Solvolytic Rearrangements of Azabicyclic Compounds. Part 1. Identification of Products

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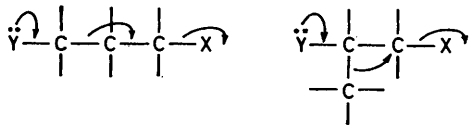
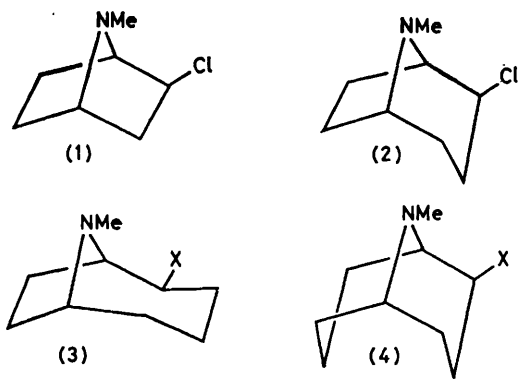
The products of solvolysis of 2β-halogeno-derivatives of 7-methyl-7-azabicyclo[2.2.1]heptane, 8-methyl-8-azabicyclo[3.2.1]octane, 9-methyl-9-azabicyclo-[4.2.1]- and -[3.3.1]-nonane, and 7-methyl-7-azabicyclo[3.2.1]-octane, have been isolated and characterised. Solvolytic rearrangement of 2-bromotropinone to a 4-hydroxy-tropan-6-one is also described.

DIRECT intramolecular interactions of a hetero-atom with a developing carbocation is well known in bicyclic systems, and commonly has rate-enhancing and product-determining effects.[1] In certain substrates only indirect interaction is sterically possible, as in the frangomeric reactions (A) studied by Grob and his co-workers,[2] in which accelerated heterolysis is nevertheless also observed. Indirect assistance is also conceivable in those heterolyses where the heteroatom can assuage the electron-deficiency resulting from Wagner–Meerwein migration (B).



(A) (B)

The product- and rate-determining consequences of type (B) interactions have been studied in only a few cases, notably in 1-substituted-bicyclo[2.2.1]hept-2-yl derivatives,[3] in the work of Martin and Bartlett [4] and Paquette and his co-workers [5] on oxygen-bridged compounds, and of Tabushi *et al.* on 7-thianorbornyl chloride.[6] Some years ago [7] we reported briefly some studies on a group of nitrogen-bridged bicyclic chlorides having



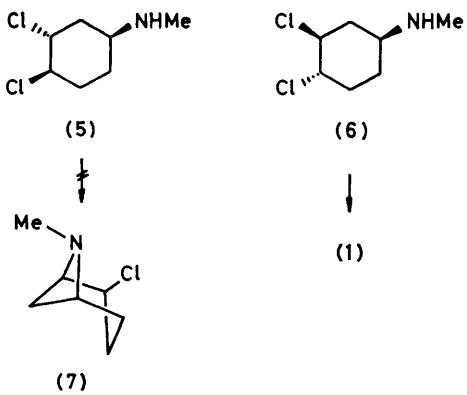
(1) (2) (3) (4)

a ; X = Cl
b ; X = Br

the appropriate stereochemistry for type (B) rearrangements and we now present a fuller account of this and subsequent work on their solvolytic behaviour.

RESULTS AND DISCUSSION

Preparations of the azabicyclic chlorides (2), (3a), and (4a) have been described previously,[8] and the 2β-bromo-analogues (3b) and (4b) were obtained similarly (see Experimental section). The other member (1) of the group has been obtained by the same general method, *i.e.* chlorination of *N*-methylcyclohex-4-enylamine hydrochloride to give a *ca.* 1 : 1 mixture of the two *trans*-dichlorides (5) and (6). These were separated either by fractional crystallisation of the hydrochlorides or by chromatography of the free bases; (6) was readily distinguished by its propensity to cyclisation, which occurred slowly at room temperature in the neat liquid, but was most efficiently accomplished by heating in dimethylformamide at 100 °C. The product (1) †



(5) (6) (1) (7)

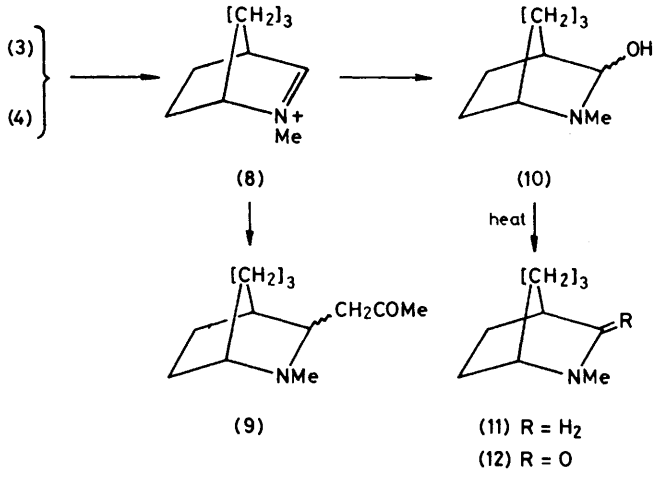
showed n.m.r. signals centred at δ 6.1 characterising the 2α-proton, consisting of four lines arising from coupling to the neighbouring 3α- (*J* 7 Hz) and 3β-protons (*J* 4.5 Hz); visible coupling to the neighbouring bridgehead proton was lacking, confirming the *exo*-orientation of the chlorine atom.[10]

The n.m.r. spectrum of the isomeric chloride (5) showed signals consistent with a chair cyclohexane containing equatorial nitrogen and *trans*-diaxial chlorine substituents ($CH_2CHClCHClCH_2$: eight-line multiplet due to AB system, each proton equally coupled to two others: $J_{AB} = J_{ae} = J_{ee} = 4.5$ Hz, $\Delta\nu_{AB} = 18.5$ Hz; C*H*NHMe: seven-line multiplet: $J_{aa} = 9$ Hz, $J_{ae} = 4.5$ Hz). This compound was largely recovered from

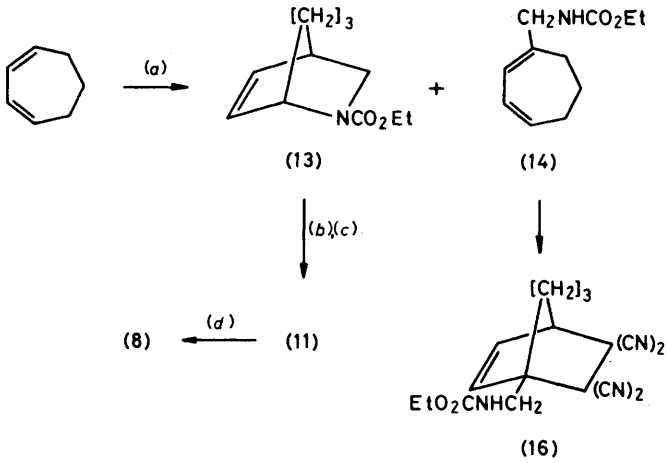
† *exo*-7-Azabicyclo[2.2.1]hept-2-yl chloride has been prepared by a different route.[9]

attempts to induce cyclisation under the conditions effective for the conversion of (6) into (1); more forcing conditions resulted in elimination to give olefinic products rather than the azabicyclo[3.1.1]heptane derivative (7).*

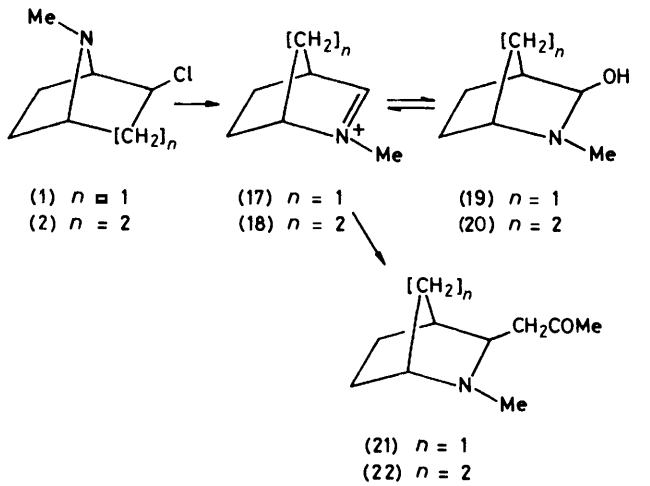
Solvolysis Products.—As previously reported [8] the isomeric 2β-chloro-9-methyl-9-azabicyclononanes (3a) and (4a) were transformed in refluxing aqueous acetone into the same ketone (9) of unknown stereochemistry. The bromo-analogues (3b) and (4b) behaved similarly, recovered yields being generally high (85%). In aqueous dioxan, rearrangement, basification, and solvent extraction afforded the oily amino-alcohol (10), characterised by conversion into the crystalline perchlorate of the cation (8), and also by thermal disproportionation (140 °C) to a mixture of the corresponding tertiary base (11) and lactam (12). Formulation of these products as derivatives of 6-azabicyclo[3.2.2]nonane was confirmed by synthesis *via* the route outlined in Scheme 1. The bicyclic adduct (13) showed the anticipated spectroscopic properties, including an AB quartet in the n.m.r. spectrum centred at τ 6.67 attributable to the NCH_2 group; only the low-field half of this signal showed appreciable coupling (J 4 Hz) to the adjacent bridgehead proton, indicating a skew conformation. Both the saturated base (11) thus prepared and the immonium salt (8) obtained from it by mercury(II) acetate oxidation were identical with samples obtained by the solvolytic route. The monocyclic adduct (14) obtained as a by-product of the diene synthesis showed u.v. absorption characteristic of a homoannular 1,3-diene and n.m.r. signals defining the three olefinic protons and the CH_2-$NHCO_2Et$ moiety. Location of the latter at the 1- rather than the 2-position of the diene was evident from the n.m.r. spectrum of the tetracyanoethylene adduct (16) which showed the presence of two adjacent olefinic protons.



Solvolysis of the homomorphic azabicyclic chlorides (1) and (2) gave similar results (Scheme 2). In aqueous acetone the rearranged acetonyl derivatives (21) and (22) appeared to be the sole products; no evidence bearing on the stereochemistry of (21) was obtained although the well-known propensity of norbornene to *exo*-attack allows a strong presumption in favour of a 2-*exo*-acetonyl substituent. In aqueous dioxan (2) was smoothly converted into the rearranged immonium cation (18), isolated as the known [12] perchlorate, but the lower homologue (1), though also readily hydrolysed, gave a product isolated by solvent extraction only with difficulty. This showed both NH and carbonyl i.r. bands, suggesting conversion of the amino-alcohol (19) into the amino-aldehyde (23). Confirmation was provided by borohydride reduction of the hydrolysate and isolation of the monocyclic amino-alcohol (24), characterised by n.m.r. and mass spectra and those of its diacetyl derivative.



SCHEME 1 (*a*) $CH_2(NHCO_2Et)_2$–BF_3·Et_2O; (*b*) H_2/Pd–C; (*c*) LAH; (*d*) $Hg(OAc)_2$



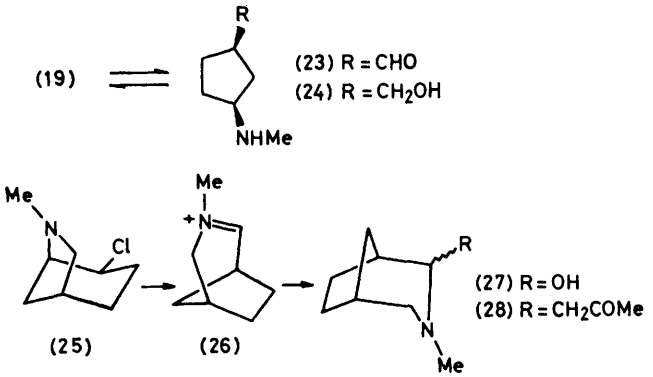
SCHEME 2

A fifth azabicyclic chloride (25), available from the cyclisation of 4-(*N*-chloro-*N*-methylamino)methylcyclo-

* 3-Bromocyclohexylamine has been reported [11] to cyclise to 7-azabicyclo[3.1.1]heptane in low yield.

hexene,[13] was also observed to rearrange stereospecifically under similar conditions, leading to derivatives (27) and (28) of the 3-azabicyclo[3.2.1]octane system, arising from the initially produced immonium cation (26).

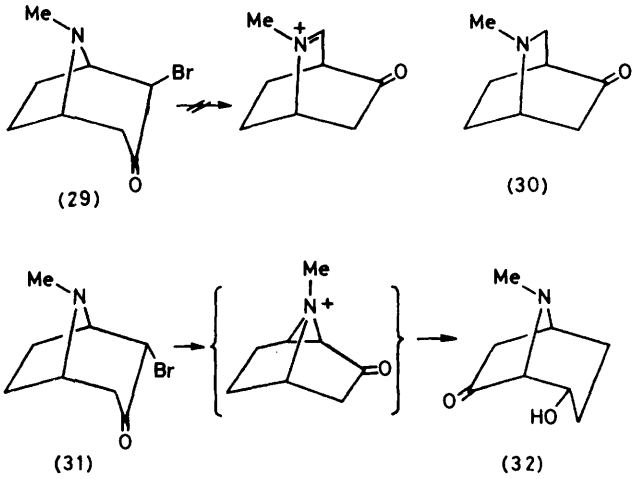
The close relationship between the tropane and isoquinuclidine ring systems established by the rearrangement of 2β-chlorotropane (2) was of interest in connection with the alkaloid dioscorine,[14] the parent ketone of which, dioscorone (30), might thus be accessible by rearrangement of an appropriately substituted tropinone.* The hydrobromide of 2β-bromotropinone (29), prepared using the procedure of Nickon,[16] was heated in aqueous acetone containing potassium carbonate; after 2 h t.l.c. analysis showed the absence of starting material and the presence of several products, one of which was an oily unstable base, isolated in 47% yield. Elemental analysis and mass spectrometry established the molecular



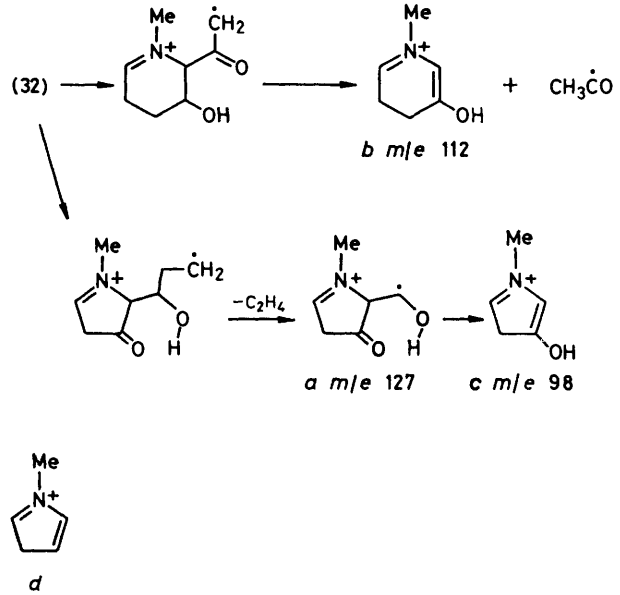
formula $C_8H_{13}NO_2$, and i.r. bands at 3 400, 2 800, and 1 740 cm^{-1} indicated the presence of OH, NMe, and five-membered ring CO groups, respectively. The ^1H n.m.r. signal arising from the alcohol α-proton showed a pattern consistent with vicinal *a,a*- and *a,e*-coupling (*J* 11.5 and 6.0 Hz) to an adjacent CH_2 in a six-membered ring, with additional splitting arising from the lower field of the two bridgehead proton signals. These data were consistent with the rearranged structure (32), arising *via* epimerisation, probably base-catalysed, of the starting bromo-ketone to the 2α-isomer (31), followed by intramolecular displacement [17] and hydrolysis of the resulting aziridinium cation.

Confirmation for structure (32) was provided by the mass spectrum in which the major daughter ions appeared at *m/e* 127, 112, and 98, corresponding to α-cleavage and fragmentation to *a*, *b*, and *c*, respectively. The absence from the mass spectrum of any significant peak at *m/e* 82 corresponding to *d*, expected to arise from a 6/7-unsubstituted tropane,[18] supported this interpretation. Other tropane derivatives briefly examined for their potential for rearrangement included the 2β-bromo-3β-hydroxy-compound, which gave only tropinone, and 2β,3α-dibromotropane, which was unchanged by prolonged refluxing in aqueous dioxan.

The product-determining role of the heteroatom bridge in the solvolyses of 2β-halogeno-azabicyclics



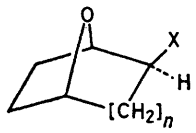
(1)—(4) is evident from the isolation only of rearranged products, formed cleanly and in generally high yield. In this they are distinguished from the behaviour of carbocyclic analogues, *e.g.* 2-*exo*-derivatives of bicyclo-[3.2.1]- and -[2.2.2]-octanes,[19] solvolysis of which leads to multiple products arising from solvent capture of interconverting pairs of bicyclic cations. In the cases of the oxygen-bridged compounds which have been studied, the *exo*-chloride (33) also gave exclusively



products arising from migration of the 1,6 σ-bond whilst being substantially less reactive than *exo*-2-norbornyl chloride.[4] Similar behaviour was shown also by the homologous 8-oxabicyclo[3.2.1]octyl *p*-bromobenzenesulphonate (OBs) (34). On the other hand, the more flexible

* A possible biogenetic role for this type of rearrangement appears to be ruled out by the recent demonstration [15] that nicotinic acid is a partial precursor for the isoquinuclidine ring of dioscorine.

exo-9-oxabicyclo[4.2.1]non-2-yl derivative (**35**) was not only less reactive than its carbocyclic counterpart but failed to undergo Wagner–Meerwein rearrangement.[5a] The bridge heteroatom here evidently provides no anchimeric assistance to ionisation, no encouragement for 1,8 σ-bond migration in the resulting cation, and exercises only an adverse inductive effect on these processes. However, it seems clear that a more weakly electronegative nitrogen



(**33**) $n = 1$, X = Cl
(**34**) $n = 2$, X = OBs
(**35**) $n = 3$, X = OBs

bridge can play a decisive product-determining role by offering to the initially formed carbocation an escape route leading to a relatively stable immonium cation; whether such participation is significant during the rate-determining ionisation is the subject of kinetic studies described in the following paper.

EXPERIMENTAL

I.r. spectra were obtained using Perkin-Elmer model 257 and Unicam SP-200G instruments; n.m.r. spectra of solutions in $CDCl_3$ were measured at 100 MHz using Perkin-Elmer R-14 and Varian XL-100 instruments, with $SiMe_4$ as internal reference. Mass spectra were recorded on an A.E.I. MS-9 spectrometer using direct insertion of samples.

Analytical g.l.c. was performed on a Pye model 104 f.i.d. chromatograph using 7-ft × 3/16-in columns packed with 100—120 mesh Supasorb (B.D.H. Ltd.) coated with 10% of silicone gum E. 30 (A), neopentylglycol succinate (B), or Carbowax 20M (C).

Preparation of Bicyclic Halides. 2β-Chloro-8-methyl-8-azabicyclo[3.2.1]octane (**2**), m.p. 30—32 °C, 2β-chloro-9-methyl-9-azabicyclo[4.2.1]nonane (**3a**), m.p. 47—48 °C, and 2β-chloro-9-methyl-9-azabicyclo[3.3.1]nonane (**4a**), m.p. 47—48 °C, were obtained as described previously.[8] Samples were purified by chromatography on alumina followed by sublimation or distillation, and were shown by g.l.c. (column B, 185 °C) to be >99% pure.

2β-Bromo-9-methyl-9-azabicyclononanes (**3b**) *and* (**4b**).—To a solution of *N*-methylcyclo-oct-4-enylamine (865 mg) in glacial acetic acid (30 cm³) stirred at 17 °C in subdued light was slowly added a solution of 10% bromine in glacial acetic acid until a pale yellow colour persisted in the reaction mixture. After 0.5 h at room temperature the solvent was removed *in vacuo* and water (100 cm³) and aqueous alkali was added until the solution was strongly alkaline. Isolation with ether gave an oil (1.28 g) shown by g.l.c. (column B) to contain two components in a 1 : 4 ratio. Chromatography on alumina and elution with 3% ether in light petroleum (b.p. 40—60 °C) gave first the minor constituent (120 mg), *2β-bromo-9-methyl-9-azabicyclo*[4.2.1]*nonane* (**3b**) as an oil, $\nu_{max.}$ (film) 2 795, 2 760 (NMe), and 1 468 cm⁻¹; τ 5.80 (1 H, t, CHBr), 6.4 br and 6.7 br (2 H, 2 × s, bridgehead protons), 7.50 (3 H, s, NMe), and 7.5—8.9 (10 H, m); *m/e* 219 and 217 (M^+), 138, 110, 96, 83, 82, and 42.

The *picrate* crystallised from aqueous ethanol as prisms, m.p. 190—195 °C (Found: C, 40.7; H, 4.2; N, 12.7. $C_{15}H_{19}BrN_4O_7$ requires C, 40.3; H, 4.3; N, 12.6%).

Further elution with ether–light petroleum gave *2β-bromo-9-methyl-9-azabicyclo*[3.3.1]*nonane* (**4b**), obtained after sublimation at 10 mmHg as crystals, m.p. 46—47 °C; $\nu_{max.}$ (Nujol) 2 810, 2 770 (NMe), 1 480, and 892 cm⁻¹; τ 5.5 (1 H, br s, CHBr), 6.8—7.3 (2 H, m, bridgehead protons), 7.4 (3 H, s, NMe), and 7.5—8.9 (10 H, m); *m/e* 219 and 217 (M^+), 138, 110, 96, 94, 82, 59, 57, and 42 (Found: C, 49.8; H, 7.7; N, 6.1. $C_9H_{16}BrN$ requires C, 49.6; H, 7.4; N, 6.4%).

2β-Chloro-7-methyl-7-azabicyclo[2.2.1]*heptane* (**1**). Cyclohexene-4-carboxylic acid was converted by thionyl chloride into the acid chloride (19.3 g), b.p. 80—81 °C at 15 mmHg (lit.,[20] 52—57 °C at 1.8 mmHg); $\nu_{max.}$ (film) 3 020 (=CH), 1 790 (C=O), and 1 650 cm⁻¹ (C=C), and thence into the azide by addition of an ethereal solution to a vigorously stirred aqueous solution of sodium azide (2 mol equiv.) cooled to 0 °C. After 1.5 h the ether layer was separated, washed with ice-cold aqueous sodium hydrogencarbonate and then with ice-water. The dried solution was evaporated *in vacuo* at 5 °C giving the crude azide (containing some isocyanate) as a colourless oil [$\nu_{max.}$ (film) 3 020 (=CH), 2 260 (N=C=O), 2 135 (CON_3), 1 710 (C=O), and 1 650 cm⁻¹ (C=C)] which was immediately dissolved in anhydrous ethanol and refluxed for 12 h. Removal of the solvent *in vacuo* afforded ethyl *N*-cyclohex-3-enylcarbamate as an oil (21.2 g, 94%) which solidified on cooling to −30 °C. Recrystallisation from light petroleum (b.p. 40—60 °C) at low temperatures afforded colourless needles, m.p. 19—27 °C (lit.,[20] oil); $\nu_{max.}$ (film) 3 310 (NH), 3 020 (=CH), 1 690 (NCO_2Et), and 1 650 cm⁻¹ (C=C); *m/e* 169 (M^+).

The urethane (21.3 g) in anhydrous ether (50 cm³) was added slowly to a stirred suspension of lithium aluminium hydride (10 g) in anhydrous ether (100 cm³). After 24 h the mixture was decomposed by cautious addition of saturated aqueous sodium potassium tartrate (250 cm³) and the product was isolated with ether. Removal of the solvent and distillation *in vacuo* gave a fraction of b.p. 48—55 °C at 15 mmHg (9.2 g, 68%), shown by g.l.c. (columns B and C) to be >95% pure *N*-methylcyclohex-3-enylamine; $\nu_{max.}$ (film) 3 290 (NH), 3 030 (=CH), 2 790 (NMe), and 1 650 cm⁻¹ (C=C). The *N-phenylurea* was obtained from ethanol as needles, m.p. 161—163 °C (Found: C, 72.7; H, 8.2; N, 11.7. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%); the *picrate* crystallised from water as needles, m.p. 131—132 °C (Found: C, 45.8; H, 4.7; N, 16.8. $C_{13}H_{16}N_4O_7$ requires C, 45.9; H, 4.7; N, 16.5%); and the *hydrochloride* separated from aqueous propan-2-ol as prisms, m.p. 168—169 °C (Found: C, 56.3; H, 9.6; N, 9.7. $C_7H_{14}ClN$ requires C, 56.0; H, 9.6; N, 9.5%).

A solution of *N*-methylcyclohex-3-enylamine hydrochloride (19.4 g) in anhydrous dichloromethane (100 cm³) was treated with dry chlorine at room temperature in subdued light until a faint yellow colour persisted in the solution. Cautious evaporation of the solvent gave a crystalline residue (27.2 g) which was treated with 10% aqueous sodium hydroxide (250 cm³) and the bases thus liberated were isolated with ether. Chromatography of a portion (14.1 g) of the oily mixture on alumina (Woelm, Activity II) and elution with ether–light petroleum (b.p. 40—60 °C) mixtures gave N-*methyl*-trans-3,cis-4-*dichlorocyclohexylamine* (**5**) (6.6 g) as an oil which slowly deposited crystals of a salt, $\nu_{max.}$ (Nujol) 2 460 cm⁻¹, on standing for several weeks, although dilute ethereal solutions were stable indefinitely. A specimen purified by preparative g.l.c. (20-ft × 3/8-in 10% E30 on 80—100 mesh silanised Supa-

sorb at 130 °C) showed $\nu_{max.}$ (film) 3 340 (NH) and 2 800 cm^{-1} (NMe); τ($CDCl_3$) 5.5—5.9 (2 H, m, CHCl), 6.9—7.3 (1 H, m, C*H*NHMe), 7.57 (3 H, s, NMe), 7.4—8.6 (6 H, m, CH_2), and 8.71 (1 H, s, N*H*Me). The *hydrochloride*, m.p. 222—223 °C, crystallised from ether–methanol (Found: C, 38.5; H, 6.4; N, 6.6; Cl, 48.3. $C_7H_{14}Cl_3N$ requires C, 38.5; H, 6.45; N, 6.4; Cl, 48.7%).

Further elution of the column with ether and then with ether–methanol gave a mixed fraction (2.9 g), followed by N-*methyl*-cis-3,trans-4-*dichlorocyclohexylamine* (6) (4.2 g) as an oil; $\nu_{max.}$ (film) 3 300 (NH) and 2 790 (NMe) cm^{-1}; τ 6.15 (2 H, m, C*H*Cl), 7.35 (1 H, m, C*H*NMe), 7.54 (3 H, s, NMe), 7.30—8.90 (6 H, m, CH_2), and 8.75 (1 H, s, N*H*Me) which also slowly deposited a crystalline salt on keeping. The *hydrochloride*, m.p. 200—203 °C, crystallised from ether–methanol (Found: C, 38.6; H, 6.4; N, 6.7; Cl, 48.5%).

A solution of *N*-methyl-*cis*-3,*trans*-4-dichlorocyclohexylamine (6) (5.02 g) in dimethylformamide (50 cm^3) was heated on a water bath for 24 h. The solution was poured into aqueous 2N-sodium hydroxide (250 cm^3) and the products were extracted with ether, the extract being passed down a column of activated alumina (200 g) and then saturated with dry hydrogen chloride. The product was collected, washed with ether, and recrystallised from ether–methanol, giving 2β-*chloro*-7-*methyl*-7-*azabicyclo*[2.2.1]*heptane hydrochloride* (2.2 g), m.p. 245—255 °C (decomp.) (Found: C, 46.2; H, 6.9; N, 7.7; Cl, 38.8. $C_7H_{13}Cl_2N$ requires C, 46.15; H, 7.2; N, 7.7; Cl, 39.0%). Basification and isolation with ether gave the base (1) as an oil distilling at 52 °C and 0.3 mmHg in >99.5% purity (g.l.c.); τ 6.14 (1 H, dd, *J* 4.5 and 6.5 Hz, CHCl), 6.66br and 6.69br (2 H, 2 × s, CHN), 7.66 (3 H, s, NMe), and 7.4—9.0 (6 H, m, methylenes); *m/e* 147 and 145 (M^+), 110, 83, 82 (base peak), and 42; *m** 46.4 ($M^+ \longrightarrow 82$), and 81.3 ($83 \longrightarrow 82$) (Found: C, 57.9; H, 7.9; N, 9.9; Cl, 24.2. $C_7H_{12}ClN$ requires C, 57.7; H, 8.3; N, 9.6; Cl, 24.4%).

Rearrangement of the 2β-*Chloro*-9-*methyl*-9-*azabicyclononanes* (3a) *and* (4a).—(a) *In aqueous acetone*. A solution of the pure chloride (200 mg) in water–acetone (2 : 1) (20 cm^3) was refluxed for 16 h. Isolation with ether and distillation of the product at 80—100 °C (bath) and 10 mmHg gave in each case 7-*acetonyl*-6-*methyl*-6-*azabicyclo*[3.2.2]*nonane* (9) as an oil (yields >90%) of >98% purity (g.l.c.); $\nu_{max.}$ (film) 2 795, 2 760 (NMe), and 1 708 cm^{-1} (CO); τ(CCl_4) 7.1—7.7 (2 H, m, CHN), 7.45 (2 H, s, CH_2CO), 7.75 (3 H, s, NMe), 7.95 (3 H, s, COMe), and 8.0—8.9 (11 H, m); *m/e* 195 (M^+), 152, 138 ($M^+ - CH_2COMe$, base peak), 110, 96, 94, 82, 70, 43, 42. The *picrate* (from ethanol) had m.p. 147—149 °C (Found: C, 51.0; H, 5.3; N, 13.6. $C_{18}H_{24}N_4O_8$ requires C, 51.2; H, 5.2; N, 13.3%).

(b) *In aqueous dioxan*. Solvolyses were carried out by refluxing solutions of the chloride (350 mg) in dioxan–water (1 : 2) (20 cm^3) for 6 h, under nitrogen. Basification and isolation by continuous ether extraction gave the crude amino-alcohol (10) [$\nu_{max.}$ (film) 3 400 (OH), 2 810, and 2 770 cm^{-1} (NMe)] as a slightly yellow oil (280 mg, 90%) which slowly deteriorated on keeping in the atmosphere. Addition of 50% perchloric acid in ethanol followed by a little ether gave the *perchlorate* (8), obtained from ethanol as needles, m.p. 252—254 °C; $\nu_{max.}$ (Nujol) 1 695 ($C\overset{+}{=}N$); *m/e* 139 (M^+), 110, 96, 82, 70, 42, and 41 (Found: C, 45.7; H, 7.0; Cl, 15.0; N, 6.0. $C_9H_{16}ClNO_4$ requires C, 45.5; H, 6.8; Cl, 14.9; N, 5.9%).

A solution of the perchlorate in 50% aqueous acetone was refluxed for 12 h. Removal of the acetone, basification, and isolation with ether gave 7-acetonyl-6-methyl-6-azabicyclo[3.2.2]nonane (9) identical (spectra and g.l.c.) with the sample obtained as described in (a).

Rearrangement of the 2β-*Bromo-compounds* (3b) *and* (4b).—Solvolysis of the 2β-bromo-9-methyl-9-azabicyclononanes in aqueous acetone were carried out as described for the chloro-compounds; conversion into the acetonyl compound (9) was almost quantitative in each case, and no other volatile product could be detected by g.l.c.

Thermolysis of the Amino-alcohol (10).—G.l.c. (column A, 140 °C) of the crude amino-alcohol obtained above showed two well differentiated peaks; preparative g.l.c. resulted in the separation of 6-*methyl*-6-*azabicyclo*[3.2.2]*nonane* (11), obtained as an oil; $\nu_{max.}$ (film) 2 785 and 2 750 cm^{-1} (NMe); τ 6.5—7.1 (3 H, m, CH_2NCH), 7.3 (3 H, s, NMe), 7.4—8.5 (11 H, m); *m/e* 139 (M^+), 111, 96, 82, and 43; the *picrate* (from aqueous ethanol), m.p. 266—268 °C (decomp.) (Found: C, 48.9; H, 5.5; N, 15.3. $C_{15}H_{20}N_4O_7$ requires C, 48.9; H, 5.5; N, 15.2%), and 6-*methyl*-7-*oxo*-6-*azabicyclo*[3.2.2]*nonane* (12), a viscous oil; $\nu_{max.}$ (film) 1 660 cm^{-1}; τ 6.55 (1 H, m, C*H*NMe), 7.05 (3 H, s, NMe), 7.4 (1 H, m, CHCO), and 8.0—8.5 (10 H, m); *m/e* 153 (M^+), 124, 111, 110, 97, 96, 82, 70, 57 {$(MeNCO)^+$, base peak}, and 42 (Found: C, 70.5; H, 10.1. $C_9H_{15}NO$ requires C, 70.6; H, 9.9%).

A solution of the lactam (43 mg) in dry ether (15 cm^3) was stirred with lithium aluminium hydride (100 mg) for 12 h and then worked up in the usual way to give a colourless oil (26 mg, 66%) shown (i.r. and g.l.c.) to be identical with the base (11) obtained as described above.

Ethyl 6-*Azabicyclo*[3.2.2]*non*-8-*ene*-6-*carboxylate* (13).—Cyclohepta-1,3-diene (14.2 g) was added dropwise during 20 min to a refluxing solution of freshly distilled boron trifluoride–ether (6.05 g) and methylenebisurethane (28.9 g) in dry benzene (200 cm^3). The reactants were refluxed for 16 h and the cooled solution was washed successively with aqueous sodium hydrogencarbonate, brine, and water, dried and evaporated *in vacuo*. The residue was extracted with several portions of boiling light petroleum (b.p. 40—60 °C), the extracts being decanted from unreacted methylenebisurethane, combined and concentrated, and chromatographed on alumina (300 g). Elution with 25% ether–light petroleum afforded *ethyl* 6-*azabicyclo*[3.2.2]*non*-8-*ene*-6-*carboxylate* (13) (3.2 g, 11%) as an oil, b.p. 75—80 °C at 0.15 mmHg; $\nu_{max.}$ (film) 3 035 (=CH), 1 690 (CO), and 1 630 cm^{-1} (C=C); τ 3.82 (2 H, t, CH=CH), 5.34 (1 H, br s, H-6), 5.86 (2 H, q, OCH_2Me), 6.52 (1 H, d) and 6.84 (1 H, dd, *J* 11.0 and 4.0 Hz) (CH_2N), 7.60 (1 H, br m, H-1), 8.2—8.5 (6 H, m), and 8.90 (3 H, t, CH_2Me); *m/e* 195 (M^+), 195, 166 (base peak), 152, 122, 108, 96, 94, 93, 67, 53, 41, and 39; *m** 141.3 ($M^+ \longrightarrow 166$) and 118.5 ($M^+ \longrightarrow 152$) (Found: C, 67.9; H, 9.1; N, 7.0. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%).

Further elution with ether afforded *ethyl* N-[(*cyclohepta*-1,3-*dienyl*)*methyl*]*carbamate* (14) (1.59 g, 5%) as a viscous oil, b.p. 93—97 °C at 0.04 mmHg; $\lambda_{max.}$ (EtOH) 250 nm (ε 9 150); $\nu_{max.}$ (film) 3 320 (NH), 3 005 (=CH), and 1 700 cm^{-1} (CO); τ 4.29 (3 H, m, =CH), 4.74 (1 H, br m, NH), 5% (2 H, q, OCH_2Me), 6.25 (2 H, d, CH_2NH), 7.70 (4 H, br m) and 8.0—8.5 (2 H, m) (other ring protons), and 8.77 (3 H, t, OCH_2Me); *m/e* 195 (M^+), 166, 106, 105, 102, 91 (base peak), 79, 78, and 77 (Found: C, 67.8; H, 8.9; N, 7.1%). A solution of this product (0.49 g) and tetracyanoethylene (0.32 g) in dry benzene (30 cm^3) was allowed

to stand at room temperature for 3 days. The reddish-brown crystals that separated were collected and recrystallised from ethanol to give the *adduct* (16) (0.28 g) as colourless prisms, m.p. 159—160 °C; $\nu_{max.}$ (Nujol) 3 370 (NH), and 1 720 cm^{-1} (CO); τ 3.20 (1 H, br m, NH), 3.49 (2 H, br s, =CH), 5.88 (2 H, q, *J* 7 Hz, OCH_2Me), 6.13 and 6.31 (2 H, dd, *J* 8 Hz, CH_2N), 7.8—8.2 (7 H, m, ring protons), and 8.89 (3 H, t, *J* 7 Hz, OCH_2Me) (Found: C, 62.9; H, 5.4; N, 21.9. $C_{17}H_{17}N_5O_2$ requires C, 63.1; H, 5.3; N, 21.7%).

6-*Methyl*-6-*azabicyclo*[3.2.2]*nonane* (11).—A solution of the 1,4-adduct (13) (1.95 g) in cyclohexane (100 cm^3) was hydrogenated over 5% palladium–charcoal (200 mg) at atmospheric pressure. Absorption of hydrogen was complete after 40 min and the filtered solution was evaporated *in vacuo*; the residue distilled at 75—81 °C (bath) and 0.04 mmHg to give *ethyl* 6-*azabicyclo*[3.2.2]*nonane*-6-*carboxylate* (1.75 g) as a colourless oil; $\nu_{max.}$ (film) 1 690 cm^{-1} (CO); τ 5.6—6.0 br (1 H, CHN), 5.90 (2 H, q, CH_2Me), 6.65 (2 H, q, NCH_2), 7.8 (1 H, br m, bridgehead proton), 7.9—8.7 (10 H, m), and 8.8 (3 H, t, CH_2Me); *m/e* 197 (M^+), 168, 154, 140, 96, 82 (base peak), 68, 56, 55, and 41; *m** 120.4 (M^+ 154) (Found: C, 66.6; H, 9.7. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.7%).

A solution of this urethane (0.87 g) in dry ether (30 cm^3) was added dropwise to a well-stirred solution of lithium aluminium hydride (0.5 g) in dry ether (30 cm^3) and the mixture was refluxed for 5 h. Work-up in the usual way gave an oil which distilled at 103—105 °C (bath) and 50 mmHg to give 6-methyl-6-azabicyclo[3.2.2]nonane, shown by g.l.c. and comparison of i.r. and n.m.r. spectra to be identical with material obtained from thermolysis of the amino-alcohol (10).

Oxidation of 6-methyl-6-azabicyclo[3.3.2]nonane (11) was carried out by stirring a solution of the base (0.85 g) and mercury(II) acetate (9.18 g) in 5% acetic acid (25 cm^3) at 105 °C for 5 h. The cooled mixture was filtered, the residue well washed with solvent, and the filtrate saturated with hydrogen sulphide. After filtering, careful addition of excess of potassium carbonate was followed by extraction with ether; the dried extract was concentrated (to 50 cm^3) and treated with 50% aqueous perchloric acid (0.5 cm^3) together with sufficient ethanol to achieve miscibility. The perchlorate (0.74 g, 51%) obtained as needles, m.p. 252—254 °C, from ethanol was identical with the sample prepared by the solvolytic route from (3) or (4).

Rearrangement of 2β-*Chloro*-8-*methyl*-8-*azabicyclo*[3.2.1]-*octane* (2).—(a) *In aqueous acetone*. A solution of the chloride (237 mg) in acetone (4 cm^3) and water (16 cm^3) was refluxed for 14 h. Removal of the acetone *in vacuo* followed by basification, isolation with ether, and distillation at 120 °C (bath) and 10 mmHg gave 3-*acetonyl*-2-*methyl*-2-*azabicyclo*[2.2.2]*octane* (22) (184 mg, 69%) of 99% purity (g.l.c.); $\nu_{max.}$ (film) 2 785, 2 760, and 1 710 cm^{-1}; τ 7.2—7.6 (2 H, m, NCH), 7.37 (2 H, s, COMe), and 8.0—9.0 (11 H, m); *m/e* 181 (M^+), 138, 125, 124 (base peak, $M^+ - CH_2CO$Me), 110, 96, 94, 82, 70, 58, and 43.

The *picrate* was obtained from ethanol as plates, m.p. 118—120 °C (Found: C, 50.0; H, 5.4; N, 13.9. $C_{17}H_{22}N_4O_8$ requires C, 49.8; H, 5.4; N, 13.7%).

(b) *In aqueous dioxan*. A solution of the chloride (90 mg) in dioxan (10 cm^3) and water (20 cm^3) was heated on a steam-bath for 6 h. Basification and isolation with ether gave an oil, $\nu_{max.}$ (film) 3 300, 2 785, and 2 760 cm^{-1}, to which addition of 50% perchloric acid in ethanol followed by trituration with ether gave the perchlorate (18), obtained from ethanol as needles, m.p. 235—236 °C (lit.,[12] 239 °C).

Rearrangement of 2β-*Chloro*-7-*methyl*-7-*azabicyclo*[2.2.1]-*heptane* (1).—(a) *In aqueous acetone*. A solution of the chloride (247 mg) in 50% aqueous acetone (15 cm^3) was refluxed for 48 h. Basification, isolation with ether, and distillation at 120 °C (bath) and 0.03 mmHg gave 3-*acetonyl*-2-*methyl*-2-*azabicyclo*[2.2.1]*heptane* (21) (200 mg); $\nu_{max.}$ (film) 2 960, 2 875, 2 782 (NMe), 1 710 (CO), 1 360, 1 165, and 930 cm^{-1}; τ 6.86 (1 H, br s, bridehead CHN), 7.36 (1 H, m, $NCHCH_2$), 7.43 (1 H, dd, *J* 5 and 2 Hz) and 7.60 (1 H d *J* 5 Hz, CH_2CO), 7.70 (3 H, s, NMe), 7.85 (3 H, s, COMe), and 7.9—8.9 (7 H, m); *m/e* 167 (M^+), 138, 124, 110 (base peak, $M^+ - CH_2$COMe), 82, and 43. The *picrate* (from ether–methanol) had m.p. 133 °C (Found: C, 48.4; H, 4.9; N, 14.3. $C_{16}H_{20}N_4O_8$ requires C, 48.5; H, 5.1; N, 14.1%).

(b) *In aqueous dioxan*. A solution of the chloride (220 mg) in water (10 ml) and dioxan (5 cm^3) was refluxed under nitrogen for 8 h. Extraction (3 × 10 cm^3) with ether gave a gum (15 mg) shown by g.l.c. to consist largely of starting material. The reaction mixture was mixed with a solution of sodium borohydride (150 mg) in water (5 cm^3) and kept for 16 h. Acidification with 4M hydrochloric acid and evaporation *in vacuo*, followed by re-basification with a paste of potassium carbonate and extraction with dichloromethane (5 × 15 cm^3) gave *cis*-3-*N*-methylaminocyclopentylmethanol (24) (168 mg, 85%), shown by g.l.c. (Column C) to be 95% pure; $\nu_{max.}$ (film) 3 290 and 3 380 cm^{-1}; τ 6.21 (1 H, s, OH), 6.56 (1 H, d, NH), 6.77 (2 H, s, CH_2OH), 7.10 (1 H, m, CHNHMe), 7.57 (3 H, d, *J* 3.0 Hz, NMe), 7.7—8.9 (7 H, m); *m/e* 129 (M^+), 110, 98, 81, and 70. The *diacetyl derivative*, obtained by treatment with warm acetic anhydride, was obtained as an oil; $\nu_{max.}$ (film) 1 749 (ester CO); τ 5.99 (2 H, dd, *J* 6.5 and 2.0 Hz, $CHCH_2OAc$), 7.14 (3 H, d, *J* 5.7 Hz, NMe), 7.91br (6 H, s, NAc and OAc), and 7.6—8.9 (8 H, m, ring protons); *m/e* 213.1356 (M^+: $C_{11}H_{19}NO_3$ requires 213.136 5), 170, 157, 155, 98, 74 (base peak), and 43.

Rearrangement of endo-4-*Chloro*-6-*methyl*-6-*azabicyclo*-[3.2.1]*octane* (25).—A solution of the chloride (273 mg) in dioxan (7 cm^3) and water (15 cm^3) was refluxed for 20 h under N_2. Basification with sodium hydroxide and continuous extraction with ether gave 3-*methyl*-3-*azabicyclo*[3.2.1]-*octan*-2-*ol* (27) (220 mg, 90%) as an oil; $\nu_{max.}$ (film) 3 460 (OH) and 2 805 cm^{-1} (NMe); addition of 50% perchloric acid in ethanol together with some ether gave the *perchlorate* (26) (220 mg), obtained from ethanol as colourless needles, m.p. 175—176 °C; $\nu_{max.}$ (Nujol) 1 700 cm^{-1} (C=N$^+$); τ 1.30 br (1 H, d, *J* 4.3 Hz, CH=N$^+$), 6.48 (3 H, s, N$^+$Me), 6.0—6.4 (2 H, m, CH_2N^+Me), 6.6—7.0 (1 H, m, CHCH=N$^+$), 7.25—7.50 (1 H, m, $CHCH_2N^+$), and 7.8—8.5 (6 H, m) (Found: C, 42.8; H, 6.6; Cl, 16.1; N, 6.6. $C_8H_{14}NClO_4$ requires C, 42.9; H, 6.3; Cl, 15.8; N, 6.3%).

Solvolysis of this chloride (25) (140 mg) in refluxing aqueous acetone (2 : 1) for 48 h under N_2 gave, after removal of the acetone, basification, and isolation in the usual way, 2-*acetonyl*-3-*methyl*-3-*azabicyclo*[3.2.1]*octane* (28) (139 mg, 89%) which was purified by chromatography on alumina (20 g, Activity II) and short-path distillation at 0.1 mmHg. A colourless oil was obtained having $\nu_{max.}$ (film) 2 780 (NMe) and 1 710 cm^{-1} (CO); τ 7.2—7.75 (5 H, m, CH_2NCHCH_2CO), 7.90 (6 H, s, NMe and COMe), 8.0—8.9 (8 H, other ring protons); *m/e* 181 (M^+), 133, 126, 125, 114, 94, 73, 72, and 58. The *picrate* crystallised from methanol giving needles, m.p. 177—178 °C (Found: C, 50.1; H,

5.6; N, 13.8. $C_{15}H_{18}N_4O_8$ requires C, 49.8; H, 5.4; N, 13.7%).

Solvolysis of 2β-*Bromo*-8-*methyl*-8-*azabicyclo*[3.2.1]*octan*-3-*one* (2β-*Bromotropinone*) (29).—Tropinone was converted into the hydrobromide of (29), m.p. 192 °C (decomp.) [lit.,[16] 192° (decomp.)], and the free base was liberated with aqueous sodium carbonate and isolated with ether, giving unstable crystals, m.p. 72—74 °C (lit.,[16] 75.5—76.5°); τ 4.94 (1 H, CHBr, d, *J* 3.6 Hz).

A solution of the pure hydrobromide (320 mg) in water (10 cm^3) and acetone (5 cm^3) containing potassium carbonate (75 mg) was refluxed for 2 h under N_2; t.l.c. then showed the absence of starting material. The mixture was extracted with ether (2 × 15 cm^3) and then with chloroform (3 × 15 cm^3); the latter extract afforded the *ketone* (32), an unstable oil (80 mg) which appeared to contain a single component on examination by t.l.c. This showed $\nu_{max.}$ (film) 3 400 (OH), 2 800 (NMe), and 1 741 cm^{-1} (CO); τ 6.01 [1 H, ddd, *J* 11.5, 6.0 and 4.0 Hz, $CH_2CH(OH)$-CHN], 6.50 (1 H, br s, OH), 6.84 (1 H, br s, CHN), 6.97 (1 H, br d, *J* 4.0 Hz, CHN), 7.54 (3 H, s, NMe), and 7.1—8.8 (6 H, m, remaining protons): *m/e* 155.0925 (M^+; $C_8H_{13}NO_2$ requires 155.0946), 127, 112, 98 (base peak), and 42. The *picrate* had m.p. 220 °C (decomp.) (Found: C, 43.8; H, 4.5; N, 14.7. $C_{14}H_{16}N_4O$ requires 43.8; H, 4.2; N, 14.6%).

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