15. A. Mannschreck, R. Radeglia, E. Grundemann, and R. Ohme, Chem. Ber., 100, 1778 (1967).

SYNTHESIS OF 3,4-DIAMINO-2,2,6,6-TETRAMETHYLPIPERIDINE-1-OXYL

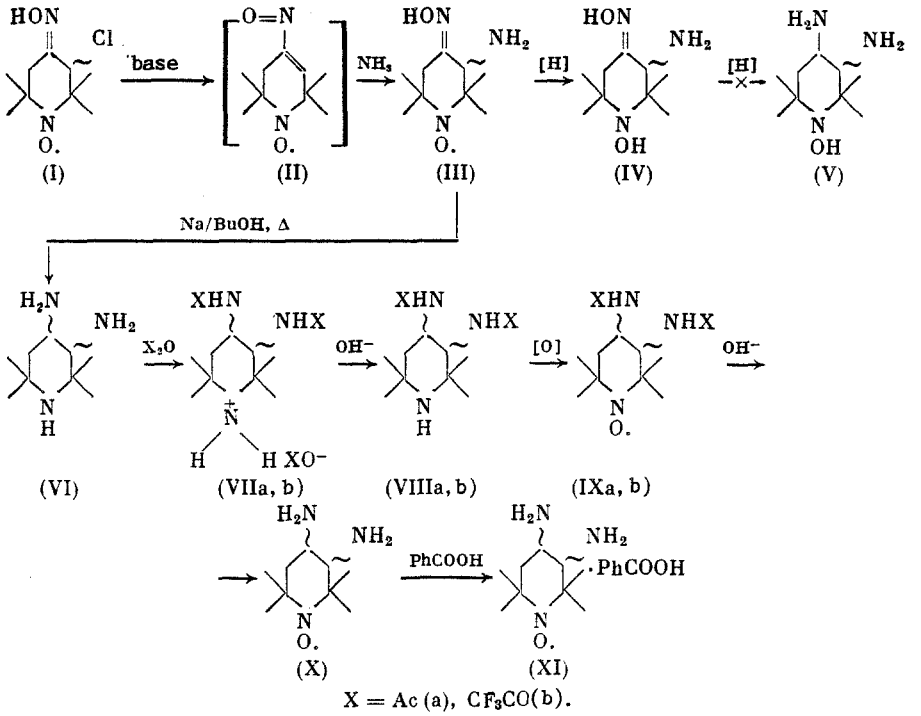
V. D. Sen'

UDC 542.91:547.822.7-31

The reaction of 4-hydroxyimino-2,2,6,6-tetramethyl-3-chloropiperidine-1-oxyl with ammonia results in the formation of 3-amino-4-hydroxyimino-2,2,6,6-tetramethylpiperidine-1-oxyl. Reduction of 3-amino-4-hydroxyimino-2,2,6,6-tetramethylpiperidine-1-oxyl to 3,4-diamino-2,2,6,6-tetramethylpiperidine, protection of the primary amino groups by acylation, followed by oxidation of the secondary amino group to a radical and removal of the acyl protection resulted in the formation of 3,4-diamino-2,2,6,6-tetramethylpiperidine-1-oxyl.

Difunctionally substituted nitroxyl radicals are of interest as rigidly binding spin labels [1], as reagents in analytical chemistry [2] and as starting compounds in the synthesis of biologically active compounds. Most of the known radicals of this type are derivatives of pyrrolidine- and imidazolidineoxyls, and only a few of them are 4,4- or 3,4-disubstituted piperidineoxyl [1].

In the present work, the synthesis of piperidineoxyl (X) was carried out starting from chlorooxime (I) [3] according to the following scheme:



Aminooxime (III) was obtained by saturating a chloroform solution of (I) with gaseous NH_3. In the course of the reaction the color of the solution changes from orange to green, which indicates the dehydrochlorination of (I) by the action of NH_3 to (II), and then the second molecule of NH_3 adds to (II) with the formation of (III), whereby the reaction mixture again becomes orange in color (cf. [4]).

In view of the ease of reduction of the nitroxyl group, the conversion of (III) into the desired diamine (X) is impossible without affecting the radical center. Simultaneously

N. N. Semenov Institute of Chemical Physics, Academy of Sciences of the USSR, Chernogolovka Branch. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2094-2098, September, 1989. Original article submitted July 22, 1988.

 0568-5230/89/3809-1928$12.50

with the reduction of the oxime group, the >NO· group can be reduced to >NOH or further to >NH with the formation of (V) or (VI), respectively. A simpler method of synthesis of (X) from (III) can be carried out via the intermediate (V) [5], since oxidizing agents, which do not require protection of the primary amino groups, such as for example the O_2/Cu^{2+} catalytic system [6], are suitable for converting hydroxylamine into radicals. In the present work, this path could not be followed, since it was impossible to obtain 1-hydroxypiperidine (V) from (III) with the reducing agents used.

The method of hydrogenation of oximes under mild conditons on the Rh/Al_2O_3 catalyst [7] was found to be ineffective for (III). Even at elevated temperatures (90°C) and H_2 pressure ($3 \cdot 10^6$ Pa) the oxime group does not react, but (III) is reduced to the corresponding hydroxylamine (IV). Treatment of (III) with an excess of $LiAlH_4$ in boiling THF leads to the same result.

Aminooxime (III) can be reduced to a 3,4-diamino derivative by the action of the classical reducing agent of oximes—metallic Na in n-butanol at elevated temperature; 3,4-diaminopiperidine (VI) is thus formed in a ~70% yield. Compound (VI) is thus obtained in a lower yield when the hydrogenation of (III) is carried out on a platinum catalyst in an acid–aqueous medium.

In order to reoxidize (VI) to a radical, the primary amino groups of this compound were protected by acylation. The diacetyl derivative (VIIa) was oxidized in an aqueous medium by means of the H_2O_2/WO_4^{2-} system at pH 10-11 [8], while the bis(trifluoroacetyl) derivative (IIIb) was oxidized by p-nitroperbenzoic acid in an organic solvent medium. The removal of the acetyl protection in compound (IXa) proceeds much more difficultly (1N KOH, 100°C, 70 h) than in (IXb) (1N KOH, 80°C, 10 min). The overall yields of (X) from (VI) on using the acetyl and trifluoroacetyl protection are 33 and 53%, respectively.

Diamine (X) was identified in the form of a well crystallizable monobenzoate (XI).

TABLE 1. IR, UV and EPR Spectra of 3,4-Disubstituted Piperidines and Piperidineoxyls

Compound	IR spectrum*		UV spectrum (in EtOH)		EPR spectrum (EtOH, 25°C)
	ν, cm^{-1}	group	λ_{max}, nm	ε, liter/(mole·cm)	a_N, mT (±0.01)
(III)	1603 1660 3240, 3320, 3390, 3587	NH_2 C=N NH, OH	224 sh 432	2800 11,5	1,55
(VI)	1590, 3200, 3290, 3365	NH_2	–	–	–
(VIIa)	1550 1630, 1647, 1685 2500, 2620, 2687 3075, 3100, 3220, 3278	CONH, AcO^- C=O NH_2^+ NH	–	–	–
(VIIIb)	1160, 1185, 1210 1565 1677, 1700, 1712, 1730 3105, 3310	CF_3 CONH C=O NH	–	–	–
(IXa)	1557 1630, 1670 3085, 3220, 3260, 3320	CONH C=O NH	243 458	2080 11,0	1,60
(IXb)	1165, 1185, 1210 1566 1700, 1735 3112, 3305	CF_3 CONH C=O NH	236 sh 463	2140 10,5	1,60
(X)	1610, 3313, 3395	NH_2	242 463	2100 10,4	1,59
(XI)	722, 1524, 1590 1622, 2155, 2565, 2635, 2730, 3335, 3400, 3430	$PhCOO^-$ NH_2, NH_3^+	227 269 sh 279 sh 459	12 500 1790 1190 11,1	1,59

*(III) – in $CHCl_3$, (VI) – oily layer, (X) – in CCl_4, remaining – in mineral oil.

The structure of the compounds obtained was confirmed by elemental analysis and spectral data (Table 1). The EPR spectra of dilute solutions of (III), (IX)-(XI) consist of three lines; the hyperfine interaction constants a_N are between 1.55 and 1.60 mT, and are typical for piperidineoxyls. In the UV spectra of the radicals there are two absorption bands of the nitroxyl group in each case. The shorter-wave band of the >NO· group of (XI) is overlapped by the absorption of the $PhCOO^-$ chromophore. In the mass spectrum of (III) the most stable primary fragmentary ions with m/z 184 and 167 are formed, probably, as a result of the elimination of NH_3 and NH_2OH, respectively, from $[M + 1]^+$ and M^+. This course of fragmentation differs from the decomposition of M^+ of monosubstituted piperidineoxyls [9].

By potentiometric titration in an aqueous solution for the 3-NH_2 group of (III), the value of $pK_a = 6.32 \pm 0.05$ was found (25°C). The absorption band of the intramolecular hydrogen bond is absent in the IR spectrum (III) in $CHCl_3$, and therefore an anti-configuration should be ascribed to compound (III). In order to evaluate the influence of the nitroxyl group on pK_a of (III), a pK_a was determined for 3-amino-2,2,5,5-tetramethylpyrrolidine-1-oxyl, in which the amino and nitroxyl group are separated by a chain of two C-atoms. The value obtained of $pK_a = 7.25 \pm 0.05$ (H_2O, 25°C) is lower by ∿3.5 units than the pK_a in primary aliphatic amines. Hence, it follows that the nitroxyl group is a strong electron acceptor, the −I-effect of which is comparable with that of the nitrile group [10]. The decrease in pK_a of (III) compared with 3-aminopyrrolidineoxyl by a further unit approximately is due to the influence of the oxime group. This fact correlates satisfactorily with the data in [11], where it was shown that in aliphatic 1,2-aminooximes, the pK_a of the amino group is 1.6 units lower than the customary value for primary amines.

Compound (VI) obtained in the reduction of (III) and its transformation products (VII)-(XI) are probably racemic trans-3,4-disubstituted piperidines (cf. [12]). The formation of only one diastereomer of (VI) is confirmed by sharp melting points (within 1°C) of its well crystallizing derivatives (IXa, b). Moreover, cis- and trans-1,2-diaminocyclohexanes are readily separated by the TLC method [13], while each of compounds (VI), (VIII)-(X) that we synthesized gives only one spot in their TLC. The confirmation for the stereostructure of the compounds obtained will be reported after additional investigations.

The author wishes to express his gratitude to V. A. Golubev and L. A. Krinitskaya for helpful comments on the results of this work.

EXPERIMENTAL

The IR spectra were obtained on a Specord 75-IR spectrophotometer, the electronic spectra on a Specord UV-VIS, the EPR spectra on a EPA-2A radiospectrometer, and the mass spectra on a Finnigan chromato-mass spectrometer (NH_3-ionization, 50 eV, temperature of ionization chamber 100°C).

3-Amino-4-hydroxyimino-2,2,6,6-tetramethylpiperidine-1-oxyl (III). In analogy to [4], by the reaction of 4.40 g of chlorooxime (I) with excess of NH_3, 3.53 g of (III) was obtained, yield 87%. Rose fine needles, mp 121-123°C (from MeCN). Found: C 54.8; H 9.35; N 20.9%. $C_9H_{18}N_3O_2$. Calculated: C 53.98; H 9.06; N 20.98%; M 200.26. Mass spectrum: m/z (intensity, %): 202 (26), 201 (70), 200 (100, M^+), 184 (59), 167 (26), 137 (25), 127 (68), 110 (29).

3,4-Diamino-2,2,6,6-tetramethylpiperidine (VI). Metallic Na (4.5 g) was added in small portions in the course of 30 min at 90-100°C, with stirring, to a solution of 5.0 g of (III) in 100 ml of n-butanol. After complete dissolution of Na, the reaction mixture was poured into 200 g of crushed ice, the aqueous layer was separated, and the butanolic layer was extracted with 3 N HCl (50 ml × 3). The aqueous extracts were combined, washed with ether and evaporated to dryness. The remaining crystals were treated with 160 ml of 25% NaOH and extracted with ether (40 ml × 5). The extract was dried over NaOH, and ether was removed. Distillation of the residue in vacuo (83-89°C/800 Pa) gave 2.9 g (68%) of (VI) in the form of a colorless oil with an aminic odor. The TLC of (VI) was carried out on Silufol plates, using an alcohol–30% aqueous NH_3 mixture (5:1) as eluent and ninhydrin as developing agent, R_f 0.22.

3,4-Diacetylamino-2,2,6,6-tetramethylpiperidinium Acetate (VIIa). A 1.76 g portion of Ac_2O was added dropwise at ∿20°C to a solution of 1.23 g of (VI) in 7 ml of DMF, and the mixture was stirred for 2 h. A 14 ml portion of dry ether was added to the suspension, and the crystals were filtered, washed with ether, and dried in vacuo. Yield, 1.44 g (63%) of (VIIa) in the form of colorless plates, mp 226-227°C (from MeCN). Found: C 57.6; H 9.42;

N 13.7%. $C_{15}H_{29}N_3O_4$. Calculated: C 57.12; H 9.27; N 13.32%: M 315.41.

3,4-Bis(trifluoroacetylamino)-2,2,6,6-tetramethylpiperidine (VIIIb). A solution of 11.0 g of $(CF_3CO)_2O$ in 10 ml of DMF was added dropwise in the course of 20 min at 0°C and with stirring in a dry atmosphere to a solution of 3.8 g of (VI) in 15 ml of DMF, and stirring was continued for another 3 h at ~20°C. A large part of the solvent was then removed from reaction mixture at 40°C under vacuum (10 Pa). The remaining oil was dissolved in 20 ml of H_2O, and the solution was made alkaline to pH 10 at 0°C with 1 N KOH. The crystals that separated out were filtered off, washed with ice water, and dried in air. The yield of (VIIIb) was 6.26 g (80%), colorless needles, mp 254-257°C (from MeCN; in a sealed capillary). Found: C 42.8; H 5.16; F 31.6; N 11.5%. $C_{13}H_{19}F_6N_3O_2$. Calculated: C 42.98; H 5.27; F 31.38; N 11.57%; M 363.30.

3,4-Diacetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl (IXa). A 30% aqueous H_2O_2 (1.4 ml) was added in the course of 1 h, in portions of 0.2 ml, with stirring, at ~20°C, to a solution of 1.26 g of (VIIa) in 4 ml of 1 N KOH containing Na_2WO_4 and Trilon B in concentrations of 10^{-2} mole/liter. After 24 h, the solution was acidified to pH 6 and extracted with ethyl acetate (5 ml × 5). From the extract 0.99 g (91%) of (IXa) was isolated rose needles, mp 246-247°C (from MeCN). Found: C 57.1; H 9.12; N 15.2%. $C_{13}H_{24}N_3O_3$. Calculated: C 57.76; H 8.95; N 15.54%; M 270.35.

3,4-Bis(trifluoroacetylamino)-2,2,6,6-tetramethylpiperidine-1-oxyl (IXb). A 3.84 g portion (calculated for 100%) of p-nitroperbenzoic acid was added to a solution of 3.63 g of (VIIIb) in 40 ml of ethyl acetate, and the mixture was stirred for 2 h at 20°C. The precipitated p-$O_2NC_6H_4COOH$ was filtered off, the filtrate was washed with cold 5% solution of $NaHCO_3$ (10 ml × 3), water, and dried over Na_2SO_4. The solvent was removed in vacuo. Yield, 3.40 g (90%) of (IXb), rose crystals, mp 251-252°C, in a sealed capillary (from 50% alcohol). Found: C 41.2; H 5.06; F 30.3; N 11.1%. $C_{13}H_{18}F_6N_3O_3$. Calculated: C 41.28; H 4.80; F 30.13; N 11.11%; M 378.29.

3,4-Diamino-2,2,6,6-tetramethylpiperidine-1-oxyl (X). A suspension of 3.03 g of (IXb) in 20 ml of 1 N KOH was heated at 80°C to complete dissolution, the solution was cooled to 20°C, saturated with potassium carbonate, and extracted with ether (40 ml × 5). The extract was dried over K_2CO_3, the ether was evaporated and the remaining red oil was distilled in vacuo (7 Pa) (bath temperature 114-117°C). The yield of (X) was 1.11 g (73%). TLC (Silufol, alcohol–THF–33% aqueous Et_2NH (6:3:1.1.5)); R_f 0.39.

(3-Amino-2,2,6,6-tetramethyl-1-oxyl-4-piperidyl)ammonium Benzoate (XI). A solution of 140 mg of PhCOOH in 2 ml of ether was added with stirring to a solution of 186 mg of (X) in 3 ml of ether. The crystals formed were separated, washed with ether, and dried in vacuo. Yield 283 mg (92%) of (XI), rose rods, mp 151-156°C (from MeCN). Found: C 62.3; H 8.38; N 13.8%. $C_{16}H_{26}N_3O_3$. Calculated: C 62.31; H 8.50; N 13.63%; M 308.40.

LITERATURE CITED

1. J. F. W. Keana, Spin Labelling in Pharmacology, Part 1, J. L. Holtzman, ed., Academic Press, N.Y. (1984).
2. P. M. Solozhenkin, Electronic Paramagnetic Resonance in Analysis of Compounds [in Russian], Donish, Dushanbe (1986), p. 98.
3. L. A. Krinitskaya and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., 391 (1983).
4. L. A. Krinitskaya and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1619 (1984).
5. M. Ya. Fioshin, I. A. Avrutskaya, N. N. Bogdanova, and I. I. Surov, Coll. Czech. Chem. Commun., 51, 1986 (1986).
6. V. A. Golubev, V. D. Sen', and E. G. Rozantsev, Symposium on Stable Nitroxide Free Radicals, Pecs, Hungary (1979), p. 38.
7. P. N. Rylander, Catalytic Hydrogenation in Organic Syntheses, Academic Press, N.Y. (1979), p. 153.
8. V. D. Sen', V. A. Golubev, and N. I. Efremova, Izv. Akad. Nauk SSSR, Ser. Khim., 61 (1982).
9. B. V. Rozynov, R. I. Zhdanov, O. S. Reshetova, et al., Izv. Akad. Nauk SSSR, Ser. Khim., 1838 (1978).
10. D. D. Perrin, B. Dempsey, E. P. Sergeant, pK_a Prediction for Organic Acids and Bases, Chapman and Hall, London (1981), p. 30.
11. R. K. Murmann, J. Am. Chem. Soc., 80, 4174 (1958).
12 F. M. Jaeger, Chem. Zbl., 1196 (1937).
13. R. Saito and Y. Kidani, Chem. Lett., 123 (1976).