$OCH_2C_6H_4$-Resin (0.53 mmol/g)[10] with the results shown in Figure 1B. The stabilities of the anchoring bonds in these resins are similar.

Acknowledgment. The author thanks Dr. F. Scheidl, Dr. T. Williams, Dr. V. Toome, Mr. S. Traiman, and their colleagues for performing physicochemical measurements and Mrs. I. D. Kulesha for providing technical assistance in a certain phase of this work.

Registry No.—I, 9003-70-7; VIII, 54276-63-0; IX, 54276-64-1; X, 51095-58-0; XI, 54276-65-2; XII, 54276-66-3; XIII, 54276-67-4; XIV, 54276-68-5; potassium acetate, 127-08-2; Boc-Ala-OH, 15761-38-3; Boc-Ala-$OCH_2C_6H_5$, 51814-54-1; Boc-Gly-OH, 4530-20-5; Boc-Gly-$OCH_2C_6H_5$, 54244-69-8; 4-(*p*-hydroxyphenyl)-2-butanone, 5471-51-2; phenyl chloroformate, 1885-14-9; 2-nitrobenzyl-*p*-nitrophenyl carbonate, 54276-69-6; 2-nitrobenzyl alcohol, 612-25-9; *p*-nitrophenyl chloroformate, 7693-46-1; 2-nitrobenzyloxycarbonylglycine, 30007-79-5; glycine, 56-40-6; Boc-Thr(Bzl)-$OCH_2C_6H_5$, 54276-70-9; Boc-Tyr(Bzl)-OH, 2130-96-3; Boc-Phe-OH, 13734-34-4; Boc-Tyr(Cl_2Bzl)-OH, 40298-71-3; Boc-Tyr(Cl_2Bzl)-$OCH_2C_6H_5$, 54244-64-3; Boc-Val-OH, 13734-41-3; Aoc-Arg(Tos)-OH, 54244-59-6; pGlu-Ser(Bzl)-Gly-NH_2, 54276-71-0; pyroglutamic acid, 16891-48-8; Boc-Ser(Bzl)-OH, 23680-31-1; pGlu-Gln-Ala-NH_2, 38357-81-2; Boc-Gln-OH, 13726-85-7; Bpoc-Leu-OH, 18634-99-6; Bpoc-Ala-OH, 23631-89-2; Bpoc-Val-OH, 25692-88-0; Bpoc-Thr(Bzl)-OH, 47733-62-0; Bpoc-Tyr(Bzl)-OH, 25692-91-5; Bpoc-Phe-OH, 40099-50-1; Fmoc-Gly-OH, 29022-11-5.

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(24) Abbreviations used: Aoc, *tert*-amyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; Bpoc, 2-(*p*-biphenylyl)-2-propyloxycarbonyl; Bzl, benzyl; Cl_2Bzl, 2,6-dichlorobenzyl; Fmoc, 9-fluorenylmethyloxycarbonyl; Tos, *p*-toluenesulfonyl; Z, benzyloxycarbonyl; Z(2-NO_2), 2-nitrobenzyloxycarbonyl; DCC, dicyclohexylcarbodiimide; DMF, dimethylformamide; DMSO, dimethyl sulfoxide.
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A Nuclear Magnetic Resonance Study of Structure in Some Bi- and Tricyclic *N*-Nitrosoamines[1]

David R. Battiste and James G. Traynham*

Coates Chemical Laboratories, Louisiana State University, Baton Rouge, Louisiana 70803

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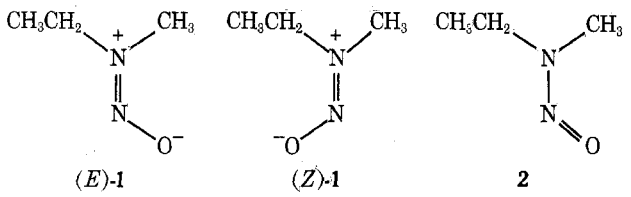
In acyclic *N*-nitrosoamines, the barrier to rotation about the N–N bond, revealed by nuclear magnetic resonance spectra, gives rise to diastereomeric structures. We have prepared a series of bi- and tricyclic *N*-nitrosoamines with a nitrogen in one of the bridges and adjacent to a bridgehead (compounds **3–7**) and investigated their structures by NMR techniques, including the use of europium shift reagent. *N*-Nitrosoamines **3** and **4** were obtained as single compounds, with the nitroso oxygen anti to the vicinal bridgehead, and **5–7** were obtained as mixtures of nonequilibrating diastereomers. The size of the heterocyclic ring influences the geometry between the bridgehead hydrogen (or methyl) and the NNO group sufficiently to account for these differences.

N-Nitrosoamines are interesting as a class of compounds because they are strongly carcinogenic and because their structures are poorly represented by conventional, uncharged valence-bond formulas. This paper is concerned with a structural study of some bi- and tricyclic compounds in which the *N*-nitrosoamine (NNO) group is a member of a ring bridge and is adjacent to a bridgehead position. The geometries of these compounds are considerably more rigid than the acyclic[2] and monocyclic[3] *N*-nitrosoamines which have been studied earlier, and they illustrate substantial 1,5 nonbonded O–H interactions that strongly influence diastereomer ratios.

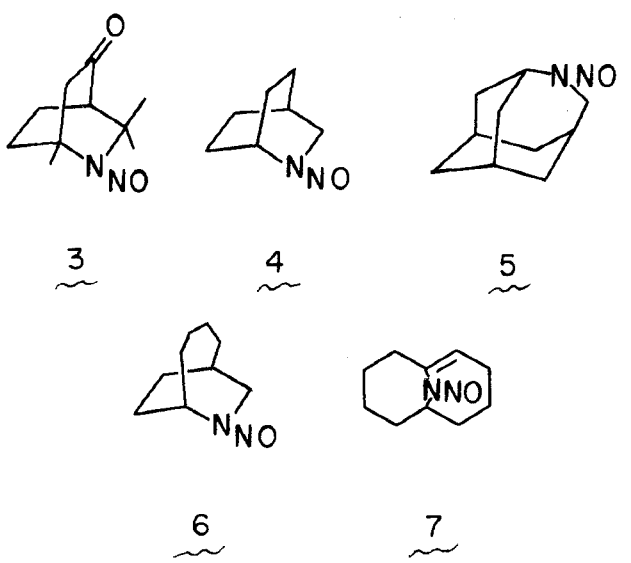
The nuclear magnetic resonance (NMR) spectrum of *N*-nitrosodimethylamine reveals that the two methyl groups are magnetically nonequivalent up to about 156°.[4] The substantial energy barrier to rotation about the N–N bond[4,5] gives rise in unsymmetrical *N*-nitrosoamines to diastereomeric structures [e.g., (*E*)-**1** and (*Z*)-**1**] which are

formed together but give distinguishable NMR spectra.[2] The downfield chemical shifts of protons in the *N*-alkyl groups are comparable to those in structurally related carbocations.[6] These data virtually require the use of a zwitterionic formulation [(*E*)-1 and (*Z*)-1] rather than a conventional uncharged one (**2**).[7]



(*E*)-1 (*Z*)-1 **2**

We have prepared several bi- and tricyclic *N*-nitrosoamines (**3–7**) and investigated their structures by NMR techniques, including the use of europium shift reagent.[3,8,9] Compounds **3** and **4** each were obtained as a single configuration, but **5**, **6**, and **7** each was obtained as a nonequilibrating mixture of isomers. The ring size of the heterocyclic ring affects the geometrical relationship between the bridgehead hydrogen and the NNO moiety enough to account for these differences.



3 **4** **5** **6** **7**

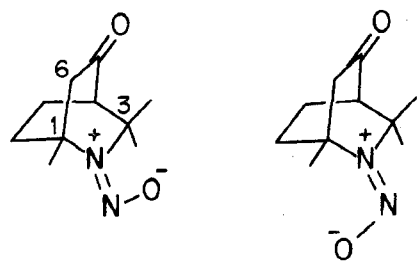
These *N*-nitrosoamines were prepared by treatment of the corresponding amines (or ammonium chlorides) with aqueous nitrous acid. The product which separated from the aqueous solution was extracted into an organic solvent or collected directly on a filter. It was used for the NMR studies without any fractionation attempts.

Compound 3. The first member of the series, *N*-nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (**3**), contains a carbonyl group and has the positions vicinal to NNO substituted by methyl groups. It was selected because of the moderate ease with which it can be synthesized from a commercially available cyclohexenone. The most striking feature in the NMR spectrum of **3** is the presence of only three methyl singlets (δ 1.24, 1.40, and 1.61). This feature suggests that only one configurational isomer is present. If both diatereomers of the *N*-nitrosoamine were present, there should be two sets of three singlets for the methyl groups, unless rapid equilibration were occurring. The spectrum also includes a doublet of doublets (dd, δ 2.46) and a doublet (δ 2.24), which are assigned to the methylene hydrogens adjacent to the carbonyl group.

The bridgehead methyl group (Me-1) is expected to be deshielded with respect to the other methyls, because it lies in the deshielding zone of the planar NNO group.[10] The geminal methyls at position 3 (Me-3) lie above and below the plane of the C-1 (C-3) NNO group and in the shielding cone of that group.[10] The exo Me-3 lies in the shielding cone of the carbonyl group and is therefore more shielded than the endo Me-3. Therefore, the Me-1 is assigned to the absorption at δ 1.61, the endo Me-3 to the one at δ 1.40, and the exo Me-3 to the one at δ 1.24.

The two diastereotopic hydrogens at position 6 (H-6) have different splitting patterns and chemical shifts. A Dreiding molecular model shows the appropriate geometry for W coupling[11] between the H-6 syn to NNO (syn H-6) and endo H-7, but such long-range coupling seems unlikely for anti H-6. Therefore, syn H-6 is assigned to the dd (J_{gem} = 18.5, J_w = 1.8 Hz) centered at δ 2.46, whereas anti H-6 is assigned to the doublet (J_{gem} = 18.5 Hz) centered at δ 2.24.

A europium shift reagent [Eu(fod)$_3$] study[3,9] confirmed the NMR assignments above and established that a single diastereomer was present. Plots of the chemical shifts of different hydrogens vs. the shift reagent/nitrosoamine mole ratios are linear and have the following slopes:[12] exo Me-3, 5.99; endo Me-3, 5.40; Me-1, 3.20; syn H-6, 5.07; and anti H-6, 4.64. The slopes for the three methyl groups are consistent with a single configuration, illustrated by formula **3a**. Were rapid equilibration between diastereomers **3a** and **3b** occurring, we would expect the difference in slopes for the Me-1 and end Me-3 to be much smaller. The larger slopes for the two Me-3 than for the Me-1, even though they lie in the shielding cone of the NNO group, are compelling evidence for the spatial relationships between each Me and the Eu complex required by formula **3a**.

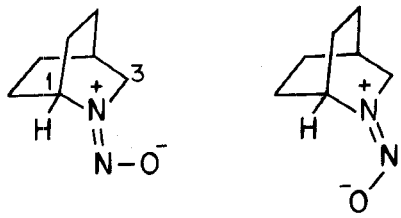


3a **3b**

Configuration **3a** is in accord with previously studied examples, for which the major *N*-nitrosoamine diastereomer in a mixture was found to have the nitroso oxygen anti to the more bulky substituent on nitrogen.[2,3] It differs from them, however, in that the methyl groups in **3** are essentially locked in place with respect to the plane of the NNO group. The steric interaction between NNO and Me-1 in configuration **3b**, unrelieved by partial rotation as is possible in acyclic *N*-nitrosoamines, is apparently too large to permit NMR-detectable amounts of **3b** to exist along with **3a**. Would a hydrogen rather than a methyl at position 1 affect the diastereomer ratio similarly? To answer that question, we prepared and investigated the parent bicyclic *N*-nitrosoamine, **4**.

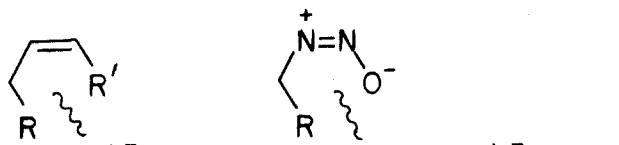
Compound 4. The NMR spectrum of *N*-nitroso-2-azabicyclo[2.2.2]octane (**4**) includes only one set of signals for the hydrogens at position 1 (H-1) and at position 3 (H-3), and it does not undergo change when the solution is cooled to −40°. These data indicate that, as with **3**, only one configuration was present. The effect of Eu shift reagent on the chemical shift of H-1 is substantially less than the effect for H-3. Linear plots of chemical shifts vs. the Eu: NNO mole ratios have slopes[12] of 4.33 for H-1 and 9.39 for H-3. Therefore H-1 must be anti to the Eu complexing site, and the configuration is represented by formula **4a**. Even a bridgehead hydrogen is sufficient to preclude the appear-

ance of NMR-detectable amounts of the diastereomer of **4a** (**4b**).



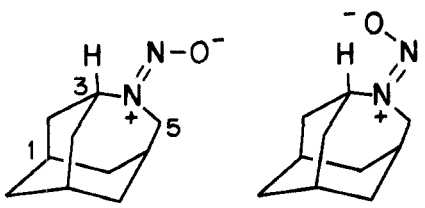
4a **4b**

The nonbonded O–H interaction which so effectively disfavors the isomers of **3** and **4** with the nitroso oxygen syn to the bridgehead is quite similar to that which has been named pseudoallylic $A^{1,3}$ strain in other systems[13] (R = H in our system).



allylic $A^{1,3}$ strain pseudo-allylic $A^{1,3}$ strain

Compound 5. The substitution pattern in the vicinity of the NNO group in **5** (*N*-nitroso-4-azahomoadamantane, *N*-nitroso-4-azatricyclo[4.3.1.$1^{3,8}$]undecane) is the same as in **4**, but the NNO group is now in a more flexible seven-membered ring. The NMR spectrum of **5** includes two doublets (^3J = 3.9 Hz), one at δ 3.65 and one at δ 4.43, with relative intensities of 87:13 and combined relative intensity equivalent to two hydrogens. These signals must be assigned to the NCH_2 (position 5, H-5) in two configurations (relative abundance 87:13) of **5** (**5a** and **5b**).[14] In accord

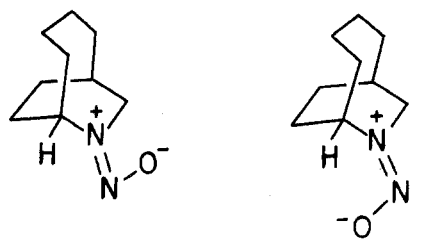


5a **5b**

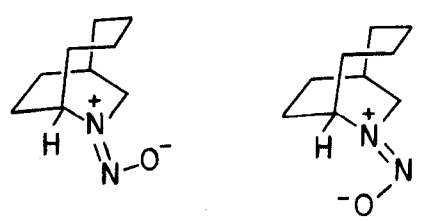
with the relative chemical shifts demonstrated for other *N*-nitrosoamines,[2] we would assign the syn H-5 (**5a**) to the δ 3.65 signal, and the anti H-5 (**5b**) to the δ 4.43 one. This assignment is confirmed by the Eu shift reagent data. The effect of the Eu reagent on the δ 3.65 signal is much larger (slope[12] = 8.02) than on the δ 4.43 signal (slope[12] = 3.85). Corresponding slopes[12] are obtained for the bridgehead hydrogen vicinal to NO (H-3): 10.1 for syn H-3, 3.85 for anti H-3.[15]

Why do we find both diastereomers of **5** but only one of **3** and **4**? The close approach of O and H-3 in a symmetrical Dreiding model of **5b** is substantially relieved by twisting along the two-atom bridge. Permitted twisting in the model of **5b** is more extensive (35–40° for the dihedral angle between the bridgehead hydrogen and the plane of the NNO group) than in the model for **4b** (dihedral angle of 10–15°). Twisting in the actual compounds is probably less than these angles, because it introduces other strains, but it is probably enough to account for the appearance of the minor diastereomer, **5b**, along with the major one, **5a**.

Compound 6. While maintaining a bridgehead and a methylene position bound to nitrogen as in **4** and **5**, *N*-nitroso-7-azabicyclo[4.2.2]decane (**6**) incorporates the NNO group into an eight-membered ring. The NMR spectrum of **6** is complex, but we have been able to make peak assignments by use of Eu shift reagent and decoupling experiments. The deciphered spectrum reveals the coexistence of four diastereomers: two configurations of the NNO group and two conformations of the eight-membered ring. Formulas **6a–d** represent these four diastereomers.



6a **6b**



6c **6d**

The NMR absorptions are described in succession from those most downfield to those most upfield. Two broad multiplets appear at δ 5.04 and 4.56. The slopes[12] for the Eu shift reagent study are 8.5 and 10.2, respectively. Therefore the δ 5.04 multiplet is assigned to the anti H-6 of **6a** and **6c**, and the δ 4.56 one to the syn H-6 of **6b** and **6d**.[16] A dd pattern is partly obscured by the δ 4.56 multiplet, but it clearly emerges when Eu shift reagent is added to the solution. It (δ 4.46) and a second dd (δ 4.09) with identical coupling constants (J_{gem} = 13.8, J_{vic} = 4.0 Hz) are affected moderately and equally by the addition of Eu shift reagent (slopes[12] of 6.3). One of these absorptions is assigned to the diastereotopic anti H-8 of **6b** or **6d**, and the other absorption to the anti H-8 of **6d** or **6b**.

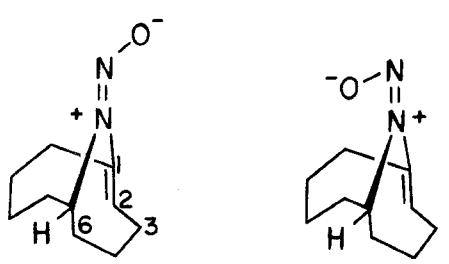
A multiplet centered at δ 3.86 and a dd centered at δ 3.18 show the same J_{gem} = 16.0 Hz and are both shifted strongly by Eu shift reagent (slopes[12] 11.9 and 10.1, respectively). These two absorptions are assigned to the diastereotopic syn H-8 of **6b** and **6d**, one to the one and one to the other. A decoupling experiment showed that all of the H-8 assigned above are coupled to the same hydrogen, presumably the bridgehead H-1, whose absorption is included in the broad envelope at δ 2.70–1.00.

We have estimated the isomer ratios by use of the ratios of integrated intensities of some absorptions in the NMR spectrum. The intensity ratio for the syn H-8 signals (δ 3.86 and 3.18) is 1:1 and that for the δ 3.18:δ 4.09 (syn H-8:anti H-8) absorptions is 58:42 (1.38:1). The ratio of the anti H-6:syn H-6 absorptions in the Eu-shifted spectra (to resolve the syn H-6 and an anti H-8 absorption) is also about 58:42. Therefore it appears that the two different ring conformers are about equally abundant in the mixture (but not rapidly equilibrating), and the two configurations of the NNO group are present in a ratio of about 58:42. The syn H-6 configuration is the less abundant one, but the geometry[14] which forces H-6 well below the plane of the NNO

group also substantially relieves the nonbonded O–H interaction, which was much more effective in compounds **3–5**.

Compound 7. *N*-Nitroso-11-azabicyclo[4.4.1]undec-1-ene (**7**) was prepared from the parent amine, which was available in our laboratory from an earlier, unrelated study.[17] Two features distinguish it from the other *N*-nitrosoamines in this series: the ring nitrogen is attached to two bridgehead carbons, and one of them is unsaturated. The NMR spectrum of **7** consists of two broadened triplets, δ 5.88 and 5.73, both with ^3J = 6.0 Hz; a broad multiplet centered near δ 5.05; and a large, broad absorption at δ 2.90–1.00. The combined area of the two triplets is equivalent to the area of the middle multiplet, and each area is equivalent to one hydrogen. The triplet absorptions are assigned to C=CH (H-2) in two configurations. The addition of Eu shift reagent resolved the middle broad multiplet into two absorptions, which appeared in a 40:60 ratio. The downfield portion, which was the lesser portion and which appeared to be centered originally at about δ 5.15, was shifted more extensively than the upfield portion, centered originally at about δ 5.02 (slopes[12] 14.4 and 5.5, respectively). The more extensively shifted absorption is assigned to syn H-6, and the other to anti H-6.[18] The major isomer again has the bridgehead H anti to the nitroso O. Even though H-6 lies essentially in the plane of the NNO group (a Dreiding model makes substantial twisting appear improbable), it is not so close to the syn-O as is the vicinal bridgehead H in **3–5**.

The spectrum for **7** does not suggest that nonequilibrating ring conformations coexist, as does the spectrum for **6**.



7a 7b

Experimental Section

Boiling and melting points are uncorrected; melting points were obtained with a Thomas-Hoover capillary melting point apparatus. Nuclear magnetic resonance (NMR) spectra were obtained on Varian Model A-60A and HA-100 spectrometers; tetramethylsilane was used as internal standard; Mr. David LaTour of these laboratories assisted with the 100-MHz spectra. Element microanalyses were obtained by Mr. Ralph Seab of these laboratories and by Galbraith Laboratories, Inc.

***N*-Nitroso-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one (3).** A mixture prepared by adding piperitenone[19] (1.40 g, 9.1 mmol) to chilled aqueous ammonia (27 ml of 28.7% solution) was stirred at 2–4° for 120 hr,[20] saturated with sodium chloride, and extracted with ethyl ether. The ether solution was extracted with 15 ml of 6 *M* hydrochloric acid. The aqueous solution was made basic (pH 11–12) and extracted with two 20-ml portions of ethyl ether. This ether extract was dried and distilled. 1,3,3-Trimethyl-2-azabicycl[2.2.2]octan-5-one,[20] bp 80–83° (0.3 mm), was obtained in 26% yield (394 mg). A portion (258 mg, 1.55 mmol) of the amine was dissolved in 12 *M* hydrochloric acid (0.17 ml). This solution was added by drops from a syringe to a stirred, ice-cold solution of sodium nitrite (140 mg, 2.0 mmol) in water (2 ml). The mixture was stirred for 0.5 hr at 0°, allowed to warm to room temperature, heated at 45–50° for 2 hr, allowed to cool, and extracted with two 3-ml portions of carbon tetrachloride. When the carbon tetrachloride was removed in vacuo, the *N*-nitrosoamine (**3**) was obtained in 38% yield (114 mg): mp 125.5–126.5°; NMR (CCl_4) δ 2.46 (dd, 1, J_{gem} = 18.5, J_w = 1.8 Hz, syn H-6), 2.24 (d, 1, J_{gem} = 18.5 Hz, anti H-6), 2.13–1.65 (m, 4, H-7 + H-8), 1.61 (s, 3, CH_3-1), 1.40 (s, 3, endo CH_3-3), and 1.24 (s, 3, exo CH_3-3).

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.2; H, 8.2; N, 14.3. Found: C, 60.9; H, 8.3; N, 14.5.

***N*-Nitroso-2-azabicyclo[2.2.2]octane (4).** A mixture prepared by adding by drops a solution of sodium nitrite (1.79 g, 2.6 mmol) in water (3 ml) to a solution of 2-azabicyclo[2.2.2]octane[21] (2.42 g, 2.2 mmol) in 8 *M* hydrochloric acid (2.7 ml) was stirred at 75–80° for 3 hr, allowed to cool to room temperature, and filtered. The collected solid (**4**) was air dried; the yield was 62% (1.78 g); mp 138.5–141.5° (lit.[22] mp 140–142°); NMR (CCl_4) δ 4.82 (br m, 1, H-1), 3.45 (d, 2, ^3J = 3.0 Hz, H-3), 2.34–1.50 (br m, 9).

***N*-Nitroso-4-azatricyclo[4.3.1.1^{3,8}]undecane (5).** 4-Azatricyclo[4.3.1.1^{3,8}]undecane[23] was synthesized by rearrangement of 2-adamantanone oxime (mp 164.5–165.5°) in polyphosphate ester[24] and reduction of the lactam with lithium aluminum hydride.[23] The ammonium chloride (mp >300°) was isolated in 34% overall yield from oxime. Nitrosation was accomplished by adding a solution of the ammonium chloride (400 mg, 2.14 mmol) in water (2 ml, containing 5 drops of 6 *M* hydrochloric acid) to a stirred solution of sodium nitrite (167 mg, 2.41 mmol) in water (1 ml) and heating the mixture at 50–60° for 1 hr. The fluffy white solid which separated was collected by filtration and dried over phosphoric anhydride in vacuo. The nitrosoamine (**5**) was obtained in 65% yield (250 mg): mp 214–214.5°; NMR ($CDCl_3$) δ 5.32 (m, H-3), 4.43 (d, ^3J = 3.8 Hz, anti H-5), 3.65 (d, ^3J = 3.5 Hz, syn H-5), 2.60–1.35 (br m, remainder of H).[25]

***N*-Nitroso-7-azabicyclo[4.2.2]decane (6).** Chlorosulfonyl isocyanate (5.7 g, 4.0 mmol) was added in 45 min to stirred cyclooctatetraene (5.2 g, 5.0 mmol) heated at 50° in a 100-ml, three-neck flask. The mixture was stirred at 50° for 7 hr. Upon cooling to room temperature, the dark mixture solidified and was dissolved in acetone (20 ml). That solution and a 4 *M* sodium hydroxide solution were added dropwise concurrently to aqueous (20 ml) acetone (10 ml). The pH was maintained at 7 and was monitored closely with a pH meter. From the resulting solution, by extraction with dichloromethane, 8-azabicyclo[4.2.2]deca-2,4,9-trien-7-one, mp 137–138° (lit.[26] mp 139–140°), was isolated in 49% yield (3.61 g).

The unsaturated lactam in methanol solution was reduced in a Paar apparatus with hydrogen and palladium on charcoal catalyst to the saturated lactam (8-azabicyclo[4.2.2]decan-7-one), mp 70–71° (lit.[27] mp 73°). The lactam (1.02 g, 6.79 mmol) was converted to the amine by reduction with lithium aluminum hydride in tetrahydrofuran solution. An ether solution of the amine was treated with hydrogen chloride; the hygroscopic ammonium chloride (444 mg, 38%) which precipitated was dried in vacuo over phosphoric anhydride.

Anal. Calcd for $C_9H_{18}ClN$: C, 61.5; H, 10.4. Found: C, 61.5; H, 10.3.

A mixture of the 7-azabicyclo[4.2.2]decane hydrochloride (100 mg), water (1.0 ml), and sodium nitrite (82.0 mg, 1.19 mmol) was heated at 50–60° for 1 hr, stirred overnight at room temperature, and filtered. The white solid *N*-nitrosoamine, **6**, was dried in vacuo over phosphoric anhydride: yield 68% (74.5 mg); mp 168–170°; NMR (CCl_4) δ 5.40 (m, anti H-6), 4.56 (m, syn H-6), 4.46 (dd, J_{gem} = 13.8, ^3J = 4.0 Hz, anti H-8), 4.09 (dd, J_{gem} = 13.8, ^3J = 4.0 Hz, anti H-8), 3.86 (br d, J_{gem} = 16.0 Hz, syn H-8), 3.18 (dd, J_{gem} = 16.0, ^3J = 6.0 Hz, syn H-8), 2.70–1.00 (br m, remainder of H).[25]

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.2; H, 9.6; N, 16.7. Found: C, 64.5; H, 9.6; N, 16.5.

***N*-Nitroso-11-azabicyclo[4.4.1]undec-1-ene (7).** To a stirred, ice-chilled sample of freshly distilled 11-azabicyclo[4.4.1]undec-1-ene[17] [bp 79–80° (3 mm), 421 mg (2.13 mmol)] was added 12 *M* hydrochloric acid (0.2 ml). After 5 min, a solution of sodium nitrite (167 mg, 242 mmol) in water (2 ml) was added to the ice-chilled, stirred ammonium chloride solution by drops. A brown solid immediately precipitated from the solution and, after the mixture had warmed to room temperature, was collected by filtration (233 mg, 61%). The crude nitrosoamine (**7**) was purified by preparative layer chromatography on silica gel with 2:1 cyclohexane–ethyl acetate: mp 65–67°; NMR (CCl_4) δ 5.88 (t, ^3J = 6.0 Hz, anti C=CH), 5.73 (t, ^3J = 6.0 Hz, syn C=CH), 5.14 (shoulder, syn H-6), 5.02 (br m anti H-6), and 2.90–1.00 (br m, remaining H).[25]

Eu Shift Reagent Studies. Europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) [Eu(fod)$_3$] was dried for at least 24 hr in vacuo over phosphoric anhydride before use. In a typical study, separate solutions of accurately weighed amounts of *N*-nitrosoamine and Eu(fod)$_3$ in the same solvent (CCl_4 or

$DCCl_3$) were prepared. The *N*-nitrosoamine solution (0.2–1 *M*) was transferred to a clean, dry NMR tube, and the spectrum was recorded. A measured amount of the $Eu(fod)_3$ solution (approximately 0.6 *M*) was added to the NMR tube from a microliter syringe, the mixture was thoroughly mixed by shaking, and the spectrum was again recorded. Further additions (6–15) and recordings were made in like manner. The ranges of Eu:NNO mole ratios for the different *N*-nitrosoamines follow ($\times 10^{-2}$): **3,** 1.68–42.1; **4,** 2.41–20.8; **5,** 2.1–23.5; **6,** 0.76–91.3; and **7,** 0.74–11.7. All of the plots of change in chemical shift vs. Eu:NNO mole ratio are linear. The data were treated by a least-squares computer program by Mr. J. H. Streiffer of these laboratories, and the calculated lines have an average correlation coefficient of 0.995 (range 0.983–0.9998). The calculated slopes[12] are reported in the discussion section.

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Registry No.—3a, 54410-47-8; **4a,** 54410-48-9; **5a,** 54410-49-0; **5b,** 54410-50-3; **6a,c,** 54410-51-4; **6b,d,** 54410-52-5; **7a,** 54410-53-6; **7b,** 54410-54-7; piperitenone, 491-09-8; 1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-5-one, 33069-72-6; sodium nitrite, 7632-00-0; 2-azabicyclo[2.2.2]octane, 280-38-6; 4-azabicyclo[4.3.1.$1^{3,8}$]undecane, 22776-74-5; 2-adamantanone oxime, 4500-12-3; cyclooctatetraene, 629-20-9; 8-azabicyclo[4.2.2]deca-2,4,9-trien-7-one, 17198-06-0; 8-azabicyclo[4.2.2]decan-7-one, 17198-07-1; 7-azabicyclo[4.2.2]decane hydrochloride, 54410-44-5; 11-azabicyclo[4.4.1]undec-1-ene, 7183-74-6.

References and Notes

(1) (a) Based on the Ph.D. Dissertation of D.R.B., Louisiana State University, Baton Rouge, La., May 1974. Grateful acknowledgment is made to the Dr. Charles E. Coates Memorial Fund of the LSU Foundation donated by George H. Coates for financial aid toward the preparation of that dissertation. (b) Presented in part at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1, 1974, No. ORGN 21.

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(12) Slopes for the Eu shift reagent plots are given in units of ppm/Eu reagent:*N*-nitrosoamine mole ratio; they were calculated by use of a least-squares computer program.

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(14) A referee cited a related example reported by J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26,** 949 (1970). Homoadamantan-4-one oxime was obtained as a single isomer (OH syn to position 5) from weakly acidic solution but as a mixture of isomers, syn:anti ~ 2:3, from strongly basic solution. This mixture ratio indicates that, for oxime formation in strongly basic solutions, stereochemical influences on or in intermediates determine isomer distribution more than do the relative energies in the oxime isomers themselves.

(15) Without Eu present, the absorptions for the syn and anti H-3 are not resolved but appear as a nearly symmetrical multiplet centered near δ 5.22. Eu complexing separates the signals, and the more extensively shifted one is assigned to syn H-3.

(16) This syn–anti assignment is clearly required by the shift reagent data but contrasts with the relative chemical shifts for syn and anti methine H in acyclic *N*-nitrosoamines.[2] Dreiding models of **6a–d** show that H-6 is forced to lie about 20° below the C-6 (C-8) NNO plane, i.e., in the shielding cone of the NNO group.[10] Shielding is more extensive on the syn side of the NNO than on the anti side.[10]

(17) R. R. Lilienthal, Ph.D. Dissertation, Louisiana State University, Baton Rouge, La., Dec 1971.

(18) Here the syn–anti assignments and relative chemical shifts agree with those for methine H in acyclic systems.[2,14] H-6 is essentially in the (deshielding) plane of the NNO group.

(19) Dr. J. J. Beereboom, Pfizer Central Research, sent us a generous gift of piperitenone (3-methyl-6-isopropylidene-2-cyclohexen-1-one), which was purified according to the procedure recommended by J. J. Beereboom, *J. Org. Chem.*, **31,** 2026 (1966): bp 90–95° (10 mm); NMR (CCl_4) δ 5.85 (m, 1, C=CH), 2.83–1.65 (m, 4, CH_2CH_2), 2.08 (s, 3, CH_3), 1.92 (s, 3, CH_3), 1.85 (s, 3, CH_3).

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(21) We acknowledge with gratitude gifts of a small sample of 2-azabicyclo[2.2.2]octane from Professor Paul Gassman, The Ohio State University, which permitted us to begin our study, and a generous one from Dr. F. J. Villani, Schering Corp., which permitted us to complete it.

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(25) For relative intensities of these NMR absorptions, see discussion section.

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