[Chem. Pharm. Bull. 16(4) 654—662 (1968)] UDC 547.891.2.07

Syntheses of Tricyclic Amines from Azabicyclic Compounds through Carbenes

Sadao Oida and Eiji Ohki

Central Research Laboratories, Sankyo Co., Ltd.[1]

(Received June 10, 1967)

It was found that the insertion reaction of a carbene produced at bridged carbon (C_9) of 3-methyl-3-azabicyclo[3.3.1]nonane proceeded exclusively into the opposite side to N-methyl group to yield 3-methyl-3-azatricyclo[6.1.0.0^{5,9}]nonane (III), while that of a carbene at bridged carbon(C_8) of 3-methyl-3-azabicyclo[3.2.1]octane was to the same side of N-methyl group to give 2-methyl-2-azatricyclo[5.1.0.0^{4,8}]octane (XV).

In a previous paper,[2] it was shown that the skeleton of 8-phenyl-3-azabicyclo[3.2.1]octane did not yield a carbonium ion like Ia, but that the skeleton of its homolog, 9-phenyl-3-azabicyclo[3.3.1]nonane easily formed a carbonium ion like Ib. This finding led us to investigate analogous carbene intermediates at the same bridged carbon of these azabicyclic compounds, because one might expect that, if any difference of skeletal strains between these bicyclo-nonane and -octane controls the formation of a carbonium ion as described before,[2] the carbene intermediates would also be affected by analogous interaction.

Following the method of Cristol and Harrington,[3] thermal decomposition of the sodium salt of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one[4] tosylhydrazone (II) was carried out at 170° in Diglyme. The resulting product was purified by fractional distillation and preparative gas chromatographty, giving a tricyclic amine (III) of bp 109—110° (77mmHg) in 67% yield. The molecular formula of III, $C_9H_{15}N$, was determined by elemental analysis, referring to its mass spectrum which exhibited a molecular ion peak at *m/e* 137 (*cf.* Fig. 1). III was also characterized as a crystalline methiodide, $C_{10}H_{18}NI \cdot 1/2H_2O$, mp 230° (decomp.), and a picrate, $C_{15}H_{18}O_7N_4$, mp 180—195°.

The tricyclic amine (III) showed no absorption in the ultraviolet region and its NMR spectrum also showed no absorption corresponding to any olefinic proton; but infrared absorption of III or its methiodide at 3030 cm^{-1} suggested the presence of a cyclopropane ring[5] in the molecule. Complex absorption at 0.8—1.1 ppm in the NMR spectrum of III would be ascribed to protons of the cyclopropane ring, but it partly fell on a region of normal methylene or methine proton absorption, giving no suggestion on the cyclopropane moiety. On the basis of these spectral data, the structure of the tricyclic amine would be designated as III or its alternate formula (IV).

The Hofmann degradation of the methiodide of III afforded an unsaturated bicyclic amine (V) which formed a crystalline hydrochloride of mp 181—183°, $C_{10}H_{18}NCl$. The presence of an exocyclic methylene group in V was shown by infrared absorptions at 3080, 1651, and 867 cm^{-1}, and the two broad absorptions at 4.96 and 4.83 ppm in its NMR spectrum. The notable end absorption of V in the ultraviolet region indicated a conjugation of the cyclopropane ring with the exocycilc methylene group.[6] Furthermore, in the NMR spectrum of the methiodide

1) Location: *2-58, Hiromachi, 1-chome, Shinagawa-ku, Tokyo.*
2) S. Oida, M. Kurabayashi, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **14**, 1418 (1966). *cf.* H.O. House, W.M. Bryant, III, *J. Org. Chem.*, **31**, 3482 (1966).
3) S.J. Cristol and J.K. Harrington, *J. Org. Chem.*, **28**, 1413 (1963).
4) H.O. House, P.P. Wickham, and H.C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1963).
5) M. Horák, J. Šmejkal, and J. Farkaš, *Collection Czech. Chem. Commun.*, **28**, 2280 (1963).
6) A.I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, London, 1964, p. 347.

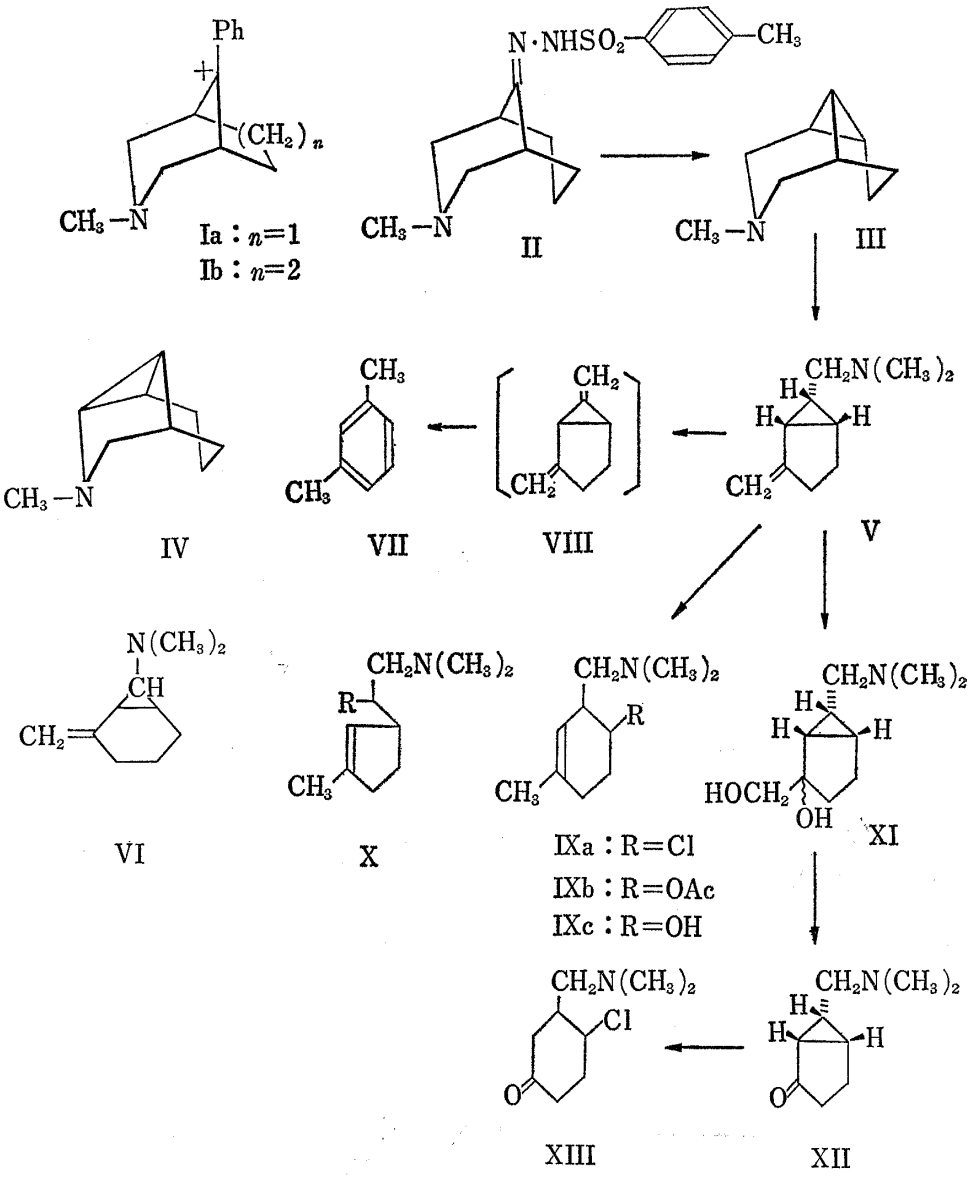

Chart 1

of V, it was possible to recognize the presence of a typical ABX-type quartet on each of the absorption centered at 3.53 and 3.10 (J_{AB}=13.5, J_{AX}=5.5, and J_{BX}=8.5 cps), indicating that the dimethylamino group was not connected with methine group, but with a methylene group like $(CH_3)_2N\text{-}CH_AH_B\text{-}CH_X\text{-}$. This fact illustrated that the alternate formula (VI) for the unsaturated bicyclic amine originating from the tricyclic amine (IV) was ruled out. Further Hofmann degradation of the methiodide of V yielded, in a good yield, *m*-xylene (VII), which was identified by means of infrared, ultraviolet, and NMR spectrometry, and by gas chromatography. Presumably, formation of VII would proceed through an unstable bicyclic diene intermediate (VIII), also supporting the above-described evidence on the structure of V.

Further proof for the conjugation of the exocyclic methylene with the cyclopropane ring in V was given by the following facts.

In contrast with the tricyclic amine (III), which was stable to acids,[7] the unsaturated bicyclic amine (V) easily took up hydrogen chloride to give a monocyclic

7) The tricyclic amine (III) was inert to hydrochloric acid in boiling ethanol, and majority of III was also recovered unaffected when heated in acetic acid for 2 days, in the presence of perchloric acid.

chloramine[8] (IXa), hydrochloride of mp 179°, which formed a methiodide of mp 166° (decomp.). Treatment of V with acetic acid in the presence of a mineral acid also yielded a monocyclic acetoxyamine[8] (IXb) (picrate, mp 155—164°) which was hydrolyzed to a hydroxyamine (IXc) of bp 130—140° (8 mmHg) (picrate, mp 148—149°). These facile uptake of acids suggested the conjugation of the cyclopropane ring with the double bond in V. In these addition products, the presence of the endo-double bond shifted from exo-position was indicated by infrared absorptions at 847—810 cm^{-1} and NMR signals at 5.0—5.4 ppm associated with one proton of the double bond, and also NMR signals at 1.63—1.72 ppm with methyl protons on the double bond.

Osmium tetroxide oxidation of V afforded a glycol (XI) of mp 76.5—78°, which was further treated with periodic acid to give a bicyclic aminoketone (XII). XII was characterized as a crystalline hydrochloride of mp 196° (decomp.) and a picrate of mp 183—186°. The infrared absorption of XII at 1715 cm^{-1} and its notable end absorption in the ultraviolet region indicated a conjugation of the cyclopropane ring with a five-membered ring ketone.[9] Furthermore, treatment of XII with hydrochloric acid gave, in a good yield, a chloroamino-ketone (XIII) which formed a hydrochloride of mp 196° (decomp.) and a picrate of mp 172—173.5°. The ultraviolet spectrum of XIII exhibited no absorption and its infrared absorption was at 1710 cm^{-1} corresponding to a saturated six-membered ring ketone.

On the basis of these data, III was disignated as 3-methyl-3-azatricyclo[6.1.0.$0^{5,9}$]nonane.

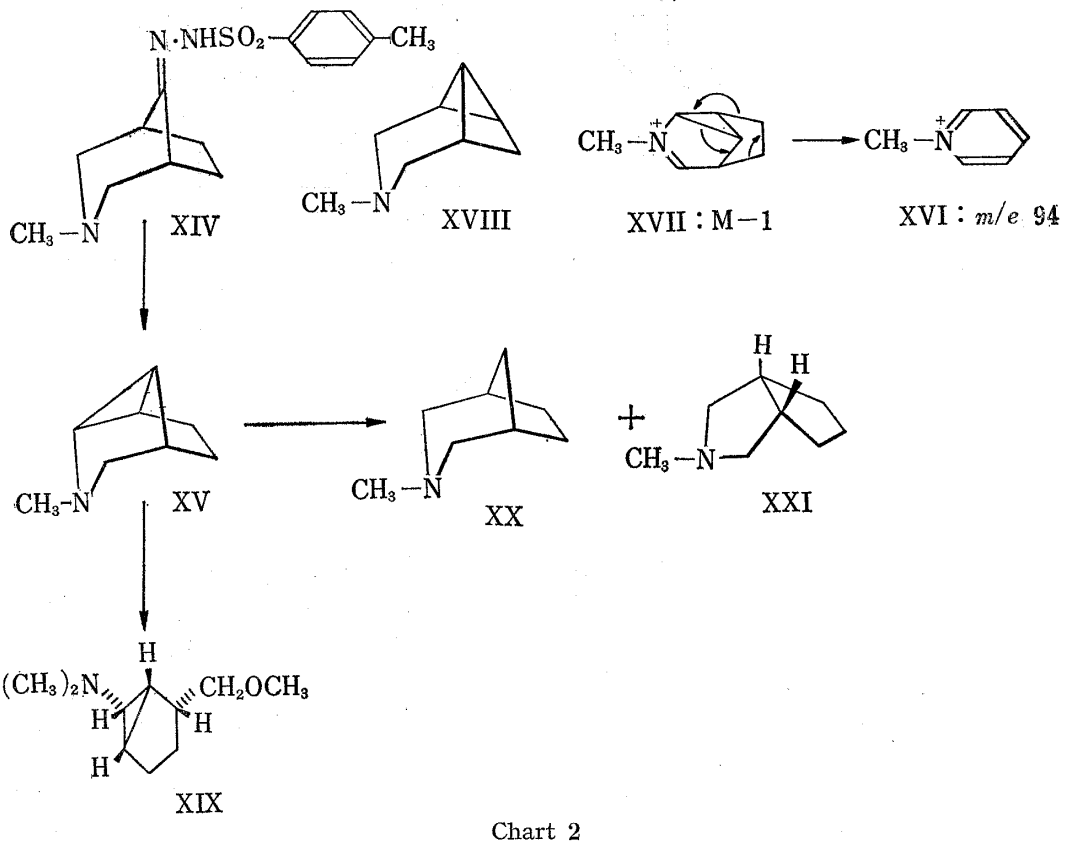

Chart 2

On the other hand, the sodium salt of 3-methyl-3-azabicyclo[3.2.1]octan-8-one[4] tosyl-hydrazone (XIV) was worked up under the same condition as for III and gave a tricyclic

8) An alternative formula (X) will be assignable for these addition products; however, formation of IX was more plausible by consideration of an 1,4-addition mode of an acid to the conjugation system from stereochemically-favored side. This coincided in the addition mode of acids to the bicyclic aminoketone (XII) described below.

9) See reference 6) p. 345.

azaoctane (XV) of bp 83—86° (75 mmHg) in 56% yield. XV was characterized as a methiodide of mp 215° (decomp.) and a picrate of mp 153° (decomp.). Molecular formula of XV was determined by elemental analyses of XV and its derivatives, and by its mass spectrometry (M^+=123). The infrared absorption of XV at 3030 cm^{-1} also indicated the presence of a cyclopropane ring.[5] Mass spectrometry of XV suggested the structure of 2-methyl-2-azatricyclo[5.1.0.$0^{4,8}$]octane, as shown in Fig. 2. The most intense fragmentation peak at *m/e* 94 was indicative of N-methylpyridinium ion (XVI) which may be generated from M-1 (XVII) by the removal of ethylene. As shown in Fig. 1, the tricyclic azanonane (III) exhibited a marked *m/e* 58 and an abundant *m/e* 57 corresponding to $(CH_3)_2N^+=CH_2$[10] and: $CH_2-N^+(CH_3)=CH_2$, which were presumably generated from the part of the molecule, $-CH_2-N(CH_3)-CH_2-$. However, the tricyclic azaoctane (XV) showed no *m/e* 58 and exhibited *m/e* 57 of low intensity, ruling out the other possible formula (XVIII) having two methylene groups at the nitrogen atom.

As for the chemical proof of XV, its Hofmann degradation reverted it to the tricyclic amine (XV) by liberation of methanol when the reaction was carried out in water, but gave a methoxyamine (XIX) when reacted in methanol. Interpretation of this result was still not obvious, but the NMR spectrum of XIX at 2.4—2.9 ppm, corresponding to one proton, was indicative of the presence of one hydrogen at the carbon bearing the dimethylamino group, also suppporting the structure of the original tricyclic amine as XV, not as XVIII. Contrasted with the tricyclic azanonane (III), which was stable to hydrogenation, XV esaily took up one mole of hydrogen to afford a mixture of 3-methyl-3-azabicyclo[3.2.1]octane (XX) and 3-methyl-3-azabicyclo[3.3.0]octane (XXI), which were identified with the synthetic samples as methiodides of mp >270° and mp 203—204.5° (decomp.), respectively. The former was synthesized by the Huang-Minlon reduction of 3-methyl-3-azabicyclo[3.2.1]octan-8-one[4] and the latter by the method of Rice and Grogan.[11] Formation of the latter also ruled out the alternative formula (XVIII). Based on these facts, the structure of the tricyclic azaoctane was designated as 2-methyl-2-azatricyclo[5.1.0.$0^{4,8}$]octane.

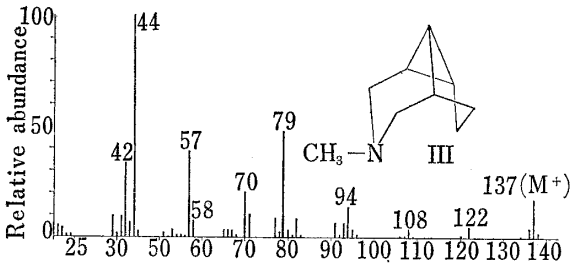

Fig. 1. Mass Spectrum of 3-Methyl-3-azatricyclo-[6.1.0.$0^{5,9}$]nonane (III)

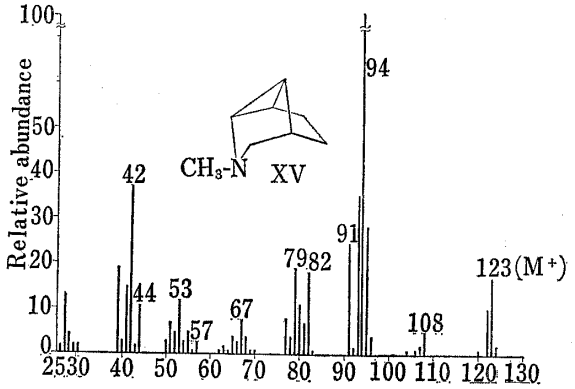

Fig. 2. Mass Spectrum of 2-Methyl-2-azatricyclo[5.1.0.$0^{4,8}$]octane (XV)

In these reactions, the by-products were also investigated in both azabicyclo-nonane and -octane compounds; but any products corresponding to an isomer of the tricyclic amine (IV or XVIII) could not be isolated.[12] Consequently, it was concluded that the insertion

10) W.M. Bryant, III, A.L. Burlingame, H.O. House, C.G. Pitt, and B.A. Tefertiller, *J. Org. Chem.*, **31**, 3120 (1966).

11) L.M. Rice and C.H. Grogan, *J. Org. Chem.*, **24**, 7 (1959).

12) A compound of mp 180° (decomp.), $C_{16}H_{23}O_2NS$, was obtained as a by-product of III in 0.2% yield and an analogous compound of mp 123—124°, $C_{15}H_{21}O_2NS$, as a by-product of XV in the same yield as descirbed in experimental. Infrared and NMR spectra of these by-products suggested their structure as XXII and XXIII respectively; however, further study on these compounds was not attempted due to the lack of samples.

reaction of these carbenes, which are assumed as intermediates in these reactions, proceeded exclusively into the opposite side of N-methyl group in the case of azabicyclononane system and into the same side in the case of azabicycloöctane.

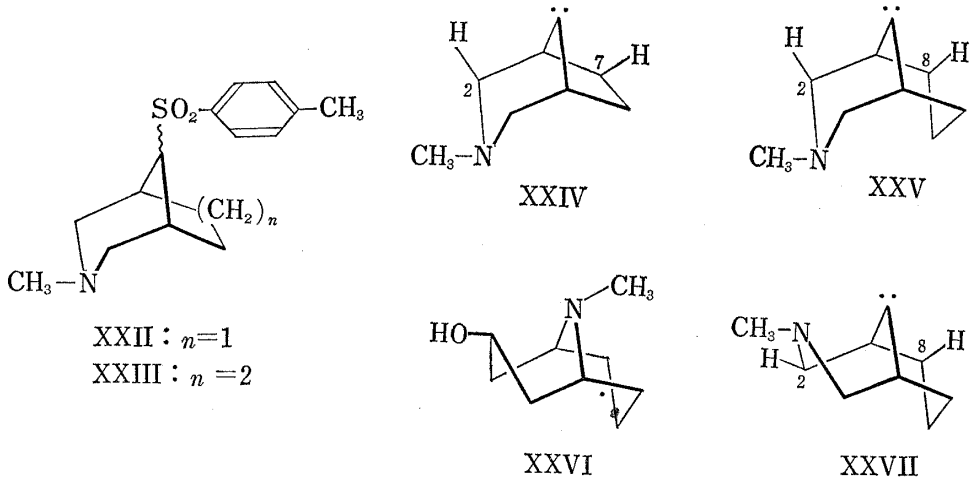

Chart 3

The insertion of the carbene (XXIV) of azabicycloöctane to the C_2–H bond may be caused due to the nearer location of the C_2–H bond than that of the C_7–H bond toward the C_8–position in the rigid skeleton of the azabicycloöctane system.[2] On the other hand, the exclusive insertion of the carbene (XXV) of azabicyclononane is a puzzle, because there is a possibility that the insertion falls in the C_2–H bond or the C_8–H bond equally. Chen and Le Feúve[13] have recently concluded from NMR analysis that 3α-granatanol exists in solution in chair–boat equilibrium predominating chair–boat conformer (XXVI). Lygo, McKenna, and Sutherland[14] also reported that the main conformer of the hydrochloride of 3-methyl-3-azabicyclo[3.3.1]-nonane in solution is the chair–chair form (like XXV), but that of the methiodide is almost exclusively the boat–chair form (like XXVII), also indicating that some substitution easily affects the skeletal conformation of the flexible 3-azabicyclononane. In the connection with these reports, one of the possible explanation on the insertion mode of XXV would be that the boat–chair conformer (XXVII) mainly participated at elevated temperature in determining the orientation of the carbene insertion reaction.

These tricyclic amines (III or XV) were unstable to air and heat; they gradually converted into a dark-brown gum in a few days by storage at room temperature. It was also found that these amines had neither spasmolytic nor hypotensive activity.

Experimental

Melting points are not corrected. Ultraviolet spectra were determined on a Beckman Model DK-2, infrared spectra on a Perkin–Elmer Model 21, proton magnetic resonance specta (NMR) on a Varian A-60 spectrometer and mass spectra[15] on a Hitachi RMU-6D mass spectrometer. The removal of solvent *in vacuo* was accomplished by a rotating flash evaporator at 20—30 mm and usually at 35—50°. Gas chromatographic measurements were carried out on a Shimadzu Model GC-IB and F & M Model 775. Plates for thin-layer chromatography were prepared with Silica Gel G (E. Merck AG) or MN Silica Gel G/UV 257

13) C.Y. Chen, R.W. Le Feúve, *Tetrahedron Letters*, **1965**, 737.
14) R. Lygo, J. McKenna, and I.O. Sutherland, *Chem. Commun.*, **1965**, 356.
15) Authors are grateful to Dr. S. Nozoe, Tokyo University, for measurements of the mass spectra and to Dr. M. Ohashi, Tokyo Kyoiku University, for helpful discussion for rational interpretations of the mass spectra.

(N. Nagel AG), and visualization of spots was usually effected by spraying Dragendorff's reagent or irradiation of ultraviolet ray.

3-Methyl-3-azabicyclo[3.3.1]nonan-9-one Tosylhydrazone (II)——To a solution of 21.0 g (0.113 mole) of tosylhydrazide in 130 ml of MeOH, 17.1 g (0.112 mole) of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one[4] was added in one portion. After addition of three drops of conc. H_2SO_4, the solution was heated on a steam bath for 15 min. The precipitate obtained by cooling was collected and washed with cold MeOH. This crude product of mp 183° (decomp.) was recrystallized from EtOH, giving 32.2 g (90% yield) of the tosylhydrazone (II) as colorless needles of mp 186° (decomp.). IR (Nujol) cm^{-1}: ν_{N-H} 3250, $\nu_{N=C}$ 1656. *Anal.* Calcd. for $C_{16}H_{23}O_2N_3S$: C, 59.09; H, 7.21; N, 13.08. Found: C, 59.71; H, 7.24; N, 13.37.

3-Methyl-3-azatricyclo[6.1.0.0^{5,9}]nonane (III)——Sodium metal (2.76 g, 0.12 mole) was dissolved in 100 ml of anhyd. MeOH in N_2 atmosphere and 38.4 g (0.12 mole) of the tosylhydrazone (II) was dissolved in the solution at room temperature with stirring. The solution was evaporated to dryness *in vacuo* and the residue was further dried over P_2O_5 in an oil bath at 100° under a reduced pressure (0.5 mm). To the sodium salt thus obtained was added 250 ml of Diglyme which was freshly distilled over $LiAlH_4$. The suspension was heated slowly in an oil bath in dry N_2 atmoshpere. Evolution of N_2 was observed at above 160° and the bath temperature was kept at 165—170° for 1.5 hr. When cooled, the mixture was poured into 200 ml of ice water and extracted with 250 ml of a mixture of ether–hexane (1:2). The organic layer was washed four times with 100 ml of H_2O and extracted twice with 200 ml of cold 10% HCl. The acidic extract was basified with conc. NH_4OH under cooling, and an oil that separated was extracted twice with 150 ml of hexane. After drying over anhyd. $MgSO_4$, the extract was evaporated and the residue distilled fractionally, giving 11.0 g of the tricyclic amine (III), bp 109—110° (77 mmHg), and 2.0 g of a high-boiling oil, bp 85—100° (4 mmHg). Gas chromatographic analysis over a column packed with 1.5% SE-30 silicone gum on Chromosorb W at 135° showed that the former was III of 95% purity and the latter contained III in 30%; the total yield of III was 67%. The analytical sample was obtained by further purification on a preparative column packed with 10% SE-30 silicone gum on Chromosorb W at 160°. IR (liquid) cm^{-1}: ν_{C-H}3030, 2790, 2720 (shoulder). NMR (CCl_4) δ ppm: 2.11 (CH_3–N–, singlet, 3H), 0.7—3.3 (complex absorption, 12H). *Anal.* Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.90; H, 10.96; N, 10.09.

The picrate of III, needles (from MeOH), mp 180—195° (decomp.), was prepared in the usual manner. *Anal.* Calcd. for $C_{15}H_{18}O_7N_4$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.30; H, 5.02; N, 15.33.

Chromatography of the distillation residue of III on silica gel afforded a compound of mp 180° (decomp.) (leaflets from MeOH) in 0.2% yield. IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1600, $\nu_{S=O}$ 1152, 1303, δ_{C-H} 820. *Anal.* Calcd. for $C_{16}H_{23}O_2NS$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.41; H, 7.99; N, 4.73.

2-Methylene-6-(N,N-dimethylamino)methylbicyclo[3.1.0]hexane (V)——The methiodide of III was prepared as follows: A solution of 11.0 g of III and 15 ml of MeI in 50 ml of ether was refluxed for 6 hr. Removal of the solvent afforded a crystalline residue which was recrystallized twice from a mixture of EtOH, acetone, and ether (1:8:2), giving 15.76 g of the methiodide of III as needles, mp 230° (decomp.). IR (Nujol) cm^{-1}: ν_{O-H} 3500, 3430. *Anal.* Calcd. for $C_{10}H_{18}NI \cdot \frac{1}{2}H_2O$: C, 41.68; H, 6.65; N, 4.86. Found: C, 41.30; H, 6.77; N, 4.61.

To a solution of 15.50 g of the methiodide of III in 15 ml of H_2O was added Ag_2O, freshly prepared from 14 g of $AgNO_3$, and the mixture was stirred for 30 min at room temperature. The solid was filtered off and the filtrate was concentrated *in vacuo* at 50° and finally distilled under a reduced pressure (80 mm); its thermal decomposition began around 110° and a degradation product containing H_2O distilled over at about 140°. After being dried over anhyd. Na_2SO_4, 7.30 g of the bicyclic amine (V) was collected. Thin-layer and gas chromatographic analyses indicated that the product contained a small amount of the tricyclic amine (III). IR (liquid) cm^{-1}: $\nu_{C=C}$ 1651, ν_{C-H} 3080, 3030, δ_{C-H} 867. UV λ_{max}^{EtOH}: 220 mμ (ε 4110). NMR ($CDCl_3$) δppm: 4.96 (broad, 1H), 4.83 (broad, 1H), 2.28 (singlet, 6H), 0.9—2.6 (complex absorption).

V formed a hydrochloride of leaflet (from EtOH–ether), mp 181—183° (decomp.), by treatment with 10% HCl in EtOH. NMR (D_2O) δppm: 5.13 (broad, 1H), 5.01 (broad, 1H), 3.30 (quartet, J=6 and 13 cps, 1H), 3.00 (quartet, J=8 and 13 cps, 1H), 2.92 (singlet, 6H), 1.1—2.4 (complex absorption). *Anal.* Calcd. for $C_{10}H_{18}NCl$: C, 63.98; H, 9.67; N, 7.46. Found: C, 63.64; H, 9.61; N, 7.37. V also formed a picrate of mp 166—168° (needles from MeOH–ether). *Anal.* Calcd. for $C_{16}H_{20}O_7N_4$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.47; H, 5.45; N, 14.83.

Hofmann Degradation of 2-Methylene-6-(N,N-dimethylamino)methylbicyclo[3.1.0]hexane (V)——The methiodide of V was prepared as follows: A solution of 0.71 g of V in 5 ml of ether was refluxed with excess of MeI for 1 hr. The crystalline residue obtained by removal of the solvent was recrystallized from a mixture of EtOH, acetone, and ether to give 1.0 g (72% yield) of the methiodide of V as a powder of mp 177—179°. NMR (D_2O) δppm: 5.14 (broad, 1H), 5.03 (broad, 1H), 3.53 (quartet, J=5.5 and 13.5 cps, 1H), 3.10 (quartet, J=8.5 and 13.5 cps, 1H), 3.17 (singlet, 9H), and 1.3—2.7 (complex absorption). *Anal.* Calcd. for $C_{11}H_{20}NI$: C, 45.06; H, 6.88; N, 4.78. Found: C, 44.89; H, 7.03; N, 4.81.

To a solution of 0.858 g of the methiodide described above in 5 ml of H_2O was added Ag_2O, which was freshly prepared from 1 g of $AgNO_3$, and the mixture was stirred for 30 min. The solid was filtered off and the filtrate was concentrated at room temperature under a reduced pressure. The resulting residue was heated

for decomposition and the degradation product containing with H_2O distilled over at 140—150° (bath temp.), giving 0.244 g of a faint yellow liquid. Using a column packed with PEG 6000, 30—60 mesh, gas chromatographic analysis at 88° indicated that the product was *m*-xylene in 93% purity. It was also shown that the product was identical with the authentic sample in comparison of infrared, ultraviolet, and NMR spectra.

1-Methyl-3-(N,N-dimethylamino)methyl-4-chlorocyclohex-1-ene (IXa)——The bicyclic amine (V) (0.482 g) was dissolved in 5 ml of 10% HCl–EtOH and the mixture was refluxed on a steam bath for 1 hr. Removal of the solvent *in vacuo* aordedff crystalline residue which was recrystallized from a mixture of EtOH–ether to give 0.36 g of a hydrochloride of IXa as fine leaflets of mp 178.5—179°. IR (Nujol) cm^{-1}: $\nu_{C=C}$ 1672, δ_{C-H} 816. NMR (D_2O) δppm: 5.17 (=CH–, broad singlet, 1H), 4.6 (–$\underset{|}{C}$H–Cl, broad, 1H), 2.96 ($(CH_3)_2N$–, singlet, 6H), 2.05—2.25 (complex absorption, 4H), 1.72 (=$\underset{|}{C}$–CH_3, triplet, J=1.5 cps, 3H). *Anal.* Calcd. for $C_{10}H_{19}NCl_2$: C, 53.58; H, 8.54; N, 6.25. Found: C, 53.40; H, 8.52; N, 6.43. The methiodide of IXa, mp 166° (decomp.), was prepared by the usual treatment with MeI. *Anal.* Calcd. for $C_{11}H_{21}NClI$: C, 40.20; H, 6.44; N, 4.26. Found:C, 39.95; H, 6.49; N, 4.14.

1-Methyl-3-(N,N-dimethylamino)methyl-4-acetoxycyclohex-1-ene (IXb)——A solution of 3.17 g of the bicyclic amine (V) and 4.2 g of 70% $HClO_4$ in 35 ml of AcOH was heated on a steam bath for 4 hr. After removal of the solvent *in vacuo*, the reaction mixture was poured into 30 ml of ice–water which was basified with dil. NH_4OH, and extracted twice with 20 ml portions of hexane. After being dried over anhyd. $MgSO_4$, removal of the solvent from the extract gave 3.09 g of an oil, which was chromatographed over 35 g of silica gel. Evaporation of the solvent from the $CHCl_3$ eluate afforded 1.88 g of IXb whose further purification was not attempted. IR (liquid) cm^{-1}: $\nu_{C=O}$ 1743, $\nu_{C=C}$ 1675 (shoulder), δ_{C-H} 847. NMR ($CDCl_3$) δppm: 5.0—5.4 (broad, 2H), 2.19 ($(CH_3)_2N$–, singlet, 6H), 2.02 (CH_3COO–, singlet, 3H), 1.70 (CH_3–$\underset{|}{C}$=, broad singlet, 3H). The picrate of IXb formed plates of mp 155—164°. *Anal.* Calcd. for $C_{18}H_{24}O_9N_4$: C, 49.09; H, 5.49; N, 12.72. Found: C, 48.87; H, 5.65; N, 12.97.

1-Methyl-3-(N,N-dimethylamino)methyl-4-hydroxycyclohex-1-ene (IXc)——Sodium metal (0.1 g) was dissolved in 10 ml of anhyd. MeOH and 1.28 g of IXb was added to the solution. The mixture was allowed to stand at room temperature overnight and then concentrated *in vacuo*. The residue was poured into 15 ml of H_2O and extracted three times with $CHCl_3$. The extract was dried over anhyd. $MgSO_4$ and evaporated *in vauco* to give 0.99 g of an oil which was distilled, giving 0.91 g of IXc, as a colorless liquid, bp 130—140° (8 mmHg) (bath temp.), IR (liquid) cm^{-1}: ν_{O-H} 3400 (broad), $\nu_{C=C}$ 1675, δ_{C-H} 835. NMR ($CDCl_3$) δppm: 5.2 (broad, 1H), 4.75 (broad, 1H), 3.95 (multiplet, 1H), 2.25 ($(CH_3)_2N$–, singlet, 6H), 1.63 (CH_3–$\underset{|}{C}$=, broad singlet, 3H). *Anal.* Calcd. for $C_{10}H_9ON$: C, 70.96; H, 11.32; N, 8.28. Found: C, 69.96; H, 11.29:; N, 8.13.

IXc formed a picrate of needles (from MeOH), mp 148—149°. *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.31; H, 5.92; N, 13.96.

2-Hydroxy-2-hydroxymethyl-6-(N,N-dimethylamino)methylbicyclo[3.1.0]hexane (XI)——A solution of 5.0 g (0.02 mole) of OsO_4 in 100 ml of anhyd. ether was dropped into a stirred solution of 3.0 g (0.02 mole) of V and 3 ml of pyridine in 50 ml of anhyd. ether under cooling. The mixture was allowed to stand at room temperature for 30 min. The solid obtained was collected, washed with 50 ml of ether, and added to a mixture of 200 ml of H_2O, 125 ml of EtOH, and 50 g of Na_2SO_3. This suspension was boiled for 6 hr under stirring. When cooled the solid was collected and washed with 100 ml of EtOH. The combined filtrate and washings were concentrated to 50 ml, and extracted five times with $CHCl_3$. The extract was dried over anhyd. $MgSO_4$, and removal of the solvent afforded 3.14 g of a yellow liquid which crystallized slowly on digesting with a mixture of 3 ml of AcOEt and 1 ml of hexane. The crystals formed were collected and recrystallized from AcOEt to 1.77 g (48% yield) of XI as prisms, mp 76.5—78°. IR (Nujol) cm^{-1}: ν_{O-H} 3450, 3380 (shoulder). NMR ($CDCl_3$) δ ppm: 3.78 (–CH_2–O–, doublet, J=11.5 cps, 1H), 3.47 (–CH_2–O–, doublet, J=11.5 cps, 1H), 2.28 ($(CH_3)_2N$–, singlet, 6H), 0.9—2.5 (complex absorption). *Anal.* Calcd. for $C_{10}H_{19}O_2N$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.74; H, 10.36; N, 7.46.

6-(N,N-Dimethylamino)methylbicyclo[3.1.0]hexan-2-one (XII)——A solution of 1.07 g of $NaIO_4$ in 12 ml of H_2O was dropped into a cooled solution of 0.93 g of XI in a mixture of 0.4 ml of AcOH and 6 ml of H_2O under stirring. The mixture was allowed to stand overnight at room temperature, then basified with 10% NaOH solution, and extracted twice with ether. After being dried over anhyd. Na_2SO_4, removal of the solvent from the extract afforded a liquid which formed a crystalline hydrochloride by treatment with 3 ml of 10% HCl–EtOH. The crude hydrochloride was washed with ether and recrystallized from EtOH to give 0.474 g (50% yield) of the hydrochloride of XII as leaflets of mp 196—197.5° (decomp.). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1715. UV λ^{EtOH}: 220 mμ (ε 830). NMR (D_2O) δ ppm: 3.19 (–CH_2–$\underset{|}{N}$–, quartet J_{AB}=13.5, J_{AX}=6.5 cps, 1H), 3.44 (–CH_2–$\underset{|}{N}$–, quartet J_{AB}=13.5, J_{BX}=6.5 cps, 1H), 2.28 ($(CH_3)_2N$–, singlet, 6H), 1.5—2.8 (complex absorption). *Anal.* Calcd. for $C_9H_{16}ONCl$: C, 56.99; H, 8.50; N, 7.39; Cl, 18.69. Found: C, 57.13; H, 8.53; N, 7.47; Cl, 18.69. The picrate of XII formed yellow prisms of mp 183—186° (decomp.). *Anal.* Calcd. for $C_{15}H_{18}O_8N_4$: C, 47.12; H, 4.75; N, 14.66. Found: C, 47.05; H, 4.95; N, 14.94.

3-(N,N-Dimethylamino)methyl-4-chlorocyclohexan-1-one (XIII)——A solution of 0.128 g of the hydrochloride of XII in 3 ml of 10% HCl–EtOH was refluxed for 3 hr. To the mixture was added 5 ml of ether and the precipitate obtained (0.123 g, 81% yield) was recrystallized from EtOH–ether to give an amorphous hydrochloride of XIII, mp 196° (decomp.). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1710. NMR (D_2O) δ ppm: 4.45—4.48 (–$\overset{|}{C}$H–Cl, broad, 1H), 2.95 ($(CH_3)_2N$–, singlet, 6H), 1.65—3.7 (complex absorption). *Anal.* Calcd. for $C_9H_{17}ONCl_2$: C, 47.80; H, 7.58; N, 6.19. Found: C, 47.48; H, 7.59; N, 6.29.

XIII formed a picrate of mp 172—173.5° (prisms from acetone). *Anal.* Calcd. for $C_{15}H_{19}O_8N_4Cl$: C, 43.02; H, 4.57; N, 13.38; Cl, 8.47. Found: C, 42.83; H, 4.71; N, 13.58; Cl, 8.33.

3-Methyl-3-azabicyclo[3.2.1]octan-8-one Tosylhydrazone (XIV)——A solution of 72.3 g (0.52 mole) of 3-methyl-3-azabicyclo[3.2.1]octan-8-one[4] and 108 g (0.58 mole) of tosylhydrazide in 750 ml of MeOH was refluxed for 5 hr. Removal of the solvent *in vacuo* afforded a crystalline residue which was washed with cooled AcOEt and recrystallized from a small amount of AcOEt to give 69.3 g (43% yield) of XIV as a faint yellow powder of mp 147° (decomp.). Analytical sample, mp 153—154° (decomp.), was prepared by further recrystallization from acetone–hexane. IR (Nujol) cm^{-1}: ν_{N-H} 3250, $\nu_{C=N}$ 1682, $\nu_{S=O}$ 1338, 1167. *Anal.* Calcd. for $C_{15}H_{21}O_2N_3S$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.37; H, 6.94; N, 13.99.

2-Methyl-2-azatricyclo[5.1.0.0^{4,8}]octane (XV)——Similar to the case for III, thermal decomposition of the sodium salt of XIV, prepared from 69.3 g (0.226 mole) of XIV and 5.5 g (0.24 mole) of Na metal in 200 ml of anhyd. MeOH, was carried out at 160—165° for 3 hr. The resulting product was purified by fractional distillation and gave 15.6 g (56% yield) of XV, as a colorless liquid, bp 83—86° (75 mmHg), whose purity was found to be over 95% by gas chromatography. Analytical sample was also prepared through preparative gas chromatography. IR (liquid) cm^{-1}: ν_{C-H} 3030, 2780. NMR (CCl_4) δ ppm: 2.47 ($CH_3\overset{|}{N}$–, singlet, 3H), 1.0—3.5 (complex absorption, 9—10H). *Anal.* Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.69; H, 10.62; N, 11. 28. XV formed a picrate of mp 153° (decomp.) (fine needles from MeOH). *Anal.* Calcd. for $C_{14}H_{16}O_7N_4$: C, 47.73; H, 4.58; N, 15.90. Found: C, 47.91; H, 4.60; N, 16.00.

Chromatography of the distillation residue of XV on silica gel afforded a compound as plates (from ether–benzene), mp 123—124°, in 0.2% yield. IR (Nujol) cm^{-1}: $\nu_{C=C}$ 1598, $\nu_{S=O}$ 1152, 1305, δ_{C-H} 808. NMR ($CDCl_3$) δ ppm: 2.20 ($CH_3\overset{|}{N}$–, singlet, 3H), 1.5—3.0 (complex absorption, 11H), 2.46 (aromatic methyl, singlet, 3H), 7.3—8.0 (aromatic proton, complex absorption, 4H). *Anal.* Calcd. for $C_{15}H_{21}O_2NS$: C, 64.48; H, 7.58; N, 5.01; S, 11.48. Found: C, 64.32; H, 7.60; N, 4.90; S, 11.24.

Hofmann Degradation of 2-Methyl-2-azatricyclo[5.1.0.0^{4,8}]octane (XV) Methiodide——A solution of 5.20 g of XV and 10 ml of MeI in 15 ml of ether was allowed to stand at room temperature overnight. The resulting precipitate (8.51 g, 76% yield) was recrystallized from acetone to a methiodide of XV as prisms of mp 215—225° (decomp.). *Anal.* Calcd. for $C_9H_{16}NI$: C, 40.77; H, 6.08; N, 5.28. Found: C, 40.57; H, 6.08; N, 5.29.

To a solution of 3 g of the methiodide of XV thus obtained dissolved in 15 ml of MeOH was added Ag_2O, freshly prepared from 4.0 g of $AgNO_3$. The suspension was stirred at room temperature for 30 min. The solid was collected and washed with MeOH. The combined filtrate and washings were evaporated *in vacuo* to leave an oil, which was heated in an oil bath under a reduced pressure (100 mmHg) and 1.10 g of 2-methoxymethyl-6-N,N-dimethylaminobicyclo[3.1.0]hexane (XIX) was obtained as a colorless oil, bp 140—150° (100 mmHg) (bath temp.). Gas chromatographic analysis showed that this oil was XIX in 96% purity, containing a small amount of the tricyclic amine (XV). Analytical sample was prepared by preparative gas chromatography. IR (liquid) cm^{-1}: ν_{C-H} 3020, 2760. NMR (CCl_4) δ ppm: 3.35 (–CH_2–O–, doublet, J=7 cps, 2H), 3.28 (CH_3O–, singlet, 3H), 2.4—2.9 (–$\overset{|}{C}$H–N–, broad, 1H), 2.21 ($(CH_3)_2N$–, singlet, 6H), 1.1—2.1 (complex absorption, 7H). *Anal.* Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32; N, 8.28. Found: C, 71.20; H, 11.35; N, 8.31.

The methiodide of XV was treated with Ag_2O using H_2O instead of MeOH as the solvent, and subsequent thermal decomposition gave XV as the main product.

Hydrogenation of 2-Methyl-2-azatricyclo[5.1.0.0^{4,8}]octane (XV)——Three grams of XV was hydrogenated over 2 g of 10% Pd–C in 60 ml of EtOH. After uptake of 1 mole of H_2, the catalyst was filtered off and to the filtrate was dropped 5 ml of conc. H_2SO_4 under cooling. The resulting mixture was concentrated, then poured into 20 g of ice–water, and basified with 10% NaOH. An oil thereby obtained was extracted with two 15 ml portions of ether. The extract was dried over anhyd. Na_2SO_4, and 5 ml of MeI was added in portions. After standing for 1 hr, the resulting precipitate was collected and washed with ether. The crude methiodide of mp 200—203° (3.84 g, 59% yield) was recrystallized from EtOH–acetone to give 3-methyl-3-azabicyclo[3.3.0]octane (XXI) methiodide, as prisms, mp 203—204.5. The product was identified with an authentic sample synthesized by the method of Rice and Grogan,[11] by mixed mp, and infrared and NMR spectrometry.

The filtrate left after the methiodide of mp 200—203° was collected was allowed to stand and slowly precipitated leaflet crystals. To this filtrate was added further 1 ml of MeI and the mixture was allowed to stand for 10 days at room temperature. The second crop of the methiodide of mp >270° thus obtained (0.97 g, 15% yield) was recrystallized from EtOH–acetone to 3-methyl-3-azabicyclo[3.2.1]octane (XX) methiodide,

as leaflets of mp >270°. This second methiodide was identified with the synthetic sample described below by mp, and infrared and NMR spectrometry.

3-Methyl-3-azabicyclo[3.2.1]octane (XX) Methiodide——A mixture of 1.90 g of 3-methyl-3-azabicyclo-[3.2.1]octan-8-one,[4] 3 ml of 80% hydrazine hydrate, 3.5 g of KOH, and 30 ml ethylene glycol was refluxed for 30 min. Then the bath temperature was gradually raised to 190—210° and the mixture was distilled. To the distillate (5—6 ml) was added 15 ml of saturated NaCl solution and the separated oil was extracted with 20 ml of ether. After being dried over anhyd. Na_2SO_4, the extract was treated with 3 ml of MeI, and allowed to stand at room temperature for 5 days, giving 2.75 g (75% yield) of the methiodide of XX as leaflets of mp >270°. *Anal.* Calcd. for $C_9H_{18}NI$: C, 40.46; H, 6.79; N, 5.24. Found: C, 40.58; H, 6.88; N, 5.54.

Acknowledgement We are grateful to Dr. G. Sunagawa, Manager, and Dr. I. Iwai, Asisistant Manager, of the Laboratories for their guidance.