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# FORMATION OF DERIVATIVES OF PYRAZINE 1,4-DIOXIDE AND 1-HYDROXYIMIDAZOLE IN THE CONDENSATION OF 1,2-HYDROXYAMINO OXIME ACETATES WITH 1-PHENYL- AND 1-(2-HETARYL)-1,2-DICARBONYL COMPOUNDS

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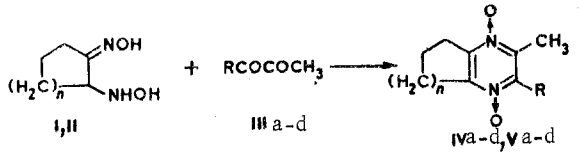
The condensation of acetates of 2-hydroxyaminocyclohexanone and 2-hydroxyaminopentanone oximes with 1-phenyl and 1-(2-hetaryl) 1,2-diketones leads to pyrazine 1,4-dioxide derivatives, whereas the condensation of 2-hydroxyaminocyclohexanone oxime acetate with 1-phenyl- and 1-(2-hetaroyl)glyoxals gives mixtures of pyrazine 1,4-dioxide and 1-hydroxyimidazole derivatives.

We have previously shown that the reaction of secondary 2-hydroxyaminocycloalkanone oximes with aliphatic 1,2-dicarbonyl compounds leads to pyrazine 1,4-dioxide derivatives [1], whereas tertiary 1,2-hydroxyamino oximes condense with diacetyl to give 1-hydroxy-2-acetyl-3-imidazoline 3-oxide derivatives [2]. In the present research we studied the reaction of acetates of 2-hydroxyaminocycloalkanone oximes with 1-phenyl and 1-(2-hetaryl) 1,2-dicarbonyl compounds, viz., both glyoxals and diketones.

2-Hydroxyaminocyclopentanone and 2-hydroxyaminocyclohexanone oximes (I, II) react with 1-phenyl- and 1-(2-hetaryl)-1,2-propanediones (IIIa-d) to give IVa-d and Va-d, the compositions of which correspond to products of condensation with splitting out of two water molecules (Table 1). The IR spectra of IVa-d and Va-d contain intense absorption of an N → O group at 1300-1380 $cm^{-1}$, and the UV spectra coincide with the spectrum of a pyrazine 1,4-dioxide derivative [3]. The PMR spectra are also in agreement with the proposed formulas (Table 2).




I, IV $n=1$; II, V $n=2$; III a R=Ph; b R=2-furyl; c R=2-thienyl, d R=5-methyl-2-furyl

Only the starting compounds were isolated in an attempt to realize the condensation of hydroxyamino oximes I and II with bifuroyl and bibenzoyl under the same conditions.

The available information on direct methods for the synthesis of pyrazine and quinoxaline 1,4-dioxide derivatives without the use of oxidation is limited [4]. At the same time, a number of pyrazine and quinoxaline dioxide derivatives are biologically active substances, particularly when there is a hetaryl substituent in the 2 position [5]. Phenyl- and hetarylglyoxals were therefore subjected to condensation in order to increase the number of pyrazine 1,4-dioxides obtained from 2-hydroxyaminocycloalkanone oximes.

In contrast to 1,2-diketones, phenyl- and hetarylglyoxals VIa-c react with hydroxyamino oximes II via two pathways to give mixtures of 1-hydroxyimidazole derivatives VIIa-c and pyrazine 1,4-dioxide derivatives VIIIa-c. Thus the condensation of II with phenylglyoxal hydrate in alcohol at 20°C for 12 h leads to a mixture of 1-hydroxy-2-benzoyl-4,5,6,7-tetra-

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TABLE 1. Melting Points, Results of Elementary Analysis, and Yields of the Compounds Obtained

| Compound | mp,[a] °C | Found, % | | | Empirical formula[b] | Calc., % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | C | H | N | |
| IVa | 206—208 | 69,4 | 5,8 | 11,7 | $C_{14}H_{14}N_2O_2$ | 69,5 | 5,8 | 11,6 | 78 |
| IVb | 184—185 | 61,5 | 5,3 | 11,7 | $C_{12}H_{12}N_2O_3$ | 62,0 | 5,2 | 12,1 | 76 |
| IVc | 142—143 | 57,9 | 4,9 | 11,1 | $C_{12}H_{12}N_2O_2S$ | 58,0 | 4,8 | 11,3 | 84 |
| IVd | 160—161 | 63,5 | 5,7 | 11,4 | $C_{13}H_{14}N_2O_3$ | 63,5 | 5,7 | 11,4 | 67 |
| Va | 182—183 | 70,4 | 6,0 | 11,2 | $C_{15}H_{16}N_2O_2$ | 70,3 | 6,2 | 10,9 | 83 |
| Vb | 153—154 | 63,4 | 5,8 | 11,2 | $C_{13}H_{14}N_2O_3$ | 63,4 | 5,7 | 11,4 | 81 |
| Vc | 162—164 | 59,1 | 5,4 | 10,5 | $C_{13}H_{14}N_2O_2S$ | 59,6 | 5,4 | 10,7 | 74 |
| Vd | 135—136 | 64,1 | 6,1 | 10,6 | $C_{14}H_{16}N_2O_3$ | 64,5 | 6,2 | 10,8 | 51 |
| VIIa | 143—145 | 60,6 | 5,3 | 9,9 | $C_{14}H_{15}N_2O_2Cl$[c] | 60,4 | 5,4 | 10,0 | 40 |
| VIIb | 107—108 | 61,8 | 5,2 | 11,9 | $C_{12}H_{12}N_2O_3$ | 62,0 | 5,2 | 12,0 | 76 |
| VIIc | 82—83 | 58,2 | 4,9 | 11,4 | $C_{12}H_{12}N_2O_2S$ | 58,0 | 4,8 | 11,3 | 67 |
| VIIIa | 153—155 | 69,9 | 5,4 | 11,7 | $C_{14}H_{14}N_2O_2$ | 69,5 | 5,8 | 11,6 | 30 |
| VIIIb | 200—201 | 61,9 | 5,2 | 11,9 | $C_{12}H_{12}N_2O_3$ | 62,0 | 5,2 | 12,0 | 1 |
| VIIIc | 211—212 | 57,8 | 4,8 | 10,9 | $C_{12}H_{12}N_2O_2S$ | 58,0 | 4,8 | 11,3 | 8 |
| IXb | 130—132 | 55,6 | 4,9 | 11,5 | $C_{11}H_{12}N_2O_4$ | 55,9 | 5,1 | 11,9 | 78 |
| IXc | 120—121 | 48,8 | 5,1 | 10,2 | $C_{11}H_{12}N_2O_3S \cdot H_2O$ | 48,8 | 5,2 | 10,3 | 71 |
| Xa | 179—180 | 68,6 | 5,4 | 12,2 | $C_{11}H_{10}N_2O_3$ | 68,6 | 5,3 | 12,3 | 55 |
| Xb | 207—208 | 61,1 | 4,6 | 13,1 | $C_{13}H_{12}N_2O_2$ | 60,5 | 4,6 | 12,8 | 1 |

[a]The compounds were crystallized: IVa, c and Vd from ethyl acetate, IVb, d, Vb, VIIa, VIIIa-c, IXb, c, and Xa from alcohol, and Va, c and VIIb from acetone (Xb was obtained without crystallization). [b]Found, respectively, for IVc, Vc, VIIc, VIIIc, and IXc: S 12.6; 12.2; 12.9; 12.7; 11.87%. Calculated: S 12.9; 12.2; 12.9; 12.9; 11.9%. [c]Analysis for the hydrochloride.

TABLE 2. Spectral Characteristics of Pyrazine 1,4-Dioxide Derivatives IV, V, VIII, and X

| Compound | UV spectrum, $\lambda_{max}$, nm (log ε) | PMR spectrum,[a] ppm |
|---|---|---|
| IVa | 243 (4,30), 253 sh. (4,24), 307 (4,31) | 6,70 (m, $C_6H_5$); 3,14 [t, 5,7-$(CH_2)_2$]; 2,20 (m, 6-$CH_2$, $CH_3$) |
| IVb | 242 (4,11), 270 (4,27), 291 (4,48) | 7,62 (m); 6,64 (m, $C_4H_3O$); 3,24 [t, 5,7-$(CH_2)_2$]; 2,62 (s, $CH_3$); 2,31 (quint., 6-$CH_2$) |
| IVc | 244 (4,25), 268 (4,15), 298 (4,39) | 7,61 (m); 7,38 (m); 7,16 (m, $C_4H_3S$); 3,24 [t, 5,7-$(CH_2)_2$]; 2,54 (s, $CH_3$); 2,24 (m, 6-$CH_2$) |
| IVd | 244 (4,05), 270 (4,12), 298 (4,48), 338 sh. (4,05) | 7,38 (d); 6,38 (d, $C_4H_2O$); 3,24 [m 5,7-$(CH_2)_2$]; 2,61 (s, pyrazine $CH_3$); 2,21 (m, furan $CH_3$, 6-$CH_2$) |
| Va | 242 (4,28), 253 sh., (4,17), 307 (4.24) | 7,34 (m, $C_6H_5$); 2,75 [m, 5,8-$(CH_2)_2$]; 2,19 (s, $CH_3$); 1,79 [m, 6,7-$(CH_2)_2$] |
| Vb | 241 (4,05), 268 (4,11), 292 (4,36) | 7,64 (m); 7,46 (m); 6,58 (m, $C_4H_3O$); 2,87 [m, 5,8-$(CH_2)_2$]; 2,64 (s, $CH_3$); 1,84 [m, 6,7-$(CH_2)_2$] |
| Vc | 244 (4,24), 266 (4,10), 297 (4,35) | 7,60—7,30 (m $C_4H_3S$); 2,92 [m 5,8-$(CH_2)_2$]; 2,57 (s, $CH_3$); 1,87 [6,7-$(CH_2)_2$] |
| Vd | 242 (4,06), 268 (4,06), 298 (4,52), 338 sh. (4,06) | 7,38 (d); 6,34 (d, $C_4H_2O$); 2,92 [m 5,8-$(CH_2)_2$]; 2,64 (s, pyrazine $CH_3$); 2,38 (s, furan $CH_3$ ); 1,88 [m, 6,7-$(CH_2)_2$] |
| VIIIa | 264 (4,34), 318 (4,21) | 8,19 (s, pyrazine H); 7,49 (m, $C_6H_5$); 2,71 [m 5,8-$(CH_2)_2$]; 1,87 [m 6,7-$(CH_2)_2$] |
| VIIIb | 270 (4,29), 295 (4,59), 320 sh. (4,30), 328 i (4,25) | 8,60 (s, pyrazine H ); 7,96 (m); 7,59 (m); 6,62 (m, $C_4H_3O$); 2,94 [m, 5,8-$(CH_2)_2$]; 1,87 [m 6,7-$(CH_2)_2$] |
| VIIIc | 272 (4,18), 304 (4,57), 338 sh. (4,17) | 8,69 (s, pyrazine H ); 7,74—7,54 (m); 7,19 (m, $C_4H_3S$), 2,92 [m, 5,8-$(CH_2)_2$]; 1,86 [m, 6,7-$(CH_2)_2$] |
| Xa | 267 (4,41), 315 (4,28) | 8,09 (s, pyrazine H ); 7,70—7,47 (m, $C_6H_5$); 3,21 [t, 5,7-$(CH_2)_2$]; 2,27 quint, , 6-$CH_2$) |
| Xb | 275 (4,29), 298 (4,53), 318 sh.. (4,28), 333sh . (4,23) | 8,54 (s, pyrazine H ); 7,99 (m); 7,61 (m); 6,70 (m $C_4H_3O$); 2,94 [m 5,7-$(CH_2)_2$]; 2,38 (m 6-$CH_2$) |

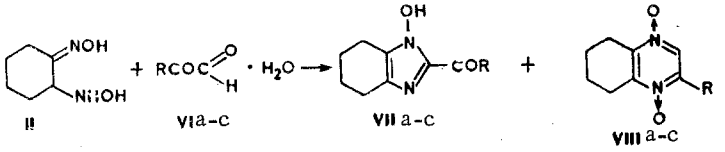
[a]The following solvents were used to record the PMR spectra: $CCl_4$ for Va, IVa, and VIIIa, $CDCl_3$ for Vb, c, IVb, c, d, VIIIb, c, and Xa, b, and $CD_3OD$ for Vd.

TABLE 3. Spectral Characteristics of 1-Hydroxyimidazole Derivatives VIIa-c and α-(2-Hetaroyl)-N-(2-hydroximinocyclopentyl)nitrones IXb, c

| Compound | IR spectrum, $cm^{-1}$ | | UV spectrum, $\lambda_{max}$, nm (log ε) | PMR spectrum,[a] ppm |
|---|---|---|---|---|
| | C=O | CH=N→O | | |
| VIIa | 1650 | | 258 (4,86), 328 (4,10) | 12,70 (OH)[b,c]; 8,57 (m); 7,51 (m, $C_6H_5$); 2,68 [m, 4,7-$(CH_2)_2$]; 1,84 [m, 5,6-$(CH_2)_2$] |
| VIIb[d] | 1630 | | 290 (4,95), 351 (4,24) | 11,50 (OH)[b,c]; 8,14 (m); 7,74 (m); 6,62 (m, $C_4H_3O$); 2,64 [m, 4,7-$(CH_2)_2$]; 1,84 [m, 5,6-$(CH_2)_2$] |
| VIIc | 1630 | | 282 (4,92), 357 (4,24) | 13,34 (OH)[b,c]; 8,64 (m); 7,64 (m); 7,10 (m, $C_4H_3S$); 2,60 [m, 4,7-$(CH_2)_2$]; 1,88 [m, 5,6-$(CH_2)_2$] |
| IXb | 1650 | 1560 | 333 (4,35) | 11,04 (s, OH)[b]; 8,49 (s, aldonitrone H); ); 8,04 (m); 7,64 (m); 6,79 (m, $C_4H_3O$); 5,30 (t, cylcopentane 1-H); 2,45—1,54[e] [3,4,5-$(CH_2)_3$] |
| IXc | 1620 | 1550 | 266 n (3,88), 312 (4,11) | 11,02 (s, OH)[b]; 8,69 (s, aldonitrone-H); 8,08 (m); 7,22 (m, $C_4H_3S$); 5,21 (t, cyclopentane 1-H.); 2,51—1,82[e] [m, 3,4,5-$(CH_2)_3$] |

[a]The following solvents were used to record the PMR spectra: $CDCl_3$ for VIIa, b, $CCl_4$ for VIIc, and $d_6$-DMSO for IXb, c. [b]Vanishes when $CD_3OD$ is added. [c]Broad signal. [d]A band at 3100-3200 $cm^{-1}$, which does not change when the solution (in $CCl_4$) is diluted, is observed in the IR spectrum of VIIb. [e]Broad signal that is partially overlapped by the signal of the undeuterated-solvent impurity.

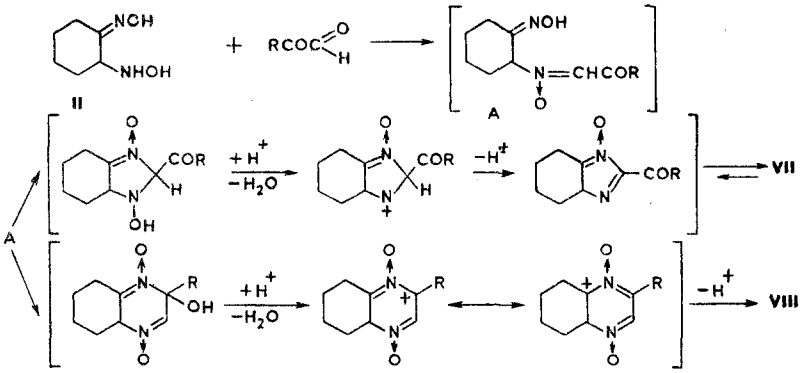
hydrobenzimidazole* (VIIa) (40%) and 2-phenyl-5,6,7,8-tetrahydroquinoxaline 1,4-dioxide (VIIIa) (30%). In contrast to phenylglyoxal, hetarylglyoxals undergo condensation with hydroxyamino oxime II to give primarily 1-hydroxyimidazole derivatives VIIb-c.




VI—VIII a R=Ph; b R=2-furyl ; c R=2-thienyl

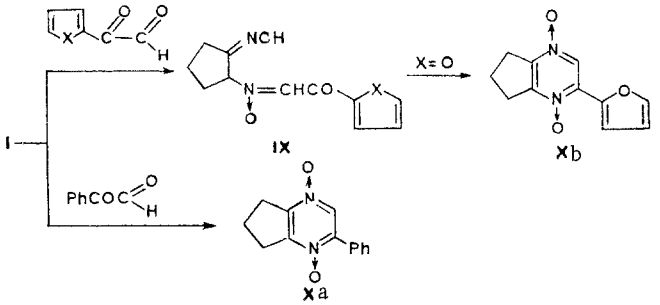
The IR spectra of VIIa-c contain intense absorption of a C=O group at 1650 $cm^{-1}$ and of an OH group at 3100-3200 $cm^{-1}$, which are linked by an intramolecular hydrogen bond. The PMR spectra of imidazoles VIIa-c contain a signal of two methylene groups in the 5 and 6 positions at 1.84 ppm, a signal of two $CH_2$ groups on the 4 and 7 positions at 2.60-2.70 ppm, signals of phenyl and hetaryl substituents at 6.50-8.70 ppm, and a signal of an OH group at 11.50-13.30 ppm, which vanishes when $CD_3OD$ is added (Table 3). The IR, UV, and PMR spectra of VIIIa-c correspond to pyrazine 1,4-dioxide derivatives (Table 2).

The formation of a mixture of 1-hydroxyimidazole and pyrazine 1,4-dioxide derivatives can be represented by a scheme in which the initially formed nitrone A can undergo cyclization at both the carbon atom of the nitrone group and at the carbon atom of the carbonyl group to give cations B and C, which by subsequent splitting out of a proton and aromatization are converted to the final products (see [1]).




*The possibility that VIIa-c exist in the tautomeric imidazole N-oxide form [6] is less likely.

The hypothetical intermediate nitrone was not isolated in the condensation of hydroxyamino oxime II with 2-hetarylglyoxals VIb, c; however, stable α-(2-furoyl)- and α-(2-theonyl)-N-(2-hydroxyiminocyclopentyl)nitrones (IXb, c) are formed in a similar reaction in the case of condensation of hydroxyamino oxime I. With respect to their compositions, IXb, c correspond to products of condensation with splitting out of one water molecule. The IR spectra of IXb, c contain intense absorption of conjugated C=N → O and C=O groups at 1550 and 1650 $cm^{-1}$, and the UV spectrum corresponds to a conjugated nitrone [7]. The PMR spectra of nitrones IXb, c contain a signal of an oxime group at 11.00 ppm, which vanishes when $CD_3OD$ is added, a signal of a hydrogen atom of an aldonitrone at 8.5-8.7 ppm, a signal of three hydrogen atoms of hetaryl rings at 7.0-8.0 ppm, and a signal of a secondary hydrogen atom of a cyclopentane ring in the 1 position in the form of a triplet (Table 3).




IX b X=O, c X=S

2-(2-Furyl)-6,7-dihydro-5H-cyclopentanopyrazine 1,4-dioxide (Xb) was obtained in low yield, along with 2-furylglyoxal aldoxime (40%), which was formed in the acidic hydrolysis of the nitrone due to transoximation, when nitrone IXb was heated with an alcohol solution of hydrochloric acid. It is interesting to note that the formation of an intermediate nitrone of the A type was not observed in the reaction of hydroxyamino oxime I with phenylglyoxal; 2-phenyl-6,7-dihydro-5H-cyclopentanopyrazine 1,4-dioxide (Xa) was isolated in 50% yield.

Thus in the present research we have expanded the range of application of the condensation of hydroxyamino oximes I and II with 1,2-diketones to obtain new pyrazine 1,4-dioxide derivatives and have also uncovered a new pathway in the reaction of hydroamino oximes with phenyl- and hetarylglyoxals IVa-c to give 1-hydroxyimidazole derivatives.

## EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of 5-7% solutions of the compounds were recorded with a Varian A-56-60 A spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The yields, melting points, and results of elementary analysis of the compounds are presented in Table 1, and their spectral characteristics are presented in Tables 2 and 3.

Condensation of Acetates of Hydroxyamino Oximes I and II with 1-Phenyl-1,2-propanedione. A 0.01-mole sample of 1-phenyl-1,2-propanedione was added to a solution of 0.01 mole of the hydroxyamino oxime acetate in 18 ml of alcohol, and the mixture was refluxed for 3 h. The alcohol was evaporated, the residue was triturated with ether, and the precipitate was removed by filtration. Pyrazines IVa and Va were purified by crystallization.

Condensation of Acetates of Hydroxyamino Oximes I and II with 1-(2-Hetaryl)-1,2-propanediones (IIIa-d). A 0.01-mole sample of 1-(2-hetaryl)-1,2-propanedione was added to a solution of 0.01 mole of the hydroxyamino oxime in 30 ml of alcohol, and the yellow solution was allowed to stand at 20°C for 12 h. The alcohol was evaporated, the residue was triturated with ether, and the precipitate was removed by filtration. Pyrazines IVb-d and Vb-d were purified by crystallization.

Condensation of the Acetate of 2-Hydroxyamino Oxime II with Phenyl- and 2-Hetarylglyoxals VIa-c. A 0.015-mole sample of hydrated glyoxal VI was added to a solution of 0.015 mole of hydroxyamino oxime II in 50 ml of alcohol, and the mixture was allowed to stand at 20°C for 12 h. The alcohol was evaporated, and 1-hydroxyimidazole derivatives VIIa-c were isolated from the residue by chromatography with a column packed with silica

gel by elution with ether. Subsequent elution with acetone gave pyrazine dioxide derivatives VIIIa-c. The substances were purified by crystallization.

2-Phenyl-6,7-dihydro-5H-cyclopentanopyrazine 1,4-Dioxide (Xa). This compound was obtained under the same conditions by condensation of hydrated phenylglyoxal with hydroxyamino oxime I. Pyrazine Xa was isolated by chromatography with a column packed with silica gel by elution with ethyl acetate and was purified by crystallization.

Condensation of the Acetate of Hydroxyamino Oxime I with 2-Furylglyoxal. A 0.01-mole sample of hydrated furylglyoxal was added to a solution of 0.01 mole of hydroxyamino oxime I in 25 ml of alcohol. After 15 min, nitrone IXb precipitated from the dark-yellow solution. The suspension was filtered, and the precipitated nitrone was washed with alcohol and purified by crystallization to give gold-yellow crystals.

Condensation of the Acetate of Hydroxyamino Oxime I with 2-Thienylglyoxal. A 0.015-mole sample of hydrated 2-thienylglyoxal was dissolved in 40 ml of water at 70°C, and 0.01 mole of hydroxyamino oxime I was added, during which gold nitrone IXc precipitated. The suspension was filtered, and the precipitated nitrone was washed with water and ether acetate and purified by crystallization.

Cyclization of Nitrone IXb. A 4-mmole sample of nitrone IXb was mixed with 15 ml of alcohol, and 2.5 ml of concentrated HCl was added, during which the nitrone dissolved with spontaneous heat evolution. After 30 min, the mixture was neutralized with dry sodium bicarbonate, the alcohol was evaporated, and the black precipitate was extracted with ether. The extract was dried with sodium sulfate, the ether was evaporated, and the residue was chromatographed with a column packed with silica gel by elution with ether to give 2-furylglyoxal aldoxime (40%). Subsequent elution with acetone gave 2-(2-furyl)-6,7-dihydro-5H-cyclopentanopyrazine 1,4-dioxide (Xb). The products were purified by crystallization. 2-Furylglyoxal aldoxime was identified from its IR spectrum by comparison with the spectrum of a genuine sample [8].

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