HALOGEN DERIVATIVES OF NITROXYL RADICALS OF IMIDAZOLINE

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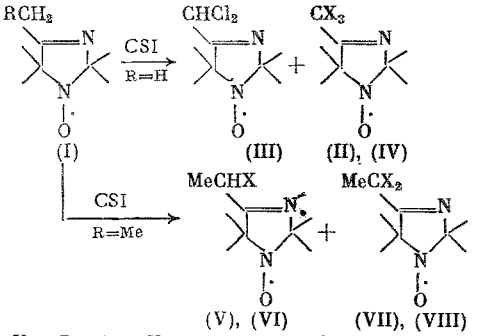
Derivatives of 4-haloalkyl-3-imidazoline 3-oxide are starting materials in the synthesis of many functional derivatives of nitroxyl radicals [1]. It was shown previously by us that analogous compounds in the 3-imidazolin-1-oxyl series are formed in moderate yield on interacting enaminoketone derivatives of imidazoline with bromine or with hypohalites [2]. A new route to the synthesis of 4-haloalkyl-3-imidazolin-1-oxyls has been investigated and some of their properties have been studied in the present work.

The interaction of imino compounds capable of enolization with halosuccinimides (HSI) leads to an α-halo substituted derivative of the imine, however, the reaction does not go selectively and leads in good yield only to polyhalogenated imino compounds [3]. Under these conditions the interaction of 2,2,4,5,5-pentamethyl-3-imidazolin-1-oxyl (Ia) with N-bromosuccinimide (BSI) in CCl_4 leads to the tribromo derivative, viz. 4-tribromomethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (II), independent of the conditions of carrying out the reaction and of the ratio of reactants, in a yield not exceeding 10%. On interacting compound (Ia) with N-chlorosuccinimide (CSI) either a mixture of 4-dichloromethyl- (III) and 4-trichloromethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (IV) was obtained or, under the action of an excess of CSI, only the trichloro derivative (IV). 4-Ethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (Ib) reacted more readily than compound (Ia) with CSI and as a result both the dihalo derivatives, 4-(1,1-dichloroethyl)- (VII) and 4-(1,1-dibromoethyl)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (VIII), and the monohalo derivatives, 4-(1-chloroethyl)- (V) and 4-(1-bromoethyl)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (VI), were successfully isolated.



R = H (a), Me (b); X = Br (II), (VI), (VIII), X = Cl (IV), (V), (VII).

Thus, the interaction of derivatives of 3-imidazoline (I) with CSI led to the formation of mono-, di- and trihalo derivatives; however, as a rule low yields and poor reproducibility made this approach less satisfactory for synthesis. It should be mentioned that halogenation of derivatives of 3-imidazoline 3-oxide under similar conditions occurred significantly more readily [4] in comparison with derivatives of 3-imidazoline which is evidently linked with the ability of imino compounds to add a molecule of halogen at the C=N bond [5]. In the case of 3-imidazoline derivatives this must lead to opening of the hetero ring. Another possible explanation is linked with the high reducing ability of the nitroxyl group in the composition of the 3-imidazoline heterocycle [6] which leads to its ready oxidation to a hydroxylammonium group and subsequent opening of the hetero ring.

A more convenient method of obtaining 4-haloalkyl derivatives of 3-imidazoline comprises halogenation of N-formyl derivatives of imidazoline (IX)* Compound (IX) is formed on treating 3-imidazoline derivatives

* For the preliminary communication see [7].

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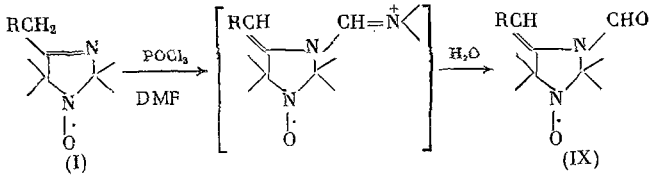
with phosphorus oxychloride in dimethylformamide (DMF) under conditions of the Vilsmeier reaction. The structure of (IXa) was confirmed by the PMR spectrum of its diamagnetic analog 4-methylene-2,2,5,5-tetramethylimidazolidin-1-oxide (X) formed on interaction of (IXa) with hydrazine hydrate.

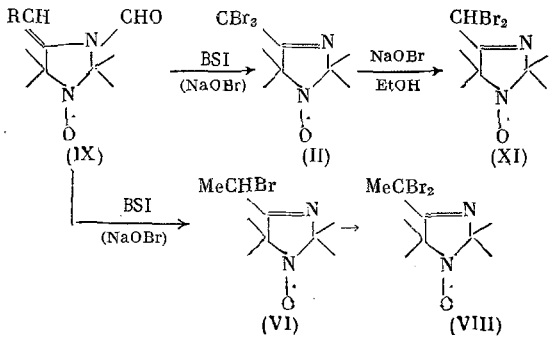


R = H (a), Me (b).

Treatment of the N-formyl derivatives (IX) with proton acids or with electrophilic reagents led to fission of the formyl group with the formation of derivatives of 3-imidazoline (I). Interaction of (IXa) with an aqueous alcohol solution of NaOBr led to the dibromo derivative (XI) after work-up [7] which was not obtained on brominating imidazoline (Ia). It was shown on further study of this reaction that the tribromo derivative (II) was formed initially. If the reaction mixture was then subjected to heating at 30-40°C compound (II) was quantitatively converted into the dibromo derivative (XI). The isolated tribromo derivative did not form dibromo derivative (XI) on interaction with an aqueous or aqueous dioxan solution of NaOBr, on interaction with an aqueous alcohol solution of NaOH the dibromo derivative was formed in trace amounts. Heating of the same aqueous alcohol solution of (II) with NaOBr led to the formation of dibromo derivative (XI) as the sole paramagnetic product. The reaction scheme seemingly includes reduction of the tribromomethyl group by the products of oxidation of ethyl alcohol by sodium hypobromite.

Thus, as a result of the interaction of compound (IXa) with NaOBr it is possible to isolate in high yield either the tribromo- (II) or the dibromomethyl derivative (XI).

It is interesting to note that this reaction is also extended to the tribromo derivative, 4-tribromomethyl-2,2,5,5-tetramethyl-3-imidazolin-3-oxide-1-oxyl (XII), the corresponding dibromo derivative (XIII) is formed in this way. The trichloro derivative (IV) did not enter into a reductive dehalogenation reaction under analogous conditions.



R = H (a), Me (b).

The interaction of (IXa) with BSI led to tribromide (II) independent of the ratio of reactants, compound (IXb) was brominated selectively under these conditions and led either to the mono- (VI) or to the dibromo derivative (VIII) depending on the ratio of reactants. The interaction of compound (IXb) with NaOBr occurred analogously and led to the formation of the bromo derivatives of imidazoline (VI) and (VIII) and it was not possible to detect their mutual interconversion under the conditions of the reaction.

Thus, the use of halogenation of derivatives of 3-imidazoline or N-formylimidazolidine made it possible to obtain mono-, di-, and trihalo derivatives of 3-imidazolin-1-oxyl.

Data on the interaction of α-halo substituted imino compounds with nucleophilic reagents are extremely limited. Consequently it seemed of interest to study the interaction of the synthesized 4-halo-methyl derivatives with certain nucleophilic reagents, particularly bases.

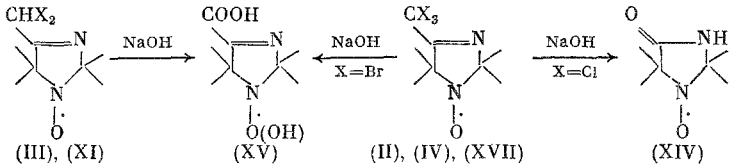
On interacting the trichloro derivative (IV) with NaOH in aqueous alcohol solution a nucleophilic substitution reaction occurred between the trichloromethyl group and hydroxyl with the formation of lactam (XIV) [8].

TABLE 1. Characteristics of Synthesized Compounds

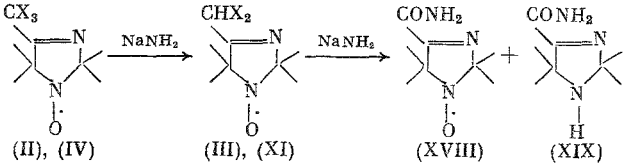
Compound	Yield, %	Mp, °C	Found/Calculated, %				Empirical formula
			C	H	Cl (Br)	N	
(III)	40	89–91	42,8 / 42,9	5,8 / 5,8	31,3 / 31,7	12,4 / 12,5	$C_8H_{13}Cl_2N_2O$
(V)	25	53–54	53,0 / 53,0	8,1 / 7,9	17,2 / 17,5	13,8 / 13,8	$C_9H_{16}ClN_2O$
(VI)	75	Oil	43,5 / 43,5	6,2 / 6,5	33,0 / 32,4	11,0 / 11,3	$C_9H_{16}BrN_2O$
(VII)	60	79–81	45,8 / 45,4	6,3 / 6,3	30,2 / 29,8	11,6 / 11,8	$C_9H_{15}Cl_2N_2O$
(VIII)	80	45–48	33,5 / 33,1	4,7 / 4,6	48,1 / 48,9	8,5 / 8,6	$C_9H_{15}Br_2N_2O$
(IX)	85	91–93	58,8 / 59,0	8,3 / 8,2	–	15,5 / 15,3	$C_9H_{15}N_2O_2$
(IXb)	75	80–81	60,6 / 60,9	8,5 / 8,6	–	14,2 / 14,2	$C_{10}H_{17}N_2O_2$
(X)	75	82–83	58,8 / 58,8	8,7 / 8,7	–	15,2 / 15,2	$C_9H_{16}N_2O_2$
(XVII)	60	104–6	31,5 / 31,7	3,8 / 4,0	26,6 / 26,4	9,1 / 9,2	$C_8H_{12}BrCl_2N_2O$

Note. Compounds (III), (V), (VII), (IX), (X), (XVII) were purified by recrystallization from hexane, (VI) chromatographically, and (VIII) by distillation.

Under similar conditions the tribromo derivative formed a carboxylic acid (XV) [9] and a small amount of dibromo derivative (XI). On increasing the reaction time (XI) was also converted into acid (XV). On interacting the dibromo (XI) or dichloro derivatives (III) [9] with NaOH acid (XV) was also formed. Based on this, it may be proposed that dibromo derivative (XI) is an intermediate reaction product. The formation of a carboxyl group on hydrolysis of the dibromomethyl group may be explained by the participation of the radical center which is reduced by this to a hydroxylamino group [10]. However, on carrying out the hydrolysis of tribromo derivative (II) in an atmosphere of argon the diamagnetic acid (XVa) was formed together with the paramagnetic compound (XV) in trace amounts. Consequently the main scheme according to which the reaction evidently proceeds is hydrolysis of the tribromomethyl grouping without participation of the radical center. It is interesting to note that under analogous conditions carboxylic acid (XV) is also formed from 4-bromodichloromethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XVII) obtained by the action of bromine on (III).



The interaction of halomethyl derivatives of 3-imidazoline with sodamide has been studied. The reaction was conducted in liquid ammonia which was used without previous drying. Under these conditions the dichloro derivative (III) was formed from the trichloro derivative (IV) as also occurred on interacting (II) with an aqueous alcohol solution of NaOBr. Treatment of dichloro derivative (III) with an excess of $NaNH_2$ led to the known amide (XVIII) [11]. On treating the same tribromo (II) or dibromo derivative (XI) with an excess of sodamide a significant amount of the dimagnetic compound (XIX) was formed in addition to amide (XVIII) [12].



The fact that the products of reaction with an excess of sodamide were the same in the case of the dibromo (XI) and tribromo (II) derivatives indicates that reaction of (II) with $NaNH_2$ evidently also proceeds through the stage of dihalo derivative (XI). The second stage, the conversion of the dihalomethyl group into

amide, occurs with the participation of the nitroxyl group (cf. [12]) which is reduced to an amino group in the case of the dibromo derivative (XI).

EXPERIMENTAL

IR spectra were described on a UR-20 spectrometer in KBr (concentration 0.25%) and in CCl_4 (concentration 5%). UV spectra were taken on a Specord UV-VIS instrument in EtOH. The identity of compounds was determined by comparison of IR and UV spectra and by thin layer chromatography on Silufol UV-254 plates. The NMR spectra were described on a Varian A-56-60A instrument. Data of elemental analysis, melting points, and yields of the synthesized compounds are given in Table 1.

4-Tribromomethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (II). a) BSI (2.4 g) and one drop conc. H_2SO_4 were added to a solution of imidazoline (Ia) (0.6 g) in CCl_4 (20 ml) freshly distilled over P_2O_5. The reaction mixture was stirred for 2 h at ~20°C, the precipitate of succinimide filtered off, and the solution evaporated. Compound (II) was isolated by chromatography on a column of silica gel, eluent was ether–hexane (1:2). Yield was 0.15 g (10%), mp 82-83°C (EtOH) (cf. [2]).

b) A solution of (IXa) (0.3 g) in EtOH (30 ml) was added dropwise with stirring and cooling to 0°C to a solution of NaOBr prepared from NaOH (2.6 g) and Br_2 (0.96 ml) in water (25 ml). The precipitated solid was filtered off, washed with water, and dried. Yield of (II) was 0.49 g (77%).

The dibromo derivative (VIII) was obtained in 60% yield from (IXb) under analogous conditions, and with insufficient NaOBr a mixture of the mono (VI) and dibromo derivative (VIII) was obtained which was separated by chromatography on silica gel, eluent was $CHCl_3$.

c) A solution of (IXa) (0.5 g) in dry CCl_4 (20 ml) was stirred with BSI (1.51 g) for 10 min, the precipitate of succinimide was filtered off, the solution evaporated, (II) was isolated by chromatography on silica gel with chloroform as eluent, and the yield was 0.7 g (60%).

Similarly (VI) was obtained in 65% yield on treating (IXb) with an equivalent amount of BSI and on treatment with an excess of reagent the dibromo derivative (VIII) was obtained in 60% yield.

4-Dichloromethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (III). A solution of imidazoline (Ia) (2 g) in dry CCl_4 (50 ml) was stirred for 48 h with CSI (1.9 g). The precipitate of succinimide was filtered off and the solution evaporated. The mixture of (III) and (IV) was separated by chromatography on a column of silica gel with $CHCl_3$ as eluent. Yield of (III) was 1.15 g.

Compound (V) 4-(1-chloroethyl)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl was obtained in a similar manner from imidazoline (Ib) by the action of an equimolar quantity of CSI. IR spectrum (KBr, ν, cm^{-1}): 1630 (C=N) and by the action of an excess of CSI 4-(1,1-dichloroethyl)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (VII) was obtained. IR spectrum (KBr, ν, cm^{-1}): 1615 (C=N). Under analogous conditions 4-(1-bromoethyl)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (VI) was obtained by the action of BSI on (Ib) at an equimolar ratio of reactants. IR spectrum (CCl_4, ν, cm^{-1}): 1630 (C=N), and with an excess of BSI 4-(1,1-dibromoethyl)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (VIII) was obtained, IR spectrum (KBr, ν, cm^{-1}): 1610 (C=N).

4-Trichloromethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (IV). CSI (20 g) and one drop of conc. H_2SO_4 were added to a solution of imidazoline (Ia) in dry CCl_4 (150 ml), the mixture was heated to boiling, and removed from the heat. When the exothermic stage of the reaction was complete the mixture was cooled, the precipitate of succinimide filtered off, the solution evaporated, and the residue recrystallized from hexane. Yield of (IV) was 10.3 g (95%), mp 123-125°C (hexane) (cf. [2]).

4-Bromodichloromethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XVII). A solution of Br_2 (0.14 ml) in MeOH (5 ml) was added dropwise with stirring and cooling to 0°C to a solution of (III) (0.3 g) and sodium methylate (0.3 g) in MeOH (20 ml). Stirring was continued for 15 min, the solution evaporated, the residue washed with dry ether, the precipitate of inorganic salt was filtered off, the solution evaporated, and (XVII) was isolated by chromatography on a column of silica gel with $CHCl_3$ as eluent. IR spectrum (KBr, ν, cm^{-1}): 1615 (C=N).

4-Dibromomethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XI) was obtained in a similar manner to the tribromo derivative (II). After adding a solution of (IXa) to the solution of NaOBr the mixture was evaporated by 2/3 at 30-40°C in vacuum with a water-jet pump. The residue was diluted with water, the precipitate of (XI) filtered off, washed with water, and dried. Yield was 90%, mp 123-125°C (hexane) (cf. [2]).

4-Dibromomethyl-2,2,5,5-tetramethyl-3-imidazolin-3-oxide-1-oxyl (XIII). A solution of NaOBr prepared from NaCH (0.6 g) and Br_2 (0.3 ml) in water (10 ml) was added in portions with stirring to a solution of (XII) (0.5 g) in EtOH (10 ml) at such a rate that the temperature of the reaction was not raised above 40°C. After the end of the addition the solution was evaporated by 2/3, the precipitated solid dibromo derivative was filtered off, washed with water, dried, and recrystallized from EtOH. Yield was 0.2 g (50%), mp 133-135°C (cf. [4]).

4-Methylene-3-formyl-2,2,5,5-tetramethylimidazolidin-1-oxyl (IXa). $POCl_3$ (3 ml) was added dropwise with stirring and cooling to dry DMF (10 ml). Stirring was continued for 10 min at ~20°C and after cooling to 0°C a solution of imidazoline (Ia) in dry DMF (3 ml) was gradually added. Stirring was continued for 1 h at ~20°C, then the mixture was poured onto ice. The solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and the solution evaporated to dryness. The residue was dissolved in a small quantity of $CHCl_3$ and filtered through a layer of Al_2O_3 (6 cm) eluting with chloroform. The solution was evaporated and (IXa) (3 g) was obtained. IR spectrum (KBr, ν, cm^{-1}): 1680 (C=O), UV spectrum, ethanol λ_{max}, nm (log ε): 233 (4.00).

Under analogous conditions 4-ethylidene-3-formyl-2,2,5,5-tetramethylimidazolin-1-oxyl (IXb) was obtained from imidazoline (Ib), IR spectrum (KBr, ν, cm^{-1}): 1630 (C=O), UV spectrum, EtOH λ_{max}, nm (log ε): 242 (390).

1-Hydroxy-4-methylene-3-formyl-2,2,5,5-tetramethylimidazolidine (X). A solution of (IXa) (0.2 g) and hydrazine hydrate (0.5 ml) in EtOH was maintained at ~20°C for 48 h, evaporated, the residue was dissolved in water, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. Compound (X) crystallized on adding hexane. Yield was 0.15 g. IR spectrum (KBr, ν, cm^{-1}): 1680 (C=O). UV spectrum (EtOH), λ_{max}, nm (log ε): 232 (3.86). PMR spectrum (CCl_4): 1.23 s (6 H) and 1.48 s (6 H, gem Me_2), 4.05 d (1 H, J = 5 Hz), and 4.44 d (1 H, CH_2, J = 5 Hz), 5.84 s (1 H, CHO).

4-Oxo-2,2,5,5-tetramethylimidazolidin-1-oxyl (XIV). A solution of (IV) (7 g) in a mixture of EtOH (100 ml) and 10% aqueous NaOH solution (50 ml) was boiled for 5 h, evaporated by 2/3, acidified to pH 4 with 5% HCl, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, evaporated, and (XIV) (4 g:95%) of mp 223-225°C (cf. [8]) was obtained.

4-Carboxy-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XV). A solution of (II) (0.45 g) in a mixture of MeOH (10 ml) and 10% NaOH solution (5 ml) was maintained at ~20°C for 6 h, evaporated by 2/3, the precipitated solid dibromo derivative (XI) was filtered off, the solution extracted with $CHCl_3$, and the extract discarded. The aqueous solution was acidified with 5% HCl to pH 3 and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solution evaporated, and (XV) of mp 115-117°C (cf. [9]) was obtained. On increasing the reaction time to 12 h the dibromo derivative (XI) was not isolated but (XV) was formed in 80% yield.

It was possible to obtain (XV) from dibromo derivative (XI) in a similar manner.

4-Dichloromethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (III). Compound (IV) (3 g) was added with stirring and cooling to −40°C to a solution of sodamide prepared from Na (1.2 g) and liquid NH_3 (150 ml). Stirring was continued for 3 h at −40 to −50°C, the excess of $NaNH_2$ was decomposed with NH_4Cl. After evaporation of NH_3 the residue was extracted with $CHCl_3$, the solid inorganic salt was filtered off, and the solution evaporated. Compound (III) was isolated by chromatography on a column of silica gel with $CHCl_3$ as eluent. Yield was 0.9 g (35%).

Under similar conditions amide (XVIII) was obtained from dichloro derivative (III) in 45% yield, mp 201-203°C (cf. [11]) and a mixture of (XVIII) and (XIX) was obtained from the tribromo (II) and dibromo derivative (XI). The mixture was separated by chromatography on a column of silica gel with $CHCl_3$−MeOH (30:1) as eluent. Yield of (XVIII) was 30%, mp 165-167°C (cf. [11]).

CONCLUSIONS

1. On halogenation of derivatives of 3-imidazoline or N-formylimidazoline mono-, di-, and trihaloalkyl derivatives of nitroxyl radicals of 3-imidazoline were obtained.

2. Participation of the radical center in reactions of the halomethyl derivatives of 3-imidazoline with nucleophilic reagents was detected and a difference was found in the direction of the reaction of chloro and bromo derivatives with bases.

3. A reductive dehalogenation reaction was discovered which led to the formation of dihalomethyl derivatives of 3-imidazoline from trihalomethyl derivatives and took place under the action of an aqueous alcohol solution of sodium hypobromite or amide in liquid ammonia.

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