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# ORGANIC RADICAL REACTIONS INVOLVING NO FREE VALENCE

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**Abstract**—Radical reactions involving no free valence have been performed and new stable free radicals of the 2,2,6,6-tetramethylpiperidine nitrogen oxide series have been synthesized.

IT IS commonly accepted that all reactions possible between radicals and molecules occur with participation of free valence (i.e. of an unpaired electron from the external molecular or atomic orbit). This point of view is shared by Steacie,[1] Walling[2] and Waters.[3]

In a discussion on free radicals, Hückel emphasizes that "though radicals do not react with each other, there always occur reactions yielding products with an even number of electrons."[4]

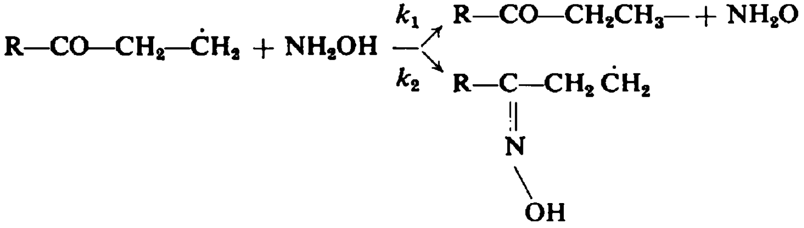
Semenov[5] classifies bimolecular reactions between free radicals and molecules as restricted to two types:

$$\dot{R}_1 + R_2{-}R_3 \rightarrow R_1{-}R_2 + \dot{R}_3$$

$$\dot{R} + A_1{=}A_2 \rightarrow R{-}A_1{-}\dot{A}_2$$

Thus until now it was considered that reactions between free radicals and molecules were impossible without the participation of an unpaired electron.

These concepts cannot, however, be a general rule. Indeed, conceive a radical possessing, along with the free valence, a certain reactive group, for instance the carbonyl group. A radical of this structure could react with an hydroxylamine molecule for example, by two routes:



$$\mathrm{R{-}CO{-}CH_2{-}\dot{C}H_2 + NH_2OH} \begin{cases} \xrightarrow{k_1} \mathrm{R{-}CO{-}CH_2CH_3{-} + NH_2\dot{O}} \\ \xrightarrow{k_2} \mathrm{R{-}\underset{\underset{\displaystyle N{-}OH}{\|}}{C}{-}CH_2\dot{C}H_2} \end{cases}$$

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[1] E. W. R. Steacie, *Atomic and Free Radical Reactions* (2nd Edition) Reinhold, New York (1954).

[2] C. Walling, *Free Radicals in Solution*. John Wiley, New York (1957).

[3] W. A. Waters, *The Chemistry of Free Radicals* (2nd Edition) Oxford University Press (1948).

[4] W. Hückel, *Theoretische Grundlagen der Organischen Chemie* BdI. Akad. Verlagsgesellschaft, Leipzig (1956).

[5] N. N. Semenov, *O nekotorykph problemakh khimicheskoi kinetiki i reaktzionnoi sposobnosti*. Moskva (1958).

From the activated complex theory,[6,7] the rate constants of these reactions will be:

$$k_1 = \varkappa \frac{kT}{h} \cdot \exp\left(-\Delta F_1^{\ddagger}/RT\right)$$

$$k_2 = \varkappa \frac{kT}{h} \cdot \exp\left(-\Delta F_2^{\ddagger}/RT\right)$$

Here $\Delta F_1^{\ddagger}$ and $\Delta F_2^{\ddagger}$ denote the increase in free energy with formation of the activated complex in the reactions under comparison.

It will readily be seen that the rate of the reaction involving no free valence will predominate when

$$\Delta F_2^{\ddagger} < \Delta F_1^{\ddagger}$$

and since

$$\Delta F^{\ddagger} = \Delta E^{\ddagger} - T\Delta S^{\ddagger}$$

$k_2$ may be higher than $k_1$, even under condition that

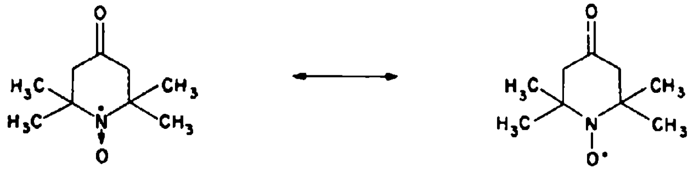
$$\Delta E_2^{\ddagger} > \Delta E_1^{\ddagger}$$

provided the activation entropy $\Delta S_1^{\ddagger}$ is considerably higher than $\Delta S_2$.$^{\ddagger}$

A sharp decrease in the rate with an increasing steric factor is often observed for organic bimolecular reactions.[8,9]

An attempt was made to direct the chemical process through the second reactive center by increasing the steric hindrance close to the atom carrying the free valence, thus leaving aside the unpaired electron.

The previously unobserved heterocyclic free radical, which a reactive carbonyl group screened from the radical center by four methyl substituents of the heminal type,



was synthesized by the authors as a structural model. This radical is very stable and under ordinary conditions it undergoes no changes for many months.

Until recently, the stability of a radical was considered to be due solely to delocalization of the unpaired electron cloud over the system of conjugated bonds in the radical.[10–12] In contrast to this, the high kinetic stability of the new radical obtained is accounted for by the low level of the ground state energy of a system with a

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[6] M. G. Evans and M. Polanyi, *Trans. Farad. Soc.* **31**, 875 (1935).

[7] S. Glasstone, K. J. Laidler and H. Eyring, *The Theory of Rate Processes.* McGraw-Hill, New York (1941).

[8] W. E. Vaughan, *J. Amer. Chem. Soc.* **54**, 3863 (1962).

[9] J. B. Harkness, G. B. Kistiakowsky and W. H. Mears, *J. Chem. Phys.* **5**, 682 (1937).

[10] O. A. Reutov, *Teoreticheskie Problemy Organicheskoi Khimii* p. 236. Moscow State University (1956).

[11] H. Beyer, *Lehrbuch der organischen Chemie* p. 412. Leipzig (1955).

[12] T. N. Temnikova, *Kurs teoreticheskikh osnov organicheskoi khimii* p. 732. GNTI, Leningrad (1959).

FIG. 1. 2,2,6,6-Tetramethyl-4-piperidone nitrogen oxide.

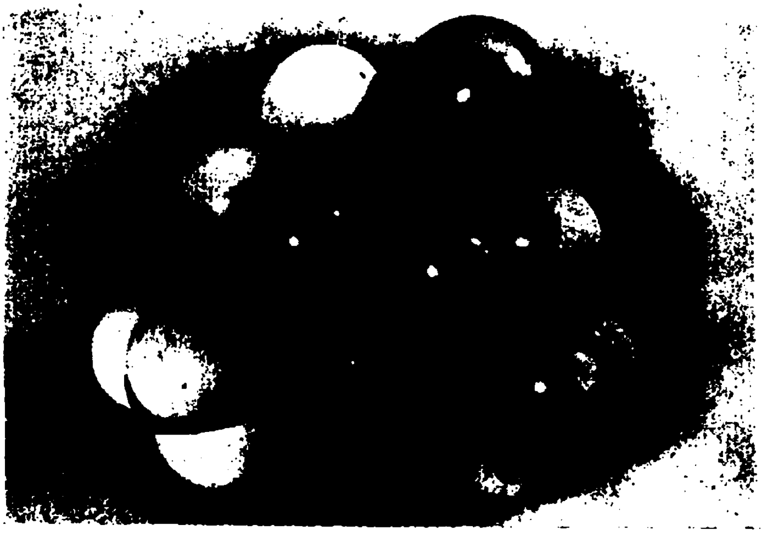


FIG. 3. 2,2,7,7-Tetramethyl-5-homopiperazinone nitrogen oxide (Structure I).

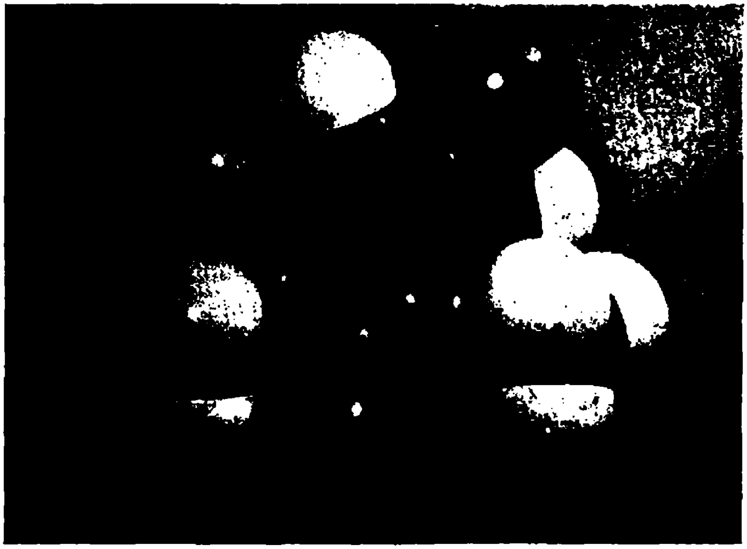


FIG. 4. 2,2,7,7-Tetramethyl-5-homopiperazinone nitrogen oxide (Structure II).

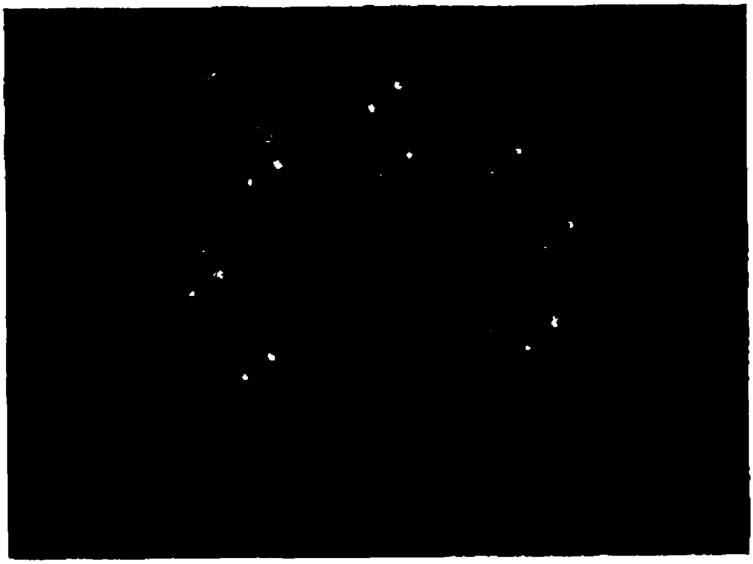


FIG. 5. 2,2,5,5-Tetramethylpiperidine nitrogen oxide.

three-electron nitrogen-oxygen bond,[13] and also by the high steric factor in the region of the free valence localization (Fig. 1).

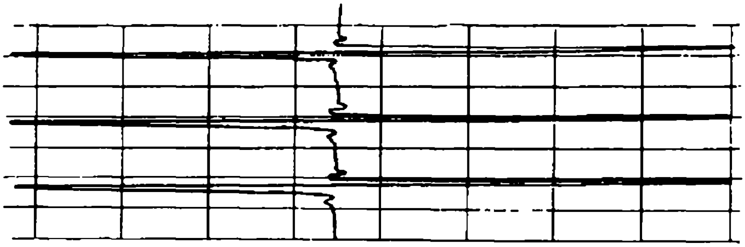
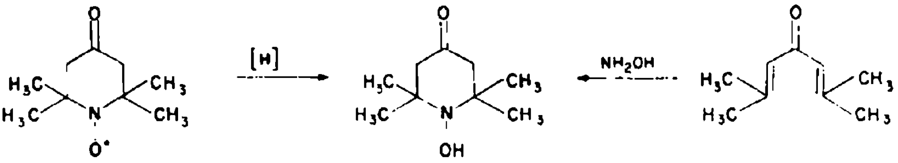


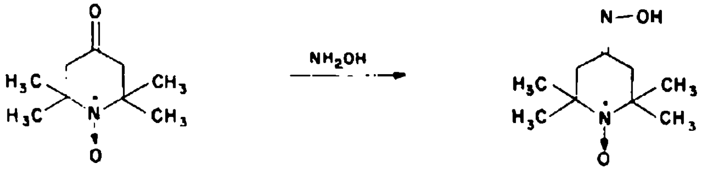
FIG. 2. ESR spectrum exhibited by a solution of 2,2,6,6-tetramethyl-4-piperidone nitrogen oxide in water.

As anticipated, the solid compound displays an ESR singlet, which passes into a triplet with a 15·3 ± 0·4 splitting between components and a g-factor of 2·0064, when the compound is dissolved in water (Fig. 2). The triplet nature of the spectrum accounted for by interaction between the magnetic moment of the unpaired electron and by that of the nitrogen nucleus of a spin equal to unity, is an indication that considerable localization of the unpaired electron cloud occurs on the heteroatom.

A study of the chemical behaviour of the new radical, shows that catalytic reduction in the presence of platinium, palladium and nickel yields a substituted diamagnetic hydroxylamine which may be synthesized from phorone and hydroxylamine:[14]



Due to considerable steric hindrance close to the heteroatom carrying the free valence, the radical readily enters into reactions characteristic of the carbonyl group without involving the free valence. An oxime radical is thus formed by reaction of 2,2,6,6-tetramethyl-4-piperidone nitrogen oxide with an aqueous solution of the hydroxylamine base.



After recrystallization from alcohol, the oxime radical displayed well defined rosy crystals, readily soluble in water, the solution being of a bright red.

The reactions of this radical semicarbazide and the 2,4-dinitrophenylhydrazine

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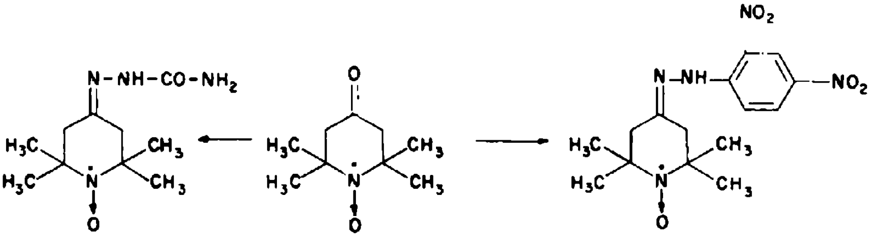
[13] J. W. Linnett, *J. Amer. Chem. Soc.* **83**, 2651 (1961).

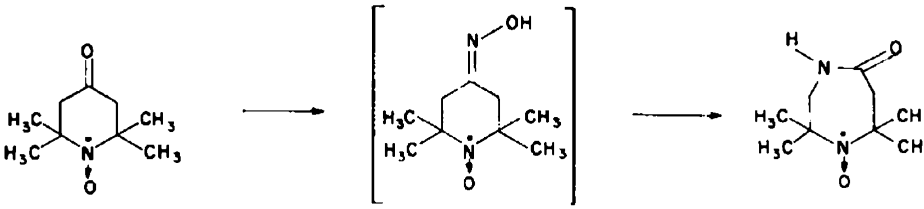
[14] F. Lehmann, *Ber. Dtsch Chem. bes.* **30**, 2736 (1897).

phoshpate occur in a similar manner, yielding a yellow semicarbazone radical and an orange 2,4-dinitrophenyl-hydrazone radical.

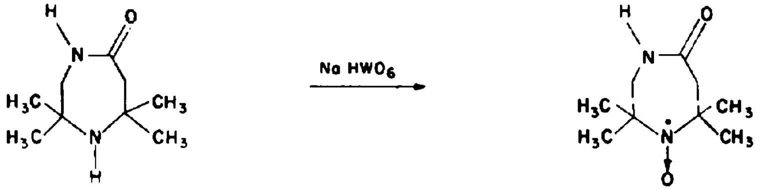


In benzene solution, the ESR singlet exhibited by solid radicals becomes a triplet identical with the initial ketone radical spectrum.[15]

The specific reactivity of the ketone radical was particularly evident from the ready rearrangement occurring in the reaction of 2,2,6,6-tetramethyl-4-piperidone nitrogen oxide with an excess of hydroxylamine hydrochloride. This reaction is spontaneous*liberating heat and yielding the 2,2,7,7-tetramethyl-5-homopiperazinone nitrogen oxide radical:[16]



The compound obtained has all the properties of 2,2,7,7-tetramethyl-5-homopiperazinone nitrogen oxide obtained by direct catalytic oxidation of the respective amine:[17]



The identity of these radicals was established by comparison of their absorption in the UV and IR, by paper chromatography, and by comparison of their melting points and mixed melting points.

A diamagnetic hydrochloride of an unidentified structure was isolated, along with the free radical, form the products of the reaction between hydroxylamine hydrochloride and the ketone radical.

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* However, the reaction is not always reproducible in the absence of thionyl chloride and sometimes, through a reason unknown, it terminates at the oxime radical step.

[15] M. B. Neiman, Yu. G. Mamedova and E. G., Rozantzev, *Azerbeidzhanskii Khim. Zh.*, No 6, 37 (1962).

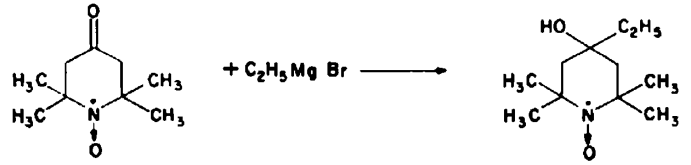
[16] E. G. Rozantzev and R. A. Papko, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, No 4, 764 (1963).

[17] E. G. Rozantzev and R. A. Papko, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, No 12, 2254 (1962).

The free 2,2,7,7-tetramethyl-5-homopiperazinone nitrogen oxide is a rosy-coloured crystalline paramagnetic compound.

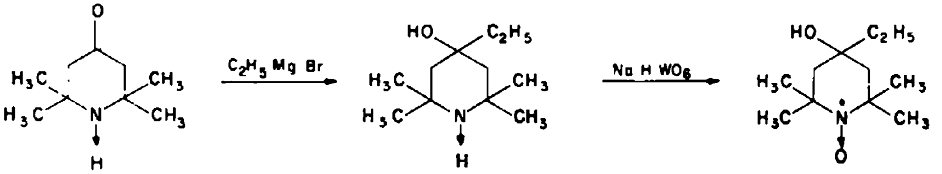
It may be seen from the molecular modes (Fig. 3 and 4) that two conformational isomers are possible for this radical.

A corresponding alcohol radical was formed by interaction of the ketone radical with ethylmagnesium bromide:



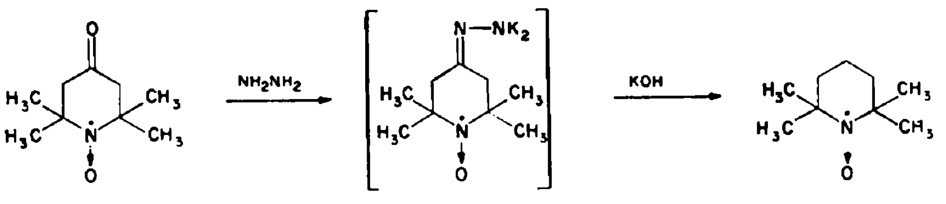
Two absorption maxima, $\lambda_{\max}$ 227 and 235 m$\mu$, characteristic of the nitrogen oxide group, were observed in the UV spectrum (n-heptane) of the alcohol radical.[18] The IR spectrum characteristic displays narrow and broad bands in the 3605 cm$^{-1}$ and 3445 cm$^{-1}$ regions, respectively which suggests the presence of an hydroxyl group in the radical.[19]

The alcohol radical was also synthesized by the following scheme:



Finally, the identity of the two alcohol radicals was verified using the thin-layer chromatography technique (aluminium oxide) with a methanol–acetone mixture as eluent (1 : 1).

The paramagnetic reduction product of the ketone radical may also be obtained by decomposition of the hydrazone radical using the Kizhner method:[20]



The radical thus obtained appeared to be identical with that synthesized by direct catalytic oxidation of 2,2,6,6-tetramethylpiperidine.

An extremely high volatility and a strong camphor like smell which may be accounted for by the globular stereometry of the radical are peculiar of this compound. (Fig. 5.)

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[18] A. Hoffman and A. Henderson, *J. Amer. Chem. Soc.* **83**, 4671 (1961).

[19] R. E. Lyle, *J. Org. Chem.* **22**, 1280 (1957).

[20] E. G. Rozantzev, Yu. G. Mamedova and M. B. Neiman, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* No **12**, 2250 (1962).

## EXPERIMENTAL

### 2,2,6,6-*Tetramethyl-4-piperidone nitrogen oxide* (I).

A solution of 1·7 g (0·01 g mole) 2,2,6,6-tetramethyl-hydroxy-4-piperidone in 25 ml anhydrous ether was boiled for 1 hr in the presence of 2·2 g (0·02 g mole) silver oxide, using a reflux condenser. After removal of the silver, the coloured solution was chromatographed on aluminium oxide; the ether evaporated and the residue recrystallized from heptane, yielding 1·27 g (74·7%) of I, m.p. 36°. (Found: C, 63·53; H, 9·60; N, 8·25; 5·9 × $10^{23}$ spin/mole $C_9H_{16}NO_2$ requires: C, 63·49; H, 9·47; N, 8·23%; 6·0 × $10^{23}$ spin/mole).

### *An oxime of* 2,2,6,6-*tetramethyl-4-piperidone nitrogen oxide* (II)

2,2,6,6-Tetramethyl-4-piperidone nitrogen oxide (1·70 g; 0·01 g mole) in 5 ml methanol were added to a solution of 0·33 g (0·01 g mole) hydroxylamine base in 5 ml methanol. After evaporation of the alcohol *in vacuo*, the residue recrystallized from anhydrous ethanol, yielding 0·95 g (51 %) of the oxime, m.p. 180°. (Found: C, 58·45; H, 9·37; N, 15·25; 6·0 × $10^{23}$ spin/mole $C_9H_{17}N_2O_2$ requires: C, 58·51; H, 9·25; N, 15·12%; 6 0 × $10^{23}$ spin/mole).

### *Semicarbazone of* 2,2,6,6-*tetramethyl-4-piperidone nitrogen oxide* (III)

A saturated aq. solution of 1·11 g (0·01 g mole) of the radical was poured into a saturated aq. solution of semicarbazide hydrochloride. The mixture was left to stand for a short time and then excess of a concentrated solution of $K_2C_2O$ added. After drying and crystallization from anhydrous alcohol, the raw product melted with decomposition above 215°. The ESR spectrum is similar to that of the initial ketone radical.

### 2,4-*Dinitrophenylhydrazone of* 2,2,6,6-*tetramethyl-4-piperidone nitrogen oxide* (IV)

The compound was precipitated when an aq. solution of the ketone radical was poured into a solution of 2,4-dinitrophenylhydrazine in 20% phosphoric acid. After washing with alcohol and drying, the compound melted with decomposition above 250°. The ESR spectrum is similar to that of the initial ketone radical.

### 2,2,7,7-*Tetramethyl-5-homopiperazinone nitrogen oxide* (V)

(a) A saturated aq. solution of 1·70 g (0·01 g mole) 2,2,6,6-tetramethyl-4-piperidone nitrogen oxide was mixed at room temperature with 0·76 g (0·011 g mole) hydroxylamine hydrochloride dissolved in the minimum amount of water. The finely crystallized orange residue was filtered off and recrystallized from ether, yielding 0·55 g (30%) of V, m.p. 162°. (Found: C, 58·40; H, 9·23; N, 15·11; 5·8 × $10^{23}$ spin/mole $C_9H_{17}N_2O_2$ requires: C, 58·51; H, 9·25; N, 15·12%; 6·0 × $10^{23}$ spin/mole).

(b) A mixture of catalytic amounts of trylon-B, sodium tungstate, 5 ml water and 3 ml 30% $H_2O_2$ were added to a solution of 3·4 g (0·02 g mole) 2,2,7,7-tetramethyl-5-homopiperazinone[15] (m.p. 147–148°) in 3 ml warm methanol. The mixture was left to stand overnight, then saturated with solid $K_2CO_3$ and extracted with ether. The combined ether extracts were dried ($K_2CO_3$), the ether evaporated, and the radical recrystallized from anhydrous ether as orange crystals (2·59 g: 70%) m.p. 163° (a mixed m.p. with the compound obtained in the preceding experiment was 162·5°). (Found: C, 58·27; H, 9·19; N, 15·16; 5·9 × $10^{23}$ spin/mole $C_9H_{17}N_2O_2$ requires: C, 58·51; H, 9·25; N, 15·12%; 6·0 × $10^{23}$ spin/mole).

### 2,2,6,6-*Tetramethyl-4-ethyl-4-piperidinol nitrogen oxide* (VI)

(a) An ether solution of ethylmagnesium bromide was prepared from 24 g (1 g atom) Mg, 109 g (1·0 g mole) ethyl bromide and 220 ml anhydrous ether in a 0·5 l. three-necked round-bottomed flask provided with a dropping funnel, a mixer and a reflux condenser carrying a $CaCl_2$ tube.2,2,6,6-Tetramethyl-4-piperidone nitrogen oxide (56·67 g; 0·3 g mole) in 100 ml anhydrous ether were then slowly added to the reacting mixture, which was heated slowly on a water bath for 4 hr, and then left to stand overnight. After removal of ether the solid reacting mass was dissolved with cooling in 15% HCl, then saturated with NaOH and extracted with ether. The combined ether extracts were dried ($K_2CO_3$) and the ether removed, yielding 48 g of the initial ketone radical.

The remaining alkaline solution was extracted with n-butanol and 5·6 g of a bright red oil representing a mixture of two radicals was separated from the combined butanol extracts. Chromatography on aluminium oxide (with a 1:1 methanol–acetone mixture as eluent) yielded 5 g (7·4%) of 2,2,6,6-tetramethyl-4-ethyl-4-piperidinol nitrogen oxide which exhibited an ESR spectrum when dissolved in benzene corresponding to a 100% content of the free radical. (Determination of active hydrogen: Weighed portion of 1050 mg. Found: 126·4 ml of $H_2$. $C_{11}H_{22}NO_2$. Calc: 125·8 ml of $H_2$.) UV spectrum: $\lambda_{max}$ 227 and 235 mμ (n-heptane). IR spectrum: 3445 $cm^{-1}$ (broad band), 3605 $cm^{-1}$ (narrow band).

(b) Trylon-B (20 ml), 15 mg sodium tungstate, 4 ml water and 2 ml 30% $H_2O_2$ were added to a solution of 1·85 g (0·01 g mole) 2,2,6,6-tetramethyl-4-ethyl-4-piperidinol (m.p. 66°) in 4 ml water. After standing 24 hr at room temperature, the mixture was saturated with solid $K_2CO_3$ and the radical extracted with ether. Chromatography on a thin layer of aluminium oxide (1:1 methanol–acetone mixture) showed that the chromatography constant $r_f$ of the compound was identical with that of VI obtained in the preceding experiment.

### 2,2,6,6-*Tetramethylpiperidine nitrogen oxide* (VII)

(a) Diethyleneglycol (100 g), 10 g (0·06 g mole) 2,2,6,6-tetramethyl-4-piperidone nitrogen oxide, 9·5 g 85% hydrazine hydrate and 15 g KOH were introduced into a 250 ml round-bottomed flask provided with a reflux condenser. The mixture was heated at 150° for 1·5 hr, then the reflux condenser was replaced and the reaction products distilled into a receiver cooled with liquid nitrogen. The distillate repeatedly extracted with ether, the combined extracts dried ($MgSO_4$), then concentrated and the radical isolated by chromatography on aluminium oxide. Recrystallization from ether yielded 0·75 g (8%) of VII, m.p. 38–39°.

(b) Trylon-B (10 mg), 15 mg sodium tungstate, 5 ml water and 1·5 ml 30% $H_2O_2$ were added to 70 g (0·005 g mole) 2,2,5,5-tetramethylpiperidine in 5 ml methanol. The mixture was left 2 days and then saturated with $K_2CO_3$ and extracted with ether and the extracts combined and dried ($K_2CO_3$). After complete evaporation of the ether in a flow of dry air, the crystalline residue was sublimed *in vacuo* yielding 0·55 g (70·5%) of VII, m.p. 37–38°. A sample mixed with the compound obtained in the preceding experiment melted at 37–39°.