PREPARATION AND ALKALINE CLEAVAGE OF 4H-IMIDAZOLE N-OXIDES

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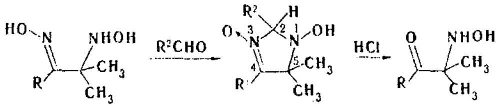
Heating 1-acyloxy-5,5-dimethyl-3-imidazoline 3-oxides in vacuo gives derivatives of 4H-imidazole 1-oxides. The reaction of the latter with alkalis is accompanied by ring opening and the formation of oximes of α-acylamino ketones.

The dehydration of 1-hydroxy-3-imidazoline 3-oxides, which, depending on the degree of substitution of the heteroring, leads to N-oxides of imidazoles and 2H-imidazoles, was previously described in [1,2]. Continuing our study of the possibilities of the synthetic use of 1-hydroxy-3-imidazoline 3-oxides, we attempted to extend the dehydration method to 5,5-dimethyl-substituted compounds of this series in order to obtain the uninvestigated 4H-imidazole N-oxides.

The condensation of N-(1-oximino-2-methyl-1-phenyl-2-propyl)hydroxylamine (Ia) with acetaldehyde and benzaldehyde and of N-(3-oximino-2-methyl-2-butyl)hydroxylamine (Ib) with acetaldehyde gives, respectively, 1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline 3-oxide (IIa), 1-hydroxy-5,5-dimethyl-2,4-diphenyl-3-imidazoline 3-oxide (IIb), and 1-hydroxy-2,4,5,5-tetramethyl-3-imidazoline 3-oxide (IIc). In alcohol IIb is in tautomeric equilibrium with N-(1-oximino-2-methyl-1-phenyl-2-propyl)-α-phenylnitrone in a ratio of 3 : 1 (see [2]).

Dehydration products are not obtained by the action of a 20% alkali solution [3] on IIa-c nor by heating them in vacuo above their melting points. Disintegration of the heteroring to form α-hydroxylamino ketones (IIIa,b) [4] does occur when they are treated with hydrogen chloride.



I II III

I a $R = C_6H_5$, b $R = CH_3$; II a $R^1 = C_6H_5$, $R^2 = CH_3$, b $R^1 = R^2 = C_6H_5$, c $R^1 = R^2 = CH_3$;
IIIa $R = C_6H_5$, b $R = CH_3$

It has been previously shown that acylation of 1-hydroxy-3-imidazoline 3-oxides facilitates dehydration [1]. Heating IIa,b with acetic anhydride and IIc with benzoic anhydride in chloroform gives monoacyl derivatives IVa-c in the IR spectra of which one observes the characteristic bands of an ester grouping – at 1220 and 1770 cm^{-1} for IVa,b and at 1250 and 1750 cm^{-1} for IVc.

The action of an alkaline solution on benzoyl derivative IVc leads to splitting out of benzoic acid and the formation of a colorless crystalline product (Vc) with the composition $C_7H_{14}N_2O_2$. The IR spectrum of this compound contains bands at 1670 and 3420 cm^{-1} with a weak component at 3460 cm^{-1}, which indicate the presence of a secondary amine group in the molecule [5], and the band of a free hydroxyl group at 3600 cm^{-1}. The compound does not absorb in the near-UV region. The PMR spectrum of this compound (Table 1) consists of a singlet from two geminal methyl groups attached to a saturated carbon atom at 8.69 ppm and of two singlets of methyl groups attached to the carbon atoms with a double bond at 8.36 and 8.23 ppm;

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TABLE 1. Chemical Shifts of the Protons (τ, ppm) in the PMR Spectra of the Compounds Obtained[a]

Compound	R^1	R^2	gem- $(CH_3)_2$
Va[b]	2,34—3,06[c]	8,33	8,59
Vb	2,36—2,81[c]	d	8,36
Vc[e]	8,36	8,23	8,69
VII	7,90	8,09[f]	8,55
VIIIa	1,36—1,82 2,33—2,56[c]	7,58	8,41
VIIIb	1,33—1,80 2,30—2,56[c]	g	8,29
VIIIc[g]	7,80	7,69	8,69

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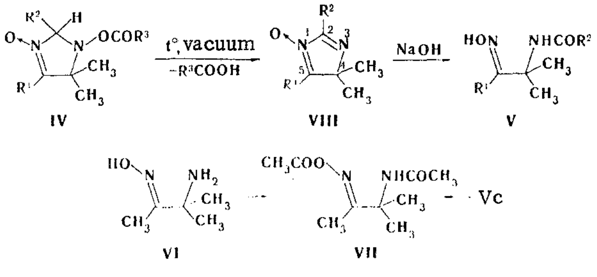
[a] The spectra were recorded for ~10% solutions in CD_3OD except where otherwise specified. [b] Recorded in d_6-DMSO with the OH signal at −0.44 ppm. [c] Complex bands of the protons of the benzene rings. [d] The R^2 signals coincide with the R^1 signals. [e] Recorded in d_6-DMSO with a broad NH signal at 2.29 ppm and an OH signal at −0.24 ppm. [f] The signal intensity corresponds to two CH_3CO groups. [g] Recorded in CCl_4.

there is a broad band of an NH group at weak field at 2.29 ppm and a distinct singlet of the hydroxyl group of the oxime group at −0.24 ppm [6,7]. Both weak-field signals disappear when deuteromethanol is added. On the basis of these data, it can be concluded that Vc has the 2-acetamido-2-methyl-3-butanone oxime structure. This compound has not been described, but the unacylated 2-amino-2-methyl-3-butanone oxime (VI) is known and is formed in the reaction of the dimer of 2-methyl-2-butene nitrosochloride with ammonia [8]. α-Amino oxime VI has complexing properties, and the oxime group consequently has the anti configuration. Heating both α-amino oxime VI and Vc in excess acetic anhydride gives the same 3-acetoximino-2-acetamido-2-methylbutane (VII).

Treatment of acetyl derivatives IVa,b with an alkali solution (with heating) gives Va,b. Since the spectral characteristics of these compounds (Table 1) are close to the spectral characteristics of Vc, the α-acylamino oxime structure (Va,b) was assigned to them by analogy. It can be assumed that the formation of Va-c begins with the cleavage of an oxygen molecule and the formation of 4H-imidazole 1-oxides and subsequent cleavage of the heteroring by the action of alkali.

When benzoyl derivative IVc is heated in vacuo, benzoic acid is split out, and an unstable oil (VIIIc) is formed. The IR spectrum of VIIIc does not contain absorption in the region of the stretching vibrations of the hydroxyl, amino, and amide groups, but there is a broad band at 1580 cm^{-1}, which is characteristic for the C=N bond in nitrones [9]. The absorption maximum in the UV spectrum is found at 280 nm (log ε 3.50), i.e., it is shifted by about 40 nm to the long-wave region as compared with starting compound IVc, which indicates the appearance of a conjugated system of multiple bonds. The singlets of two geminal methyl groups at 8.69 ppm and of two methyl groups at 7.80 and 7.69 ppm are observed in the PMR spectrum of VIIIc, and this, together with the optical-spectroscopy data, indicates the 2,4,4,5-tetramethyl-4H-imidazole 1-oxide structure. An almost quantitative yield of Vc is obtained by the action of aqueous alkali (with heating) on freshly prepared VIIIc.



IVa $R^1=C_6H_5$, $R^2=R^3=CH_3$; b $R^1=R^2=C_6H_5$, $R^3=CH_3$; c $R^1=R^2=CH_3$, $R^3=C_6H_5$;
VIII a $R^1=C_6H_5$, $R^2=CH_3$; b $R^1=R^2=C_6H_5$; c $R^1=R^2=CH_3$
Va $R^1=C_6H_5$, $R^2=CH_3$; b $R^1=R^2=C_6H_5$; c $R^1=R^2=CH_3$

TABLE 2. Synthesized Compounds

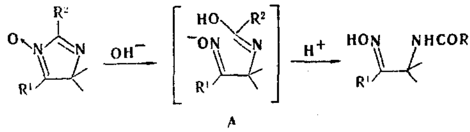
Comp.	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
IIa[a]	133—135	$C_{12}H_{14}N_2O_2$	65,5	7,3	12,7	65,5	7,3	12,7	92
IIb[b]	162—164	$C_{17}H_{18}N_2O_2$	72,3	6,5	10,3	72,3	6,4	9,9	82
IIc[b]	96—97	$C_7H_{14}N_2O_2$	53,1	9,0	17,7	53,1	9,0	17,7	86
IVa[b]	121—123	$C_{14}H_{18}N_2O_3$	64,0	6,7	10,8	64,1	6,9	10,8	75
IVb[b]	154—156	$C_{19}H_{20}N_2O_3$	70,9	6,2	8,8	70,5	6,2	8,7	70
IVc[c]	106—108	$C_{14}H_{18}N_2O_3$	64,1	6,7	10,7	64,1	6,9	10,8	55
Va[d]	193—194	$C_{12}H_{16}N_2O_2$	64,8	6,8	12,6	65,5	7,3	12,7	75
Vb[a]	179—181	$C_{17}H_{18}N_2O_3$	72,7	6,5	9,8	72,3	6,4	9,9	60
Vc[e]	174—175	$C_7H_{14}N_2O_2$	53,1	9,0	17,4	53,1	8,9	17,7	81
VII[f]	67—69	$C_9H_{16}N_2O_3$	54,1	7,8	14,0	54,0	8,0	14,0	96
VIIIa[g]	105—106	$C_{12}H_{14}N_2O$	71,1	7,0	14,1	71,3	6,9	13,8	93
VIIIb[g]	127—130	$C_{17}H_{16}N_2O$	77,0	5,8	11,1	77,4	6,1	10,6	87
VIIIc[h]	oil	$C_7H_{12}N_2O$	59,5	8,2	19,8	60,0	8,6	20,0	53

[a] From ethyl acetate. [b] From alcohol. [c] From alcohol–ether. [d] From chloroform. [e] From alcohol–ethyl acetate. [f] From ether. [g] From cyclohexane. [h] The analytical and spectral characteristics were obtained for freshly prepared compounds, since changes are observed in the IR spectrum after about 20 h.

When acetyl derivative IVa is heated in vacuo, a yellow crystalline substance (VIIIa) sublimes. This substance proved to be stable and was resublimed. The composition of VIIIa corresponds to splitting out of a molecule of acetic acid from IVa. The position of the absorption maximum in its UV spectrum (λ_{max} 324 nm, log ε 3.86) is shifted to the long-wave region by about 30 nm as compared with the position of the maximum in the spectrum of starting IVa, which is apparently also a consequence of the appearance of an additional multiple bond. The PMR spectrum of VIIIa contains a singlet from two geminal methyl groups at 8.41 ppm, a singlet of one methyl group at 7.58 ppm, and two complex bands at 1.36-1.82 and 2.33-2.56 ppm (the intensity ratio is 2 : 3), which correspond to the five protons of the benzene ring. The separation into two signals is apparently due to the electron-acceptor properties of the nitrone grouping [6, 10]. On the basis of these data, the 2,4,4-trimethyl-5-phenyl-4H-imidazole 1-oxide structure was assigned to VIIIa. 4,4-Dimethyl-2,5-diphenyl-4H-imidazole 1-oxide (VIIIb) was similarly obtained by in vacuo heat treatment of acetyl derivative IVb.

Heating of VIIIa,b with aqueous alkali gives crystalline products Va and Vb, which are close to Vc with respect to their properties and spectral characteristics, which indicates that they have the structures of the anti isomers of the oximes of α-acetamidoisobutyrophenone (Va) and α-benzamidoisobutyrophenone (Vb).

The formation of α-acylamino ketones during the action of alkali on 4H-imidazole 1-oxides can be represented as being the result of attack on the 2 position of the heteroring by the hydroxyl ion with ring opening and the formation of the enol form of the amide (structure A).



A

Data on the transformations of 4H-imidazole 1-oxides on reaction with hydrogen chloride will be published in our next communication.

EXPERIMENTAL*

The IR spectra of KBr pellets of solids (0.25%, pellet thickness 1 mm) and CCl_4 solutions (5%, layer thickness 0.1 mm) were recorded with a UR-10 spectrophotometer. The UV spectra of alcohol solutions were recorded with a Unicam SP-700c spectrophotometer. The PMR spectra were recorded with a Varian A-56-60A spectrometer with hexamethyldisiloxane (9.96τ) as the internal standard. The melting points, results of elementary analysis, yields, and spectral characteristics of the compounds obtained are presented in Tables 1 and 2.

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*Performed with the participation of L. Z. Kuleshina.

Condensation of α-Hydroxylamino Oximes with Aldehydes. A fourfold excess of acetaldehyde in 30 ml of absolute alcohol was added to 0.02 mole of α-hydroxylamino oxime Ia,b in 40 ml of absolute alcohol, and the mixture was refluxed for 10 min. The solvent was removed by distillation, absolute ether was added to the oily residue, and the crystalline precipitate of IIa or IIc, respectively, was removed by filtration.

Benzaldehyde (0.011 mole) was added to 0.01 mole of α-hydroxylamino oxime Ia in 20 ml of absolute alcohol and the mixture was refluxed for 30 min. The solvent was removed by distillation, absolute ether was added, and the precipitated IIb was removed by filtration. UV spectra: λ_{max}, nm (log ε): IIa 292 (3.98), IIb 290 (4.12), IIc 235 (3.72).

Acylation of 1-Hydroxy-3-imidazoline 3-Oxides. A 0.018-mole sample of acetic (for IIa,b) or benzoic (for IIc) anhydride was added to a suspension of 0.014 mole of 1-hydroxy-3-imidazoline 3-oxide in 50 ml of chloroform, and the mixture was refluxed for 30 min, cooled, washed with 5% potassium carbonate solution and water, and dried over magnesium sulfate. The solvent was removed by vacuum distillation, and the residual oil was diluted with absolute ether. The precipitate was removed by filtration. UV spectra, λ_{max}, nm (log ε): IVa 292 (3.96), IVb 290 (4.13), IVc 237 (3.66).

Action of Alkali on 1-Acyloxy-3-imidazoline 3-Oxides. A 0.02-mole sample of IVa-c was refluxed for 2-2.5 h in 12-15 ml of 10-20% sodium hydroxide solution. The solution was neutralized to pH 6 with 10% HCl and extracted with chloroform. The solution was dried over magnesium sulfate, and the solvent was vacuum-evaporated. The residual oil was diluted with absolute alcohol–ether to precipitate Va-c.

3-Acetoximino-2-acetamido-2-methyl-3-butane (VII). A 0.01-mole sample of α-amino oxime VI [10] was dissolved in 10 ml of acetic anhydride, and the solution was refluxed for 10 min, cooled, and poured into water. The solvent was removed by distillation, and the oil was dried and dissolved in ether. The precipitated VII was removed by filtration.

A 0.01-mole sample of α-acetamido oxime Va,c was refluxed for 5 min in 2 ml of acetic anhydride, and the mixture was worked up as in the preceding case. According to the IR spectra and melting point of a mixture of the product with VII, the compound obtained from Vc was identical to VII.

4H-Imidazole 1-Oxides. The acetyl derivatives were heated in vacuo (2-3 mm) in a sublimator at 150° (IVa) or 170° (IVb). The products (VIIIa,b) were resublimed at 120-130° (2-3 mm). UV spectra, λ_{max}, nm (log ε): VIIIa 324 (3.86), VIIIb 336 (3.94).

Benzoyl derivative IVc was sublimed at 140° (2-3 mm). The resulting oil was dissolved in water, and the aqueous solution was treated with ether to remove the benzoic acid. The water was vacuum-evaporated, and the residue was dissolved in chloroform. The chloroform solution was dried over magnesium sulfate, the solvent was removed by distillation, and the oil was sublimed repeatedly. Compound VIIIc was unstable and decomposed on standing at room temperature. UV spectrum: λ_{max} 280 nm (log ε 3.50).

Action of Alkali on 4H-Imidazole 1-Oxides. A suspension of 0.02 mole of VIIIa,b or freshly distilled VIIIc in 15 ml of 10% sodium hydroxide solution was refluxed for 15 min. The solution was cooled and neutralized with 10% HCl to pH 6, and the precipitate was removed by filtration and crystallized. According to the IR spectra and melting points of mixtures of the products with genuine samples of Va-c, the compounds were identical to Va-c, respectively.

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