PRODUCTION OF STABLE NITROXIDE RADICALS

OF 3-IMIDAZOLINE-3-OXIDE

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We demonstrated earlier [1] that the condensation of $\operatorname{anti-\alpha-hydroxylaminooximes}$ with the hydroxylamino group at a tertiary carbon atom with acetone in sealed ampoules leads to 1-hydroxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxides. Since these compounds contain not only a nitrone group in the heterocycle, but also a hydroxylamino group shielded by two tert-alkyl groups, their oxidation led to stable nitroxides [2]. In this work the replacement of acetone by its diethylketal permitted not only a facilitation of the reaction and an increase in the yields of the condensation products, but also its extension to a larger number of compounds.

Heating of N-(1-oximino-2-methyl-1-phenylpropyl-2)-(Ia), N-(3-oximino-2-methylbutyl-2)-(Ib), N-(1-oximino-2-methylpropyl-2)-(Ic), N-(1-oximino-1-methyl-2-phenylpropyl-2)-(Id), and N-(1-oximino-2methylcyclohexyl-2)-(Ie) hydroxylamines with an excess of acetone diethylketal leads to colorless crystalline substances (IIa-e), corresponding in composition to the condensation products of compounds (Ia-e) with acetone with elimination of a water molecule. The use of acetates of α -hydroxylaminooximes (Ib, e) [3] increases the yields of the condensation products (IIb, e).

The absorption characteristic of 4-phenyl-3-imidazoline-3-oxides [4] is observed in the UV and IR spectra of compound (II) (Table 1). The UV spectra of the remaining condensation products (IIb-e) are practically identical to one another and close to the UV spectrum of 2-methylpyrroline-1-oxide [8]. The IR spectra of compounds (IIb-e) contain intense bands close to 1200 cm⁻¹, which can be assigned to the semipolar N \rightarrow O bond, and characteristic bands in the region of 1620-1630 cm⁻¹, corresponding to the vibrations of the C = N group in nitrones [6]. These data permitted the assignment of the structure 1-hy-droxy-2,2,5,5-tetramethyl-4-phenyl-(IIa), 1-hydroxy-2,2,4,5-pentamethyl-(IIb), 1-hydroxy-2,2,5-tetramethyl-4,5-tetramethyl-5-phenyl-(IId), and 1-hydroxy-2,2,5-trimethyl-4,5-tetramethyl-4,5-tetramethylene-(IIe) 3-imidazoline-3-oxides to the condensation products:



The PMR spectra of the compounds obtained (IIa, b, d, e) agree with their structure and are cited separately [7]. In the PMR spectrum of compound (IIc) there are two singlets at 8.68 and 8.51 ppm, corresponding to methyl groups in the 5- and 2-positions, and a singlet at 2.92 ppm of the proton of the aldonitrone group. The signals of the methyl groups were assigned by comparison with the PMR spectrum of compound (II'c), produced by condensation of compound (Ic) with the diethylketal of hexadeuteroacetone, in which the band of the methyl groups in the 2-position is absent.

It is interesting that the condensation of α -hydroxylaminooximes (Ib, e) with the diethylketal of hexadeuteroacetone gives compounds in whose PMR spectra not only the signals of the geminal methyl groups

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| Compound | | | | | Found, 7/0 | | Empirical | Ö | alculated, | 9/0 | | |
|-------------|--------------------------|-----------|------------------|--------------|------------------|--------------|---|------|------------|------|------|---------------------------------------|
| No. | Time, n | Yield, % | Mp. C. | υ | Η | N | formula | υ | Н | z | | $\lambda_{\max, \min(1g\varepsilon)}$ |
| IIa | Ω | 67 | 193—194 [1] | 66,7 66,8 | 7,9 8,1 | 12,0 12,2 | $C_{13}H_8N_{\perp}O_{\lambda}$ | 66,7 | 7,7 | 12,0 | 1560 | 220 286 (3,95) |
| IIb | 0,3 | 4 09 | 196-198 [1] | 55,8 55,4 | 9 9 7 3 | 16,2 16,0 | C ₈ H ₁₆ N ₂ O ₂ | 55,8 | 9,3 | 16,3 | 1630 | 230 (4,00) |
| IIc | 2,5 | 25 | 162—163 | 53,5 53,6 | හ හ හ හ | 17,7 | C7H14N2O2 | 53,2 | 8,9 | 17,7 | 1612 | 234 (3,95) |
| IId | ų | 30 | 206—207 | 66,4 66,5 | 7,8 7,6 | 11,9 12,0 | C ₁₃ H ₁₈ N ₂ O ₂ | 66,6 | 7,7 | 12,0 | 1620 | 230 (4,03) |
| IIe | 3° 2 | 57† | 172174 | 60,6 60,3 | | 14,5 14,4 | C ₁₀ H ₁₈ N ₂ O ₂ | 60,6 | 9,2 | 14,1 | 1630 | 232 (3,90) |
| * From alco | hol. $f \alpha$ -hydr | oxylamino | oximes were used | d in the re | action, | | | | | | | |

TABLE 1. 1-Hydroxy-2,2,5,5-tetrasubstituted-3-imidazoline-3-oxides (IIa-e)

| (IIIa-e) |
|----------|
| Radicals |
| Free |
| -1-oxy |
| 3-oxide |
| zoline- |
| -imida |
| ituted-3 |
| rasubsti |
| 5-Teti |
| 2,2,5,5 |
| 5. 5. |
| TABLE |

| | ()(2(2). | D TOTT | n-noimineane | | | -onten- | T OVA T TCC T | rautoare | | | | |
|-------------|----------|-------------|--------------|----------------|------------|--------------|---|----------|------------|------|------------------|-------------------------------------|
| Compound | | | | | Found, 껴 | | Empirical | O | alculated, | 10 | | |
| No. | Time, h | Yield,% | Mp, °C | υ | Н | N | formula | υ | Н | N | cm ⁻¹ | $\lambda_{max'} m(\lg \varepsilon)$ |
| IIIa | 20 | 80* | 104-105 [1] | 66,5 66,3 | 7,4 | 12,3 12,5 | C ₁₈ H ₁₇ N ₅ O ₃ | 66,9 | 7,3 | 12,0 | 1540 | 224 (3,90) 285 (4,00) |
| IIIb | 9 | 74† | 94-97 [1] | 55,9 55,7 | 0.8 0,8 | 16,4 16,1 | C ₈ H ₁₅ N ₂ O ₂ | 56,1 | 8,8 | 16,4 | 1610 | 234 (4,11) |
| IIIc | 0,4 | 32† | 100-103 | 53,9 54,0 | 8,1 8,2 | 17,9 | C7H13N202 | 53,5 | 8°33 | 17,8 | 1595 | 236 (4,05) |
| PIII | 9 | 20 * | 116—117 | $66,7 \\ 67,1$ | 7,2 | 11,9 12,2 | C ₁₃ H ₁₇ N ₂ O ₂ | 66,99 | 7,3 | 12,0 | 1600 | 234 (4,18) |
| IIIe | 9 | 40* | 103-105 | 61,0 60,9 | 8,6 8,8 | 13,6 13,9 | C10H17N2O2 | 60,9 | 8,6 | 14,2 | 1610 | 238 (4,16) |
| * In ether, | | | | | | | | | | | | |

† In benzene.

in the 2-position, but also those of the methyl and methylene groups in the 4-position of the heterocycle, corresponding to the α -position of the nitrone group (II'b, e), are absent. Exchange for deuterium can occur both during the process of condensation and in the final product. Thus, heating the compound (IIb) with the diethylketal of hexadeuteroacetone in the presence of deuteroacetic acid leads to the compound (II'b), the PMR spectrum of which, in contrast to the spectrum of compound (IIb), does not contain the signal of the methyl group in the 4-position at 8.00 ppm. The formation of compound (II'b) occurs readily in D₂O in the presence of alkali, which is explained by the mobility of the hydrogens of the methyl group of the α -carbon atom of the nitrone group with respect to nucleophilic reagents [6]



The condensation products (IIa-e) have high melting points, are sparingly soluble in nonpolar organic solvents, comparatively readily soluble in alcohol, and some (IIb, c) are soluble in water. These compounds (IIa-e) are stable during storage in air, while 1-hydroxy-2,2,6,6-tetramethylpiperidines are oxidized to nitroxides under these conditions [8].

The oxidation of compounds (IIa-e) with lead dioxide in benzene or ether leads to the nitroxides, 2,2,5,5-tetramethyl-4-phenyl-(IIIa), 2,2,4,5,5-pentamethyl-(IIIb), 2,2,5,5-tetramethyl-(IIIc), 2,2,4,5-tetramethyl-5-phenyl-(IIId), and 2,2,5-trimethyl-4,5-tetramethylene-(IIIe) 3-imidazoline-3-oxide-1-oxy free radicals. The compounds obtained are colored orange or yellow, have substantially lower melting points, and are better soluble in organic solvents than the starting material (IIa-e); they are stable to chromatography on silica gel.

They can be stored for a long time in the crystalline state at 0° without decomposition; storage of the radical (IIIc) requires a lower temperature. In solution, these radicals are less stable. When an ether solution of the radical (IIIb) stands for two to three days, the starting material of the condensation (IIb) precipitates with a small yield. The radical (IIIa) is stable to heating, and in reduction with hydrazine hydrate it smoothly forms compound (IIa).

The EPR spectra of compounds (IIIa-e) represent a triplet with hyperfine splitting constant ~14.5 Oe, characteristic of nitroxides [2]. As we go to radicals, the IR spectra change negligibly; the bands of the OH group at 1000-1040 and 3600 cm⁻¹ disappear, the band of the nitrone group C = N is shifted by 20 cm⁻¹ toward lower frequencies (Table 2). In the UV spectra of the radicals (IIIa-e), a bathochromic shift of the band of the nitrone group at 230 nm and an increase in its intensity are observed. Evidently there is an interference of the absorptions of the nitrone and nitroxide groups, since the electronic spectrum of ditert-butyl nitroxide consists of bands at λ_{max} 238 nm (log ε 3.33) and λ_{max} 465 nm (log ε 0.95) [9]. Increasing the concentration and a change to heptane in a number of cases (IIIa, b, e) permit absorption at λ_{max} 420-450 nm to be observed (log ε 0.6) (see also [10]). The PMR spectra of the radicals are discussed together with the spectra of diamagnetic compounds in [7].

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument in tablets of KBr (concentration 0.25%, thickness 1 mm) and in solutions of CCl_4 . The UV spectra were recorded on a "Unicam-SP-700c" instrument in alcohol. The PMR spectra were taken on a "Varian A-56-60A" instrument in CD_3OD (concentration 3-5%) with hexamethyldisiloxane as the internal standard (9.96 ppm).

 α -Hydroxylaminooximes (Ia, b, c, e) were described earlier [3]; the compound (Id) was produced analogously to [3], mp 132-133° (from alcohol). Found: C 62.0; 62.2; H 7.1; 7.1; N 14.5; 14.5%. C₁₀H₁₄N₂O₂. Calculated: C 61.8; H 7.3; N 14.4%.

Diethylketals of acetone and hexadeuteroacetone were produced by the interaction of ketones with orthoformic ester in the presence of catalytic amounts of conc. H_2SO_4 , followed by neutralization with an alcohol solution of sodium ethylate, bp 114°.

<u>Condensation of α -Hydroxylaminooximes (Ia-e) with the Diethylketal of Acetone</u>. A solution of 16.0 g of compound (Ia) in 50 ml of the diethylketal of acetone was boiled for ~5 h (until the appearance of a yellow color). The (IIa) that precipitated after cooling was filtered off, weight 13.0 g. Compounds (IIc, d) were produced under the same conditions. Condensation of acetates of the α -hydroxylaminooximes (Ib, e) [3] under similar conditions leads to the compounds (IIb, e). The reaction times, yields, melting points, data of elementary analysis, and spectral characteristics of the condensation products (IIa-e) are cited in Table 1.

Condensation of compounds (Ib, c, e) with the diethylketal of hexadeuteroacetone was conducted under analogous conditions. PMR spectra of the compounds: (II'b) 8.70 ppm (two CH₃ groups in the 5-position); (II'c) 8.68 ppm (two CH₃ groups in the 5-position), 2.92 ppm (α -H); (II'e) 8.63 ppm (one CH₃ in the 5-position), 8-9 ppm (compound band of the CH₂ groups of the cyclohexane ring).

Deuteroexchange of the Protons of the Methyl Group in the 4-Position of the Compound (IIb). Heating compound (IIb) for 3 h with the diethylketal of hexadeuteroacetone in the presence of deuteroacetic acid leads to the product of exchange (II"b). The compound (II"b) is also formed when compound (IIb) is heated in a 0.1 N solution of KOH in D_2O to 50° for 15 min, followed by 2-h exposure at 20°. The PMR spectrum of compound (II"b): 8.56 ppm (two CH₃ groups in the 2-position), 8.70 ppm (two CH₃ groups in the 5-position).

Oxidation of 1-Hydroxy-2,2,5,5-tetrasubstituted-3-imidazoline-3-oxides (IIa-e). A 5.0 g portion of compound (IIa) was ground with 50 g lead dioxide and shaken with dry ether for 20 h. The solution was filtered off, evaporated, and the orange precipitate of (IIIa) recrystallized from heptane, weight 4.0 g. The radicals (IIb-e) were produced similarly and purified by recrystallization from ether with cooling. The radical (IIId) was purified by chromatography on silica gel in a mixture of chloroform and alcohol (40:1); the solvent was evaporated, and after the addition of heptane, a yellow crystalline precipitate (IIId) separated. The conditions of the reaction, yields, melting points, data of elemental analysis, and spectral characteristics of the radicals (IIIa-e) are cited in Table 2.

Reduction of the Radical (IIIa) by Hydrazine Hydrate. To a solution of 0.1 g of the radical (IIIa) in 4 ml of alcohol we added 0.05 ml of hydrazine hydrate. After standing for 1 h at 20°, the solution was decolorized. The alcohol was evaporated, the residue washed with water, weight 0.06 g, mp 192-194° (from alcohol). The compound obtained proved identical with the compound (IIa) according to melting point and IR spectrum.

CONCLUSIONS

1. The condensation of α -hydroxylaminooximes with the hydroxylamino group at a tertiary carbon atom with the diethylketal of acetone leads to 1-hydroxy-2,2,5,5-tetrasubstituted-3-imidazoline-3-oxides. The use of acetates of α -hydroxylaminooximes in a number of cases permits an appreciable increase in the yields of the condensation products.

2. The possibility of exchange of the protons of the α -methyl and α -methylene groups of the ketonitrone groups of 3-imidazoline-3-oxides for deuterium was detected.

3. Stable nitroxides were produced by oxidation of 1-hydroxy-2,2,5,5-tetrasubstituted-3-imidazoline-3-oxides with lead dioxide.

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