Studies on Stable Free Radicals. V[1]

Reactivity of a Stable Free Radical, 2,2,6,6-Tetramethyl-4-oxopiperidine-1-oxyl

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A stable *N*-oxyl radical, 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (I), afforded 1-hydroxy-2,2,6,6-tetramethyl-3-(2,2,6,6-tetramethyl-4-oxopiperidinoxy)-4-oxopiperidine (IX) by hydrogen-abstraction followed by the coupling reaction of the *N*-oxyl radical I with the *C* radical III derived from I. The product IX was characterized as the monoacetate (X), monobenzoate (XI), urethane (XII), semicarbazone (XIII), triol (XIV), triacetate (XV), and a new *N*-oxyl radical (XVI). It has been confirmed that i) the extremely stable *N*-oxyl radical abstracts the α-methylene-hydrogen of the ketone which affords a thermodynamically stable conjugated ketone, ii) radical I acts as a scavenger toward a *C*-radical intermediate and iii) the decomposition of radical I proceeds *via* the *C*-radical to give phorone (V).

Recently, the fact that 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (I) and its analogs are extremely stable free radicals[2] has been established by the elegant studies of Rozantzev and his co-workers.[2a] In spite of the stabilization of radical I, it was found that these radicals still have the ability to act as a hydrogen abstracting agent,[3] an oxdizing agent,[3f,4] and a radical scavenger.[3d-g] In addition, we found that the *N*-oxyl I decomposed to give the corresponding hydroxylamine II and phorone (V) by heating, but did not decompose by the action of light.[3g]. The probable mechanism for the decomposition of radical I is shown in Chart 1. The free radical intermediate III, which would be generated by the abstraction of an α-methylene ketone hydrogen by another radical I (=I'), was proposed.[3g] This mechanism was supported by the fact that the original radical I trapped intermediate III to give the coupling reaction product, 1-hydroxy-2,2,6,6-tetramethyl-3-(2,2,6,6-tetramethyl-4-oxopiperidinoxy)-4-oxopiperidine (IX) (Chart II).

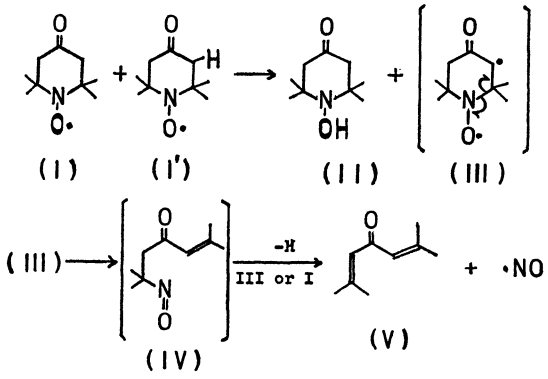


Chart 1

Results and Discussion

When crystals of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (I) were allowed to stand at room temperature for six months, the paramagnetic substance liquefied with subsequent formation of a grey precipitate (mp 139—140°C) which was shown to be diamagnetic by an ESR technique. Further, this product IX could be isolated as a by-product, when the *N*-oxyl I was prepared from the corresponding hindered amine[5] at temperatures 50—60°C. Elemental analysis, molecular weight determination and mass spectral data gave the formula $C_{18}H_{34}N_2O_4$ which corresponded to an O,O coupled dimer (VII) or an aldol condensation product (VIII). Structures VII and VIII were eliminated for the following reasons. In the IR spectrum, this product had a carbonyl band at 1720 cm^{-1} and a hydroxy band at 3360 cm^{-1}. In the NMR(τ)(100 Mc, in $CDCl_3$), it had a broad singlet at 5.25—5.60 (1H), a doublet at 5.74 (1H, J=1.5 Hz), a doublet at 7.12 (1H, J=12.0 Hz), a doublet of doublets at 7.61 (1H, J=12.0 Hz, 1.5 Hz), a broad apparent triplet due to an AA'BB' system (4H, J= *ca.* 15 Hz), and five singlets due to unequivalent methyl proton signals 8.65, 8.70, 8.72, 8.76 and 8.81 (24 H). From these spectral data, the structure of the product, $C_{18}H_{34}N_2O_4$, was assigned to be 1-hydroxy-2,2,6,6-tetramethyl-3-(2,2,6,6-tetramethyl-4-oxopiperidinoxy)-4-oxopiperidine (IX). The product IX was treated with acetic anhydride, benzoic anhydride, phenyl isocyanate, semicarbazide or sodium borohydride to give a monoacetate (X), a monobenzoate (XI), an urethane (XII), a disemicarbazone (XIII) or a triol (XIV),[6] respectively (Chart II). The derivatives X, XI and XII had no hydroxy band in the IR spectra. On exposure to air, triol XIV changed into 2,2,6,6-tetra-

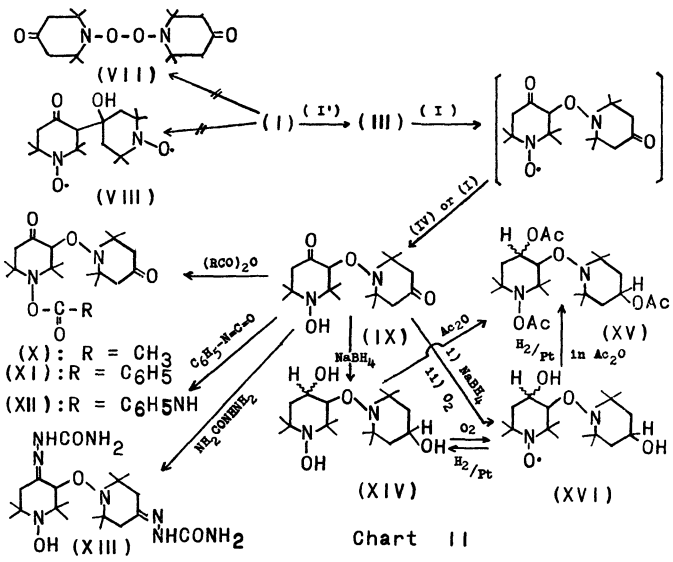
1) Part IV. Ref. 3 g.

2) a) E. G. Rozantzev, "Free Nitroxyl Radicals," Plenum Press, New York, N. Y. (1970), p. 1. b) A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals," Acad. Press, New York, N. Y. (1968), p. 180. c) K. Murayama, *Uki Gosei Kagaku Kyokai Shi*, **29**, 366 (1971).

3) a) M. S. Khloplyankina, A. L. Buchachenko, M. B. Neiman, and A. G. Vasil'eva, *Kinetika i Kataliz*, **6**, 394 (1965). b) A. L. Buchachenko, O. P. Sukhanova, L. A. Kalashnikova, and M. B. Neiman, *ibid.*, **6**, 601 (1965). c) V. V. Gur'yanova, B. M. Kovarskaya, L. A. Krinitskaya, M. B. Neiman, and E. G. Rozantzev, *Vysokomolekul Soedin*, **7**, 1515 (1965). d) E. G. Rozantzev and V. A. Golubev, *Izv. Akad. Nauk SSSR, Ser. Khim*, **1966**, 891. e) K. Murayama, S. Morimura, and T. Yoshioka, This Bulletin, **42**, 1640 (1969). f) K. Murayama and T. Yoshioka, *ibid.*, **42**, 1942 (1969). g) K. Murayama and T. Yoshioka, *ibid.*, **42**, 2307 (1969).

4) a) C. M. Poleos, N. M. Karayannis, and M. M. Labes, *Chem. Commun.*, **1970**, 195. b) K. Murayama, S. Morimura, and T. Yoshioka, Presented at the 90 th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July, 1970, Preprints of the Meeting, No. II (1970), p. II—57.

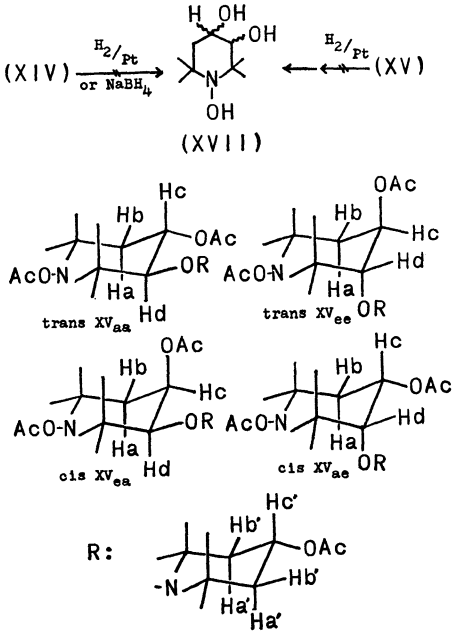
5) a) F. Francis, *J. Chem. Soc.*, **1927**, 2897. b) D. Mackay and W. A. Waters, *ibid.*, *C*, **1966**, 813. c) K. Murayama, S. Morimura, O. Amakasu, T. Toda, and E. Yamao, *Nippon Kagaku Zasshi*, **90**, 296 (1969).



methyl-3-(2,2,6,6-tetramethyl-4-oxopiperidinoxy)-4-oxopiperidine-1-oxyl (XVI). When the new *N*-oxyl radical XVI was hydrogenated in the presence of the Adams catalyst in acetic anhydride solution, the corresponding triacetate (XV),[6] which was identical with triacetate derived from triol XIV, was obtained in good yield. These chemical reactivities corresponded to the properties of the assigned structure IX.

Thus we confirmed that i) the extremely stable *N*-oxyl radical I abstracted the α-methylene-hydrogen of the ketone which could give a thermodynamically stable conjugated ketone[3], ii) the radical I trapped a *C*-radical intermediate such as III, and iii) the decomposition of the radical I proceeded *via* the *C*-radical such as III to give phorone (V).

6) a) No antipode of triol XIV or triacetare XV was found. b) We were unable to establish the relative configuration of triol XIV and triacetate XV since the reductive cleavage of the C–N bond in XIV and XV to the corresponding 3,4-diol(triol XVII), which would be characterized as the acetonide, was unsuccessful using sodium borohydride or hydrogen in the presence of the Adams catalyst.



Further, the magnitude of the chemical shift and the coupling constant in the proton magnetic resonance was unreliable for configurational study because of the absence of the antipode of triol XIV and triacetate XV, and of the uncertainty in the conformation of the heterocyclic(piperidine) ring: the magnitude of the coupling constant (JHdHc=2.7 Hz) eliminated the *trans* XV_{aa}. However, the *trans* XV_{ee} and the *cis* XV_{ae} (or XV_{ea}) were undistinguishable by the coupling constant.

Experimental

All the melting points were uncorrected.

Unless otherwise stated, the IR spectra were determined by means of Nujol mull, and the molecular weight was determined by V. O. P. method. Mass spectra were obtained using a JEOL-JMS-OIS mass spectrometer.

1-Hydroxy-2,2,6,6-tetramethyl-3-(2,2,6,6-tetramethyl-4-oxopiperidinoxy)-4-oxopiperidine (IX). *a) From the N-Oxyl I*: When 1 kg of the crystals of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (I)[3,5c] was allowed to stand for six months at room temperature, the crystals liquefied and then gave rise to *ca.* 100 g of a grey precipitate. The precipitate was filtered and washed with cold ether three times. The crude product was recrystallized from benzene to afford colorless prisms, mp 139—149°C (decomp.). The prisms were dried at 80°C for 3 hr under diminished pressure to give an analytically pure sample. Found: C, 63.43; H, 9.39; N, 8.33%; MW, 361.4 (in acetone). Calcd for $C_{18}H_{32}N_2O_4$: C, 63.50; H, 9.47; N, 8.23%; MW, 340.5. IR (cm^{-1}): ν_{O-H} 3360, $\nu_{C=O}$ 1720. NMR(τ)(in $CDCl_3$)(100 Mc): a broad singlet at 5.25—5.60 (1H), a doublet at 5.74 (1H, J=1.5 Hz), a doublet at 7.12 (1H, J=12.0 Hz), a doublet of doublets at 7.61 (1H, J=12.0 Hz, 1.5 Hz), a broad apparent triplet due to an AA'BB' system (4H, J=*ca.* 15 Hz) and five singlets due to unequivalent methyl proton signals at 8.65, 8.70, 8.72, 8.76 and 8.81 (24H).

b) From 2,2,6,6-Tetramethyl-4-oxopiperidine[5]: 2,2,6,6-Tetramethyl-4-oxopiperidine was oxidized with a 33% aqueous hydrogen peroxide solution at 50—60°C in the presence of EDTA and sodium tungstate. The reaction mixture was then saturated with potassium carbonate, and extracted with benzene. The benzene layer was washed with water saturated with sodium chloride and dried with potassium carbonate, and then the benzene solution was concentrated under

diminished pressure. The crude crystals, which separated from the reaction mixture, were filtered and washed with cold ether. The crude product was recrystallized from benzene to give an analytically pure sample, mp 139—140°C (decomp.), which was identical with the sample obtained by the above procedure *a*).

Monoacetate (X) of the Hydroxypiperidone IX. A solution of 0.5 g (1.47×10^{-3} mol) of IX in 1.5 m*l* of acetic anhydride was allowed to stand at room temperature for 18 hr. Evaporation of the solvent *in vacuo* gave an oily product. After the crude oil, dissolved with petroleum ether, was treated with active charcoal, pure crystals (0.4 g, 71.5%) were gradually obtained on concentration of the solution, and were recrystallized from petroleum ether three times to give an analytically pure sample, mp 89—90°C. Found: C, 62.90; H, 9.00; N, 7.33%; MW, 396.6 (in $CHCl_3$), 376 (in CCl_4). Calcd for $C_{20}H_{34}N_2O_5$: C, 62.83; H, 8.98; N, 7.35%; MW, 382.49. IR (cm^{-1}) (Grating): no ν_{O-H}; $\nu_{C=O}$ 1767,[7] 1745, 1722; (in CCl_4): 1785, 1745, 1725.

Monobenzoate (XI) of the Hydroxypiperidone IX. Into a mixture of 1.5 g (4.42×10^{-3} mol) of IX, 2.0 g (8.85×10^{-3} mol) of benzoic anhydride and 2.0 g (1.45×10^{-2} mol) of potassium carbonate in 4.0 m*l* of benzene was added slowly and dropwise 0.1 g of water with vigorous stirring at room temperature. Stirring was continued for 24 hr at room temperature after the evolution of carbon dioxide had ceased. The benzene layer was separated and washed with 5% aqueous solution of potassium carbonate and dried with potassium carbonate. The crude oil, obtained by evaporation of benzene *in vacuo*, solidified upon being scratched in a small amount of petroleum ether, (1.65 g, 84.5%). The crude crystals were dissolved in a small amount of benzene followed by addition of petroleum ether to give an analytically pure sample, mp 153.5-154.5°C. Found: C, 67.77; H, 8.15; N, 6.07%. Calcd for $C_{25}H_{36}N_2O_5$: C, 67.57; H, 8.16; N, 6.30%. IR (cm^{-1}): no ν_{O-H}; $\nu_{C=O}$ 1747, 1725.

Urethane (XII) of the Hydroxypiperidone IX. The ketone IX, 1.0 g (2.94×10^{-3} mol) exothermally dissolved at once in 0.6 g (5.04×10^{-3} mol) of pheny isocyanate, and the crude solid which separated was washed with petroleum ether, (1.3 g, 96.5%). An analytically pure sample was obtained by recrystallization from 95% ethanol, mp 147—148°C (decomp.). Found: C, 65.53; H, 8.18; N, 9.04%, MW, 488.5 (in acetone). Calcd for $C_{25}H_{37}N_3O_5$: C, 65.36; H, 8.13; N, 9.15%; MW, 459. IR(cm^{-1}): ν_{N-H} 3290; $\nu_{C=O}$ 1745, 1722.

Disemicarbazone (XIII) of the Hydroxypiperidone IX. Into a mixture of 0.34 g(1.00×10^{-3} mol) of IX and 0.3 g (3.66×10^{-3} mol) of sodium acetate in 4 m*l* of water was added gradually 0.3 g (2.70×10^{-3} mol) of semicarbazide hydrochloride with stirring for 3 hr at room temperature. The ketone IX dissolved and gave the crystals of the semicarbazone (0.35 g, 77.2%). An analytically pure sample was obtained by recrystallization from ethanol, mp 136°C (decomp.). Found: C, 52.79; H, 8.52; N, 24.39%. Calcd for $C_{20}H_{38}N_8O_4$: C, 52.84; H, 8.42; N, 24.65%. IR (cm^{-1}): ν_{O-H} 3460; ν_{N-H} 3350, 3270; $\nu_{C=O}$ 1678.

1,4-Dihydroxy-2,2,6,6-tetramethyl-3-(4-hydroxy-2,2,6,6-tetramethylpiperidinoxy)piperidine (=triol) (XIV). a) From the Hydroxypiperidone IX: Into a solution of 1.0 g (2.94×10^{-3} mol) of ketone IX in 20 m*l* of methanol was added ten 0.1 g portions (2.64×10^{-2} mol) of sodium borohydride under a nitrogen atmosphere for 5 hr at room temperature; then was added a solution of 0.5 g of ammonium chloride in 5 m*l* of water at 5°C. The solution was evaporated *in vacuo* to give a residue. The triol XIV was carefully extracted with absolute ethanol from the residue under nitrogen and obtained as an unstable crude product (0.75 g, 75%), which was recrystallized from methanol to give an analytically pure sample mp 168—171°C (decomp.).[6,8] Found: C, 63.07; H, 10.42; N, 8.27%. Calcd for $C_{18}H_{36}N_2O_4$: C, 62.77; H, 10.53; N, 8.13%. MS: M^+, *m/e* 343. IR (cm^{-1}): ν_{O-H} 3350; ν_{C-O} 1055.

b) From 2,2,6,6-tetramethyl-3-(2,2,6,6-tetramethyl-4-hydroxypiperidinoxy)-4-hydroxypiperidine-1-oxyl (=the diol-N-oxyl) (XVI): A solution of 0.1 g(2.94×10^{-4} mol) of the diol-*N*-oxyl XVI in 6 m*l* of methanol was shaken with hydrogen for 5 hr in the presence of the Adams catalyst until the yellow color disappeared. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. After the residue was dissolved into a small amount of ether without exposure to air, the ethereal solution was diluted with petroleum ether. Gradually the unstable triol XIV crystallized, (84 mg, 84%), mp 167—171°C.[8]

1,4-Diacetoxy-2,2,6,6-tetramethyl-3-(4-acetoxy-2,2,6,6-tetramethylpiperidinoxy)piperidine (=triacetate) (XV). a) From the Diol-N-oxyl XVI: The diol-*N*-oxyl XVI, 2.0 g (5.82×10^{-3} mol), was dissolved in 60 m*l* of acetic anhydride and hydrogenated at room temperature for 5 hr in the presence of the Adams catalyst, until the yellow coloration of XVI disappeared. The catalyst was filtered off and 60 m*l* of pyridine was added into the filtrate. The reaction mixture was allowed to stand at room temperature for 24 hr. The solvent was then evaporated under reduced pressure. The crude oil obtained was dissolved in benzene, and the benzene layer was washed with a saturated aqueous solution of sodium bicarbonate. After the benzene was evaporated *in vacuo*, the residue solidified upon being scratched in a small amount of petroleum ether (2.2 g, 81.5%). The crude product obtained was recrystallized from petroleum benzine to afford an analytically pure sample, mp 173°C. Found: C, 61.50; H, 8.86; N, 5.96%. Calcd for $C_{24}H_{42}N_2O_7$: C, 61.25; H, 9.00; N, 5.95%. MS: M^+ *m/e* 470. IR (cm^{-1}): $\nu_{C=O}$ 1772, 1740. NMR(τ)(in C_5D_5N, 100 Mc)[6]: a doublet of doublets of doublets at 4.46 (1 Hc, J_{HcHb}=3.5 Hz, J_{HcHa}=3.0 Hz, and J_{HcHb}=2.7 Hz), a triplet of triplets at 4.90 (1 Hc′, $J_{Hc'Ha'}$=11.0 Hz, $J_{Hc'Hb'}$=5.0 Hz), a doublet at 5.93 (1 Hd, J_{HdHc}=2.7 Hz), doublets of doublets at 7.74 (1Hb, J_{HbHa}=15.5 Hz, J_{HbHc}=3.5 Hz) and at 8.19 (1 Ha, J_{HaHb}=15.5 Hz, J_{HaHc}=3.0 Hz), three singlets due to acetyl protons at 7.81 (3H), 7.97 (3H) and 8.01 (3H), and seven singlets due to methyl protons at 8.47 (3H), 8.52 (3H), 8.69 (3H), 8.77 (3H), 8.83 (6H), 8.87 (3H) and 8.92 (3H). Signals due to Ha′ and Hb′ overlapped with those due to the methyl protons and Ha at 8.5—8.1.

b) From the Triol XIV: A solution of 2.0 g (5.82×10^{-3} mol) of the triol XIV in 6 m*l* of acetic anhydride and 6 m*l* of pyridine was allowed to stand for 24 hr at room temperature. When the solvent was evaporated under reduced pressure, the crude product obtained was dissolved into benzene. The benzene layer was washed with a saturated aqueous solution of sodium bicarbonate. After the benzene was evaporated *in vacuo*, the residue solidified upon being scratched in a small amount of petroleum ether, (2.2 g, 81.8%), which was identical with the sample obtained by the above procedure *a*) (from XVI).

2,2,6,6-Tetramethyl-3-(2,2,6,6-tetramethyl-4-hydroxypiperidinoxy)-4-hydroxypiperidine-1-oxyl (=diol-N-oxyl) (XVI). a) From the Hydroxypiperidone IX: Into a solution of 0.6 g

7) O. Exner and B. Kanáč, *Collection Czech. Chem. Commun.*, **25**, 2530 (1960).

8) The crystals turned yellow on exposure to air.

(1.77×10^{-3} mol) of IX in 20 m*l* of methanol was added six 100 mg portions (1.58×10^{-2} mol) of sodium borohydride in the presence of oxygen (air) at room temperature. After additional stirring for 10 hr, a solution of 0.3 g of ammonium chloride in 5 m*l* of water was added into the mixture at 5°C. The solvents (methanol and water) were evaporated *in vacuo*. Extraction of *N*-oxyl XVI with absolute ethanol from the reaction mixture followed by evaporation *in vacuo* gave yellow paramagnetic crystals, (0.47 g, 78%), which was dissolved in a small amount of methanol and diluted with petroleum ether to give an analytically pure sample, mp 183—184°C (decomp.). Found: C, 63.07; H, 10.09; N, 8.21%; MW, 383.6 (in acetone). Calcd for $C_{18}H_{35}N_2O_4$: C, 62.91; H, 10.28; N, 8.17%; MW, 343. MS: M^+ *m/e* 343.258 (Calcd 343.259). IR (cm^{-1}): ν_{O-H} 3400; ν_{C-O} 1040.

b) From the triol XIV: When a solution of triol XIV in methanol was treated under an oxygen (air) atmosphere, the solution turned yellow. After the solution was allowed to stand at room temperature for two days, evaporation of methanol gave yellow crystals. The crude crystals were recrystallized from ether to give an analytically pure sample, mp 183—184°C (decomp.), which was identical with the sample obtained by the above procedure *a*) (from IX).

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