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AN UNEXPECTED FORMATION OF A NEW 3-IMIDAZOLINE FREE RADICAL.

E.A.V. Rijk* and G.I. Tesser
Laboratory for Organic Chemistry, Cath. University of Nijmegen
Toernooiveld, 6525 ED Nijmegen, The Netherlands

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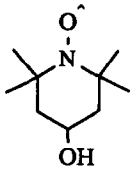
ABSTRACT
A new 3-imidazoline has been formed unexpectedly in the reaction between 2,4-dibromo-2,4-dimethylpentanone-3 and concentrated aqueous ammonia. A crystalline nitroxide formed upon oxidation with hydrogen peroxide. Its identity has been proved by X-ray analysis. A feasible mechanism for the present reaction is given.

Introduction

Part of our program is devoted to the incorporation of nitroxide free radicals in nucleotide chains[1]. For this purpose the readily available piperidine derivative **1**[2] (TEMPO-OL) was incorporated into a tri-2'-deoxyadenylate, the latter being used to study the interaction of DNA with single stranded DNA-binding protein, with the aid of NMR[3].

In order to induce minimal distortion of the system under study, a need was felt for a spinlabel smaller than **1**. A good candidate would be compound **2**, but its synthesis is cumbersome[4].



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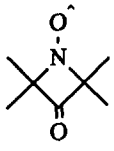

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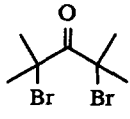

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Therefore, we wished to devise a shorter and more efficient synthesis, but we arrived at the unexpected formation of an imidazoline derivative. The present communication deals with this process and with its reaction mechanism.

Results

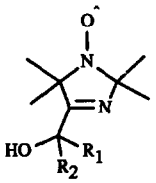
One of the shortest and formally most simple routes to compound **2** consists of the ammonolysis of dibromoketone **3** and subsequent oxidation of the formed hindered amine.

Thus, a two-phase mixture of dibromoketone **3** and excess aqueous ammonia was vigorously stirred, until a homogenous solution was obtained. Upon saturation of this solution with potassium carbonate a slightly coloured oil separated, which was subsequently oxidized with hydrogen peroxide and a trace of tungstate as the catalyst. Thinlayer chromatography showed only one

UV-quenching spot, which turned blue when sprayed with a mixture of 1% potassium ferricyanide and 15% ferric chloride hexahydrate in water (1:1, v/v). This reagent has been employed formerly for the chromatographical detection of nitroxide free radicals[5]. Fortunately the nitroxide could be isolated as a highly crystalline solid.

The isolated crystals, when subjected to analytical evaluation, soon appeared not to represent the desired azetidinone **2**, but to have a different constitution. Although the existence of the nitroxide moiety was unquestionably demonstrated by ESR (a_n= 17.5 G), mass spectra and elemental analysis indicated the compound to have the formula $C_{10}H_{19}N_2O_2$.

Since NMR and IR spectra did not present clear insight into the structure, we decided to establish it unambiguously by means of X-ray analysis[6]. This revealed the compound to be 1-methyl-1-[4-(1-oxyl-2,2,5,5-tetramethyl-3-imidazolyl)]ethanol **4a** (figure 1, R_1=R_2=CH_3)[7].



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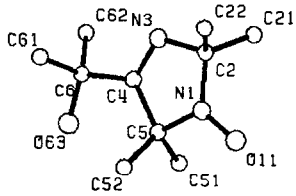
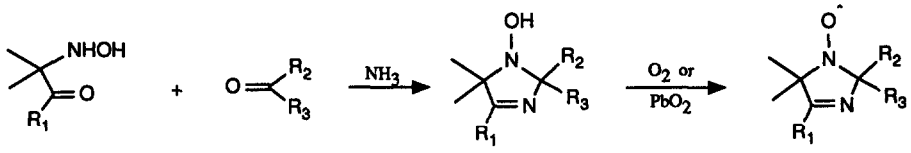


***Figure 1:** Structure of nitroxide **4a** (R_1=R_2=CH_3) according to X-ray analysis.*

Discussion

Volodarsky et al.[8,9] have been the first who described 3-imidazoline free radicals. In their approach, 1,2-hydroxylaminoketones **5** were reacted with ketones and ammonia, yielding the colourless N-hydroxy imidazolines **6**, which were oxidized to the nitroxides **7** (scheme 1).



5 **6** **7**

***Scheme 1:** Synthesis of 3-imidazoline nitroxide radicals according to Volodarsky et al.*

The primary (**4b**, R_1=R_2=H) and secondary (**4c**, R_1=H, R_2=CH_3) alcohols have been synthesized by reduction of their parent carbonyl compounds. It is obvious that our imidazoline **4a** with the tertiary alcohol can not be achieved in this way, so the here reported synthesis is a valuable complement of the general route to 3-imidazoline free radicals.

3-imidazoline nitroxides have been used as chelating agents. For example, the carboxylic acid **8** proved to be capable of chelation without involvement of the free radical moiety[8]. Although the

electronic and conformational requirements for chelation are present in the alcohols **4** (figure 2),

8 **4**

Figure 2: *Organometallic adducts of the carboxylic acid **8** and the alcohols **4**.*

organometallic adducts of them are not known, presumably since the basic conditions required for formation of these compounds are too demanding; both alcohols **4b** and **4c** are oxidized by the nitroxide moiety to the aldehyde or ketone, using basic conditions. Since the tertiary alcohol **4a** is insensitive to oxidative conditions, it meets the requirements for chelation better than the alcohols **4b** and **4c** do.

Knowing the structure of the formed nitroxide, an exact interpretation of the spectra was possible. The ^{1}H-NMR spectrum (figure 3) showed the presence of 2 broad signals shifted far upfield: -9.28 ppm and -15.57 ppm.

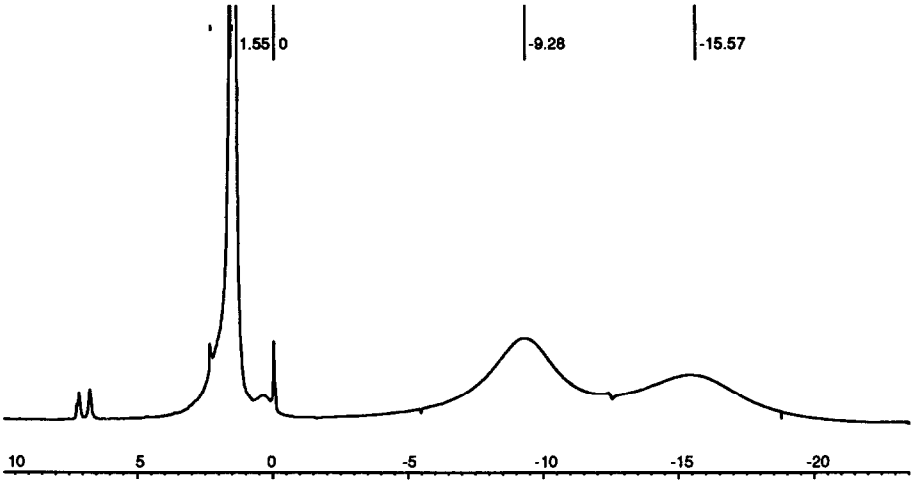


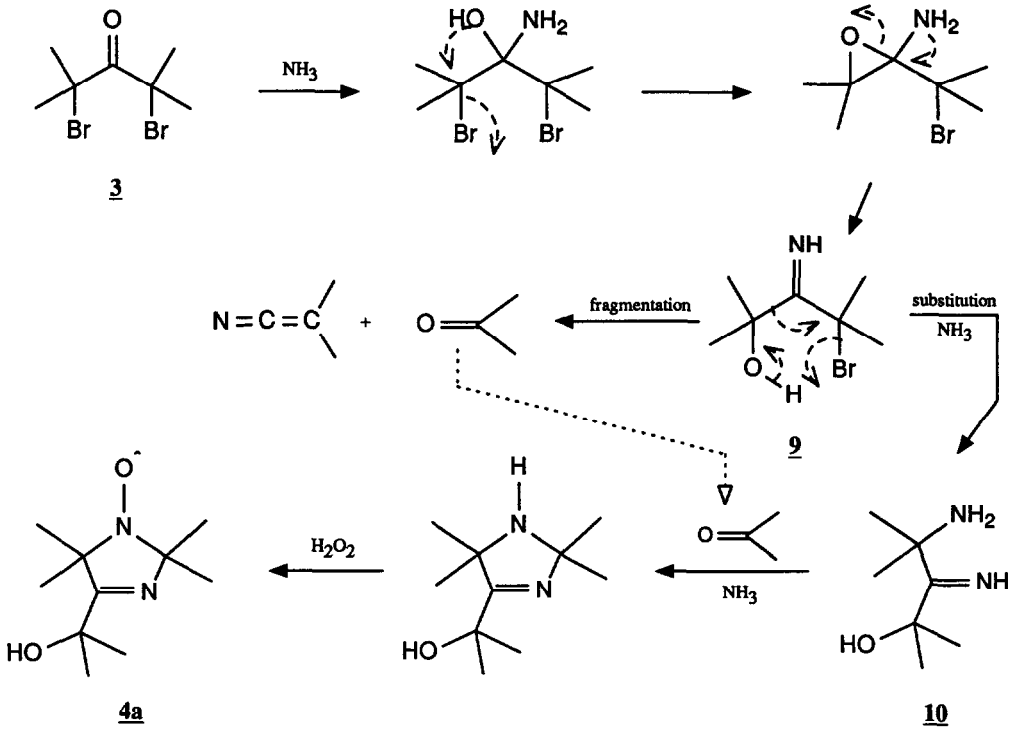
Figure 3: *^{1}H-NMR spectrum of nitroxide **4a**.*

This behaviour is characteristic for 3-imidazoline free radicals as has been described by Volodarsky et al.[8]. The upfield shifted signals arise from the four α-methyl groups of the nitroxide, which experience the magnetic field of the nitroxide moiety. As a result of unsymmetrical

distribution of charge in the molecule, caused by the imine, the methyl groups on C_2 experience less shielding than those on C_5. Consequently, the C_2-methyls appear at lower field relative to the C_5-methyls.

A small quantity was reduced with hydrogen, using palladium on carbon as the catalyst. In the formed hydroxylamine, the C_2- and C_5-methyls are shifted back to normal positions and are hardly distinguishable of each other; 1.464 and 1.477 ppm. The singlet of the methyl groups on C_6 appeared at 1.55 ppm, in both the nitroxide and the hydroxylamine, showing that the field strength of the unpaired electron rapidly decreases with increasing distance.

A feasible mechanism for the presently unanticipated reaction is given in scheme 2. Amines are reported to react with α-bromoketones to give α-hydroxyimines, epoxides being formed as intermediates[10]. This renders the γ-hydroxy bromide **9**, which is formed after attack of NH_3 on the α,α'-dibromoketone, an acceptable intermediate. We postulate that compound **9** plays a key role in the pathway: Apart from its tendency to undergo a fragmentation[11], whereby acetone is formed, it can also react with a second molecule of NH_3 to give the 1,2-aminoimine **10**, which will yield the 3-imidazoline on reaction with the formed acetone[12].



***Scheme 2:** Tentative mechanism of the formation of 1-methyl-1-[4-(1-oxyl-2,2,5,5-tetramethyl-3-imidazolyl)] ethanol.*

Experimental

2,4-dimethyl-pentanone-3 was purchased from Aldrich.

Thin layer chromatography (TLC) was performed on precoated silica-gel plates, F_{254}. The plates were developed with ethylacetate. Detection of the nitroxide free radical is performed by spraying with a freshly prepared mixture of 1% $K_3Fe(CN)_6$ and 15% $FeCl_3.6H_2O$ in water (1:1, v/v). The nitroxides reduce the reagent and produce Prussian blue spots.

^{1}H-NMR and ^{13}C-NMR spectra of the nitroxide were recorded on a Bruker AM 400. For ^{1}H-NMR spectra of the reduced compound a Bruker WH 90 was used. Spectra were recorded in $CDCL_3$, using TMS as internal standard.

ESR-spectra were recorded on a Bruker ESP 300.

Melting points were determined in a closed capillary using a Tottoli apparatus and are not corrected.

Mass spectra were recorded on a VG-7070E using an Electron Impact (EI) technique.

IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer.

2,4-dibromo-2,4-dimethylpentanone-3 (3).

2,4-dibromo-2,4-dimethylpentanone-3 was synthesized by slow addition of 1 mole bromine to an ice-cooled solution of 1 mole (114 grams) 2,4-dimethylpentanone-3 in 200 ml acetic acid. A catalytic amount of HBr was added to start reaction. A second mole of bromine was then added at reflux temperature. After completion of the addition, acetic acid was removed by evaporation, the residue was washed with a concentrated aqueous solution of Na_2CO_3 and finally distilled in vacuum. B.p.$^{13\text{-}14\ mm}$: 89-91°C. ^{1}H-NMR($CDCl_3$): δ=2.16 ppm.

1-methyl-1-[4-(1-oxyl-2,2,5,5-tetramethyl-3-imidazolyl)]ethanol (4a).

A mixture of 140 grams 2,4-dibromo-2,4-dimethylpentanone-3 and 1 litre of concentrated aqueous ammonia was stirred vigorously until a homogeneous solution was obtained (1-2 days, dependent on the speed of mixing). Saturation with K_2CO_3 caused the separation of an oil which was taken up in Et_2O. Drying of the organic layer with K_2CO_3 and evaporation of ether yielded 62 grams of a slightly coloured oil.

The oil was dissolved in 400 ml water, containing 1.6 grams of Na_2WO_4 and oxidized with 100 ml of a 35% solution of H_2O_2 in water (g/g). After 2 hours the aqueous layer was saturated with NaCl, causing the phase separation. The bright yellow organic phase was taken up in Et_2O and separated. The aqueous layer was extracted three times more with little portions of Et_2O. Evaporation of the combined organic layers gave 24 grams yellow oil, which crystallized partly. The partly crystallized residue, containing some impurities, was dissolved in 150 ml Et_2O and shaken with 150 ml of a concentrated aqueous solution of NaCl. The two-phase mixture was poured into a beaker and left standing at the air, causing slow evaporation of the ethereal layer. The impurities were forced into the aqueous layer, as a result of this treatment, leaving yellow crystals floating on the watersurface. These were filtered off and washed with concentrated aqueous NaCl solution. The isolated crystals were subsequently dissolved in a small quantity of Et_2O, residual NaCl was filtered

off and the organic layer evaporated, yielding 11.5 grams (22% based on reacted 2,4-dibromo-2,4-dimethylpentanone-3). Chromatographic pure. M.p.: 156-158°C. Analytically pure crystals could be obtained by sublimation or recrystallisation from n-hexane.

Elemental analysis:	calculated:	C: 60,27%	H: 9,61%	N: 14,06%
($C_{10}H_{19}N_2O_2$)	found:	C: 60,25%	H: 9,59%	N: 13,74%.

Mass(EI+): 200 (M^++H), 199 (M^+). ^{1}H-NMR($CDCl_3$): δ=1.55 ppm (s), 1-methyl and ethanol-CH_3; -9.28 ppm (broad s), 2-$(CH_3)_2$; -15.57 ppm (broad s), 5-$(CH_3)_2$. ^{1}H-NMR($CDCl_3$) of the reduced compound (H_2, 10% Pd on C): δ=1.464 and 1.477 ppm (2 singlets, 12H), imidazolyl-CH_3; 1.55 ppm (s, 6H), CH_3. ^{13}C-NMR($CDCl_3$): δ=29,7 ppm; 35,7 ppm; 84,6 ppm; 152,0 ppm. IR(KBr): μ=3250-3500 cm^{-1}(OH in H-bridge); 2980, 2940 and 2870 cm^{-1}(methyl); 1630 cm^{-1}(C=N).

References and Notes.

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2. Please note: The use of ^ to designate the unpaired electron in the nitroxide moiety, is not the authors choice, but a peculiarity of the chemical texteditor used (ChemText™).
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