR spectra were recorded on a Varian A-56-60A spectrometer with HMDS and tert-butanol (aqueous solutions) as internal standard. The IR and UV spectra of compounds IIa-c, IVb, Va,b, and VI are given in [11].

The characteristics of compounds synthesized are given in Tables 1 and 2.

N-(1,1-Dimethyl-2-oxo-2-phenylethyl)-2-chloroacetohydroxamic Acid (IIb) and 2-Methyl-1-phenyl-2-chloroacetoxyamino-1-propanone (III). A solution of 4.7 ml (62 mmoles) of chloroacetyl chloride in 45 ml of THF is added in the course of 30 min, with stirring and cooling on an ice bath, to a solution of 10 g (56 mmoles) of Ib [12] and 9.4 ml (67 mmoles) of triethylamine in 170 ml of THF. The reaction mixture is stirred at room temperature for 2 h, and filtered. The filtrate is evaporated and the residue is treated with ethyl acetate. The solution is washed with water, dried over magnesium sulfate, and evaporated. The residue is ground in a mixture of ether and petroleum ether, and the precipitate is filtered. Yield 6.7 g (47%) of IIb. From the filtrate, by chromatography on silica gel (eluent, chloroform), 5.7 g (40%) of III are isolated.

N-(1,1-Dimethyl-2-oxopropyl)-2-chloroacetohydroxamic acid (IIa) is obtained in a similar way in a yield of 38% from 1,2-hydroxylamino ketone hydrochloride (Ia•HCl) [13], using a two-fold excess of triethylamine.

N-(1-Methyl-2-oxo-2-phenylethyl)-2-chloroacetohydroxamic Acid (IIc). A 7.62 g portion (55 mmoles) of K_2CO_3 and 20 ml of water are added to a solution of 10 g (61 mmoles) of Ic [12] in 300 ml of ether, and then, with stirring and cooling, a solution of 4.6 ml (61 mmoles) of chloroacetyl chloride in 40 ml of ether is added in the course of 1 h. The mixture is stirred at room temperature for 1 h. The ether layer is separated, washed with 0.1 N HCl, water, dried over magnesium sulfate, and evaporate. The residue is ground in a mixture of ether and hexane, and the precipitate is filtered to yield 6.20 g (42%) of IIc.

N-(1,1-Dimethyl-2-oxopropyl)-2-urotropinium-acetohydroxamic acid chloride (Va). Urotropin (1.57 g, 11.2 mmoles) is added in portions to a solution of 1.8 g (9.3 mmoles) of IIa in 150 ml of dry acetonitrile, and the mixture is stirred for 20 h. The precipitate that separates is filtered. Yield, 2.66 g (89%) of Va.

N-(1,1-Dimethyl-2-oxo-2-phenylethyl)-2-urotropiniumacetohydroxamic Acid Chloride (Vb) is obtained in a similar way, in a yield of 92%.

N-(1,1-Dimethyl-2-oxopropyl)-2-azidoacetohydroxamic Acid (VIIIa). A mixture of 4.4 g (23 mmoles) of IIa and 1.62 g (25 mmoles) of sodium azide in 40 ml of dry DMFA is stirred at room temperature for 24 h. The sodium chloride precipitate is filtered and DMFA is distilled *in vacuo*. The residue is ground in ether, the precipitate is filtered to yield 2.20 g (50%) of VIIIa.

N-(1,1-Dimethyl-2-oxo-2-phenylethyl)-2-azidoacetohydroxamic Acid (VIIIb). A mixture of 7.43 g (28 mmoles) of IIb and 2.08 g (32 mmoles) of sodium azide in 50 ml of dry DMFA is stirred for 24 h at room temperature. The sodium chloride precipitate is filtered and DMFA is distilled *in vacuo* The residue is treated with ether, the ether solution is washed with water, dried over magnesium sulfate, and evaporated. The residue is ground in ether, and the precipitate is filtered. Yield, 4 g (53%) of VIIIb.

1-Hydroxy-5,6,6-trimethyl-2-oxo-1,2,3,6-tetrahydropyrazine (IVa). A. A solution of 3.9 ml of 25% aqueous ammonia in 5 ml of alcohol is added to a solution of 0.5 g (2.6 mmoles) of IIa in 10 ml of dioxane, and the mixture is left to stand for 3 days. The solvent is evaporated, and from the residue 0.03 g (8%) of IVa is isolated by chromatography on silica gel (eluent, a 20:1 chloroform–alcohol mixture).

B. A solution of 0.3 g (0.9 mmole) of Va in 10 ml of ethanol and 10 ml of 0.1 N HCl is allowed to stand for 24 h. The solvent is evaporated and 0.02 g (10%) of IVa is isolated in a similar way as in experiment A.

C. Triphenylphosphine (0.87 g, 3.3 mmoles) is added in portions to a solution of 0.6 g (3 mmoles) of VIIIa in 10 ml of dry THF, and the mixture is allowed to stand for 24 h. The solvent is evaporated and 0.37 g (79%) of IVa is isolated in a similar way as in experiment A.

1-Hydroxy-6,6-dimethyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrazine (IVb). A. A solution of 2.9 ml of 25% aqueous ammonia in 5 ml of alcohol is added to a solution of 0.50 g (1.9 mmole) of IIb in 10 ml of dioxane, and the mixture is allowed to stand for 2 days. Alcohol and dioxane are evaporated and the residue is treated by 3 ml of water, and extracted by ethyl acetate. The ethyl acetate solution is dried over magnesium sulfate, evaporated, and the residue is ground with ether. The precipitate is filtered to yield 0.07 g (17%) of IVb.

B. A solution of 7.65 g (19 mmoles) of Vb in 100 ml of ethanol and 100 ml of 0.1 N HCl is allowed to stand for 24 h. The alcohol is evaporated, and the precipitate that separates from water is filtered to yield 2.5 g (59%) of IVb. An additional amount of 0.5 g (12%) of IVb is isolated from the filtrate.

C. Compound IVb is obtained from azide VIIIb in a similar way as IVa by the method C, yield 53%.

6-Methyl-2-oxo-5-phenyl-1,2-dihydropyrazine (VI). A solution of 0.5 g (2.1 mmoles) of IIc, 1.6 ml of 2 N HCl and 0.5 g (3.6 mmoles) of urotropin in 7 ml of methanol is boiled for 10 h. The precipitate that separates on cooling, is filtered to yield 0.14 g (36%) of VI.

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SYNTHESIS OF 1-ALKYL(ARALKYL)-4-ACYL-2-PIPERAZINONES

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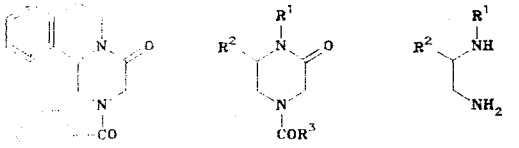
1-Alkyl(aralkyl)-4-acyl-2-piperazinones are formed in high yields during selective acylation of N-monosubstituted ethylenediamines by benzoyl and cyclohexylcarbonyl chlorides in the presence of pyridine hydrochloride and treatment of the reaction products with chloroacetyl chloride in the presence of potassium tert-butylate.

Among 2-piperazinones, having different biological activities [1-3], the little investigated 4-acyl derivatives are of special interest, since the 4-acyl-2-piperazinone fragment is included in the structure of a new anthelmintic prasiquantel (I) [4] with a broad spectrum of activity. The aim of the present work was to find suitable method for the synthesis of 1-alkyl(aralkyl)-4-acyl-2-piperazinones (IIa-g). Compounds IIa-g were selected as the object products, since they contain the same functional groups as prasiquantel, and have a similar lyophilicity.

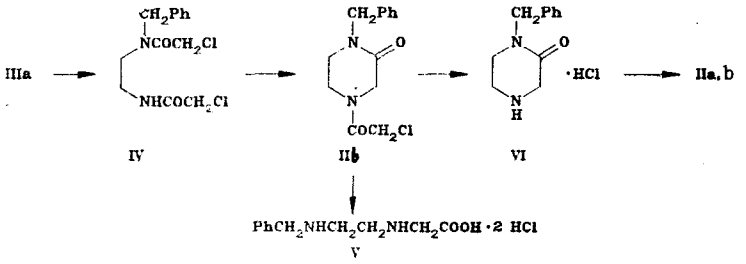
In the course of the investigation, we studied schemes of synthesis of compound IIa-g, based on the use of available N-monosubstituted ethylenediamines IIIa-c.



I IIa-h IIIa-c

IIa-c,f IIIa R^1=$PhCH_2$, IId,e IIIb R^1=$PhCH_2CH_2$, IIfg, IIIc R^1=Et; IIa-e,h IIIa,b R^2=H, IIf,g IIIc R^2=Ph; IIa,d,f R^3=Ph, b R^3=4-$NO_2C_6H_4$, c,e,g R^3=cyclohexyl h R^3=$ClCH_2$

Taking compound IIIa as an example, we first studied the variant of the synthesis of 2-piperazinones, which gives the formation of a hetero ring by the cyclization of the bis-chloroacetyl derivative IV by the action of a strong base, and the subsequent elimination of the chloroacetyl group.



IIIa → IV → IIb → VI ·HCl → IIa,b

IIb → $PhCH_2NHCH_2CH_2NHCH_2COOH \cdot 2\,HCl$ V

During the acylation of compound IIIa by chloroacetyl chloride, the derivative IV is obtained in high yield. By the action of potassium tert-butylate, this converts into piperazinone IIh in a yield of 37% only. Even mild acidic hydrolysis of compound IIh results not

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