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OXIDATION OF DI-tert-ALKYLHYDROXYLAMINES TO NITROXIDE RADICALS BY NITROUS ACID

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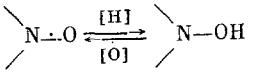
Stable nitroxide radicals and di-tert-alkylhydroxylamines are interconverted in oxidation–reduction reactions:



Therefore, it is possible to protect the nitroxide functional group by reducing it to the hydroxylamine group. The reverse transition to the nitroxide radical requires use of oxidants; the ones usually used are oxygen [1, 2], potassium ferricyanide [3], lead or manganese dioxide [4, 5] and peroxy acids [6]. The oxidants are selected for various reasons, including the ease with which the hydroxylamino group is oxidized. The presence in the hydroxylamine molecule of functional groups which form hydrogen bonds with the proton of the hydroxylamine group hinders oxidation [2].

Previously it has been assumed that all di-tert-alkylhydroxylamines are oxidized by atmospheric oxygen and lead dioxide [7]. At the present time, many dialkylhydroxylamines are known which are stable to the action of oxygen (3-N-oxides of 1-hydroxyimidazolines [5]), and also to lead and manganese dioxide (3-halo-4-oxo-2,2,6,6-tetramethyl-1-hydroxypiperidines [8]).

The most active oxidants for hydroxylamines are the peroxy acids. However, their use is associated with certain complications. Such as, they induce "peroxidation" of nitroxide radicals to oxoammonium salts [9]; furthermore they require use of alkaline reagents to separate the acids formed, which is undesirable for materials which are labile to bases.

The difficulties which we encountered upon oxidation to the nitroxide radicals of 3-halo-4-oxo-2,2,6,6-tetramethyl-1-hydroxypiperidines and also their oximes forced us to look for new reagents for oxidation of di-tert-alkylhydroxylamines.

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TABLE 1. Oxidation of 2,2,6,6-Tetramethyl-1-hydroxypiperidines by Nitrous Acid

Hydroxylamine	Oxidation method	Nitroxide	Yield of nitroxide, %	mp of nitroxide, °C	Lit. cited.
(Ia)	A	(IVa)	97	33,5–35,5	[7]
(Ib)	A	(IVb)	88	68,5–70,5 (cyclohexane)	[7]
(Ic)	A	(IVc)	81	174,5–176 (CCl_4)	[7]
(Ic)	B	(IVc)	81	174,5–176 (CCl_4)	[7]
(Id)	A	(IVd)	76	85–86,5 (hexane)	[8]
(Ie)	B	(IVe)	60*	75,5–77,5 (hexane)	[8]
(If)	A	(IVf)	70	122,5–124,5 (CCl_4)	
(If)	B	(IVf)	62*	118,5–120	
(II)	A	(V)	72	169–170	[11]
(III)	A	(VI)	60	104–105 (hexane)	[5]

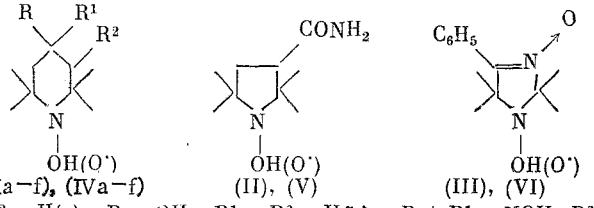
*The yield is indicated on the basis of the hydrochloride of (Ia).

We have found that nitrous acid, formed upon reaction of sodium nitrite with salts of di-tert-alkylhydroxylamines or with acids, oxidizes the hydroxylamino group to nitroxide according to the scheme

$$R_2N - OH \cdot HCl + NaNO_2 \rightarrow R_2N - OH + HNO_2 + NaCl$$
$$R_2N - OH + HNO_2 \rightarrow R_2N \dot{-} O + NO + H_2O$$

apparently analogously to oxidation of phenols to quinones by nitrous acid [10].

In this work, we oxidized by nitrous acid the heterocyclic hydroxylamines – derivatives of the sterically hindered 1-hydroxypiperidine (Ia-f), 1-hydroxypyrrolidine (II), and 1-hydroxyimidazoline (III) – with formation of the nitroxide radicals (IVa-f), (V), and (VI)



(Ia–f), (IVa–f) (II), (V) (III), (VI)

$R + R^1 = O$; $R^2 = H$(a); $R = OH$, $R^1 = R^2 = H$(b); $R + R^1 = NOH$, $R^2 = H$(c) $R + R^1 = O$, $R^2 = Cl$(d); $R + R^1 = O$, $R^2 = Br$(e); $R + R^1 = NOH$, $R^2 = Cl$(f)

The reaction was carried out in aqueous solution [compounds (Ia, b)], in two-phase solvent–water systems [(Ic-e), (III)] or in aqueous suspension [(If), (II)]. As a rule, in order to obtain complete oxidation we used a twofold excess of nitrous acid. A larger excess of HNO_2 is undesirable due to build-up of significant amounts of NO_2, which oxidizes the nitroxide group. The unreacted acid was neutralized or washed off with water. The oxidation was accomplished in two variants, depending on whether the dialkylhydroxylamine to be oxidized was in the free-base form (method A) or in the salt form (method B), and also depending on the stability to acid medium of the nitroxide radical formed. Method A involved adding the calculated amount of acid to an aqueous solution or suspension of dialkylhydroxylamine and an excess of $NaNO_2$. Method B involved adding a solution of $NaNO_2$ to an aqueous solution containing the salt of the dialkylhydroxylamine (and the acid, if necessary). The nitroxide radicals were separated by extraction or filtration. The results of the experiments are given in Table 1, from which it is evident that oxidation of dialkylhydroxylamines by nitrous acid proceeds with good yields. We should point out that upon oxidation of the oxime of hydroxylamine (If), deoximation is not observed upon treatment with nitrous acid. In the case of the oxime (Ic), partial cleavage of the hydroxyimino group occurs; therefore, we used one equivalent of HNO_2 for the oxidation.

The advantage of the proposed method is the possibility for oxidation of hydroxylamines in the form of their salts, while other oxidants react only with the free bases. This

circumstance allows us to use the previously proposed method for conversion of nitroxides to salts of hydroxylamines [4, 12] in order to protect the N–O group. For example, the bromoketone–nitroxide (IVe) cannot be obtained directly by bromination of the ketone–nitroxide (IVa). In order to obtain (IVe), the nitroxide (IVa) is converted to the hydrochloride of the hydroxylamine (Ia) [12], is brominated [8], and [without separating (Ie)] the reaction mass is oxidized by nitrous acid. Analogously, in order to obtain nitroxide (IVf), it has proven to be more efficient to not separate in pure form the hydroxylamines (Id) and (If) after chlorination and reaction with $NH_2OH \cdot HCl$. The reaction mass obtained after chlorination of the hydrochloride of ketone (Ia) is treated with $NH_2OH \cdot HCl$ and then, after formation of the hydrochloride of the oxime chloride (If), it is treated with an excess of $NaNO_2$.

EXPERIMENTAL

The IR spectra were recorded on the UR-20 instrument in KBr tablets. Compounds (Ia-c) were obtained according to the procedure in [2, 4]; compounds (Id, e), according to [8]; (II), according to [13]; (III), according to [5]. The oxidation was monitored using TLC on Silufol plates (Czechoslovakia) in a chloroform–ether (3:1) system. The compounds obtained were identified chromatographically and also from the lack of a depression in the melting point of a mixture of the test sample and known samples.

Oxidation of 2,2,6,6-Tetramethyl-4-oxo-1-hydroxypiperidine (Ia). To a solution of 0.34 g (2 mmole) of (Ia) and 0.35 g (5 mmole) of $NaNO_2$ in 5 ml water, with stirring 8 ml 0.5 N HCl was slowly added dropwise. After 15 min, the reaction mass was saturated with K_2CO_3 and extracted three times with benzene. The benzene extract was evaporated; obtained in the residue was 0.33 g of 2,2,6,6-tetramethyl-4-oxo-piperidine-1-oxide (IVa).

Oxidation of 2,2,6,6-Tetramethyl-1,4-dihydroxypiperidine (Ib). The experiment was carried out analogously to the preceding experiment. After saturation of the reaction mass with K_2CO_3, the product was extracted with ether. After drying and evaporation of the ether extract, 0.30 g of 2,2,6,6-tetramethyl-4-hydroxypiperidine-1-oxide (IVb) was obtained.

Oxidation of 2,2,6,6-Tetramethyl-4-hydroxyimino-1-hydroxypiperidine (Ic). To a mixture of 0.37 g (2 mmole) of (Ic) in 10 ml ether and 0.21 g (3 mmole) of $NaNO_2$ in 5 ml water was added 4.5 ml of 0.5 N HCl dropwise with stirring. Further treatment was carried out as described in the preceding experiment. Obtained was 0.31 g of 2,2,6,6-tetramethyl-4-hydroxyiminopiperidine-1-oxide (IVc).

Oxidation of 2,2,6,6-Tetramethyl-3-chloro-4-oxo-1-hydroxypiperidine (Id). To a solution of 0.41 g (2 mmole) of (Id) in 10 ml benzene was added in one step 0.21 g (3 mmole) of $NaNO_2$ in 5 ml water; and then 4.5 ml of 0.5 N HCl was slowly added dropwise with stirring. After 15 min, the benzene layer was separated, washed twice with water and evaporated under vacuum. The residue was crystallized from hexane. Obtained was 0.31 g of 2,2,6,6-tetramethyl-3-chloro-4-oxopiperidine-1-oxide (IVd).

Oxidation of 2,2,6,6-Tetramethyl-3-bromo-4-oxo-1-hydroxypiperidine (Ie). To a solution of 0.41 g (2 mmole) of the hydrochloride of (Ia) in 5 ml chloroform was added 0.1 ml (2 mmole) of Br_2. After completion of the reaction with bromine, to the solution with stirring a solution of 0.35 g (5 mmole) of $NaNO_2$ in 5 ml water was added dropwise. The chloroform layer was separated, washed twice with water, and dried with anhydrous $MgSO_4$. The solvent was evaporated and the residue was crystallized from hexane. Obtained was 0.30 g of 2,2,6,6-tetramethyl-3-bromo-4-oxo-piperidine-1-oxide (IVe).

2,2,6,6-Tetramethyl-3-chloro-4-hydroxyimino-1-hydroxypiperidine (If). To a solution of 0.90 g (4.38 mmole) of (Id) in alcohol was added 5 ml water and 0.75 g (10.8 mmole) of $NH_2OH \cdot HCl$, and the mixture was allowed to stand for a day. Then the alcohol was evaporated under vacuum, the residue was treated with a solution of 0.90 g (10.7 mmole) $NaHCO_3$ in 15 ml water; and the residue (If) was filtered by suction, washed with water, and dried. Obtained was 0.69 g (71%) (If), mp 121.5-123.5°C (CCl_4). Unstable, decomposed upon crystallization. Found: C 48.18; H 7.59; N 12.17; Cl 18.97%. $C_9H_{17}N_2O_2Cl$. Calculated: C 48.98; H 7.76; N 12.69; Cl 16.06%. IR spectrum (ν, cm^{-1}): 3320 (OH); 1635 (C=N).

2,2,6,6-Tetramethyl-3-chloro-4-hydroxyiminopiperidine-1-oxide (Vf). To a solution of 0.41 g (2 mmole) of (IVd) in 5 ml alcohol and 3 ml water was added 0.17 g (2.4 mmole) of $NH_2OH \cdot HCl$ and 0.20 g (2.4 mmole) of $NaHCO_3$ and the mixture was allowed to stand for a day. Then the alcohol was evaporated under vacuum, the residue of the oxime chloride (IVf) was filtered by suction, washed with water, and dried. Obtained was 0.31 g (70%) of (IVf), mp

122.5-124.5°C (CCl_4). Found: C 49.01; H 7.25; N 12.70; Cl 15.65%. $C_9H_{16}N_2O_2Cl$. Calculated: C 49.20; H 7.34; N 12.75; Cl 16.14%. IR spectrum (ν, cm^{-1}): 3300 (OH); 1650 (C=N).

Oxidation of 2,2,6,6-Tetramethyl-3-chloro-4-hydroxyimino-1-hydroxypiperidine (If). To an aqueous solution of 0.35 g (5 mmole) of $NaNO_2$ in 5 ml water was added 0.44 g (2 mmole) of (If). To the suspension formed was slowly added dropwise 8 ml of 0.5 N HCl. The mixture was stirred for 1 h. The residue was filtered by suction, washed with water, and dried. Obtained was 0.31 g (70%) of 2,2,6,6-tetramethyl-3-chloro-hydroxyiminopiperidine-1-oxide (IVf), mp 118.5-120°C; no depression of the melting point with the sample obtained in the preceding experiment.

Oxidation of 2,2,5,5-Tetramethyl-3-carbamido-1-hydroxypyrrolidine (II). To an aqueous suspension of 0.29 g (1.56 mmole) of (II) was added 0.22 g (3.19 mmole) of $NaNO_2$ and then 7 ml of 0.5 N HCl was slowly added dropwise with stirring. After 15 min, the reaction mass was saturated with K_2CO_3 and extracted three times with chloroform. The extract was dried with anhydrous $MgSO_4$ and evaporated. In the residue: 0.21 g of 2,2,5,5-tetramethyl-3-carbamido-pyrrolidine-1-oxide (V).

Oxidation of 2,2,5,5-Tetramethyl-1-hydroxy-4-phenylimidazoline-3-oxide (III). To a solution of 0.47 g (2 mmole) of (II) in 20 ml chloroform was added 0.70 g (10 mmole) of $NaNO_2$ in 10 ml water, and then 20 ml 0.5 N HCl was slowly added dropwise with stirring. After 30 min, the reaction mass was neutralized with 1.5 g K_2CO_3; the chloroform layer was separated and evaporated. The residue was crystallized from hexane. Obtained was 0.28 g of 2,2,5,5-tetramethyl-1-oxyl-4-phenylimidazoline-3-oxide (VI).

CONCLUSIONS

1. We have developed a convenient preparative method for obtaining nitroxide radicals by oxidation of di-tert-alkylhydroxylamines and their salts by nitrous acid.

2. We propose protection of the nitride functional group by conversion of the nitroxide radical to the salt of the hydroxylamine, and removal of the protection by oxidation with nitrous acid.

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