Pergamon

Tetrahedron 54 (1998) 10899–10914

TETRAHEDRON

Manipulation of Substituents at Nitrogen in Tropanes, Homotropanes, and Dehydro- Derivatives

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Received 10 June 1998; revised 1 July 1998; accepted 2 July 1998

Abstract: Trop-6-ene (8-methyl-8-azabicyclo[3.2.1]oct-6-ene) and substituted *N*-benzylnortrop-6-enes are synthesised. *N*-Debenzylation of tropanes fails using a wide variety of non-hydrogenolytic conditions despite effective application in model piperidine derivatives; debenzylation of homotropanes is more successful, giving norhomotropane and norhomotrop-7-ene. Bridged *N*-benzyl compounds react more slowly than *N*-methyl analogues with chloroformates; the resulting quaternary intermediates are more prone than the *N*-methyl analogues to suffer competitive reversion to the starting amine, especially in the tropanes, consistent with slower S_N2 attack at the benzylic carbon during decomposition; the use of an *N*-*p*-methoxybenzyl group does allow partial debenzylation to nortrop-6-ene, suggesting greater S_N1 character in the decomposition step in this case. 'Equatorial' attack is preferred in methylation of *N*-benzyl-nortrop-6-ene and -homotrop-7-ene with CH_3I; subsequent reductive debenzylation of the quaternary salt achieves overall replacement of *N*-benzyl by *N*-methyl in both cases. VT NMR studies show the presence of a single 'equatorial' invertomer (Cl *syn*- to the 2C-bridge) in *N*-chloro-norhomotropanes and -7-enes and, by analogy, in the *N*-alkyl compounds.
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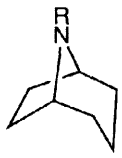
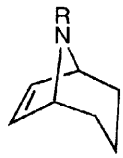
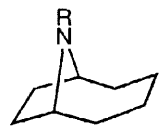
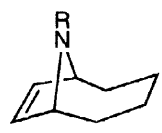
Introduction

We wished to develop a practical route to the bicyclic secondary amines nortrop-6-ene (**2b**) and norhomotrop-7-ene (**4b**) and hence make a wider range of novel *N*-substituted derivatives. We required examples of the dehydro- derivatives for our studies of the effects of unsaturation (as well as variation of *N*-substitution) on the inversion process at nitrogen[1,2] and on the ^{15}N NMR spectra[2c] of azabicycles. We also wished to extend our investigations into the influence of ring size and *N*-substituents in controlling facial selectivity in attack on π-bonds in azabicyclic ring systems.[3] The *N*-methyl group is a feature of the majority of natural tropanes but nor-derivatives, for example the recently discovered calystegines, are assuming greater importance; nor- derivatives of lower and higher homologues are typified by epibatidine and anatoxin-a, respectively. Historically, the *N*-demethylation of natural tropanes has been a well-established route to nor-compounds but we are aware of no such studies on 6,7-dehydro compounds. A direct route to the unsaturated analogue (**2b**) from cyclohepta-1,3-diene had proceeded in disappointingly low yield[1] and we therefore investigated the preparation of (**2a**) with a view to subsequent demethylation. Hydrogenolytic removal of *N*-benzyl groups is traditional but is clearly inapplicable to dehydro-compounds; we have therefore explored the non-hydrogenolytic removal of *N*-benzyl groups in view of the greater ease of preparation of the range of *N*-benzyl derivatives (**1c**) - (**4c**).[1,4] Unexpected difficulties led us to extend the investigation to include the more electron-rich *p*-methoxybenzyl derivative (**2d**).

R = CH_3	**(1a)** tropane	**(2a)** trop-6-ene	**(3a)** homotropane	**(4a)** homotrop-7-ene
R = H	**(1b)**	**(2b)**	**(3b)**	**(4b)**
R = $-CH_2-C_6H_5$	**(1c)**	**(2c)**	**(3c)**	**(4c)**
R = $-CH_2-C_6H_4-OMe$	**(1d)**	**(2d)**	R = Cl **(3e)**	**(4e)**

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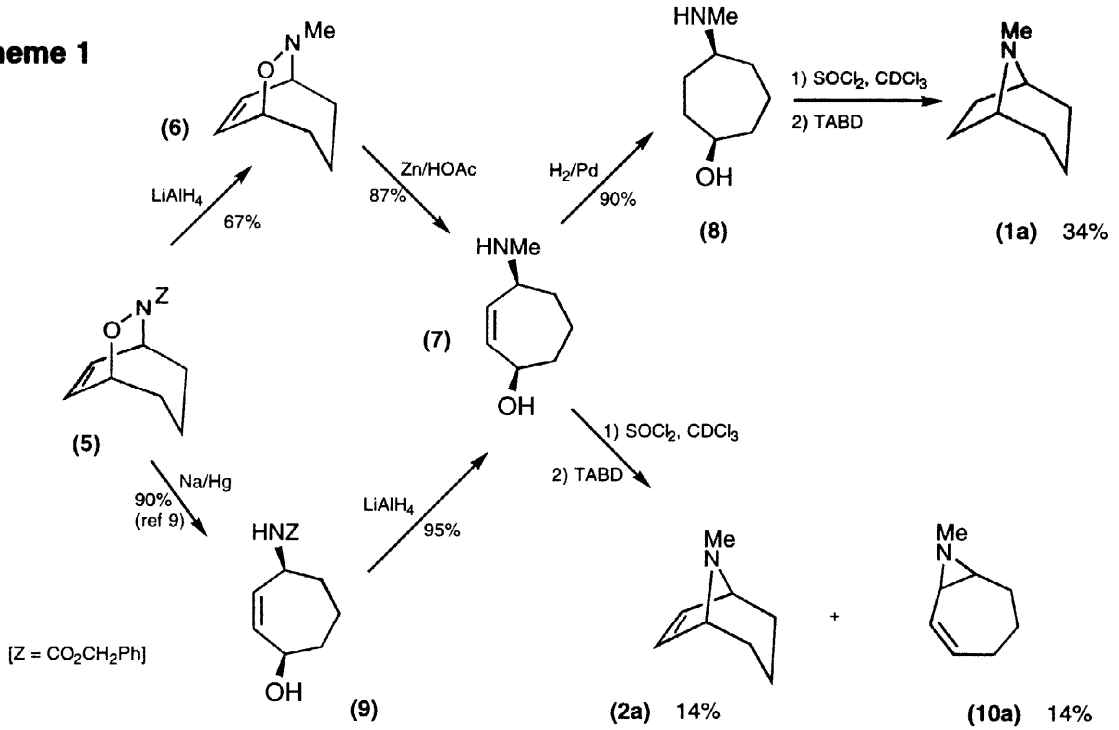
PII: S0040-4020(98)00643-7

Study of the exchange of groups at bridging nitrogen *via* quaternisation/de-quaternisation raised questions about the preferred configuration at nitrogen in homotropanes and homotrop-7-enes. We have therefore investigated conformational preferences at nitrogen in these higher homologues using *N*-chloro- derivatives.

Synthesis of *N*-substituted nortropanes and dehydro-derivatives

The direct approach to nortropane (**1b**) and nortrop-6-ene (**2b**) involved conversion of the primary amines 4-aminocycloheptanol and 4-aminocyclohept-2-enol into the corresponding *trans*-chloroamines followed by cyclisation with base but these reactions gave very low yields. We therefore chose trop-6-ene (**2a**) for our initial studies.

Scheme 1



The *N*-methyl compounds (**1a**) and (**2a**) were prepared from (**5**)[1] as shown in Scheme 1. The conversion of (**5**) into (**7**) *via* (**6**) gave an overall yield of 58% and the alternative sequence *via* (**9**)[5] is preferable (86%).

Hydrogenation of (**7**) gave (**8**) but attempts to cyclise (**8**) using thionyl chloride followed by pyridine[1] were unsuccessful. In contrast, thionyl chloride followed by diisopropylamine did induce cyclisation to (**1a**) (as shown by NMR analysis) but separation of diisopropylamine from the product by chromatography was not practicable. Following unsuccessful work with anhydrous potassium carbonate and ultrasound,[1] cyclisation of (**8**) was finally achieved using thionyl chloride in $CDCl_3$ (the reaction was monitored by ^1H NMR spectroscopy) followed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene crosslinked with 2% divinylbenzene (TABD). The polymer-supported base allowed easy separation of the product and, after chromatography, tropane (**1a**) was isolated in 34% yield. However, application of these optimised conditions to the unsaturated analogue (**2a**) (an excess of lithium chloride was also added to the solution containing the amino-alcohol prior to addition of the thionyl chloride) gave trop-6-ene (**2a**) in only 14% yield together with a similar amount of the isomeric aziridine (**10a**). Attempts to achieve bicyclisation of (**9**) prior to reduction of the benzyloxycarbonyl group with hydride failed, despite the use of a range of conditions.

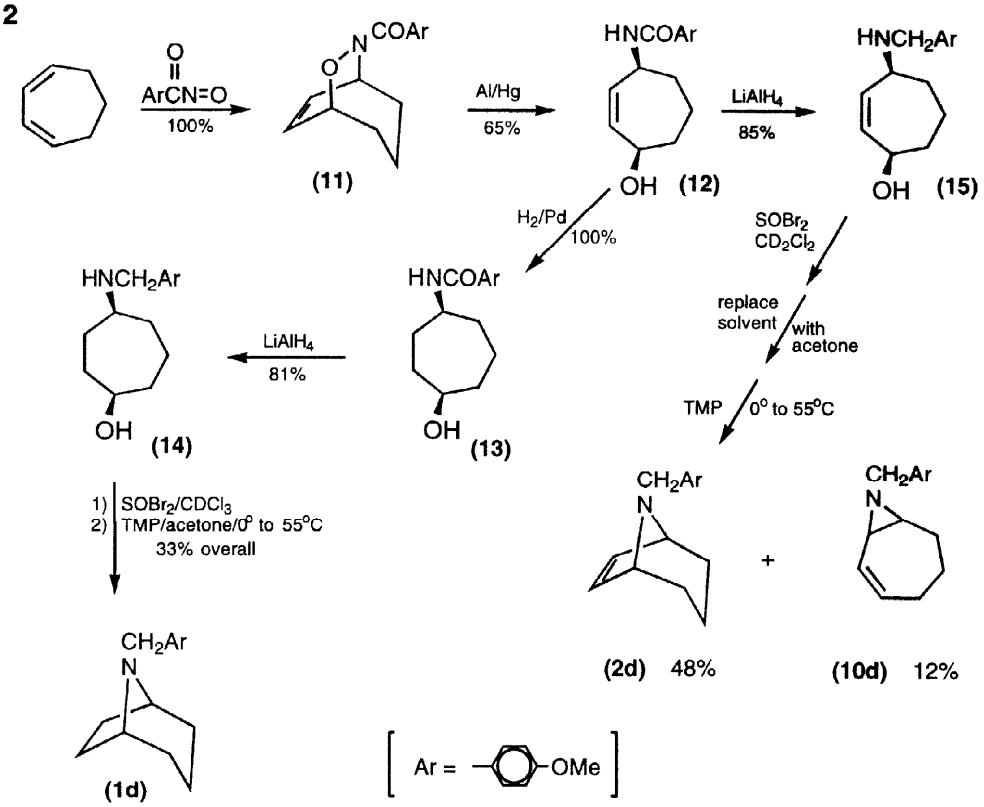
The yield of (**2a**) was better than that achieved in cyclisation of the primary amine[1] but remained too low for it to be considered as an attractive substrate for demethylation. This was unfortunate in view of the many reagents described below which have been developed specifically in order to achieve demethylation of nitrogen in tropanes and other alkaloids but have not been applied to 6,7-dehydrotropanes.

The direct production of simple *N*-protected tropanes by cyclisation of *N*-benzoyl intermediates also gave limited success in early studies[1] and, in any case, the hydrolytic removal of the *N*-benzoyl group from *N*-benzoylnortropane has been reported to fail.[6] In contrast, the *N*-benzyl derivatives of nortropane and nortrop-

6-ene were obtained in good yield from the corresponding *N*-benzyl precursors[1] and were therefore attractive candidates for deprotection, although non-hydrogenolytic methods are needed for the unsaturated compounds.

In order to take advantage of the smoother cyclisation using a benzylamino nitrogen but also to provide an *N*-substituent which should be even more susceptible to reductive removal, we turned to the *N*-(*p*-methoxybenzyl) analogues (**1d**) and (**2d**). These were synthesised using a similar approach to that established previously for (**1c**) and (**2c**) (Scheme 2).

Scheme 2



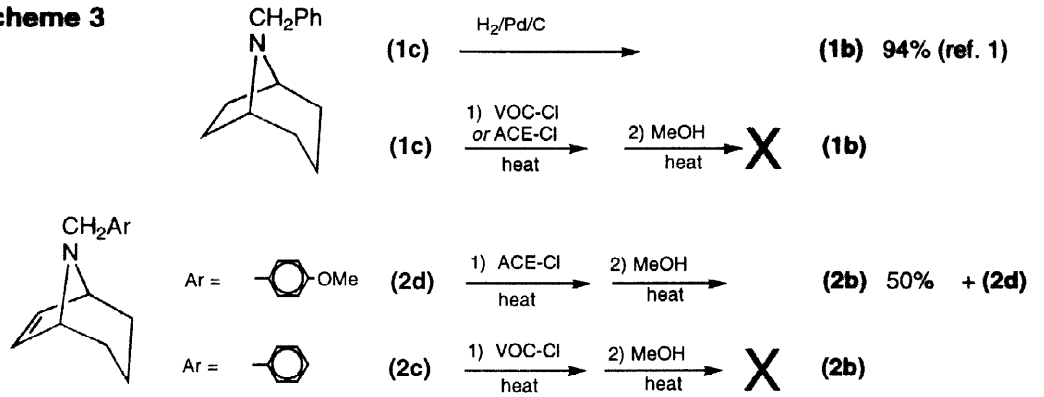
In view of the pronounced dependence of the bicyclisation reaction on conditions, exploratory work on this step was performed using the saturated compound (**14**). The conversion of (**14**) into (**1d**) using thionyl chloride followed by anhydrous pyridine or anhydrous potassium carbonate with ultrasound failed. However, successful cyclisation of (**14**) was achieved in 33% yield using thionyl bromide in $CDCl_3$ (to generate the intermediate trans-4-bromoaminocycloheptane as the hydrobromide salt) followed by replacement of the solvent by acetone and heating at 50°C with anhydrous tetramethylpiperidine (TMP).[1] Application of these conditions to the unsaturated analogue (**15**) produced an encouraging 48% yield of *N*-(*p*-methoxybenzyl)-nortrop-6-ene (**2d**) accompanied by 12% of the aziridine (**10d**) from the competing S_N2' reaction (Scheme 2).

Nortropanes and nortrop-6-enes by debenzylation at nitrogen

The hydrogenolytic removal of *N*-benzyl and *N*-benzyloxycarbonyl groups from tropane and homotropane derivatives yields the nor- systems smoothly. For example, removal of the *N*-benzyl group from *N*-benzylnortropane (**1c**) using Pd/C gives (**1b**) in 94% yield[1] (Scheme 3). Whilst a range of conditions for *N*-debenzylation has been described in the literature,[7] yields have often varied greatly and few studies have involved bicyclic N. We were unable to debenzylate (**2c**) with, for example, Na/NH_3 (and with other alkali metals in liquid ammonia),[1] phenyl chloroformate,[8a] vinyl chloroformate (VOC-Cl),[8b] or α-chloroethyl chloroformate (ACE-Cl).[8c] In model experiments, debenzylation of (**1c**) itself with VOC-Cl or ACE-Cl gave only unchanged starting material. We found this surprising, especially when we subsequently demonstrated that *N*-benzyl piperidine was debenzylated successfully under these conditions (Scheme 4), and we turned to the more electron rich *N*-*p*-methoxybenzyl analogue (**2d**). Addition of ACE-Cl to (**2d**) followed by heating at reflux for 24h, removal of solvent, heating the residue in methanol, and basification during an aqueous work-up, led to formation of nortop-6-ene (**2b**) in approximately 50% yield (NMR). The production of (**2b**) was easily

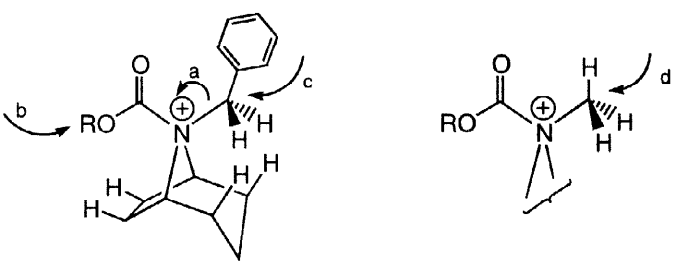
demonstrated using ^{1}H NMR spectroscopy but starting material was also recovered. The ^{13}C NMR spectrum of (**2b**) was especially diagnostic showing only four signals.

Scheme 3



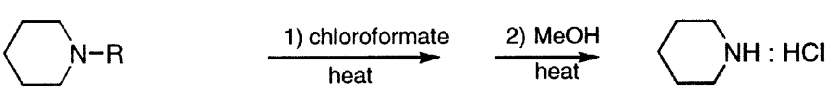
The improvement in the case of the methoxybenzyl compound strongly suggests that, in this case, there is substantial S_N1 character in the breakdown of the quaternary salt formed in the reaction with chloroformate (Figure 1; path a). This presumably allows for more effective competition with the two alternative processes: nucleophilic attack at the benzyloxycarbonyl group (path b)[8a] which leads back to starting *N*-benzyl amine, and S_N2 attack at the benzylic carbon (path c) which is more hindered in this conformationally restricted system. We assume that the greater success of tropane demethylation reactions with chloroformates relies upon easier S_N2 attack at the methyl carbon in the quaternary intermediate (path d) in competition with attack at the alkoxycarbonyl group. The effective demethylation of tropine (tropan-3α-ol) using ACE-Cl,[8c] (67% yield in our hands) supports this. It must be emphasised that the observations in these azabicyclic systems differ from results from simple tertiary cyclohexylamines where conformational restrictions are relaxed and where *N*-debenzylation reasonably takes precedence over *N*-demethylation using chloroformates.[9]

Figure 1



We performed model studies with *N*-ethyl-, *N*-benzyl-, and *N*-*p*-methoxybenzyl-piperidines (**16a-c**) in the hope of defining the factors limiting the removal of the *N*-substituent but the deprotection using VOC-Cl was actually successful in every case (Scheme 4). The use of VOC-Cl[8b] and ACE-Cl[8c] with (**16a**) has been reported previously and we obtained unoptimised yields (Scheme 4) which were close to the literature values. Again, conformational freedom in the monocycles appears to avoid the problems encountered in tropanes.

Scheme 4



(16a)	R = CH_2CH_3	ACE-Cl	77%
(16a)	R = CH_2CH_3	VOC-Cl	83%
(16b)	R = CH_2Ph	VOC-Cl	85%
(16c)	R = CH_2-(4-OMe-Ph)	VOC-Cl	88%
(16d)	R = CH_2-(3,4-di-OMe-Ph)		

In contrast, attempts to debenzylate (**16b,c,d**) using a range of other literature procedures led to varying degrees of success. Compounds (**16c,d**) were isolated unchanged from sulphuric acid in TFA/anisole[10] and

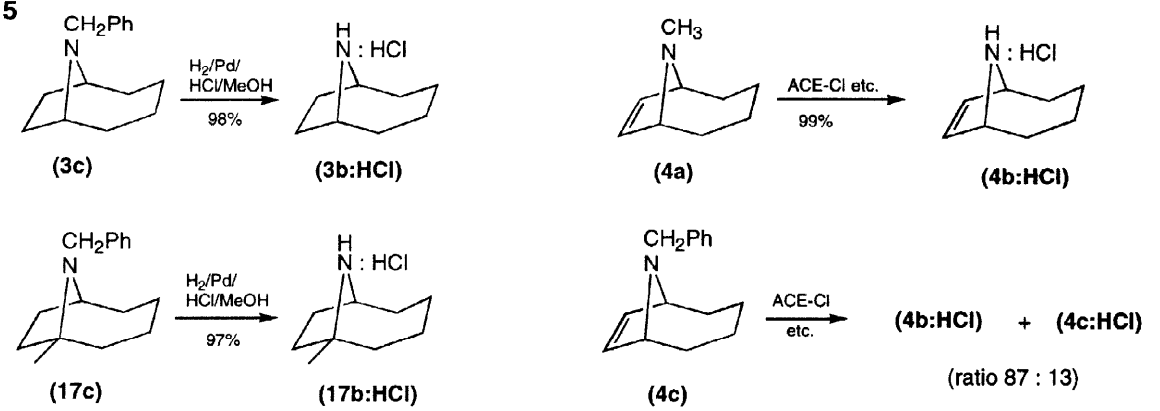
(16c) was unchanged on treatment with DDQ.[11] *N*-Benzylpiperidine (16b) was debenzylated successfully under Fe(II)-catalysed dealkylation conditions[12] although it survived a photosensitised single electron transfer reaction[13] unchanged. Details are recorded in the Experimental section but these results discouraged us from applying these methods to the *N*-benzylnortropanes.

N-Debenzylation using chloroformates is clearly not routinely applicable in the tropane series, even when steps are taken to ensure that the (slower[16b]) initial quaternisation reactions of the *N*-benzyl amines with chloroformates proceed to completion. This contrasts, not only with the behaviour of simple monocyclic analogues (where debenzylation occurs cleanly), but also with that of the homotropanes discussed below.[14a]

Norhomotropanes and norhomotrop-7-enes by dealkylation at nitrogen

The efficient synthesis of *N*-benzyl derivatives of the higher homologues (3c) and (4c), the *N*-methyl compounds (3a) and (4a), and 1-methyl- derivatives has already been described[4] but dealkylation at nitrogen in these compounds has not been investigated. Hydrogenolytic debenzylation of (3c) (as the hydrochloride) gave the hydrochloride of the parent secondary amine, norhomotropane (9-azabicyclo-[4.2.1]nonane) (3b) in high yield. This method is clearly applicable to all the saturated *N*-benzyl derivatives described earlier[4] and is also illustrated by the efficient formation of (17b:HCl) from (17c) (Scheme 5).

Scheme 5



Reductive debenzylation of the unsaturated amine (4c) using sodium metal in liquid ammonia was unsuccessful. The application of Fe(II)-catalysed dealkylation conditions[12] to (4c) also led only to recovery of starting material despite successful debenzylation of *N*-benzylpiperidine (16b) in a control experiment.

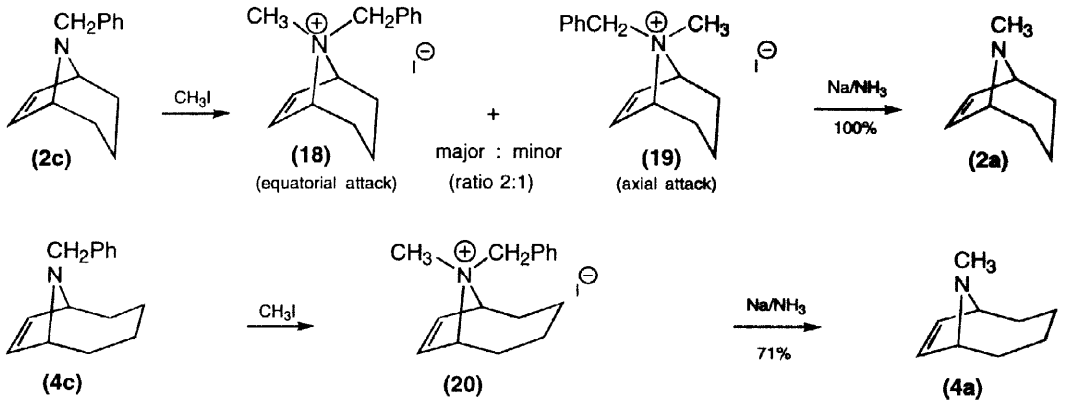
N-Deprotection of (4a) and (4c) using ACE-Cl was achieved following experiments using ^{1}H NMR spectroscopy to monitor the progress of the conversions. Addition of ACE-Cl to a dry solution of (4a) in $CDCl_3$ at 0°C resulted in immediate loss of the signals due to (4a) in the ^{1}H NMR spectrum with simultaneous formation of a signal at δ 4.7 (attributed to the bridgehead protons of the quaternary intermediate) together with a less intense signal at δ 4.25 (which was found to be associated with the corresponding protons of (4a:HCl)) although full spectral analysis was not possible. Addition of methanol and subsequent heating led to the isolation of (4b:HCl) and (4a:HCl) (ratio 79:21 by NMR). Importantly, when the reaction of the *N*-methyl analogue (4a) was repeated on a larger scale using freshly dried and distilled dichloromethane and with additional drying of the solution of the amine using anhydrous potassium carbonate prior to addition of the ACE-Cl, a significant improvement was noted. Completion of the procedure by heating with methanol gave pure (4b:HCl) in 99% yield with no trace of the (4a) isolated from the first experiment.

In contrast, treatment of the *N*-benzyl analogue (4c) with ACE-Cl produced no change at 0°C. It was necessary to heat the mixture for 24 hours at 60°C to achieve the loss of all of the ^{1}H NMR signals due to (4c); new signals appeared at δ 4.7 (major) and 4.35 (minor). Methanolysis then led to isolation of (4b:HCl) and (4c:HCl) (ratio 87:13 by NMR). The recovery of small amounts of the starting amine (4c) was thought to be due to the presence of traces of water, leading to competitive decomposition of the quaternary intermediate by the alternative pathway (path b). The reaction of (4c) was therefore repeated with scrupulous exclusion of moisture but this did not lead to further improvement.[14b] Nevertheless, the greater conformational flexibility of the homotropane ring system[23] clearly extends to (4c); this reduces the restrictions found in tropanes (Figure 1) to a useful extent and allows debenzylation without the need for a more electron-releasing aryl ring.

Exchange of *N*-Substituents by Methylation/Debenzylation

Cleavage of a benzyl group from a quaternary ammonium salt should be much easier than from a neutral amine and would normally be expected to occur in preference to loss of a methyl group. The benzyl amine (**2c**) was therefore methylated by heating with a large excess of iodomethane in an equivalent volume of acetone.[15] The product was isolated in 74% yield and was shown to be a mixture of two stereoisomeric quaternary ammonium salts (**18**) and (**19**) in the ratio *ca.* 2:1.

Scheme 6



The methyl singlet in the ^{1}H NMR spectrum of the major diastereoisomer appeared at δ 3.14 (upfield of that due to the minor diastereoisomer at δ 3.41); it was assumed to be in the shielding cone of the double bond and was therefore assigned to (**18**). Similarly, the signal due to the benzylic methylene group of the minor diastereoisomer appeared at δ 5.00 (upfield of that due to the major diastereoisomer at δ 5.29) and was assigned to (**19**). This preference for equatorial attack was anticipated on the basis of earlier work on tropane quaternisation.[16] The quaternary salts (**18**) and (**19**) showed resistance to reductive debenzylation with sodium amalgam (Emde reduction)[17] or thiophenol/base.[18] However, treatment with sodium in liquid ammonia led to successful debenzylation, giving (**2a**) in quantitative yield[14c] showing that both stereoisomers had reacted.

Methylation of (**4c**) using iodomethane gave a single stereoisomer which was assigned the structure (**20**) on the basis of close similarity to the ^{1}H NMR spectrum of (**18**). Treatment with sodium amalgam gave partial debenzylation but some unchanged quaternary salt was also recovered. The use of sodium in liquid ammonia was preferable and led to complete debenzylation; (**4a**) was isolated in 71% yield.

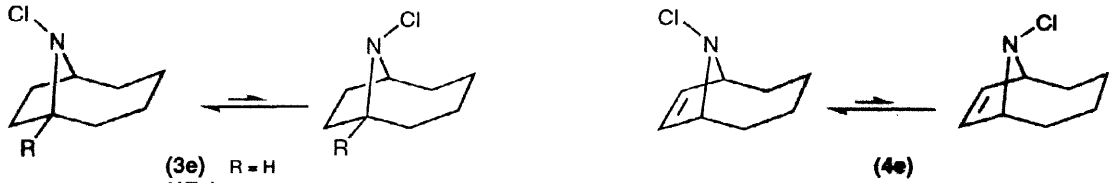
This constitutes a practical method for exchange of an *N*-benzyl group by *N*-methyl in both the tropane and homotropane ring systems.

Nitrogen Inversion Studies

The invertomer preference at neutral nitrogen is of interest in view of the 'equatorial' approach of electrophiles to the nitrogen during quaternisation reactions in both the tropenes and homotropenes studied here. The methyl group in tropane itself has been shown to prefer the 'equatorial' position (*syn-* to the 2-carbon bridge)[19] so that the lone pair is 'axial'. We have shown that this preference is maintained in *N*-benzyl and *N*-chloro derivatives.[1] Inversion barriers in unstrained *N*-alkyl amines are low[20] and our earlier ^{15}N NMR measurements[2c] had suggested that the barrier-raising 'bicyclic effect' would not be of major consequence in the homotropane ring system.[21] In view of the substantial increase in the inversion barrier routinely observed in *N*-chloro-compounds, we turned to the derivatives (**3e**), (**4e**), and (**17e**) (Figure 2) on the basis of our earlier observations[1,2] that the higher barriers in the *N*-chloro- compounds allow more reliable measurements at more accessible temperatures. Importantly, invertomer ratios for *N*-chloro- derivatives are generally very similar to those for the corresponding *N*-methyl compounds in a wide range of azabicyclic systems.[22]

In the event, the ^{1}H NMR spectra of these compounds were unchanged down to 213 K. We must conclude either that the nitrogen inversion barriers are very significantly lower than those observed in the tropanes[1] (and that coalescence has not yet been reached) or that the invertomer preferences are heavily weighted in favour of one conformer, presumably the syn- invertomer shown in Figure 2. This latter alternative is more likely and would agree with the syn- preference reported for the *N*-methyl in homotropane itself.[23]

Figure 2



(3e) R = H
(17e) R = CH_3

(4e)

The behaviour of the ethano-bridged compounds (**3e**) and (**17e**) is consistent with that observed for *N*-benzyl- and *N*-chloronortropane[1] where the invertomer having the *N*-substituent syn- to the 2-carbon bridge dominates at equilibrium (>95%). The effect of unsaturation in the 2-carbon bridge in the tropanes is to increase further the relative proportion of the invertomer having the *N*-substituent syn- to the 2-carbon (etheno-) bridge, largely as a result of reduced steric interactions.[1,2] It is therefore not surprising that the corresponding syn- invertomer should also dominate in the case of the dehydro-homotropane derivative (**4e**).

Following considerable early controversy,[16b] it is now accepted that 'equatorial' attack (over the ethano-bridge) is generally preferred in tropane quaternisations. The apparent contradiction between the preference for an equatorial substituent (axial lone pair) in the *N*-alkyl compounds and the preponderance of equatorial attack on the nitrogen has been discussed in detail in terms of the Curtin-Hammett principle;[24] the reaction in tropanes proceeds *via* the minor invertomer since it provides access to the lower energy transition state. The balance of developing interactions between the incoming electrophile and the axial 2,4-hydrogens *versus* the *exo*-6,7-hydrogens has been been invoked,[16b] although this explanation fails when applied to certain bulky electrophiles which can lead to a relative increase in axial attack.[16a] On this basis, removal of the *exo*-6,7 hydrogens in (**2c**) might be expected to tip the balance even further towards equatorial attack (on the less abundant invertomer) since any developing interaction with the 6,7- bridge is reduced even further. This is the reverse of what is observed; axial attack now accounts for about one third of the product (Scheme 6) although this ratio is very similar to that already recorded in the methylation of *N*-benzylnortropane (**1c**)[15b] where the *exo*-6,7 hydrogens are present. The factors controlling stereoselectivity in tropane quaternisation remain complex. The formation of only (**20**) from methylation of the unsaturated homologue (**4c**) means that, whatever the precise conformation of the 4-carbon bridge, the 7,8-dehydrohomotropanes also conform to the general preference in both ring systems not only for an 'equatorial' substituent but also for 'equatorial' attack on the less-abundant invertomer.

Summary

Difficulties in preparing the 6,7-dehydro- derivative of tropane (**2a**) meant that this was not a practical substrate for removal of the *N*-methyl group to produce (**2b**). The corresponding *N*-benzyl derivatives of nortropane (**1c**) and nortrop-6-ene (**2c**) were synthesised but removal of the benzyl group using chloroformates and other non-hydrogenolytic conditions was surprisingly unsuccessful, despite effective application of the same method to simple piperidine derivatives. It appears that steric restrictions on the S_N2 decomposition pathway for the quaternary intermediates in chloroformate-induced debenzylation (Figure 1 paths c & d) provide the key to the change in the balance of reactivity in tropanes allowing intrusion of the alternative return to starting amine (path b). An improvement to the debenzylation pathway in tropanes came only with the use of a more electron-rich benzyl group, probably as a result of greater S_N1 character in the C-N cleavage step during the debenzylation (path a). This led to partial formation of nortrop-6-ene (**2b**) from the *N*-*p*-methoxybenzyl derivative (**2d**). The *N*-deprotection of *N*-methyl and *N*-benzyl derivatives of homotropanes and 6,7-dehydro-homotropanes was easier than in tropanes, probably as a result of greater conformational freedom in the same key step. Careful exclusion of water was especially important in cases where the normal decomposition pathway was slowed. Methylation at nitrogen in (**4c**) was completely diastereoselective (approach over the etheno-bridge) despite the fact that this involves preferential attack on the minor invertomer, as inferred from VT NMR work with *N*-chloro analogues. Conversion of the *N*-benzyl derivatives of nortrop-6-ene and norhomotrop-7-ene [(**2c**) and (**4c**) respectively] into the corresponding *N*-methyl derivatives [(**2a**) and (**4a**)] was also possible *via* consecutive methylation and reductive debenzylation.

Experimental

NMR spectra were recorded on Varian EM 390 (90 MHz), Bruker ARX 250, or AM 300 spectrometers. Spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as internal reference unless indicated otherwise. Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), br (broad); protons identified as NH or OH were shown to be exchangeable with D_2O. In the ^{13}C spectra, (s), (d), (t), (q), are used to indicate quaternary, methine, methylene and methyl carbons respectively, as shown by off-resonance decoupling or DEPT experiments.

IR spectra were recorded on a Perkin-Elmer 298 spectrometer as solutions in CH_2Cl_2 unless indicated otherwise. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad), v (very). Mass spectra were measured routinely on a VG Micromass 14 spectrometer and were obtained using ionisation by electron impact unless stated otherwise; intensities are given as percentages of the base peak. Accurate mass measurements were obtained using a Kratos Concept mass spectrometer or through the EPSRC service at the University College of Swansea. Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected. Combustion Analyses were performed by CHN Analysis Ltd. of South Wigston, Leicester or Butterworth Laboratories Ltd., Teddington, Middlesex.

Reactions were performed under dry nitrogen using solvents dried by standard methods. Diethyl ether was dried over sodium wire and distilled from lithium aluminium hydride. Dichloromethane was distilled from calcium hydride. Petroleum ether and ethyl acetate were distilled prior to use. Methanol was purified with magnesium and iodine.[25] Tetrahydrofuran was distilled from sodium-benzophenone. Triethylamine and pyridine were distilled from KOH. Other solvents were dried and purified by standard methods.[26] Flash chromatography was carried out using Merck Kieselgel 60 (230 - 400 mesh). Thin-layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60 - 254).

Compound (**5**) was prepared as described in reference 1 but the yield was improved by the use of a rigorously purified sample of benzyl *N*-hydroxycarbamate.[5] Conversion of (**5**) into (**9**) was described earlier (compound (**10**) in reference 5) as was the synthesis of compounds (**3c**), (**4a**) and (**4c**).[4]

N-Methyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (6)

A solution of *N*-(benzyloxycarbonyl)-8-oxa-9-azabicyclo[3.2.2]non-6-ene (**5**) (1.50 g, 5.79 mmol) in dry tetrahydrofuran (50 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.95 g, 25.14 mmol) in dry tetrahydrofuran (50 ml). After refluxing for 10h, excess hydride was destroyed by the addition of water-saturated diethyl ether. The resulting mixture was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure to yield an orange oil. The crude material was purified by flash chromatography (59:40:1 diethyl ether:petroleum ether (b.p. 40-60°C):triethylamine) to afford (**6**) as a colourless oil (0.54 g, 67%), R_f 0.2. δ_H (300 MHz, $CDCl_3$): 1.18 - 1.94 (series of m, 6H), 2.58 (s, 3H), 3.47 (m, 1H), 4.44 (m, 1H), 6.13 (brdd, J = 9.2, 6.9 Hz, 1H), 6.32 (ddd, J = 9.2, 6.4, 1.5 Hz, 1H). δ_C (75 MHz, $CDCl_3$): 18.5 (t), 31.8 (t), 45.6 (q), 61.0 (d), 71.9 (d), 126.8 (d), 127.9 (d). ν_{max} (CH_2Cl_2): 3680w, 3620w, 3020s, 2980m, 2935m, 1515w, 1430w, 1255w, 1210s cm^{-1}. $^m/z$ (%): 139 (M^+, 14), 110 (12), 94 (28), 79 (64), 77 (15), 40 (30), 32 (100); $C_8H_{14}NO$ [MH^+] requires $^m/z$ 140.1075; observed 140.1087.

Cis-4-(Methylamino)cyclohept-2-enol (7) [from (6)]

Zinc powder (2.97 g, 45.44 mmol) was added to a stirred solution of (**6**) (0.36 g, 2.61 mmol) in glacial acetic acid (15 ml) at 0°C. The reaction mixture was heated at 50 - 60°C for 4 h and then filtered. The residue was washed with glacial acetic acid (10 ml) and the combined extracts evaporated under reduced pressure. The crude product was cooled, basified with concentrated ammonia solution and extracted with dichloromethane (6 x 30 ml). The combined organic layers were dried with Na_2SO_4 and the solvent removed under reduced pressure to yield (**7**) as a pale yellow solid (0.32 g, 87%) identical to the sample prepared by hydride reduction of (**9**).

Cis-4-(Methylamino)cyclohept-2-enol (7) [from (9)]

A solution of (**9**) (1.50 g, 5.74 mmol) in dry tetrahydrofuran (30 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.95 g, 24.92 mmol) in dry tetrahydrofuran (20 ml). After heating under reflux for 10 h, excess hydride was destroyed by the addition of water-saturated diethyl ether. The resulting mixture was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure to yield a yellow oil. The crude material was dissolved in diethyl ether (20 ml), and washed with 2M (aq) hydrochloric acid (2 x 25 ml). The combined aqueous extracts were then washed with fresh diethyl ether (3 x 25 ml) before being basified with 2M (aq) sodium hydroxide. The aqueous solution was extracted with dichloromethane (10 x 20 ml) and the combined organic extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure to afford (**7**) as a pale yellow solid (0.54 g, 66%). An analytical sample was prepared by

recrystallisation from petroleum ether (b.p. 80 - 100°C), m.p. 62 - 64°C. δ_H (300 MHz, $CDCl_3$): 1.54 - 1.84 (series of m, 6 H), 2.39 (s, 3H), 3.13 (td, J = 6.5, 1.8 Hz, 1H), 4.18 (td, J = 6.8, 1.7 Hz, 1H), 5.84 (dd, J = 11.4, 6.2 Hz, 1H), 6.13 (dd, J = 11.4, 6.3 Hz, 1H). δ_C (75 MHz), $CDCl_3$): 21.0 (t), 31.5 (t), 34.1 (q), 34.3 (d), 57.7 (d), 68.2 (d), 134.7 (d), 138.8 (d). ν_{max} (CH_2Cl_2): 3690w, 3600w, 3050s, 2980s, 2930m, 1600w, 1545w, 1440m, 1420s, 1260s, cm^{-1}. $^m/z$ (%): 141 (M^+, 21), 123 (10), 96 (60), 94 (21), 91 (15), 82 (16), 81 (16), 70 (100), 68 (19), 57 (20), 44 (22), 42 (29), 41 (18), 32 (19). Found: C, 68.20; H, 10.41; N, 9.73%. $C_8H_{15}NO$ requires: C, 68.04; H, 10.71; N, 9.92%.

In a later experiment,[5] a flask containing lithium aluminium hydride (0.115 g, 3.02 mmol) in dry tetrahydrofuran (2 ml) was alternately evacuated and purged with nitrogen and then cooled to 0°C. A solution of (**9**) (0.459 g, 1.76 mmol) in dry tetrahydrofuran (18 ml) was added dropwise from a syringe. The mixture was allowed to warm and was then heated under reflux for 3 h. Excess hydride was destroyed by the addition of water-saturated diethyl ether and the resulting mixture was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The steps involving washing with aqueous solutions (above) were omitted and, after flash chromatography using methanol : dichloromethane (5:95) (through which ammonia had been bubbled), a sample of (**7**) was obtained in improved yield (0.263 g, 95%).

Cis-4-(Methylamino)cycloheptanol (8)

A solution of (**7**) (0.32 g, 2.25 mmol) in methanol (30 ml) was hydrogenated at atmospheric pressure with a catalytic amount (*ca.* 15 mg) of 5% palladium on charcoal. After 16 h the catalyst was filtered off and the solvent was evaporated under reduced pressure to yield (**8**) as a pale yellow oil (0.29 g, 90%). δ_H (300 MHz, $CDCl_3$): 1.35 - 1.90 (series of m, 10H), 2.38 (s, 3H), 2.79 (m, 1H), 3.23 (brs, exch., 1H), 3.98 (m, 1H). δ_C (75 MHz, $CDCl_3$): 18.3 (t), 28.6 (t), 32.6 (t), 34.0 (q), 34.3 (t), 35.7 (t), 57.7 (d), 69.2 (d). ν_{max} (CH_2Cl_2): 3690w, 3600w, 3050s, 2980s, 2940s, 2860m, 1660w, 1600w, 1540w, 1460m, 1440s, 1420s, 1265s cm^{-1}. $^m/z$ (%): 144 (MH^+, 100), 130 (3), 100 (3), 70 (11), 44 (6); $C_8H_{18}NO$ [MH^+] requires $^m/z$ 144.1388; observed 144.1388.

Tropane (1a)

Thionyl chloride (18.9 µl, 0.26 mmol) was added dropwise to a solution of (**8**) (0.034 g, 0.24 mmol) in dry deuteriochloroform (1 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and it was monitored periodically by 90 MHz ^1H NMR spectroscopy. After 10 min., the NMR spectrum contained new signals, which were assigned to the alkyl chlorosulphite derivative. δ_H (90 MHz, $CDCl_3$): 1.80 - 2.60 (brm, 10H), 2.74 (brm, 3H), 3.28 (brm, 1H), 4.40 (brm, 1H), 9.25 (brs, 2H, NH_2^+). After 19.5 h, the NMR spectrum showed that the alkyl chlorosulphite intermediate had completely decomposed, giving the hydrochloride salt of the trans-1,4-chloroamine. The heterogeneous polymer-supported base, TABD (1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene crosslinked with 2% divinylbenzene) (0.2 g), was then added and the suspension was rocked for 12h. The base was removed by filtration under a nitrogen atmosphere and the filtrate was basified with gaseous ammonia. The white solid produced was removed by filtration and the ^1H NMR spectrum of the crude solution showed that the desired compound (**1a**) had been formed. Purification was effected by flash chromatography (using a solution of diethyl ether saturated with ammonia as eluent) to afford (**1a**) as a pale yellow oil (0.01 g, 34%), R_f 0.22, showing NMR spectra in agreement with those in the literature.[6]

Trop-6-ene (2a) [and the isomeric aziridine (10a)]

Thionyl chloride (161.1 µl, 2.21 mmol) was added dropwise to a solution of (**7**) (0.29 g, 2.03 mmol) and anhydrous lithium chloride (0.40 g) in dry deuteriochloroform (8 ml) at 0°C and the progress of the reaction was monitored by ^1H NMR spectroscopy. The reaction mixture was sonicated for 3 h before being left overnight at room temperature. Subsequently, the heterogeneous polymer-supported base TABD (1.6 g), was added and the resulting suspension was rocked for 12 h. The base was removed by filtration under a nitrogen atmosphere and the filtrate was basified with gaseous ammonia. The white precipitate formed was removed by filtration and the solvent was evaporated under reduced pressure to give an orange oil which was purified by flash chromatography [9:1, diethyl ether:petroleum ether (b.p. 40 - 60°C) saturated with gaseous ammonia]. The aziridine (**10a**) was eluted first and was isolated as a colourless oil (0.034 g, 13.5%), R_f 0.48. δ_H (300 MHz, $CDCl_3$): 1.25 -2.06 (series of m, 8H), 2.43 (s, 3H), 5.62 (m, 1H), 6.00 (brdd, J = 11.5, 5.7 Hz, 1H). The ^1H NMR spectrum was very similar to spectra of the corresponding *N*-benzyl compound (reported earlier as compound (**27**) in reference 1) and the *N*-*p*-methoxybenzyl analogue (**10d**) described below. Further elution gave (**2a**) as a colourless oil (0.035 g, 14%), R_f 0.34. δ_H (300 MHz, $CDCl_3$): 1.25 - 2.06 (series of m, 6H), 2.21 (s, 3H), 3.40 (brd, J = 2.5 Hz, 2H), 5.86 (s, 2H). $^m/z$ (%): 123 (M^+, 36), 108 (14), 94 (100), 80 (16), 70 (21), 57 (26); $C_8H_{13}N$ [M^+] requires $^m/z$ 123.1048; observed 123.1048.

***N*-(*p*-Methoxybenzoyl)-8-oxa-9-azabicyclo[3.2.2]non-6-ene (11)**

Cyclohepta-1,3-diene (2.0 g, 21.24 mmol) was added to a suspension of tetramethylammonium periodate

(7.84 g, 29.58 mmol) in chloroform (140 ml). A solution of *p*-methoxybenzohydroxamic acid (6.2 g, 30.24 mmol) in dimethylformamide (20 ml) and chloroform (60 ml) was added dropwise to this mixture, with stirring at room temperature, over 20 min. The resulting mixture was left to stir for a further 22 h and the chloroform was removed under reduced pressure. The residue was dissolved in diethyl ether (400 ml) and washed with water (4 x 100 ml). The organic layer was separated, dried with $MgSO_4$, and the solvent was removed under reduced pressure to yield an orange gum which was purified by flash chromatography (9:1 diethyl ether: petroleum ether (b.p. 40 - 60 °C)) to afford (**11**) as a pale pink waxy solid (5.49 g, 100%), R_f 0.36. An analytical sample was prepared by recrystallisation from petroleum ether (b.p. 80 - 100 °C), m.p. 62 - 64°C. δ_H (300 MHz, $CDCl_3$) [spectrum broadened owing to slow *N*-CO bond rotation]: 1.35 - 1.90 (series of m, 6H), 3.80 (s, 3H), 4.74 (brs, 1H), 5.40 (brs, 1H) 6.28 (brt, J = 3.7 Hz, 2H), 6.87 and 7.73 (AA'BB', 4H). δ_C (75 MHz, $CDCl_3$): 18.4 (t), 28.4 (t), 30.0 (t), 55.0 (q), 76.1 (d), 112.8 (d), 126.5 (s), 127.5 (d), 129.0 (d), 130.5 (d), 161.0 (s). ν_{max} (CH_2Cl_2): 3020m, 2940s, 2870w, 2840m, 1635s, 1600s, 1570s, 1505s, 1430s, 1375s, 1300s, 1240s, 1215s cm^{-1}. $^m/z$ (%): 259 (M^+, 7), 243 (4), 152 (11), 135 (100), 107 (7), 92 (7), 77 (13), 32 (71). Found: C, 69.26; H, 6.42; N, 5.25%. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40%.

Cis-4-(*p*-Methoxybenzoylamino)cyclohept-2-enol (12)

A solution of (**11**) (5.96 g, 0.02 mol) in aqueous tetrahydrofuran (THF:H_2O, 10:1) (140 ml) was cooled to 0°C with stirring under nitrogen. Aluminium amalgam [prepared by sequential exposure (10 - 20s) of small strips of aluminium foil (5.38 g, 0.20 mol) to 1M (aq) potassium hydroxide solution, distilled water, aqueous mercuric chloride solution (0.5%), distilled water, and tetrahydrofuran] was then added to the solution of (**11**). Stirring was continued at 0°C for 2 days. Subsequently, fresh amalgam (from 1.8 g, 0.07 mol of aluminium foil) was added to the reaction mixture and stirring was continued at 0°C for a further 3 days. The reaction mixture was diluted with THF (410 ml), stirred vigorously for 1.5 h, and then filtered through a pad of celite. The filtrate was diluted with toluene and concentrated in vacuo to give a yellow-white solid. Trituration with diethyl ether afforded (**12**) as an insoluble white crystalline material (3.92 g, 65%). An analytical sample was prepared by recrystallisation from toluene, m.p. 177 - 178°C. δ_H (300 MHz, CD_3OD); 1.50 - 2.07 (series of m, 6H), 3.83 (s, 3H), 4.37 (brd, J = 10.2 Hz, 1H), 4.61 (brd, J = 8.6 Hz, 1H), 5.64 (brdt, J = 12.0, 3.0 Hz, 1H), 5.78 (brdt, J = 12.0, 2.6 Hz, 1H), 6.96 and 7.79 (AA'BB', 4H). δ_C (75 MHz, CD_3OD): 26.4 (t), 34.9 (t), 37.0 (t), 52.3 (d), 55.9 (q), 72.5 (d), 114.6 (d), 127.8 (s), 130.1 (d), 133.7 (d), 138.8 (d), 163.8 (s), 168.7 (s). ν_{max} (CH_2Cl_2): 3350w, 3310w, 2915s, 2460s, 2400w, 1620s, 1570m, 1450s, 1435m, 1375m cm^{-1}. $^m/z$ (%): 261 (M^+, 1), 243 (13), 152 (26), 135 (100), 107 (8), 92 (10), 77 (13), 32 (73). Found: C, 68.74; H, 7.32; N, 5.28%. $C_{15}H_{19}NO_3$ requires: C, 68.94; H, 7.33; N, 5.36%.

Cis-4-(*p*-Methoxybenzoylamino)cycloheptanol (13)

A solution of (**12**) (1.0 g, 3.83 mmol) in methanol (40 ml) was hydrogenated at atmospheric pressure using 5% palladium on charcoal (*ca.* 20 mg). After 16h, the catalyst was filtered off; removal of solvent under reduced pressure gave (**13**) as a white crystalline solid (1.01 g, 100%). An analytical sample was prepared by recrystallisation from toluene, m.p. 98 - 99°C. δ_H (300 MHz, CD_3OD): 1.25 - 2.17 (series of m, 10H), 3.80 (s, 3H), 3.86 (m, 1H), 4.03 (m, 1H), 6.93 and 7.77 (AA'BB', 4H). δ_C (75 MHz, CD_3OD): 21.8 (t), 29.6 (t), 33.8 (t), 36.4 (t), 38.4 (t), 52.1 (d), 56.2 (q), 72.2 (d), 114.9 (d), 128.3 (s), 130.4 (d), 163.9 (s), 168.9 (s). ν_{max} (CH_2Cl_2): 3330w, 2940s, 2850s, 1620m, 1600m, 1570w, 1525m, 1500m, 1460s, 1375m, 1250m cm^{-1}. $^m/z$ (%): 263 (M^+) (13), 152 (16), 135 (100), 107 (16), 92 (23), 77 (31), 64 (13). $C_{15}H_{21}NO_3$ [MH^+] requires 264.1599; observed 264.1600. Found: C, 68.37; H, 7.94; N, 5.13%. $C_{15}H_{21}NO_3$ requires C, 68.41; H, 8.04; N, 5.32%.

Cis-4-(*p*-Methoxybenzylamino)cycloheptanol (14)

A solution of (**13**) (0.71 g, 2.20 mmol) in dry tetrahydrofuran (22 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.44 g, 11.70 mmol) in dry tetrahydrofuran (52 ml). After heating at reflux for 10h, the excess hydride was destroyed by addition of water-saturated diethyl ether. The resulting mixture was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to yield a yellow oil. Subsequent purification by flash chromatography (95:4:1 diethyl ether:methanol:triethylamine) afforded (**14**) as a colourless oil (0.55 g, 81%), R_f 0.20. δ_H (300 MHz, $CDCl_3$): 1.40 - 1.98 (series of m, 10H), 2.99 (m, 1H), 3.14 (brs, exch, 1H) 3.63 & 3.72 (AB quartet, J = 12.6 Hz, 2H), 3.78 (s, 3H), 4.02 (m, 1H), 6.86 and 7.24 (AA'BB', 4H). δ_C (75 MHz, $CDCl_3$): 18.2 (t), 28.9 (t), 32.7 (t), 34.4 (t), 35.5 (t), 50.9 (t), 55.1 (d), 55.3 (q), 69.1 (d), 113.9 (d), 129.4 (d), 131.7 (s), 158.8 (s). ν_{max} (CH_2Cl_2): 3600w, 3180w, 3040m, 2930m, 2850m, 1610w, 1510m, 1460m, 1240s cm^{-1}. $^m/z$ (%): 249 (M^+, 3), 176 (9), 136 (4), 121 (100), 91 (7), 84 (9), 77 (7), 41 (9); $C_{15}H_{24}NO_2$ [MH^+] requires $^m/z$ 250.1807; observed 250.1807.

Cis-4-(*p*-Methoxybenzylamino)cyclohept-2-enol (15)

A solution of (**12**) (0.71 g, 2.27 mmol) in dry tetrahydrofuran (23 ml) was added dropwise to a stirred

slurry of lithium aluminium hydride (0.42 g, 11.06 mmol) in dry tetrahydrofuran (49 ml). After heating at reflux for 10 h, excess hydride was destroyed by addition of water-saturated diethyl ether. The resulting mixture was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure to yield a yellow, glassy solid. Subsequent purification by flash chromatography (95:4:1 diethyl ether:methanol:triethylamine) afforded **(15)** as a white crystalline solid (0.57 g, 85%), R_f 0.46. An analytical sample was prepared by recrystallisation from toluene, m.p. 39 - 40°C. δ_H (300 MHz, $CDCl_3$): 1.55 - 1.84 (series of m, 5H), 2.17 - 2.32 (m, 1H), 3.27 (td, J = 6.4, 1.8 Hz, 1H), 3.63 & 3.73 (AB quartet, J = 12.6 Hz, 2H), 3.77 (s, 3H), 4.19 (td, J = 6.8, 1.6 Hz, 1H), 5.86 (dd, J = 11.4, 6.2 Hz, 1H), 6.15 (dd, J = 11.4, 6.3 Hz, 1H), 6.85 and 7.21 (AA'BB', 4H). δ_C (75 MHz, $CDCl_3$): 21.2 (t), 31.8 (t), 34.3 (t), 51.0 (t), 55.1 (d), 55.2 (q), 68.2 (d), 113.9 (d), 129.4 (d), 131.6 (s), 134.6 (d), 139.0 (d), 158.8 (s). ν_{max} (CH_2Cl_2): 3595w, 3110w, 3040m, 2980m, 2920m, 1605w, 1510m, 1420m, 1250s cm^{-1}. $^m/z$ (%): 247 (M^+, 7), 229 (8), 122 (16), 121 (100), 91 (13), 77 (15), 32 (21). Found: C, 72.69; H, 8.77; N, 5.72%. $C_{15}H_{21}NO_2$ requires: C, 72.84; H, 8.56; N, 5.66%.

***N-p*-Methoxybenzylnortropane (1d)**

Thionyl bromide (19.45 µl, 0.25 mmol) was added dropwise to a stirred solution of **(14)** (0.052 g, 0.21 mmol) in dry deuteriochloroform (1 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24 h. The solvent was removed under reduced pressure and replaced by dry acetone (1 ml). After cooling to 0°C, anhydrous 2,2,6,6-tetramethylpiperidine (TMP) (120 µl) was added and the solution was left to warm to room temperature, whereupon it was heated at 50°C for 5 h.

The solvent was removed under reduced pressure and the solid residue was triturated with diethyl ether. The combined ethereal extracts were basified with gaseous ammonia and the white solid which formed was removed by filtration. Evaporation of solvent under reduced pressure left an orange oil. Purification by flash chromatography (80:19:1, petroleum ether (40 - 60°C):diethyl ether:triethylamine) afforded **(1d)** as a colourless oil (0.016 g, 33%), R_f 0.21. δ_H (300 MHz, $CDCl_3$): 1.27 - 2.05 (series of m, 10H), 3.15 (brt, J = 3.2 Hz, 2H), 3.45 (s, 2H), 3.79 (s, 3H), 6.84 and 7.29 (AA'BB', 4H). δ_C (75 MHz, $CDCl_3$): 16.8 (t), 26.4 (t), 31.4 (t), 55.2 (q), 56.3 (t), 59.3 (d), 113.5 (d), 129.7 (d), 132.2 (s), 158.4 (s). ν_{max} (CH_2Cl_2): 2930s, 2865m, 2830m, 1600w, 1505m, 1230m cm^{-1}. $^m/z$ (%): 231 (M^+, 87), 202 (11), 188 (24), 134 (23), 121 (97), 110 (13), 94 (23), 77 (26), 55 (30), 41 (51); $C_{15}H_{21}NO$ [M^+] requires $^m/z$ 231.1623; observed 231.1623.

***N-p*-Methoxybenzylnortrop-6-ene (2d) [and the isomeric aziridine (10d)]**

Thionyl bromide (73.85 µl, 0.95 mmol) was added dropwise to a stirred solution of **(15)** (0.20 g, 0.79 mmol) in dry deuteriochloroform (4 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24 h. The solvent was removed under reduced pressure and replaced with dry acetone (4 ml). After cooling to 0°C, anhydrous TMP (455 µl) was added and the solution was left to warm to room temperature, whereupon it was heated at 50°C for 5 h.

The reaction mixture was worked up as described above for **(1d)** and provided a crude orange oil. Purification was effected by flash chromatography (70:29:1, petroleum ether (40 - 60°C):diethyl ether:triethylamine). The aziridine **(10d)** was eluted first and was isolated as a colourless oil (0.022 g, 12%), R_f 0.31. δ_H (300 MHz, $CDCl_3$): 1.51 - 2.27 (series of m, 8H), 3.28 (d, J = 13.4 Hz, 1H), 3.74 (d, J = 8.4 Hz 1H), 3.79 (s, 3H), 5.65 (ddd, J = 11.3, 6.4, 3.6 Hz, 1H), 5.83 (ddd, J = 11.6, 4.1, 2.7 Hz, 1H), 6.85 and 7.27 (AA'BB', 4H); δ_C (75 MHz, $CDCl_3$): 23.5 (CH_2), 29.8 (CH_2), 31.2 (CH_2), 42.8 (CH), 47.5 (CH), 55.2 (CH_3), 64.5 (CH_2), 113.6 (CH), 126.2 (CH), 128.8 (CH), 131.8 (C), 133.3 (CH), 158.5 (C); ν_{max} (CH_2Cl_2): 3000m, 2920s, 2830m, 1605m, 1505s, 1235s cm^{-1}; $^m/z$ (%): 229 (M^+, 21), 169 (10), 121 (100), 108 (49), 91 (37), 81 (60), 65 (20), 53 (36), 41 (51); $C_{15}H_{19}NO$ [M^+] requires $^m/z$ 229.1467; observed 229.1467.

Further elution gave the desired compound **(2d)** as a colourless oil (0.088 g, 48%), R_f 0.20: δ_H (300 MHz, $CDCl_3$): 1.22 - 1.75 (series of m, 6H), 3.41 (s, 2H), 3.43 (brd, J = 2.6 Hz, 2H), 3.77 (s, 3H), 5.89 (s, 2H), 6.83 and 7.26 (AA'BB', 4H); δ_C (75 MHz, $CDCl_3$): 16.6 (CH_2), 25.6 (CH_2), 55.2 (CH_3), 57.1 (CH_2), 65.1 (CH), 113.5 (CH), 129.2 (CH), 129.8 (CH), 132.3 (C), 158.3 (C); ν_{max} (CH_2Cl_2): 2930s, 2830m, 1605w, 1580w, 1505m, 1450w, 1325w, 1235m cm^{-1}; $^m/z$ (%): 229 (M^+, 70), 200 (4), 169 (6), 149 (4), 121 (100), 108 (13), 94 (27), 77(34), 41 (36); $C_{15}H_{19}NO$ [M^+] requires $^m/z$ 229.1467; observed 229.1467.

Nortop-6-ene (2b) [from (2d)]

α-Chloroethyl chloroformate (ACE-Cl, 241.1 µl, 2.23 mmol) was added dropwise to a stirred solution of **(2d)** (0.26 g, 1.12 mmol) in dry dichloromethane at 0°C over 15 min.. The mixture was allowed to warm to room temperature and was then heated under reflux for 24 h. The solvent was removed under reduced pressure and the residue dissolved in dry methanol (6 ml). The resulting solution was heated at 60°C for 2 h and evaporated to yield a yellow solid. Partial purification was achieved by dissolution in water (2 ml) and washing with diethyl ether (3 x 4 ml). The aqueous layer was then basified with 2M aqueous sodium hydroxide and the product extracted into dichloromethane (10 x 2 ml). The combined organic extracts were dried with Na_2SO_4

and the solvent removed under reduced pressure to yield a yellow oil. A ^{1}H NMR spectrum revealed the presence of some unchanged (**2d**) together with a product identified as the nor-compound (**2b**) in a yield of 50% (estimated by NMR integration). A sample was chromatographed on silica using chloroform : methanol : triethylamine (87:12:1) to give (**2b**) as a colourless oil. It was not easy to identify the fractions containing (**2b**) from the small-scale chromatographic separation since the compound is not UV-active and does not stain with iodine (R_f = 0.19). δ_H (300 MHz, $CDCl_3$): 1.44 - 2.22 (series of m, 6H), 4.30 (brs, 2H), 5.08 (brs, 1H, exch), 6.09 (s, 2H); δ_C (75 MHz, $CDCl_3$): 22.4 (CH_2), 29.7 (CH_2), 58.7 (CH), 129.0 (CH); ν_{max} (CH_2Cl_2): 3660w, 3450w, 2960s, 2930s, 2860m, 1660w, 1610m, 1590m, 1510w, 1450w, 1395w cm^{-1}; ^{m}/z (%): 110 (MH^+, 100), 105 (11), 88 (56), 80 (10), 74 (6); $C_7H_{11}N$ [M^+] requires ^{m}/z 109.0891; observed 109.0892.

Preparation of *N*-benzylpiperidine (16b)

N-Benzoylpiperidine was prepared by a standard method[27] and was isolated as a viscous, straw-coloured oil in a yield of 93%. It was used without further purification. A solution of *N*-benzoylpiperidine (0.79 g, 4.2 mmol) in dry diethyl ether (20 ml) was added dropwise to a stirred slurry of lithium aluminium hydride(0.69 g, 18.23 mmol) in diethyl ether (30 ml). After heating at reflux overnight, the solution was cooled and excess hydride destroyed by careful addition of water-saturated diethyl ether. After drying with $MgSO_4$, evaporation under reduced pressure gave (**16b**) as a colourless oil (0.62 g, 85%). δ_H (90 MHz, $CDCl_3$): 1.41 (brm, 6H), 2.30 (brm, 4H), 3.38 (s, 2H), 7.19 (s, 5H).

Preparation of *N*-*p*-methoxybenzylpiperidine (16c)

p-Methoxybenzoyl chloride (5.52 g, 0.032 mol) was added carefully, with cooling, over a period of 1 h to a stirred solution of sodium hydroxide (1.51 g, 0.038 mol), piperidine (2.9 ml, 0.029 mol) and water (12 ml). After stirring for 1 h, the oily layer was extracted into dichloromethane (3 x 20 ml) and the combined organic extracts were washed with water (20 ml) and dried with Na_2SO_4. Evaporation of the solvent under reduced pressure afforded *N*-*p*-methoxybenzoylpiperidine as a yellow oil (5.59 g, 87%) which was not purified further. δ_H (90 MHz, $CDCl_3$): 1.59 (brs, 6H), 3.48 (brs, 4H), 3.71 (s, 3H), 6.83 and 7.19 (AA'BB', 4H).
A solution of the *N*-*p*-methoxybenzoylpiperidine (1.37 g, 6.24 mmol) in dry diethyl ether (50 ml) was added to stirred slurry of lithium aluminium hydride (1.03 g, 27.12 mmol) in diethyl ether (30 ml) as described for (**16a**). A similar work-up procedure gave (**16c**) as a colourless oil (1.06 g, 83%). δ_H (90 MHz, $CDCl_3$): 1.35 (brm, 6H), 2.31 (brm, 4H), 3.34 (s, 2H), 6.76 and 7.13 (AA'BB', 4H).

Preparation of *N*-3,4-dimethoxybenzylpiperidine (16d)

3,4-Dimethoxybenzoyl chloride (1.47 g, 7.33 mmol) was added to a mixture of sodium hydroxide (0.38 g, 9.54 mmol), piperidine (0.73 ml, 7.33 mmol) and water (3.83 ml) as described above for (**16c**). The product (**16d**) was isolated as a colourless oil (1.64 g, 90%). δ_H (90 MHz, $CDCl_3$): 1.56 (brs, 6H), 3.44 (brs, 4H), 3.79 (s, 6H), 6.82 (m, 3H).

Debenzylation of (16a,b,c) with VOC-Cl

A solution of vinyl chloroformate (127.5 µl, 1.5 mmol) in dry dichloromethane (10 ml) was cooled to 0°C, a solution of the *N*-substituted piperidine (1.16 mmol) in dry dichloromethane (10 ml) was added dropwise, and the reaction mixture allowed to warm to room temperature. After heating at reflux for 4h, a small aliquot was removed and evaporated; a ^{1}H NMR spectrum confirmed that the reaction with VOC-Cl was complete. Hydrogen chloride was bubbled through the reaction mixture and the solvent was removed under reduced pressure. The residue was dissolved in methanol (30 ml) and heated at 50 - 60°C for 4.5 h. The mixture was evaporated under reduced pressure to leave piperidine hydrochloride as a white solid in each case after trituration with cold diethyl ether (yields varied from 83 - 88%).

Reaction of (16a) with ACE-Cl

ACE-Cl (291 µl, 1.5 mmol) was added dropwise from a micro-syringe over a period of 10 mins to a stirred solution of *N*-ethyl piperidine (0.23 g, 2.07 mmol) in dry 1,2-dichloroethane (10 ml) at 0°C. After heating at reflux for 3 h, the solvent was removed under reduced pressure, methanol (20 ml) was added, and the resulting solution was heated at 50°C for 3 h. After cooling, removal of solvent, and recrystallisation from ethanol, piperidine hydrochloride was obtained as a white crystalline solid (0.19 g, 77%).

Unsuccessful attempts to remove benzyl and *p*-methoxybenzyl groups from cyclic and bicyclic amines

i) Chloroformates Application of the methods based on VOC-Cl and ACE-Cl (as described above for (**16a,b,c**)) to the following compounds led to re-isolation of unchanged starting material as the hydrochloride salt in each case. *N*-Benzylnortropane (**1c**) gave only starting material with VOC-Cl and with ACE-Cl; following recognition of the importance of total exclusion of water, the latter reaction was repeated with extreme precautions but gave the same result.[14b]

N-Benzylnortrop-6-ene (**2c**) gave only starting material with VOC-Cl.

ii) Sulphuric acid in TFA/Anisole[10] 5% Sulphuric acid in trifluoroacetic acid (TFA)/anisole has been used removal of electron-rich benzyl groups (including *p*-methoxybenzyl and 3,4-dimethoxybenzyl groups) from tertiary amines. Attempted removal of the *p*-methoxybenzyl group from *N*-*p*-methoxybenzylpiperidine (**16c**) and from (**16d**) using these conditions gave only the TFA salt of the starting material.

iii) Photosensitised single electron transfer[13] Application of this debenzylation method is illustrated using (**16b**). A mixture of acetonitrile:water (7:3) (37 ml) containing (**16b**) (0.12 g, 0.69 mmol, 1.85 x 10^{-2} M) and 9,10-dicyanoanthracene (0.001g, 0.003 mmol, 8.3 x 10^{-5} M) (prepared from sodium 9,10-anthraquinone α-sulphonate[28] as described in reference 29) in a pyrex tube was irradiated in a Rayonet reactor fitted with 3500 Å lamps. The reaction was monitored using TLC but after 10 h, only starting material was present. A sample was removed and the only amine isolated was (**16b**) as shown by ^{1}H NMR spectroscopy. Irradiation using 3000Å lamps for a period of 24 h produced only starting material.

The same procedure was also applied to *N*-benzylpyrrolidine without success.

iv) Fe(II)-Catalysed dealkylation of tertiary amines[12] A stirred solution of *N*-benzyl-9-azabicyclo[4.2.1]non-7-ene (**4c**) (0.057 g, 0.268 mmol) in dichloromethane (0.5 ml) was cooled to 0°C and treated with m-chloroperoxybenzoic acid (0.058 g, 0.268 mmol, 80% purity) in several portions. Subsequently, a 1N aqueous solution of iron(II)chloride was added and stirring was continued at -10° to 0°C for a further 7 h, before being left overnight at 4°C. The mixture was treated with a 2M solution of aqueous hydrochloric acid (1.3 ml) and the dichloromethane was removed under reduced pressure. The aqueous residue was washed with diethyl ether (2 x 1.5 ml), basified with 2M aqueous sodium hydroxide, and extracted with dichloromethane (10 x 2 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure to afford a yellow/orange oil. Trituration with cold petroleum ether (b.p. 60 - 80°C) removed the colour, leaving a white solid identified by ^{1}H NMR as the hydrochloride salt of the starting material (**4c**).

The validity of the method in our hands was confirmed by application to *N*-benzylpiperidine (**16b**). The product was isolated (in 65% yield) as piperidine hydrochloride (the organic extracts were treated with gaseous HCl, prior to evaporation of the solvent).

v) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[11] A solution of (**16c**) (0.20 g, 0.98 mmol) in dichloromethane (7 ml) was added dropwise to a stirred solution of DDQ (0.44 g, 1.95 mmol) in dichloromethane (8 ml), followed by addition of water (0.4 ml). The resulting mixture was stirred at room temperature for 48 h. After washing with aqueous sodium metabisulphite (15%, 3 x 15 ml) and aqueous sodium bicarbonate (15%, 3 x 15 ml), the organic layer was dried with $MgSO_4$. Acidification with gaseous HCl, followed by evaporation of solvent, gave only the HCl salt of starting material (**16c**).

vi) Alkali metals in liquid ammonia The isolation of only starting material from attempted debenzylation of (**2c**) with alkali metals in liquid ammonia has been reported previously.[1] A similar result was obtained from (**4c**) with sodium in liquid ammonia.

Demethylation of tropan-3α-ol with ACE-Cl

This literature procedure[8b] was performed on a commercial sample of tropan-3α-ol to confirm the viability of the method. ACE-Cl (185.4 µl, 1.72 mmol) was added dropwise to a stirred solution of tropan-3α-ol (0.24 g, 1.72 mmol) in dry 1,2-dichloroethane (10 ml) at 0°C over 15 min and the mixture was heated at reflux for 7 h. The solvent was removed under reduced pressure and the residue dissolved in methanol (10 ml). The solution was heated at 50°C for 3h. Removal of the solvent under reduced pressure left a pale yellow solid which was purified by recrystallisation from ethanol to give nortropan-3α-ol hydrochloride as fine white crystals (0.19 g, 67%), m.p. 199 - 201°C (lit.[30] m.p. 200°C).

9-Azabicyclo[4.2.1]nonane (Norhomotropane) (3b) [by debenzylation of (3c)]

A solution of (**3c**)[4] (0.19 g, 0.88 mmol) in dry methanol (9 ml) was acidified with gaseous hydrogen chloride and hydrogenated at atmospheric pressure in the presence of 10% palladium on charcoal. After 16 h, the solution was filtered through celite and then through a Millipore 0.2Mµ Millex-FG disposable filter giving a clear solution which was evaporated under reduced pressure to yield (**3b:HCl**) (0.139 g, 98%) as a white, hygroscopic solid. δ_H (300 MHz, $CDCl_3$): 1.40 - 2.50 (brm, 12H), 4.19 (brs, 2H), 9.01 and 9.88 (each vbrs, NH_2^+); δ_C (75 MHz, $CDCl_3$): 23.2, 29.7, 31.6 (3 x CH_2), 57.2 (CH); ν_{max} (CH_2Cl_2): 2930brs, 2800brs, 2760brs, 2710m, 2650m, 2560m, 2500m, 1590s, 1470brm, 1265w cm^{-1}; ^{m}/z (%): 125 (M^+-HCl, 36), 96 (18), 82 (100), 69 (44), 68 (81), 56 (21), 43 (36), 42 (37), 41 (86), 39 (75).

Basification with NaOH (aq), extraction into dichloromethane, and addition of one equivalent of picric acid (220 mg, 0.86 mmol), gave the picrate of (**3b**), m.p. 229 - 230°C (decomp.) from ethanol [lit.[31] m.p. 228°C (decomp.)]. Found : C, 47.95; H, 5.13; N, 15.76%. $C_8H_{15}N$:$C_6H_3N_3O_7$ requires: C, 47.46; H, 5.12; N, 15.81%.

9-Azabicyclo[4.2.1]non-7-ene (Norhomotrop-7-ene) (4b) [by demethylation of (4a)]

α-Chloroethyl chloroformate (2.456 ml, 22.74 mmol) was added dropwise, under dry nitrogen, to a stirred solution of **(4a)**[4] (1.04 g, 7.58 mmol) in dry dichloromethane (10 ml) [this solution had previously been dried over anhydrous potassium carbonate] and the solution was heated at 35°C for 4 h. The solvent was removed under reduced pressure and the residue dissolved in methanol (20 ml) and heated at 55°C for 3 h. The solvent was evaporated under reduced pressure to yield **(4b:HCl)** (1.203 g, 99%) as a white hygroscopic solid. δ_H (300 MHz, $CDCl_3$): 1.40 - 2.50 (brm, 8H), 4.69 (brs, 2H), 5.86 (s, 2H), 9.31 and 10.35 (each vbrs, NH_2^+); δ_C (75 MHz, $CDCl_3$): 23.2 & 29.1 (CH_2), 62.3 (CH), 129.7 (CH); ν_{max} (CH_2Cl_2): 2930brs, 2810m, 2790m, 2740m, 2690m, 2650m, 2610m, 2540m, 1710m, 1580s, 1450brm, 1410m, 1360m, 1220w cm^{-1}; $^m/z$ (%): 123 (M^+-HCl, 12), 94 (16), 80 (100), 67 (38), 53 (10), 41 (36), 40 (12), 39 (40).

The picrate of **(4b)** was prepared [as described above for **(3b)**] and had m.p. 226 - 227°C (decomp.) from ethanol. Found : C, 48.11; H, 4.58; N, 15.69%. $C_8H_{13}N{:}C_6H_3N_3O_7$ requires: C, 47.73; H, 4.58; N, 15.90%.

9-Azabicyclo[4.2.1]non-7-ene (Norhomotrop-7-ene) (4b) [by debenzylation of (4c)]

Partial debenzylation was achieved by treatment of **(4c)**[4] (0.17 g, 0.80 mmol) with ACE-Cl (432μl, 4 mmol) in $CDCl_3$ (2 ml). No reaction occurred at 0°C and the mixture was heated at 60°C for a total of 24 h until all the signals corresponding to **(4c)** had disappeared. The solvent was removed and, after heating in methanol (as described in the previous experiment), the product was isolated as an oily yellow solid (122 mg) which was shown to consist of a mixture of **(4b:HCl)** and **(4c:HCl)** in a ratio of 87:13 as shown by integration of ^1H and ^{13}C NMR spectra.

1-Methyl-9-azabicyclo[4.2.1]nonane (17b)

The hydrochloride salt **(17b:HCl)** (0.778 g, 97%) was prepared from **(17c)**[4] (1.05 g, 4.58 mmol) as described for **(3b:HCl)** above. δ_H (300 MHz, $CDCl_3$): 1.55 - 2.27 (m, 11H), 1.70 (s, 3H), 2.50 (m, 1H), 4.19 (brm, 1H), 9.27 (vbrd, J = 10.2 Hz, NH^+), 9.63 (vbrs, 1H, NH^+); δ_C (75 MHz, $CDCl_3$): 22.2 & 22.3 (CH_2), 26.1 (CH_3), 29.8, 30.0, 35.2, 38.9 (4 x CH_2), 55.9 (CH), 66.1 (C); ν_{max} (CH_2Cl_2): 2930brs, 2800brs, 2720brs, 2490m, 1590s, 1475m, 1465m, 1420m, 1380m, 1210w cm^{-1}; $^m/z$ (%): 139 (M^+-HCl, 25), 110 (10), 96 (74), 84, (57), 82 (100), 79 (45), 67 (26), 55 (21), 41 (40).

The picrate of **(17b)** was prepared [as described above for **(3b)**] and had m.p. 275 - 276°C (decomp.) from ethanol. Found: C, 49.05; H, 5.45; N, 15.00% $C_9H_{17}N{:}C_6H_3N_3O_7$ requires: C, 48.91; H, 5.47; N, 15.21%.

Quaternisation of (2c) with iodomethane; formation of (18) and (19)

Iodomethane (400 μl, 6.43 mmol) was added from a microsyringe to a solution of **(2c)** (0.13 g, 0.63 mmol) in dry acetone (400 μl) at 0°C. After heating at reflux for 3h, the solvent was removed under reduced pressure to yield an orange solid. This was analysed by ^1H NMR spectroscopy and shown to contain the salts **(18)** and **(19)** in a ratio of 2:1. Trituration with cold acetone afforded the mixture of salts as a yellow solid (0.16 g, 74%). δ_H (300 MHz, $CDCl_3$): *major diastereoisomer* **(18)** 1.64 - 1.92 (series of m, 4H), 2.63 (m, 2H), 3.14 (s, 3H), 4.79 (brs, 2H), 5.29 (s, 2H), 6.29 (s, 2H), 7.46 (m, 5H); *minor diastereoisomer* **(19)** 1.64 - 1.92 (series of m, 4H), 2.17 (m, 2H), 3.41 (s, 3H), 4.67 (brs, 2H), 5.0 (s, 2H), 6.42 (s, 2H), 7.71 (m, 5H). δ_C (75 MHz, $CDCl_3$): *major diastereoisomer* **(18)** 13.7 (CH_2), 20.5 (CH_2), 49.0 (CH_3), 66.6 (CH_2), 73.2 (CH), 130.6 (CH), 130.7 (C), 130.9, 132.1, 134.1 (3 x CH); *minor diastereoisomer* **(19)** 13.3 (CH_2), 20.8 (CH_2), 41.1 (CH_3), 59.3 (CH_2), 75.1 (CH), 129.5 (C), 130.4, 130.8, 131.6, 132.9 (4 x CH). ν_{max} (nujol mull): 3050w, 3010w, 2970w, 2960m, 2940m, 1460m, 1450s, 1375m, 1330m, 1265s, 1210w cm^{-1}. $^m/z$ (%): 214 (M^+ - I^-)(9), 200 (97), 145 (36), 124, (20), 110 (11), 44 (3).

Unsuccessful debenzylation of (18) / (19)

i) using Emde reduction[17] A solution of **(18)** and **(19)** (0.093 g, 0.27 mmol) in water (4 ml) was heated to reflux and sodium amalgam, (3.00 g) was added in portions over 30 min. The reaction mixture was maintained at reflux for a further 7 h. The solution was then decanted from the mercury residue and acidified with 2M HCl. The solvent was removed under reduced pressure to leave a yellow/white solid which was repeatedly triturated with chloroform. The combined extracts were dried and evaporated to yield an orange oil which showed only the presence of unreacted starting material when examined by ^1H NMR.

ii) using thiophenol.[18] A sample of **(18)** and **(19)** (0.076 g, 0.223 mmol) was added to a solution of thiophenol (46.0 μl, 0.45 mmol) in a 20% aqueous solution of sodium hydroxide (90.0 μl) in a reacti-vial. The vial was sealed and heated at 90°C for 7 h. The aqueous solution was extracted with dichloromethane (6 x 1 ml) and the combined organic extracts were dried. Evaporation of the solvent left only starting material.

Trop-6-ene (2a) by reductive debenzylation of (18) / (19)

A small sample of **(18)** and **(19)** (10 mg, 0.0296 mmol) in the minimum of dry THF (0.5 ml) was added to dry, distilled liquid ammonia (*ca.* 4 ml) containing the minimum amount of sodium necessary to achieve a

blue solution. The solution was left to stir and reflux at -33°C for 2 h after which time to solution was quenched with solid ammonium chloride until the blue colour disappeared. The ammonia was allowed to evaporate, the residue was extracted with dichloromethane, and the solution was filtered. HCl gas was bubbled through the solution which was then evaporated under reduced pressure to yield **(2a:HCl)** (4.6 mg, 98%) as a white solid, δ_H (250 MHz, $CDCl_3$): 1.5 - 2.7 (complex, 6H), 2.76 (d, J ≈ 5 Hz, 3H, NMe), 4.12 (br, 2H, $H_{1,5}$), 6.04 (s, 2H, $H_{6,7}$), 11.1 (br, 1H, NH^+). The solution was basified with anhydrous K_2CO_3 to yield the free amine **(2a)** which showed identical spectroscopic properties to an authentic sample (above).

_N_-Methyl-_N_-benzyl-9-azabicyclo[4.2.1]non-7-enium iodide (20)

Iodomethane (300 µl, 4.82 mmol) was added to a solution of **(4c)** (0.105 g, 0.491 mmol) in dry acetone (300 µl) at 0°C. The mixture was heated at reflux for 6 h; evaporation left an orange solid which was triturated with cold acetone to yield **(20)** as a pale yellow solid. δ_H (300 MHz, $CDCl_3$): 1.86 - 1.90 (m, 2H), 2.08 - 2.17 (m, 4H), 2.61 - 2.69 (m, 2H), 3.20 (s, 3H), 4.98 (brm, 2H), 5.28 (s, 2H), 6.18 (s, 2H), 7.45 - 7.48 (m, 3H), 7.75 - 7.80 (m, 2H; δ_C (75 MHz, $CDCl_3$): 23.2 & 27.1 (CH_2), 52.1 (CH_3), 56.8 (CH_2Ph), 129.0 (C), 129.6, 130.1, 130.3, 131.5 (aryl and alkenyl CH).

_N_-Methyl-9-azabicyclo[4.2.1]non-7-ene (4a) from reduction of (20)

a. A suspension of **(20)** (0.10 g, 0.282 mmol)in dry THF (3 ml) was treated with sodium in liquid ammonia as described for the formation of **(2a)**. The HCl salt of **(4a)** (0.035 g, 71%) was isolated as a white solid, δ_H (90 MHz, $CDCl_3$): 1.4 - 2.7 (series of m, 8H), 3.0 (d, J ≈ 5 Hz, 3H, methyl), 4.3 (brd, J ≈ 6 Hz, 2H, $H_{1,6}$), 5.9 (s, 2H, $H_{7,8}$), 7.2 (br, 1H, NH^+). The solution was basified with ammonia gas and filtered to yield the free amine **(4a)** which showed identical spectroscopic properties to an authentic sample.[4]

b. Treatment of **(20)** with sodium amalgam [as described above for debenzylation of **(18) / (19)**] gave a product which was shown by NMR to be a 1:1 mixture of **(20)** and **(4a:HCl)** but was not purified.

_N_-Chloro-9-azabicyclo[4.2.1]nonane (3e)

A solution of the **(3b:HCl)** (0.13 g, 0.80 mmol) in water (10 ml) was treated with sodium hypochlorite (5% chlorine content; 18 ml) and stirred at room temperature for 1 h. The product was extracted into $CFCl_3$ (3 x 10 ml) and the combined organic layers were dried over $MgSO_4$. The product was handled in solution which was concentrated by evaporation of the solvent under a gentle stream of nitrogen. Complete removal of the solvent left **(3e)** as a pale yellow oil (0.119 g, 93%). δ_H (300 MHz, $CFCl_3$): 1.28 - 1.72 (series of m, 8H), 1.90 - 2.01 (m, 2H), 2.42 - 2.58 (m, 2H), 3.89 (m, 2H). δ_C (75 MHz, $CFCl_3$): 25.6, 32.0, 36.2 (3 x CH_2), 76.0 (CH). $^m/z$ (%) (CI): 162 (^{37}Cl MH^+, 30), 160 (^{35}Cl MH^+, 97), 124 (100), 102 (9), 96 (11), 82 (38), 69 (39), 68 (73), 55 (11), 41 (19); $C_8H_{14}N^{35}Cl$ (MH^+) requires $^m/z$ 160.0893; found 160.089.

_N_-Chloro-9-azabicyclo[4.2.1]non-7-ene (4e)

A solution of the picrate of **(4b)** (0.274 g, 0.78 mmol) was converted into **(4e)** (0.120 g, 98%) as described for **(3e)**. δ_H (300 MHz, $CFCl_3$): 1.33 - 1.63 (series of m, 6H), 1.90 - 2.01 (m, 2H), 4.27 (ddd, J = 6.6, 1.8, 1.0 Hz, 2H), 5.82 (d, J = 1.0 Hz, 2H). δ_C (75 MHz, $CFCl_3$): 24.5 & 31.9 (CH_2), 80.6 (CH), 130.8 (=CH). $^m/z$ (%) (CI): 160 (^{37}Cl MH^+, 5), 158 (^{35}Cl MH^+, 17), 124 (13), 114 (18), 94 (10), 81 (23), 80 (100), 67 (26), 53 (8); $C_8H_{12}N^{35}Cl$ (M^+) requires $^m/z$ 157.0660; found 157.066.

_N_-Chloro-1-methyl-9-azabicyclo[4.2.1]nonane (17e)

A solution of **(17b:HCl)** (0.10 g, 0.60 mmol) was converted into **(17e)** (0.099 g, 95%) as described for **(3e)**. δ_H (300 MHz, $CFCl_3$): 1.29 (s, 3H), 1.49 - 1.96 (m, 10H), 2.17 - 2.32 (m, 2H), 3.82 (m, 1H). δ_C (75 MHz, $CFCl_3$): 25.6 & 25.7 (CH_2), 30.1 (CH_3), 30.2, 35.3, 36.4, 42.0 (4 x CH_2), 68.3 (CH), 70.2 (C). $^m/z$ (%) (CI): 176 (^{37}Cl MH^+, 4), 174 (^{35}Cl MH^+, 13), 158 (2), 140 (100), 122 (3), 106 (8), 96 (13), 82 (12), 58 (5), 44 (10); $C_9H_{16}N^{35}Cl$ (M^+) requires $^m/z$ 173.0970; found 173.097.

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14. **a.** Difficulties with the removal of *N*-benzyl groups using ACE-Cl are not confined to tropanes; initial attempts with other azabicyclic systems including *N*-benzyl-2-azabicyclo[2.2.1]hept-5-ene and *N*-benzyl-2-azabicyclo[2.2.2]hept-6-ene also gave only unchanged starting material: Howarth, N.M., unpublished.
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