Face Selection in Reactions of 5,7-Diazaadamantan-2-one Derivatives: Mutual Influence of Remote Substituents

Elena M. Gonikberg and William J. le Noble*

Department of Chemistry, State University of New York, Stony Brook, New York 11794

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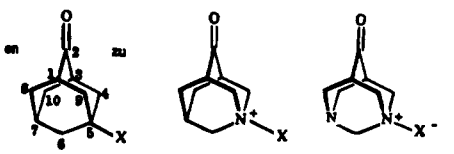
When one of the nitrogen atoms in 5,7-diazaadamantan-2-one[1] (**4**) is quaternized, for example, as in **3**-O, carbonyl reduction occurs principally at the *zu* face to give alcohol (*E*)-**6**-O, in accord with Cieplak-type transition state hyperconjugation. The ratio in this reduction is somewhat less than in that of the previously reported monoaza *N*-oxide **2**-O, which is attributed to the effect of hyperconjugation in the initial state of **3**-O. If the parent diaza ketone **4** is reduced first to the corresponding diaza alcohol **5** and if this is then oxidized to **6**-O, the *Z*-isomer is the principal product. The stereochemistry of this latter reaction is also considered to be a result of extended hyperconjugation. Virtually identical data are obtained with the methyl iodide salts. It is concluded that the effect of remote substituents is mutual and that this fact can be exploited to influence, even reverse, the stereochemical outcome of a synthesis by manipulation of the *sequence* of the individual steps.

Introduction

The subject of face selection in addition and elimination processes continues to engage the interest of many chemists.[2] Our own efforts in this arena have been concentrated on electronic effects; they were based on 2-adamantanone and its derivatives as the stereochemical test device with which to probe face differentiation, a substituent at the remote 5-position serving as both polarizer and indicator.[3] These probes have the dual advantage[4] of a virtual steric equivalence of the two faces at C-2 and of avoiding the conformational uncertainty that characterizes such studies with open-chain compounds or even simple rings. One disadvantage of the use of remote substitution to create face differentiation is of course the fact that the consequent product and rate ratios are rather modest (except in solvolysis[5] and its reverse, carbocation capture[6]). In order to bring about more robust ratios, we recently began[7] to use an isoelectronic analog of our mainstay **1**-F in which the C-F group is replaced by an N-O function, as in **2**-O. The positive charge at this bridgehead site does indeed produce product ratios 1 order of magnitude larger than those observed with **1**-F.[8] Virtually identical increases in these ratios were seen with an analogous betaine, **2**-$CH_2CO_2^-$, and the methyl iodide derivative, **2**-MeI.



1-X **2-X** **3-X**

We have now exploited this opportunity still further by substituting the other remote bridgehead site (C-7-H) by nitrogen as well; this gives rise to the still isoelectronic 5,7-diazaadamantan-2-one derivative **3**-O. Several reasons underlie our predilection of this structure. Firstly, **3**-X has the same esthetically pleasing symmetry as do the parent ketones **1**-X. Secondly, it restores the differentiating groups to the same distant positions that we dealt with in compounds **1**. Thirdly, we anticipated that hyperconjugation in the initial state might affect the outcome, by transferring positive charge from one nitrogen to the other in the N–C–N (aminal) chain segment. Lastly, the most important to us, we hoped that the chemical sensitivity of nitrogen (as compared to that of C-H) might allow us to study interactions between the substituents N-5 and C-2 in *both* directions. These last two speculations are elaborated further below.

Results and Discussion

Diaza alcohol **5** has been described by Stetter,[9] but his preparation from the precursor 1,3-bis-phenylthio ketone involves an elaborate and difficult-to-reproduce four-step procedure: diacetylation with concomitant loss of formaldehyde, Raney nickel desulfurization with simultaneous reduction of the carbonyl group, hydrolysis of the bis-acetamide, and, finally, reintroduction of formaldehyde. He attempted to achieve the same result in a single direct step by means of Raney nickel but reported that this reaction produced only a small amount of the

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(1) The correct name for this compound is 1,3-diazaadamantan-6-one. For the sake for convenience, we have again used the numbering system based on structure **1** throughout this paper. In those structures in which neither nitrogen atom is quaternary and in which C-2 is tetragonal and carries one substituent, this substituent is understood to "point to the right".

(2) A summary is scheduled to appear in the form of a tetrahedron report by B. Gung.

(3) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

(4) For a listing of other probes chemists have used to address this question, see: Kaselj, M.; Adcock, J. L.; Luo, H.; Zhang, H.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 7088.

(5) (a) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3839. (b) Adcock, W.; Coope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411.

(6) (a) Lin, M.-h.; Cheung, C.-K.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 6562. (b) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874.

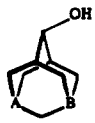
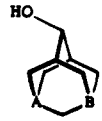
(7) Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916. See also: Fernandez, M. J.; Galvez, E.; Lorente, A.; Iriepa, I.; Soler, J. A. *J. Heterocycl. Chem.* **1989**, *26*, 307.

(8) Lau, J.; Gonikberg, E. M.; Hung, J.-t.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421.

(9) Stetter, H.; Dieminger, K.; Rauscher, E. *Chem. Ber.* **1959**, *92*, 2057.

0022-3263/95/1960-7751$09.00/0

Table 1. ^{13}C NMR Resonances of Mono- and Diazaadamantane Derivatives in D_2O

structure	A	B	compd	C-1,3	C-2	C-4,9	C-6	C-7	C-8,10
	HC	N		47.26	221.44	59.22	56.31	25.99	37.64
	N	N	**4**	47.73	208.20	58.37	71.92		58.37
	HC	NO	**2**-O	39.98	92.76	68.55	71.64	28.49	28.76
	N	NO	**3**-O	45.16	96.11	71.04	87.26		54.12
	ON	NO	**7**	45.59	93.68	69.46	89.63		69.46
	HC	N		33.74	73.06	52.13	58.55	26.20	35.20
	N	N	**5**	34.35	73.57	52.75	74.65		57.84
	HC	NO		36.37	71.33	75.67	67.90	28.60	28.50
	N	NO	(*Z*)-**6**-O	39.20	69.35	67.60	87.12		55.06
	ON	NO	**8**	41.04	68.14	66.36	89.49		70.30
	HC	N		33.95	72.96	57.82	58.84	26.73	29.46
	HC	NO		35.22	72.04	70.62	69.11	29.48	25.91
	N	NO	(*E*)-**6**-O	37.93	70.59	71.80	87.54		50.56

bis-thio alcohol. Kuznetsov and Zefirov[10] later noted that 1-(phenylthio)-5,7-diazaadamantan-2-one upon treatment with Raney nickel smoothly eliminates sulfur with simultaneous reduction of the keto group; this led us to try the direct conversion into **5** once again, with Raney nickel in 2-propanol. NMR monitoring of the reaction showed that the carbonyl reduction occurs first and that subsequent desulfurization does take place to produce a complex and viscous mixture; **5** could be isolated from it in 21% yield. This is comparable to the overall yield obtained by Stetter, but the savings in time and reagents are considerable. The oxidation of the alcohol to give ketone **4** was also improved over the tedious procedure of Kuthan *et al.*,[11] who used chromium trioxide in acetic acid to obtain a 48% yield. Use of silver carbonate on celite as the oxidizing agent in a very simple procedure[12] led to an 83% yield. Careful oxidation of **4** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the mono-*N*-oxide **3**-O.

The ^{13}C NMR spectra were analyzed thoroughly because they form the basis of the assignments of configuration as well as of the analyses. The resonances could be readily assigned on the basis of DEPT experiments and comparisons with the previously studied monoaza analogs; the results are given in Table 1.

The first two ketones mentioned in the Table have the carbonyl resonances in their normal low-field positions, but when one or both of the amine functions are converted into the *N*-oxides, these resonances (in D_2O) move upfield by well over 100 ppm. This is attributed to diol formation as we have discussed previously.[7] Several of the compounds were also measured in other media ($CDCl_3$, DMSO-d_6, and methanol-d_4). The data are reported in the supporting information; here it need be mentioned only that both the ^{13}C and ^1H NMR spectra are strongly solvent and pH dependent.

Reduction of **3**-O with sodium borohydride gave a mixture of two diastereomeric alcohols which was analyzed as depicted in Figure 1. The additivity calculations were based on the six mono-*N*-oxides described in Table 1, and the figure clearly shows that the calculated values of the resonances of C-4,9 and C-8,10 agree well with those observed. The bridgehead proton signals were also well separated, and integration proved the ratio to be 88:12, with the *E*-isomer being the major one.

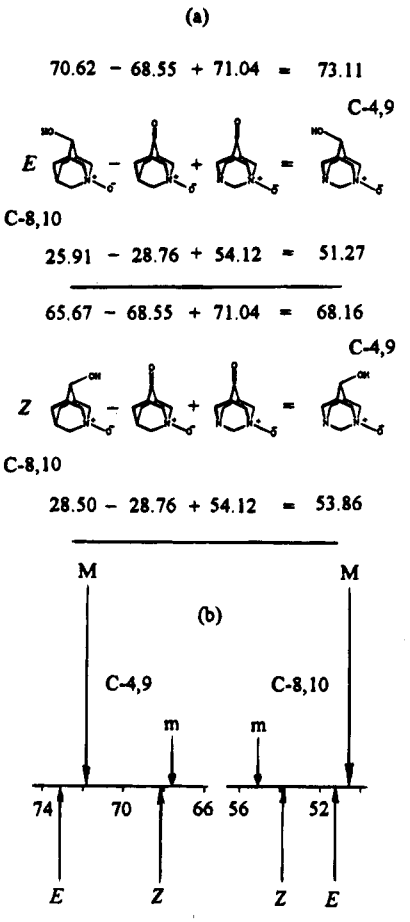
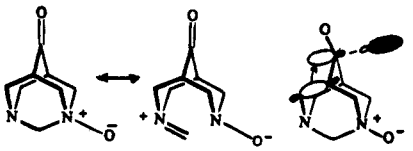


Figure 1. (a) How the chemical shifts of the signals of C-4,9 and C-8,10 in (*E*)- and (*Z*)-**6**-O are calculated from those in known model compounds. (b) Match between the computed values and the major (M) and minor (m) signals observed in the reduction of **3**-O. The major and minor signals are reversed in the mixture obtained in the oxidation of **5**; see also Figure 2.

This ratio, although substantial compared to that observed in the reduction of **1**-F, is less than one-half of that obtained with **2**-O. As noted, this was anticipated as X-ray diffraction studies have shown[13] the effect of ground state hyperconjugation to be large in aminals in

(10) Kuznetsov, A. I.; Zefirov, N. S. *Russ. Chem. Rev.* **1989**, *58*, 1033.
(11) Kuthan, J.; Palecek, J.; Musil, L. *Collect. Czech Chem. Commun.* **1973**, *38*, 3491.
(12) (a) Fetizon, M.; Golfier, M. *C. R. Acad. Sci. Paris* **1968**, *267c*, 900. (b) Dekkers, A. W. J. D.; Verhoeven, J. W.; Speckamp, W. N. *Tetrahedron* **1973**, *29*, 1691.
(13) (a) Kurkutova, E. N.; Goncharov, A. V.; Zefirov, N. S.; Palyulin, V. A. *Zh. Strukt. Khim.* **1976**, *17*, 591. (b) McCabe, P. H.; Milne, N. J.; Sim, G. A. *Acta Crystallogr.* **1989**, *C45*, 114. (c) Goncharov, A. V.; Panov, V. N.; Maleev, V. N.; Potekhin, K. A.; Kurkutova, E. N.; Struchkov, Y. T.; Palyulin, V. A.; Zefirov, N. S. *Dokl. Akad. Nauk. SSSR* **1991**, *318*, 148.

which one nitrogen atom is quaternized; the two C–N bonds may differ in length by well over 0.1 Å. As a result, the positive charge of the quaternary nitrogen is partly transferred to the formally neutral nitrogen, and of course this tempers the difference in donating ability of the two pairs of bonds that are vicinal to and periplanar with the carbonyl group in the transition state of nucleophilic addition. The preference of the nucleophile for the *zu* face is in the same direction as in **1**-F and **2**-O, thus further supporting our position that transition state hyperconjugation in the Cieplak sense controls the stereochemistry.



We had an additional interest in this system, namely, to pursue the preparation of alcohols **6**-O from the other direction: *i.e.*, by the oxidation of one nitrogen atom in the C_2-symmetrical alcohol **5**. The idea was that the transition state of that reaction should be subject to the same type of stabilization that characterizes the addition process to the trigonal carbon in **3**-O: Then, as just noted, the vicinal bonds least deactivated by the amine oxide function control the stereochemistry. In the oxidation to be considered now, the vicinal bonds antiperiplanar to the C-2-H function should control the favored configuration. Thus, the *Z*-isomer should now dominate. And indeed, when that reaction was carried out, this isomer was found to be in excess by a factor of 69:31 (see Figure 2). The two ways to produce alcohol **6**-O from **4** are characterized by opposite stereochemistry, as shown in Scheme 1; the changeover is brought about but by the *sequence* of the two steps! A similar study was carried through in its entirety with the methyl iodide salt **3**-MeI, and the results were almost identical. Thus, reduction of this salt gave the two alcohols in the ratio *E*:*Z* = 89:11; methylation of **5** gave the same two isomers in the ratio 30:70. Here, also, the stereochemistry is determined by the sequence of the two steps leading from **4** to **6**-MeI.[14]

There are a few precedents for this type of phenomenon. Thus, while the reduction of 5-bromoadamantan-2-one is known[3] to give an excess of the corresponding *E*-alcohol, W.-S. Chung has determined that this bromide hydrolyzes more slowly than the *Z*-isomer.[15] Adcock and his co-workers have concluded[16] that the ^{19}F NMR spectra of 5-substituted 2-fluoroadamantanes are affected more strongly by the substituent if the C–F and C–X bonds are antiperiplanar than if they are synperiplanar. They attributed this effect to "double hyperconjugation"; we prefer the term "extended hyperconjugation" since the effect may well be demonstrable over even greater distances.[17]

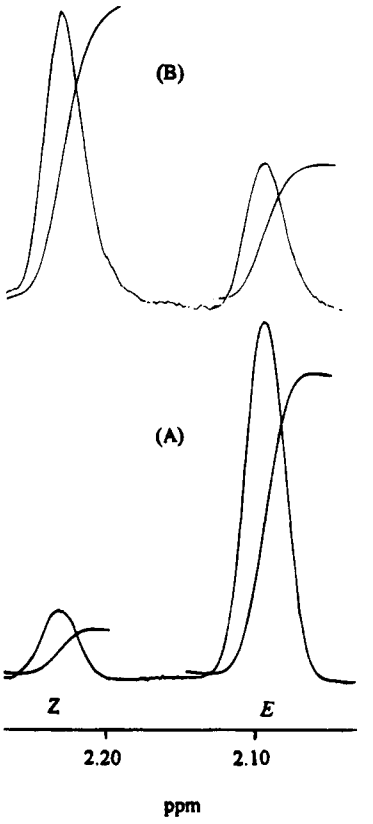
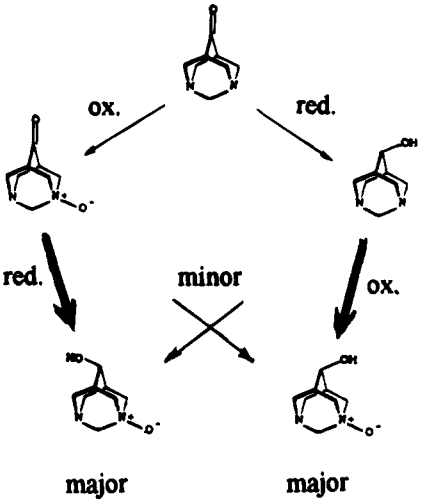
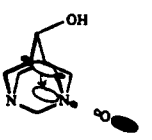


Figure 2. Resonances of H-1,3 in mixtures of the isomers of (*E*)- and (*Z*)-**6**-O in (A) the reduction of **3**-O and (B) the oxidation of **5**.

Scheme 1





The strength of the influence of the 2-substituent on the stereochemistry of oxidation appears to be reduced

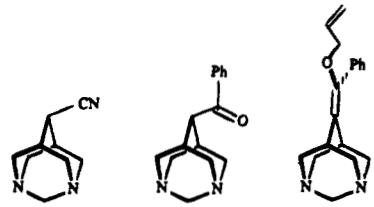
(14) An effort was made to see whether we could also find the result of the effect in the monoreduction of the bis-*N*-oxide **8**, which could be prepared from ketone **7**. Unfortunately, this attempt was thwarted by the competing reduction of the second oxide function and by the poor solubility of **8** in acetonitrile, the recommended solvent (Balicki, R. *Chem. Ber.* **1990**, *123*, 647).

(15) Chung, W.-S. Personal communication.

(16) (a) Adcock, W.; Trout, N. A. *J. Org. Chem.* **1991**, *56*, 3229. (b) Adcock, W.; Coope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411. (c)) Adcock, W.; Krstic, A. R.; Duggan, P. J.; Shiner, V. J.; Coope, J.; Ensinger, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 3140. (d) Adcock, W.; Iyer, V. S. *Magn. Reson. Chem.* **1991**, *29*, 381.

(17) (a) Oevering, H.; Paddon-Row, M. N.; Heppener, M.; Oliver, A. M.; Cotsaris, E.; Verhoeven, J. W.; Hush, N. S. *J. Am. Chem. Soc.* **1987**, *109*, 3258. (b) Kroon, J.; Oliver, A. M.; Paddon-Row, M. N.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 4868.

if its inductive power is; this is suggested by the following two experiments. Compounds **9** and **10** became available in the course of an unsuccessful effort to prepare ether **11** (with which we hoped to study the stereochemsitry of the Claisen rearrangement as we previously did with the monoaza analog[8]). The oxidation of **9** and **10** with 1 equiv



9 **10** **11**

of *m*-CPBA gave *E*/*Z*-mixtures of the mono-*N*-oxides with the *Z*-isomer in excess but now only by the small margins of 52:48 and 55:45, respectively. The isomers were readily identified in both cases by applying the ^{13}C NMR additivity procedure, as detailed in the experimental part and the supporting information pages.

We conclude as follows. The conversion of 5,7-diazaadamantan-2-one into the corresponding alcohols in which one of the nitrogen atoms is quaternized has a stereochemistry which depends on the sequence of the reduction and quaternization steps: If reduction is carried out first, the *Z*-product is predominant, and if quaternization is done first, then the *E*-product is obtained in excess. This demonstrates that the influence of substituents is mutual even when they are bound to carbons separated by three single bonds and that this fact can be exploited in synthetic sequences to affect favorable stereochemical outcomes. The interaction between the substituents is not quite as strong as the one observed earlier in quaternized 5-azaadamantan-2-ones; we attribute this fact to hyperconjugation in the initial state of the quaternized 5,7-diaza analog.

Experimental Section

1,3-Bis(phenylthio)-5,7-diazaadamantan-2-one. This compound was prepared according to the directions by Stetter.[9] ^1H NMR ($CDCl_3$): δ 7.30–7.60 (m, 10 H, Ph), 3.78 (s, 2 H, H-6), 3.36 and 3.26 (d, d, J = 12.5 Hz, 4 H, 4 H, H-4,8–10, ax, eq). ^{13}C NMR ($CDCl_3$): δ 200.96 (C-2), 137.74, 129.45, 128.98 and 128.02 (Ph), 71.58 (C-6), 64.20 (C-4,8–10), 59.46 (C-1,3).

5,7-Diazaadamantan-2-ol (5). To a suspension of 10 g of this ketone in 250 mL of 2-propanol was added 100 g of Raney nickel in 2-propanol with stirring and reflux in three portions at 10 h intervals; the hot solution was carefully decanted before the addition of each batch. After NMR analysis indicated complete reduction, the mixture was filtered through Celite and the filtrate reduced to a small volume of a yellow oil. Crystals (1.2 g, 21%) were obtained after treatment with acetonitrile (5 mL). Mp (sealed capillary): 267 °C dec (lit.[9] mp 270 °C dec). ^1H NMR (D_2O, pH 13): δ 4.23 (s, 1 H, H-2), 4.00 (s, 2 H, H-6), 3.43 (d, J = 13 Hz, 2 H, H-4,9, ax), 3.34 (d, J = 13 Hz, 2 H, H-8,10, ax), 3.07 (d, J = 13 Hz, 4 H, H-4,8–10, eq), 1.65 (s, 2 H, H-1,3). The assignments are based on COSY data. ^{13}C NMR (D_2O, pH 13): δ 74.65 (C-6), 73.57 (C-2), 57.84 (C-8,10), 52.75 (C-4,9), 34.35 (C-1,3). The assignments are based on data for the 5-azaadamantan-2-ols[7] and a DEPT experiment.

5,7-Diazaadamantan-2-one (4). A mixture of **5** (0.500 g, 3.2 mM), benzene (300 mL), and silver carbonate/Celite according to Fetizon[12] was stirred and heated to reflux overnight. After filtration of the black solid and evaporation of solvent, the residue was sublimed at 90 °C and 2 Torr to give **4** in 83% yield (0.415 g). Mp (sealed capillary): 253 °C dec (lit.[11,18] mp 92 °C). The ^1H NMR spectrum agreed with that published.[11] ^{13}C NMR (D_2O): δ 208.20 (C-2), 71.92 (C-6), 58.37 (C-4,8–10), 47.73 (C-1,3).

5,7-Diazaadamantan-2-one *N*-Oxide (3-O). A solution of *m*-CPBA (100 mg, 0.60 mM)) in methylene chloride (5 mL) was gradually added to a solution of **4** (75 mg, 0.50 mM) in the same solvent (5 mL). The mixture was stirred at room temperature for 2 h. Reduction to small volume gave a white residue which was extracted with water (3 × 5 mL). Evaporation of the water yielded the mono-*N*-oxide in 91% yield (77 mg). Mp: 272 °C dec. MS: m/z = 168 (M^+), 152 (M − 16); loss of oxygen under these conditions is common.[19] ^1H NMR (D_2O, pH adjusted to 13):[20] δ 4.09 (s, 2 H, H-6), 3.72 (d, J = 11 Hz, 2 H) and 3.27 (d, J = 11 Hz, 2 H, H-4,9, ax, eq), 3.17 (d, J = 13.5 Hz, 2 H) and 2.99 (d, J = 13.5 Hz, 2 H, H-8,10, ax, eq), 1.83 (s, 2 H, H-1,3). ^{13}C NMR (D_2O): δ 96.11 (C-2, gem diol), 87.26 (C-6), 71.04 (C-4,9), 54.12 (C-8,10), 45.16 (C-1,3). The assignments are based on known data for 5-azaadamantan-2-one *N*-oxide.[7]

In the presence of a 2-fold excess of *m*-CPBA, the *N*,*N*′-dioxide is formed with 90% yield. Mp: 195 °C dec. MS: 184 (M^+), 168 (M − O), 152 (M − 2O). ^1H NMR (D_2O at pH 13): δ 4.40 (s, 2 H, H-6), 3.97 (d, J = 11.5 Hz, 4 H) and 3.48 (d, J = 11.5 Hz, 4 H, H-4,8–10), 2.26 (s, 2 H, H-1,3). ^{13}C NMR (D_2O): δ 93.68 (C-2), 89.63 (C-6), 69.46 (C-4,8-10), 45.59 (C-1,3).

***(E)*- and *(Z)*-5,7-Diazaadamantan-2-ol 5-*N*-Oxide [*(E)*- and *(Z)*-6-O]. (a) By Reduction of 3-O.** Compound **3**-O (40 mg, 0.24 mM) was reduced with sodium borohydride (10 mg, 0.26 mM) in 1 mL of D_2O at pH 13. After 3 h of stirring at room temperature, the mixture of alcohols (*E*)- and (*Z*)-**6**-O was analyzed as described in the text; the ratio was found to be 88:12, respectively.

(b) By Oxidation of 5. A solution of *m*-CPBA (50 mg, 0.3 mM) in methylene chloride (5 mL) was slowly added to a solution of **5** (40 mg, 0.26 mM) in the same solvent (5 mL). Cloudiness set in after 0.5 h of stirring at room temperature. The solvent was evaporated and the residue extracted with D_2O (1 mL). This solution of **6**-O was analyzed by means of NMR as described in the text and found to have an *E*/*Z*-ratio of 31:69, respectively. (*E*)-**6**-O: ^1H NMR (D_2O at pH 13) δ 4.24 (bs, 3 H, H-2,6), 3.59 (m, 4 H), 3.48 (d, J = 13.5 Hz, 2 H) and 3.02 (d, J = 13.5 Hz, 2 H, H-4,8–10), 2.10 (s, 2 H, H-1,3); ^{13}C NMR δ 87.54 (C-6), 71.80 (C-4,9), 70.59 (C-2), 50.56 (C-8,10), 37.93 (C-1,3).

***(Z)*-6-O**: ^1H NMR δ 4.17 (s, 2 H, H-6), 3.98 (s, 1 H, H-2), 3.75 (d, J = 10 Hz, 2 H), 3.35 (d, J = 10 Hz, 2 H), 3.25 (d, J = 13.5 Hz, 2 H), and 2.96 (d, J = 13.5 Hz, 2 H, H-4,8–10), 2.21 (s, 2 H, H-1,3); ^{13}C NMR δ 87.12 (C-6), 69.35 (C-2), 67.60 (C-4,9), 55.06 (C-8,10), 39.20 (C-1,3). The ^1H NMR assignments were facilitated by the wide divergence in composition between the two solutions; the ^{13}C NMR assignments were additionally based on the known data for the 5-azaadamantan-2-ol *N*-oxides published previously.[7]

In the presence of a 2-fold excess of *m*-CPBA, the mixtures were transformed into the single bis-*N*-oxide **8**. ^1H NMR (D_2O, pH 13): δ 4.33 (s, 2 H, H-6), 3.98 (s, 2 H, H-2), 3.92 (d, J = 11.5 Hz, 2 H) and 3.39 (d, J = 11.5 Hz, 2 H, H-4,9, ax, eq), 3.68 (d, J = 12.5 Hz, 2 H) and 3.56 (d, J = 12.5 Hz, 2 H, H-8,-10, ax, eq), 2.26 (s, 2 H, H-1,3). ^{13}C NMR: δ 89.49 (C-6), 70.30 (C-8,10), 68.14 (C-2), 66.36 (C-4,9), 41.04 (C-1,3). The assignments were based on data published[21] for *N*,*N*′-dimethyl-5,7-diazaadamantan-2-ol diiodide.

***N*-Methyl-5,7-diazaadamantan-2-one Iodide (3-MeI).** Iodomethane (2 drops, *ca.* 0.5 mM) was added to a solution of

(18) We have no explanation for the large difference in melting point. The literature value[11] is almost certainly in error; this conclusion is based on the agreement between the ^1H NMR spectra and on a comparison of melting points for other adamantane derivatives.

(19) Kliegel, W.; Franckenstein, G.-H. *Liebigs Ann. Chem.* **1976**, 2294.

(20) For the *N*-oxides as well as for the quaternary methyl salts, the chemical shifts for all of the nuclei depend strongly on the nature of the solvent and, if in D_2O, on the pH of the solution (see supporting information, NMR spectra of **3**-O in $CDCl_3$ and D_2O at pH 4 and 13).

(21) Fernandez, M. J.; Galvez, E.; Lorente, A.; Camunas, J. A.; Sanz, J.; Fonseca, I. *Heterocycl. Chem.* **1990**, *27*, 1355.

4 (40 mg, 0.26 mM) in methylene chloride (5 mL). A white precipitate formed in the next 0.5 h. The solvent was evaporated to give 66 mg of the title salt (87%). ^{1}H NMR (D_2O at pH 13): δ 4.55 (s, 2 H, H-6), 3.88 (d, J = 12 Hz, 2 H) and 3.70 (d, J = 12 Hz, 2 H, H-4,9), 3.37 (d, J = 14 Hz, 2 H) and 3.29 (d, J = 14 Hz, 2 H, H-8,10), 2.86 (s, 3 H, *N*-Me), 2.16 (s, 2 H, H-1,3). ^{13}C NMR (D_2O): δ 80.15 (C-6), 63.26 (C-4,9), 51.00 (C-8,10), 50.90 (*N*-Me), 39.06 (C-1,3). C-2 was not observed. Use of an excess of methyl iodide did not lead to the formation of the diiodide.[22]

(*E*)- and (*Z*)-*N*-Methyl-5,7-diazaadamantan-2-ol Iodide [(*E*)- and (*Z*)-6-MeI]. (a) By Reduction of 3-MeI. Compound **3**-MeI (66 mg, 0.22 mM) was reduced with sodium borohydride (10 mg, 0.26 mM) in D_2O (1 mL) at pH 13. After 5 min of stirring at room temperature, the mixture of alcohols was analyzed by means of NMR as described in the text; the *E*/*Z*-ratio was found to be 89:11, respectively.

(b) By Methylation of 5. The methylation experiment was identical with that reported for **4**. The *E*/*Z*-ratio in this instance was 30:70, respectively. (*E*)-**6**-MeI: ^{1}H NMR (D_2O at pH 13) δ 4.61 (s, 2 H, H-6), 4.38 (s, 1 H, H-2), 3.83 (d, J = 13 Hz, 2 H), 3.72 (d, J = 13 Hz, 2 H), 3.54 (d, J = 14 Hz, 2 H) and 3.14 (d, J = 14 Hz, 2 H, H-4,8–10), 2.89 (s, 3 H, *N*-Me), 2.12 (s, 2 H, H-1,3); ^{13}C NMR δ 80.71 (C-6), 67.17 (C-2), 65.95 (C-4,9), 49.90 (*N*-Me), 47.64 (C-8,10), 31.55 (C-1,3).

(*Z*)-6-MeI: ^{1}H NMR δ 4.52 (s, 2 H, H-6), 4.15 (s, 1 H, H-2), 3.86 (d, J = 13 Hz, 2 H), 3.57 (d, J = 13 Hz, 2 H), 3.39 (d, J = 14 Hz, 2 H), 3.12 (d, J = 14 Hz, 2 H, H-4,8–10), 2.84 (s, 3 H, *N*-Me), 2.18 (s, 2 H, H-1,3); ^{13}C NMR δ 80.30 (C-6), 63.96 (C-2), 59.45 (C-4), 52.09 (C-8,10), 50.30 (*N*-Me), 32.43 (C-1,3). The assignments were made in the same way as those for the *N*-oxides.

2-Cyano-5,7-diazaadamantane (9) and Its Mono-*N*-oxides. This compound was prepared from **4** by means of the van Leusen procedure.[23] A white solid was obtained in 64% yield. MS: 163 (M^+). ^{1}H NMR ($CDCl_3$): δ 4.15 (s, 2 H, H-6), 3.64–3.20 (m, 9H, H-2,4,8–10), 1.69 (s, 2 H, H-1,3). ^{13}C NMR: δ 120.45 (C≡N), 74.03 (C-6), 56.85 (C-8,10), 53.68 (C-4,9), 35.63 (C-2), 27.56 (C-1,3).

A solution of **9** (40 mg, 0.25 mM) in methylene chloride (5 mL) was treated by the dropwise addition of a solution of *m*-CPBA (50 mg) in the same solvent (5 mL); after 2 h of stirring at room temperature, the solvent was evaporated, the white residue was extracted with water, and the water was evaporated under vacuum to give a mixture of the two isomeric *N*-oxides which was analyzed by NMR. ^{1}H NMR ($CDCl_3$): δ 4.70 (major) and 4.59 (minor) (s, s, H-6), 4.2–2.9 (m, H-2,4,8-10), 2.41 (major) and 2.39 (minor) (H-1,3). Integration of the H-6 signals gave a ratio of *Z*:*E* = 52:48; the assignment rests on the previous observations in this research that the *Z*-isomer always has H-6 at lower field. ^{13}C NMR: δ 118.43 and 118.03 (C≡N), 85.49 and 85.28 (C-6), 67.84 (C-4,9, minor), 65.60 (C-4,9, major), 53.11 (C-8,10, major), 50.51 (C-8,10, minor), 32.24 and 32.13 (C-2), 31.79 and 31.52 (C-1,3). The assignment was based on additivity calculations (see supporting information), which agreed with the one based on ^{1}H NMR.

5,7-Diazaadamant-2-yl Phenyl Ketone (10) and Its *N*-Oxides. A 2.0 M solution of phenyllithium (5 mL) was added dropwise to a solution of **9** (550 mg) in dry benzene over a 15 min period. After the mixture was stirred for 4 h at room temperature, the reaction was cautiously quenched with water (2 mL), and the aqueous layer was separated and extracted with methylene chloride. The combined organic solution was concentrated, and acetone and concentrated HCl were added (5 mL each); the mixture was heated to reflux for 4 h, cooled, neutralized, and extracted with methylene chloride. Chromatography (basic alumina, 15% hexane in ethyl acetate) gave **10** (320 mg) as a yellow oil. MS: 242 (M^+). ^{1}H NMR ($CDCl_3$): δ 8.0–7.4 (m, 5 H, Ph), 4.16 (s, 2 H, H-6), 3.86 (s, 1 H, H-2), 3.64–3.10 (m, 8 H, H-4,8–10), 1.88 (s, 2 H, H-1,3). ^{13}C NMR: δ 202.10 (C=O), 136.34, 132.75, 128.68 and 128.11 (Ph), 74.55 (C-6)), 56.29 (C-8,10), 53.52 (C-4,9), 50.34 (C-2), 28.32 (C-1,3).

Oxidation of a solution of this compound (60 mg, 0.25 mM) in methylene chloride (5 mL) with *m*-CPBA (50 mg) in the same solvent (5 mL) as described above gave a mixture of the *E*- and *Z*-oxides. ^{1}H NMR ($CDCl_3$): δ 8.0–7.4 (m, Ph), 4.46 (major) and 4.40 (minor) (s, s, H-6), 4.2–3.0 (m, H-2,4,8-10), 2.59 (major) and 2.55 (minor) (H-1,3). Integration of the H-6 signals gave a ratio of *Z*:*E* = 55:45. ^{13}C NMR: δ 199.6 (C=O), 136.4, 133.7, 133.3, 129.7, 129.1, 128.2, 127.6 (Ph), 86.76 and 86.19 (C-6), 71.05 (C-4,9, minor), 66.53 (C-4,9, major), 55.69 (C-8,10, major), 50.68 (C-8,10, minor), 46.67 and 46.47 (C-2), 31.60 (C-1,3). The assignments were made in the same way as those of the oxides of compound **9**.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and mass spectral information for all new compounds (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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