Studies on Stable Free Radicals. XIII.[1] Synthesis and ESR Spectral Properties of Hindered Piperazine *N*-Oxyls

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New hindered 3,5-dioxopiperazines (VII, IX), hindered piperazines (VIII, X), and the corresponding *N*-oxyls (XI, XIII, XII, and XIV) were synthesized. The substituent and solvent effects of the nitrogen coupling constants (a_N) in the *N*-oxyls were measured and compared with each other; the introduction of carbonyl groups at the *C*-3 and *C*-5 ring positions decreased these values, which increased in a protic polar solvent.

Many papers have recently reported synthetic methods for and the properties of extremely stable free radicals.[2] Especially, the introduction of *N*-oxyl into such heterocyclic rings as pyrrolines (I), pyrrolidines (II), piperidines (III), oxazolines (IV),[3] imidazolines (V),[4] and imidazolidines (VI)[5] were synthesized in number (Chart 1), and some of them were found useful as a radical scavenger,[5] and oxidizing agent,[5] and a spin labeling compound.[6]

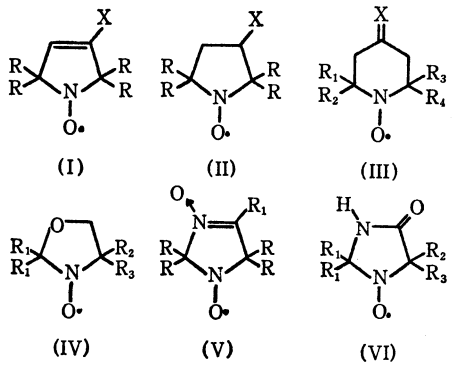
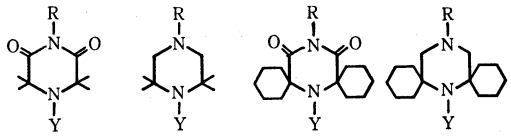


Chart 1.

However, piperazine *N*-oxyls have not as yet been reported, although some hindered piperazines are known;[7] this may be because of the difficulties in the direct oxidation of such hindered piperazines, as will be discussed later.

This paper will describe the synthesis of new hindered piperazine *N*-oxyls, their chemical properties, and their ESR coupling constants (a_N). The substituent and solvent effects on the coupling constant in the *N*-oxyls are of interest in connection with those of the piperidine *N*-oxyls (III).[8] Chart 2 summarizes starting hindered amines and the corresponding *N*-oxyls.



Y=H	$VII_{H,B,C}$	$VIII_{H,B}$	$IX_{H,B,C}$	$X_{H,B}$
Y=O·	$XI_{H,B,C}$	XII_B	$XIII_{H,B,C}$	XIV_B

H : R=H, B : R=$CH_2C_6H_5$, C : R=COOEt

Chart 2.

Results and Discussion

I. The Synthesis of 3,5-Dioxopiperazines, VII and IX. The starting amine, IX_H (R=H), was synthesized from bis(1-cyanocyclohexyl)amine (XV), itself derived from an aminonitrile of cyclohexanone, in a concentrated sulfuric acid solution according to a literature procedure.[7] Although the application of this method to the synthesis of VII_H met with failure, the following method, using basic conditions, successfully led to the formation of VII_H (Chart 3): the treatment of an aminonitrile of acetone with potassium hydroxide in refluxing methanol gave VII_H, plus 2,2,5,5-tetramethyl-4-oxoimidazolidine (XVI).[5] The alkylation or acylation of VII_H or IX_H gave the corresponding 4-substituted derivatives; after VII_H or IX_H was treated with sodium hydride in *N*,*N*-dimethylformamide (DMF), benzylation or carbethoxylation of the resulting Na-salts gave VII_B, IX_B (R=$CH_2C_6H_5$), VII_C, IX_C (R=COOEt) (Chart 4).

Piperazines $VIII_{H,B}$ and $X_{H,B}$ were synthesized by

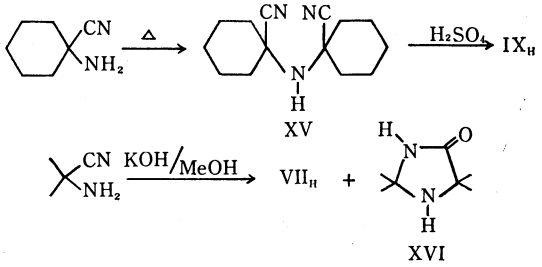


Chart 3.

1) Part XII: T. Toda, E. Mori, and K. Murayama, This Bulletin, **45**, 1852 (1972).

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

3) a) J. F. W. Keana, S. B. Keana, and D. Beetham, *J. Amer. Chem. Soc.*, **89**, 3055 (1967). b) J. F. W. Keana and R. J. Dinerstein, *ibid.*, **93**, 2808 (1971).

4) L. B. Volodarsky, G. A. Kutikova, R. Z. Sagdeev, and Yu, N. Molin, *Tetrahedron Lett.*, **1968**, 1065.

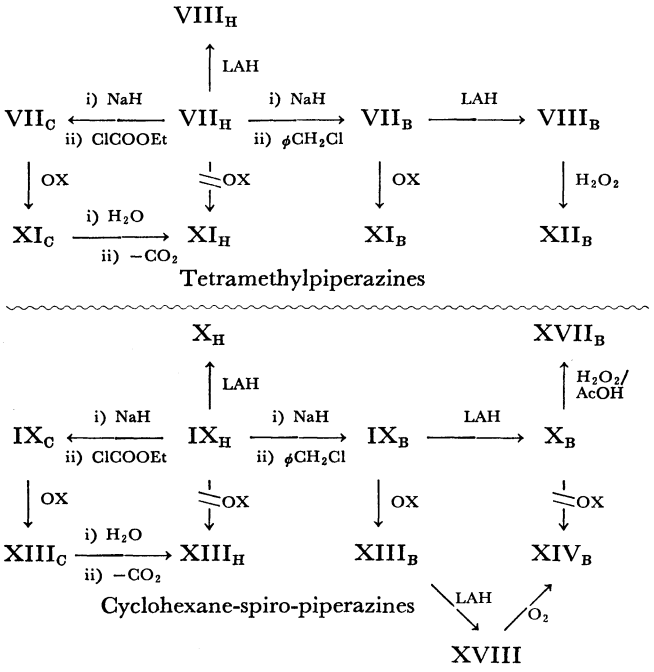
5) K. Murayama, S. Morimura, and T. Yoshioka, This Bulletin, **42**, 1640 (1969).

6) a) T. L. Stone, T. Buckman, P. L. Nordio, and H. M. McConnell, *Proc. Nat. Acad. Sci. U. S.*, **54**, 1010 (1965). b) H. M. McConnell and B. G. McFarland, *Quart. Rev. Biophys.*, **3**, 91 (1970).

7) a) R. Sudo and S. Ichihara, This Bulletin, **36**, 34 (1963). b) E. F. J. Duynstee, M. E. A. F. Mevis, H. K. Ostendorf, and D. J. D. Kock, *Rec. Trav. Chim. Pays-Bas*, **87**, 945 (1968).

8) a) Ref. 1-c), p. 194. b) R. Briere, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, **1965**, 3273.

the reduction of the coresponding dioxopiperazines, $VII_{H,B}$ and $IX_{H,B}$ respectively, with lithium aluminum hydride (LAH). (Chart IV)



B: $C_6H_5CH_2$, OX: oxidiation

Chart 4.

II. Oxidation of the Dioxopiperazines VII and IX to the Corresponding N-*Oxyls, XI and XIII.* The direct oxidation of the 4-unsubstituted dioxopiperazines, VII_H and IX_H, to XI_H and $XIII_H$ respectively was unsuccessful (Chart 4.); when *m*-chloroperbenzoic acid (CPBA) was used as an oxidizing agent, a rapid decomposition of VII_H and IX_H occurred with blue coloration, and none of the desired *N*-oxyls XI_H and $XIII_H$ were formed. Using 30% aqueous hydrogen peroxide in the presence of EDTA and sodium tungstate did not afford the desired products. However, the 4-substituted dioxopiperazines, $VII_{B,C}$ and $IX_{B,C}$, were oxidized with CPBA or 30% aqueous hydrogen peroxide to give the desired *N*-oxyls, $XI_{B,C}$ and $XIII_{B,C}$ respectively. The relative ease of the formation of the cyclohexane-spiro-piperazine-*N*-oxyl, $XIII_B$, was observed by comparing the degree of orange coloration; it was smaller than that of the tetramethyl-*N*-oxyl XI_B upon the oxidation of the corresponding amines with 30% aqueous hydrogen peroxide in methanol in the presence of the catalysts.

The 4-unsubstituted derivatives, VII_H and IX_H, were synthesized by the hydrolysis of XI_C and $XIII_C$, respectively, followed by spontaneous decarboxylation.

III. Oxidation of the VIII and X Piperazines to the XII and XIV N-*Oxyls.* The direct oxidation of the VIII and X piperazines should require controlled reaction conditions because of the presence of the *tert*-amine group. In fact, the oxidation of $XIII_B$ and X_B with CPBA met with failure; a rapid decomposition occurred, with a green coloration, and one of the the desrifed *N*-oxyls XII or XIV were obtained. On the other hand, the oxidation of $VIII_B$ (the tetramethylpiperazine derivative) with 30% aqueous hydrogen peroxide in the presence of the catalyst *in methanol* was successful in producing the desired *N*-oxyl, XII_B. The application of this procedure to the oxidation of X_B (cyclohexane-spiro-piperazine derivative) was, however, unsuccessful; X_B was recovered quantitatively under the same reaction conditions.

The difference in the reactivity between $VIII_B$ and X_B, or that between VII_B and IX_B, described above, may be explained by the steric effect at *C*-2 and *C*-6 in the ring. The same relationship has been observed in the imidazolidine series[5] and in the piperidine series.[9]

The oxidation of X_B with 30% aqueous hydrogen peroxide in the presence of the catalyst gave an undesirable product, N^1-oxyl-N^4-oxide ($XVII_B$) *in acetic acid.*

Since the direct oxidation of X_B failed to produce XIV_B, another route was attempted; we reduced[10] the 3,5-dioxo derivative, $XIII_B$, with LAH to give the corresponding hydroxylamine (XVIII), which was then oxidized with air[11], thus affording the dseired *N*-oxyl, XIV_B.

IV. Coupling Constants (a_N) in the ESR Spectra. The ESR spectra of the piperazine *N*-oxyls were measured in a 10^{-3} M solution, using Fremy's salt as the reference. Table 1 summarizes the substituent effects on the nitrogen-coupling constant (a_N) in the piperazine *N*-oxyls, and shows that carbonyl groups at *C*-3 and *C*-5 or a nitroxide group at *N*-4 decrease the value by about 1.0 gauss, *e.g.*, XI_B, XII_B, and $XVII_B$. This suggests that the unpaired electron distribution is altered to a small extent by a dipolar field effect. A similar trend has been observed with the ipperidine *N*-oxyl series.[8] Anomalously, the *N*-oxyl $XIII_C$

Table 1. Substituent effects in ESR spectra of the piperazines (10^{-3} M in CH_2Cl_2)

Compound	a_N gauss ±0.1	Compound	a_N gauss ±0.1
XI_C	14.5	$XIII_C$	13.7
XI_B	14.5	$XIII_B$	14.2
XI_H	14.7	$XIII_H$	14.5
—	—	$XVII_B$	14.7
XII_B	15.8	XIV_B	15.5

Table 2. Solvent effects in ESR spectra of the piperazines (10^{-3} M)

Compound	CH_2Cl_2	C_6H_6	CH_3OH
XI_C	14.5	14.5	15.0
XI_B	14.5	14.5	14.9
XI_H	14.7	14.8	15.0
XII_B	15.8	15.8	16.4

9) T. Yoshioka, S. Higashida, and K. Murayama, This Bulletin, **45**, 636. (1972).

10) V. A. Golubev, E. G. Rozantzev, and M. B. Neiman, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1965**, 1927.

11) E. G. Rozantzev and V. A. Golubev, *ibid.*, **1966**, 891.

exhibited a relative low value (13.7); no reasonable explanation of this has been proposed because of the uncertainty of the conformation.

Table 2 shows solvent effects which are attributable to the hydrogen bonding between the *N*-oxyl and solvent (HS), altering the unpaired electron distirbution in favor of the (B) form, *i.e.*, the form with the more nucleophilic oxygen atom,[8] as is shown in Chart 5.

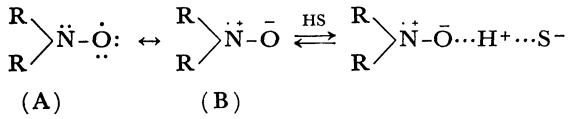


Chart 5.

Experimental

All the melting points are uncorrected.

Unless otherwise stated, the IR spectra were taken with a Hitachi EPI-S2 spectrometer (Nujol mull); the NMR spectra, with a Varian A-60 using tetramethylsilane as the internal standard; the Mass spectra, with a JEOL-JMS-OIS app aratus, and the ESR spectra, with a Hitachi MES 4001 type X-band spectrometer employing 100 kc modulation. Table 3 shows the formula molecular ion peak, mp, bp, yield, and result of elemental analysis of all the prdoucts; the IR spectra are shown in Table 4, and the NMR in Table 5.

2,2,6,6-Tetramethyl-3,5-dioxopiperazine (VII_H). A solution of 100 g (1.19 mol) of an aminonitrile of acetone and 26.6 g (474 mmol) of potassium hydroxide in 1000 m*l* of methanol was refluxed for 7 hr. Then 49.2 g (479 mmol) of a 35% aqueous hydrochloric acid solution was added into the reaction mixture to neutralize the used potassium hydroxide with stirring at 20°C. After 1 hr, the potassium chloride thus produced was removed by filtration; the filtrate was evaporated *in vacuo* to give a semi-solid, which was then washed at room temperature with 1000 m*l* of benzene in order to separate the oxoimidazolidine, XVI. The treatment of the obtained insoluble solid with a solution of 90.1 g of 35% aqueous hydrochloric acid in 180 m*l* of methanol gave 40.2 g of the monohydrochloride of VII_H. Recrystallization from water gave pure prisms. The hydrochloride was dissolved in water on heating and was neutarlized with potassium carbonate. The extract with chloroform from the mixture was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give the free base, VII_H, which was subsequently recrystallized from DMF to give colorless needles.

2,2,6,6-Tetramethyl-3,5-dioxo-4-benzylpiperazine (VII_B). Into a solution of 28.5 g (168 mmol) of VII_H in 500 m*l* of dry DMF, were added thirteen 0.5 g-portions (9.65 g, 201 mmol) of 50% sodium hydride (Nujol dispersion) with stirring at 40°C. After the vigorous evolution of hydrogen had ceased, the reaction mixture was stirred for 1 hr at 40°C. Into the mixture we then added a solution of 28.4 g (224 mmol) of benzyl chloride in 50 m*l* of dry DMF at 45—50°C. After stirring overnight at room temperature, the DMF was evaporated *in vacuo* to give a residue, which was dissolved in benzene (200 m*l*) and water (200 m*l*). The separated benzene layer was washed with water, dried over anhydrous magnesium sulfate, and treated with active charcoal. The evaporation of the benzene *in cacuo* left an oil, which was then dissolved in petroleum benzine and cooled

Table 3. Piperazines and piperazine-*N*-oxyles

Compound	Formula	M^+ (*m/e*)	Mp or bp °C	Yield (%)	Elemental analysis (Found/Calcd)			
					C	H	N	Cl
VII_H	$C_8H_{14}N_2O_2$	170	236—238 (DMF)	89.5[a]	56.71/56.47	8.48/8.29	16.68/16.47	
$VII_H \cdot HCl$	$C_8H_{15}N_2O_2Cl$	—	>250 (H_2O)	32.8	46.41/46.49	7.60/7.31	13.52/13.56	17.12/17.19
VII_B	$C_{15}H_{20}N_2O_2$	260	79—80 (petr. benzine)	62.7	69.02/69.23	7.78/7.76	10.89/10.77	
VII_C	$C_{11}H_{18}N_2O_4$	242	104—105 (ethanol)	56.5	54.66/54.53	7.52/7.49	11.77/11.56	
$VIII_H$	$C_8H_{18}N_2$	142	74—75 (petr. ether)	61.5	65.63/65.93[b]	12.59/12.64	19.02/19.23	
$VIII_H \cdot 2HCl$	$C_8H_{20}N_2Cl_2$	—	>200 (ethanol)	>95	44.48/44.73	9.39/9.38	12.81/13.04	32.89/33.01
$VIII_B$	$C_{15}H_{24}N_2$	232	104—105/1 mmHg	75.5	77.47/77.53	10.30/10.41	11.77/12.06	
IX_B	$C_{21}H_{28}N_2O_2$	340	92—93 (petr. benzine)	75.8	73.96/74.08	8.55/8.29	8.34/8.23	
$IX_B \cdot HCl$	$C_{21}H_{29}N_2O_2Cl$	—	250 (ethanol)	>95	66.62/66.84	7.80/7.75	7.76/7.43	9.44/9.39
IX_C	$C_{17}H_{26}N_2O_4$	322	102—105 (*n*-hexane)	62.4	63.50/63.33	8.11/8.13	8.97/8.69	
X_H	$C_{14}H_{26}N_2$	222	88—89 (*n*-hexane)	74.4	75.38/75.68	11.77/11.80	12.79/12.61	
X_B	$C_{21}H_{32}N_2$	312	91—93 (petr. benzine)	78.6	80.83/80.71	10.36/10.32	8.95/8.97	
XI_H	$C_8H_{13}N_2O_3$	185	150—160 (ether)[c]	60.7	51.91/51.89	7.07/7.08	15.17/15.14	
XI_B	$C_{15}H_{19}N_2O_3$	275	71.5—72.5 (detr. ether)	47.4	65.70/65.45	7.02/6.98	10.04/10.18	
XI_C	$C_{11}H_{17}N_2O_5$	257	99—101 (ether)	66.2	51.36/51.36	6.96/6.68	10.83/10.89	
XII_B	$C_{15}H_{23}N_2O$	247	61.5—62.5 (petr. ether)	29.4	72.64/72.87	9.42/9.39	11.32/11.34	
$XIII_H$	$C_{14}H_{21}N_2O_3$	265	174—175 (99.5% ethanol)	67.2	63.41/63.40	8.01/8.00	10.79/10.57	
$XIII_B$	$C_{21}H_{27}N_2O_3$	355	50—51 (*n*-hexane)	61.0	70.75/70.99	7.52/7.61	8.05/7.89	
$XIII_C$	$C_{17}H_{25}N_2O_5$	337	73—74 (*n*-hexane)	62.5	60.38/60.51	7.52/7.47	8.13/8.31	
XIV_B	$C_{21}H_{31}N_2O$	327	143—144 (*n*-hexane)	95.0	76.92/77.06	9.53/9.57	8.54/8.56	
$XVII_B$	$C_{21}H_{31}N_2O_2$	343	163—164 (methanol)	68.0	73.50/73.46	9.31/9.13	8.23/8.16	

a) from $VII_H \cdot HCl$. b) sublimes under reduced pressure; calcd for $C_8H_{18}N_2 \cdot 1/5\,H_2O$. c) on a hot plate.

12) F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Amer. Chem. Soc.*, **88**, 149, 157 (1966).

Table 4. IR Spectra of the products (cm^{-1})

VII_H	3300(w)	3170(m)	3050(m)	1725		1700		1290		
IX_H	3310(w)	3170(m)	3045(m)	1727		1675(br)		1285		
XI_H	3220	3115(m)		1735		1710	1420	1315		
$XIII_H$	3220	3095		1724		1695(br)	1400	1322		
VII_B	3350(m)			1715		1660			755	700
IX_B	3320(w)			1720		1670			745	695
XI_B				1738		1675	1425		750	695
$XIII_B$				1736(m)		1690	1420(sh)		740	695
VII_C	3360		1788[a]	1730		1690	1380(m)			
IX_C	3350		1783[a]	1737		1700	1375(m)			
XI_C			1785[a]	1740	1720(sh)	1700	1380	1305		
$XIII_C$			1785[a]	1736		1700	1384(m)	1315		
$VIII_B^l$	—								740	700
X_B	—								730	695
XII_B							1400(m)		750	700
XIV_B							1405(w)		745	695
$VIII_H$	3250									
X_H	3250									

br=broad, l=liquid film, a) Ref. 12

Table 5. NMR Spectra of the piperazines

Compound	Solvent	Chemical shift at τ, (Coupling constant J (Hz))			
VII_H	d_6-DMF				8.60(12H, s)
$VIII_H$	CCl_4			7.58(4H, s)	8.94(12H, s)
X_H	$CDCl_3$			7.35(4H, s)	8.1—9.0(20H, broad)
VII_B	$CDCl_3$	2.70(5H, s)	5.04(2H, s)		8.60(12H, s)
$VIII_B$	CCl_4	2.75(5H, m)	6.58(2H, s)	7.96(4H, s)	8.90(12H, s)
IX_B	CCl_4	2.5—3.0(5H, m)	5.17(2H, s)		7.8—9.0(20H, broad)
X_B	CCl_4	2.76(5H, m)	6.61(2H, s)	7.88(4H, s)	8.1—9.0(20H, broad)
VII_C	CCl_4		5.50(2H, q, J=7.0)	8.59(12H, s)	8.61(3H, t, J=7)

at 5°C to give 27.4 g of colorless prisms of VII_B.

2,2,6,6-Tetramethyl-3,5-dioxo-4-carbethoxypiperazine (VII_C). This was prepared from VII_H and ethyl chlorocarbonate in a manner similar to that described above; the extract with benzene from the reaction mixture was washed with ice-water (7—10°C).

2,2,6,6-Tetramethylpiperazine ($VIII_H$). To a suspension of 9.1 g (240 mmol) of LAH in 1000 m*l* of dry ether, we added twenty 0.5-g portions (58.8 mmol) of VII_H at 5—8°C. The resulting solution was stirred for 30 min at 5°C and then refluxed for 1 hr. On cooling to room temperature, a solution of 34.3 g of ethyl acetate in 60 m*l* of ether was added to the resulting mixture in order to decompose the excess LAH. After the reaction mixture had been kept at room temperature for 1 hr, a solution of 2.3 g of sodium hydroxide in 45 m*l* of water was added at 5°C into the mixture, and then the mixture was stirred for 1 hr at room temperature. The ether layer was separated and dried over anhydrous magnesium sulfate. The evaporation of the ether give 5.1 g of crude crystals, which readily sublimed *in vacuo*. The amine, $VIII_H$, turned yellow on exposure to air.

2,2,6,6-Tetramethyl-4-benzylpiperazine ($VIII_B$) was synthesized from VII_B in a manner similar to that described above (in tetrahydrofuran (THF), at 15—20°C).

Cyclohexane-1-spiro-2'-(3',5'-dioxopiperazine)-6'-spiro-1''-cyclohexane (IX_H) was synthesized by the literature procedure.[7]

Cyclohexane-1-spiro-2'-(3',5'-dioxo-4'-benzylpiperazine)-6'-spiro-1''-cyclohexane (IX_B) was prepared from IX_H at 65°C as colorless prisms by a procedure similar to that used in the synthesis of VII_B.

Cyclohexane-1-spiro-2'-piperazine-6'-spiro-1''-cyclohexane (X_H) was prepared from IX_H in ether at 5—8°C in a manner similar to that used in the synthesis of $VIII_H$.

Cyclohexane-1-spiro-2'-(4'-benzylpiperazine)-6'-spiro-1''-cyclohexane (X_B) was similarly prepared from IX_B in ether at 5—8°C.

Oxidation of the Piperazines. 2,2,6,6-Tetramethyl-3,5-dioxopiperazine-1-oxyl (XI_H). By the Direct Oxidation of VII_H. i) With 30% Aqueous Hydrogen Peroxide in the Presence of EDTA and Sodium Tungstate (HPO) in Methanol: Into a suspension of 0.1 g (0.589 mmol) of VII_H in 3.0 g of methanol, was slowly added 1.5 g (13.2 mmol) of HPO. The solution was allowed to stand for 5 days at room temperature. No desired reddish-orange solution, which would indicate the formation of *N*-oxyls, was obtained; the mixture merely turned pale yellow. The methanol was evaporated *in vacuo*, and 15 m*l* of benzene and 0.5 g of potassium carbonate were added to the mixture in order to decompose the excess hydrogen peroxide. The resulting mixture was stirred at room temperature overnight. When the benzene layer, separated from the reaction mixture, was evaporated *in vacuo*, it gave none of the desired prroduct, XI_H.

ii) With HPO in Acetic Acid: None of the desired product ws obtained.

iii) With CPBA in Dichloromethane: Into a solution of 0.1 g (0.589 mmol) of VII_H in 10 m*l* of dichloromethane, was slowly added 0.3 g (1.74 mmol) of CPBA at room temperature. The solution gradually turned blue and then discolored; none of the desired reddish-orange solution was observed. When the dichloromethane was evaporated *in vacuo* after washing with a 10% aqueous solution of potassium carbonate, it gave no *N*-oxyl.

By Hydrolysis Followed by the Decarboxylation of VII_C. Into 2.5 g of a 9.15×10^{-3}% solution (0.264 μmol) of potassium hydroxide in methanol, was added 67.7 mg (0.264 μmol) of VII_C at room temperature. The mixture was allowed to stand for 1 hr at room temperature; then the methanol was evaporated *in vacuo* below room temperature to leave a residue, which was washed with ether three times to remove the VII_C. The residue was then dissolved in methanol and treated with a solution of an equimolar hydrogen chloride in methanol at 10°C. The methanol was removed *in vacuo*, and the resuting residue was extracted with ether. The concentration of the extract gave yellow prisms. A small piece of the prisms gradually sublimed at 150—160°C (on the hot plate of a micro melting-point apparatus).

2,2,6,6-Tetramethyl-3,5-dioxo-4-benzylpiperazine-1-oxyl (XI_B). To a solution of 3.0 g (11.5 mmol) of VII_B in 10 m*l* of acetic acid, was added dropwise 5.25 g (46.2 mmol) of HPO at 20°C. The solution was then allowed to stand at room temperature. After 3 days the solution began to turn reddish. After standing for additional 4 days, 100 m*l* of benzene and 23.7 g potassium carbonate were added to the reaction mixture below 15°C in order to neutralize the acetic acid employed as a solvent and in order to decompose the excess hydrogen peroxide. The suspension was stirred for 2 hr at room temperature. Separation, drying over potassium carbonate, and the evaporation of the benzene gave 4.1 g of a reddish oil, which was then chromatographed on 100 g Brockmann aluminum oxide, using petroleum benzine as the eluent. The subsequent evaporation of the elute *in vacuo* left a reddish oil, which crystallized on standing overnight (1.5 g). Recrystallization gave reddish-orange neeldes. As a by-product along with XI_B, *2,2,6,6-tetramethyl-3,5-dioxo-4-benzyl-1-hydroxypiperazine* was obtained from an ether-elute; mp 97—98°C (from petroleum ether); (1.2 g, 44%). Found: C, 64.95, H; 7.29, N; 9.96%. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.22, H; 7.32, N; 10.14%. IR(cm^{-1}): 3450, 1735, 1675, 735, and 700.

2,2,6,6-Tetramethyl-3,5-dioxo-4-carbethoxypiperazine-1-oxyl (XI_C) was prepared by the oxidation of VII_C with CPBA in a procedure similar to that described above; the extract was washed with water below 10°C.

2,2,6,6-Tetramethyl-4-benzylpiperazine-1-oxyl (XII_B). i) Oxidation of $VIII_B$ with CPBA: As soon as a solution of 0.6 g (3.48 mmol) of CPBA in 10 m*l* of dichloromethane was added dropwise to a solution of 0.25 g (1.08 mmol) of $VIII_B$ in 10 m*l* of dichloromethane at 15°C, a rapid decomposition of $VIII_B$ occurred with green coloration; none of the desired *N*-oxyl was obtained.

ii) Oxidation of $VIII_B$ with HPO in Methanol: To a solution of 1.92 g (8.28 mmol) of $VIII_B$ in 5 m*l* of methanol, was added dropwise 3.0 g (26.5 mmol) of HPO at room temperature. After the reaction mixture had been allowed to stand for 20 hr at room temperature, 10 more grams of HPO were added to the mixture. After standing overnight, a reddish oil separated spontaneously. To the mixture was then added 50 ml of benzene and 5 g of potassium carbonate. Vigorous stirring was continued for 3 hr, and then the benzene layer was separated, washed with water saturated with sodium chloride, and dried over anhydrous magnesium sulfate. The subsequent removal of the benzene left 1.7 g of a reddish oil, which was chromatographed on 100 g of a silica gel (M. WOELM for Dry-Column Chromatography) using petroleum benzine as the eluent. The evaporation of the elute *in vacuo* gave 0.6 g of reddish crystals.

Cyclohexane-1-spiro-2'-(3',5'-dioxopiperazine-1'-oxyl)-6'-spiro-1''-cyclohexane ($XIII_H$). The direct oxidation of IX_H with HPO or CPBA failed to produce $XIII_H$ in a manner similar to that used for the oxidation of VII_H. However, hydrolysis, followed by decarboxylation of $XIII_C$, gave $XIII_H$ in a procedure similar to that used for VII_C.

Cyclohexane-1-spiro-2'-(3',5'-dioxo-4'-benzylpiperazine-1'-oxyl)-6'-spiro-1''-cyclohexane ($XIII_B$). i) To a suspension of 0.1 g (0.294 mmol) of IX_B in 0.7 m*l* of acetic acid, was added dropwise 0.35 g (3.08 mmol) of HPO. The suspension was then stirred at room temperature. After 2 days, a reddish oil separated spontaneously from the acetic acid. To the mixture, after 4 days, were addde 5 m*l* of benzene and 0.2 g of potassium carbonate at room temperature in order to neutralize the acetic acid and in order to decompose the excess hydrogen peroxide. The resulting suspension was stirred at room temperature for 2 hr. The benzene was then evaporated *in vacuo* to give 0.109 g of a reddish oil. The oil was dissolved in a small amount of *n*-hexane and cooled at −5—0°C overnight to give reddish crystals.

ii) To a solution of 4.0 g (11.7 mmol) of IX_B in 800 m*l* of dichloromethane, was gradually added 8.0 g (46.6 mmol) of crystals of CPBA at room temperature. The reaction mixture immediately turned red, and was then kept for 5 days at room temperature. The resulting solution was washed with 200 m*l* of a 10% aqueous potassium carbonate solution three times and with water. After the solution had then been dried over potassium carbonate, the removal of the solvent left a reddish oil, which was chromatographed on 100 g of Brockmann aluminum oxide using petroleum benzine as the eluent. The evaporation of the elute gave 2.5 g of crude crystals, which were recrystallized to give pure reddish crystals. The physical data completely accorded with those of the sample obtained by *Method i)* above.

Cyclohexane-1-spiro-2'-(3',5'-dioxo-4'-carbethoxypiperazine-1'-oxyl)-6'-spiro-1''-cyclohexane ($XIII_C$) was synthesized from IX_C in a manner similar to that used in the synthesis of XI_C; a reddish oil obtained by the evaporation of the extract solidified during 3 days' storage at −10—0°C. The solid was washed with cold (−50°C) *n*-hexane and chromatographed on silica gel using *n*-hexane–ether (9 : 1) to give reddish-orange prisms.

Cyclohexane-1-spiro-2'-(4'-benzylpiperazine-1'-oxyl)-6'-spiro-1''-cyclohexane (XIV_B). i) Oxidation of X_B with CPBA: An attempt to do this in a manner similar to that used in the oxidation of $VIII_B$ met with failure.

ii) Oxidation of X_B with HPO in Methanol: A mixture of 0.2 g (0.641 mmol) of X_B, 0.5 g (4.42 mmol) of HPO and 2 m*l* of methanol was stirred at room temperature. After 6 days, the starting amine was quantitatively revovered.

iii) Oxidation of X_B with HPO in Acetic Acid: This gave none of the desired product, but another product, *cyclohexane-1-spiro-2'-(4'-benzylpiperazine-1'-oxyl-4'-oxide)-6'-spiro-1''-cyclohexane ($XVII_B$)*, when conducted in a manner similar to that used in the preparation of $XIII_B$.

iv) Reduction of $XIII_B$ with LAH Followed by the Air-Oxidation of the Resulting Hydroxyl Amine (XVIII): Into a suspension of 0.248 g (6.5 mmol) of LAH in 6 ml of dry ether, was gradually added 0.5 g (1.41 mmol) of $XIII_B$ at room temperature. The ether was refluxed for 30 min and then allowed to stand at room temperature. After 12 hr, the

reddish solution gradually became colorless. The discolored solution was poured into ice-water, and the mixture was stirred at room temperature for 3 days while being exposed to air. The ether layer gradually turned red again and was separated, washed with water three times, dried over anhydrous magnesium sulfate, treated with active charcoal, and evaporated *in vacuo* to give 0.437 g of crude crystals, which gave reddish crystals upon recrystallization.

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