FORMATION OF 2-IMIDAZOLINE DERIVATIVES IN THE REACTION OF 1,2-HYDROXYAMINO OXIMES WITH PHENYL- AND METHYLGLYOXAL

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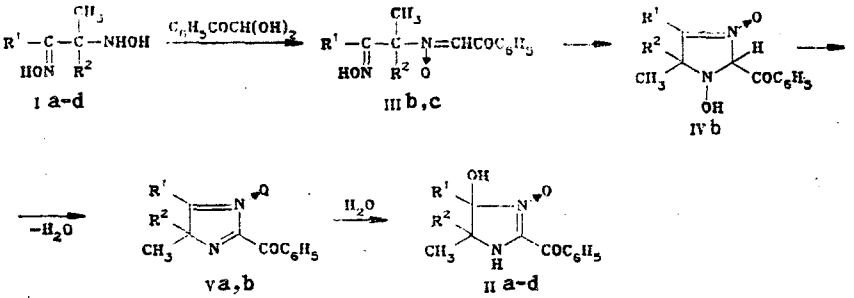
2-Acyl-4-hydroxy-2-imidazoline 3-oxide derivatives were obtained by the reaction of 1,2-hydroxyamino oximes with a hydroxyamino group attached to a tertiary carbon atom with phenyl- and methylglyoxal.

In a previous study of the reaction of 1,2-hydroxyamino oximes with hydroxyamino group attached to a tertiary carbon atom it was shown that the reaction of acyclic 1,2-hydroxyamino oximes Ia, b with diacetyl leads to 2-acetyl-3-imidazoline 3-oxides [1], whereas the reaction of both alicyclic 1,2-hydroxyamino oxime Id and acyclic 1,2-hydroxyamino oxime Ic with an aldoxime group with 1,2-dicarbonyl compounds leads to 2,3-dihydropyrazine 1,4-dioxide derivatives [2, 3]. In the present research we studied the reaction of the same 1,2-hydroxyamino oximes Ia-d with phenyl- and methylglyoxal.

The reaction of Ia-d with phenylglyoxal hydrate in tetrahydrofuran at 20°C for 8-18 days or by refluxing for 2-6 h led to IIa-d (Table 1), the compositions of which correspond to products of condensation with splitting out of a molecule of water. The IR spectra of KBr pellets of IIa-d (Table 2) contain intense bands at 1610-1620 and 1665-1675 cm^{-1}, whereas the IR spectra of 1% solutions in $CHCl_3$ contain bands at ~3410 and at 3575-3590 cm^{-1}, which made it possible to assume the presence of C=N, C=O, NH, and OH bonds. Compounds IIa-d have similar UV spectra with maxima at 256-257 and 320-322 nm (Table 2); this constitutes evidence for the presence of the same chromophore system. These data, as well as data from the PMR and ^{13}C NMR spectra (Table 2), made it possible to assign the 2-benzoyl-4-hydroxy-5,5-dimethyl-4R^1-2-imidazoline 3-oxide structure to IIa-c and the 2-benzoyl-3a-hydroxy-7a-methyl-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole 3-oxide structure to IId. The most characteristic signals in the PMR spectrum of IIc are doublets of methylidyne and hydroxy protons at 5.01 and 5.78 ppm, respectively (Table 2); only a singlet of a methylidyne proton is observed when deuteromethanol is added to the solution. The spectral data (Table 2) make it possible to assume the absence of tautomeric equilibria between IIa-d and their possible N-hydroxy forms (see [4, 5]).

To ascertain the schemes of the formation of IIa-d we conducted a study on the isolation of intermediates. When we decreased the time of the reaction of Ib with phenylglyoxal hydrate to 18 h at 20°C, we obtained a compound, to which we assigned the N-(2-hydroximino-



I—V a $R^1=C_6H_5$; b $R^1=CH_3$; c $R^1=H$; a-c $R^2=CH_3$; d $R^1+R^2=(CH_2)_4$

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TABLE 1. Characteristics of the Compounds Obtained

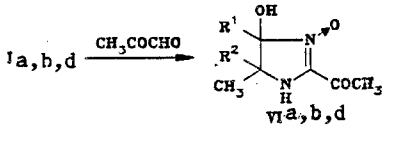
Compound	T_{mp}*, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
II	146—147	69,6	5,8	9,0	$C_{18}H_{18}N_2O_3$	69,7	5,9	9,0	83
II	139—141	63,1	6,3	11,2	$C_{13}H_{16}N_2O_3$	62,9	6,5	11,3	45
II	161—163	61,5	5,9	11,9	$C_{12}H_{14}N_2O_3$	61,5	6,0	12,0	12
II	164—166	66,2	6,2	10,1	$C_{15}H_{18}N_2O_3$	65,7	6,6	10,2	80
III	133—134	62,9	6,3	11,3	$C_{13}H_{16}N_2O_3$	62,9	6,5	11,3	65
III	148—150	61,9	6,0	12,0	$C_{12}H_{14}N_2O_3$	61,5	6,0	12,0	72
IV	140—145	62,9	6,4	11,1	$C_{13}H_{16}N_2O_3$	62,9	6,5	11,3	94
V	138—142	74,5	5,7	9,5	$C_{18}H_{16}N_2O_2$	74,0	5,5	9,6	68
VI	214—215	63,0	6,2	11,0	$C_{13}H_{16}N_2O_3$	62,9	6,5	11,3	70
VI	96—99	51,9	7,5	15,0	$C_8H_{14}N_2O_3$	51,6	7,6	15,0	42
VI	142—143	56,6	7,7	12,7	$C_{10}H_{16}N_2O_3$	56,6	7,6	13,2	49

*The compounds were crystallized: IIa, d, Va, and VIa, b, d from alcohol, IIb from ethyl acetate, IIc from toluene, and IIIb, c from acetone.

1,1-dimethylpropyl)-α-benzoylnitrone structure (IIIb) on the basis of spectral data and the results of elementary analysis. Under similar conditions we obtained α-benzoylnitrone IIIc from Ic. Intense bands at 1525-1530 and 1665 cm^{-1}, which correspond to stretching vibrations of conjugated nitrone and carbonyl groups [6], are observed in the IR spectra of IIIb, c. Compound IIIb is unstable, and in solution it undergoes quantitative conversion to 2-benzoyl-4-hydroxy-4,5,5-trimethyl-2-imidazolin-3-oxide (IIb).

The addition of catalytic amounts of p-toluenesulfonic acid to a solution of α-benzoylnitrone IIIb in alcohol led to 2-benzoyl-1-hydroxy-4,5,5-trimethyl-3-imidazoline 3-oxide (IVb), which is isomeric in composition to IIIb. The UV spectrum of IVb (Table 2) is the superimposition of the absorptions of two chromophore systems, viz., benzoyl and alkylnitrone systems. A quartet of a methylidyne proton (2-H) at 6.17 ppm and a doublet of protons of a methyl group (4-CH_3) at 2.10 ppm, which is due to long-range spin-spin coupling, is observed in the PMR spectrum of IVb; this is possible only for a cyclic structure. 3-Imidazoline 3-oxide IVb is a less stable compound than its acyclic isomer α-benzoylnitrone IIIb. 2-Imidazoline IIb is formed quantitatively when IVb is heated in alcohol or when a solution in chloroform is maintained in the presence of aluminum oxide at 20°C. 4H-Imidazole Vb, the subsequent covalent addition to which of a molecule of water [7, 8] leads to 2-imidazoline IIb, is evidently formed in the dehydration of IVb. In fact, maintenance of solutions of IIIb and IVb in tetrahydrofuran at 20°C leads to an intermediate [monitoring by thin-layer chromatography (TLC)], which is converted to 2-imidazoline IIb and is most likely 4H-imidazole Vb; however, we were unable to isolate the latter. Intermediate 4H-imidazole Va was isolated in the reaction of Ia with phenylglyoxal hydrate at 20°C for 30 h. The greater stability of 4H-imidazole Va as compared with 4H-imidazole Vb can be explained by conjugation of the phenyl group in the 5 position with the imidazole ring, which stabilizes the diazadiene structure of 4H-imidazole Va. Maintenance of a solution of Va in tetrahydrofuran in the presence of catalytic amounts of p-toluenesulfonic acid for 24 h at 20°C leads smoothly to the product of covalent hydration of 4H-imidazole Va, viz., 2-benzoyl-4-hydroxy-5,5-dimethyl-4-phenyl-2-imidazoline 3-oxide (IIa) (see [7, 8]).

The reaction of Ia, b, d with methylglyoxal gives 2-acetyl-2-imidazolines VIa, b, d, the spectral characteristics of which are similar to the spectral characteristics of IIa-d (Table 2). Bands at 3410 and 3570-3585 cm^{-1}, which correspond to stretching vibrations of NH and OH bonds, respectively, are observed in the IR specta (1% solutions in $CHCl_3$) of VIa, c, d.



VIa,b,d

Thus in the case of the reaction of 1,2-hydroxyamino oximes with a hydroxyamino group attached to a tertiary carbon atom with phenylglyoxal hydrate it was shown that the

TABLE 2. Spectral Characteristics of II-VI

Compound	IR spectrum, cm^{-1} (in KBr)	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum,* ppm
IIa	1620, 1670, 3375, 3415	257 (4,02), 322 sh (3,32)	1,07 (3H, s, 5-CH_3); 1,37 (3H, s, 5-CH_3); 3,14 (1H, s, 4-OH); 5,87 (1H, br. s, NH); 7,2—7,8, 8,1—8,4 (10H, m, 2-COC_6H_5, 4-C_6H_5)
IIb	1615, 1665, 3365, 3420	256 (4,02), 321 sh (3,31)	1,21 (3H, s, 5-CH_3); 1,36 (3H, s, 5-CH_3); 1,45 (3H, s, 4-CH_3); 5,13 (1H, s, 4-OH); 6,17 (1H, br.s, NH); 7,2—7,7, 8,0—8,2 (5H, m, 2-COC_6H_5)
IIc	1610, 1665, 3385	256 (4,03), 321 sh (3,34)	1,20 (3H, s, 5-CH_3); 1,29 (3H, s, 5-CH_3); 5,01 (1H, d, J=5,0 Hz, 4-H); 5,78 (1H, d, J=5,0 Hz, 4-OH); 6,27 (1H, br.s, NH); 7,2—7,7, 8,0—8,2 (5H, m, 2-COC_6H_5)
IId	1620, 1675, 3325, 3390	256 (4,00), 324 (3,30)	1,31 (3H, s, 7*a*-CH_3); 1,4—2,2 (8H, m, CH_2); 3,14 (1H, s, 3*a*-OH); 5,70 (1H, br.s, NH); 7,2—7,7, 8,0—8,5 (5H, m, 2-COC_6H_5)
IIIb	1530, 1665, 3355	259 (3,94), 312 (4,15)	1,81 (6H, s, CH_3); 1,96 (3H, s, CH_3); 7,8—8,1, 8,2—8,4 (5H, m, C_6H_5); 8,50 (1H, s, CH)
IIIc	1525, 1665, 3370	259 (3,90), 308 (4,17)	1,79 (6H, s, CH_3); 7,7—8,0, 8,1—8,4 (5H, m, C_6H_5); 8,00 (1H, s, CH); 8,48 (1H, s, CH)
IVb	1625, 1695, 3205	245 (4,35)	1,17 (3H, s, 5-CH_3); 1,38 (3H, s, 5-CH_3); 2,10 (3H, d, J=1,5 Hz, 4-CH_3); 6,17 (1H, q, J=1,5 Hz, 2-H); 7,4—7,7, 8,0—8,2 (5H, m, 2-COC_6H_5)
Va	1680	241 sh (4,16), 261 (4,24), 313 sh (4,00), 339 (4,06)	1,80 (6H, s, 4,4-CH_3); 7,4—7,7, 7,9—8,1, 8,4—8,7 (10H, m, 2-COC_6H_5, 5-C_6H_5)
VIa	1630, 1710, 3340	291 (3,52)	0,96 (3H, s, 5-CH_3); 1,27 (3H, s, 5-CH_3); 2,40 (3H, s, 2-$COCH_3$); 3,20 (1H, s, 4-OH); 5,54 (1H, br. s, NH); 7,2—7,7 (5H, m, 4-C_6H_5)
VIb	1630, 1700, 3280, 3390	292 (3,54)	1,10 (3H, s, 5-CH_3); 1,26 (3H, s, 5-CH_3); 1,50 (3H, s, 4-CH_3); 2,36 (3H, s, 2-$COCH_3$); 3,36 (1H, s, 4-OH); 5,46 (1H, br.s, NH)
VId	1635, 1720, 3375, 3420	294 (3,46)	1,32 (3H, s, 7*a*-CH_3); 1,4—2,1 (8H, m, CH_2); 2,41 (3H, s, 2-$COCH_3$); 3,19 (1H, s, 3*a*-OH); 5,44 (1H, br.s, NH)

*The PMR spectra of the compounds were recorded in various solvents: IIa, d and VIa, b, d in $CDCl_3$, IIIb, c and IVb in CD_3OD, IIb,c in $(CD_3)_2CO$, and Va in CCl_4. ^{13}C NMR spectrum (δ, ppm) of IIb in DMSO: 21.0, 23.1, 25.7 (4,5,5-CH_3); 53.1 [$C_{(5)}$], 96.5 [$C_{(4)}$]; 128.0, 130.4, 133.1, 135.6 (C_6H_5); 148.5 [$C_{(2)}$]; 187.6 (C=O). ^{13}C NMR spectrum (δ, ppm) of VIa in DMSO: 23.8, 25.2, 26.7 (2-$COCH_3$, 5,5-CH_3); 54.3 [$C_{(5)}$]; 98.0 [$C_{(4)}$]; 128.3, 128.7, 129.0, 140.0 (C_6H_5); 148.0 [$C_{(2)}$]; 194.0 (C=O).

formation of 2-acyl-4-hydroxy-2-imidazoline 3-oxides occurs through intermediate 1-hydroxy-3-imidazoline 3-oxides. These hydroxides are readily dehydrated with the formation of 4H-imidazoles, the covalent addition to which of a molecule of water gives 2-acyl-4-hydroxy-2-imidazoline 3-oxides.

EXPERIMENTAL

The IR spectra of KBr pellets or solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A-56/60A spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The ^{13}C NMR spectra were recorded with a Brucker HX-90 spectrometer (22.63 MHz). The course of the reactions was monitored by TLC (Silufol UV-254) with development with UV light and iodine vapors. 1,2-Hydroxyamino oximes Ia-d produced by the Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR, were used.

N-(2-Hydroximino-1,1-dimethylpropyl)-α-benzoylnitrone (IIIb). A 6.6 g (50-mmole) sample of Ib was added to a solution of 7.6 g (50 mmole) of phenylglyoxal hydrate in 60 ml of tetrahydrofuran, after which the mixture was maintained at 20°C for 18 h. The yellow crystals were removed by filtration to give 5.35 g of IIIb. An additional 2.64 g of the substance was obtained from the filtrate by evaporation and treatment with ether.

N-(2-Hydroximino-1,1-dimethylethyl)-α-benzoylnitrone (IIIc). A solution of 3.04 g (20 mmole) of phenylglyoxal hydrate in 8 ml of alcohol was added with stirring to a solution of 2.36 g (20 mmole) of Ic in 25 ml of water, after which the mixture was stirred at 20°C for 17 h. The resulting precipitate was removed by filtration. The yield was 3.50 g.

2-Benzoyl-1-hydroxy-4,5,5-trimethyl-3-imidazoline 3-Oxide (IVb). A) A 0.04 g (0.2 mmole) sample of p-toluenesulfonic acid was added to a suspension of 1.0 g (4 mmole) of IIIb in 20 ml of alcohol, and the mixture was stirred for 5 min. The unchanged nitrone IIIb was removed by filtration, and the filtrate was evaporated. The residue was treated with 5 ml of ethyl acetate, and the precipitate was removed by filtration. The yield was 0.94 g.

B) A solution of 0.1 g (0.4 mmole) of nitrone IIIb in 5 ml of tetrahydrofuran was maintained at 20°C for 2 days, after which the resulting precipitate was removed by filtration. The yield was 0.03 g (30%).

2-Benzoyl-4,4-dimethyl-5-phenyl-4H-imidazole 1-Oxide (Va). A 0.51-g (2.62 mmole) sample of Ia was added to a solution of 0.39 g (2.62 mmole) of phenylglyoxal hydrate in 5 ml of tetrahydrofuran. After 24 h, the solution was evaporated, and the residue was treated with ethyl acetate. The ethyl acetate solution was washed with water, dried with magnesium sulfate, and evaporated. The residue was treated with ether, and the precipitate was removed by filtration. The yield was 0.52 g.

2-Benzoyl-4-hydroxy-5,5-dimethyl-4-phenyl-2-imidazoline 3-Oxide (II). A) A 0.51 g (2.62 mmole) sample of Ia was added to a solution of 0.39 g (2.62 mmole) of phenylglyoxal hydrate in 3 ml of tetrahydrofuran. After 8 days, the solution was evaporated, and the residue was treated with ethyl acetate. The ethyl acetate solution was washed with water, dried with magnesium sulfate, and evaporated. The residue was treated with ether, and the precipitate was removed by filtration. The yield was 0.68 g.

B) A 0.5 ml sample of water and 0.01 g (0.05 mmole) of p-toluenesulfonic acid were added to a solution of 0.1 g (0.34 mmole) of 4H-imidazole Va in 3 ml of tetrahydrofuran. After 24 h, the solution was evaporated, the residue was treated with ether, and the precipitate was removed by filtration. The yield was 0.08 g (75%).

2-Benzoyl-4-hydroxy-4,5,5-trimethyl-2-imidazoline 3 Oxide (IIb). A) This compound was obtained from Ib in 45% yield in analogy to the preparation of oxide IIa by method A; the reaction time was 11 days.

B) A solution of 1.0 g (4.1 mmole) of IIIb in 5 ml of tetrahydrofuran was maintained at 20°C for 12 days, after which it was evaporated. The residue was treated with ether, and the precipitate was removed by filtration. The yield was 0.7 g (70%).

C) A 0.2 g (0.8 mmole) sample of IVb was added with stirring to a suspension of 5 g of aluminum oxide in 20 ml of chloroform, and the mixture was maintained at 20°C for 2.5 h.

The aluminum oxide was removed by filtration and washed with methanol, and the combined filtrates were evaporated. The residue was treated with petroleum ether–ether (3:1), and the precipitate was removed by filtration. The yield was 0.08 g (40%).

2-Benzoyl-4-hydroxy-5,5-dimethyl-2-imidazolin-3-Oxide (IIc). This compound was obtained in 12% yield from Ic in analogy to the method used to prepare oxide IIa by method A; the reaction time was 18 days. The product was isolated by treatment with ether and subsequent cooling.

2-Benzoyl-3a-hydroxy-7a-methyl-3a,4,5,6,7,7a-hexa-hydro-1H-benzimidazole 3-Oxide (IId). A solution of 1.52 g (10 mmole) of phenylglyoxal hydrate in 20 ml of tetrahydrofuran was added to a solution of 2.18 g (10 mmole) of the acetate of Id in 30 ml of tetrahydrofuran, and the mixture was refluxed for 3 h. The solution was evaporated, the residue was treated with ethyl acetate, and the precipitate was removed by filtration to give 2.20 g of oxide IId.

Oxides IIa-c were similarly obtained from the corresponding oximes Ia, c and the acetate of oxime Ib by refluxing in tetrahydrofuran for 6h, 2.5 h, and 30 min, respectively.

2-Acetyl-4-hydroxy-5,5-dimethyl-4-phenyl-2-imidazolin-3-Oxide (VIa). A solution of 2.16 g (30 mmole) on methylglyoxal in 5 ml of tetrahydrofuran was added to a solution of 5.82 g (30 mmole) of oxime Ia in 25 ml of tetrahydrofuran, and the mixture was refluxed for 4 h. It was then cooled, and the resulting precipitate was removed by filtration. The yield was 3.1 g. An additional 2.12 g of product was obtained from the filtrate after evaporation and subsequent chromatography with a column packed with silica gel (elution with chloroform).

2-Acetyl-4-hydroxy-4,5,5-trimethyl-2-imidazoline 3-Oxide (VIb). A solution of 2.7 g (37 mmole) of methylglyoxal in 15 ml of tetrahydrofuran was added to a solution of 3.8 g (20 mmole) of the acetate of oxime Ib in 10 ml of tetrahydrofuran, after which the mixture was refluxed for 6 h. The solution was evaporated, and the residue was chromatographed with a column packed with silica gel (elution with chloroform). The yield was 1.63 g.

2-Acetyl-3a-hydroxy-7a-methyl-3a,4,5,6,7,7a-hexa-hydro-1H-benzimidazole 3 Oxide (VId). A solution of 1.0 g (14 mmole) of methylglyoxal in 10 ml of tetrahydrofuran was added to a solution of 1.42 g (9 mmole) of oxime Id in 5 ml of tetrahydrofuran, and the mixture was maintained at 20°C for 24 h. The solution was evaporated, and the residue was chromatographed with a column packed with silica gel (elution with chloroform). The yield was 0.88 g.

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