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MEISENHEIMER AND OTHER REARRANGEMENTS OF *N*-OXIDES DERIVED FROM 2-AZABICYCLO[2.2.1]HEPT-5-ENES; THE INFLUENCE OF REACTION CONDITIONS AND STEREOCHEMISTRY AT NITROGEN

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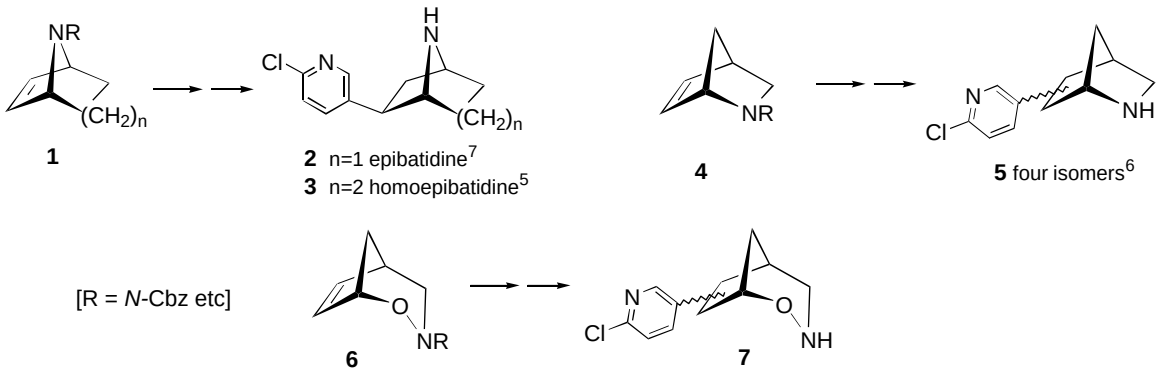
Abstract – *N*-Benzyl-2-azabicyclo[2.2.1]hept-5-ene reacts rapidly with *m*-CPBA and, on basification, a single *N*-oxide is released which rapidly forms *N*-benzyl-2-oxa-3-azabicyclo[3.2.1]oct-6-ene *via* a Meisenheimer rearrangement at room temperature. In addition, competition from a formal Cope elimination in a non-planar system leads to novel substituted cyclopentadienes; these show unusual VT NMR behavior and an unusually high J_{gem} value of 23.8 Hz is observed in one isomer at low temperature as a result of diastereotopicity induced by slow inversion at nitrogen in the side chain. *N*-Benzyl-2-azabicyclo[2.2.1]heptane forms two stable *N*-oxides with *m*-CPBA. Invertomer preferences are measured in the starting amines and the relationship between invertomer ratios, *N*-oxide stereochemistry, and rearrangement pathways is explored.

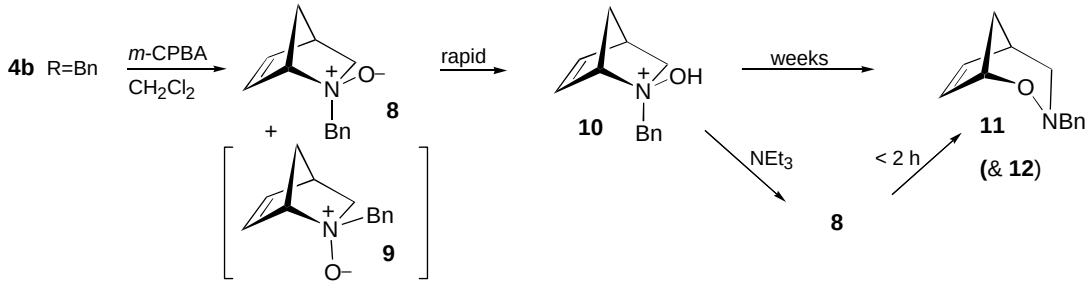
The Meisenheimer rearrangement of amine *N*-oxides[1] is of synthetic value[2] and is also of mechanistic interest.[3] Bicyclic amine oxides offer additional mechanistic complexity since the oxidation of an unsymmetrical amine produces two diastereoisomeric *N*-oxides and these have the potential to react at different rates[4] and to give different products. Our work on the synthesis of high-affinity nicotinic acetylcholine receptor (nAChR) ligands has produced homologues **(3)**[5] and isomers **(5)**[6] of epibatidine **(2)**[7] (Scheme 1) and we chose the bicyclic oxazine **(6)** as an attractive target for production of further variants of **2** including **7**. Four stereoisomers of **7** are possible, and we wished to explore the possibility of facial selectivity in studies of double bond functionalisation, for example, using reductive Heck chemistry.[7b] In exploring an approach to the intermediate **(6)** based on the Meisenheimer rearrangement of **4**, we found a more complex picture which has relevance to recent studies by others.[8,9]

Dedicated with great pleasure to Professor Leo A. Paquette on the occasion of his 70th birthday.



Scheme 1

We expected to obtain the two *N*-oxides **(8)** and (**9)** on treatment of the amine **(4b)**[10] with *m*-CPBA[11] and, whilst NMR spectral analysis suggested a single initial product, there was evidence for further changes with time. The isolated product mixtures varied with reaction conditions, timing, work-up procedures, and attempted chromatographic separations but the picture shown in Scheme 2 gradually emerged.

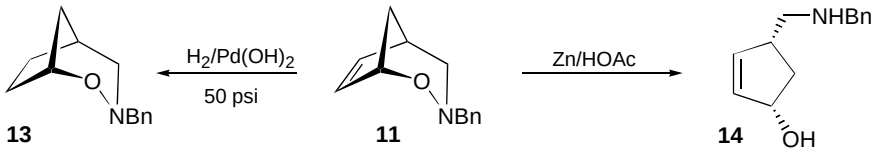


Scheme 2

After addition of *m*-CPBA to **4b** in $CDCl_3$ in an NMR tube, the NMR spectrum immediately showed a single major product which we believe to the protonated *N*-oxide **(10)** (formed by rapid protonation of **8** by the *m*-CBA formed in the reaction). It was shown to be the *exo*-isomer by detailed ^{1}H NMR chemical shift comparisons with the *exo*- and *endo*- quaternary salts produced by 'kinetic protonation' of *N*-methyl **(4a)**[12] and *N*-benzyl **(4b)** derivatives. NOESY studies showed that both $H_{3\text{-}endo}$ and H_6 in **(10)** had nOe interactions with the benzylic protons but $H_{3\text{-}exo}$ did not. The signals due to **10** gradually decreased over a period of days,[13] to be replaced by signals assigned to the Meisenheimer rearrangement product **(11)**, one other major product **(12)** (discussed later), together with unidentified minor products. Integration against an internal standard showed the yield of **11** to be *ca.* 41%. The very slow rearrangement of the first-formed **10** contrasts with the rapid rearrangement (3-5 sec) in the closely related work of Bailey.[8b] Our understanding and control of our chemistry really only began to develop when we re-considered the importance of base in these reactions, established in the work of Cope and Wragg.[3] Thus, when *m*-CPBA was added to **4b** in an NMR tube in $CDCl_3$ followed by shaking for *ca*. 5 sec and immediate addition of triethylamine, the NMR spectrum showed the presence of the *N*-oxide **(8)**. On standing at room

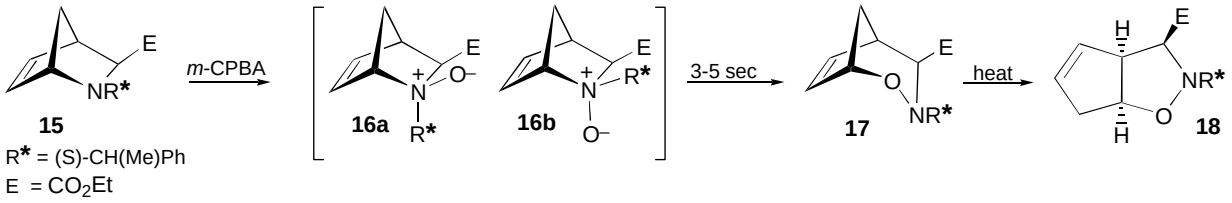
temperature, peaks assigned to the oxazine **(11)** [together with **(12)**] began to appear and the loss of **8** was complete within 2 hours. The two major products had similar R_f values and a small sample of the oxazine **(11)** was obtained in early work only after repeated chromatography. Spectroscopic data for **11** were fully in accord with the assigned structure (Table 2 in the EXPERIMENTAL).

The simplest and most effective conversion into pure **11** was achieved by shaking a mixture of **4b** with *m*-CPBA in chloroform for one minute followed immediately by loading on to a short column of basic alumina.[14] The first fraction eluted from the column with chloroform consisted of **11** (37% yield).



Scheme 3

Hydrogenation of the double bond in **11** gave **13** with retention of the *N*-benzyl group and the N-O bond (Scheme 3). Cleavage of the N-O bond with Zn/AcOH gave **14**; homonuclear spin-decoupling allowed full analysis and assignment of the NMR spectrum of **14**.[8c] Attempts to increase the yield of **11** using H_2O_2 or by the use of *t*-butyl peroxide/$VO(acac)_2$[15] were unsuccessful. In the light of the work of Bailey (Scheme 4), the possibility of further rearrangement of **11** to give the corresponding bicyclic oxazine corresponding to **18** was considered but no change was observed on refluxing a sample of **11** in dichloromethane for 48 h.



Scheme 4

The difference in the rate of rearrangement in our work (days) when compared with that of Bailey[8] (seconds) in a very similar system becomes less significant if it is assumed that the rapid reaction observed by Bailey is actually a consequence of basification (quenching). In contrast to the higher temperatures needed to achieve rearrangement in many other systems,[1] the easier C_1-N bond cleavage in the 2-azanorbornene systems is presumably a result of intrinsic strain. Perhaps the additional substituent at C_3 in **15** contributes to the additional acceleration in this case. The *N*-oxide **(16b)** (having the *exo*-R* substituent) is considered to be the key intermediate in this work[8] in which case the interaction between the ester group and the sterically demanding *N*-substituent would lead to additional strain and a consequent rate increase. We have no information on the ratio **16a**: **16b**;[16] however support for **16b**

is provided by the absence of an alternative rearrangement product which could, in principle, have occurred from **16a** if this stereoisomer had been present. This 'further rearrangement' was uncovered after a chromatography fraction containing both **11** and the second major product **(12)** began to deposit crystals. Trituration of other column fractions, after seeding and cooling, provided more crystalline material and the isomeric structures **(12b,c)** were finally deduced with the aid of a crystal structure determination (Figure 1) and NMR spectral analysis.

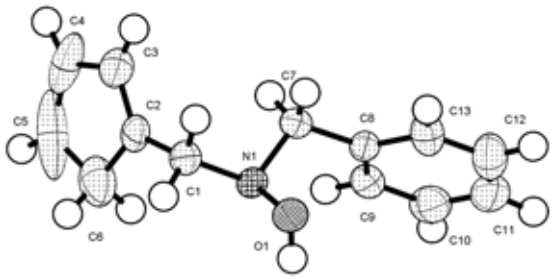
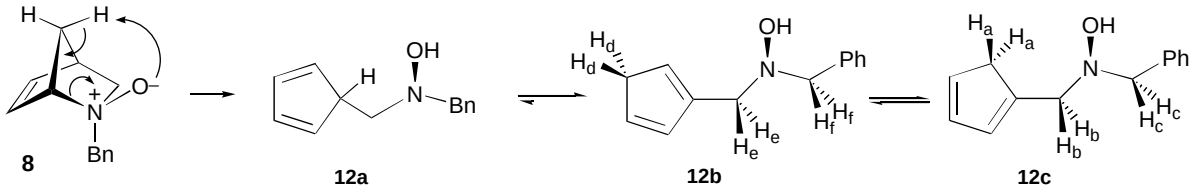


Figure 1. X-ray crystal structure for compound(s) (12) showing the atom label scheme and 50% displacement ellipsoids.[17]

Signals corresponding to both **11** and **12b,c** appeared in the NMR spectrum during the experiment described above and the yield of **12** was estimated to be *ca.* 33% by NMR spectrometry. The product is clearly the result of competition from a formal Cope elimination (Scheme 5), a process which was considered unlikely at the outset in view of the difficulty in achieving a planar transition state.[18]



Scheme 5

Figure 2a **Figure 2b**

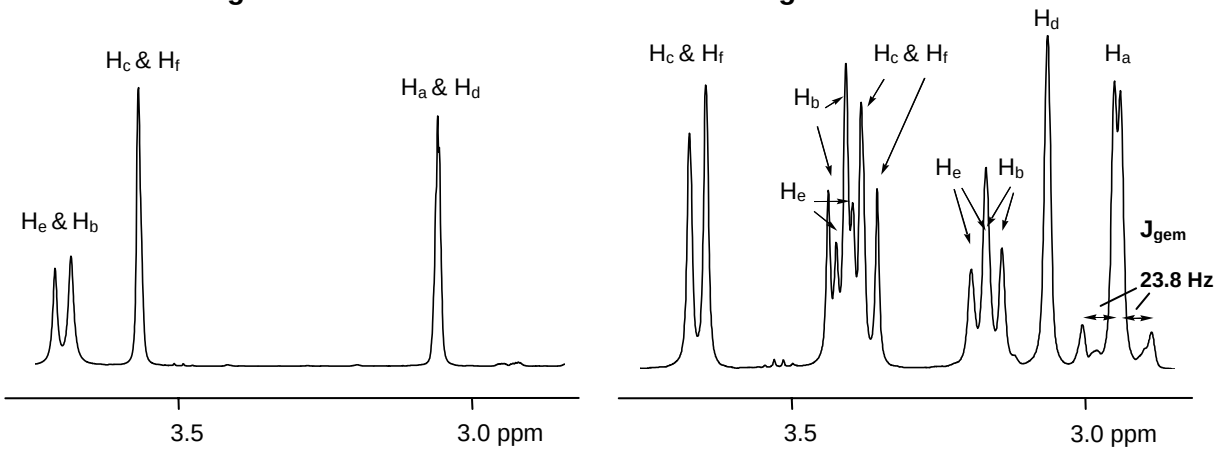
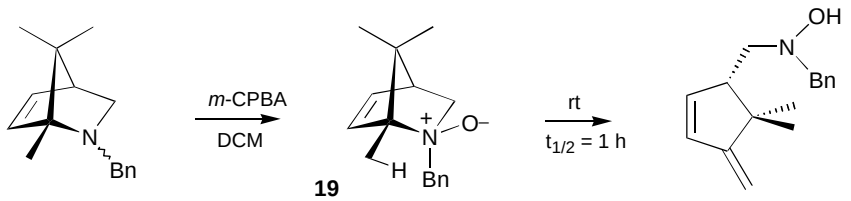


Figure 2. Partial ^{1}H NMR spectra of 12b and 12c at (a) 25^{o}C and (b) –60^{o}C

The complex ^{1}H NMR spectra were assigned with the aid of VT measurements. Integration of the spectrum at 25°C showed that the kinetic product **(12a)** was not present to a measurable extent at equilibrium and gave a ratio of **12b**:**12c** of 41:59. The picture in Scheme 5 is consistent with the uncertainty at the positions labeled as C3-C6 in the cyclopentadiene ring and the clear sp^2 character of C2.[17] The ^{1}H NMR spectrum coalesced at *ca.* 0°C and sharpened as the temperature was lowered further but became unexpectedly complex at –60°C. The presence of signals due to both **12b** and **12c** at room temperature shows that the 1,5-sigmatropic shifts are not the cause of the VT changes which can, instead, be explained by slow inversion at the hydroxylamine nitrogen. This is confirmed by the signals for hydrogens H_b/H_e and H_c/H_f which are equivalent (singlets) at room temperature but become diastereotopic at –60°C as a result of the chiral nitrogen and therefore appear as AB systems.

The contrast in the behaviour of the signals for H_a and H_d is of particular interest. At –60°C the geminal pair H_d remain a singlet as a result of the distance from the chiral nitrogen. However, the protons H_a are closer to the nitrogen and clearly become diastereotopic, revealing an AB system with an extraordinary geminal coupling constant of 23.8 Hz, higher than any geminal proton-proton coupling in our experience. Over a period of months at 4°C, **12a** and **12b** was converted completely into a mixture of unknown products which are assumed to be Diels-Alder cycloadducts.

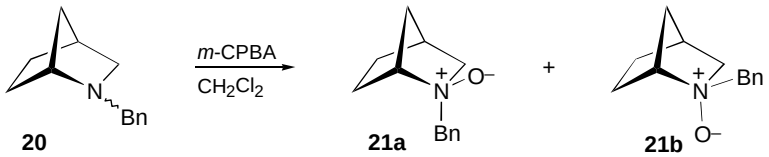
Coldham[9] has described an analogous Cope elimination in a system which also has difficulty in attaining a planar transition state (Scheme 6); the alternative β-carbon (the 1-methyl group) provides the hydrogen since a 7-*syn* hydrogen is unavailable. In this work, the initial *N*-oxide **(19)** rapidly undergoes Cope elimination after a basic work-up. However in deuteriochloroform and, more importantly, without the basic work-up, the *N*-oxide salt is stable, providing a direct analogy with our observations.



Scheme 6

We saw no products which could be assigned to sigmatropic rearrangements involving the *N*-benzyl substituent in these reactions. Our work confirms the well established preference for migration of allyl over benzyl in the Meisenheimer rearrangement.[1,3b]

In order to try to encourage the alternative benzyl migration, we examined the behaviour of the saturated *N*-benzylamine **(20)** (Scheme 7) which was made by hydrogenation of **4b**.



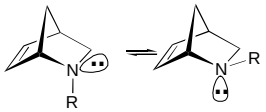
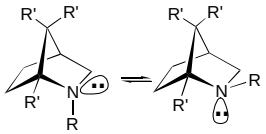
Scheme 7

Addition of *m*-CPBA to **20** in $CDCl_3$ immediately gave *exo*- and *endo*- *N*-oxides **(21a)** and (**21b)** (presumably protonated) in a ratio of 70:30.[19] After 2 days at room temperature, there was no change and NEt_3 was added. Heating at 40°C was followed by replacement of solvent with toluene-d_8 and further heating for 2 days at 75°C. Finally, the sample was heated to 150°C with loss of solvent but the NMR spectrum of the residue showed only the two *N*-oxides **(21a)** and (**21b)**.

MECHANISTIC DISCUSSION

The allylic stabilization in the intermediate **(22)** is clearly essential for cleavage of the N-C_1 bond and benzylic stabilization is not sufficient to allow competition from the alternative rearrangement, not least because benzyl migration would involve no release of bicyclic ring strain. It is interesting to note that whilst **22** leads to the Meisenheimer rearrangement product, it could conceivably provide an alternative to the concerted Cope elimination involving H_{7syn} in producing **12**. The work described in Scheme 4 is thought to proceed *via* the *N*-oxide **(16b)** and hence the intermediate **(23)**;[8a] rapid ring closure of **23** would explain the lack of competition from the formal Cope elimination (which would have led to derivatives of **12**) and would also explain the ready rearrangement to **18** (which is consistent with an '*endo*-' oxyanion and which does not compete in our work). With this in mind, it seemed pertinent to consider existing work on the invertomer preferences in *N*-alkyl norbornenes and norbornanes such as **(4)**, (**20)** and (**24)** and their relationship to the observed stereoselectivities in *N*-oxide formation (Table 1).

We have previously reported invertomer ratios for **4a** and **24** based on kinetic protonation experiments[12] and we find similar ratios for the *N*-benzyl analogues **(4b)** and (**20)** in this work. We hoped to find a direct relationship between invertomer preferences and the *N*-oxide configurations in this work following earlier results from the 5,6-benzo- derivative of the *N*-methyl-7-azabicyclo[2.2.1]heptadiene system where the 93:7 preference for the amine invertomer having the lone pair *anti*- to the benzo group[20] was matched by a 91:9 ratio of *N*-oxides with the major diastereoisomer also having the oxyanion *anti*-.[4a]

		***N*-oxide (*endo*-R)**	***N*-oxide (*exo*-R)**
4a R = Me[12]	77 : 23		
4b R = Bn	80 : 20	*ca.* 100%	
			
24 R = Me; R' = H[12]	24 : 76		
20 R = Bn; R' = H	36 : 64	70%	30%
R = Bn; R' = Me[9]	major : minor *	86%	14%

Invertomer ratios from kinetic protonation studies[12a] except for * which is assumed on steric grounds

Table 1. Invertomer ratios and *N*-oxide ratios

However, it can be seen that not all of the lone pair preferences of the amines in Table 1 correlate with the *exo-/endo-* configuration of the oxyanion in the derived *N*-oxides. There is a preference for *N*-oxidation from the *exo*-face of the azabicyclic system in all of the examples shown in Table 1, despite the differences in invertomer preference in the amine substrates and despite potential steric hindrance by the *syn*-7-methyl substituent in the work in Scheme 6.[9] The absence of a direct relationship in these examples is presumably a consequence of the complexities of kinetic *versus* thermodynamic control in reactions at an inverting nitrogen.[21] The results of Bailey (Scheme 4) make the picture more complex. The major invertomer in the free amine **(15)** is presumably that in which the *N*-substituent is *endo-* and it might therefore be conjectured that the peroxyacid would also approach the rapidly inverting nitrogen in **15** from the *exo-* face whereas the *endo-N*-oxide is actually formed. Whilst this may minimize interactions between the oxidizing agent and the *exo-* ester substituent at C3, it puts both the ester and R group *exo-* in the *N*-oxide. Clearly the introduction of a sterically-demanding *N*-substituent and an additional ester group adjacent to the reactive nitrogen in **15** alters the balance of reactivity substantially. Of course, there is no bar to total reaction *via* the minor invertomer if that pathway has the lower activation energy and if N-inversion is rapid in comparison with the rate of quaternisation.

EXPERIMENTAL

^{1}H and ^{13}C NMR (DEPT) data were recorded at 250 MHz and 63 MHz unless otherwise stated. Variable temperature and NOESY data were recorded at 400 MHz. Chemical shifts are given in ppm (δ) relative to the internal standard (TMS). NMR spectral data for some new compounds are provided in Tables 2 and 3, together with selected comparison data. Routine mass spectra were measured on a Micromass Quattro LC spectrometer (electrospray) and accurate mass measurements using a Kratos Concept mass spectrometer

(FAB). Flash chromatography was carried out using silica gel (60). Thin-layer chromatography was conducted on 60-254 plates with triethylamine added to solvents for amine separations.

Reaction of (4b) with *m*-CPBA; formation of *N*-benzyl-2-oxa-3-azabicyclo[3.2.1]oct-6-ene (11)

To the amine **(4b)**[10] (6.31 g, 34.12 mmol) in dry dichloromethane (650 mL) was added *m*-CPBA (57-86% pure, 14.41 g, minimum 47.6 mmol) and the solution stirred at rt under nitrogen for 3 days. The mixture was then heated under reflux over night, cooled, and washed with saturated $NaHCO_3$ (3x500 mL) and water (2x500 mL). The organic layers were combined and dried over $MgSO_4$ and the solvent removed under reduced pressure to leave a highly viscous brown oil (5.58 g). TLC analysis (3:1 hexane:ether with 1% triethylamine) showed a mixture of compounds; column chromatography using the same solvent mixture gave **11** (2.34 g; 34%) together with a co-running impurity which was later separated by crystallization and shown to be the cyclopentadiene isomers **(12)**. Repeated chromatography provided a small sample of pure **11** as a pale yellow oil.

Small-scale reactions were performed in NMR tubes and monitored by ^{1}H NMR spectroscopy. In a typical reaction, *m*-CPBA (57 - 86%, 27 mg, minimum 0.089 mmol) was added to a solution of the amine **(4b)** (11 mg, 0.059 mmol) in $CDCl_3$ (1.5 mL) followed by a known amount of cyclohexane (measured by weight and volume). Immediate formation of the protonated *N*-oxide **(10)** (NMR data in Table 3) was followed, over a period of days, by gradual replacement of the peaks assigned to **10** by new peaks due to **11** and **12**. In another reaction, the mixture was shaken for *ca.* 5 sec after addition of *m*-CPBA and triethylamine (2 μL, 0.10 mmol) was added. Similar changes occurred, but over a shorter period of 2 h.

Preferred method for isolation of *N*-benzyl-2-oxa-3-azabicyclo[3.2.1]oct-6-ene (11)

Compound **(4b)** (0.212 g, 1.146 mmol) was dissolved in $CHCl_3$ (5 mL), *m*-CPBA (57-86% pure, 0.360 g, minimum 1.189mmol) was added and the mixture was shaken for one minute before being loaded onto a basic alumina column and left over night. Elution with $CHCl_3$ gave **11** (0.085 g, 37%) as the first fraction [later fractions also contained **12**, together with other unidentified materials]. ^{1}H NMR spectral data are shown in Table 2. ^{13}C NMR (76 MHz, $CDCl_3$): δ 39.0 (C_5), 44.8 (C_8), 58.8 (C_4/CH_2Ph), 62.9 (C_4/ CH_2Ph), 81.1 (C_1), 128.8 (C_6), 138.5 (C_7), 127.4, 128.5, 129.4 (aryl CH), 139.1 (aryl C). ν_{max} (film) 2962, 1496, 1453, 1327, 1074 cm^{-1}. m/z: 201.11528; $C_{13}H_{15}NO$ [MH^+] requires m/z 201.11536.

***N*-Benzyl-*N*-cyclopenta-1,3-dienylmethylhydroxylamine (12b) and *N*-benzyl-*N*-cyclopenta-1,4-dienylmethylhydroxylamine (12c)**

This mixture of compounds was isolated from the treatment of **4b** with *m*-CPBA when column fractions containing **11** and **12** deposited crystals on standing (R_f 0.52 in 3:1 hexane:ether + 1% triethylamine) and was identified using an X-Ray crystal structure.[17] VT NMR experiments were run at rt and at 10^o intervals down to –60^{o}C ^{1}H NMR (400 MHz, $CDCl_3$ rt): **12b**: δ 3.02 (s, 2H, H_3), 3.59 (s, 2H, CH_2-Ph), 3.75 (s, 2H, H_6), 6.23 (s, 1H, H_2), 6.40 – 6.59 (m, 2H, H_4 and H_5), 7.26 – 7.37 (m, 5H, Ph); **12c**: δ 3.02

(s, 2H, H_5), 3.59 (s, 2H, CH_2-Ph), 3.72 (s, 2H, H_6), 6.40 – 6.59 (m, 3H, H_2, H_3 and H_4), 7.26 – 7.37 (m, 5H, Ph). ^{1}H NMR (400 MHz, $CDCl_3$, -60°C): **12b**: δ 3.00 (s, 2H, H_3), 3.13, 3.38 (AB, 2H, H_6), 3.34, 3.67 (AB, 2H, CH_2-Ph), 6.27 (s, 1H, H_2), 6.40 – 6.47 (m, 2H, H_4 and H_5), 7.27 – 7.37 (m, 5H, Ph); **(12c)**: 2.84, 2.89 (AB, 2H, H_5), 3.10, 3.40 (AB, m, H_6), 3.34, 3.67 (AB, m, CH_2-Ph), 6.40 – 6.47 (m, 3H, H_2, H_3 and H_4), 7.27 – 7.37 (m, 5H, Ph). ^{13}C NMR (63 MHz, $CDCl_3$): **12b** (minor): δ 41.8, 59.1, 63.9 (3 x CH_2); **12c** (major): 43.8, 59.8, 63.8 (3 x CH_2); alkene and aryl signals for both isomers appeared as a complex pattern from 127 - 145 ppm. m/z: 201.11541; $C_{13}H_{15}NO$ [MH+] requires 201.11536.

3-Benzyl-2-oxa-3-azabicyclo[3.2.1]octane (13)

Compound **(11)** (0.213 g, 1.060 mmol) was dissolved in ethanol (150 mL), palladium hydroxide (~0.5 g) was added and the mixture shaken under a hydrogen atmosphere (~50 psi) for 24 h.[22] The reaction was filtered, the solvent removed under reduced pressure, and the resulting oil purified by column chromatography (3:1 hexane:ether with 1% triethylamine R_f = 0.68) giving **13** (0.114 g, 53%). ^{1}H NMR spectral data are shown in Table 2. ^{13}C NMR (63 MHz, $CDCl_3$): δ 28.6 (C_6/C_7), 30.7 (C_6/C_7), 34.9 (C_5), 38.6 (C_8), 63.1 (C_4/CH_2Ph), 63.3 (C_4/CH_2Ph) 80.1 (C_1), 127.3, 128.6, 129.0, (aryl CH),138.4 (aryl C). υ_{max} (film) 2945, 1496, 1454, 1301, 1171, 1060 cm^{-1}. m/z: 203.13107; $C_{13}H_{17}NO$ [MH+] requires 203.13101.

	11	**11:H$^+$**	**17^{8a} a**	**13**	***N*-Tosyl analogue of 11^{23}**
H_1	4.64 br s	5.01 br s	4.55 br s		4.78 m
H_{4x}	2.85 br d	3.84 br d	-	2.75 dddd	3.63 dddd
H_{4n}	2.60 d	3.22 d	3.80 d	2.51 d	2.86 dd
H_5	2.73 br d	2.99 br s	3.15 br d	2.31 br dd	2.80
H_6	6.43 dd	6.67 dd	6.50 dd	H_{6n} 1.86 dd **b** H_{6x} 1.61-1.67 m	6.48
H_7	6.09 dd	6.31 dd	6.10 dd	H_{7n} 2.20 dd **b** H_{7x} 1.61-1.67 m	6.08
H_{8s}	1.82 br m	1.98 br d	1.95 d	1.29 m **c**	1.80
H_{8a}	1.71 d	1.81 d	1.68 ddd	1.69 brdd **c**	1.55 d
CH_2-Ph	3.83, 4.01 AB	4.36, 4.50 AB			
$J_{1,7}$	2.3 Hz	2.3	2.6	-	2.7
$J_{1,8a}$	-	-	3.2	-	
$J_{4x,4n}$	10.8	11.4	-	10.4	10.9
$J_{4,5}$	2.9	2.9	3.8	4.4	2.7
$J_{5,6}$	-	-	1.9	$J_{5n,5x}$ 8.6	
$J_{5,8a}$	-	-	1.7	$J_{6n,6x}$ 8.6	
$J_{6,7}$	5.6	5.3	5.6	$J_{8s,8a}$ 11.4	5.8
$J_{8a,8s}$	10.2	11.4	10.7	-	11.0

Additional data for 17^{8a} and the *N*-tosyl analogue of 11[23] are included for comparison.
All spectra in $CDCl_3$ at 298K Data assigned with the aid of homonuclear spin-decoupling studies.
a Selected data only; **b** These assignments may be reversed; **c** These assignments may be reversed.

Table 2. ^{1}H NMR spectral data for 2-oxa-3-azabicyclo[3.2.1]octanes and -enes

4-(Benzylaminomethyl)cyclopent-2-enol (14)

To the amine **(11)** (0.200 g, 0.995 mmol) in 10% aqueous acetic acid (8 mL) and THF (6 mL) was added zinc powder (~0.5 g) and the mixture stirred at rt for 24 h. After filtration, the solution was basified with aq. NaOH and extracted with ethyl acetate (3x50 mL). The organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure to give a pale yellow oil (1.55 g, 77%). ^{1}H NMR (400 MHz, C_6D_6): δ 1.55 (br d, 1H, H_{5a} *J* 13.3 Hz), 2.15 (dd, 1H, H_6 *J* 11.4, 3.3 Hz), 2.17 (ddd, 1H, H_{5s} *J* 13.3, 8.1, 6.7 Hz), 2.37 (dd, 1H, H_6 *J* 11.4, 3.3 Hz), 2.52 (dddddd, 1H, H_4 *J* 8.1, 3.3, 3.3, 2.6, 1.5, 1.2 Hz), 3.44 and 3.52 (AB, 2H, CH_2Ph *J* ≈14 Hz), 4.75 (dddd, 1H, H_1 *J* 6.7, 2.6, 1.1, 0.5 Hz), 5.48 (ddd, 1H, H_3 5.5, 1.2, 0.5 Hz), 6.10 (ddd, 1H, H_2 *J* 5.5, 2.6, 1.2 Hz), 7.14-7.28 (m, 5H, Ph) [H_{5a} and H_{5s} are defined here as *syn*- and *anti*- to the OH and alkylamino- side chains; OH and NH signals were not seen]. ^{13}C NMR (63 MHz, $CDCl_3$): δ 39.8 (C_5), 44.6 (C_4), 50.0 and 54.8 (NCH_2), 74.7 (C_1), 134.6 (C_2), 136.9 (C_3), 127.7, 128.7, 129.0 (aryl CH), 139.6 (aryl C). υ_{max} (film) 2926, 1453, 1058 cm^{-1}. m/z: 204.13879; $C_{13}H_{18}NO$ [MH^+] requires 204.13884.

2-Benzyl-2-azabicyclo[2.2.1]heptane (20)

Palladium on carbon (~0.5 g) was added to **(4b)** (0.504 g, 2.72 mmol) in dry methanol (10 mL) and stirred under hydrogen for a total of 1 h. After filtration, the solvent was removed under reduced pressure to afford **20** as a yellow oil (0.407 g, 80%). A sample (0.236 g) was purified by column chromatography (70% ethyl acetate, 25% hexane, 4% methanol, 1% triethylamine) and provided 0.030 g (13%) of pure **20** together with 0.140 g (59%) in a lower state of purity. ^{1}H NMR spectral data are in Table 3. ^{13}C NMR (63 MHz, $CDCl_3$) 27.2 (CH_2, C_5/C_6), 29.2 (CH_2, C_5/C_6), 36.2 (CH_2, C_7), 38.4 (CH, C_4), 59.3 (CH_2, C_3/CH_2Ph), 60.3 (CH_2, C_3/CH_2Ph), 60.9 (CH, C_1), 127, 128.6, 128.9, 140.7 (aryl CH). υ_{max} (film) 2958, 1494, 1452, 1367, 1299, 1211, 1154, 1028 cm^{-1}. m/z: 188.14401; $C_{13}H_{18}N$ [MH^+] requires 188.14392.

***N*-Benzyl-2-azabicyclo[2.2.1]heptane *N*-oxides (21a,b)**

m-CPBA (57-86% pure, 0.042 g, minimum 1.39 mmol) in $CDCl_3$ (~0.2 mL) was added to **(20)** (0.021 g, 0.112 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube. The *N*-oxides **(21a)**, **(21b)** were formed immediately and the mixture was monitored by ^{1}H NMR spectroscopy at intervals. There was no change after two days and triethylamine (0.023 mL, 0.168 mmol) was added. No change occurred during 5 days at rt nor after heating at 40°C for 4 h. After evaporation of solvent under nitrogen and replacement by toluene-d_8, the sample was heated at 75°C for *ca.* 48 h. After further heating overnight at 140°C (which led to evaporation of solvent) the *N*-oxides were recovered unchanged. ^{1}H NMR spectra are shown in Table 3.

Protonation of *N*-benzyl-2-azabicyclo[2.2.1]hept-5-ene (4b) and *N*-benzyl-2-azabicyclo[2.2.1]-heptane (20)

In a typical experiment, the amine **(4b)** (0.1 g, 0.54 mmol) was added to a solution of trifluoroacetic acid:$CDCl_3$ (1:4, 0.5 mL) at rt and NMR spectra (Table 3) were recorded immediately.

	4b	**4b:H$^+$ (*exo*-Bn)**	**4b:H$^+$ (*endo*-Bn)**	**10**		**20**	**21b**	**21a**
H_1	4.87 br s	**a**	4.38 br s	4.86 br s	H_1	3.20 br s	4.56 br s	4.31 br s
H_{3x}	4.06 dd	2.84 dd	3.59 ddd	4.04 dd	H_{3x}	2.77 ddd	3.78 ddd	4.01 ddd
H_{3n}	3.37 dd	2.97 ddd	2.23 dd	3.33 dd	H_{3n}	2.24 dd	3.38 dd	3.50 dd
H_4	3.40 br s	3.33 br s	3.27 br s	3.40 br s	H_4	2.33 br s	2.66 s	2.73 s
H_5	6.87 dm	6.51 dm	6.81 dm	6.87 dd	H_{5x}	1.55 m	1.51-2.83 m	1.51-2.83 m
					H_{5n}	1.81 m		
H_6	6.47 dd	6.18 dd	6.43 dd	6.48 dd	H_{6x}	1.42 ddd		
					H_{6n}	1.32 m		
H_{7s}	2.78 br d	2.02 br d	1.89 br d	2.83 br d	H_{7s}	1.69 ddddd		
H_{7a}	2.01 br d	1.81 br d	1.72 br d	2.03 br d	H_{7a}	1.24 dd		
CH_2Ph	4.65, 4.91 AB	4.18, 4.41 **b**	3.82, 3.95 **b**	4.65, 4.90 AB	CH_2Ph	3.64 s	4.90, 5.05 AB	4.84, 5.21 AB
$J_{1,6}$	2.6	2.6	2.6	2.6	$J_{3x,3n}$	9.1	12.1	12.2
$J_{3x,3n}$	11.3	10.2	10.2	11.2	$J_{3x,4}$	~3.5	3.6	3.6
$J_{3x,4}$	3.1	3.2	3.5	3.1	$J_{3x,5x}$	~3	Not resolved	2.4
$J_{3n,7a}$	2.4	2.3	2.3	2.4	$J_{3n,7a}$	1.0	-	-
$J_{5,6}$	5.5	5.6	5.9	5.0	$J_{4,5x}$	~3.1	-	-
$J_{7a,7s}$	10.1	10.5	10.2	10.1	$J_{4,5n}$	~2.5	-	-
$J_{Bn,Bn}$	13.0	12.9	12.9	12.8	$J_{4,7s}$	~2	-	-
$J_{NHx,3x}$	-	-	6.4	-	$J_{5n,7s}$	~2	-	-
$J_{NHn,3n}$	-	6.4	-	-	$J_{6n,7s}$	~2	-	-
$J_{NH,Bn}$	-	7.0	7.0	-	$J_{7a,7s}$	9.5	-	-
C_1	64.7	70.0	68.7	81.5 **c**				
C_3	53.0	52.9	52.3	68.5				
C_4	44.4	43.7	43.4	43.4				
C_5	136.7	143.6	145.4	146.3				
C_6	131.4	132.4	130.5	131.3				
C_7	48.6	44.8	47.6	47.9				
CH_2Ph	59.6	59.3	57.1	69.2 **c**				

All spectra in $CDCl_3$ at 298K. See reference 12a for comparison data for N-Me analogues **a** Not seen in spectrum; may be hidden beneath *endo*-Bn H_1 signal; **b** AB system also couples to N-H proton; **c** These assignments may be reversed

Table 3. NMR spectral data for protonated amines and *N*-oxides.

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