PREPARATION OF 2,3- AND 2,5-DIHYDROPYRAZINE 1,4-DIOXIDES FROM 2-HYDROXYAMINO-2-METHYLPROPANAL OXIME AND SOME OF THEIR PROPERTIES

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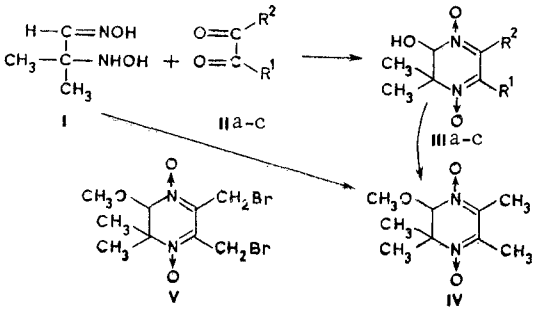
3-Hydroxy-2,3-dihydropyrazine 1,4-dioxide derivatives were obtained by condensation of 2-hydroxyamino-2-methylpropanal oxime with glyoxal, diacetyl, and 1,2-cyclohexanedione in water, and 3-methoxy-2,3-dihydropyrazine 1,4-dioxide was obtained by condensation with diacetyl in methanol. 2,5-Dihydropyrazine 1,4-dioxide is formed when 2-hydroxyamino-2-methylpropanal oxime is heated in a solution of acetone and dilute hydrochloridic acid. The reduction of 3-hydroxy- and 3-methoxy-2,3-dihydropyrazine 1,4-dioxides and 2,5-dihydropyrazine 1,4-dioxide leads to 1,4-dihydroxypiperazines, and the bromination of 3-methoxy-2,3-dihydropyrazine 1,4-dioxide gives 5,6-bis(bromomethyl)-3-methoxy-2,3-dihydropyrazine 1,4-dioxide. 1,4-Dihydroxy-2,5-piperazinedione was obtained by oxidation of 2,5-dihydropyrazine 1,4-dioxide.

It has previously been shown that the reaction of tertiary acyclic 1,2-hydroxyamino oximes with diacetyl gives 2-acetyl-1-hydroxy-3-imidazoline oxides — starting compounds for the preparation of nitroxyl radicals with a functional group in the 2 position of the heteroring [1, 2]. However, the reaction of tertiary alicyclic 1,2-hydroxyamino oximes with 1,2-dicarbonyl compounds leads to 2-hydroxy-2,3-dihydropyrazine 1,4-dioxide derivatives [3]. In a continuation of these investigations we studied the reaction of 2-hydroxyamino-2-methylpropanal oxime* (I) — a tertiary alicyclic 1,2-hydroxyamino oxime that contains an aldoxime group — with 1,2-dicarbonyl compounds IIa-c.

The reaction of 1,2-hydroxyamino oxime I with glyoxal (IIa), diacetyl (IIb), and 1,2-cyclohexanedione (IIc) in water gives 3-hydroxy-2,2-dimethyl- (IIIa) and 3-hydroxy-2,2,5,6-tetramethyl-2,3-dihydropyrazine 1,4-dioxide (IIIb) and 3-hydroxy-2,2-dimethyl-2,3,5,6,7,8-hexahydroquinoxaline 1,4-dioxide (IIIc), respectively. When IIIb is heated in methanol in the presence of p-toluenesulfonic acid, it is converted to 2,2,5,6-tetramethyl-3-methoxy-2,3-dihydropyrazine 1,4-dioxide (IV). The same compound (IV) is formed in the condensation of 1,2-hydroxyamino oxime I with diacetyl (IIb) in methanol.



II, III a $R^1=R^2=H$, b $R^1=R^2=CH_3$, c R^1, $R^2=(CH_2)_4$

*Compound I, which was previously [4] described as N-(1-oximino-2-methyl-2-propyl)hydroxylamine, was named in accordance with the IUPAC rules [5].

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TABLE 1. Spectral Characteristics of Dihydropyrazines and Piperazines

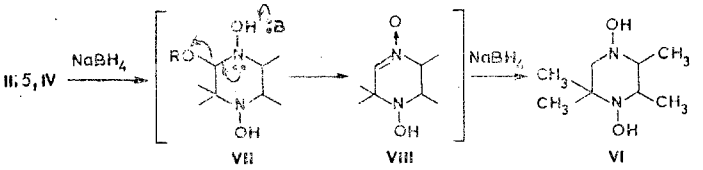
Compound	IR spectrum,[a] cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum,[b] ppm
IIIa	1535, 1580 (C=N)	357 (4.16)	1,27 (3H, s, 2-CH_3); 1,34 (3H, s, 2-CH_3); 4,82 (1H, s, 3-H); 7,20 (2H, s, 5,6-H)
IIIb	1505, 1576 (C=N)	345 (4.14)	1,41 (6H, s, 2,2-CH_3); 2,17 (3H, s, 5- or 6-CH_3); 2,24 (3H, s, 5- or 6-CH_3); 4,97 (1H, s, 3-H); 7,74 (1H, s, 3-OH)
IIIc	1500, 1574 (C=N)	350 (4,19)	1,41 (3H, s, 2-CH_3); 1,51 (3H, s, 2-CH_3); 1,67 (4H, m, 6,7-CH_2); 2,67 (4H, m, 5,8-CH_2); 4,94 (1H, s, 3-H); 7,24 (1H, s, 3-OH)
IV	1508, 1562 (C=N)	348 (4,21)	1,32 (3H, s, 2-CH_3); 1,42 (3H, s, 2-CH_3); 2,09 (3H, s, 5- or 6-CH_3); 2,15 (3H, s, 5- or 6-CH_3); 3,54 (3H, s, 3-OCH_3); 4,60 (1H, s, 3H)
V	1506, 1547 (C=N)	270 (4,12), 368 (4,07)	1,41 (3H, s, 2-CH_3); 1,51 (3H, s, 2-CH_3); 3,62 (3H, s, 3-OCH_3); 4,55 (1H, s, 3-H); 4,29, 4,59 (H_AH_B, J_{AB} = =11.0 Hz, 5- or 6-CH_2Br); 4,37, 4,62 (H_AH_B, J_{AB} = =11,0 Hz, 5- or 6-CH_2Br)
VI			1,21 (3H, d, J=6,4 Hz, 5- or 6-CH_3), 1,25 (3H, s, 2-CH_3); 1,34 (3H, d, J=6,4 Hz, 5- or 6-CH_3); 1,48 (3H, s, 2-CH_3); 2,93 (1H, d, J=10,4 Hz, 3-H); 3,25 (1H, d, J=10,4 Hz, 3-H); 3,48 (2H, m, 5,6-H); 7,22 (1H, s, OH); 7,59 (1H, s, OH)
IX	1607 (C=N)	234 (4,22)	1,96 (12H, s, 2,2,5,5-CH_3); 8,74 (2H, s, 3,6-H)
XII	—	—	1,00 (12H, s, 2,2,5,5-CH_3); 2,57 (4H, s, 3,6-CH_2); 7,03 (2H, br.s, 1,4-OH)
XIII	1672 (C=O)	—	1,39 (12H, s, 3,3,6,6-CH_3); 9,84 (2H, s, 1,4-OH)

[a]The assignment to C=N vibrations was made in analogy with [8]. [b]The PMR spectra were obtained from solutions in $(CD_3)_2SO$ (IIIa, XII, and XIII), $CDCl_3$ (IIIb, IIIc, and V), $(CD_3)_2CO$ (IV), and CD_3OD (IX). The PMR spectrum of VI in pyridine was recorded with a Bruker WP-200SY spectrometer, and signals of only one isomer were observed; the position of the OH band was determined from a solution in $(CD_3)_2SO$.

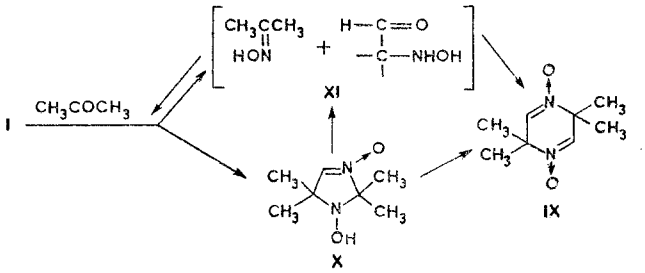
The IR spectra of IIIb, c (in CCl_4 and $CHCl_3$) contain broad bands at 3000-3500 cm^{-1} of an OH group tied up in an intramolecular hydrogen bond, the position of which does not change upon dilution (CCl_4). The UV spectra of derivatives IIIa-c and IV (Table 1) are similar to the UV spectra of the known 2-hydroxy-2,3-dihydropyrazine 1,4-dioxides [3]. The PMR spectra of IIIa-c and IV (Table 1) do not contradict the structures presented above.

Thus, as in the case of tertiary acyclic 1,2-hydroxyamino oximes, the condensation of tertiary acyclic 1,2-hydroxyamino oxime I, which contains an alkoxime group, with 1,2-dicarbonyl compounds IIa-c leads to the formation of dinitrone systems, viz., 2,3-dihydropyrazine 1,4-dioxides IIIa-c. The reactivity of the dinitrone grouping can be used for the introduction of functional groups such as a halogen atom in the α position of the nitrone group [6, 7], and reduction [7] could lead to piperazine derivatives. Treatment of IV with bromine in dioxane led to 5,6-bis(bromomethyl)-2,2-dimethyl-3-methoxy-2,3-dihydropyrazine 1,4-dioxide (V). In contrast to starting IV, two absorption maxima at 270 (log ε 4.12) and 368 nm (log ε 4.11) are observed in the UV spectrum of V (Table 1) (see [3, 6]). It should be noted that in the PMR spectrum of V (Table 1) the methylene protons of the two bromomethyl groups are not equivalent and are observed in the form of two superimposed quartets (A_1B_1 and A_2B_2 systems).

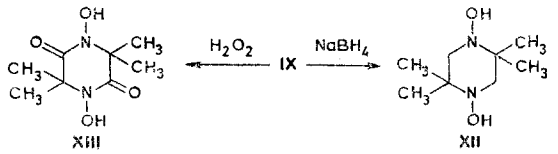
The reduction of IIIb and IV with $NaBH_4$ in water led to the formation of the same VI, i.e., 1,4-dihydroxy-2,2,5,6-tetramethylpiperazine. The chemical shifts in the PMR spectrum of VI (Table 1) and the nonequivalence of the protons of the methylene group in the 3 position of the heteroring and the protons of the two geminal methyl groups in the 2 position of the heteroring are in agreement with this structure. The reduction of IIIb and IV evidently proceeds via the following scheme: The reduction of the two nitrone groups leads to 1,3,4-trihydroxy(or 1,4-dihydroxy-3-methoxy)piperazine VII, and subsequent elimination of water (or methanol) gives tetrahydropyrazine VIII, which is then reduced to VI.



In a study of the properties of 1,2-hydroxyamino oxime I we observed that it is converted to 2,2,5,5-tetramethyl-2,5-dihydropyrazine 1,4-dioxide (IX) when it is heated in acetone with dilute hydrochloric acid solution. Compound IX is not formed in appreciable amounts (according to TLC) when acetone is replaced by ethanol, and starting 1,2-hydroxyamino oxime I is isolated. Compound IX is also formed when 1-hydroxy-2,2,5,5-tetramethyl-3-imidazoline 3-oxide (X) [9] is heated in dilute hydrochloric acid solution. This result makes it possible to assume that the formation of IX proceeds through the initial formation of 3-imidazoline 3-oxide X, which is converted to final product IX under the reaction conditions. However, transoximation of 1,2-hydroxyamino oxime I in acetone in the presence of hydrochloric acid with subsequent condensation of two molecules of intermediate 1,2-hydroxyamino aldehyde XI is not excluded.



Compound IX is readily reduced by $NaBH_4$ in water to give 1,4-dihydroxy-2,2,5,5-tetramethylpiperazine (XII), whereas oxidation with hydrogen peroxide (see [7]) leads to 1,4-dihydroxy-3,3,6,6-tetramethyl-2,5-piperazinedione (XIII) viz., a compound of the series of cyclic hydroxamic acids that are attracting the attention of researchers in connection with their potential biological activity [10, 11]. Treatment of IX with hydroxylamine or hydroxylamine acetate leads to 1,2-hydroxyamino oxime I or its acetate [4], respectively.



Thus dihydropyrazine 1,4-dioxides with both conjugated and isolated nitrone groups can be synthesized from 1,2-hydroxyamino oxime I.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in alcohol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with Varian A-56-60A (60 MHz) and Bruker WP-200SY (200 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The course of the reactions was monitored on Silufol UV-254 plates with development with UV light and iodine vapors. 1,2-Hydroxyamino oxime I produced in the chemical pilot plant of the Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Academy of Sciences of the USSR was used in this research.

3-Hydroxy-2,2-dimethyl-2,3-dihydropyrazine 1,4-Dioxide (IIIa). A 0.58-g (10 mmole) sample of glyoxal IIa (a 25% aqueous solution) was added to a solution of 1.18 g (10 mmole) of I in 30 ml of water. After 24 h, the solution was evaporated, and the residue was triturated with acetone. The precipitate was removed by filtration to give 0.68 g of IIIa. The filtrate was evaporated, and the residue was chromatographed with a column packed with silica gel (elution with ethyl acetate and acetone) to give an additional 0.36 g of IIIa.

3-Hydroxy-2,2,5,6-tetramethyl-2,3-dihydropyrazine 1,4-Dioxide (IIIb). A 0.86-g (10 mmole) sample of diacetyl (IIb) was added to a solution of 0.59 g (5 mmole) of I in 20 ml

TABLE 2. Dihydropyrazines and Piperazines

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IIIa	162—164[a] (dec.)	45,4	6,4	17,5	$C_6H_{10}N_2O_3$	45,6	6,4	17,7	66
IIIb	148—150[b] (dec.)	51,7	7,8	15,1	$C_8H_{14}N_2O_3$	51,6	7,6	15,0	75
IIIc	133—134[c] (dec.)	56,9	7,1	12,6	$C_{10}H_{16}N_2O_3$	56,6	7,6	13,2	77
IV	163—165[c]	53,9	7,8	13,9	$C_9H_{16}N_2O_3$	54,0	8,1	14,0	56
V	122—123[d] (dec.)	30,1	4,0	7,7	$C_9H_{14}Br_2N_2O_3$ [e]	30,2	3,9	7,8	34
VI	184—185[f, g]	55,1	10,9	16,1	$C_8H_{18}N_2O_2$	55,1	10,4	16,1	88
IX	298—300[a]	56,3	8,3	16,6	$C_8H_{14}N_2O_2$	56,4	8,3	16,5	97
XII	224—225[g, h]	55,3	10,0	16,4	$C_8H_{18}N_2O_2$	55,1	10,4	16,1	88
XIII	300—303[a, g]	47,8	7,1	14,0	$C_8H_{14}N_2O_4$	47,5	7,0	13,9	57

[a]From alcohol. [b]From ethyl acetate. [c]From acetone. [d]From carbon tetrachloride. [e]Found: Br 44.4%. Calculated: Br 44.6%. [f]From dimethyl sulfoxide. [g]The melting point was determined in a sealed capillary. [h]From DMF.

of water. After 24 h, the solution was saturated with sodium chloride and extracted with chloroform. The chloroform solution was dried with magnesium sulfate and evaporated, the residue was triturated in ethyl acetate—ether (1:1), and the precipitate was removed by filtration to give 0.70 g of IIIb.

3-Hydroxy-2,2-dimethyl-2,3,5,6,7,8-hexahydroquinoxaline 1,4-dioxide (IIIc) was similarly obtained using an equimolar ratio of I and IIc.

2,2,5,6-Tetramethyl-3-methoxy-2,3-dihydropyrazine 1,4-Dioxide (IV). A) A solution of 0.59 g (5 mmole) of I and 0.86 g (10 mmole) of diacetyl (IIb) in 15 ml of methanol was refluxed for 2 h, after which it was evaporated, and the residue was triturated with ethyl acetate. The precipitate was removed by filtration to give 0.40 g of IV. The filtrate was evaporated, and the residue was chromatographed with a column packed with silica gel (elution with ethyl acetate and acetone) to give an additional 0.16 g of IV.

B) A solution of 186 mg (1 mmole) of IIIb and 4 mg of p-toluenesulfonic acid in 5 ml of methanol was refluxed for 30 min, after which it was evaporated, and the residue was triturated with ether. The precipitate was removed by filtration to give 70 mg (35%) of IV.

5,6-Bis(bromomethyl)-2,2-dimethyl-3-methoxy-2,3-dihydropyrazine 1,4-Dioxide (V). A solution of 1.60 g (10 mmole) of bromine in 10 ml of dry dioxane was added dropwise to a cooled (to −5°C) solution of 1.00 g (5 mmole) of IV in 20 ml of dry dioxane, and the mixture was allowed to stand for 2 h. It was then poured into water, and the aqueous mixture was extracted with chloroform. The chloroform solution was washed with water until the wash water had pH 7, after which it was dried with magnesium sulfate and evaporated. The residue was triturated with diethyl ether, and the precipitate was removed by filtration to give 0.60 g of V.

1,4-Dihydroxy-2,2,5,6-tetramethylpiperazine (VI). A solution of 1.25 g (33 mmole) of $NaBH_4$ in 50 ml of water was added with stirring at 0°C to a solution of 2.18 g (11.7 mmole) of IIIb in 20 ml of water, after which the mixture was maintained at this temperature for 30 min and then at room temperature for 20 h. The precipitate was removed by filtration to give 0.78 g of VI. Extraction of the aqueous solution gave an additional 0.91 g of VI.

Reduction of IV under similar conditions gave VI in 62% yield.

2,2,5,5-Tetramethyl-2,5-dihydropyrazine 1,4-Dioxide (IX). A) A solution of 1.50 g (12.7 mmole) of I in 10 ml of acetone and 10 ml of 0.5% hydrochloric acid was refluxed for 10 h, after which it was evaporated, and the residue was treated with ethyl acetate. The precipitated was removed by filtration to give 1.05 g of IX.

B) A solution of 6.00 g (38 mmole) of X [9] in 50 ml of 0.5% hydrochloric acid was refluxed for 3 h, after which it was evaporated, and the residue was treated with ethyl acetate. The precipitate was removed by filtration to give 2.17 g (67%) of IX.

1,4-Dihydroxy-2,2,5,5-tetramethylpiperazine (XII). A 0.45-g (11.8 mmole) sample of $NaBH_4$ was added in portions with stirring at 0°C to a solution of 2.00 g (11.8 mmole) of IX

in 70 ml of water, and the mixture was maintained at this temperature for 1 h. The precipitate was removed by filtration to give 1.80 g of XII.

1,4-Dihydroxy-3,3,6,6-tetramethyl-2,5-piperazinedione (XIII). A solution of 0.25 g (1.47 mmole) of IX in 5 ml of 30% H_2O_2 was allowed to stand for 6 days, after which the precipitate was removed by filtration to give 0.17 g of XIII.

Reaction of 2,5-Dihydropyrazine 1,4-Dioxide IX with Hydroxylamine and Hydroxylamine Acetate. A solution of 0.23 g (1.35 mmole) of IX and 0.31 g (3.33 mmole) of hydroxylamine acetate in 6 ml of methanol was allowed to stand for 24 h, after which it was evaporated. The residue was treated with ether, and the precipitate was removed by filtration to give 0.47 g (98%) of the acetate of 1,2-hydroxyamino oxime I. The IR spectrum of the salt obtained coincided with the IR spectrum of a genuine sample [4].

The reaction of IX with free hydroxylamine under similar conditions gave 1,2-hydroxyamino oxime I in 85% yield.

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