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4- AND 5-HYDROXYLAMINOTHIAZOLIDINE-2-THIONES. REACTION WITH 4-NITROBENZALDEHYDE

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Stable nitrones are formed in the condensation of 5-hydroxylaminothiazolidine-2-thiones with 4-nitrobenzaldehyde. At the same time, nitrones obtained from the isomeric 4-hydroxylaminothiazolidine-2-thiones, as well as 4-hydroxylaminoimidazolidin-2-one, can undergo rearrangement to E- or Z-O-substituted 4-nitrobenzaldoximes, depending on the structure and the reaction conditions.

In a continuation of our research on the synthesis and study of the reactivities of hydroxylaminothia(imida)zolidine-2-thiones(ones) [1, 2] we examined their reaction with 4-nitrobenzaldehyde.

Thus, regardless of the structures of substituents R^1—R^4, 5-hydroxylaminothiazolidine-2-thiones I react with the aldehyde to give stable [N-(thiazolidine-2-thion-5-yl)-C-(4-nitrophenyl)]nitrones IIa,b [1] and IIc,d; it is best to carry out the reaction in the presence of 4-toluenesulfonic acid (TSA).

In the case of the isomeric 4-hydroxylaminothiazolidine-2-thiones III, however, the corresponding nitrones Va-e can be obtained only in the absence of TSA and when R^1 = H. Similar conditions are also necessary for the formation of nitrone VI from 4-hydroxylaminoimidazolidin-2-one IV.

A completely different situation arises when the reaction of 4-hydroxylamino derivatives III and IV with the aldehyde is carried out in the presence of TSA and, in the case of the sterically hindered hydroxylamines IIIf,g (R^1 = CH_3), also without it. Although they do have the empirical formulas of the corresponding nitrones, the UV spectra (ethanol) of the resulting VIIa-g and VIII do not contain the absorption at 340-350 nm that is characteristic for nitrones [1], a 0.1-0.4 ppm shift of the signal of the azomethine proton to weaker field as compared with the PMR spectra of nitrones III is observed in their PMR spectra, and the IR spectra (KBr) do not contain bands of stretching vibrations of an N—O bond but do contain bands at 900-1000 cm^{-1}, which are more characteristic for the vibrations of an oxime group [3]. In addition, VII and VIII do not react with sodium borohydride [3].

An O-substituted 4-nitrobenzaldoxime structure can be assigned to VII and VIII on the basis of these data. The alternative synthesis of VIIc and VIII by the reaction of, respectively, 4-hydroxythiazolidine-2-thione IXa and 4-hydroxyimidazolidin-2-one IXc with E-4-nitrobenzaldoxime [2] makes it possible to conclude that the oxime group of derivatives VII and VIII has an E configuration.

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We also established that, in contrast to nitrones II, nitrones V and VI undergo rearrangement to the corresponding oximes VII and VIII when they are heated in the presence of TSA.

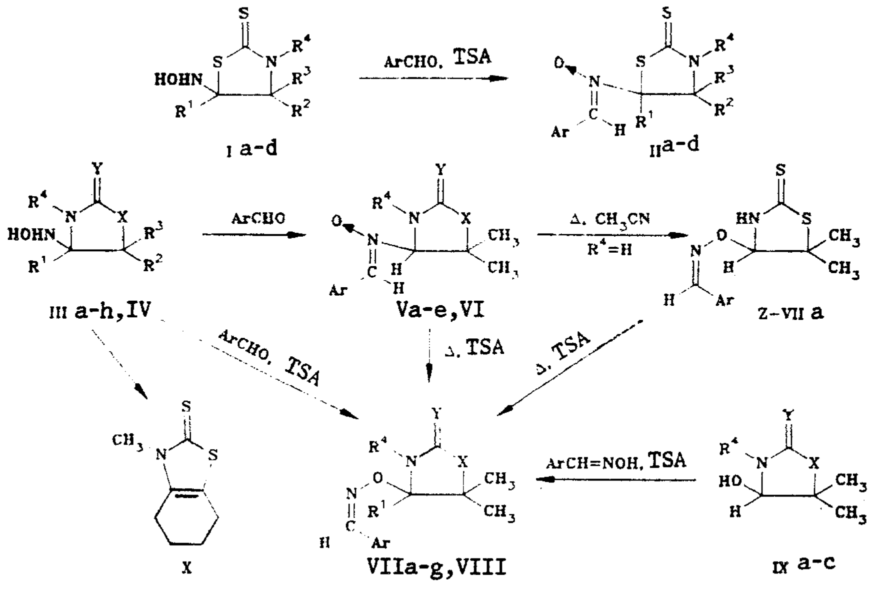
In addition, we noted that, according to TLC data, hydroxy products IX and the E-4-nitrobenzaldoxime are present in the reaction mixtures in all cases involving the formation of oximes, while carrying out the rearrangement of nitrone Vb ($R^4 = CH_3$) in the presence of hydroxy derivative IXb ($R^4 = CH_2C_6H_5$) leads to a mixture of oximes VIIb and VIIe.

The results obtained attest that nitrones V and VI, like 4-hydroxylamino derivatives III and IV [1, 2, 4], under acid-catalysis conditions, in contrast to isomeric compounds I and II, undergo hydrolysis to the corresponding 4-hydroxy derivatives IX, as well as the E-4-nitrobenzaldoxime, which are known [2] to readily react with one another (acid catalysis) to give oximes VII and VIII (see Scheme 1).

The formation of oximes VIIf, g ($R^1 = CH_3$) also in the absence of TSA is evidently due to the instability of the resulting nitrones as a consequence of the greater steric hindrance. In the case of hydroxylamine IIIh [$R^1 + R^2 = (CH_2)_4$], however, 4-thiazoline-2-thione X was isolated instead of the expected nitrone or oxime [1].

The properties of nitrone Va ($R^4 = H$) should be dealt with separately. In contrast to the rest of the synthesized nitrones, which can be recrystallized from alcohol, nitrone Va is converted to 4-ethoxythiazolidine-2-thione XI and the thermodynamically less favorable Z-4-nitrobenzaldoxime XII upon brief heating in alcohol. However, heating in dry acetonitrile is accompanied by its rearrangement to a substituted 4-nitrobenzaldoxime with a Z configuration of the oxime group (Z-VIIa). At the same time, the oxime obtained in the condensation of hydroxylamine IIIa with the aldehyde in the presence of TSA has an E configuration (E-VIIa). The E- and Z-isomeric assignments were made from PMR spectroscopic data. Thus the signal of the H—C=N proton of oxime E-VIIa is located at weaker field by 0.62 ppm as compared with the corresponding signal of Z-VIIa; this is due to the anisotropic deshielding effect of the OH group, which is cis-oriented with respect to it [5] (see Scheme 2).

Scheme 1



I, II a $R^1+R^2=(CH_2)_4$, $R^3=H$, $R^4=CH_3$, b $R^1=H$, $R^2=R^3=R^4=CH_3$, c $R^1=R^2=R^3=R^4=CH_3$, d $R^1=R^2=R^3=CH_3$, $R^4=H$; III a–e $R^1=H$, $R^2=R^3=CH_3$, f, g $R^1=R^2=R^3=CH_3$, h $R^1+R^2=(CH_2)_4$, $R^3=H$, a, f $R^4=H$, b, g, h $R^4=CH_3$, c $R^4=i\text{-}C_3H_7$, d $R^4=C_6H_5$, e $R^4=CH_2C_6H_5$, a-h $X=Y=S$; IV $R^1=H$, $R^2=R^3=CH_3$, $R^4=C_6H_5$ $X=NCH_3$, $Y=O$; V a $R^4=H$, b $R^4=CH_3$, c $R^4=i\text{-}C_3H_7$, d $R^4=C_6H_5$, e $R^4=CH_2C_6H_5$, a–e $X=Y=S$; VI $R^4=C_6H_5$, $X=NCH_3$, $Y=O$; VII a–e $R^1=H$, f, g $R^1=CH_3$, a, f $R^4=H$, b, g $R^4=CH$, c $R^4=i\text{-}CH_3H_7$, d $R^4=C_6H_5$, e $R^4=CH_2C_6H_5$, $X=Y=S$; VIII $R^1=H$, $R^4=C_6H_5$, $X=NCH_3$, $Y=O$; IX a $R^4=i\text{-}C_3H_7$, b $R^4=CH_2C_6H_5$, c $R^4=C_6H_5$, a, b $X=Y=S$, c $X=NCH_3$, $Y=O$; $Ar=4\text{-}NO_2C_6H_4$

The reduction of nitrone Va with sodium borohydride does not lead to the expected N,N-disubstituted hydroxylamine. The Z-4-nitrobenzaldoxime and 5,5-dimethylthiazolidine-2-thione (XIII) are isolated in this case.

Such properties of nitrone Va are evidently associated with the presence of a labile hydrogen atom in the 3 position of the heteroring. It may be assumed that the intermediate formation of a 3-thiazoline-2-thione (A) and Z-benzaldoxime XII occurs during the examined reactions. Thiazoline A reacts with alcohol to give ethoxy derivative XI, while it is reduced by sodium borohydride to give XIII. Oxime Z-VIIa evidently can also be formed in the reaction

TABLE 1. Characteristics of II, V-VIII, XI, and XIII and PMR Spectra (d_6-DMSO) of IId, Va-c, VIIa-c,e,f, XI, and XIII

Compound	Chemical shifts, δ, ppm (SSCC, Hz)							
	empirical formula	mp, °C	CH or CCH$_3$ [or CH$_2$]	C(CH$_3$)$_2$	R^4	CH=N→O. CH=N—,s	Ar, m	yield, %
II c	$C_{14}H_{17}N_3O_3S_2$	123						50
II d	$C_{13}H_{15}N_3O_3S_2$	107 ... 109	1,99s	1,28; 1,46	10,46 (br.s, H)	8,29	8,06 ... 86,3	62
V a	$C_{12}H_{13}N_3O_3S_2$	131 ... 132	5,83s	1,40; 1,69	10,53 (br.s, H)	8,24	8,0 ... 8,55	92
V b	$C_{13}H_{15}N_3O_3S_2$	173 ... 175	6,0s	1,39; 1,65	3,15 (s, H)	8,18	8,06 ... 8,66	67
V c	$C_{15}H_{19}N_3O_3S_2$	167 ... 170	6,19s	1,35; 1,58	1,09 d, 1,28 d, 5,74 m [$J=7{,}5$, CH(CH$_3$)$_2$]	8,45	8,01 ... 8,50	45
V d	$C_{18}H_{17}N_3O_3S_2$	189 ... 191						53
V e	$C_{19}H_{19}N_3O_3S_2$	162 ... 164						68
VI	$C_{19}H_{20}N_4O_4$	210 ... 212						75
E-VII a	$C_{12}H_{13}N_3O_3S_2$	148 ... 149	5,62s	1,46; 1,59	10,95 (br. s, H)	8,58	7,73 ... 8,40	96
Z-VII a	$C_{12}H_{13}N_3O_3S_2$	146 ... 147	5,62s	1,48; 1,60	10,98 (br. s H)	7,96	8,06 ... 8,40	60
VII b	$C_{13}H_{15}N_3O_3S_2$	164 ... 166	5,88s	1,44; 1,60	3,31 (s, CH$_3$)	8,62	7,75 ... 8,40	61
VII c	$C_{15}H_{19}N_3O_3S_2$	163 ... 165	6,04s	1,43; 1,54	1,2 d, 1,31 d, 4,88 m [$J=7{,}5$, CH(CH$_3$)$_2$]	8,55	7,84 ... 8,33	71
VII d	$C_{18}H_{17}N_3O_3S_2$	154 ... 156						90
VII e	$C_{19}H_{19}N_3O_3S_2$	91 ... 92	5,63s	1,44; 1,46	4,54, 5,51 [AB-system ($J=15$), CH$_2$C$_6$H$_5$]	8,48	7,65 ... 8,36	65
VII f	$C_{13}H_{15}N_3O_3S_2$	142 ... 144	1,50s	1,46; 1,65	10,91 (br s, H)	8,44	7,73 ... 8,36	61
VII g	$C_{14}H_{17}N_3O_3S_2$	106 ... 108						50
VIII	$C_{19}H_{20}N_4O_4$	145 ... 147						62
XI*	$C_7H_{13}NOS_2$	135 ... 137	—	1,46; 1,56	For C$_2$H$_5$O: 1,16 t [$J=7{,}5$, CH$_3$]; 3,38 ... 3,94 [2H, AB-part of an ABX$_3$-system, where X$_3$–CH$_3$ protons]			49
XIII	$C_5H_9NS_2$	159 ... 160**	3,69 d ($J=1{,}5$)	1,50	—	—	—	40

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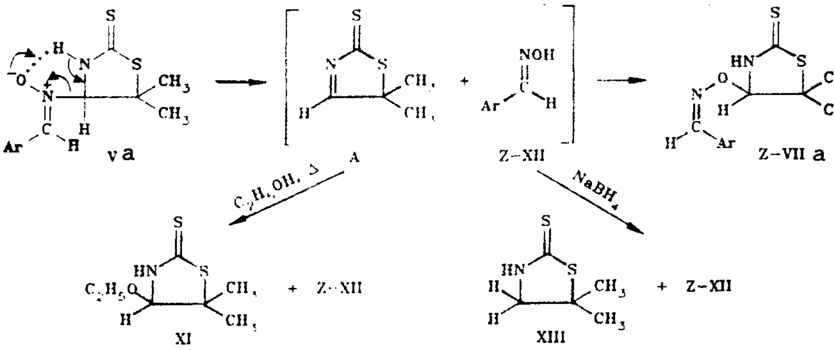
*Benzene, mp 162-163°C [8].

**In $(CD_3)_2CO$.

of thiazoline A with oxime Z-XII; however, the possibility of the realization in this case also of intramolecular isomerization similar to that which occurs in the rearrangement of N-acylnitrones to Z-O-carbamoyloximes [6, 7] cannot be excluded.

Scheme 2



The isolation of Z-4-nitrobenzaldoxime XII and the formation of oxime VIIa make it possible to assume that nitrone Va also has a Z configuration; the other nitrones, viz., II, V, and VI (comparison of the PMR data), also probably have the same configuration.

EXPERIMENTAL

The IR spectra of KBr pellets and solutions of the compounds in CCl_4 were recorded with a Perkin—Elmer spectrometer. The UV spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with Varian FT-80A (80 MHz) and Bruker HX-90E (90 MHz) spectrometers with tetramethylsilane (TMS) as the internal standard. The course of the reactions was monitored on Silufol UV-254 plates in a benzene—acetone (3:1) system.

The characteristics of the compounds are presented in Table 1.

The I-III and IX used in this research were obtained by the methods in [1, 3].

[(N-Thiazolidine-2-thion-4-yl)- or (N-Imidazolidin-2-on-4-yl)-C-(4-nitrophenyl)]nitrones V and VI. A. A solution of 3 mmole of 4-nitrobenzaldehyde in 5 ml of absolute alcohol was added to a solution of 3 mmole of hydroxylamine IIIa, b or IV in 10 ml of absolute alcohol, the mixture was maintained at 20°C for 5 h, and the resulting precipitate was removed by filtration. This procedure was used to obtain Va, b and VI.

B. A mixture of equimolar amounts of hydroxylamine IIIc-e and 4-nitrobenzaldehyde was refluxed in absolute alcohol for 10 min, after which the alcohol was removed, the residue was treated with a small amount of alcohol, and the precipitate was removed by filtration. This procedure gave Vc-e.

Oximes VIIf,g were obtained by a similar method from IIIf,g by refluxing the reaction mixtures for 3 h.

[(N-Thiazolidine-2-thion-5-yl)-C-(4-nitrophenyl)]nitrones II and O-(Thiazolidine-2-thion-4-yl)- or O-(Imidazolidin-2-on-4-yl)-4-nitrobenzaldoximes VII and VIII. A mixture of equimolar amounts of hydroxylamine Ic,d, IIIa-g, or IV and 4-nitrobenzaldehyde was refluxed in benzene with a Dean—Stark adapter in the presence of catalytic amounts of toluenesulfonic acid (TSA). At the end of the reaction the benzene was evaporated (monitoring by TLC, 30 min), and the residue was treated with a small amount of ether. The crystallized precipitate was removed by filtration to give, respectively, nitrones IIc,d and oximes VIIa-g and VIII.

Reaction of 4-Hydroxylaminothiazolidine-2-thione IIIh with 4-Nitrobenzaldehyde. A mixture of equimolar amounts of hydroxylamine IIIh and 4-nitrobenzaldehyde in benzene was refluxed in the presence and absence of TSA. At the end of the reaction (monitoring by TLC) the benzene was evaporated, and the precipitate was recrystallized from petroleum ether (40-70°C). This procedure gave a compound that was identical, according to the IR spectrum, to thiazoline-2-thione X [1] in 45% yield. According to TLC data, E-4-nitrobenzaldoxime XII was present in the reaction mixture.

Alternative Synthesis of Oximes VIIc and VIII. Equimolar amounts of hydroxy derivative IXa,c and E-4-nitrobenzaldoxime were refluxed in benzene with a Dean—Stark adapter in the presence of catalytic amounts of TSA. At the end of the reaction (monitoring by TLC) the reaction mixture was filtered, the solvent was evaporated, and the residue was treated with ether. This procedure gave compounds with IR spectra that were identical to the IR spectra of oximes VIIc and VIII, respectively.

Rearrangement of Nitrones Vb, c and VI to Oximes VIIb, c and VIII and of Oxime Z-VIIa to Oxime E-VIIa. A suspension of 1 mmole of nitrone Vb,c or VI or oxime Z-VIIa in 5 ml of benzene was refluxed in the presence of TSA. At the end of the reaction (monitoring by TLC, ≈15 min) the reaction mass was filtered, the benzene was evaporated, the residue was treated with 2 ml of ether, and the precipitate was removed by filtration. This procedure gave oximes VIIb, c, VIII, and E-VIIa.

Rearrangement of Nitrone Vb to Oxime VIIb in the Presence of 4-Hydroxy Derivative IXb. A mixture of 1 mmole of nitrone Vb and 0.5 mmole of IXb in 15 ml of benzene was treated as in the preceding method. Compounds VIIb,e were isolated by TLC [Silufol, elution with benzene—acetone (3:1)].

Rearrangement of Nitrone Va to Oxime Z-VIIa. A solution of 2 mmole of nitrone Va in 30 ml of dry acetonitrile (dried with magnesium sulfate for 24 h) was refluxed for 5 min. At the end of the reaction (monitoring by TLC) the acetonitrile was evaporated, the residue was treated with 3 ml of ether, and the precipitate was removed by filtration to give oxime Z-VIIa.

Ethanolysis of Nitrone VIIa. A solution of 1.5 mmole of nitrone VIIa in 10 ml of absolute alcohol was refluxed for 15 min. The alcohol was then evaporated, the residue was treated with 2 ml of alcohol, and the precipitate was removed by filtration to give 0.11 g (57%) of Z-4-nitrobenzaldoxime XII. The IR spectrum was identical to the IR spectrum of a genuine sample. The filtrate remaining after isolation of the Z-oxime was evaporated, the residue was treated with 10 ml of ether, and the mixture was filtered. The ether was evaporated, and the residue was recrystallized from hexane to give 0.12 g of 4-ethoxythiazolidine-2-thione XI. IR spectrum (KBr): 1480, 1345, 1275, 1210, 1145, 1095, 1020, 990, 690 cm^{-1}.

Reduction of Nitrone VIIa. A 2-mmole sample of sodium borohydride was added in portions with stirring to a solution of 1 mmole of nitrone VIIa in 50 ml of tetrahydrofuran and 10 ml of alcohol, and the mixture was stirred for ≈30 min at 20°C. It was then filtered, and the filtrate was evaporated. The residue was treated with 20 ml of water, and the residue was removed by filtration and recrystallized from benzene to give Z-4-nitrobenzaldoxime XII in 70% yield. The IR spectrum was identical to the IR spectrum of a genuine sample. A second reaction product was extracted from the aqueous filtrate with ether (30 3-ml portions). The ether extract was dried with magnesium sulfate, the ether was evaporated, and the residue was crystallized with hexane to give XIII. IR spectrum (KBr): 1510, 1300, 1055, 1030 cm^{-1}; (CCl_4): 3420 cm^{-1} (NH).

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