Reduction-Oxidation of Berbine *N*-Oxides with Aerated Sodium in Liquid Ammonia

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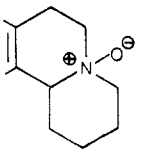
Reduction-oxidation of *trans*- or *cis*-canadine *N*-oxide (**3** or **12**) in aerated sodium in liquid ammonia yields nitrone **4** and a little of amine **5**. Photolysis of **4** in methanol gives rise to amide **8**, lactam **9**, and methyl ether **10**. Attempted reduction-oxidation of either *trans*- or *cis*-xylopinine *N*-oxides (**14** or **15**) furnishes only amine **16**. The two *N*-oxides of nandinine (**20**) proved to be only sparingly soluble in the reaction medium and thus provided only limited yields of nitrone **23**. The yield of nitrone is also curtailed if a methyl group is present at C-13 of the starting berbine *N*-oxide.

The Birch-type reduction of various tetrahydroisoquinoline *N*-oxides (**1**) is known to generate secondary amines **2** in good yields through cleavage of the central carbon to nitrogen bond.[1]



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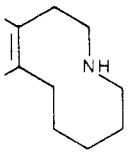

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Initial attempts on our part to extend this sodium in liquid ammonia reduction to the known *trans*-*N*-oxide **3**[2] of (±)-canadine yielded ill-defined products. Following various attempts to modify the experimental conditions, it was found that a colorless crystalline product could be obtained in up to 70% yield when a slurry of *trans*-canadine *N*-oxide (**3**) in warm THF or toluene was first added to distilled liquid ammonia, resulting in a nearly homogeneous mixture. Small chunks of metallic sodium were then cautiously and slowly added so that no permanent blue coloration developed. An additional and critical requirement was that a stream of dry air be continuously passed over the suspension during and immediately after the addition of the sodium chunks. The product was only sparingly soluble in chloroform and proved to be insoluble in most other organic solvents. Analysis indicated the molecular formula $C_{20}H_{21}O_5N$, corresponding to that for the starting *N*-oxide **3**.

The NMR spectrum of the product presents a complex picture, but its most outstanding feature is a one-proton doublet of doublets at δ 6.98 characteristic of the vinylic proton of a nitrone, suggesting structure **4** (see Scheme I). Such an assignment is supported by the ^{13}C NMR spectrum, obtained in trifluoroacetic acid (see Experimental Section), which shows a doublet at 167.0 ppm (J_{CH} = 107.2 Hz) assignable to C-6.

A minor product in the reduction-oxidation of canadine *N*-oxide was a crystalline material, usually obtained in less than 5% yield. Its analytical and spectral characteristics pointed to amine **5**. Acetylation of **5** with acetic anhydride in pyridine readily furnished amide **6**, ν_{max} ($CHCl_3$) 1621 cm^{-1}. Finally, 21% of the starting *N*-oxide **3** was also recovered.

A mechanism which explains the formation of the nitrone **4** as well as that of the minor product **5** is presented below and is based in part on previously reported studies on the oxidation of simple aliphatic hydroxylamines.[3] The initial *trans*-*N*-oxide **3** undergoes reductive fission of the central N-7 to C-14 bond with formation of a net negatively charged species which is then protonated to furnish the key nitrogen oxide radical **3a**. Further reduction and protonation lead to hydroxylamine **3b** whose anion can be converted to nitrone **4** through the intermediacy of radical anion **3c**. Alternatively, hydroxylamine **3b** can undergo dehydration and reduction to furnish amine **5**. It is worth noting that hydrogen abstraction to produce **3c** occurs at C-6 rather than at the benzylic C-8 site which is sterically hindered by the presence of the C-9 methoxyl group.

Reaction of **4** with acetic anhydride in pyridine in the presence of a catalytic amount of 4-(dimethylamino)-pyridine gave a 67% yield of the crystalline imide **7** [ν_{max} (KBr) 1698 cm^{-1} (br)] with a characteristic acetyl NMR singlet at δ 2.35. The genesis of imide **7** is rationalized in the sequence shown in Scheme II.

Photolysis of **4** in methanol using a low-pressure ultraviolet lamp provided three products. Two of these, amide **8** and lactam **9** (Chart I), obtained in 17% and 45% yields, respectively, had been prepared very recently in our laboratory through the direct photolysis of *trans*-canadine *N*-oxide (**3**),[2] and their genesis from **3** had been explained in terms of the intermediate oxaziridine **4a** which is a valence tautomer of nitrone **4**. The third and minor product from the photolysis was methyl ether **10** [9%; ν_{max} (KBr) 1645 and 3290 cm^{-1}] whose formation could be suppressed by running the photolysis in acetonitrile.

Trimethoxyphosphite is known to add to the iminium double bond of a nitrone in a transformation which can also deoxygenate the nitrone.[4] When trimethoxyphosphite was added to nitrone **4**, crystalline amino phosphonate **11** was obtained; ν_{max} (Nujol) 3307 cm^{-1}.

Initial attempts to oxidize (±)-canadine with *m*-chloroperbenzoic acid had produced only the *trans*-*N*-oxide **3**.[2] A careful reexamination of this reaction showed that when the oxidation and workup are carried out consistently below 30 °C, *cis*-canadine *N*-oxide (**12**,[5] Chart II) may also be obtained, albeit in a 20:1 ratio in favor of the trans isomer. Subsequent treatment of the *cis*-*N*-oxide **12** under our reduction-oxidation conditions supplied nitrone **4** in 16% yield, with only a trace amount of amine **5**.

The known berbine (±)-xylopinine (**13**) upon oxidation with *m*-chloroperbenzoic acid gives rise to a 13:1 separable

(1) J. P. Yardley, *Synthesis*, 543 (1973).
(2) P. Chinnasamy, R. D. Minard, and M. Shamma, *Tetrahedron*, **36**, 1515 (1980).
(3) D. H. Johnson, M. A. Thorold, and R. Trappe, *J. Chem. Soc.*, 1093 (1956).
(4) P. Milliet and X. Lusinchi, *Tetrahedron*, **35**, 43 (1979).
(5) It has been shown that the ^{13}C NMR chemical shifts of C-6 and C-13 are critical in differentiating *trans*- from *cis*-berbine *N*-oxide: C. Tani, N. Nagakura, S. Hattori, and N. Masaki, *Chem. Lett.*, 1081 (1975).

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Scheme I

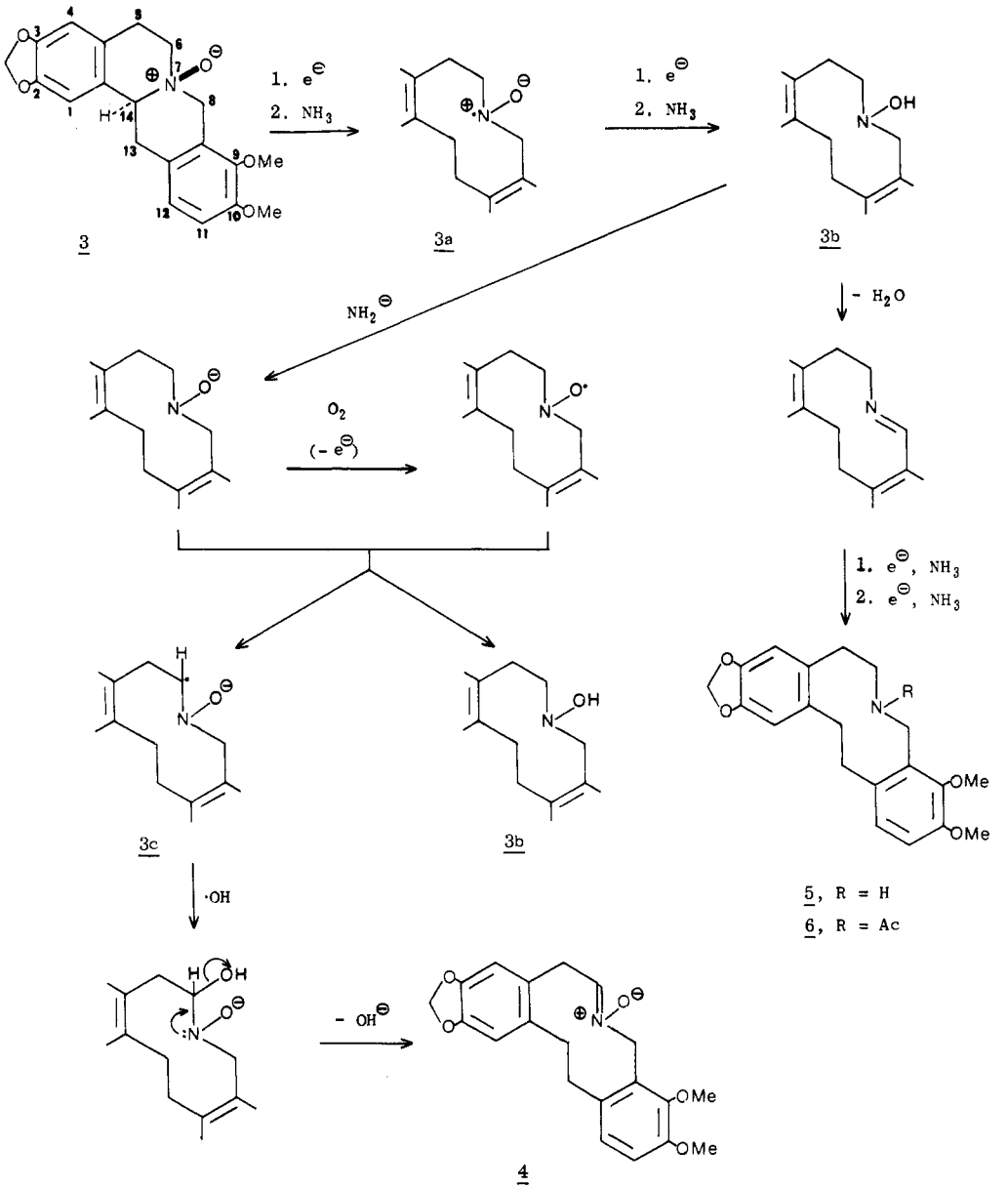
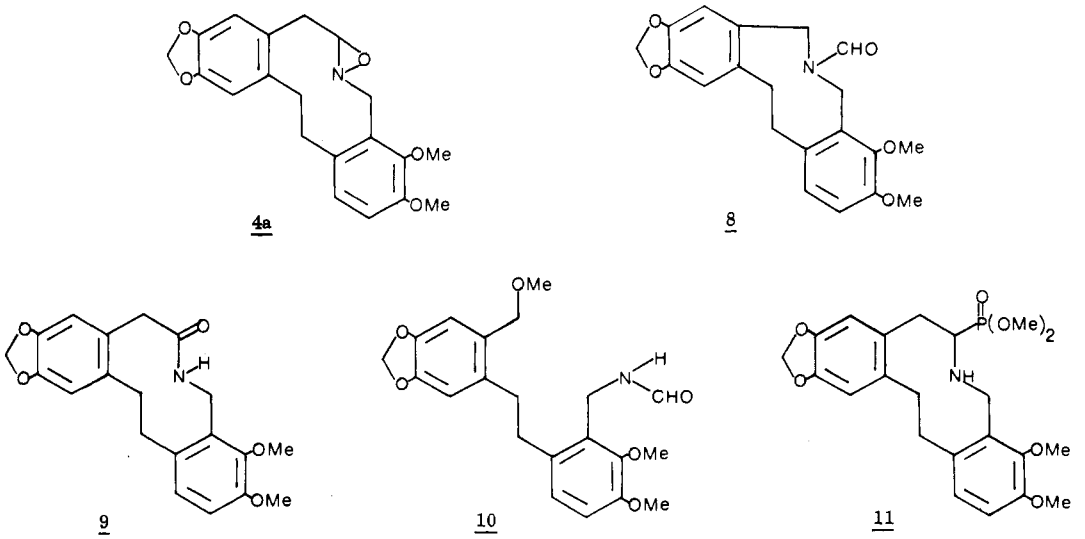


Chart I



mixture of *trans*-*N*-oxide **14** and cis analogue **15**.[2] Attempted reductive oxidation of either of these two *N*-oxides provided in good yield only the straight reduction product, namely, amine **16**. More specifically, the *trans*-

Scheme II

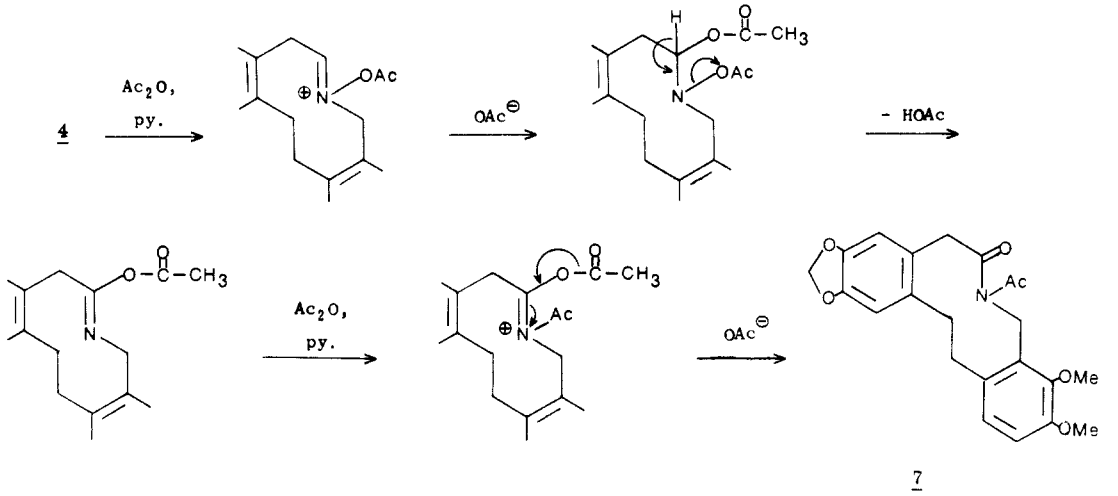
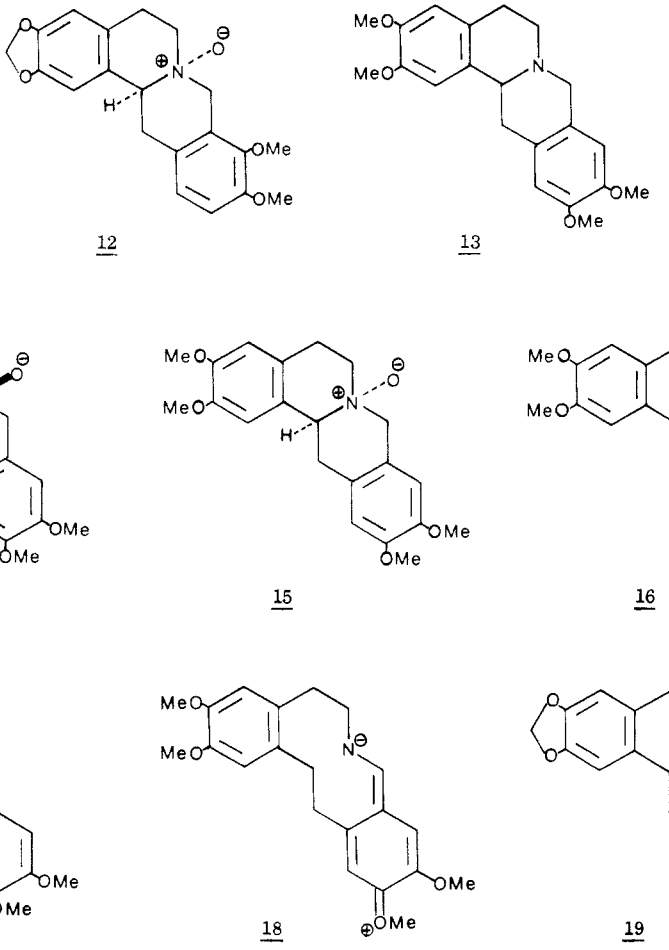


Chart II



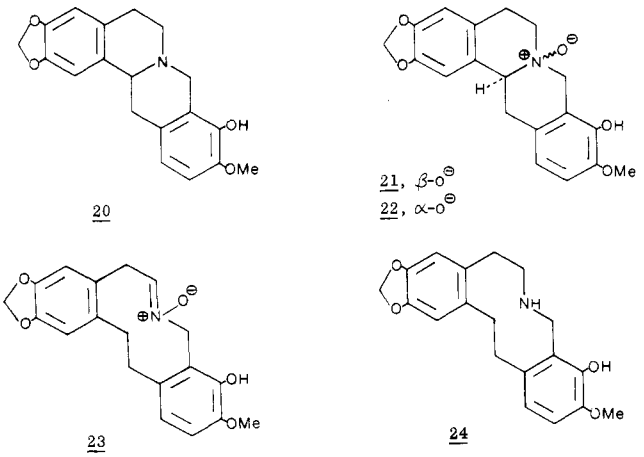
N-oxide **14** furnished a 45% yield of amine **16**, while the yield was increased to 54% when the reaction was run under a nitrogen atmosphere. Similarly, with *cis*-*N*-oxide **15**, the yields of **16** were 55% and 71% with and without the presence of air, respectively.

The reason for the facile formation of amine **16** to the detriment of its corresponding nitrone can be explained by intermediate **17** which must be formed from the corresponding hydroxylamine. Species **17** is stabilized by resonance through the canonical resonating form **18** which incorporates a trans quinone methide system. The analogous resonating form in the canadine series would be **19** which is an *o*-quinone methide and is, therefore, thermodynamically less favored.

(±)-Nandinine (**20**, Chart III), which corresponds to the racemate of tetrahydroberberrubine,[6] was oxidized with *m*-chloroperbenzoic acid to give in 5:1 ratio a separable mixture of the corresponding *trans*- (**21**) and *cis*- (**22**) *N*-oxides. The sodium salts of both *N*-oxides were sparingly soluble in the reductive liquid ammonia system so

(6) Berberrubine is prepared from berberine by refluxing with sodium iodide in pyridine. Sodium borohydride in methanol reduction of berberrubine iodide affords (±)-nandinine.

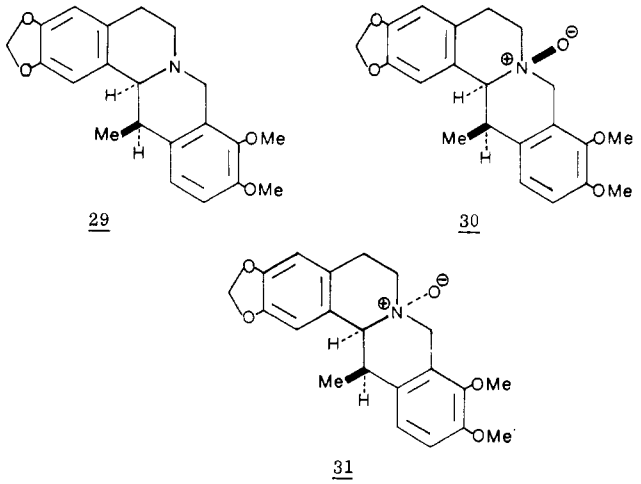
Chart III



that substantial quantities of starting *N*-oxides were recovered. From *trans*-*N*-oxide **21** was obtained a 2% yield of nitrone **23**, accompanied by amine **24** in 10% yield and 41% recovery of *N*-oxide **21**. *cis*-*N*-Oxide **22** provided a 2% yield of nitrone **23**, none of amine **24**, and, significantly, a 50% recovery of starting *cis*-*N*-oxide.

The yield of nitrone is also seriously curtailed if a methyl group is present at C-13 of the starting berbine *N*-oxide. Thus, (±)-mesothalictricavine (**25**,[7a] Chart IV), which exists in the preferred conformation **25a**,[7b] gave only *cis*-*N*-oxide **26** upon oxidation with *m*-chloroperbenzoic acid. Treatment of this material with sodium in liquid ammonia and air led to nitrone **27** in 10% yield, accompanied by a 5% yield of hydroxylamine **28**. At the same time, the starting *N*-oxide **26** was also recovered in 25% yield. It is known that hydroxylamines can in some cases be oxidized by cupric acetate to the nitrone,[8] and, indeed, oxidation of **28** with this reagent resulted in formation of nitrone **27**.

Along the same lines, *m*-chloroperbenzoic acid oxidation of (±)-thalictricavine (**29**)[7] supplied an 11:1 separable mixture of *trans*- and *cis*-*N*-oxides (**30** and **31**). Reaction of *trans*-*N*-oxide **30** with aerated sodium in liquid ammonia gave only a 1% yield of nitrone **27** together with 18% of recovered starting material.



We are presently engaged in a search for other compounds whose reduction–oxidation with aerated sodium in liquid ammonia will lead to unusual chemistry.

Experimental Section

General Procedures. Mass spectra were determined at 70 eV. Methane gas was used in the chemical ionization mass spectra. All ^{1}H NMR spectra were taken in deuteriochloroform except where specified otherwise. All ^{13}C NMR spectra were obtained on a Varian CFT-20 spectrometer; chemical shift assignments with identical superscripts (dagger, double dagger, or asterisk) are interchangeable. TLC was on Merck F-254 precoated silica gel plates. The developing medium was chloroform–methanol (98:2) except where stated differently. Spots were visualized under ultraviolet light or by spraying with chloroplatinate reagent. For convenience, the numbering system adopted for all derivatives of berberine is that of the mother compound.

***trans*- and *cis*-*N*-Oxides of Canadine (3 and 12).** (±)-Canadine (2.0 g) was dissolved in methylene chloride (50 mL) and the solution cooled to 20 °C. *m*-Chloroperbenzoic acid (2 g) was then added over 15 min with stirring. The mixture was stirred 1 h at room temperature. The solution was washed with aqueous sodium bicarbonate and dried, and the solvent was evaporated. The crude product was chromatographed on a neutral alumina column (Brockmann activity 1, 80–200 mesh) by eluting first with chloroform and then with chloroform–methanol. Unreacted canadine was followed first by **3**; 990 mg (47%); mp 205–206 °C (acetone–$CHCl_3$) [lit.[2] mp 203–204 °C (MeOH)]; ^{13}C NMR (C-F_3COOD) 25.35 (C-5), 31.08 (C-13), 57.46 (OCH_3), 62.80 (OCH_3), 66.00 (C-6), 66.69 (C-8), 72.18 (C-14), 103.67 (OCH_2O), 107.07 (C-1), 110.39 (C-4), 116.58 (C-11), 127.76 (C-12), 120.55† (C-12a), 123.38† (C-8a), 125.01‡ (C-4a), 125.62‡ (C-14a), 146.12 (C-10), 150.00* (C-3), 150.49* (C-2), 153.16 ppm (C-9).

The fraction eluting with 2–5% methanol in chloroform proved to be **12**: 50 mg (2.4%); mp 144 °C (acetone) or mp 210 °C (acetone); ^{13}C NMR ($CDCl_3$) 25.16 (C-5), 35.00 (C-13), 55.60 (OCH_3), 57.74 (C-6), 60.20 (OCH_3), 64.79 (C-8), 70.40 (C-14), 100.81 (OCH_2O), 106.42 (C-1), 108.57 (C-4), 112.19 (C-11), 121.96† (C-12a), 123.12† (C-8a and C-12), 123.28† (C-14a), 126.99† (C-4a), 144.85‡ (C-10), 146.09‡ (C-2), 146.94‡ (C-3), 150.72 ppm (C-9); mass spectrum, *m*/*e* (relative intensity) 355 (M^+, 1), 339 (51), 338 (39), 147 (16), 164 (base), 149 (40).

Anal. Calcd for $C_{20}H_{21}O_5N{\cdot}CH_3COCH_3$: C, 66.81; H, 6.58. Found: C, 66.89; H, 6.45.

Reduction-Oxidation of 3. A slurry of **3** (200 mg) in warm THF (10 mL) was added to 100 mL of distilled ammonia. The mixture was stirred for 10 min. A small chunk of sodium was then added under reflux, while at the same time the mixture was being continuously stirred and a stream of dry air was being passed. After the transitory blue color had disappeared, other chunks of sodium were added in the same fashion. This process took 6 h, with dry air being continuously passed over the suspension. The ammonia was then allowed to dry overnight. Water and chloroform were added to the residue. The organic layer was dried and the solvent evaporated. The residue gave colorless crystals of **4**: 70 mg (35%); mp 273 °C (MeOH–$CHCl_3$); λ_{max} 288 (sh), 296 nm (log ϵ 3.89, 3.84); ^{1}H NMR (200 MHz) δ 2.21–2.93 (4 H, m, H-13 and H-14), 3.13 (1 H, ddd, J_{gem} = 15.4 Hz, $J_{5B,6}$ = 2.2 Hz, $J_{5B,8B}$ = 2.3 Hz, H-5B), 3.87 (3 H, s, OCH_3), 4.01 (3 H, s, OCH_3), 4.54 (1 H, dd, J_{gem} = 15.4 Hz, $J_{5A,6}$ = 10.0 Hz, H-5A), 4.69 (1 H, d, J_{gem} = 12.7 Hz, H-8A), 5.66 (1 H, dd, J_{gem} = 12.7 Hz, $J_{5B,8B}$ = 2.3 Hz, H-8B), 5.96 (2 H, s, OCH_2O), 6.74 (1 H, s, H-1 or H-4), 6.78 (1 H, s, H-1 or H-4), 6.88 (1 H, d, $J_{11,12}$ = 8.4 Hz, H-11 or H-12), 6.95 (1 H, d, $J_{11,12}$ = 8.4 Hz, H-11 or H-12), 6.98 (1 H, dd, $J_{5A,6}$ = 10.0 Hz, $J_{5B,6}$ = 2.2 Hz); ^{13}C NMR (CF_3C-OOD) 35.54 (C-5), 36.86 (C-13), 38.44 (C-14), 61.18 (C-8), 57.32 (OCH_3), 63.68 (OCH_3), 103.43 (OCH_2O), 112.40 (C-4), 113.31 (C-1), 117.37 (C-11), 129.75 (C-12), 121.04† (C-12a), 122.68† (C-8a), 136.07‡ (C-4a), 139.31‡ (C-14a), 148.98 (C-10), 149.53* (C-3), 150.67* (C-2), 153.32 (C-9), 167.03 ppm (C-6, J_{CH} = 107.2 Hz); mass spectrum, *m*/*e* (relative intensity) 355 (M^+, 54.1), 339 (67), 338 (base), 191 (30), 190 (43), 174 (36), 165 (50), 164 (54), 149 (81).

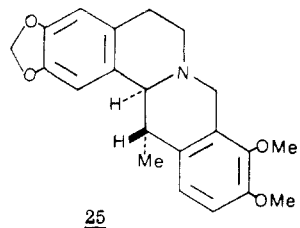
Anal. Calcd for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96. Found: C, 67.55; H, 5.88.

The mother liquor was concentrated and subjected to TLC to give **5**: 6 mg (3%); mp 143–144 °C (acetone–ether); ^{1}H NMR (60 MHz) δ 2.5–3.1 (4 H, m, H-13 and H-14), 3.01 (4 H, br s, H-5 and

(7) (a) N. Takao and K. Iwasa, *Chem. Pharm. Bull.*, **24**, 3185 (1976); (b) N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *ibid.*, **25**, 1426 (1977).

(8) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).

Chart IV



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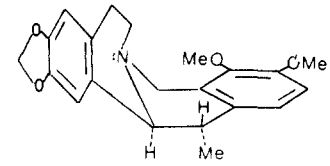

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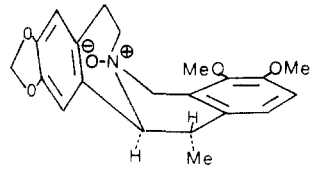

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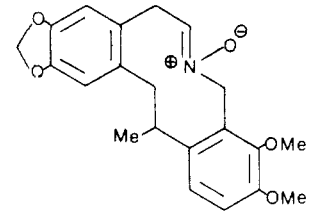

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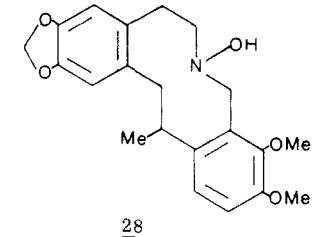

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H-6), 3.80 (6 H, s, 2 OCH_3), 3.88 (2 H, s, H-8), 4.10 (1 H, br, NH), 5.83 (2 H, s, OCH_2O), 6.52 (1 H, s, H-1 or H-4), 6.57 (1 H, s, H-1 and H-4), 6.73 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-11 or H-12), 6.83 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-10 or H-11); mass spectrum, *m/e* (relative intensity) 341 (M^+, base), 310 (48), 192 (74), 176 (26), 154 (48), 149 (59). Acetylation with acetic anhydride in pyridine at room temperature and workup gave oily amide **6**: mass spectrum, *m/e* (relative intensity) 383 (M^+, $C_{22}H_{25}O_5N$, base), 324 (33), 297 (33), 222 (24), 180 (24), 176 (18), 165 (32), 164 (30), 149 (62).

From the above reduction–oxidation was also recovered 41 mg (21%) of starting *N*-oxide.

When toluene was substituted for THF in the above reduction–oxidation, **4** (135 mg, 70%), **5** (10 mg, 5%), and starting *N*-oxide (3 mg, 2%) were obtained.

All of the above yields are average rather than maximum.

Acetylation of Nitrone 4. A mixture of **4** (100 mg), pyridine (10 mL), acetic anhydride (0.5 mL), and 4-(dimethylamino)-pyridine (1 drop), was heated for 5 min until the nitrone was dissolved. The mixture was then allowed to stand for 30 min. The solvent was evaporated, and methanol was added. The solvent was again evaporated. The resulting crude crystals of **7** were recrystallized from $CHCl_3$–MeOH: 75 mg (67%); mp 201–202 °C; ^1H NMR (200 MHz) δ 2.35 (3 H, s, $COCH_3$), 2.05–2.74 (4 H, m, H-13 and 14), 3.78 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.48 and 4.26 (2 H, dd, J_{gem} = 14.7 Hz, H-5), 5.02 and 5.06 (2 H, dd, J_{gem} = 15.0 Hz, H-8), 5.94 (2 H, s, OCH_2O), 6.71 (1 H, s, H-1 or H-4), 6.81 (1 H, s, H-1 or H-4), 6.89 and 7.00 (2 H, dd, J = 8.4 Hz, H-11 and H-12); mass spectrum, *m/e* (relative intensity) 397 (M^+, base), 338 (61), 321 (15), 310 (13), 297 (21), 222 (12), 180 (23), 175 (15), 165 (15), 164 (62), 149 (60), 148 (25), 147 (24).

Anal. Calcd for $C_{22}H_{23}O_6N$: C, 66.46; H, 5.83; N, 3.52. Found: C, 66.19; H, 5.95; N, 3.59.

Photolysis of Nitrone 4. A suspension of **4** (200 mg) in methanol (100 mL) was irradiated under nitrogen for 5 h with a Pen Ray low-pressure mercury lamp. The solvent was evaporated and the residue triturated with hot chloroform. The white solid was filtered and washed with chloroform and ether to give **9** [90 mg (45%); mp >300 °C [lit. mp >250 °C (MeOH)]][2] identical with material obtained by direct photolysis of **3**.

The above mother liquor was evaporated, and the resulting crystals of **8** were recrystallized from chloroform–methanol [34 mg (17%); mp 223 °C [lit. mp 228–230 °C (MeOH)]][2] and were again identical with material obtained by direct photolysis of **3**.

The second mother liquor was subjected to TLC to supply **10**: 17 mg (9%); mp 123 °C (acetone); ^1H NMR (200 MHz) δ 2.8–2.9 (4 H, m, H-13 and H-14), 3.32 (3 H, s, CH_2OCH_3), 4.30 (2 H, (2 H, br s, H-5), 4.46 and 4.49 (2 H, dd, J_{gem} = 15.0 Hz, H-8), 3.86 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 5.93 (2 H, s, OCH_2O), 6.71 (1 H, s, H-1 or H-4), 6.80 (1 H, s, H-1 or H-4), 6.80 (1 H, d, $J_{11,12}$ = 8.3 Hz, H-11 or H-12), 6.91 (1 H, d, $J_{11,12}$ = 8.3 Hz, H-11 or H-12); mass spectrum, *m/e* (relative intensity) 387 (M^+, $C_{21}H_{25}O_6N$, 3), 355 (75), 310 (24), 297 (17), 208 (22), 180 (13), 165 (29), 149 (base).

When the photolysis was repeated with acetonitrile instead of methanol, **9** was obtained (40 mg, 40%) together with **8** (22 mg, 22%).

Reaction of 4 with Trimethoxyphosphite. A mixture of nitrone **4** (200 mg), trimethoxyphosphite (12 mL), and triethylamine (1 mL) was refluxed until all the nitrone was dissolved (~7 h). The solvent was completely evaporated by codistillation with benzene. The residue was partitioned between ammonium hydroxide and chloroform. The organic layer was dried and the solvent evaporated. The residue was purified by TLC to give **11**: 45 mg (18%); mp 150–151 °C (acetone); ^1H NMR (200 MHz) δ 1.61 (1 H, br, NH), 3.83 and 3.87 (6 H, dd, $J_{H,P}$ = 10.4 Hz, 2 OCH_3 nonequivalent), 3.79 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 3.53 and 4.40 (2 H, dd, J_{gem} = 13.8 Hz, H-8), 5.91 (2 H, s, OCH_2O), 6.75 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-11 or H-12), 6.90 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-11 or H-12), 6.67 (1 H, s, H-1 or H-4), 6.72 (1 H, s, H-1 or H-4); mass spectrum, *m/e* (relative intensity) 450 (M^+, $C_{22}H_{28}O_7NP$, 3), 339 [base, M – $(CH_3O)_2PO$], 191 (61), 190 (38), 186 (70), 185 (45), 174 (32), 164 (25), 149 (51).

Reduction–Oxidation of 12. A slurry of **12** (200 mg) in warm THF (or warm toluene) was treated as with **3**. Workup afforded **4** (33–34 mg, 16–17%) and a trace amount of amine **5**.

Reduction–Oxidation of 14. A slurry of **14**[2] (200 mg) in warm toluene (10 mL) was added to distilled liquid ammonia (125 mL). Workup as above gave a residue which was subjected to TLC to furnish **16**: 87 mg (45%); mp 159–160 °C (acetone–ether); ^1H NMR (60 MHz) δ 1.15 (1 H, br, NH), 2.5–3.2 (8 H, m, 4 CH_2), 3.83 (12 H, s, 4 OCH_3), 3.87 (2 H, s, H-8), 6.57 (3 H, br s, 3 Ar H), 6.67 (1 H, s, Ar H); mass spectrum, *m/e* (relative intensity) 357 (M^+, $C_{21}H_{27}O_4N$, 78), 328 (46), 326 (33), 313 (19), 297 (18), 192 (82), 177 (16), 176 (17), 165 (base), 164 (81); chemical ionization mass spectrum, *m/e* 358 [(M + 1)$^+$], 386 [(M + 29)$^+$].

When nitrogen instead of oxygen gas was bubbled through the reaction mixture, **16** was obtained (104 mg, 54%).

Reduction–Oxidation of 15. A slurry of **15**[2] (80 mg) in warm toluene (10 mL) was added to distilled liquid ammonia (100 mL) in the presence of air. Workup gave **16** (42 mg, 55%).

In a separate experiment, when nitrogen gas was bubbled through the reacting mixture, **16** was obtained (34 mg, 71%).

***trans*-Nandinine *N*-Oxide (21) and *cis*-Nandinine *N*-Oxide (22).** Nandinine (**20**, 4 g) was treated with *m*-chloroperbenzoic acid as in the above oxidations. The product crystallized from hot methanol to give *trans*-*N*-oxide **21**: 2.8 g (67%); mp 224–225 °C (methanol); ^1H NMR (60 MHz, $CDCl_3$–CF_3COOD) δ 3.83 (3 H, s, OCH_3), 4.65 and 5.18 (2 H, dd, J_{gem} = 16.0 Hz, H-8), 5.92 (2 H, s, OCH_2O), 6.62 (1 H, s, H-1 or H-4), 6.67 (1 H, s, H-1 or H-4), 6.78 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-11 or H-12), 6.82 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-11 or H-12); ^{13}C NMR ($CDCl_3$–CF_3COOD) 23.75 (C-5), 29.46 (C-13), 56.13 (OCH_3), 63.44 (C-6), 64.26 (C-8), 70.0 (C-14), 101.72 (OCH_2O), 104.96 (C-1), 108.29 (C-4), 111.39 (C-8a), 111.67 (C-11), 119.62 (C-12), 121.70† (C-12a), 122.59† (C-4a), 123.58† (C-1a), 142.34 (C-9), 145.37 (C-10), 147.91* (C-3), 148.28* ppm (C-2); mass spectrum, *m/e* (relative intensity) 325 (M^+ –

O, $C_{19}H_{19}O_4N$, 52), 324 (30), 308 (12), 176 (base), 174 (26), 150 (54), 135 (19).

The methanolic solution was further evaporated and the residue recrystallized from methanol–ethyl acetate to give *cis*-*N*-oxide **22**: 545 mg (13%); mp 185–187 °C; ^{1}H NMR (60 MHz, $CDCl_3$–CF_3COOD) δ 3.82 (3 H, s, OCH_3), 4.62 and 5.30 (2 H, dd, J_{gem} = 16.0 Hz, H-8), 5.92 (2 H, s, OCH_2O), 6.58 (1 H, s, H-1 or H-4), 6.63 (1 H, s, H-1 or H-4), 6.77 (2 H, br s, H-11 and H-12); mass spectrum, *m/e* (relative intensity) 325 (M^+ – O, $C_{19}H_{19}O_4N$, 58), 324 (36), 323 (29), 308 (32), 176 (base), 174 (25), 150 (48), 135 (15).

Reduction-Oxidation of 21. The *trans*-*N*-oxide **21** (200 mg) was treated as described above for **3**. Starting material was recovered (82 mg, 41%). The mother liquor was subjected to TLC to give two products. The amorphous product **24** (20 mg, 10%) exhibits the following: ^{1}H NMR (60 MHz) δ 3.75 (3 H, s, OCH_3), 3.88 (2 H, s, H-8), 6.40 (1 H, s), 6.48 (1 H, s), 6.52 (2 H, br s, H-11 and H-12); mass spectrum, *m/e* (relative intensity) 341 (M^+, $C_{19}H_{21}O_4N$, 43), 325 (base), 324 (82), 176 (39), 174 (32), 165 (26), 150 (38), 149 (38), 135 (33).

For compound **23**: 3 mg (2%); mp 219–223 °C; ^{1}H NMR (200 MHz) δ 3.90 (3 H, s, OCH_3), 3.48 (1 H, br d, J_{gem} = 15.8 Hz, H-5A), 4.53 (1 H, dd, J_{gem} = 15.8 Hz, $J_{5B,6}$ = 10.1 Hz, H-5B), 4.91 (1 H, d, J_{gem} = 13.6 Hz, H-8A), 5.92 (1 H, d, J_{gem} = 13.6 Hz, H-8B), 6.00 (2 H, s, OCH_2O), 6.76 (1 H, s, H-1 or H-4), 6.79 (1 H, s, H-1 or H-4), 6.79 (1 H, d, $J_{11,12}$ = 8.4 Hz, H-11 or H-12), 6.87 (1 H, d, $J_{11,12}$ = 8.4 Hz H-11 or H-12), 7.79 (1 H, d, $J_{5B,6}$ = 10.1 Hz, H-6); mass spectrum, *m/e* (relative intensity) 327 (M^+, $C_{19}H_{19}O_5N$, 82), 296 (38), 178 (58), 149 (base), 135 (23).

Reduction–Oxidation of 22. The *cis*-*N*-oxide **22** (200 mg) was treated as described above for **3**. Some starting material (100 mg, 50%) was recovered. The remaining product was subjected to TLC to give **23** (2%).

Mesothalictricavine *N*-Oxide (26). To an ice-cold solution of **25** (1.56 g) in methylene chloride (110 mL) was added *m*-chloroperbenzoic acid (1.25 g) over 50 min with stirring. The mixture was stirred for another 3 h with cooling. The solution was then washed with sodium bicarbonate solution and with water. The organic layer was dried and the solvent evaporated. The residue crystallized from chloroform–ethyl acetate to give *cis*-*N*-oxide **26**: 1.335 g (82%); mp 221–222 °C; ^{1}H NMR (60 MHz) δ 1.47 (3 H, d, *J* = 7.0 Hz, CCH_3), 3.78 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.99 (1 H, d, *J* = 9.2 Hz, H-14), 5.86 (2 H, m, OCH_2O), 6.60 (2 H, s, H-1 and H-4), 6.85 (2 H, s, H-11 and 12); ^{13}C NMR ($CDCl_3$) 20.04 (CCH_3), 23.40 (C-5), 40.63 (C-13), 54.26 (C-6), 54.63 (OCH_3), 59.42 (OCH_3), 65.81 (C-8), 77.0 (C-14), 99.69 (OCH_2O), 107.52 (C-1), 107.67 (C-4), 111.57 (C-11), 121.53 (C-12), 122.24† (C-8a and C-14a), 125.99† (C-4a), 127.10 (C-12a), 143.60‡ (C-10, 144.43‡ (C-2), 145.84‡ (C-3), 149.76 ppm (C-9); mass spectrum, *m/e* 369 (M^+, 0.6), 364 (0.4), 353 (20), 351 (14), 350 (12), 178 (base), 163 (20).

Anal. Calcd for $C_{21}H_{23}O_5N$: C, 68.28, H, 6.28. Found: C, 67.78; H, 6.38.

Reduction–Oxidation of 26. A slurry of **26** (200 mg) in warm toluene (100 mL) was added to 100 mL of distilled liquid ammonia. A small chunk of sodium was then added under reflux, while dry air was passed over the system. This slow addition of sodium was continued for 2.5 h. The resulting mixture was stirred under air for an additional 3 h. The resulting slurry was diluted with water and extracted with chloroform. Workup and TLC afforded nitrone **27**: 20 mg (10%); mp 240–241.5 °C (acetone); ^{1}H NMR (200 MHz) δ 1.40 (3 H, d, *J* = 6.6 Hz, CCH_3), 2.16 (1 H, dd, J_{gem} = 13.9 Hz and $J_{13,14}$ = 10.9 Hz, H-14A), 2.49 (1 H, d, J_{gem} = 13.9 Hz, H-14B), 2.85 (1 H, m, H-13), 3.13 (1 H, dt, J_{gem} = 15.6 Hz, $J_{5A,6}$ = 2.5 Hz, $J_{5A,8B}$ = 2.5 Hz, H-5A), 3.88 (3 H, s, OCH_3), 4.03 (3 H, s, OCH_3), 4.54 (1 H, dd, J_{gem} = 15.6 Hz, $J_{5B,}$,6 = 9.9 Hz, H-5B), 4.77 (1 H, d, J_{gem} = 12.5 Hz, H-8A), 5.69 (1 H, dd, J_{gem} = 12.5 Hz, $J_{5A,5B}$ = 2.5 Hz, H-8B), 5.96 (2 H, s, OCH_2O), 6.74 (1 H, s, H-1 or H-4), 6.77 (1 H, s, H-1 or H-4), 6.93 (1 H, d, $J_{11,12}$ = 8.6 Hz, H-11 or H-12), 7.10 (1 H, d, $J_{11,12}$ = 8.6 Hz, H-11 or H-12); mass spectrum, *m/e* (relative intensity) 369 (M^+, $C_{21}H_{23}O_5N$, 21), 352 (58), 338 (23), 205 (48), 178 (base), 163 (40), 160 (55), 149 (25), 148 (28). There was also obtained hydroxylamine **28**: 9 mg (5%); mp 150–151 °C (ether); ^{1}H NMR (60 MHz) δ 1.38 (3 H, d, *J* = 7.0 Hz, CCH_3), 3.75 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 4.05 and 4.33 (2 H, dd, J_{gem} = 14.0 Hz, H-8), 5.80 (2 H, s, OCH_2O), 6.55 (1 H, s, H-1 or H-4), 6.58 (1 H, s, H-1 or H-4), 6.75 (1 H, d, $J_{11,12}$ = 8.4 Hz, H-11 or H-12), 6.93 (1 H, d, $J_{11,12}$ = 8.4 Hz, H-11 or H-12); mass spectrum, *m/e* (relative intensity) 371 (M^+, $C_{21}H_{25}O_4N$, 27), 353 (49), 338 (21), 326 (27), 325 (28), 311 (26), 222 (32), 204 (32), 178 (80), 177 (71), 163 (59), 162 (44), 149 (base). Starting compound (50 mg) was also recovered.

Conversion of Hydroxylamine 28 to Nitrone 27. Compound **28** (1 mg) and a trace amount of cupric acetate were dissolved in 60% aqueous ethanol (10 mL) containing ammonium hydroxide (0.01 mL), and air was bubbled through the solution for 3.5 h. Concentration to 5 mL and extraction with chloroform gave **27**.

***trans*-Thalictricavine *N*-Oxide (30) and *cis*-Thalictricavine *N*-Oxide (31).** Thalictricavine (**29**; 3 g) was dissolved in methylene chloride (90 mL), the solution cooled in ice water, and *m*-chloroperbenzoic acid (2 g) added with stirring for 30 min. The mixture was stirred 2 h at near 5 °C. The solution was washed with sodium bicarbonate solution and water. The workup gave a residue which crystallized from chloroform–ethyl acetate and corresponded to **30**: 2.62 g (83%); mp 206–208 °C; ^{1}H NMR (60 MHz) δ 1.58 (3 H, d, *J* = 6.8 Hz, CCH_3), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.43 and 4.70 (2 H, dd, J_{gem} = 15.0 Hz, H-8), 4.48 (1 H, d, $J_{13,14}$ = 4.0 Hz, H-14), 5.87 (2 H, s, OCH_2O), 6.63 (2 H, s, H-1 and H-4), 6.87 (1 H, d, $J_{11,12}$ = 8.3 Hz, H-11 or H-12), 7.03 (1 H, d, $J_{11,12}$ = 8.3 Hz, H-11 or H-12); ^{13}C NMR ($CDCl_3$) 17.88 (CCH_3), 24.69 (C-5), 34.51 (C-13), 55.65 (OCH_3), 60.10 (OCH_3), 65.54 (C-6), 68.64 (C-8), 68.93 (C-14), 100.83 (OCH_2O), 106.17 (C-1), 108.58 (C-4), 112.0 (C-11), 123.66 (C-12), 122.18† (C-14a), 123.96† (C-8a), 126.94 (C-4a), 131.23 (C-12a), 145.17 (C-10), 146.41‡ (C-2), 146.57‡ (C-3), 150.05 ppm (C-9); mass spectrum, *m/e* (relative intensity) 369 (M^+, 0.6), 353 (31), 351 (19), 350 (17), 338 (6.6), 336 (5.7), 178 (base), 163 (20).

Anal. Calcd for $C_{21}H_{23}O_5N \cdot {}^1/_2CH_3COOC_2H_5$: C, 66.81; H, 6.58. Found: C, 67.19; H, 6.46.

Recrystallization of the mother liquor fraction gave *cis*-*N*-oxide **31**: 240 mg (8%); mp 184.5–186 °C (acetone); ^{1}H NMR (200 MHz) δ 1.04 (3 H, d, *J* = 7.6 Hz, CCH_3), 3.84 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.62 (1 H, d, $J_{13,14}$ = 6.4 Hz, H-14), 4.76 and 4.87 (2 H, dd, J_{gem} = 16.4 Hz, H-8), 5.94 (2 H, m, OCH_2O), 6.55 (1 H, s, H-1), 6.70 (1 H, s, H-4), 6.93 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-11 or H-12), 7.00 (1 H, d, $J_{11,12}$ = 8.5 Hz, H-11 or H-12); ^{13}C NMR ($CDCl_3$) 18.40 (CCH_3), 25.16 (C-5), 37.37 (C-13), 56.0 (OCH_3), 59.02 (C-6), 60.60 (OCH_3), 67.09 (C-8), 74.53 (C-14), 101.09 (OCH_2O), 107.26 (C-1), 108.45 (C-4), 112.92 (C-11), 123.47 (C-12), 123.09 (C-8a), 125.25 (C-14a), 125.53 (C-4a), 128.67 (C-12a), 144.96 (C-10), 146.48 (C-2), 147.17 (C-3), 151.01 ppm (C-9); mass spectrum, *m/e* (relative intensity) 369 (M^+, $C_{21}H_{23}O_5N$, 0.5), 353 (27), 351 (26), 350 (22), 338 (6.3), 336 (8.1), 178 (base), 163 (18).

Reduction–Oxidation of 30. A slurry of **30** (200 mg) in warm toluene (10 mL) was added to 100 mL of distilled liquid ammonia. Reduction and air oxidation as described above for **3** produced a film which was subjected to TLC to give nitrone **27** [1.3 mg (1%); mp 238–245 °C ($CHCl_3$–MeOH)] together with 35 mg (18%) of starting material.

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