Studies on Stable Free Radicals. IX.[1] Peroxy Acid Oxidation of Hindered Secondary Amines to Nitroxide Radicals

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The hindered secondary amines, 2,2,6,6-tetramethyl-4-oxopiperidine (II) and 1,9-diaza-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]undecane (VI), were oxidized with *m*-chloroperbenzoic acid, and the corresponding hydroxylamine (III) and *N*-oxyl-hydroxylamine (VIII), respectively, were isolated. The further oxidation of III and VIII with the peracid afforded the corresponding nitroxide radical IV and IX, in good yields respectively. The stoichiometry of the oxidation reaction of the hydroxylamine III to the nitroxide radical IV was elucidated on the basis of the ESR signal intensities of oxidation products at various molar ratios with the peracid and III. An ESR study of the 1-^{15}N-labelled *N*-oxyl-hydroxylamine (XII) indicated that there was an intramolecular hydrogen transfer between >N–OH and >N–O· groups in the *N*-oxyl-hydroxylamines VIII and XII.

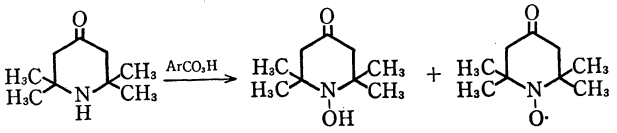
The peracid oxidation of organic molecules in a solution are known to proceed *via* heterolytic[2] or homolytic[3] processes. Organic peracids have been found to be good reagents for the oxidation of hindered secondary amines to the corresponding nitroxide radicals.[4,5] Recently, Duynstee and his co-workers[6] studied the oxidation of a hindered secondary amine (I) with perbenzoic acid to the corresponding nitroxide radical and suggested that the reaction proceeds through the corresponding hydroxylamine, although no hydroxylamine intermediate was isolated.

(I)

In the present work, we isolated the intermediate hydroxyl-amine (III) and *N*-oxyl-hydroxylamine (VIII) in the oxidation of 2,2,6,6-tetramethyl-4-oxopiperidine (triacetonamine) (II) and 1,9-diaza-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]undecane (pentacetonediamine) (VI)[7] with *m*-chloroperbenzoic acid respectively, and found that when the *N*-oxyl-hydroxylamine VIII resulted, there was an intramolecular hydrogen transfer between the >N–OH and >N–O· groups.

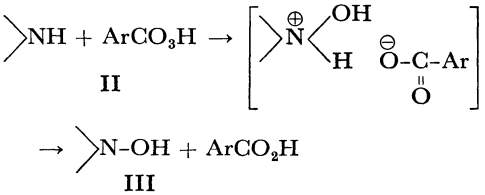
Results and Discussion

Oxidation of Triacetonamine (II). The reaction of the amine II with 1 mol-equivalent of *m*-chloroperbenzoic acid in chloroform at room temperature afforded 1-hydroxy-2,2,6,6-tetramethyl-4-oxopiperidine (III) (40.7%), the corresponding nitroxide radical (IV) (30.3%), and some unchanged amine II (16.0%).



(II) (III) (IV)

Using 2 mol-equivalents of the peracid under the same reaction conditions, the amine II formed the nitroxide radical IV in good yield (91.0%). The formation of the hydroxylamine III must be due to a nucleophilic attack of the amine II on a hydroxy group of the peracid, by analogy to the oxidation of aniline with the peracid to phenylhydroxylamine.[8]



The further oxidation of the hydroxylamine III with 1 mol-equivalent of the peracid gave the nitroxide radical IV quantitatively. We attempted to follow this peracid oxidation process of the hydroxylamine III to the nitroxide radical IV in detail. Attempts to titrate the remaining peracid in the reaction mixture by means of iodometry were unsuccessful, since the nitroxide radical formed also liberated iodine from potassium iodide. Therefore, we estimated the yield of the nitroxide radical IV by comparing its ESR signal intensities with those of a standard sample IV. Table 1 summarizes the results of this estimation and proves the stoichiometry of this oxidation reaction to be as follows:

$$2\,\rangle\text{N–OH} + \text{ArCO}_3\text{H} \rightarrow 2\,\rangle\text{N–O}\cdot + \text{ArCO}_2\text{H} + \text{H}_2\text{O}.$$

This shows that the yield of the nitroxide radical IV is not affected by the addition of an efficient radical scavenger, 1,3,5-trinitrobenzene.[9] Moreover, in the oxidation reaction, the coupled product[10] of the

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4) K. Tokumaru, H. Sakuragi, and O. Simamura, *Tetrahedron Lett.*, **1964**, 3945.

5) G. Chapelet-Letourneux, H. Lamaire, and A Rassat, *Bull. Chim. Soc. Fr.*, **1966**, 3283.

6) E. F. J. Duynstee, M. E. A. Mevis, H. K. Ostendorf, and R. J. De Kock, *Rec. Trav. Chim. Pays-Bas*, **87**, 945 (1968).

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8) K. M. Ibne-Rasa and J. O. Edward, *J. Amer. Chem. Soc.*, **84**, 763 (1962).

9) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *ibid*, **72**, 5426 (1950).

10) E. G. Rozantzev and V. A. Golubev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1966**, 891.

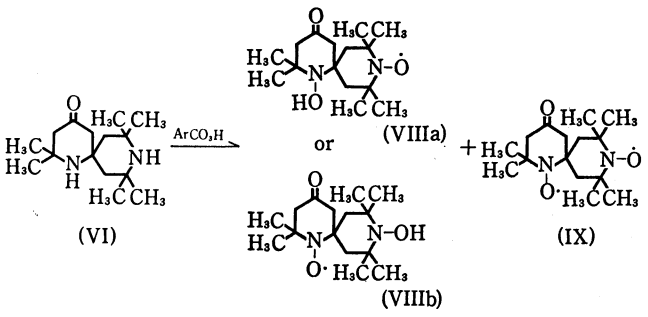
Table 1. Stoichiometry of the reaction of the hydroxylamine III with the peracid in benzene

Molar concentration × 10^3		
Solution[a]		Nitroxide radical (IV)[b,c]
Hydroxylamine	Peracid	
3	4	3
3	3	3
3[d]	3	3
3	1.5	3
3[d]	1.5	3
3	1	2[e]

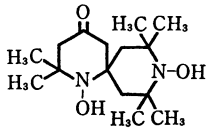
a) A solution of the hydroxylamine III (5 m*l*, 6×10^{-3} M) and a solution of the peracid were combined to 10 m*l* total volume.
b) Measurements were carried out in the same sample tube under the same conditions after 100 sec reaction time at room temperature.
c) The ESR signal intensities were compared with those of the pure nitroxide radical IV in the same sample tube under the same conditions.
d) 1,3,5-Trinitrobenzene (50 mg) was added. The ESR signal intensity of the pure nitroxide radical IV itself in solution was not influenced by an addition of 1,3,5-trinitrobenzene.
e) The ESR signal intensity did not increased after an additional 1 hr reaction time.

free radical IV with a phenyl radical arising from the peracid was not found, and no evolution of carbon dioxide was observed. From these results, this oxidation reaction is presumed to proceed through an ionic process[11], but we have no conclusive proof for this reaction mechanism.

Oxidation of Pentacetonediamine (VI). The similar treatment of pentacetonediamine (VI) with *m*-chloroperbenzoic acid in chloroform afforded two products melting at 113°C (A) and at 145°C (B). The product A was identified as 1,9-diaza-2,2,8,8,-10,10-hexamethyl-4-oxo-spiro[5.5]undecane-1,9-dioxyl



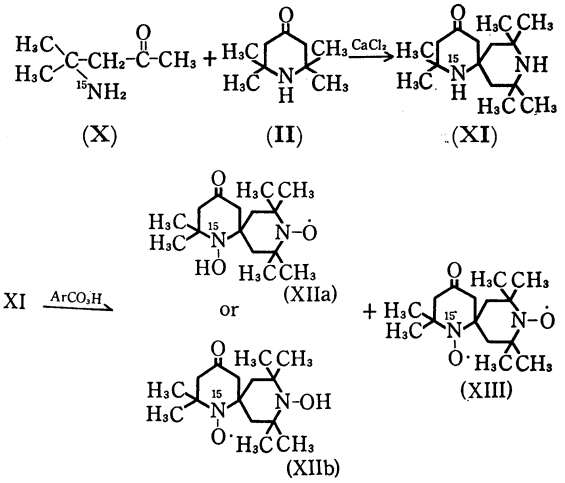
(IX) by elementary analysis and by an IR spectral comparison with an authentic sample.[7] The product B was formulated as $C_{15}H_{27}O_3N_2$ and shown to be a *N*-oxyl-hydroxylamine (VIIIa) or (VIIIb) by its spectral data (mass, IR, and ESR). No other possible intermediary products including dihydroxylamine (VII) were obtained under the present reaction conditions. As in the case of the hydroxylamine III, the further peracid oxidation of VIII gave the nitroxide biradical IX in a good yield.



(VII)

In order to determine the structure of VIII, the following isotope-labelling experiments were carried out.

The 1-^{15}N-labelled pentacetonediamine (XI) was prepared by the reaction of 4-amino(^{15}N)-4-methyl-pentan-2-one (X) with II and then, submitted to peracid oxidation to give a biradical (XIII) and a *N*-oxyl-hydroxylamine compound (XIIa or XIIb).



The structure of *N*-oxyl-hydroxylamine XII may be determined by the ESR measurements, since triplet lines due to the interaction with the ^{14}N-nucleus can be expected for the structure XIIa, while doublet lines due to the interaction of the ^{15}N-nucleus can be expected for the structure XIIb. The ESR spectrum of the product XII (Fig. 1) showed five lines, suggesting the existence of mixture of these isomers XIIa and XIIb, but the intensity of the doublet lines (due to ^{15}N-nucleus) increased at higher temperatures and decreased at lower temperatures reversibly. This suggests the existence of an equilibrium between XIIa and XIIb in solution; such as equilibrium may result from an intramolecular hydrogen exchange between >N–OH and >N–O· groups in a solution of a 10^{-4} M concentration. The equilibrium constants were obtained from the ratio of the area of triplet lines to that of doublet lines at various temperatures; they are plotted to determine the equilibrium enthalpy and entropy in Fig. 2.

Since the difference in the structures of the two isomers is very small, the small enthalpy and entropy values seem to be reasonable. The molecular model of VIII indicates that the >N–OH and >N–O· groups can approach each other closely when one

11) Blackly and Reinhard [*J. Amer. Chem. Soc.*, **87**, 802 (1965)] have reported that bis(trifluoromethyl)nitroxide radicals exist in equilibrium wtith its dimer in $CFCl_3$:
$2(CF_3)_2N\text{-}O\cdot \rightleftarrows (CF_3)_2N\text{-}O\text{-}O\text{-}N(CF_3)_2$.
In this oxidation process, homolysis of the peroxide (V) might be involved: >N-O-O-N< (V) ⟶ 2 >N-O· (IV).

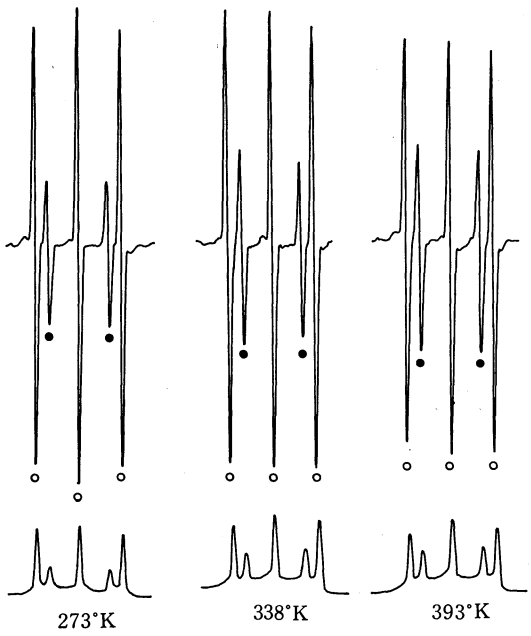


Fig. 1. ESR spectra of XII in toluene at 10^{-4} M concentration.
In the bottom half of the figure are given the integrated spectra: ○ triplet lines due to ^{14}N nucleus ($a_{^{14}N}=15.2$ G).
● doublet lines due to ^{15}N nucleus ($a_{^{15}N}=23.3$ G).

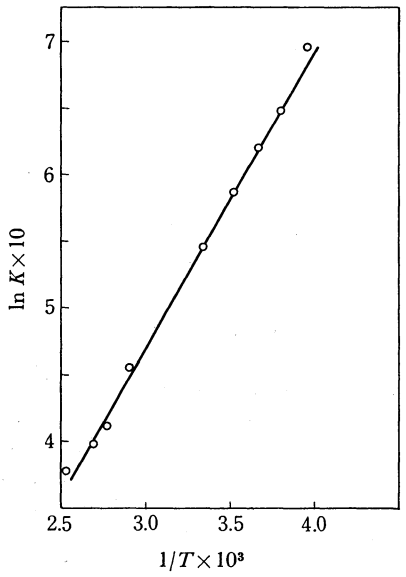


Fig. 2. Plot of ln K against $1/T$.
$\Delta H_0=-1.09$ kcal/mol
$\Delta S=0.253$ e.u.

piperidine ring is twisted[12] and the other piperidine ring is in a chair form,[13] and *vice versa*. Therefore, it may be considered that such an intramolecular transfer of a hydrogen between >N–OH and >N–O· groups in VIII is possible and that the structure VIIIa is a predominant isomer at ordinary temperatures; these conclusions are based on the results of the ESR measurement of XII at various temperatures.

Recently, Poindexter and Glazer[14] have suggested, on the basis of studies of dynamic nuclear polarizability, that a nitroxide radical III and dimethyl phosphite form a transient hydrogen bond between P–H and ·O–N<. Our results concerned the intramolecular hydrogen exchange also suggest the formation of a transient hydrogen bond between >N–OH and >N–O· groups in the transition state.

It has been reported[6,15] that the mass spectra of stable nitroxide radicals exhibit a characteristic peak corresponding to $(M+1)^+$ in addition to the molecular ion peak; the $(M+1)^+$ peak was assigned to hydroxylamine formed by the hydrogen abstraction of the nitroxide radical from water or the free radical compound. In VIII, a prominent $(M+1)^+$ peak was observed, as is shown in Fig. 3, but the mass spectrum

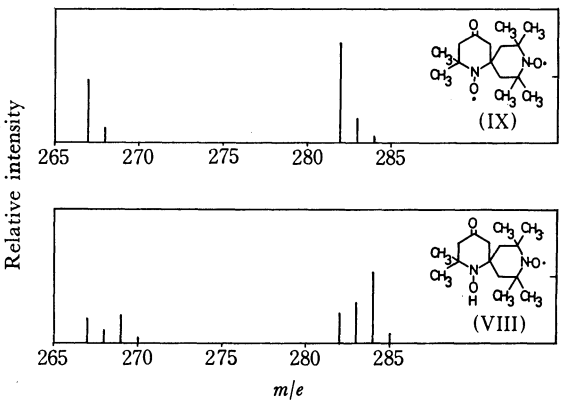


Fig. 3. Mass spectra of VIIIa and IX.

of the biradical IX did not show such a characteristic $(M+1)^+$ peak. This suggests that a hydrogen of the hydroxy group in VIII may be easily abstracted to give the dihydroxylamine VII and the biradical IX in a mass spectrometer.

Experimental

The melting points are uncorrected. The IR spectra were determined by means of Nujol mulls or liquid films. The mass spectra were obtained using a JEOL-JMS-OIS mass spectrometer at 75 eV. The ESR spectra were recorded using a Hitachi MES 4001 spectrometer employing 100 kc modulation at X-band in conjunction with a Hitachi MES 4701 thermo controller, the sample temperature being measured with a copper-constantan thermocouple. The integrated curves were obtained using a Hitachi 4703 integrator. The splitting constants and g-values were measured relative to the aqueous solution of Fremy's salt.

m-*Chloroperbenzoic Acid.* The commercially-available *m*-chloroperbenzoic acid (PBA) used here had a purity of 85.5%, as determined by iodometric analysis.

Oxidation of 2,2,6,6-Tetramethyl-4-oxopiperidine (II). a): A solution of 8.1 g (40 mmol) of PBA in 60 m*l* of chloroform was slowly stirred into a solution of 6.2 g (40 mmol) of 2,2,6,6-tetramethyl-4-oxopiperidine (II) in 50 m*l* of chloroform at ice-water-bath temperature. The solu-

12) E. G. Rozantzev and E. N. Gur'yanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1966**, 979.
13) C. Y. Chen and R. J. W. LéFevre, *J. Chem. Soc.*, **1965**, 3467.
14) E. H. Poindexter and R. L. Glazer, *J. Amer. Chem. Soc.*, **92**, 4784 (1970).
15) A. Morrison and A. P. Davies, *Org. Mass. Spect.*, **3**, 353 (1970).

tion was allowed to stand for an additional 24 hr at room temperature. Then, the solution was washed with 100 m*l* of aqueous sodium hydroxide (40%), dried over potassium carbonate, and freed of the solvent by evaporation under reduced pressure. The oily residue (6.0 g) was chromatographed on a column of aluminum oxide, and the column was eluted successively with petroleum ether, benzene, and methanol.

1). From petroleum ether eluates, 1.0 g (16.0%) of II was recovered. Confirmation was done by means of an IR spectral comparison with the starting material.

2). From benzene eluates, 2.1 g (30.3%) of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (IV) was obtained. It was identified by a comparison of the melting point (36°C) and the IR and ESR spectra with those of an authentic sample.[7]

3). From methanol eluates, 2.8 g (40.7%) of 1-hydroxy-2,2,6,6-tetramethyl-4-oxopiperidine (III) was isolated; it was identified by comparing its melting point (mp 90—91°C) and IR spectrum with those of an authentic sample.[10] Found: C, 63.06; H, 10.01; N, 8.18%. Calcd for $C_9H_{17}O_2N$: C, 63.13; H, 10.00; N, 8.18%.

b): In a way similar to that described above, the reaction of 6.2 g (40 mmol) of II with 16.2 g (80 mmol) of PBA in chloroform gave 6.3 g of an oily residue. By column chromatography on aluminum oxide, 6.2 g (91.0%) of IV was obtained. It was identified by means of its melting point (mp 36°C), and IR and ESR spectra.

Oxidation of 1-Hydroxy-2,2,6,6-tetramethyl-4-oxopiperidine (III). The reactions described below were carried out under a nitrogen atmosphere, leading to a trap filled with an aqueous barium hydroxide solution.

a): A solution of 1.0 g (5 mmol) of PBA in 60 m*l* of chloroform was stirred into a solution of 1.7 g (10 mmol) of III in 40 m*l* of chloroform at room temperature. The solution was then stirred for an additional 3 hr at room temperature.

At this point, the yield of IV was 67%, as was determined by comparing the ESR signal intensity of the reaction mixture with that of the standard sample IV in chloroform. Then, the solution was washed with 40 m*l* of aqueous sodium hydroxide (40%), dried over potassium carbonate, and evaporated under vacuum. The resulting oil was chromatographed on a column of aluminum oxide. The benzene eluates afforded 1.1 g (64.6%) of IV, and the methanol eluates gave 0.2 g (11.7%) of the unchanged starting hydroxylamine III. These compounds were identified by a comparison of the IR spectra and the melting points with those of the respective authentic samples.

b): A solution of 1.0 g (5 mmol) of PBA in 60 m*l* of benzene was stirred into a solution of 1.7 g (10 mmol) of III in 40 m*l* of benzene at room temperature. The solution was then stirred for an additional 1.5 hr at room temperature. At this point, the yield of IV was 100%, as was determined by comparing the ESR signal intensity of the reaction mixture with that of the standard sample IV in benzene. The column chromatography of the oily material obtained in a a way similar to that described above gave 1.3 g (75.0%) of IV. In these reactions a) and b), no detectable precipitates of barium carbonate were observed in the trap.

Oxidation of 1,9-Diaza-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]undecane (VI).[7] A solution of 6.1 g (30 mmol) of PBA in 60 m*l* of chloroform was added to a stirred solution of 2.5 g (10 mmol) of VI in 50 m*l* of chloroform under ice-water cooling and the solution was stirred for an additional 15 min under ice-water cooling. The solution was washed with 70 m*l* of aqueous sodium hydroxide (40%), dried over potassium carbonate, and evaporated under vacuum. The resulting oil solidified upon the addition of petroleum ether and 1.6 g of the crystalline solid was separated by filtration. This crude material was dissolved in 5 m*l* of benzene and placed onto a column of aluminum oxide. The column was eluted successively with petroleum ether, benzene, and methanol. The benzene eluates afforded 0.8 g (28.4%) of 1,9-diaza-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]-undecane-1,9-dioxyl (IX). Recrystallization from petroleum benzine gave a pure sample; mp 112—113°C. Found: C, 63.81; H, 9.35; N, 10.04%. Calcd for $C_{15}H_{26}O_3N_2$: C, 63.80; H, 9.28; N, 9.92%. IR (cm^{-1}): $\nu_{C=O}$ 1728. From the methanol eluates, 0.6 g (21.2%) of 1,9-diaza-1-hydroxy-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]undecane-9-oxyl (VIIIa) was obtained. By the recrystallization of the crude material from cyclohexane, an analytically pure sample was obtained; mp 145—146°C. Found: C, 63.58; H, 9.60; N, 9.76%. Calcd for $C_{15}H_{27}O_3N_2$: C, 63.57; H, 9.60; N, 9.88%. IR (cm^{-1}): $\nu_{C=O}$ 1728, ν_{OH} 3400. ESR (in toluene): $a_N=15.0\pm0.1$ gauss. $g=2.0060\pm0.0001$.

Oxidation of 1,9-Diaza-1-hydroxy-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]undecane-9-oxyl (VIIIa). A solution of 1.2 g (6 mmol) of PBA in 20 m*l* of benzene was stirred into a solution of 1.7 g (6 mmol) of VIIIa in 20 m*l* of benzene at room temperature, after which the solution was stirred for an additional 3 hr at room temperature. The solution was then treated by a procedure similar to that described above, and the resulting oil was chromatographed on a column of aluminum oxide. The benzene eluates afforded 1.3 g (71.5%) of IX, which was identified by comparing its melting point (mp 112—113°C) and IR spectrum with those of an authentic sample.

Oxidation of 1,9-Diaza(1-^{15}N)-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]undecane (XI). Similarly as described above, 1.0 g of the crystalline solid was obtained from 2.5 g (10 mmol) of XI. By means of column chromatography, from 1.0 g of the crystalline solid, 0.35 g (12.7%) of XIII and 0.65 g (23.0%) of XIIa were obtained. Pure samples were obtained by recrystallization. XIII : mp 112—113°C (from petroleum benzine). XIIa : mp 145—146°C (from cyclohexane), ESR (in toluene): $a_{^{14}N}=15.2\pm0.1$ gauss. $a_{^{15}N}=23.3\pm0.1$ gauss. $g=2.0056\pm0.0001$.

Synthesis of 2-Amino-^{15}N-2-methylpentan-4-one (X). To a stirred solution of 14.1 g (0.26 mol) of ammonium chloride-^{15}N (90% ^{15}N contents)[16] and 14.6 g (0.26 mmol) of potassium hydroxide in 50 m*l* of water at room temperature was added 14.7 g (0.15 mol) of mesityl oxide. The solution was then stirred continuously for 18 hr at room temperature, after which 10.0 g of potassium carbonate was added into the stirred solution at 0—5°C. An oil separated and was extracted into 100 m*l* of ether, dried over potassium carbonate, and evaporated under reduced pressure. The resulting oil was distilled to give X; bp 55—58°C/15 mmHg; yield, 10.8 g (62.1%). IR (cm^{-1}): $\nu_{C=O}$ 1760, ν_{NH} 3550, 3360 and 3280.

Synthesis of 1,9-Diaza(1-^{15}N)-2,2,8,8,10,10-hexamethyl-4-oxo-spiro[5.5]undecane (XI). By the reaction of 10.8 g (94 mmol) of X and 8.3 g (54 mmol) of II with calcium chloride (0.3 g), 4.6 g (50.0%) of XI was obtained in the same way as has been reported previously.[7] The recrystallization from cyclohexane gave an analytically pure sample; mp 91—95°C (This mp corresponds to that of the monohydrate of XI). Found: C, 66.31; H, 11.12; N, 10.85%.

16) Available from The Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan.

Calcd for $C_{15}H_{30}O_2N^{15}N$: C, 66.39; H, 11.14; N, 10.69%. IR(cm^{-1}): $\nu_{C=O}$ 1708, ν_{NH} 3150 and 3330. Mass spectrum: $M^+=253$.

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