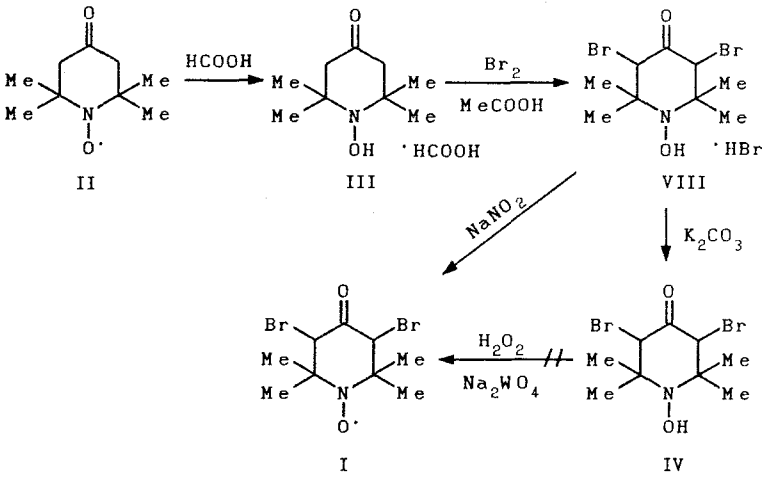
SYNTHESIS AND PROPERTIES OF 3,5-DIBROMO-4-OXO-2,2,6,6-TETRAMETHYLPIPERIDINE-1-OXYL RADICAL

I. Yu. Zhukova, E. Sh. Kagan, and V. A. Smirnov

Bromination of 1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine gives 3,5-dibromo-1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine hydrobromide. Oxidation of the latter generates 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperdine-1-oxyl radical, which represents a convenient acylating spin trap.

3,5-Dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl radical (I) can be used as the starting material for the synthesis of a variety of 2,2,5,5-pyrroline-1-oxyl derivatives. It is known that the former compound can be prepared by oxidation of 3,5-dibromo-2,2,6,6-tetramethylpiperidine with m-chloroperbenzoic acid in ether [1]. In the present paper we have shown that this compound can also be prepared conveniently from 4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl.

Since nitroxyl radicals in the 2,2,6,6-tetramethylpiperidine series are unstable in acidic media [2, 3], 4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl was converted in an initial step to the corresponding hydroxylamine III, which was then brominated to give dibromide IV.

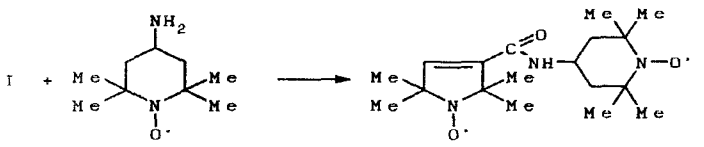


Generally speaking, di-tert-hydroxylamines can be readily oxidized to their corresponding nitroxyl radical derivatives using manganese dioxide, lead dioxide, or even with oxygen in air. However, like several other hydroxylamines in the α-halo-4-oxo-2,2,6,6-tetramethylpiperidine series [4], dibromide IV is stable with respect to reaction with these reagents. This substrate is also not oxidized by action of hydrogen peroxide–sodium tungstenate. The material is easily oxidized to its corresponding nitroxyl radical I by nitrous acid [5]. This method can be used for the preparative-scale synthesis of radical I, since it does not require isolation of the intermediate products and the overall yield is 61%.

S. Ordzhonikidze Novocherkassk Polytechnic Institute, Novocherkassk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 73-74, January, 1992. Original article submitted May 31, 1990.

0009-3122/92/2801-0064$12.50

Radical I undergoes the Favorskii rearrangement upon reaction with amines, to give 3-carboxamido-2,2,5,5-tetramethylpyrroline-1-oxyl derivatives. In accord with this general reaction, treatment of radical I 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (V) results in the formatio of 4-(2,2,5,5-tetramethyl-pyrroline-1-oxyl-3-carboxamidoyl)-2,2,6,6-tetramethylpiperidine-1-oxyl (VI), while reaction with aqueous ammonia gives 3-carboxamido-2,2,5,5-tetramethylpyrrolidine (VII).



V VI

In contrast to the behavior of radical I, however, hydroxylamine IV reacts with ammonia and primary amines to generate complex product mixtures, whose composition and structure have not been determined.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 spectrophotometer using Vaseline mulls, while EPR spectra were measured using benzene solutions on a Minsk 22-M spectrometer.

The results of C, H, N elemental analysis agreed with calculations.

3,5-Dibromo-1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine Hydrobromide (VIII, $C_9H_{15}Br_2NO_2 \cdot HBr$). Compound II (17 g, 0.1 mole) was dissolved in 30 ml glacial acetic acid and the solution was cooled in ice to 15°C; 7.3 g (6 ml, 0.16 moles) formic acid was then added gradually. Carbon dioxide was evolved. The resulting hydroxylamine salt III which formed [2] was used without prior isolation. To the above solution of hydroxylamine salt III was added a solution of 32 g (0.2 moles) bromine in 50 ml glacial acetic acid, while the entire mixture was being continuously cooled to 15-20°C. After 10-12 h the solution turned colorless and a precipitate formed, which was separated, washed with acetic acid and ether, and finally dried in air. Compound VIII was obtained in the form of colorless crystals, mp 175-177°C. Yield 31 g (75%).

3,5-Dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (I, $C_9H_{14}Br_2NO_2$). Compound VIII (31 g, 0.75 moles) was mixed with 200 ml chloroform. The resulting suspension was cooled to 20°C and stirred while a solution containing 8 g (0.12 moles) nitrous acid in 100 ml water was added; afterwards, with continuous stirring, 16 ml of 0.5 M HCl solution was added dropwise (the pH of the solution should not be below 3). After 15 min the chloroform layer was separated and washed with water (3 × 25 ml), and the solvent was evaporated under vacuum. Compound I was obtained in the form of orange crystals, mp 160-161°C. Yield 20 g (61%), based on the amount of II starting material. The IR spectrum of this newly prepared material was identical with that of an authentic sample of I [1].

3,5-Dibromo-1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine (IV, $C_9H_{15}Br_2NO_2$). Compound VIII (10.3 g, 0.025 moles) was suspended in a solution of 2.6 g anhydrous sodium carbonate at 3-5°C. After 15 min the resulting precipitate was removed by filtration, air dried, and crystallized from ethyl acetate. Colorless crystals which decomposed at the melting point were obtained. Yield 7.5 g (93%).

4-(2,2,5,5-Tetramethylpyrroline-1-oxyl-carboxamidoyl)-2,2,6,6-tetramethyl-piperidine-1-oxyl(VI,$C_{18}H_{31}N_3O_3$). A solution was formed from 30 ml methylene chloride and 1 g (5.8 mmoles) 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl with 1.1 g (11.6 mmoles) triethylamine. This solution was then treated with 1.9 g (5.8 mmoles) compound I. The mixture was stirred for 5 h at 20°C, washed with water (3 × 20 ml), and the solvent was evaporated to give an orange crystalline residue, which was then recrystallized from isopropyl alcohol, mp 192-194°C. EPR spectrum: 5 lines. Yield 1.4 g (72%).

3-Carboxamido-2,2,5,5-tetramethylpyrrolidine (VII, $C_9H_{16}N_2O$). To 2 g (5.8 mmoles) radical I was added 20 ml ammonia, and the resulting suspension was stirred for 4-5 h. The yellow precipitate which formed was removed by filtration, and to the filtrate was added 1.5 g potassium hydroxide to salt out any dissolved radical VII. Amide VII was obtained in the form of yellow crystals, mp 204-205°C (ethanol). Overall yield 0.5 g (91%). A mixed melting point probe with an authentic sample [2] did not give a melting point depression.

LITERATURE CITED

1. N. W. Alcock, B. T. Golding, P. V. Ioannou, and J. F. Sawyer, Tetrahedron, **33**, 2969 (1977).

2. É. G. Rozantsev, Free Iminoxyl Radicals, Khimiya, Moscow (1970).
3. É. G. Rozantsev, E. Sh. Kagan, and V. D. Sholle, Nitroxyl Radicals, Nauka, Moscow (1987), p. 5.
4. L. A. Krinitskaya and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 443 (1982).
5. L. A. Krinitskaya and L. B. Volodarskii, Izv. Akad. Nauk SSSR. Ser. Khim., No. 2, 391 (1983).