Studies on Intramolecular Cycloadditions Involving 3-Oxidopyridinium

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3-Oxidopyridinium derivatives bearing a pendant pent-4-enyl group at either N-1 or C-2 undergo intramolecular cycloadditions to form tricyclic systems. The chemistry of these cycloadducts has been explored, and that from the 2-substituted series compared to the cycloadduct from the corresponding pyrylium analogue; the nitrogen containing systems exhibit different chemical reactions in which the nucleophilicity of the nitrogen atom dominates. Quaternisation of the nitrogen atom and base treatment leads to opening of the aza-bridge. In contrast to the oxygen containing systems, no skeletal rearrangements (*e.g.* of the perhydroazulene to decalin type) were observed.

There is a growing recognition of the value of intramolecular 1,3-dipolar cycloadditions in synthesis. They provide a method for constructing, in one operation, complex polycyclic molecules with a high degree of stereocontrol and consequently have been widely applied in the synthesis of natural products.[1]

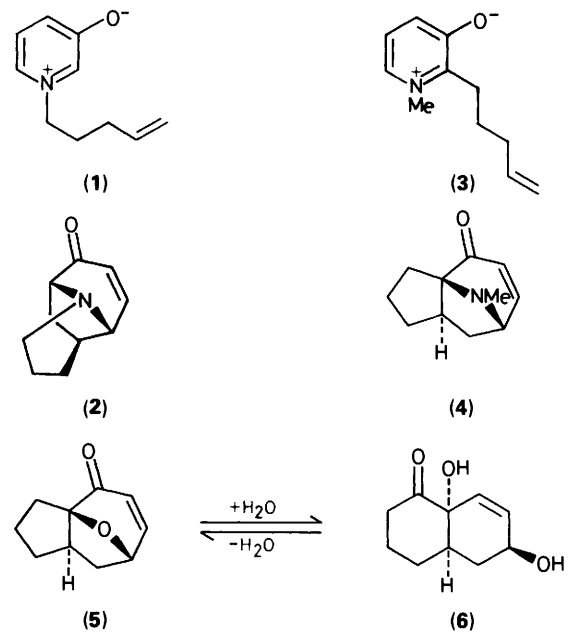
In spite of the copious literature dealing with intermolecular cycloadditions of 3-oxidopyridinium betaines,[2] the intramolecular variant has been largely neglected, presumably because setting up the appropriate systems is a little more difficult. In 1976 we reported the intramolecular cycloaddition of the *N*-substituted betaine (**1**) to give the tricyclic adduct (**2**),[3] in which the direction of addition was as predicted by frontier molecular orbital calculations.[4] Recently, Ravindranathan has prepared a number of intramolecular cycloadducts starting with *N*-homoallylpyridine betaines.[5]

In this paper we report on further chemical reactions of the cycloadduct (**2**) and also the behaviour of the 2-substituted betaine (**3**), a route to which has just become available.[6]

Compared to the properties of the corresponding oxidopyrylium system, cycloaddition of both the betaines (**1**) and (**3**) is sluggish and can only be effected by heating at temperatures above 150 °C. Use of acetonitrile as solvent was beneficial and, in the former case, allowed a yield of 64% of the cycloadduct (**2**) to be isolated, twice that previously reported.[3] The betaine (**3**) also underwent thermal cycloaddition to give the cycloadduct (**4**) in high yield. The stereochemistry of the latter was initially assumed to be the same as that observed for the corresponding oxygen system; subsequent chemical behaviour confirmed this assignment.

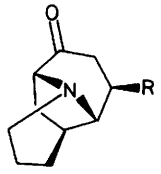
The rigidity of the tricyclic systems (**2**) and (**4**) was expected to allow highly stereoselective manipulation. Furthermore, it was of interest to compare the behaviour of these compounds to those of the oxygen containing systems, such as (**5**) (obtained by cycloaddition of the related 3-oxidopyrylium derivatives[7]), which can undergo rearrangement to the corresponding decalone system, *e.g.* (**6**). This process has been exploited in the synthesis of several natural products.[8]

Compound (**2**) reacts with lithium dimethylcuprate to give the conjugate adduct (**7**), attack occurring on the least hindered face of the enone, *syn* to the nitrogen bridge. Catalytic reduction of compound (**2**), using palladium on carbon as catalyst, leads to smooth reduction of the double bond and formation of the ketone (**8**). Addition of methylmagnesium bromide to either of the saturated ketones (**7**) or (**8**) yields, as a single product, the alcohols (**9**) and (**10**), respectively. The direction of attack (*vide infra*) is probably dictated by steric factors, addition occurring from the least hindered face, although some co-ordination of the organocuprate to the nitrogen atom cannot be ruled out.

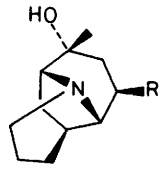


By comparison, the cycloadduct (**4**) did not behave so cleanly. Conjugate addition gave two products, assigned as the methylated ketones (**11**) and (**12**), in a 1:1 ratio. The presence of the *N*-methyl group serves to clutter the aza bridged face of the structure leading to addition across both faces of the enone. In the subsequent reaction with methylmagnesium bromide to produce the alcohol, the methyl ketone (**11**) gives only one product, assigned as the *anti*-alcohol (**13**),† whilst the ketone (**12**), in which the two methyl groups both serve to inhibit attack from the aza-bridged face, gives not only the *anti*-alcohol (**15**)

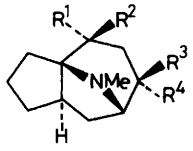
† The convention used in earlier papers is used here; the group mentioned is *syn* when on the same side (β) as the heterocyclic heteroatom and *anti* when on the opposite side (α).



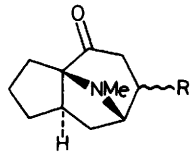
(7) R = Me
(8) R = H



(9) R = Me
(10) R = H



(13) R^1 = OH, R^2 = R^4 = Me, R^3 = H
(14) R^1 = R^3 = Me, R^2 = OH, R^4 = H
(15) R^1 = OH, R^2 = R^3 = Me, R^4 = H
(17) R^1 = OH, R^2 = Me, R^3 = R^4 = H



(11) R = ---Me
(12) R = ▬ Me
(16) R = H

Table. Chemical shifts (δ) of methyl groups in methylated adducts.

Compound	$\hat{2}$-Me	Assigned[a]	$\hat{3}$-Me	Assigned
(7)	1.15	β	—	
(9)	1.07	β	1.43	β
(10)	—		1.37	β
(11)	0.95	α	—	
(12)	1.20	β	—	
(13)	0.80	α	1.35	β
(14)	1.10	β	1.05	α
(15)	1.10	β	1.35	β

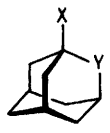
[a] β indicates *syn* to aza-bridge, α indicates *anti* to aza bridge.

but also the *syn*-alcohol (**14**), in a ratio of 1:2 respectively. For this system, the saturated ketone (**16**) gives only the *anti*-alcohol (**17**).

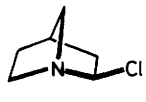
Structural assignments for the various methylated systems (**7**), (**9**)–(**15**), and (**17**) relied on detailed NMR studies, in which the chemical shifts of the methyl groups themselves were valuable (Table). Methyl groups *syn* to the aza bridge were consistently at lower field (δ > 1.0) compared to those in the *anti*-position (δ ≤ 1.0).

It was anticipated that the aza-bridged alcohols would react in a similar manner to that observed for the analogous oxygen bridged systems, *viz.* carbon skeletal rearrangements [*cf.* (**5**) to (**6**)]. Furthermore it was of interest to explore the rate of such

(18) Y = O, X = leaving group (l.g.)
(19) Y = NMe, X = l.g.
(20) Y = CH_2, X = l.g.



(21) Y = heteroatom, X = l.g.



(22)

rearrangements. A substituent directly bonded to a carbon which is developing a positive charge in an ionic reaction can influence the rate of the reaction by donating or withdrawing electrons from the reaction centre, either by resonance effects or polar effects.[9] The latter can be realised in terms of a composite of field (through-space) and inductive (through-bond) effects.

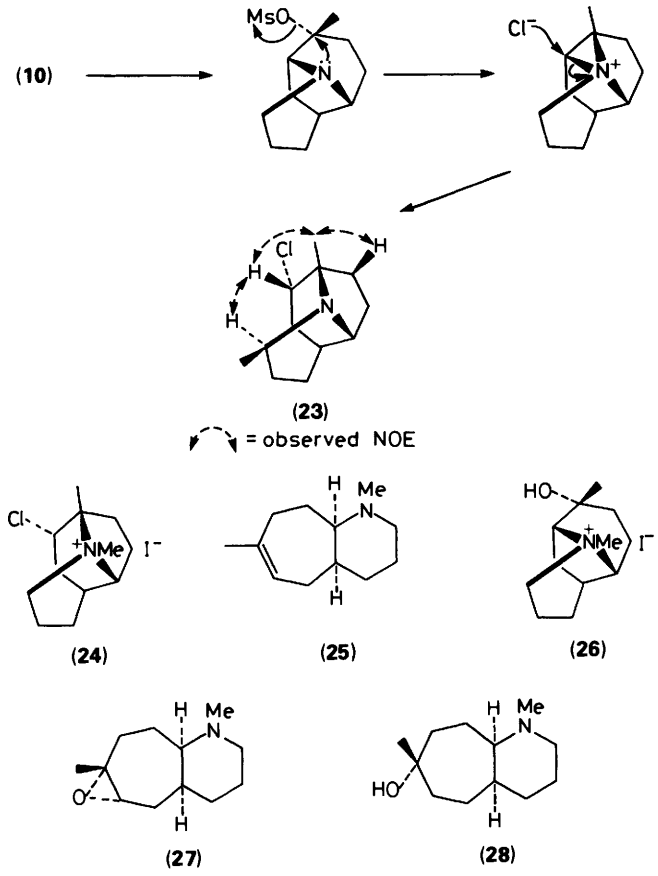
A number of publications have dealt with the effect of heteroatoms (N, O, and S) on the stability of an adjacent bridgehead carbonium ion in bi- and tricyclic systems.[9–15] The inductive order for stabilisation is CH_2 > NMe > O but this effect is usually dominated by resonance effects.[10] The involvement of resonance is most pronounced when nitrogen is adjacent to the bridgehead carbonium ion[11] and some spectacular rate effects have been observed.[9,12] Much effort has been devoted to the study of the angular dependence of the resonance effect. For example, in the 2-aza-substituted bicyclo[3.3.1]-nonane (**19**), compared to the carboncyclic parent (**20**), the NMe group increases reactivity by a factor of 10^7; this is 3 times faster than for the 2-oxa-substituted system (**18**).[12] Meyer utilised the geometry of the 1-adamantyl system (**21**), which imposes a perpendicular twist on the lone pairs of the 2-heteroatoms relative to the adjacent, vacant carbon p-orbital, to demonstrate that the resonance contribution depends on the degree of orbital overlap.[9] In this case the nitrogen derivative (Y = NMe) is 357-fold more reactive than the carbon analogue (Y = CH_2), which in turn is 10^3 times more reactive than the oxygen derivative (Y = O). Only in the case of the rigid bicycloheptane (**22**) has an α-nitrogen atom been found to decrease reactivity (20-fold),[13] but even in this case resonance stabilisation must still occur because an α-nitrogen atom is expected to inductively destabilise a carbonium ion by a factor of *ca.* 10^5. In the light of this background and a precedent for the skeletal rearrangement in bridged aza-systems,[16] the behaviour of some of the alcohols described above was examined.

Unlike the oxygen systems, treatment of the alcohols (**10**) and (**17**) with a range of Lewis acids failed to give rearrangement products, and a complex mixture of products was formed from which no keto-compounds could be extracted. Presumably, the nitrogen atom forms strong complexes with the Lewis acids thus inhibiting its involvement by the resonance effect.

Treatment of the alcohol (**10**) with methanesulphonyl chloride at 0 °C immediately gave a single product, shown to be a new secondary chloride (**23**). That this had the rearranged structure indicated was supported by extensive NMR studies. Neighbouring NOEs were seen between the indicated positions [see structure (**23**)]. The chloride (**23**) was stable to heat, with no reversion to the starting skeleton. Presumably the lone pair on the nitrogen atom is constrained to point away from the chlorine atom by the presence of the ring bridges and hence the structural conversion of (**10**) to (**23**) is essentially irreversible. Presumably the rearrangement proceeds *via* an intermediate aziridinium species[17] (see Scheme 1). Further confirmation of the structure (**23**) was obtained by treating the methiodide (**24**), itself obtained by heating the chloride with methyl iodide in acetonitrile, with sodium metal in THF[18] to afford the alkene (**25**) in excellent yield.

The starting alcohol (**10**) was also quaternised with methyl iodide to give the salt (**26**) and this was treated with silver oxide. Rather than undergoing a Hofmann elimination, participation of the alcohol group produced the epoxide (**27**), thus helping to confirm the earlier stereochemical assignments. Reduction of this epoxide with lithium in ethylenediamine[19] gave the tertiary alcohol (**28**).

In contrast to the alcohol (**10**), the alcohol (**17**) produced only complex mixtures on treatment with methanesulphonyl chloride. However, (**17**) could be quaternised with methyl iodide to give the salt (**29**), and treatment of this with silver oxide again



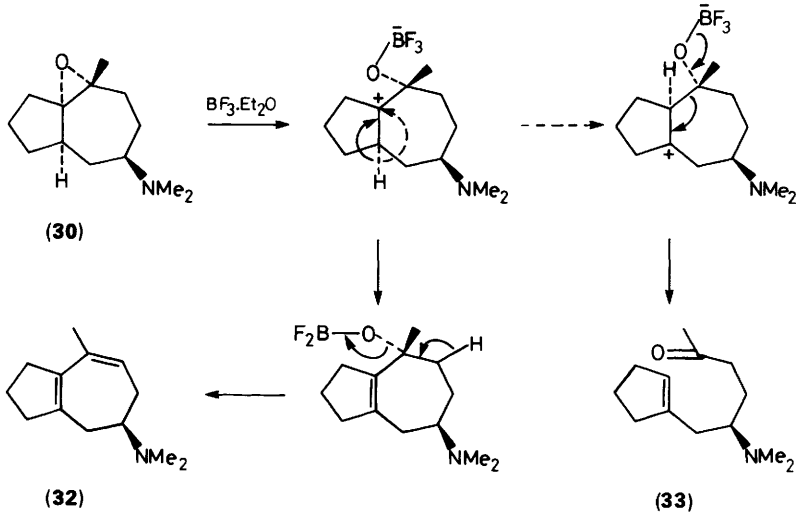
Scheme 1.

produced an epoxide, (**30**) in good yield. Reduction of (**30**) with lithium metal also gave a tertiary alcohol, which contained a tertiary methyl group, indicating that reduction had occurred at the ring junction side of the epoxide to give the alcohol (**31**). Since reduction occurs by a two-step electron donation, the more stable *trans*-junction would be anticipated,[20] as shown, although this assignment was not proved.

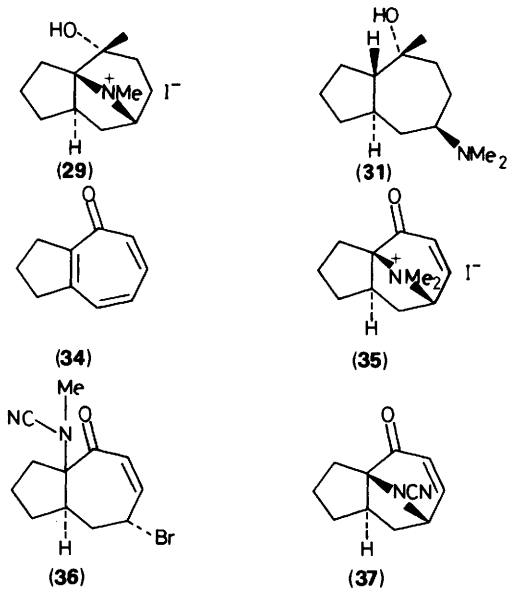
The acid-catalysed isomerisation of tetra-substituted epoxides has been reported to effect rearrangement to, *e.g.*, spiroketones,[21] so the behaviour of the epoxide (**30**) was studied. With boron trifluoride–ether at 0 °C a rapid and clean reaction occurred to produce two products. The major product, isolated in 54% yield, was isomeric with the starting epoxide but its ^{1}H NMR spectrum indicated the presence of a methyl ketone and a single vinyl proton, the dimethylamino substituent remaining intact. Extensive proton and carbon NMR studies showed the presence of the cyclopent-1-enyl and $CO{\cdot}CH_2CH_2CHNMe_2$ fragments, pointing to the assigned structure (**33**). The minor product isolated from the attempted rearrangement was found to have lost one molecule of water from the starting epoxide. Although this material only showed one vinylic proton in its NMR spectrum, it did show the presence of a vinylic methyl group and of the starting dimethylamino group; the UV spectrum also showed the presence of a conjugated diene, λ_{max} 245 nm, indicative of a substituted homoannular diene and leading to the assigned structure (**32**). A possible mechanism for the formation of these products is outlined in Scheme 2. No skeletal rearrangement products were observed.

One final reaction was explored, the attempted conversion of the ketone (**4**) to the corresponding tropone (**31**). The methiodide (**35**) could be prepared but did not react under a variety of conditions normally employed for the Hofmann elimination reaction; stronger conditions led to extensive decomposition. The von Braun reaction on the ketone (**4**), using cyanogen bromide,[22] gave a mixture of two products, the ring-opened product (**36**) and the cyanamide (**37**); the ratio of products was solvent dependent, benzene yielding a 1:12 ratio, respectively. Heating the ring-opened product gave some cyanamide as well as starting ketone, demonstrating the reversibility of the reaction under these conditions. Attempts to effect elimination of the bromine and cyanamide groups, by treatment with strong base, only produced complex mixtures.

To summarise the above results: intramolecular cycloaddition of simple 3-oxidopyridinium derivatives proceeds less readily than in the corresponding pyrylium systems. Whereas the nitrogen containing adducts also show considerable stereocontrolled reactivity, skeletal rearrangement reactions were not observed and through space interactions were preferred, for example, to form transient aziridinium species.



Scheme 2.



Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained from chloroform solutions recorded on a Perkin-Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded using a Varian EM360A (60 MHz) spectrometer, a Jeol FX90Q (90 MHz) spectrometer, or a Bruker AM400 (400 MHz) spectrometer, using deuteriochloroform as solvent and tetramethylsilane as internal reference. ^{13}C NMR spectra were determined on the Jeol FX90Q (22.5 MHz), using deuteriochloroform as solvent and tetramethylsilane as internal reference. Accurate mass measurements were determined using an AEI-Kratos MS9/50 spectrometer. Elemental analyses were determined by the Microanalytical Laboratory, School of Chemistry, University of Leeds.

Reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with a 0.25 mm layer of Merck Kieselgel 60 GF_{254}. Reaction product mixtures were usually processed by chromatography through either Merck silica gel (60G) or MN-Kieselgel 60 230–400 mesh (CAMLAB) under slight pressure; solvent mixtures are cited in ratios of volumes before mixing. Generally, reaction solvents were removed, after drying over anhydrous sodium sulphate, under reduced pressure using a rotary evaporator. Solvents were dried and distilled following standard procedures before use.[23] Light petroleum refers to the fraction of boiling range 40–60 °C; ether refers to diethyl ether. All reactions involving air-sensitive materials were conducted under an atmosphere of dry, oxygen-free nitrogen. The term brine refers to saturated aqueous sodium chloride solution. Small scale distillations were conducted using a bulb-to-bulb distillation oven under reduced pressure.

Formation and Cyclisation of the Betaine (**1**).—3-Hydroxy-1-(pent-4-enyl)pyridinium bromide[3] (32.32 g, 0.132 mol) was treated with Amberlite IRA-410 ion exchange resin (OH^- form) (80 g) in acetonitrile (500 ml) for 16 h before filtering and evaporation to give the betaine (19.51 g, 97%) as a viscous oil. Acetonitrile (50 ml) was added and the mixture was heated in a glass-lined autoclave at 160 °C for 20 h. The solvent was removed under reduced pressure and the product chromatographed through silica gel, using 2:3 ethyl acetate–light petroleum as eluant, to give 11-aza-4-oxotricyclo[5.4.0.0^{5,11}]-undec-2-ene (**2**) (13.65 g, 70%) as a viscous, pale yellow oil. The material showed the same properties as that prepared previously;[3] δ_H(400 MHz) 1.30 (1 H, m), 1.58 (2 H, m), 1.73 (2 H, m), 1.98 (1 H, dd, *J* 7.5 and 13 Hz), 2.35 (1 H, m), 2.90 (2 H, m, 10-H_2), 3.52 (1 H, d, *J* 5.5 Hz, 7-H), 3.63 (1 H, m, *J* 7 Hz, 5-H), 5.83 (1 H, dd, *J* 10, 1 Hz, 3-H), and 7.06 (1 H, dd, *J* 10, 5.5 Hz, 2-H). (Calc. for $C_{10}H_{13}NO$: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.4; H, 7.9; N, 8.7%).

11-*Aza*-11-*methyl*-10-*oxotricyclo*[5.3.1.0^{1,5}]*undec*-8-*ene* (**4**).—3-Hydroxy-2-(pent-4-enyl)pyridine[6] (7.08 g, 43.4 mmol) and iodomethane (3.5 ml, 56.2 mmol) in acetontrile (250 ml) were heated at reflux for 24 h. Removal of the excess of reagent and solvent under reduced pressure afforded 3-*hydroxy*-1-*methyl*-2-(*pent*-4-*enyl*)*pyridinium iodide* as a crystalline white solid (11.26, 85%), m.p. 133 °C (from acetone–ether); ν_{max} 3 400–2 250, 1 590, 1 475, and 1 315 cm^{-1}; δ_H(90 MHz) 1.80 (2 H, m, 2′-H_2), 2.25 (2 H, m, 3′-H_2), 3.05 (2 H, m, 1′-H_2), 4.37 (3 H, s, 1-Me), 4.95–5.2 (2 H, m, vinyl H), 5.6–6.1 (1 H, m, vinyl H), 7.55 (1 H, dd, *J* 6, 8 Hz, 5-H), 8.25 (1 H, d, *J* 6 Hz, 4-H), and 8.65 (1 H, d, *J* 8 Hz, 6-H) (Found: C, 43.1; H, 5.2; N, 4.45; I, 41.6. $C_{11}H_{16}INO$ requires C, 43.3; H, 5.3; N, 4.6; I, 41.6%).

The pyridinium iodide (13.27 g, 43.4 mmol) was stirred with an excess of Amberlite IRA-410 ion exchange resin (OH^- form) (40 g) in acetonitrile for 16 h. Filtration and removal of the solvent afforded the *betaine* (**3**) (7.55 g, 98%) as a viscous, orange gum, ν_{max} 2 940, 1 580, 1 490, 1 330, and 920 cm^{-1} (Found: M^+, 177.115 05. $C_{11}H_{15}NO$ requires *M*, 177.115 358).

Heating the betaine (**3**) (7.55 g, 42.7 mmol) in acetonitrile (100 ml) at 160 °C in a sealed tube for 16 h afforded, after removal of solvent and chromatography through silica gel, using 2:3 ethyl acetate–light petroleum as eluant, the *title cycloadduct* (6.88 g, 91%), as a pale yellow oil, b.p. 90 °C/1 mmHg; ν_{max} 2 950, 1 680, 1 450, 1 175, and 740 cm^{-1}; δ_H(90 MHz) 1.3–2.4 (9 H, m), 2.29 (3 H, s, MeN), 3.83 (1 H, t, *J* 5 Hz, 7-H), 5.98 (1 H, d, *J* 10 Hz, 9-H), and 6.79 (1 H, dd, *J* 5, 10 Hz, 8-H) (Found: C, 74.8; H, 8.7; N, 8.0. $C_{11}H_{15}NO$ requires C, 74.6; H, 8.5; N, 7.9%).

Conjugate Methyl Addition to the Ketones (**2**) *and* (**4**).—(a) *Ketone* (**2**). Methyl-lithium (24.5 ml, 1.5M in ether) was added dropwise to a stirred suspension of copper(I) bromide–dimethyl sulphide (3.7 g, 18 mmol) in dry ether (100 ml) at 0 °C. The resultant colourless solution was cooled to −20 °C before addition of the cycloadduct (2.0 g, 12.3 mmol) in ether (15 ml). After stirring the mixture at room temperature for 1 h, the reaction was poured into brine, extracted with ether (5 × 75 ml), and the combined organic extracts were dried and the solvent removed. The residue was chromatographed through silica gel, using 1:3 ethyl acetate–hexane as eluant, to yield 11-*aza*-2β-*methyl*-4-*oxotricyclo*[5.4.0^{5,11}]*undecane* (**7**) (1.9 g, 86%) as a colourless oil, ν_{max} 2 940, 1 720, 1 450, and 1 105 cm^{-1}; δ_H(60 MHz) 1.15 (3 H, d, *J* 7 Hz, 2β-Me), 1.3–2.1 (8 H, m), 2.2–2.35 (2 H, m, 3-H_2), 2.8–3.1 (3 H, m, 1-H and 10-H_2), and 3.5 (1 H, m, 5-H) (Found: C, 73.9; H, 9.4; N, 7.8. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.6; N, 7.8%).

(b) *Ketone* (**4**). In a similar manner, the ketone (3 g, 17 mmol) was reacted with lithium dimethylcuprate [from copper(I) bromide–dimethyl sulphide (4.7 g) and methyl-lithium (34 ml, 1.5M)] in ether (200 ml), and the mixture worked up to give an oil, shown to be a mixture of isomers. Chromatography through silica gel, using 1:3 ethyl acetate–hexane as eluant, afforded, initially, 11-*aza*-8β,11-*dimethyl*-10-*oxotricyclo*-[5.3.1.0^{1,5}]*undecane* (**12**) (1.46 g, 45%), ν_{max} 2 950, 1 705, 1 450, 1 240, 1 180, and 1 125 cm^{-1}; δ_H(60 MHz) 1.2 (3 H, d, *J* 7 Hz, 8β-Me), 1.2–2.6 (12 H, m), 2.5 (3 H, s, MeN), and 3.25 (1 H, m, 7-H) (Found: C, 74.7; H, 10.2; N, 7.4. $C_{12}H_{19}NO$ requires C, 74.6; H, 9.9; N, 7.3%).

Further elution gave the corresponding 8α-*methyl isomer* (**11**)

(1.58 g, 48%), ν_{max} 2 950, 1 705, 1 450, 1 170, and 1 120 cm^{-1}; δ_H(60 MHz) 0.95 (3 H, d, *J* 7 Hz, 8α-Me), 1.2–2.7 (12 H, m), 2.35 (3 H, s, NMe), and 3.25 (1 H, m, 7-H) (Found: M^+, 193.146 51. $C_{12}H_{19}NO$ requires *M*, 193.146 656).

Reduction of the Cycloadducts (**2**) *and* (**4**).—(a) *Ketone* (**2**). The cycloadduct (6 g, 36.8 mmol) in ethanol (100 ml) was hydrogenated at atmospheric pressure and temperature, using 5% Pd/C (0.6 g) as catalyst. After filtering and removal of the solvent, the residue was chromatographed through silica gel, using 10:1 ethyl acetate–methanol as solvent, to yield 11-*aza*-4-*oxotricyclo*[5.4.0.0^{5,11}]*undecane* (**8**) (5.59 g, 92%) as a colourless gum, ν_{max} 2 940, 1 725, 1 450, 1 235, and 1 100 cm^{-1}; δ_H(60 MHz) 1.2–2.3 (9 H, m), 2.35 (2 H, m, 10-H_2), 2.8–3.3 (3 H, m, 3-H_2 and 1-H), and 3.55 (1 H, m, 5-H) (Found: M^+, 165.115 19. $C_{10}H_{15}NO$ requires *M*, 165.115 36).

(b) *Ketone* (**4**). In a similar manner the ketone (**4**) (4 mg, 22.6 mmol) was hydrogenated using 5% Pd/C (0.5 g) as catalyst. Work-up and chromatography gave 11-*aza*-1-*methyl*-10-*oxotricyclo*[5.3.1.0^{1,5}]*undecane* (**16**) (3.73 g, 92%), ν_{max} 2 940, 1 705, 1 450, 1 215, and 1 110 cm^{-1}; δ_H(60 MHz) 1.3–2.6 (13 H, m), 2.35 (3 H, s, NMe), and 3.5 (1 H, m, 7-H) (Found: C, 73.6; H, 9.6; N, 8.2. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.6; N, 7.8%).

Addition of Methylmagnesium Iodide to the Ketones (**7**), (**8**), (**11**), (**12**), *and* (**16**).—*General method.* A solution of the ketone (1 equiv.) in ether (1 ml per mmol) was added to a freshly prepared solution of methylmagnesium iodide (2 equiv.) in ether (5 ml per mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, then poured into brine (10 ml per mmol). The aqueous layer was saturated with NH_4Cl and extracted with ether (× 4). The organic phases were collected, dried, and the solvent removed. The residue was chromatographed through silica gel, using 20:1 ethyl acetate–methanol as eluant, to give the corresponding alcohol. All the ketones, except for (**12**), gave a single major product. The products showed the following properties:

From ketone (**7**) (0.35 g, 1.96 mmol) was obtained 11-*aza*-2β,4β-*dimethyl*-4α-*hydroxytricyclo*[5.4.0.0^{1,5}]*undecane* (**9**) (0.32 g, 84%), as a colourless solid, m.p. 68–69 °C (subl.); ν_{max} 3 400, 2 930, 1 470, 1 130, and 925 cm^{-1}; δ_H(400 MHz) 1.06 (3 H, d, *J* 7.5 Hz, 2β-Me), 1.17–1.26 (3 H, m), 1.43 (3 H, s, 4β-Me), 1.54 (2 H, m), 1.60–1.67 (5 H, m), 2.00 (1 H, dd, *J* 7, 13.4 Hz, 3-H), 2.10 (1 H, dd, *J* 5, 7 Hz, 5-H), 2.52 (1 H, s, OH), and 2.82–2.88 (3 H, m, 1-H, 10-H_2) (Found: C, 73.8; H, 10.8; N, 7.2. $C_{12}H_{21}NO$ requires C, 73.8; H, 10.8; N, 7.2%).

From ketone (**8**) (5 g, 30.3 mmol) was obtained 11-*aza*-4α-*hydroxy*-4β-*methyltricyclo*[5.4.0.0^{1,5}]*undecane* (**10**) (3.9 g, 71%) as a white solid, m.p. 71–73 °C; ν_{max} 3 600, 2 940, 1 140, and 945 cm^{-1}; δ_H(400 MHz) 1.23 (1 H, m), 1.37 (3 H, s, 4β-Me), 1.37–1.72 (9 H, m), 1.95 (1 H, ddd, *J* 1.5, 7, 13.5 Hz, 3-H), 2.12 (1 H, dd, *J* 5.5, 7 Hz, 5-H), and 2.77–2.97 (4 H, m, 1-H, 10-H_2, OH) (Found: C, 72.6; H, 7.7; N, 7.7. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.6; N, 7.7%).

From ketone (**11**) (1.43 g, 7.4 mmol) was obtained 11-*aza*-10α-*hydroxy*-8α,10β,11-*trimethyltricyclo*[5.3.1.0^{1,5}]*undecane* (**13**) (1.14 g, 74%) as a colourless gum, ν_{max} 3 450, 2 940, 1 460, 1 340, 1 150, and 935 cm^{-1}; δ_H(60 MHz) 1.2–2.1 (13 H, m), 1.3 (3 H, s, 10-Me), 2.45 (3 H, s, NMe), 2.6 (1 H, m, 9-H), and 3.3 (1 H, m, 7-H) (Found: C, 74.5; H, 11.2; N, 6.7. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.1; N, 6.7%).

From ketone (**12**) (1.3 g, 6.7 mmol) was obtained a 2:1 mixture of the alcohols (**14**) and (**15**). The former, 11-*aza*-10β-*hydroxy*-8β,10α,11-*trimethyltricyclo*[5.3.1.0^{1,5}]*undecane* (0.737 g, 53%) was obtained as a colourless, viscous oil, ν_{max} 3 460, 2 940, 1 450, and 1 160 cm^{-1}; δ_H(60 MHz) 1.05 (3 H, s, 10α-Me), 1.1 (3 H, d, *J* 7 Hz, 8β-Me), 1.2–2.3 (13 H, m), 2.5 (3 H, s, NMe), and 2.9 (1 H, m, 7-H) (Found: M^+, 209.177 85. $C_{13}H_{23}NO$ requires *M*, 209.177 96). The latter 10α-*alcohol* (0.358 g, 26%) was also obtained as a viscous oil, ν_{max} 3 460, 2 940, 1 460, 1 370, and 1 160 cm^{-1}; δ_H(60 MHz) 1.10 (3 H, d, *J* 7 Hz, 8β-Me), 1.2–2.1 (13 H, m), 1.35 (3 H, s, 10β-Me), 2.4 (3 H, s, NMe), and 2.95 (1 H, m, 7-H) (Found: C, 74.7; H, 11.1; N, 6.8. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.1; N, 6.7%).

The ketone (**16**) (3.0 g) gave 11-*aza*-10α-*hydroxy*-10β,11-*dimethyltricyclo*[5.3.1.0^{1,5}]*undecane* (**17**) (2.8 g, 86%) as a colourless oil, ν_{max} 3 450, 2 940, 1 460, 1 340, 1 150, and 935 cm^{-1}; δ_H(60 MHz) 1.2–2.1 (13 H, m), 1.30 (3 H, s, 10β-Me), 2.45 (3 H, s, NMe), 2.6 (1 H, m, 9-H), and 3.3 (1 H, m, 7-H) (Found: C, 73.7; H, 10.8; N, 7.1. $C_{12}H_{21}NO$ requires C, 73.8; H, 10.8; N, 7.2%).

Reaction of the Alcohol (**10**) *with Methanesulphonyl Chloride.*—Methanesulphonyl chloride (0.34 ml, 4.4 mmol) was added dropwise to a stirred solution of the alcohol (0.76 g, 4.2 mmol) and triethylamine (1 ml, 7.2 mmol) in dichloromethane (20 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and left stirring for a total of 2 h then poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (3 × 50 ml). The organic extract was dried and evaporated, then chromatography of the residue through silica gel, using 20:1 ethyl acetate–methanol as eluant, gave 11-*aza*-5-*chloro*-4-*methyltricyclo*[5.4.0.0^{4,11}]*undecane* (**23**) (0.622 g, 74%) as a colourless solid, m.p. 40 °C, by bulb-to-bulb distillation at 100 °C/0.6 mmHg; ν_{max} 2 940, 1 450, 1 375, 1 190, 1 155, and 695 cm^{-1}; δ_H(400 MHz) 1.26 (3 H, s, 4-Me), 1.41 (1 H, ddd, *J* 1.5, 6, 14 Hz, 3β-H), 1.43–1.55 (3 H, m), 1.64 (1 H, m, 7-H), 1.78 (2 H, m), 1.95 (1 H, m, 2α-H), 2.04 (1 H, ddt, *J* 1.5, 7, 14.1 Hz, 6β-H), 2.25 (1 H, ddd, *J* 6, 12 Hz, 2β-H), 3.07 (1 H, dd, *J* 6, 12.5, 15.1, 10α-H), 3.19 (1 H, dd, *J* 6.1, 15 Hz, 10β-H), 3.2 (1 H, m, 1-H), and 4.36 (1 H, ddd, *J* 1.5, 7, 11 Hz, 5β-H). NOEs were observed between the protons indicated in structure (**23**) (Found: C, 66.3; H, 9.1; N, 7.2; Cl, 17.2. $C_{11}H_{18}ClN$ requires C, 66.2; H, 9.1; N, 7.0; Cl, 17.7%).

Reductive Cleavage of the Chloride (**23**).—The chloride (0.4 g, 2.0 mmol) was heated to reflux with methyl iodide (0.5 ml) and acetonitrile (10 ml) for 12 h. The resulting precipitate was collected and recrystallised from aqueous ethanol to give the quaternary salt (**24**) as a colourless solid (0.64 g, 93%), m.p. 240 °C. A portion of the salt (0.145 g, 0.42 mmol) was heated in refluxing THF (10 ml) in the presence of finely divided sodium metal (0.2 g, 8.7 mmol) for 16 h. The reaction mixture was carefully quenched with water (10 ml) and extracted with ether (3 × 30 ml). The organic extract was dried and evaporated, and the residue was distilled (150 °C/2 mmHg) to give 11-*aza*-4,11-*dimethyl*-1α,7α-*bicyclo*[5.4.0]*dec*-4-*ene* (**25**) (69 mg, 91%) as a mobile oil; ν_{max} 2 920, 1 640, 1 440, and 1 375 cm^{-1}; δ_H(360 MHz) 1.35–1.65 (5 H, m), 1.68 (3 H, s, 4-Me), 1.70–1.83 (3 H, m), 1.90–2.05 (2 H, m), 2.15 (1 H, m), 2.26 (3 H, s, NMe), 2.32 (1 H, m, 10-H), 2.50 (1 H, m, 10-H), 2.65 (1 H, m, 1-H), and 5.38 (1 H, m, 5-H) (Found: C, 80.2; H, 11.8; N, 7.7. $C_{12}H_{21}N$ requires C, 80.4; H, 11.8; N, 7.8%).

11-*Aza*-4β,11-*dimethyl*-4α,5α-*epoxy*-1α,7α-*bicyclo*[5.4.0]-*undecane* (**27**).—The alcohol (**10**) (1.0 g, 5.5 mmol) was heated with an excess of iodomethane (3 ml) in acetonitrile (50 ml) at reflux for 20 h. The precipitate was collected and recrystallised from aqueous ethanol to give the *quaternary salt* (**26**) (1.7 g, 95%), m.p. 280 °C (decomp.) (Found: C, 44.8; H, 7.1; N, 4.4, I, 39.1. $C_{12}H_{22}INO$ requires C, 44.6; H, 6.9; N, 4.3; I, 39.3%).

A portion of the salt (0.625 g, 1.9 mmol) was stirred with freshly prepared silver oxide (6.2 g, 27 mmol) in water (100 ml) for 2 h at room temperature. The mixture was filtered, the filtrate evaporated to dryness under reduced pressure, and the

residue distilled at 150 °C/0.8 mmHg to give the *title epoxide* (0.34 g, 90%) as a colourless oil, ν_{max} 2 940, 2 795, 1 450, 1 385, 1 280, 1 210, 1 140, 1 045, and 920 cm^{-1}; δ_H(360 MHz) 1.30 (3 H, s, Me), 1.45–1.75 (9 H, m), 1.95 (2 H, m), 2.15 (1 H, m, 10-H), 2.21 (3 H, s, NMe), 2.43 (1 H, m, *J* 13 Hz, 10-H), 2.72 (1 H, m, 1-H), and 2.83 (1 H, dd, *J* 3, 6 Hz, 5β-H) (Found: C, 73.6; H, 10.7; N, 7.3. $C_{12}H_{21}NO$ requires C, 73.8; H, 10.7; N, 7.2%).

5β-*Dimethylamino*-1α,2α-*epoxy*-2β-*methyl*-1α,7α-*bicyclo*-[5.3.0]*decane* (**30**).—The alcohol (**17**) (2.64 g, 13.5 mmol) was treated with methyl iodide (3 ml, 48 mmol) as described above to yield, after recrystallisation from aqueous ethanol, the quaternary salt (**29**) (4.1 g, 89%) as a colourless solid, m.p. 270 °C (Found: C, 46.4; H, 7.1; N, 4.4; I, 37.5. $C_{13}H_{24}INO$ requires C, 46.3; H, 7.1; N, 4.2; I, 37.7%).

A portion of the salt (1.5 g, 4.45 mmol) was treated with silver oxide, as described above, to yield the *title epoxide* (0.856 g, 92%) as a viscous oil, ν_{max} 2 930, 2 780, 1 455, 1 380, 1 150, 1 090, 1 045, and 880 cm^{-1}; δ_H(360 MHz) 1.38 (3 H, s, 2β-Me), 1.3–1.6 (6 H, m), 1.62–1.78 (3 H, m), 1.99 (2 H, m, 3-H_2 or 10-H_2), 2.10 (2 H, m, 3-H_2 or 10-H_2), 2.23 (6 H, s, NMe_2), and 2.33 (1 H, m, 5-H) (Found: C, 74.6; H, 11.0; N, 7.0. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.1; N, 6.7%).

Reduction of the Epoxides (**27**) *and* (**30**).—(a) *Epoxide* (**27**). Finely divided lithium metal (15 mg, 2.1 mmol) was added to a stirred solution of the epoxide (75 mg, 0.38 mmol) in dry ethylenediamine (5 ml) at room temperature and the mixture was then heated to 50 °C for 1 h. The solution was cooled and the excess of lithium destroyed by the careful addition of water (1 ml). The mixture was diluted with ether (20 ml) and the organic phase washed with water (3 × 30 ml), dried, and evaporated to give an oil which was distilled (bulb-to-bulb) to give 11-*aza*-4β,11-*dimethyl*-4α-*hydroxy*-1α,7α-*bicyclo*[5.4.0]*undecane* (**28**) (56 mg, 74%), ν_{max} 3 370, 2 930, 1 440, 1 130, and 1 030 cm^{-1}; δ_H(90 MHz) 1.25 (3 H, s, Me), 1.4–1.9 (14 H, m), 2.0–2.3 (3 H, m, 1-H, 10-H_2), and 2.2 (3 H, s, NMe) (Found: M^+, 197.178 48. $C_{12}H_{23}NO$ requires *M*, 197.177 96).

(b) *Epoxide* (**30**). The epoxide (0.1 g, 0.48 mmol) was treated with lithium metal (20 mg) in ethylenediamine as described above to yield 5β-(*dimethylamino*)-2α-*hydroxy*-2β-*methyl*-1β,7α-*bicyclo*[5.3.0]*decane* (**31**) (85 mg, 85%), ν_{max} 3 420, 2 940, 1 460, 1 375, and 1 030 cm^{-1}; δ_H(360 MHz) 1.18 (3 H, s, 2β-Me), 1.2–2.05 (15 H, m), 2.25 (6 H, m, NMe_2), and 2.46 (1 H, m, 5-H) (Found: M^+, 211.193 44. $C_{13}H_{25}NO$ requires *M*, 211.193 60).

Reaction of the Epoxide (**30**) *with Boron Trifluoride Etherate*.—Boron trifluoride etherate (0.3 ml, 2.4 mmol) was added dropwise to a solution of the epoxide (0.165 g, 0.8 mmol) in ether (10 ml) at 0 °C. After 5 min the solution was poured into saturated aqueous sodium hydrogen carbonate (10 ml) and the aqueous phase was extracted with ether (4 × 20 ml). The combined extracts were dried and evaporated under reduced pressure and the residue chromatographed through silica gel, using 1:3 ethyl acetate–methanol as eluant, to give, in order of elution:

1-(1-*Cyclopentenyl*)-2-(*dimethylamino*)*hexan*-5-*one* (**33**) (88 mg, 54%), b.p. 110 °C/0.8 mmHg; ν_{max} 2 940, 1 715, 1 455, 1 360, 1 160, and 1 100 cm^{-1}; δ_H(360 MHz) 1.5–1.7 (2 H, m), 1.80–1.93 (3 H, m), 2.12 (3 H, s, MeCO), 2.17 (1 H, m), 2.18 (6 H, s, NMe_2), 2.2–2.35 (4 H, m), 2.36–2.58 (3 H, m), and 5.35 (1 H, m, vinylic H) (Found: C, 74.3; H, 11.1; N, 6.8. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.1; N, 6.7%).

5-*Dimethylamino*-8-*methyl*-1,2,3,4,5,6-*hexahydrocyclopentacycloheptane* (**32**) (44 mg, 27%) as a colourless oil, b.p. 130 °C/1 mmHg; ν_{max} 2 940, 1 450, and 1 040 cm^{-1}; λ_{max}(EtOH) 245 nm (ε 7 100); δ_H(360 MHz) 1.77 (3 H, s, Me), 1.82 (2 H, m), 2.05 (1 H, m), 2.25 (6 H, s, NMe_2), 2.30 (2 H, m), 2.47 (5 H, m), 2.90 (1 H, m), and 5.55 (1 H, t, *J* 8 Hz, 4-H) (Found: M^+, 191.167 29. $C_{13}H_{21}N$ requires *M*, 191.167 39).

Treatment of the Ketone (**4**) *with Cyanogen Bromide*.—A solution of the ketone (0.10 g, 0.56 mmol) in benzene (2 ml) was added dropwise over 12 h to a solution of cyanogen bromide (1 g, 9.4 mmol) in benzene (1 ml) at 50 °C. After a further 3 h the reaction mixture was diluted with ether (20 ml) and poured into water (25 ml). The aqueous phase was extracted with ether (3 × 25 ml) and the combined extracts were washed with brine and then dried. Removal of the solvents and chromatography of the residue on silica gel, using ethyl acetate–light petroleum (1:2) as eluant gave, initially, 5α-*bromo*-1β-*methylcyanamido*)*bicyclo*-[5.3.0]*dec*-3-*en*-2-*one* (**36**) (14 mg, 9%), ν_{max} 2 960, 2 215, and 1 680 cm^{-1}; δ_H(400 MHz) 1.78–2.13 (5 H, m), 2.33 (1 H, ddd, $J_{7,6\alpha}$ 2 Hz, $J_{5\beta,6\alpha}$ 3 Hz, $J_{6\beta,6\alpha}$ 17 Hz, 6α-H), 2.41 (1 H, ddd, *J* 8, 10, 15 Hz, CH), 2.68 (3 H, s, NMe), 2.72 (1 H, m, 7-H), 3.07 (1 H, ddd, $J_{5\beta,6\beta}$ 4 Hz, $J_{7,6\beta}$ 2 Hz, $J_{6\alpha,6\beta}$ 17 Hz, 6β-H), 5.02 (1 H, ddd, *J* 3, 4, 7 Hz, 5β-H), 5.86 (1 H, dd, *J* 0.5, 13 Hz, 3-H), and 6.54 (1 H, ddd, *J* 0.5, 7, 13 Hz, 4-H); *m/z* 204 (100%, M^+ − Br), 175 (56), 122 (44), 97 (50), 81 (58). This material was followed by 11-*aza*-11-*cyano*-10-*oxotricyclo*[5.3.1.0^{1,5}]*undec*-8-*ene* (**37**) (88 mg, 83%), m.p. 101–102 °C; ν_{max} 2 960, 2 220, and 1 695 cm^{-1}; δ_H(400 MHz) 1.64 (1 H, m), 1.80–2.15 (6 H, m), 2.43 (2 H, m), 4.53 (1 H, dd, *J* 5, 6 Hz, 7-H), 6.08 (1 H, d, *J* 10 Hz, 9-H), and 7.15 (1 H, dd, *J* 5, 10 Hz, 8-H) (Found: C, 70.2; H, 6.45; N, 14.65. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%).

When the reaction was repeated in ether, the products (**36**) and (**37**) were formed in a 1:12 ratio in an overall yield of 65%. Heating compound (**36**) afforded more of the cyclic derivative (**37**) as well as some of the starting ketone (**4**).

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