RECYCLIZATION OF THE IMIDAZOLINE RING IN NITROXYL RADICAL DERIVATIVES OF 3-IMIDAZOLINE FOLLOWING OXIDATION BY HALOGENS AND NITROUS ACID

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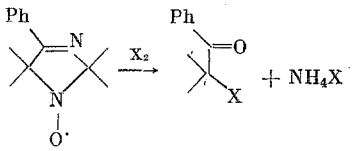
Nitroxyl radicals (NR) of the piperidine, pyrroline, and pyrrolidine series, together with di-tert-butylnitroxyl, diarylnitroxyls, and α-nitronylnitroxyls are known to be oxidized by oxidizing agents such as halogens, to oxoammonium salts [1, 2]. The behavior of 3-imidazoline and 3-imidazoline 3-oxide NR towards halogens has not been studied, but it has been shown that some 3-imidazoline and 3-imidazoline 3-oxide NR are stable towards oxidizing agents such as nitrosobenzene, sodium hypobromite, amyl nitrite, and halosuccinimides [3]. This communication describes the reaction of some 3-imidazoline and 3-imidazoline 3-oxide NR with the strong oxidizing agents, halogens and HNO_2.

The compounds selected as models were 2,2,5,5-tetramethyl-4-phenyl-3-imidazolin-1-oxyl (I) and its N-oxide (II). The radical (II) was stable towards solutions of iodine, bromine, and chlorine in chloroform over periods of several days, whereas the radical (I), which did not contain the N-oxide grouping, was stable towards iodine, but on treatment with bromine and chlorine decomposed over a period of 1 h to form 2-halo-2-methyl-1-phenyl-1-propanones (IIIa and b). Ammonium halides (IVa and b) were also formed.



(I) (IIIa, b) (IVa, b) X = Br(a), Cl(b).

This difference in the behavior of radicals (I) and (II) towards halogens may be due to one-electron oxidation of the nitroxyl group to oxoammonium in (I) in the first step, followed by fission of the heterocyclic ring. According to Usvyatsov et al. [4], 3-imidazoline NR are oxidized in this way, resistance to oxidation being strongly dependent on the presence of an N-oxide oxygen atom, and weakly dependent on the substituent in the 4 position of the heterocycle. The nitroxyl radicals of 3-imidazoline 3-oxide are very weak reducing agents [4], and hence they are stable towards halogens. 3-Imidazoline NR are stronger reducing agents [4], enabling them to be oxidized by chlorine and bromine. The weak dependence of the oxidizing potential on the substituent in the 4 position of the heterocycle [4] suggests that 3-imidazoline NR such as (I) will react with chlorine and bromine.

In fact, 4-carboxy-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl 3-oxide fails to react with halogens, whereas 4-carboxy-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (Va) reacts with bromine over a period of ~ 10 min to form a single product (VIa). By analogy with (I), the reaction product would be expected to be 3-bromo-3-methyl-2-oxobutyric acid or its degradation products. However, from mass spectrometry and elemental analysis, (VIa) had the molecular formula $C_8H_{12}BrNO_2$, indicating that an atom of bromine had been added to the acid (Va), accompanied by loss of a hydrogen atom and the nitroxyl group (as shown by the retention of the ^{15}N label when the reaction was carried out with the 3-imidazoline ring labelled in the 3 position). Absorption above 3000 cm^{-1} was absent from the IR spectrum of (VIa), but bands at 1780 (C = O) and 1635 cm^{-1} (C = N), typical of 3-oxazolin-5-ones [5], were present. The PMR spectrum of (VIa) consisted of a singlet at 2.10 ppm due to the protons of the bromoisopropyl group (cf. [6]), and a singlet at 1.56 ppm due to the gem-methyl groups in the 2 position of the 3-oxazolin-5-one ring [5]. These observations enable (VIa) to be identified as 2,2-dimethyl-4-(1-bromo-1-methylethyl)-3-oxazolin-5-one. This structure is confirmed by the ^{13}C NMR spectrum. Compound (VIa) is reduced by $NaBH_4$ at the

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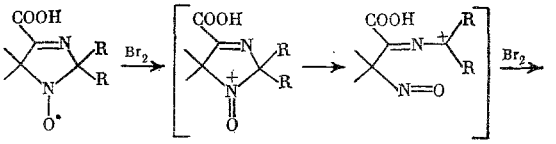
TABLE 1. Yields, Melting Points, and Elemental Analyses for the Compounds Obtained

Compound	Yield, %	mp, °C	Found, %				Molecular formula	Calculated, %			
			C	H	N	Br		C	H	N	Br
(Va)	85	117–118[a]	51,7	6,7	15,0	–	$C_8H_{13}N_2O_3$	51,9	7,0	15,1	–
(Vb)	60	115–117 [b]	56,7	6,8	13,0	–	$C_{10}H_{15}N_2O_3$	56,9	7,1	13,3	–
(VIa)	85	58–60[c]	40,7	5,1	6,0	33,7	$C_8H_{12}BrNO_2$	41,1	5,1	6,0	34,2
(VIb)	70	52–55[c]	45,8	5,3	5,1	30,7	$C_{10}H_{14}BrNO_2$	46,2	5,4	5,4	30,8
(VII)	40	104–106[c]	40,9	6,2	6,4	33,3	$C_8H_{14}BrNO_2$	40,7	5,9	5,9	33,9
(IXc)	90	200–203[d]	57,6	7,7	20,0	–	$C_{10}H_{16}N_3O_2$	57,1	7,6	20,0	–
(Xa)	80	121–122[e]	41,4	5,4	11,9	33,8	$C_8H_{13}BrN_2O$	41,2	5,6	12,0	34,3
(Xb)	90	83–84[e]	43,8	6,2	11,1	31,9	$C_9H_{15}BrN_2O$	43,7	6,1	11,4	32,4
(Xc)	75	125–127[e]	46,4	5,9	10,6	30,9	$C_{10}H_{15}BrN_2O$	46,3	5,8	10,8	30,9
(XII)	37	108–110[f]	52,3	7,0	14,9	–	$C_8H_{12}N_2O_3$	52,2	6,5	15,2	–
(XIII)	50	81–82[f]	43,5	5,7	9,7	28,8	$C_{10}H_{16}BrN_2O_2$	43,5	5,8	10,1	29,0
(XIV)	85	96–98[c]	67,6	9,7	16,8	–	$C_{14}H_{24}N_3O$	67,2	9,6	16,8	–
(XV)	60	165–168[f]	57,3	7,3	20,0	–	$C_{10}H_{16}N_3O_2$	57,2	7,6	20,0	–

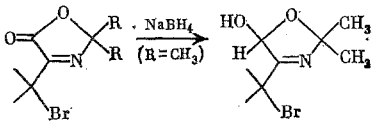
[a] Purified by chromatography (SiO_2, $CHCl_3$).
[b] Not purified.
[c] Sublimed.
[d] From $CHCl_3$
[e] From hexane.
[f] From ethanol.

lactone group to form 2,2-dimethyl-4-(1-bromo-1-methylethyl)-5-hydroxy-3-oxazoline (VII). Similarly, Br_2 treatment of 5,5'-dimethyl-4-carboxy-2-spiropentane-3-imidazolin-1-oxyl (Vb) gave 2-spiropentane-4-(1-bromo-1-methylethyl)-3-oxazolin-5-one (VIb).

Thus, bromine oxidation of the acids (Va and b) results in fission of the imidazoline ring with the formation of the oxazolone ring. Recyclization of acids (Va and b) may be represented as a sequence in which the reaction is initiated by oxidation of the nitroxyl group to the oxoammonium group, followed by fission of the N^1-C^1 bond of the imidazoline ring, the resulting carbocation reacting with the COOH group. The nitroso group in the nitrosoisopropyl moiety is replaced by bromine.



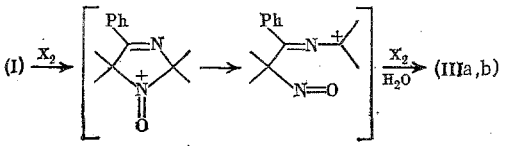
(Va, b)



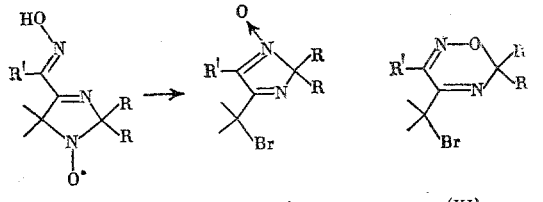
(VIa,b). (VII)

$R = CH_3$ (a); $R + R = (CH_2)_4$ (b)

The feasibility of the replacement of the N = O group by Br is indicated by the formation of (IIIa) on treatment of a suspension of 2-methyl-2-nitroso-1-phenyl-1-propanone (VIII) in $CHCl_3$ with bromine (cf. [7]). It follows that the formation of the haloketones (IIIa and b) from (I) probably proceeds similarly, with oxidation of the NO· group to oxoammonium, with subsequent replacement of the N = O group by Br, and hydrolysis of the imino group



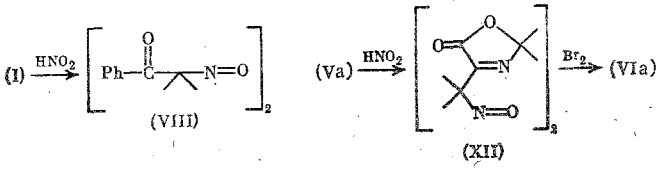
Similarly, bromine reacts with the oximes of 4-formyl- (IXa) and 4-acetyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (IXb) and 4-formyl-5,5-dimethyl-2-spiropentane-3-imidazolin-1-oxyl (IXc). It would be expected that the reaction products would be either derivatives of 2H-imidazole 1-oxide (X) if attack by the carbocation occurred at the unshared electron pair of the N atom of the oxime group, or derivatives of 6H-1,2,5-oxadiazine (XI), if attack occurs at the O atom. The UV spectra of the products show absorptions for (Xa) at 284 nm (log ε 3.92), for (Xb) at 290 nm (log ε 3.87), and for (Xc) at 288 nm (log ε 3.86), indicating the 2H-imidazole 1-oxide structure (cf. [8]), since 6H-1,2,5-oxadiazines should absorb, like the conjugated oxime ethers, at ~240 nm [9]. The IR and PMR spectra of (Xa-c) are in accordance with the 2H-imidazole 1-oxide structure



(IXa-c) (Ya-c) (XI)

$R = CH_3$, $R' = H$ (a); $R = R' = CH_3$ (b); $R + R = (CH_2)_4$, $R' = H$ (c).

Nitroxyl radicals in 3-imidazoline are also oxidized by HNO_2 with opening of the heterocycle. Radical (I) forms the nitrosoketone (VIII), and the acid (Va) recyclizes to 2,2-dimethyl-4-(1-nitroso-1-methylethyl)-3-oxazolin-5-one (XII)



(VIII) (XII)

The IR spectrum of (XII) in KBr shows bands for the 3-oxazolin-5-one ring at 1780 (C = O) and 1640 cm^{-1} (C = N), and a strong band at 1280 cm^{-1} typical of trans-nitroso dimers [10]. In $CHCl_3$ solution, a band appears at 1570 cm^{-1} due to stretching vibrations of the N = O bond in monomeric nitroso compounds [10]. When a solution of (XII) in alcohol is heated, it becomes blue in color. The UV spectra of (VIII) and (XII) in alcohol show no absorption above 270 nm, indicating that the dimers dissociate readily, since in KBr the compounds (VIII) and (XII) absorb at 310 cm^{-1} (in a region characteristic of dimeric nitroso compounds). Confirmation of the structure of (XII) is provided by replacement of the nitroso group by bromine on treatment with bromine, to form the oxazolone (VIa).

Thus, the bromine or HNO_2 oxidation of 3-imidazoline NR containing a functional group in the 4 position of the heterocyclic ring, which readily loses a proton, results in opening of the imidazoline ring with the formation of a new heterocyclic system.

EXPERIMENTAL

IR spectra were obtained on UR-20 and Perkin–Elmer-180 instruments in KBr (concentration 0.25%), and in solution in CCl_4 and $CHCl_3$ (concentrations 1-5%); UV spectra were obtained on Specord UV-VIS and SF-16 instruments in ethanol; and PMR spectra were obtained on a Varian A 56-60A for 10% solutions in CCl_4, with TMS as the internal standard. ^{13}C NMR spectra were obtained on a Bruker X-90 spectrometer for the 50% solution in CCl_4. The yields, melting points, and elemental analyses of the compounds obtained are shown in Table 1.

Reaction of 2,2,5,5-Tetramethyl-4-phenyl-3-imidazolin-1-oxyl (I) with Bromine and Chlorine. To a solution of 0.22 g of (I) [3] in 10 ml of chloroform was added dropwise with stirring 0.13 ml of bromine. The mixture was kept for 1 h, the precipitate of ammonium bromide filtered off, the filtrate evaporated, and the residue chromatographed on a silica gel column using chloroform as eluent. There was obtained 0.22 g (96%) of the bromoketone (IIIa), the spectral properties of which were identical with those of a bromoketone obtained by an independent method. Similarly, treatment of (I) with a solution of chlorine in chloroform gave the chloroketone (IIIb) in 98% yield.

4-Carboxy-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (Va). A solution of 1 g of the appropriate sodium salt [3] in 10 ml of water was acidified with 7% HCl to pH 1, extracted with chloroform, the extract dried over magnesium sulfate, filtered, and the chloroform evaporated. IR spectrum (KBr, cm^{-1}): 1730 (C = O), 1640 (C = N). UV spectrum (λ_{max}, nm): 241 (log ε 3.26).

4-Formyl-5,5-dimethyl-2-spiropentane-3-imidazolin-1-oxyl Oxime (IXc). Oxidation of 4,5,5-trimethyl-2-spiropentane-3-imidazoline 3-oxide [11] followed by bromination of the nitroxyl radical obtained with NBS [3] afforded 4-bromomethyl-5,5-dimethyl-2-spiropentane-3-imidazoline-1-oxyl 3-oxide (XIII). Treatment of (XIII) with tert-butylamine [3] gave 4-tert-butyliminomethyl-5,5-dimethyl-2-spiropentane-3-imidazolin-1-oxyl (XIV), treatment of which with hydroxylamine hydrochloride [3] gave (IXc).

5,5-Dimethyl-4-carboxy-2-spiropentane-3-imidazolin-1-oxyl (Vb). Treatment of (XIV) with hydroxylamine-O-sulfonic acid followed by oxidation with hydrogen peroxide [3] and hydrolysis gave 5,5-dimethyl-4-carboxamido-2-spiropentane-3-imidazolin-1-oxyl (XV). A suspension of 0.4 g of the amide (XV) in a solution of 0.2 g of NaOH in 5 ml of water was boiled for 6 h, cooled, acidified with 7% HCl to pH 1-2, extracted with chloroform, dried over magnesium sulfate, and the solvent evaporated. The acid (Vb) was reprecipitated from its alkali solution with hydrochloric acid.

Reaction of Radicals (Va and b) and (IXa-c) with Bromine. To a solution or suspension of 0.003 mole of the radical in 30 ml of chloroform was added with stirring 0.003 mole of bromine. After 30 min, the solvent was distilled off, and the residue chromatographed on a silica gel column (eluent, chloroform).

2,2-Dimethyl-4-(1-bromo-1-methylethyl)-3-oxazolin-5-one (VIa). ^{13}C NMR spectrum (δ, ppm): 162.17 and 161.44 (C = O and C = N), 102.65 (CBr), 53.47 (C), 30.15 and 25.04 (CH_3). Mass spectrum: 233 (M^+), 154 ($M^+ - Br$), 110 ($M^+ - Br - CO_2$). UV spectrum (λ_{max}, nm): 289 (log ε 2.19).

2-Spiropentane-4-(1-bromo-1-methylethyl)-3-oxazolin-5-one (VIb). IR spectrum (KBr, cm^{-1}): 1780 (C = O), 1640 (C = N). PMR spectrum (δ, ppm): 2.10 s (6H, CH_3), 2.00 br (8H, $(CH_2)_4$).

2,2-Dimethyl-4-(1-bromo-1-methylethyl)-2H-imidazole 1-Oxide (Xa). IR spectrum (KBr, cm^{-1}): 1590 (C = N), 1515 (C = NO). PMR spectrum (δ, ppm): 7.38 s (1H, CH =), 2.04 s (6H, CH_3CBr), 1.45 s (6H, 2-CH_3).

2,2,5-Trimethyl-4-(1-bromo-1-methylethyl)-2H-imidazole 1-Oxide (Xb). IR spectrum (KBr, cm^{-1}): 1580 (C = N), 1490 (C = NO). PMR spectrum (δ, ppm): 2.30 s (3H, 5-CH_3), 2.06 s (6H, CH_3CBr), 1.40 s (6H, 2-CH_3).

2-Spiropentane-4-(1-bromo-1-methylethyl)-2H-imidazoline 1-Oxide (Xc). IR spectrum (KBr, cm^{-1}): 1580 (C = N), 1508 (C = NO). PMR spectrum (δ, ppm): 7.33 s (1H, CH =), 2.00 br (12H, CH_3CBr and 2-CH_3).

2,2-Dimethyl-4-(1-bromo-1-methylethyl)-5-hydroxy-3-oxazoline (VII). To a solution of 0.2 g of (VIa) in 5 ml of alcohol was added with stirring a solution of 0.07 g of $NaBH_4$ in 5 ml of water. After 1 h, the alcohol was distilled off, the aqueous solution extracted with chloroform, and the extract dried over magnesium sulfate, filtered, and the chloroform removed to give 0.07 g of (VII). IR spectrum (CCl_4, cm^{-1}): 3620 (free OH), 3420 br (bound OH), 1650 (C = N). PMR spectrum (δ, ppm): 6.37 s (1H, CH), 2.10 (6H, CH_3CBr), 1.54 and 1.46 s (3H and 3H, 2-CH_3 and 2-CH_3).

Reaction of Radicals (I) and (Va) with Nitrous Acid. To a solution of 0.17 g of (I) in 4 ml of alcohol was added with stirring a solution of 0.2 g of sodium nitrite in 2 ml of water, acidified to pH 2 with 7% hydrochloric acid, and kept for 1 day. The precipitated (VIII) was filtered off, and washed with water. The spectral characteristics of (VIII) were identical with those of the nitrosoketone prepared as in [12]. To a solution of 0.19 g of the acid (Va) in 0.5 ml of alcohol was added a solution of 0.07 g of sodium nitrite in 2 ml of water, and the solution was acidified to pH 2 with 7% hydrochloric acid. The precipitate of (XII) was filtered off and washed with water. PMR spectrum (δ, ppm): 1.73 s (6H, CH_3CNO), 1.60 s (6H, 2-CH_3).

Reaction of (VIII) and (XII) with Bromine. To a suspension or solution of 0.001 mole of the nitroso compound in 5 ml of chloroform was added 0.001 mole of bromine. The reaction was followed chromatographically. When the nitroso compound had disappeared, the solvent was distilled off, and the residue chromatographed on a silica gel column (eluent, chloroform). Yield of the bromoketone (IIIa) 90%, and of (VIa), 85%.

CONCLUSIONS

1. Nitroxyl radicals in 3-imidazoline 3-oxide are not oxidized by halogens, whereas nitroxyl radicals in 3-imidazoline react with chlorine, bromine, and nitrous acid with fission of the imidazoline ring.

2. 4-Carboxy-3-imidazoline-1-oxyls on treatment with bromine and nitrous acid undergo recyclization to 3-oxazolin-5-ones.

3. Bromine treatment of 4-formyl- and 4-acetyl-3-imidazolin-1-oxyl oximes results in recyclization to 2H-imidazole 1-oxides.

LITERATURE CITED

1. É. G. Rozantsev and V. D. Sholle, The Organic Chemistry of Free Radicals [in Russian], Khimiya, Moscow (1979), p. 202.
2. V. D. Pokhodenko, A. A. Beloded, and V. G. Koshechko, Redox Reactions of Free Radicals [in Russian], Naukova Dumka, Kiev (1977), p. 81.
3. L. B. Volodarsky, I. A. Grigor'ev, and R. Z. Sagdeev, Biological Magnetic Resonance (L. J. Berliner and J. Reuben, editors), New York–London (1980), p. 169.
4. A. A. Usvyatsov, I. M. Medvedeva, and L. B. Volodarskii, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 9, Issue 4, 138 (1980).
5. R. J. Stoodley and R. B. Wilkins, J. Chem. Soc., Perkin Trans. 1, 716 (1975).
6. F. Weygand, W. Steglich, D. Mayer, and W. von Philipsborn, Chem. Ber., 97, 2023 (1964).
7. B. L. Dyamkin, A. A. Gevorkyan, and I. L. Knunyants, Izv. Akad. Nauk SSSR, Ser. Khim., 1873 (1965).
8. Yu. G. Putsykin and L. B. Volodarskii, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 9, Issue 4, 86 (1969).
9. I. A. Grigor'ev, G. I. Shchukin, A. G. Druganov, and L. B. Volodarskii, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 2, Issue 1, 80 (1979).
10. G. Foyer (editor), The Chemistry of Nitro and Nitroso Groups [Russian translation], Vol. 1, Mir, Moscow (1972), p. 100.
11. V. V. Martin and L. B. Volodarskii, Khim. Geterotsikl. Soedin., 103 (1979).
12. L. A. Tikhonova and L. B. Volodarskii, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 2, Issue 1, 103 (1977).