SYNTHESIS OF BIFUNCTIONAL DERIVATIVES OF NITROXYL RADICALS OF IMIDAZOLINE

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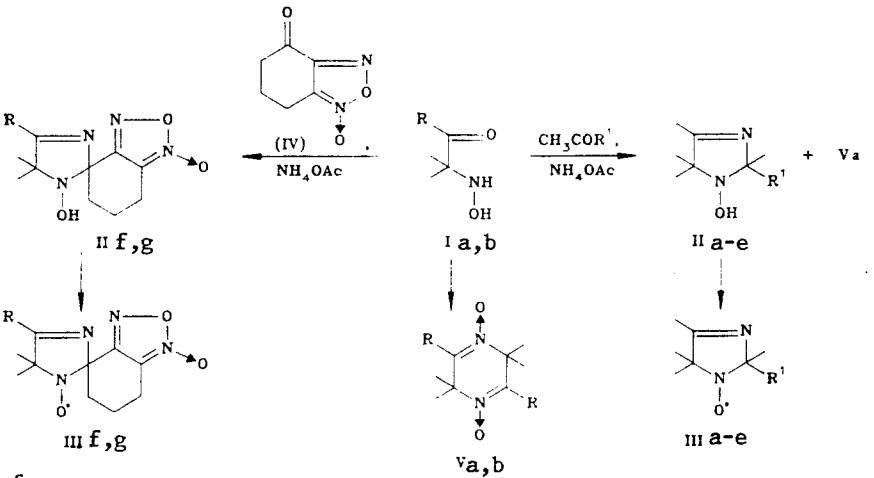
3-Imidazoline derivatives that contain a substituent with a functional group in the 2 position of the hetero-ring were obtained by the reaction of 1,2-hydroxyamino ketones with functionally substituted ketones and ammonia. The use of the reactivity of the endocyclic imino group makes it possible to accomplish the synthesis of a number of bifunctional derivatives of nitroxyl radicals of imidazoline and imidazolidine.

It is known that 3-imidazoline derivatives II, the oxidation of which leads to the formation of nitroxyl radicals III, are obtained as a result of the reaction of 1,2-hydroxyamino ketones I with methyl alkyl ketones, cycloalkyl ketones, keto stearic acid esters, and ammonia or ammonium acetate [1]. We have previously shown that the reactivity of the imino group in the composition of the 3-imidazoline heteroring makes it possible to obtain various functional derivatives of nitroxyl radicals of 3-imidazoline and imidazolidine [1-6].

The aim of the present research was to study the possibility of the condensation of I with functionally substituted ketones to form 3-imidazoline derivatives containing, in the 2 position of the heteroring, a substituent with a functional group that could be used as spin labels in molecular biology and as spin-labeled chelate-forming reagents in analytical chemistry [1]. The further use of the reactivity of the imino group in the composition of the heteroring and its activating effect on the methyl group in the 4 position subsequently made it possible to accomplish the synthesis of bifunctional derivatives of nitroxyl radicals.



Ia, IIf, IIIf, Va R=CH_3, Ib, IIg, IIIg, Vb R=C_6H_5; II, III a R^1=C_6H_5, b R^1=p-$NO_2C_6H_4$, c R^1=$CO_2C_2H_5$, d R^1=$CH_2CH_2CO_2CH_3$, e R^1=p-$NH_2C_6H_4$

The corresponding 1-hydroxy-3-imidazoline derivatives II are formed smoothly when hydroxyamino ketone Ia is heated in methanol in the presence of ammonium acetate with acetophenone, p-nitroacetophenone, ethyl pyruvate, or methyl levulinate, as well as with ketone IV. The structures of the synthesized compounds are confirmed by their spectral characteristics (Tables 1 and 2) and by the ease of formation of the corresponding nitroxyl radicals III upon oxidation of these compounds with MnO_2 in ether or chloroform. It should be noted that in cases in which the reaction is not complete after 5 h, a significant amount

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TABLE 1. Characteristics of the Synthesized Compounds

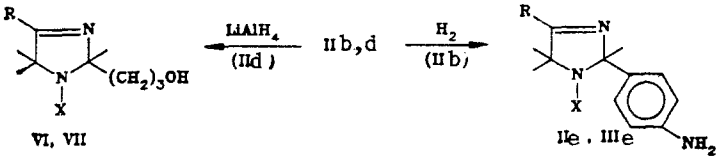
Compound	Empirical formula	mp,* °C	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max} (log ε)	Yield, %
IIa	$C_{13}H_{18}N_2O$	193...194	1650 (C=N), 160 (C=C)	—	65
IIb	$C_{13}H_{17}N_3O_3$	168...171	1645 (C=N), 1605 (C=C), 1515, 1350 (NO_2)	273 (4,05)	70
IIc	$C_{10}H_{18}N_2O_3$	112...114	1655 (C=N), 1725 (C=O), 3570 (OH)	—	50
IId	$C_{11}H_{20}N_2O_3$	128...129	1645 (C=N), 1725 (C=O)	—	75
IIe	$C_{13}H_{19}N_3O$	176...178	1650 (C=N), 1620, 3370, 3215 (NH_2)	243 (4,16)	60
IIf	$C_{11}H_{16}N_4O_3$	192...193	1625, 1650 (C=N)	270 (3,82)	70
IIg	$C_{15}H_{18}N_4O_3$	146...147	1615 (C=N)	252 (4,15)	60
IIIa	$C_{13}H_{17}N_2O$	Oil	1640 (C=N), 1600 (C=C)	—	95
IIIb	$C_{13}H_{16}N_3O_3$	105...106	1640 (C=N), 1600 (C=C), 1345, 1515 (NO_2)	265 (4,0)	95
IIIc	$C_{10}H_{17}N_2O_3$	Oil	1635 (C=N), 1750 (C=O)	—	95
IIId	$C_{11}H_{19}N_2O_3$	Oil	1640 (C=N), 1735 (C=O)	—	95
IIIe	$C_{13}H_{18}N_3O$	171...174	1645 (C=N), 3240, 3355, 3415 (NH_2)	245 (4,18)	80
IIIf	$C_{11}H_{15}N_4O_3$	147...149	1625, 1650 (C=N)	275 (3,9)	95
IIIg	$C_{16}H_{17}N_4O_3$	164...166	1615 (C=N)	255 (4,22)	95
Va	$C_{10}H_{18}N_2O_2$	217...218	1585 (C=N)	230 (4,32)	80
Vb	$C_{20}H_{22}N_2O_2$	297...298	1570 (C=N)	243 (4,16)	70
VII	$C_{10}H_{19}N_2O_2$	Oil	1645 (C=N), 3630 (OH)	—	70
VIII	$C_{11}H_{19}N_2O_3 \cdot BH_3$	98...99	1650 (C=N), 1740 (C=O)	—	55
IX	$C_{11}H_{21}N_2O_3$	Oil	1740 (C=O)	—	55
X	$C_{10}H_{17}N_2O_3$	125...127	1635 (C=N), 1710 (C=O)	—	85
XI	$C_{10}H_{18}N_3O_2$	99...102	1620, 1670 ($CONH_2$), 1645 (C=N), 3210, 3410 (NH_2)	—	85
XIII	$C_{13}H_{25}N_2O_7$	113...115	1680 (C=N), 1745 (C=O)	—	100
XIV	$C_{12}H_{23}N_2O_3$	Oil	1735 (C=O)	—	60
XV	$C_{11}H_{21}N_2O_3$	95...97	1730 (C=O)	—	85
XVII	$C_{14}H_{22}ClN_2O_4$	100...102	1560, 1660 (C=C—C=O), 1740 (C=O)	310 (4,39)	30
XVIII	$C_{13}H_{20}ClN_2O_4$	184...186	1535, 1605 (C=C—C=O), 1720 (C=O)	312 (4,39)	60
XIX	$C_{13}H_{20}IN_2O_4$	179...180	1525, 1605 (C=C—C=O), 1710	323 (4,27)	60
XXb	$C_{14}H_{16}N_3O_4$	137...138	1660, 1680 (C=O), 1625 (C=C), 1350, 1560, (NO_2)	259 (4,13) 316 (4,03)	100
XXd	$C_{12}H_{19}N_2O_4$	Oil	1645, 1665, 1695 (C=C, C=O), 1740 (C=O)	—	75
XXIb	$C_{13}H_{13}Br_3N_3O_3$	100...102	1615 (C=N), 1345, 1515 (NO_2)	263 (4,07)	60
XXId	$C_{11}H_{16}Br_3N_2O_3$	Oil	1610 (C=N), 1740 (C=O)	—	40
XXII	$C_{10}H_{15}Br_2N_3O_3$	142...143	1635 (C=N), 1705 (C=O)	—	25
XXIII	$C_{13}H_{14}N_3O_5 \cdot H_2O$	120...122	1610, 1625 (C=C, C=N), 1365, 1540 (NO_2)	266 (4,12)	80
XXIV	$C_{14}H_{16}N_3O_5$	113...114	1605, 1620 (C=C), (C=N), 1730 (C=O), 1350, 1545, (NO_2)	264 (4,12)	96
XXV	$C_{10}H_{18}N_3O_4$	134...135	1620 (N—C=C—NO_2), 3120 (NH), 3490 (OH)	342 (4,31)	30
XXVI	$C_{16}H_{20}N_3O_4$	171...173	1610 (N—C=C—NO_2), 1685 (C=O), 3130, 3300 (NH)	244 (4,18) 343 (4,23)	15

TABLE 2. PMR Spectra of Derivatives of 3-Imidazoline and Dihydropyrazine

Compound	δ, ppm
IIa	1,02 (s, 3H); 1,17 (s, 3H); 1,45 (s, 3H); 1,88 (s, 3H); 7,4 (m, 3H); 7,65 (s, 1H)
IIb	1,06 (s, 3H); 1,22 (s, 3H); 1,50 (s, 3H); 1,94 (s, 3H); 8,0 (m, 4H)
IIc	1,1 (t, J=7 Hz, 3H); 1,13 (s, 6H); 1,36 (s, 3H); 1,88 (s, 3H); 4,05 (q, J=7Hz, 2H); 7,93 (s, 1H)
IId	1,07 (s, 6H); 1,12 (s, 3H); 1,80 (s, 3H); 2,2 (m, 4H); 3,58 (s, 3H); 7,34 (s, 1H)
Va	1,56 (s, 12H); 2,04 (s, 6H)
Vb	1,74 (s, 12H); 7,4 (m, 10H)

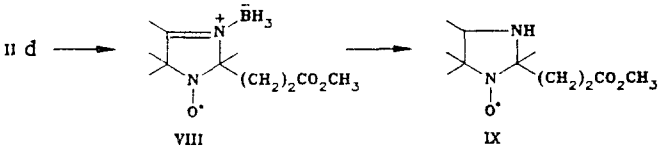
of pyrazine Va – the product of condensation of two molecules of amino ketone Ia – accumulates in the reaction mixture. Compound Va is formed in high yield when ketone Ia is refluxed in methanol in the presence of ammonium acetate. Compound Ib is less active in the condensation reaction, which takes place satisfactorily only with ketone IV, although the formation of pyrazine Vb is also observed in this case. The reaction of Ib with the other ketones enumerated above, just like heating in the presence of ammonium acetate in methanol, leads to pyrazine Vb. The condensation of hydroxyamino ketones I with both benzophenone and with p-aminoacetophenone for the direct introduction of an amino group into the composition of the imidazoline molecule cannot be accomplished under these conditions.

Since the imino group in the composition of the 3-imidazoline heteroring is not reduced either by the action of lithium aluminum hydride or by hydrogen over a catalyst (Pd/C) [4], the selective reduction of the nitro group in imidazoline IIb to give amino derivative IIe and of the ester grouping in IId to a hydroxy group (to give VI) can be accomplished. The oxidation of IIe and VI leads smoothly to nitroxyl radicals IIIe and VII, respectively.

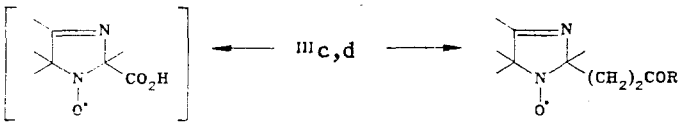


IIe, VI X=OH, IIIe, VII X=O·

On the other hand, the imino group in the composition of the heteroring is reduced with retention of the ester group as in [4]. Thus, the reaction of imidazoline IId with diborane and subsequent oxidation with MnO_2 give adduct (with borane) VIII, which forms imidazolidine IX on standing in a methanol solution of CH_3ONa. The reaction of ester IId with hydroxylamine or hydrazine hydrate leads to cleavage of the imidazoline heteroring.

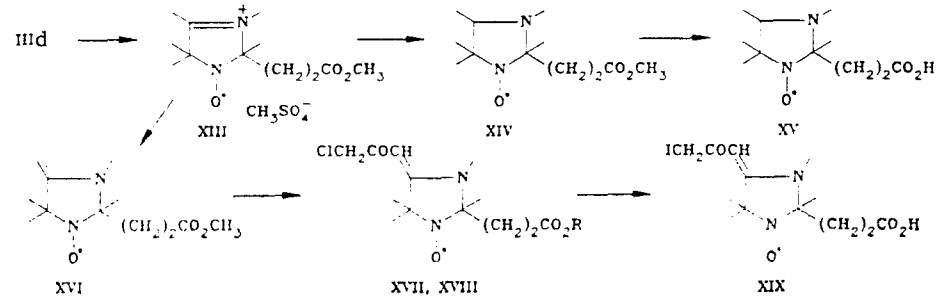


The action of aqueous alcoholic alkali on ester IIId gives acid X, while treatment of IIId with ammonium hydroxide leads to amide XI. The reactions of both diamagnetic ester IIc and the corresponding radical IIIc with NaOH proceed extremely readily; however, the corresponding carboxylic acid XII cannot be isolated in free form, since it decomposes rapidly at pH < 9.



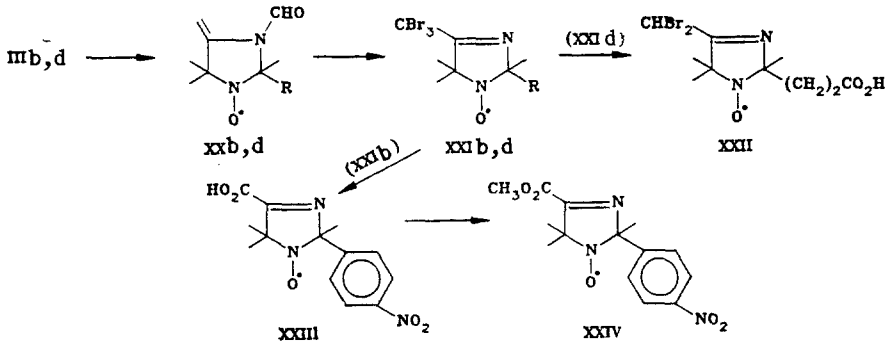
X R=OH; XI R=NH_2

Thus the condensation of hydroxyamino ketones with functionally substituted ketones and subsequent modification of the entering functional group make it possible to obtain nitroxyl radicals of 3-imidazoline containing, in the 2 position of the heteroring, a substituent with a nitro, hydroxy, amino, carboxy, carbamoyl, or ester group, in addition to an imino group in the composition of the heteroring. In order to study the possibility of the synthesis of bifunctional derivatives of nitroxyl radicals of imidazoline and imidazolidine we examined the reactions of 2-functionally substituted 3-imidazoline derivatives with the participation of the imino group entering into the composition of the heteroring.



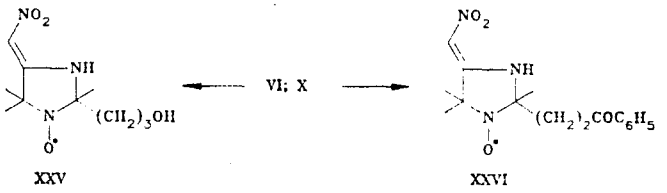
XVII R=CH_3; XVIII R=H

The reaction of ester IIId with dimethyl sulfate as in [1] leads to the formation of imidazolinium salt XIII, the reduction of which with sodium borohydride leads smoothly to a mixture of two diastereomeric esters XIV. Enamino ketone XVII is obtained in the reaction of enamine XVI, obtained by neutralization of imidazolinium salt XIII, with chloroacetyl chloride, as in [6]. Hydrolysis of the ester group and subsequent replacement of the chlorine atom by an iodine atom lead to XIX, which is simultaneously an acylating and alkylating spin label.



As we have previously demonstrated, to obtain halomethyl derivatives of nitroxyl radicals of 3-imidazoline it is expedient to introduce enamides rather than 4-methyl-3-imidazolines II into the halogenation reaction [3]. Enamides XX are formed in the reaction of imidazolines IIIb, d with $POCl_3$ in DMF. Treatment of XX with sodium hypobromite in aqueous dioxane solution or with N-bromosuccinimide leads to tribromomethyl derivatives XXI. Brief heating of tribromo derivative XXId in aqueous alcoholic alkali leads to dibromo derivative XXII, while prolonged maintenance of XXIb under the same conditions gives carboxylic acid XXIII, which forms esters XXIV on treatment with diazomethane.

The reaction of VI with methyl nitrate in the presence of phenyllithium leads, after oxidation, to nitroenamino alcohol XXV (see [5]). Under similar conditions the action of methyl nitrate on acid X unexpectedly gives XXVI which, according to the results of elementary analysis and mass spectroscopy, has the empirical formula $C_{16}H_{20}N_3O_4$ and, according to its spectral characteristics, contains a nitroenamino grouping (see [5]) and a phenacyl group; this makes it possible to assign the 2-(3-oxo-3-phenylpropyl)-4-nitromethylene-2,5,5-trimethylimidazolidine 1-oxide structure to it.



EXPERIMENTAL

The IR spectra of suspensions in KBr (c 0.25%) and solutions in CCl_4 (c 5%) were recorded with a UR-20 spectrometer. The UV spectra of solutions in alcohol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in d_6-DMSO were recorded with a Varian A-56-60A spectrometer.

The characteristics of the synthesized compounds are presented in Table 1. The results of elementary analysis for C, H, N, and Hal were in agreement with the calculated values.

Condensation of Hydroxyamino Ketones I with Ketones (general method). A mixture of 20 mmoles of the hydrochloride of hydroxyamino ketone I, 20 mmoles of the ketone, and 80 mmoles of ammonium acetate in 50 ml of methanol was refluxed for 3-5 h (monitoring by TLC on Silufol, elution with ether or $CHCl_3$–methanol, development with iodine vapors). After cooling, the precipitated imidazoline IIf was removed by filtration, washed with water, and dried. In the case of the remaining ketones the solution was evaporated and diluted with water, and the precipitated imidazolines IIa-d were removed by filtration and washed with water. Imidazoline IIg was extracted with $CHCl_3$, the extract was dried with $MgSO_4$, the solution was evaporated, and IIg was isolated by chromatography with a column packed with silica gel by elution with chloroform.

2,2,3,5,5,6-Hexamethyl-3,6-dihydropyrazine 1,4-Dioxide (Va). This compound was isolated from the aqueous solution after separation of the precipitated imidazoline II by extraction with $CHCl_3$. The extract was dried and evaporated, the residue was diluted with a small amount of ether, and the precipitated pyrazine Va was removed by filtration.

To obtain pyrazines V, a mixture of 10 mmoles of hydroxyamino ketone I and 40 mmoles of ammonium acetate was refluxed in methanol for 20 h, and the products were isolated as indicated above for pyrazine Va.

The oxidation of imidazolines II and VI to nitroxyl radicals III and VII, respectively, was accomplished by the action of MnO_2 in ether or $CHCl_3$ as in [1].

2-(4-Aminophenyl)-1-hydroxy-2,4,5,5-tetramethyl-3-imidazoline (IIe). A mixture of 0.5 g (1.9 mmoles) of imidazoline IIb and 0.2 g of the catalyst (5% Pd/C) in 40 ml of alcohol was hydrogenated with hydrogen at 20°C and atmospheric pressure until hydrogen absorption ceased (~2 h). The catalyst was removed by filtration, the solution was evaporated, the residue was diluted with a mixture of 5 ml of hexane and 5 ml of ether, and the precipitated IIe was removed by filtration.

2-(3-Hydroxypropyl)-2,4,5,5-tetramethyl-3-imidazoline 1-Oxyl (VII). A solution of 0.46 g (2 mmoles) of imidazoline IId in 10 ml of dry THF was added dropwise with stirring in the course of 20 min to a suspension of 0.34 g (10 mmoles) of lithium aluminum hydride in 15 ml of dry THF, after which 10 ml of ethyl acetate was added, and the solution was evaporated. The residue was extracted with $CHCl_3$, the extract was dried with $MgSO_4$, and the drying agent was removed by filtration. A 2-g sample of MnO_2 was added to the filtrate, and the mixture was stirred for 2 h at 20°C. The excess oxidizing agent was removed by filtration, the solution was evaporated, and VII was isolated by chromatography with a column packed with silica gel by elution with chloroform–methanol (20:1).

2-(2-Methoxycarbonylethyl)-2,4,5,5-tetramethyl-3-imidazoline 1-Oxyl-3-borane (VIII). A 0.5-ml (4 mmoles) sample of boron trifluoride etherate was added dropwise with stirring and cooling to 0°C to a suspension of 0.7 g (3 mmoles) of imidazoline IId and 0.12 g (3 mmoles) of $NaBH_4$ in 20 ml of dry THF, after which the solution was evaporated. The residue was diluted with 20 ml of ether and 20 ml of water, and shaken; the ether layer was separated, and the aqueous layer was extracted with ether (two 20-ml portions). The combined extract was dried with $MgSO_4$, the drying agent was removed by filtration, 3 g of MnO_2 was added, and the mixture was stirred for 30 min at 20°C. The excess drying agent was removed by filtration, and VIII was isolated by chromatography with a column packed with silica gel by elution with ether–hexane (1:1).

2-(2-Methoxycarbonylethyl)-2,4,5,5-tetramethylimidazolidine 1-Oxyl (IX). This compound was obtained from adduct VIII under the conditions in [4].

2-(2-Carboxyethyl)-2,4,5,5-tetramethyl-3-imidazolidine 1-Oxyl (X), 2-(2-Carboxyethyl)-2,3,4,5,5-pentamethylimidazolidine 1-Oxyl (XII), and 2-(2-Carboxyethyl)-4-(2-oxo-3-chloropropylidene)-2,3,5,5-tetramethylimidazolidine 1-Oxyl (XVIII). These compounds were obtained by alkaline hydrolysis of the corresponding esters by the action of an aqueous alcohol solution of alkali on them. **2-(2-Carbamoylethyl)-2,4,5,5-tetramethyl-3-imidazoline 1-oxyl (X)** was obtained by the action of 25% ammonium hydroxide on ester IIId.

2-(2-Methoxycarbonylethyl)-2,3,4,5,5-pentamethyl-3-imidazolinium 1-Oxyl Methylsulfate (XIII). This compound was obtained by the action of dimethyl sulfate on ester IIId under the conditions in [1].

2-(2-Methoxycarbonylethyl)-2,3,4,5,5-pentamethylimidazolidine 1-Oxyl (XIV). This compound was obtained by reduction of methylsulfate XIII with $NaBH_4$ by the method in [1].

2-(2-Methoxycarbonylethyl)-4-(2-oxo-3-chloropropylidene)-2,3,5,5-tetramethylimidazolidine 1-Oxyl (XVII). This compound was obtained from methylsulfate XIII as in [6].

4-(3-Iodo-2-oxopropylidene)-2-(2-carboxyethyl)-2,3,5,5-tetramethylimidazolidine 1-Oxyl (XIX). This compound was obtained by the action of NaI in acetone on enamino ketone XVIII by the method in [6].

2-(2-Methoxycarbonylethyl)-4-methylene-2,5,5-trimethyl-3-formylimidazolidine 1-Oxyl (XXd). A 0.3-ml (3 mmoles) sample of $POCl_3$ was added with stirring and cooling to 0°C to 5 ml of dry DMF. Stirring was continued for 15 min at 20°C, after which the solution was cooled to 0°C, and a solution of 0.46 g (2 mmoles) of imidazoline IIId in 5 ml of dry DMF was added dropwise with stirring. The mixture was stirred for 15 min, after which it was poured into a mixture of 20 g of ice and 2 g of Na_2CO_3. The solution was made alkaline to pH 10-12 with 10% NaOH and extracted rapidly with ether (three 40-ml portions). The extract was washed with water (five 25-ml portions) and dried with $MgSO_4$, the solution was evaporated, and XXIId was purified by chromatography with a column packed with silica gel by elution with ether–hexane (1:1).

Under similar conditions the action of $POCl_3$ in DMF on imidazoline IIIb gave enamide XXb, which was purified by recrystallization from hexane–ethyl acetate (1:1).

2-(2-Methoxycarbonylethyl)-4-tribromomethyl-2,5,5-trimethyl-3-imidazoline 1-Oxyl (XXId). This compound was obtained by the action of N-bromosuccinimide on enamide XXd in CCl_4 as in [3].

2-(4-Nitrophenyl)-4-tribromomethyl-2,5,5-trimethyl-3-imidazoline 1-Oxyl (XXIb). A solution of 0.29 g (1 mmole) of enamide XXb in 10 ml of dioxane was added dropwise with stirring and cooling to 0°C to a solution of NaOBr prepared from 0.45 ml (8 mmoles) of bromine and 0.75 g (18 mmoles) of NaOH in 10 ml of water, after which the reaction mixture was diluted with 30 ml of ice water, and the precipitated XXIb was removed by filtration, washed with water, and dried.

4-Dibromomethyl-2-(2-carboxyethyl)-2,5,5-trimethyl-3-imidazoline 1-Oxyl (XXII). A solution of 0.2 g of tribromo derivative XXId in a mixture of 10 ml of ethanol and 3 ml of 10% NaOH solution was heated at 40°C for 15 min, after which the alcohol was evaporated, and the residue was neutralized with 5% HCl solution, saturated with NaCl, and extracted with ethyl acetate (three 20-ml portions). The extract was dried with $MgSO_4$, the solution was evaporated, and XXII was isolated by chromatography with a column packed with silica gel by elution with chloroform–methanol (5:1).

4-Carboxy-2-(4-nitrophenyl)-2,5,5-trimethyl-3-imidazoline 1-Oxyl (XXIII). This compound was obtained from tribromo derivative XXIb as in [3].

4-Methoxycarbonyl-2-(4-nitrophenyl)-2,5,5-trimethyl-3-imidazoline 1-Oxyl (XXIV). This compound was obtained by the action of diazomethane on acid XXIII.

4-Nitromethylene-2-(3-hydroxy-1-propyl)-2,5,5-trimethylimidazolidine 1-Oxyl (XXV) and Nitroenamino Ketone XXVI. These compounds were obtained by the action of methyl nitrate on imidazolines VI and X, respectively, as in [5]. According to the mass-spectrometric data, XXVI had M^+ 318 (calculated M 318).

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