CHEMISTRY OF α-HYDROXYAMINO OXIMES

X. Condensation of anti-α-Hydroxyamino Oximes with Ketones and the Production of 2-Isoimidazole N-Oxides*

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The reaction of anti-α-hydroxyamino oximes with ketones gives substituted 1-hydroxy-3-imidazoline 3-oxides. The action of hydrogen chloride on the latter and on their acetyl derivatives leads to the isomeric 2-isoimidazole N-oxides differing by the position of the N-oxide oxygen in the isoimidazole ring. The structure of the latter compounds has been established by means of IR, UV, and PMR spectra and has been confirmed by independent synthesis.

It has been shown previously [2] that the direction of the reaction of α-hydroxyamino oximes with aliphatic aldehydes depends on the configuration of the oxime group: the syn isomers give derivatives of 4H-1,2,5-oxadiazine and the anti-isomers derivatives of 3-imidazoline-3-oxide. The latter, under certain conditions, are converted into the isomeric imidazole N-oxides differing by the position of the N-oxide oxygen in the imidazole ring [3].

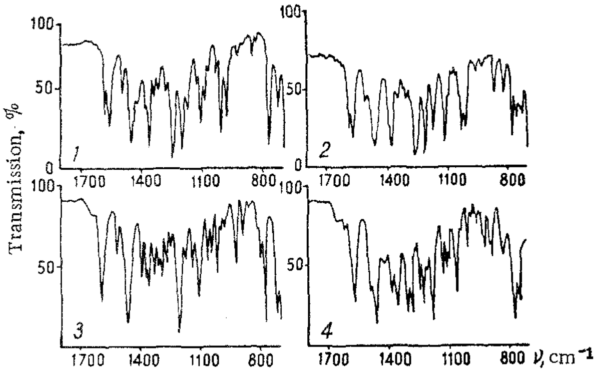
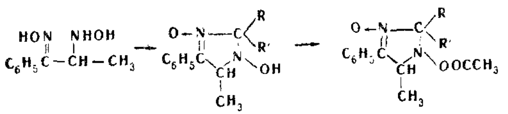


Fig. 1. IR spectra in KBr: 1) II, 2) III, 3) IV, 4) VIII.

In the present work we have studied the condensation of anti-α-hydroxyamino oximes with ketones. The reactions of N-(1-anti-hydroxyimino-1-phenyl-2-propyl)hydroxylamine (I) with acetone, methyl ethyl ketone, and cyclohexanone gave the colorless crystalline substances II, III, and IV, corresponding in composition to the products of the condensation of compound I and the corresponding ketone with the elimination of a molecule of water.



I

II $R = R' = CH_3$
III $R = CH_3$, $R' = C_2H_5$
IV $RR' = (-CH_2-)_5$

V $R = R' = CH_3$
VI $RR' = (-CH_2-)_5$
XII $R = H$, $R' = CH_3$

The UV spectra of II, III, and IV are identical with one another and are similar to the UV spectra of N-methyl-α-phenylnitrone, which shows the presence in them of the phenylnitrone grouping $O \leftarrow N{=}C{-}C_6H_5$ [2] The IR spectra of these compounds (II, III, and IV) have intense absorption bands at 1205, 1208, and 1203 cm^{-1}, respectively (Fig. 1), which can be assigned to the stretching vibrations of the semipolar N → O bond (cf. [4]). The broad absorption bands with maxima at 3180, 3190, and 3240 cm^{-1}, respectively, show the presence of an OH group participating in a hydrogen bond. In the IR spectra of the acetyl derivatives of II and IV (V and VI), this band has disappeared and the bands of the ester grouping —CO—O—at 1220 and 1765 and at 1225 and 1775 cm^{-1}, respectively, have appeared. The IR spectra of the acetyl derivatives V and VI are practically identical with those of II and IV.

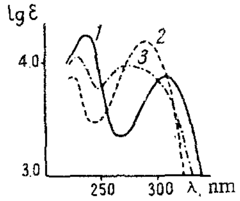


Fig. 2. UV spectra in ethanol: 1) X, 2) V, 3) XIV.

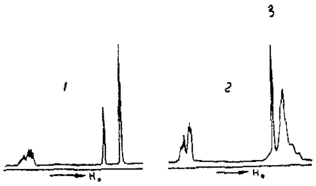


Fig. 3. PMR spectra in $CDCl_3$: 1) X, 2) XI.

A consideration of the spectral characteristics and the results of elementary analysis has permitted compounds II, III, and IV to be assigned the structures 1-hydroxy-2,2,5-trimethyl-4-phenyl-, 1-hydroxy-2-ethyl-2,5-dimethyl-4-phenyl-, and 1-hydroxy-5-methyl-2,2-pentamethylene-4-phenyl-3-imidazoline 3-oxides and V and VI the structures of the O-acetyl derivatives of II and IV.

It was to be expected that other anti-α-hydroxyamino oximes would also give condensation products of analogous structure with ketones. In fact, the re-

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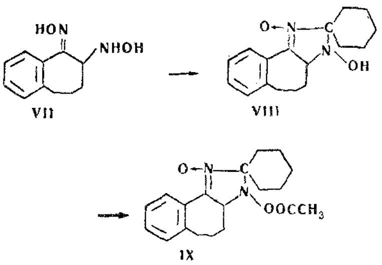
*For communication IX, see [1].

Table 1

1-Hydroxy 3-imidazoline 3-Oxides and Their Acetyl-Derivatives

Compound	Mp, °C	Empirical formula	Found, %			Calculated, %		
			C	H	N	C	H	N
II	148—150	$C_{12}H_{16}N_2O_2$	65.6; 66.1	7.4; 7.5	12.4; 12.6	65.5	7.3	12.7
III	123—125	$C_{13}H_{18}N_2O_2$	66.4; 66.3	7.7; 7.9	11.8; 12.0	66.8	7.7	11.9
IV	184—186	$C_{15}H_{20}N_2O_2$	69.4; 69.6	7.4; 7.4	10.5; 10.8	69.4	7.7	10.8
V	112—114	$C_{14}H_{18}N_2O_3$	64.4; 64.3	7.3; 7.1	11.0; 11.0	64.1	6.9	10.7
VI	133—135	$C_{17}H_{22}N_2O_3$	67.8; 67.8	7.5; 7.6	9.4; 9.6	67.8	7.3	9.3
VIII	191—193	$C_{17}H_{22}N_2O_2$	71.5; 71.7	7.7; 7.7	9.9; 10.0	71.3	7.7	9.8
IX	139—141	$C_{19}H_{24}N_2O_3$	69.3; 69.4	7.2; 7.2	8.3; 8.3	69.6	7.3	8.5

action of N-(1-hydroxyimino-2,3-benzocyclohept-7-yl)hydroxylamine (VII) with cyclohexanone gave a condensation product with the composition $C_{17}H_{22}N_2O_2$ (VIII) to which, on the basis of a consideration of the IR spectrum (1176 cm^{-1}, N → O) and UV spectrum (λ_{max} 296 nm, log ε 4.08), the structure of 1-hydroxy-2,2-pentamethylene-2',3'-benzocyclopentane [7',1': 5,4] 3-imidazoline-3-oxide has been assigned. The treatment of VIII with acetic anhydride led to the O-acetyl derivative IX.



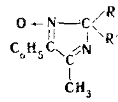
VII VIII IX

Under the action of dilute hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine, compound II was readily hydrolyzed, giving acetone 2,4-dinitrophenylhydrazone and the initial α-hydroxyamino oxime I. It was not possible to split off acetic acid by heating V in vacuum to the melting point (cf. [5]), but the treatment of ethanolic solutions of V and VI with hydrogen chloride led to compounds X and XI, the compositions of which corresponded to the products of the elimination of a molecule of acetic acid from V and VI.

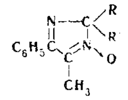
The IR spectra of X and XI (in CCl_4) lack absorption in the region of the stretching vibrations of a hydroxy group. Compounds **X and XI** have similar UV spectra which differ considerably from the spectra of the initial V and VI (Fig. 2). However, while the transition from 1-acetoxy-2,5-dimethyl-4-phenyl-3-imidazoline 3-oxide (XII) to 2,5-dimethyl-4-phenylimidazole 3-oxide (XIII) is accompanied by the complete disappearance of the long-wave band with λ_{max} 290 nm (log ε 4.19) [5], corresponding to the absorption of the $O \leftarrow N{=}C{-}C_6H_5$ grouping, in the UV spectra of X and XI the absorption in this region is preserved (Fig. 2). This is apparently due to the fact that compounds X and XI retain the chromophoric system of the phenylnitrone grouping.

In the PMR spectrum of X (Fig. 3), recorded for a 30% solution in $CDCl_3$, there are two well-defined singlets at 8.51 and 7.62 ppm [the chemical shifts of the protons are given on Tiers' scale] and a complex band with a center at 2.44 ppm with an intensity ratio close to 6 : 3 : 5. The band at 8.51 ppm corresponds to the six hydrogen atoms of two methyl groups attached to carbon atom 2, that at 7.62 ppm to the three hydrogen atoms of the single methyl group attached to carbon atom 5, and that at 2.44 ppm to the five hydrogen atoms of the phenyl residue. In the PMR spectrum of XI (Fig. 3) taken under the same conditions there is a broad band of the ten hydrogen atoms of the cyclohexene ring at 8.22 ppm, a well-defined singlet of the three hydrogen atoms of the methyl group at 7.50 ppm, and a complex band of the five aromatic hydrogen atoms at 2.59 ppm.

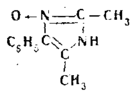
On the basis of their elementary analyses and IR, UV, and PMR spectra, it may be concluded that X has the structure of 2,2, 5-trimethyl-4-phenyl-2-iso-imidazole 3-oxide and XI that of 5-methyl-2,2-pentamethylene-4-phenyl-2-iso-imidazole 3-oxide.



X R = R' = CH_3
XI RR' = $(-CH_2-)_5$



XIV R = R' = CH_3
XV RR' = $(-CH_2-)_5$



XIII

In studying the conversion of hydroxyimidazoline N-oxides into 2-iso-imidazole N-oxides, we treated

Table 2

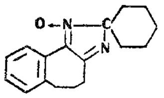
2-Isoimidazole N-Oxides

Compound	Mp, °C	Empirical formula	Found, %			Calculated, %		
			C	H	N	C	H	N
X	77—79	$C_{12}H_{14}N_2O$	71.2; 71.5	7.0; 7.1	13.9; 14.2	71.2	7.0	13.8
XI	78—80	$C_{15}H_{18}N_2O$	74.0; 74.2	7.5; 7.6	11.5; 11.6	74.4	7.4	11.6
XIV	83—85	$C_{12}H_{14}N_2O$	71.3; 71.4	7.0; 7.0	13.7; 13.8	71.2	7.0	13.8
XV	76—78	$C_{15}H_{18}N_2O$	74.0; 74.1	7.5; 7.6	11.5; 11.6	74.4	7.4	11.6
XVIII	128—130	$C_{17}H_{20}N_2O$	76.0; 76.1	7.3; 7.5	10.3; 10.6	76.2	7.5	10.4
XIX	138—140	$C_{17}H_{20}N_2O$	76.0; 76.2	7.4; 7.7	10.4; 10.4	76.2	7.5	10.4

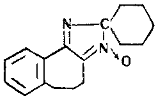
an ethanolic solution of the unacylated compound II with hydrogen chloride and obtained compound XIV, which had the same composition as X but differed from it in respect of melting point and IR and UV spectra. Similarly, from IV we obtained compound XV, which again differed from XI in its melting point and spectral characteristics.

The IR spectra of XIV and XV (in CCl_4) lacked absorption in the region of the stretching vibrations of a free hydroxy group. The UV spectra of XIV and XV (Fig. 2) were practically identical with one another, but differed both from the spectra of the initial compounds II and IV and from the spectra of imidazole N-oxides [5]. The PMR spectrum of XIV was similar in respect of the position of the bands (8.43, 7.68, and 2.36 ppm) and in the ratio of the intensities (6: 3: 5) to the PMR spectrum of X. The PMR spectrum of XV (8.16, 7.74, and 2.44 ppm, ratio of intensities 10: 3: 5) was likewise similar to the PMR spectrum of XI.

On the basis of what has been said, it may be concluded that XIV and XV are isomers of X and XI respectively, and differ from them only by the position of the N-oxide in the isoimidazole ring. Consequently, XIV has been ascribed the structure of 2, 2, 4-trimethyl-5-phenyl-2-isoimidazole 3-oxide and XV that of 4-methyl-2, 2-pentamethylene-5-phenyl-2-isoimidazole 3-oxide.



XVIII



XIX

Analogously, from IX we obtained 2, 2-pentamethyllene-2', 3'-benzocyclopentano-[7',1': 5, 4]-2-isoimidazole 3-oxide (XVIII) and from (VIII) 2,2-pentamethylene-2',3'-benzocycloheptano[7',1': 4,5]-2-isoimidazole 3-oxide (XIX).

The 2-isoimidazoles have begun to attract attention only comparatively recently [6], although they have been postulated as intermediates in the formation of N-substituted imidazoles [7]. There is still less information in the literature on N-oxides of 2-isoimidazoles [8–10]. Consequently, it seemed to us to be desirable to attempt to obtain these compounds by an independent route. For this purpose, we used a synthesis analogous to that given in the literature [11] for imidazole N-oxides (see also [5]). The reaction of acetone and ammonia with α-phenyl-α-isonitrosoacetone gave a compound identical with X and that with α-isonitrosopropio-phenone gave a compound identical with XIV. Under the same conditions, the reaction with cyclohexanone led to compounds identical with XI and XV.

EXPERIMENTAL

The IR spectra were recorded on a UR-10 spectrophotometer: for solid samples compared with potassium bromide (concentration 0.5%, tablet thickness 1 mm) and for solutions in CCl_4 (concentration 5%, layer thickness 0.1 mm). The UV spectra were taken on an SF-4-spectrophotometer; ethanol was used as the solvent. The PMR spectra were recorded for 30% solutions in $CDCl_3$ on a TsLA-5535 (40 MHz) instrument. Hexamethyldisiloxane was used as internal standard [12].

Condensation of α-hydroxyamino oximes with ketones. A tenfold excess of the appropriate ketone was added to 1.0 g of an α-hydroxyamino oxime. In the case of II and III, 1 ml of water was also added to the mixture. The solution was boiled for 30 min (in the case of VIII, for 5 min) and evaporated to dryness. The residue was crystallized, II from benzene, III from a mixture of benzene and ethanol, and IV and VIII from ethanol. The yields of condensation products amounted to 90–100%. The melting points and the elementary analysis of the compounds obtained are given in Table 1.

Acylation of the 1-hydroxy-3-imidazoline 3-oxides. Acetic anhydride (0.5 ml) was added to a suspension of 1.0 g of II in 15 ml of chloroform and the mixture was boiled for 30 min, after which it was cooled, washed with 5% sodium carbonate solution and water, dried with magnesium sulfate, and the solvent was distilled off in vacuum. The residue was recrystallized from cyclohexane. The acetylation of IV and VIII was carried out similarly. Compound VI was crystallized from cyclohexane and IX from ethanol. The yields of the acylation products amounted to 70–90%. The melting points and elementary analyses of the compounds obtained are given in Table 1.

Preparation of 2-isoimidazole N-oxides. The acetyl derivative of 1-hydroxy-3-imidazoline-3-oxide was dissolved in ethanol and then hydrogen chloride was passed through the solution and it was diluted with ether. The hydrochloride that precipitated was dissolved in methanol and the solution was saturated with ammonia, diluted with ether, and filtered, and the solvent was driven off. The compounds X, XI, and XVIII obtained in this way were crystallized from n-hexane. The saturation with hydrogen chloride of ethanolic solutions of the unacylated 1-hydroxy-3-imidazoline 3-oxides and the subsequent treatment of the hydrochlorides in a manner similar to that described above gave XIV, XV, and XIX, which were crystallized from n-hexane. The yields of the 2-isoimidazole N-oxides amounted to 70–90%. The melting points and elementary analyses of the 2-isoimidazole N-oxides and their hydrochlorides are given in Tables 2 and 3.

Independent synthesis of the 2-isoimidazole N-oxides. A solution of α-isonitroso-α-phenylacetone in ethanol was treated with a threefold excess by weight of the appropriate ketone and also with an excess of ~30% aqueous ammonia. After 4 hr, the solvent was distilled off in vacuum and the residual crystalline product (X, XI) was recrystallized from n-hexane. Compounds XIV and XV were synthesized similarly from α-isonitrosopropiophenone. The compounds X, XI, XIV, and XV obtained by this method were completely identical with the substances obtained from II, IV, V, and VI, respectively (from their IR spectra and melting points).

Hydrolysis of 1-hydroxy-2,2,5-trimethyl-4-phenyl-3-imidazoline 3-oxide (II). A heated solution of 0.137 g of 2,4-dinitrophenylhydrazine and 0.5 ml of 20% hydrochloric acid in 5 ml of ethanol was

Table 3

2-Isoimidazole N-Oxide Hydrochlorides

Compound	Mp, °C	Empirical formula	Found, %				Calculated, %			
			C	H	N	Cl	C	H	N	Cl
X · HCl	178–180	$C_{12}H_{14}N_2O \cdot HCl$	59.8; 59.8	6.6; 6.6	11.8; 12.0	14.3; 14.4	60.4	6.3	11.7	14.9
XI · HCl	198–200	$C_{15}H_{18}N_2O \cdot HCl$	64.7; 65.0	6.7; 6.8	9.7; 9.9	12.6; 12.7	64.7	6.9	10.0	12.7
XIV · HCl	182–184	$C_{12}H_{14}N_2O \cdot HCl$	60.5; 60.9	6.0; 6.3	11.8; 11.9	14.8; 15.2	60.4	6.3	11.7	14.9
XV · HCl	178–180	$C_{15}H_{18}N_2O \cdot HCl$	64.3; 64.4	6.8; 6.9	10.0; 10.3	12.4; 12.6	64.7	6.9	10.0	12.7

added to a heated solution of 0.150 g of **II** in 7 ml of ethanol and the mixture was heated to the boil and then cooled. The acetone 2,4-dinitrophenylhydrazone that separated out was filtered off; 0.11 g (69%), mp 125°–126° C (from ethanol). The filtrate was evaporated to minimum volume, diluted with a double volume of water, and neutralized with 10% sodium hydroxide solution. The precipitate that separated out was filtered off; 0.04 g (38%), mp 162°–164° C, giving no depression in admixture with compound **I**; the IR spectra of this compound and of **I** also proved to be identical.

REFERENCES

1. L. B. Volodarskii and A. N. Lysak, KhGS [Chemistry of Heterocyclic Compounds], 904, 1967.
2. L. B. Volodarskii, A. N. Lysak, and V. A. Koptyug, KhGS [Chemistry of Heterocyclic Compounds], 766, 1966.
3. L. B. Volodarskii, A. N. Lysak, and V. A. Koptyug, Tetrah. let., 1565, 1965.
4. I. Thesing and W. Sirrenberg, Chem. Ber., 92, 1748, 1959.
5. L. B. Volodarskii and A. N. Lysak, KhGS, collection 1, p. 109, 1967.
6. F. Asinger, M. Thiel, and R. Sowada, Mon., 90, 402, 1959.
7. M. Weiss, J. Am. Chem. Soc., **74**, 5193, 1952.
8. T. J. Haley, A. M. Flesher and L. Mavis, Nat., **195**, 1012, 1962.
9. T. J. Haley, Giorn. Ital. Chemioterap., **6–9**, 213, 1962; C. A., **58**, 12847a, 1963.
10. J. E. Baldwin and N. N. Rogers, Chem. Commun., 524, 1965.
11. F. J. Allan and G. G. Allan, Chem. and Ind., 1837, 1964.
12. H. Schmidbaur, J. Am. Chem. Soc., 85, 2336, 1963.

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