SYNTHESIS OF NITROXYL RADICALS OF 3-IMIDAZOLINE-3-OXIDE CONTAINING THE PHENYLAMINO GROUP, THEIR DIAZOTIZATION AND AZOCOUPLING

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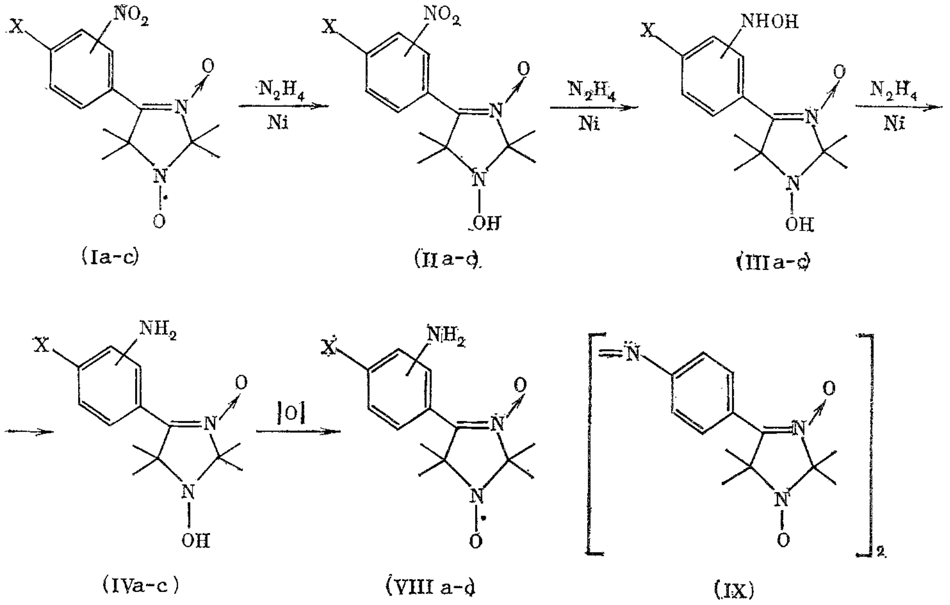
Nitroxyl radicals containing the phenylamine group can be used as spin labels introduced by diazotization and azocoupling. However the majority of nitroxyl radicals are unstable in acidic media and in the presence of $NaNO_2$ [1]. The unusual resistance of nitroxyl radicals of 3-imidazoline-3-oxide to the action of acids and oxidizing agents [2] allows one to assume their stability in diazotization and azocoupling.

We studied the possibility of synthesizing such compounds starting from the previously obtained 4-nitroaryl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl (Ia-c) [2, 3]. The most selective method of nitro group reduction in these compounds, in which the nitroxyl fragment is reduced only to a hydroxylamino group, proved to be the action of hydrazine hydrate in the presence of Raney nickel. The nitroxyl fragment is reduced faster than the nitro group. Formation of 1-oxy compounds (IIa-c) [3] was observed by TLC. Upon reduction of radical (Ia) the reaction can be stopped at the hydroxylamino derivative (IIIa)



(Ia-c) (IIa-c) (IIIa-c) (1)

(IVa-c) (VIIIa-c) (IX)

X = H, substituent NO_2, NHOH, or NH_2 ortho to the imidazoline ring (a); substituent = X in p-position (b); X = CH_3, substituent in m-position (c).

Compounds (IVa-c) and (IIIa) are colorless crystalline substances. In order to confirm the structure of (IIIa) and (IVa) 4-(2-aminophenyl)- and 4-(2-hydroxylaminophenyl)-1-methoxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxides (VI) and (VII) were obtained by reduction of 1-methoxy-4-(2-nitrophenyl)-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (V). They are significantly more soluble in nonpolar solvents compared to (IIIa) and (IVa), which permitted the recording of their IR spectra in CCl_4 and $CHCl_3$.

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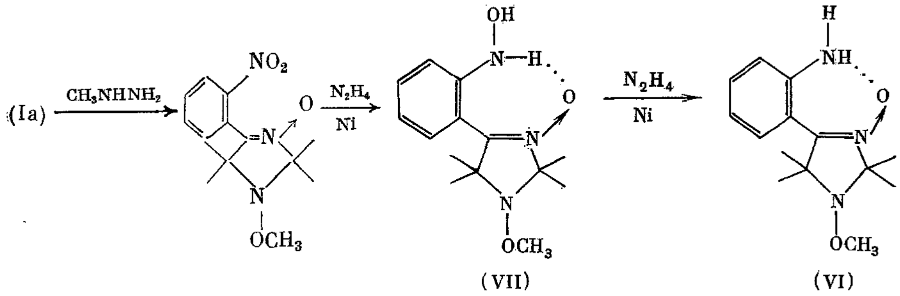
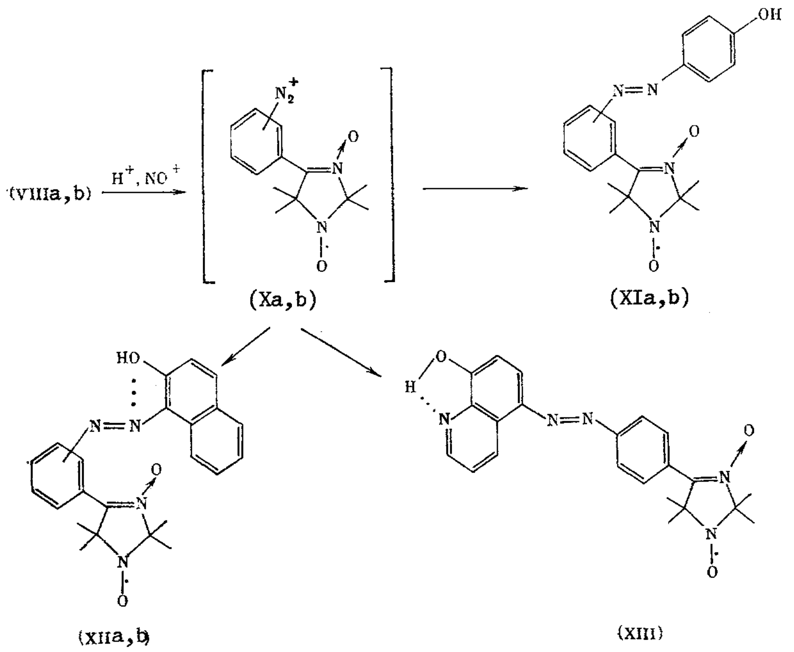


(2)

The presence of a wide band due to the bound NH group in the IR spectrum of these compounds indicates formation of an intramolecular H-bond (IMHB) (Table 1). In the UV spectra of (IIIa), (IVa), (VI), and (VII) the absorption maxima are at 330 nm. This shows that unlike 4-(2-nitroaryl)-3-imidazoline-3-oxides (Ia) and (IIa) which do not absorb above 250 nm [3], in (IIIa), (IVa), (VI), and (VII) the benzene ring is conjugated with the nitrone group. This is explained by the smaller volume of the amino- and hydroxylamino group compared to NO_2 and the possibility of IMHB formation in these comopunds. In the ^{13}C NMR spectra of (IVa), (VI), and (VII) the nitrone C atom signal is observed at 7 ppm lower field in comparison with the meta- and para substituted derivatives (IVb, c) the signals of which are typical of nitrones [4, 5]. The observed downfield shift of (IVa), (VI), and (VII), according to data of [6], indicates the presence of a IMHB with the nitrone O atom.

Upon oxidation of 4-aminoaryl-1-oxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxides (IVa-c) with PbO_2 or atmospheric O_2 in the presence of copper salts [7] the orange crystalline (VIIIa-c) are formed with high yields. Upon oxidation of (IVb) besides (VIIIb) a small amount of bright red biradical (IX)



(3)

is formed ($|J/a| = 20 \pm 2$ in toluene, $|J/a| = 10 \pm 1$ in chloroform). Biradical (IX) is formed also upon oxidation under the same conditions from (VIIIb). Similar biradicals are not formed by oxidation of radical (VIIIa), hydroxylamino derivative (IIIa) or its mixture with (IVa).

Radicals (VIIIa, b) dissolve in dilute aqueous acids, forming paramagnetic solutions, from which they can be quantitatively isolated after neutralization. Addition of $NaNO_2$ to these solutions with cooling to 0°C leads to deepening of color due to formation of diazonium salts (Xa, b) which undergo azocoupling with phenol, 2-naphthol, and 8-oxyquinoline with formation of compounds (XI) – (XIII).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	Melting point, deg C	Found/Calculated, percent C	H	N	Molecular formula	UV spectrum λ, nm (log ε)	IR spectrum ν, cm⁻¹, KBr
(IIIa)	90	170–172	59,2/58,9	7,3/7,2	16,0/15,8	$C_{13}H_{19}N_3O_3$	230(4,31), 260(3,94), 330(3,44)	3430, 3100–3300 (NHOH, 1-NOH), 1005 (1-NOH)
(IVa)	90	215–218	62,3/62,6	7,7/7,7	16,8/16,9	$C_{13}H_{19}N_3O_2$	230(4,40), 260(3,94), 330(3.58)	1630 (NH_2), 1005 (1-NOH)
(IVb)	85	230–233	62,7/62,6	7,7/7,7	16,6/16,9	$C_{13}H_{19}N_3O_2$	230(4,06), 330(4,33)	1640 (NH_2), 1010 (1-NOH)
(IVc)	67	180–183	63,6/63,9	8,2/8,2	14,8/15,0	$C_{14}H_{21}N_3O_2$	240(4,20), 295(4,00)	1640(NH_2), 1015 (1-NOH)
(V)	30	78–80	57,0/57,3	6,6/6,5	14,6/14,3	$C_{14}H_{19}N_3O_4$	250(4,11)	1530, 1360 (NO_2), 1050 ($NOCH_3$)
(VI)	80	129–131	63,9/63,9	8,1/8,0	16,2/15,8	$C_{14}H_{21}N_3O_2$	230(4,40), 260(3,92) 330(3,54)	1640(NH_2), 1060($NOCH_3$), 3430, 3250(NH_2) *
(VII)	75	120–123	59,9/60,2	7,7/7,6	15,0/15,0	$C_{14}H_{21}N_3O_3$	230(4,29), 260(3,93) 330(3,50)	3300–3400 (NH) **, 3580 (NOH) **, 1060($NOCH_3$)
(VIIIa)	80	104–106	62,6/62,9	7,2/7,3	16,9/16,9	$C_{13}H_{18}N_3O_2$	230(4,35), 340(3,45)	1640, 3430, 3250 (NH_2) *
(VIIIb)	50	171–173	62,9/62,9	7,3/7,3	16,8/16,9	$C_{13}H_{18}N_3O_2$	235(4,06), 340(4,39)	1645, 3510, 3420 (NH_2) **
(VIIIc)	80	136–137	64,4/64,1	7,5/7,7	15,7/16,0	$C_{14}H_{20}N_3O_2$	240(4,28), 295(4,07)	1630, 3450, 3330 (NH_2) **
(IX)	14	213–217	63,4/63,4	6,5/6,6	17,2/17,1	$C_{26}H_{32}N_6O_4$	235(4,25), 380(4,34)	
(XIa)	90	167–170	64,5/64,6	6,0/6,0	15,6/15,9	$C_{19}H_{21}N_4O_3$	360(4,43)	3500 (OH) **
(XIb)	90	183–186	64,5/64,6	6,1/6,0	15,9/15,9	$C_{19}H_{21}N_4O_3$	380(4,47)	3500 (OH) **
(XIIa)	80	196–198	68,6/68,5	5,8/5,8	13,9/13,9	$C_{23}H_{23}N_4O_3$	310(3,98), 480(4,15)	
(XIIb)	80	218–221	68,8/68,5	5,7/5,8	13,8/13,9	$C_{23}H_{23}N_4O_3$	330(4,23), 500(4,45)	
(XIII)	80	186–189	65,4/65,3	5,5/5,5	17,4/17,3	$C_{22}H_{22}N_5O_3$	240(4,54), 420(4,42)	3400 (OH) **

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*In CCl_4.
**In $CHCl_8$.

Compounds (XIa, b), (XIIa, b) and (XIII) are stable orange crystalline substances with intense maxima in the UV spectra, shifted to longer wavelength in alkaline media. In the IR spectra of (XIIa, b) OH bands are not observed because of strong IMHB.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer in KBr pellets (concentration 0.25%, l = 1 mm) or CCl_4 or $CHCl_3$ (concentration 1%, l = 0.4 mm). UV spectra were taken on a Specord UV-VIS spectrometer in ethanol. Data of IR and UV spectra, elementary analysis, yields, and melting temperatures are shown in Table 1. The PMR spectral parameters, recorded on a Varian A56-60 A instrument in 5-10% $(CD_3)_2CO$ or $(CD_3)_2SO$ solutions (internal standard HMDS, 0.04 ppm from TMC) are shown in Table 2. The ^{13}C NMR spectra were recorded on a Bruker HX-90 spectrometer with 10% solutions (Table 3) and the EPR spectra on a Bruker ER-200D spectrometer.

TABLE 2. Data of PMR Spectra of Diamagnetic Compounds

Compound	2,2,5,5-$(CH_3)_4$, 12 H, s, ppm	Aromatic protons, ppm	Other signals, ppm
(IIIa) *	1,37, 1,50	8,3m (1H), 7,3 m (3H)	
(IVa) *	1,33, 1,49	7,0 m (4H)	8,3s (1H, OH) 5,23w (2H, NH_2)
(IVc) *	1,46	7,6m (3H)	2,14s (3H, CH_3) 4,5 w (2H, NH_2)
(IVb) *	1,39, 1,42	6,48, 7,95, AA'BB', J=8 Hz	8,01s (1H, OH) 5,48w (2H, NH_2)
(V) *	1,52, 1,53	8,2–7,6 m (4H)	3,74s (3H, CH_3)
(VI) **	1,44, 1,58	7,0m (4H)	3,75s (3H, CH_3) 5,07w (2H, NH_2)
(VII) **	1,46, 1,60	7,5m (3H) 8,6m (1H)	3,68s (3H, CH_3) 7,56s (1H, OH) 6,90 w (1H, NH)

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*In $(CD_3)_2SO$.
**In $(CD_3)_2CO$.

TABLE 3. Data of ^{13}C NMR Spectra

Compound	2-CH_3	5-CH_3	C^2	C^5	C=N	*o*	*m*	*p*	C_i	CH_3
(IVa) [a]	23,4	23,4	89,0	66,7	145,4	148,2 127,2	115,6 117,0	129,7	111,9	
(IVb) [b]	23,1	24,0	88,2	65,6	140,2	128,2	111,9	149,2	114,0	
(IVc) [b]	23,1	23,8	88,9	65,9	140,2	112,2 114,9	145,4 128,7	125,2	122,2	16,2
(VI) [c]	24,9 [d]	24,9 [d]	90,8	68,7	147,2	148,4 128,0	117,8 118,4	131,0	113,0	64,5
(VII) [c]	25,5 [d]	25,5 [d]	90,9	68,9	146,7	151,3 127,3	113,8 119,5	131,1	111,2	64,9

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[a] In CH_3OH.
[b] In DMSO.
[c] In $CHCl_3$.
[d] Wide signal, see [5].

4-(2-Aminophenol)-1-oxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IVa). To a suspension of 4 g (14.4 mmole) radical (Ia) or the corresponding 1-oxy compound (IIa) in 60 ml ethanol 2 g of Raney nickel W2 and 20 ml 80% hydrazine hydrate were added. The mixture was boiled and stirred for 1.5 h, then the catalyst was filtered and the solvent evaporated. To the residue 30 ml water was added and the precipitate was filtered off, washed with 100 ml water and 20 ml ether and recrystallized from ethanol. The yield of (IVa) was 3.3 g. Analogously from 0.5 g (1.7 mmole) of (Ic) or (IIc) 0.3 g of 4-(3-amino-4-methylphenyl)-1-oxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IVc) was obtained, and from 0.5 g (1.7 mmole) of (V) 0.33 g of 4-(2-aminophenyl)-1-methoxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (VI) was obtained. In these cases the precipitate was not washed with ether. Reduction of (Ib) was carried out at 25°C. From 1 g of (Ib) 0.76 g of 4-(4-aminophenyl)-1-oxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IVb) was obtained.

4-(2-Hydroxylaminophenyl)-1-oxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IIIa). To a suspension of 1 g (3.6 mmole) of radical (Ia) in 50 ml ethanol 0.05 g of Raney Ni W2 and 5 ml 80% hydrazine hydrate was added and the mixture was stirred for ∿3 h, the reaction being followed by TLC (Silufol, λ 240 nm, chloroform:ethanol = 25:1), until the disappearance of (IIa) (R_f(IIa) = R_f(IVa). The mixture was treated as in the above experiment. Analogously, from 0.5 g of (V) 0.4 g of 4-(2-hydroxylaminophenyl)-1-methoxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (VII) was obtained. In this case the precipitate was not washed with ether.

1-Methoxy-4-(2-nitrophenyl)-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (V) was obtained by reaction of radical (Ia) with methyl hydrazine [8].

4-Aminoaryl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyls (VIIIa-c). a) A suspension of 2 mmole (IVa-c) and 1.5 g (6 mmole) PbO_2 in 20 ml acetone was stirred for 10-15 h until disappearance of the starting substance. TLC: Silufol, λ 240 nm, chloroform:ethanol =

25:1. The precipitate was filtered and the acetone evaporated. Radicals (VIIIa-c) were isolated by chromatography with silica gel upon elution with chloroform. The yield of (VIIIa) (from pentane) was 80%, of (VIIIc) (from benzene) 80%, of (VIIIb) (from benzene) 50%, and of biradical (IX) (from acetone) was 14%. Upon oxidation of (VIIIb) formation of biradical (IX) was observed by TLC.

b) To a suspension of 7.5 mmole (IVa-c) in 30 ml methanol a solution of 0.05 g $Cu(OAc)_2$ in 2 ml 25% aqueous ammonia was added and air was blown through the suspension until complete dissolution of the precipitate (4-5 h) plus an extra 0.5 h. The methanol was evaporated and to the residue 30 ml 10% aqueous NH_3 was added and extracted with chloroform 10 × 10 ml. The extract was dried with $MgSO_4$ and evaporated to dryness. The yield of (VIIIa, c) was 80%. During oxidation of (IVb) the mixture was separated as in method a. The yield of (VIIIb) was 50% and of biradical (IX) was 10%.

Diazotization and Azocoupling. To a solution of 0.2 g (0.8 mmole) of (VIIIa, b) in 4 ml 1 N HCl at 0°C a solution of 80 mg (1 mmole) of $NaNO_2$ in 1 ml water was added dropwise. The solution was kept for 0.5 h and filtered. To the filtrate a solution of 0.2 g NaOAc in 1.5 ml water and a solution of 90 mg (1 mmole) phenol or 120 mg (0.83 mmole) 2-naphthol or 120 mg (0.83 mmole) 8-oxyquinoline in 4 ml 2% NaOH was added. The precipitate was filtered off. Compound (XIa, b) was isolated on a chromatographic column with silica gel upon elution with chloroform. For isolation of (XIIa, b) silica gel washed with solutions of benzohydroxamic acid and 8-oxyquinoline was used. All compounds were recrystallized from a hexane–ethyl acetate mixture.

CONCLUSIONS

1. By reduction of 4-nitroaryl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl with hydrazine hydrate in the presence of Raney Ni, 1-oxy-4-aminoaryl-3-imidazoline-3-oxides were obtained, which upon oxidation form stable nitroxyl radicals containing the aminoaryl group.

2. Upon diazotization of 4-aminophenyl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyls the corresponding diazonium salts are formed, which undergo coupling with phenol, 2-naphthol, and 8-oxyquinoline with preservation of the radical center.

LITERATURE CITED

1. É. G. Rozantsev and V. D. Sholle, Organic Chemistry of Free Radicals [in Russian], Khimiya, Moscow (1979).
2. L. B. Volodarsky, I. A. Grigor'ev, L. N. Grigor'eva, and I. A. Kirilyuk, Tetrahedron Lett., 25, 5809 (1984).
3. L. B. Volodarskii, I. A. Grigor'ev, L. N. Grigor'eva, et al., Zh. Org. Khim., 21, 433 (1985).
4. I. A. Grigor'ev, V. V. Martin, G. I. Shchukin, et al., Khim. Geterotsikl. Soedin., 247 (1985).
5. I. A. Grigor'ev, G. I. Shchukin, V. V. Martin, and V. I. Mamatyuk, Khim. Geterotsikl. Soedin., 252 (1985).
6. I. A. Grigor'ev, V. I. Mamatyuk, G. I. Shchukin, et al., Khim. Geterotsikl. Soedin., 1065 (1986).
7. M. A. Schwartz, J. W. Parce, and H. M. McConnell, J. Am. Chem. Soc., 101, 3592 (1979).
8. G. I. Shchukin, I. A. Grigor'ev, and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., 2357 (1983).