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Studies on 1-Azabicyclo Compounds. XXVI.[1] Synthesis of Ten-membered Ring Amines from 9a-Cyanomethyl-, 9a-Ethoxycarbonylmethyl-, and 1-Ethoxycarbonyl-octahydroquinolizine[2]

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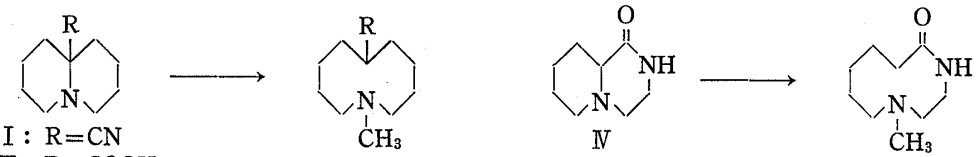
Quaternization of 9a-cyanomethyl- and 9a-ethoxycarbonylmethyl-octahydroquinolizine (VI and XI) with methyl iodide afforded *cis* (VIIa and XIIa) and *trans* methiodides (VIIb and XIIb), respectively. On treatment with lithium in liquid ammonia, the methiodides (VIIa, XIIa, and XXIV) gave the ten-membered ring amines (VIII, XIII, and XXV), respectively, in moderate yields, however, the methiodide (XXIX) gave only the demethylated product (XXVIII). And the methiodide (VIIa) yielded also the decyanated amines (IX and X) as the by-products. The formation of the ten-membered ring amines (VIII, XIII, and XXV) was proved to proceed as shown in Chart 5 *via* the unsaturated ten-membered ring amines (XVII, XVIII, and XXX), which were actually derived from the methiodides (VIIa, XIIa, and XXIV), respectively. On the other hand, treatment of VIIa and XIIa with sodium ethoxide afforded the endocyclic olefinic ring amines (XV and XVI), which were shown to be obtained by isomerization of the initially formed exocyclic olefinic ring amines (XVII and XVIII), respectively.

Previously ten-membered ring amines have been synthesized[4] by the Birch reduction of the methiodides of 9a-cyano-, 9a-carboxy-, 9a-carbamoyl-octahydroquinolizine (I, II, III), and octahydropyrido[1,2-*a*]pyrazine (IV). The present paper deals with the application of this reaction to the homologous compounds inserted a methylene between the octahydroquinolizine ring and the 9a-substituents in the molecules of I and II, namely, 9a-cyanomethyl-, 9a-ethoxycarbonylmethyl-octahydroquinolizine (VI, XI) and 1-ethoxycarbonyloctahydroquinolizine (XXII), the last of which has the methylene of the 9a-substituent in the octahydroquinolizine ring in the molecule of XI. The reaction mechanism and the effect of the inserted methylene on the reaction in comparison with the case of I—IV are also presented.



I : R=CN
II : R=COOH
III : R=CONH$_2$

IV

Chart 1

1) Part XXV: H. Kato, *Yakugaku Zasshi*, **95**, 830 (1975).
2) A part of this work was presented at 39th meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, October 1974.
3) Location: *a) Takara-machi, Kanazawa, 920, Japan; b) Tatekawa-machi, Katsuyama, 911, Japan.*
4) *a*) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1363 (1969); *b*) Y. Arata and T. Kobayashi, *ibid.*, **20**, 325 (1972); *c*) Y. Arata and Y. Nakagawa, *ibid.*, **21**, 1248 (1973); *d*) Y. Arata, T. Kikuti, M. Takahashi, and T. Aoki, *ibid.*, **22**, 1003 (1974).

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Quaternization of 9a-cyanomethyloctahydroquinolizine[5] (VI), derived from $\Delta^{1,9a}$-hexahydroquinolizine[6] (V) and cyanoacetic acid, with methyl iodide afforded two isomeric methiodides, VIIa, mp 278—280° (decomp.), and VIIb, mp 278—281° (decomp.), in the 3:1 ratio. Generally the N^+-methyl signal of *cis* 9a-substituted octahydroquinolizine methiodide resonates at higher field than that of the corresponding *trans* methiodide except for the methiodides having a triple bond directly at C-9a such as 9a-cyano and 9a-ethynyl derivatives in the nuclear magnetic resonance (NMR) spectrum.[7] And it was also found that the stereochemistry of these methiodides can be unequivocally established from their ^{13}C-NMR spectra.[7] Based on the above generality, the stereochemistry of VIIa, NMR τ: 6.87 (N^+—CH_3), and VIIb, NMR τ: 6.65 (N^+—CH_3), could be assigned to be *cis* and *trans*, respectively. These assignments were confirmed from their ^{13}C-NMR spectra (see Experimental).

The Birch reduction of VIIa with 2 molar equivalents of lithium in liquid ammonia (Li/NH_3) followed by column chromatographic separation afforded the expected ten-membered ring amine (VIII), *m/e* 194 (M^+), in 57% yield along with the decyanated amine (IX), *m/e* 167 (M^+), in 6% yield. The former showed a band at 2240 cm^{-1} (CN) in the infrared (IR) spectrum, a signal at 7.87 τ (3H, singlet, N–CH_3) and no C-methyl or vinyl signal in its NMR spectrum, substantiating its structure as depicted. The structure of the latter was verified from its spectral data; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (C=C), NMR τ: 5.20 (2H, multiplet, W_H=3 Hz, >C=C$\underline{H}_2$), 7.90 (3H, singlet, N–CH_3). When treated with excess lithium (7 molar equivalents) in liquid ammonia, VIIa gave a mixture of basic substances in 8% yield, which were proved to consist of two components in the 1:3 ratio exhibiting a molecular ion peak at *m/e* 169 and *m/e* 167 by the gas chromatographic and mass spectrometric method (GC–mass). The mass spectrum of the major component was identical with that of IX obtained above. The structure of the minor component was established to be X by the following synthesis. A further treatment of VIII with Li/NH_3 resulted in reductive decyanation giving the methyl derivative (X), *m/e* 169 (M^+), NMR τ: 9.18 (3H, doublet, J=6 Hz, >CH–C$\underline{H}_3$), in 11% yield, the mass spectrum of which was identical with that of the minor component described above. Reaction of VIIa with sodium in liquid ammonia afforded the similar results in the case of the Li/NH_3 reduction.

Thus, the Birch reduction of VIIa effected the selective cleavage of the C_{9a}–N^+ bond and partial decyanation to afford the ten-membered ring amines (VIII, IX, and X), and the yields and the ratio of the products were found to depend on the ammount of lithium used.

Condensation of V with monoethyl malonate gave 9a-ethoxycarbonylmethyloctahydroquinolizine (XI), IR $\nu_{max}^{liq.}$ cm^{-1}: 2800, 2760, 2680 (Bohlmann bands), 1720 (C=O), in 88% yield. Quaternization of XI with methyl iodide afforded the *cis* methiodide (XIIa), mp 195—198°, NMR τ: 6.92 (N^+—CH_3), and the *trans* methiodide (XIIb), mp 212—214°, NMR τ: 6.70 (N^+—CH_3), in the 3:2 ratio. Treatment of XIIa with Li/NH_3 effected reductive cleavage of the C_{9a}–N^+ bond and reduction of the ester group giving the ten-membered ring amino-alcohol (XIII), the picrate, mp 103—104°, in 59% yield. The product showed a band at 3330 cm^{-1} (OH) in its IR spectrum, signals at 6.32 (2H, triplet, J=6.5 Hz, $CH_2C\underline{H}_2OH$), 7.68 (1H, singlet, OH), 7.85 τ (3H, singlet, N–CH_3), and no C-methyl signal in its NMR spectrum. Further proof for the structure of XIII was obtained by the alternative synthesis of XIII from VIII. On being heated in an ethanolic solution containing hydrogen chloride, the nitrile (VIII) was converted to the ester (XIV), which was reduced with lithium aluminum hydride (LAH) to furnish the alcohol (XIII). The alcohol thus obtained was identified with XIII derived from XIIa by IR and NMR spectra and mixed melting point determination of their picrates.

5) N. Kumagawa, K. Suzuki, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **21**, 1601 (1973).
6) N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, **78**, 1987 (1956).
7) *a*) Y. Arata, T. Aoki, M. Hanaoka, and M. Kamei, *Chem. Pharm. Bull.* (Tokyo), **23**, 333 (1975); *b*) Y. Arata, M. Hanaoka, and S.K. Kim, *ibid.*, **23**, 1142 (1975).

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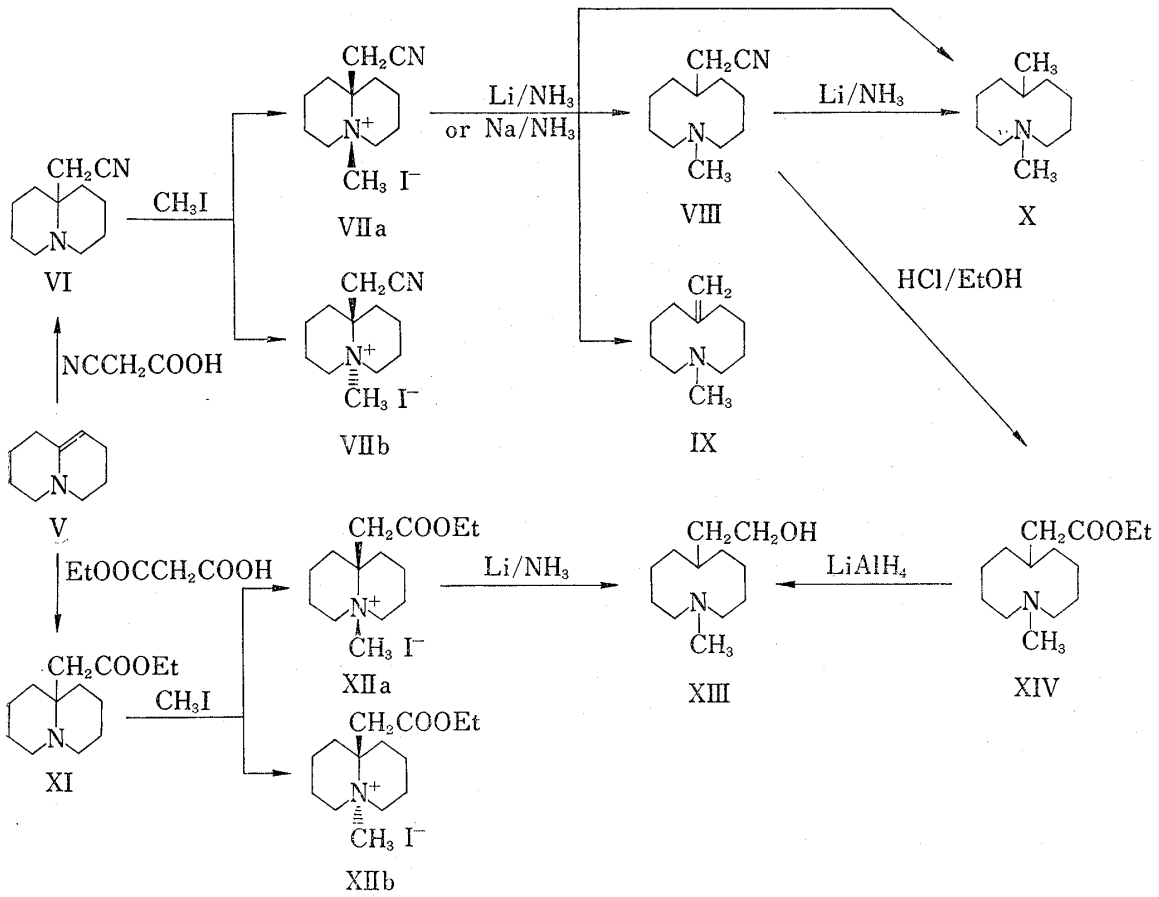

Chart 2

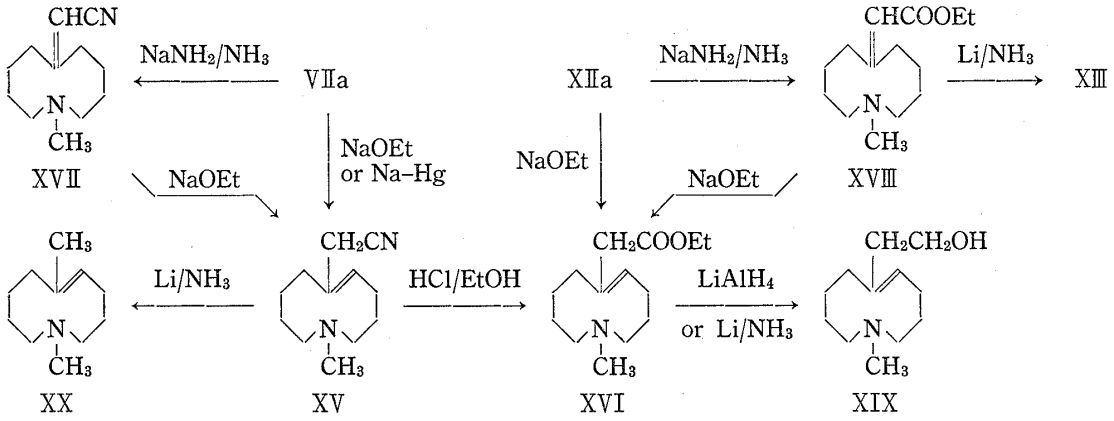

Chart 3

On the other hand, reaction of VIIa with sodium ethoxide or sodium amalgam afforded the ten-membered endocyclic amino-olefin (XV), *m/e* 192 (M^+), in 80% or 55% yield. The structure of XV was elucidated from its spectral data; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), NMR τ: 4.45 (1H, triplet, J=8 Hz, >C=C<u>H</u>CH_2), 6.96 (2H, singlet, CH_2CN), 7.86 (3H, singlet, N–CH_3). On similar treatment with sodium ethoxide, the methiodide (XIIa) gave the endocyclic olefinic ester (XVI), *m/e* 239 (M^+), the picrate, mp 122—123°, the structure of which was deduced from its spectral data; IR $\nu_{max}^{liq.}$ cm^{-1}: 1735 (C=O), NMR τ: 4.70 (1H, triplet, J=8 Hz, >C=C<u>H</u>CH_2), and further confirmed by the conversion of XV into XVI. Heating of XV in an ethanolic solution containing hydrogen chloride yielded the ester, which was identified with XVI by IR and NMR spectra and mixed melting point determination of their picrates.

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Reinecke, *et al.*[8] have reported that on treatment with sodium ethoxide, 8a-ethoxycarbonylmethylindolizidine methiodide provided an endocyclic olefin, which was probably produced by isomerization of an unstable exocyclic olefin as an intermediate. The endocyclic olefins (XV and XVI) might be also formed from the methiodides (VIIa and XIIa) *via* the exocyclic olefins (XVII and XVIII), respectively. In order to prove the above assumption, the methiodide (VIIa) was reacted with sodium amide in liquid ammonia to produce the key intermediate, the exocyclic olefin (XVII), *m/e* 192 (M^+), in 50% yield. In agreement with the structure of XVII, the product showed bands at 2200 (CN) and 1615 cm^{-1} (C=C) in its IR spectrum and signals at 4.93 (1H, multiplet, W_H=3 Hz, >C=CHCN) and 7.93 τ (3H, singlet, N–CH_3) in its NMR spectrum. On treatment with sodium ethoxide, XVII isomerized to the endocyclic olefin (XV), which was identical in all respects with that obtained directly from VIIa. Similarly, treatment of the methiodide (XIIa) with sodium amide in liquid ammonia afforded the exocyclic olefin (XVIII), *m/e* 239 (M^+), IR $\nu_{max}^{liq.}$ cm^{-1}: 1710 (C=O), 1630 (C=C), which, on treatment with sodium ethoxide, isomerized to the endocyclic olefin (XVI).

Reduction of XVI with LAH or Li/NH_3 gave the alcohol (XIX), and reduction of XV with Li/NH_3 afforded the decyanated product (XX). Catalytic hydrogenation of XV, XVI, XIX, and XX was attempted but only the starting materials were recovered unchanged. The stereochemistries of Δ^5-octahydro-1-methylazecines (XV, XVI, XIX, and XX) were remained undetermined.

Reduction of 1-ethoxycarbonyl-$\Delta^{1,9a}$-hexahydroquinolizine[9] (XXI), derived from V with ethyl chlorocarbonate, with sodium borohydride in ethanol gave two isomeric octahydroquinolizines, XXII,[9] the picrate, mp 133—135°, and XXIII, the picrate, mp 185—186°, in the 10:1 ratio. Catalytic hydrogenation of XIX over platinic oxide, however, afforded XXII as a sole product. Dehydrogenation of XXII with mercuric acetate gave XXI. Treatment of the methiodide (XXIV), mp 203—205°, of XXII with Li/NH_3 effected the cleavage of the central C_{9a}–N^+ bond and reduction of the ester group to give the ten-membered ring amino-alcohol (XXV) in 55% yield. The product showed the signals at 6.58 (2H, doublet, J=6 Hz, >CHC$\underline{H}_2$OH), 7.75 (1H, singlet, OH), 7.87 τ (3H, singlet, N–CH_3), and no C-methyl signal in its NMR spectrum. Reaction of XXI with methyl iodide afforded the C-methylation product (XXVI), NMR τ: 5.22 (1H, triplet, J=4 Hz, $CH_2C\underline{H}$=C<), 8.70 (3H, singlet, >C–CH_3), and not the normal methiodide, because of the low basicity of XXI in the nature of vinylogous amide. Reduction of XXVI with sodium borohydride gave the octahydroquinolizine (XXVII) as a sole product, which, on further reduction with LAH, gave the alcohol (XXVIII), mp 89—90°. The IR spectrum of the alcohol in a diluted carbon tetrachloride solution showed bands at 3250 cm^{-1} due to the hydroxyl group bonded with the nitrogen and at 2760, 2680 cm^{-1} due to the Bohlmann bands, establishing the stereochemistry of XXVIII and XXVII as depicted.

Reduction of the methiodide (XXIX) of XXVII with Li/NH_3 did not give the expected ten-membered ring amine but the demethylated alcohol (XXVIII), which was identical with that obtained above. The different behaviour of XXIV and XXIX in the Birch reduction would provide an important clue for solving the reaction mechanism. Namely, the hydrogen at α-position to the ethoxycarbonyl group of XXIV is attacked by the amide anion to induce the β-elimination to the intermediate, α,β-unsaturated amino-alcohol (XXX), which is then reduced[4c,10] to give the saturated amino-alcohol (XXV), whereas XXIX has not such an activated hydrogen in its molecule giving only the demethylated product (XXVIII). In order to confirm the above interpretation, the methiodide (XXIV) was reacted with sodium amide

8) M.G. Reinecke, L.R. Kray, and R.F. Francis, *J. Org. Chem.*, **37**, 3489 (1972).
9) F. Bohlmann and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964).
10) *cf. a*) D.H.R. Barton and C.H. Robinson, *J. Chem. Soc.*, **1954**, 3045; *b*) G. Stork and S.D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960); *c*) G. Stork and J. Tsuji, *ibid.*, **83**, 2783 (1961).

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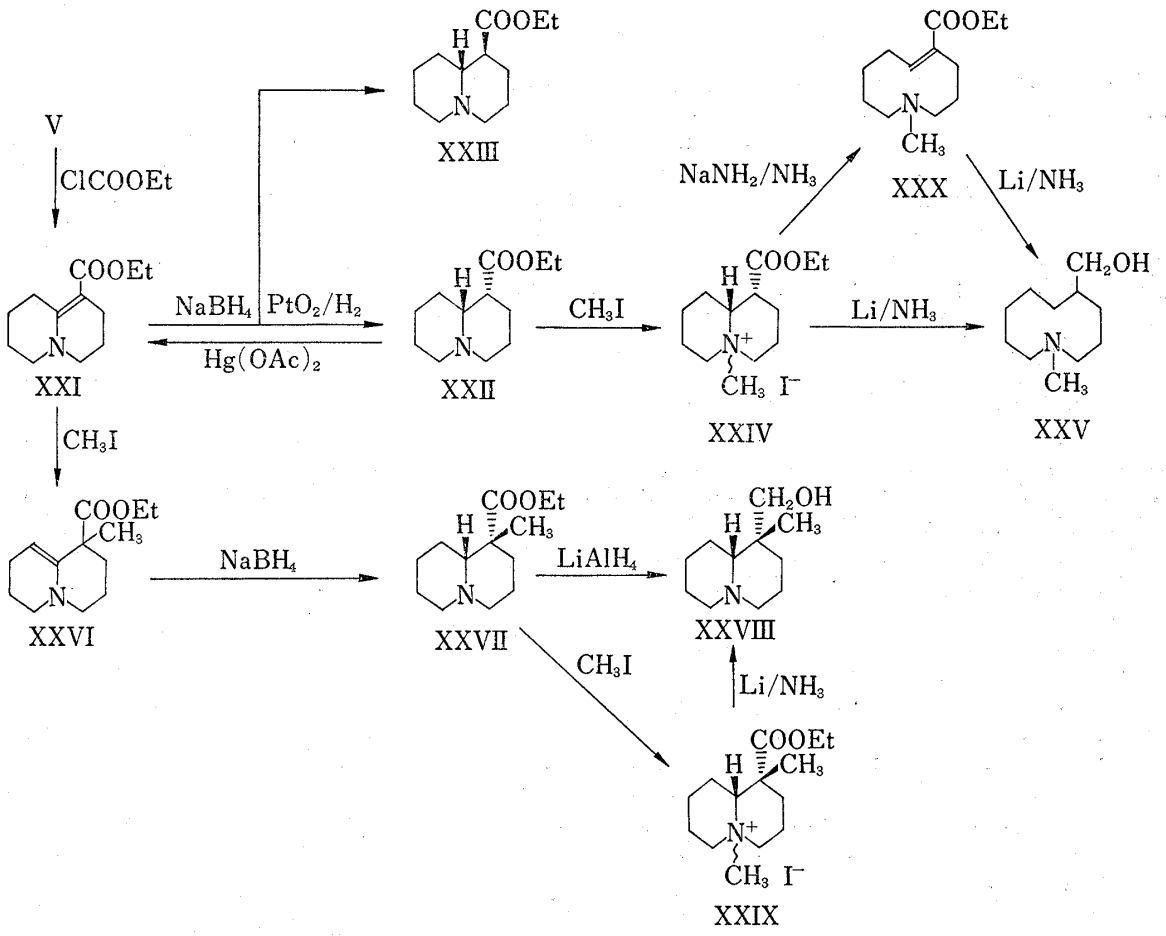

Chart 4

in liquid ammonia to produce the intermediate, the α,β-unsaturated ester (XXX) in 57% yield. The product showed bands at 1705 (C=O) and 1640 cm^{-1} (C=C) in its IR spectrum, and signals at 3.22 (1H, triplet, J=8 Hz, >C=C<u>H</u>CH_2) and 7.88 τ (3H, singlet, N-CH_3) in its NMR spectrum. Subsequent reduction of XXX with Li/NH_3 afforded the amino-alcohol, which was identical with XXV obtained directly from XXIV in all respects. The similar mechanism could be operative for the formation of the ten-membered ring amines (VIII and XIII) from the methiodides (VIIa and XIIa), respectively, as shown in Chart 5. In fact, XVIII was reduced with Li/NH_3 to give the amino-alcohol (XIII).

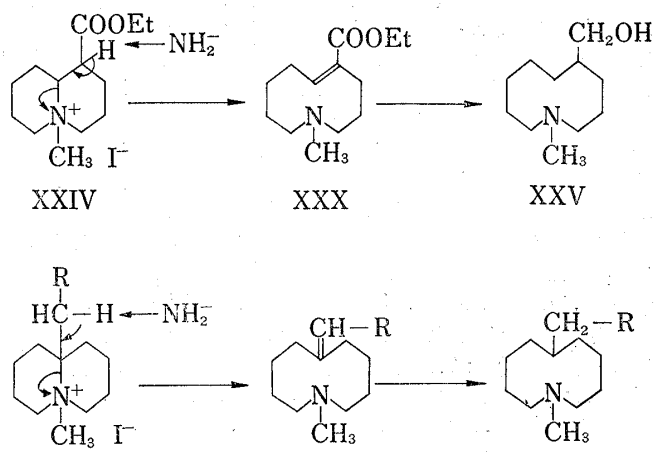

Chart 5

Thus, the Birch reduction of the methiodides (VIIa, XIIa, and XXIV) afforded successfully the ten-membered ring amines (VIII, XIII, and XXV) in *ca.* 60% yields, respectively. The reaction mechanism was clarified as shown in Chart 5. These yields are lower than those (70—80%) obtained by the Birch reduction of the methiodides of I, III, and IV.

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Experimental[11]

9a-Cyanomethyloctahydroquinolizine (VI)——According to the method of Sekiya, *et al.*[5] VI was obtained from V as colorless prisms, mp 65—66° (lit.[5] mp 60—61°).

The Methiodides (VIIa and VIIb): A solution of VI (1.0 g) and CH_3I (2.4 g) was kept standing at room temperature for 5 days. The precipitate was collected by filtration and recrystallized from MeOH to give VIIa (0.8 g, 44%) as colorless needles, mp 278—280° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN). NMR (D_2O) τ: 6.87 (3H, s, N^+-CH_3). ^{13}C-NMR ppm: 116.13 (CN), 70.14 (C_{10}), 64.44 (C_4 or C_6), 61.09 (C_6 or C_4), 49.51 (N^+-CH_3), 33.07 (C_1 or C_9), 29.61 (C_9 or C_1), 26.58 ($\underline{C}H_2CN$), 21.36 (C_3, C_7), 18.75 (C_2, C_8). *Anal.* Calcd. for $C_{12}H_{21}N_2I$: C, 45.01; H, 6.61; N, 8.75. Found: C, 44.81; H, 6.63; N, 8.52.

The filtrate and mother liquor of recrystallization were combined, evaporated *in vacuo*, and washed with ether to give a mixture of VIIa and VIIb (0.76 g, 42%) in the 1: 1 ratio. NMR (D_2O) τ: 6.65 (3/2 H, s, N^+-CH_3), 6.87 (3/2 H, s, N^+-CH_3). The mixture was recrystallized from MeOH twice, and the mother liquor was evaporated *in vacuo* and the residue was recrystallized from MeOH to give VIIb as colorless prisms, mp 278—281° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN). NMR (D_2O) τ: 6.65 (3H, s, N^+-CH_3). ^{13}C-NMR ppm: 111.88 (CN), 70.74 (C_{10}), 61.95 (C_4, C_6), 45.20 (N^+-CH_3), 30.64 (C_1, C_9), 21.78 ($\underline{C}H_2CN$), 20.26 (C_3, C_7), 17.90 (C_2, C_8). *Anal.* Calcd. for $C_{12}H_{21}N_2I$: C, 45.01; H, 6.61; N, 8.75. Found: C, 44.84; H, 6.61; N, 8.57.

Reduction of VIIa with Li/NH_3 (Formation of 6-Cyanomethyl-1-methyldecahydroazecine (VIII), 1-Methyl-6-methylenedecahydroazecine (IX), and 1,6-Dimethyldecahydroazecine (X))——1) To a solution of VIIa (1.0 g) in liq. NH_3 (300 ml) was added Li (50 mg) in small portions with stirring. After evaporation of NH_3, the residue was shaken with H_2O and ether. The ether layer was washed with H_2O, dried, and evaporated *in vacuo*. The residue was chromatographed on alumina using *n*-hexane and benzene as eluents.

The fraction eluted with *n*-hexane gave IX (32 mg, 6%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH_3), 1640 (C=C). NMR ($CDCl_3$) τ: 5.20 (2H, m, W_H=3 Hz, >C=CH_2), 7.90 (3H, s, N-CH_3). Mass Spectrum *m/e*: 167 (M^+). The picrate: yellow needles, mp>300° (EtOH). *Anal.* Calcd. for $C_{17}H_{24}O_7N_4$: C, 51.51; H, 6.10; N, 14.14. Found: C, 51.59; H, 6.27; N, 14.02.

The fraction eluted with benzene gave VIII (348 mg, 57%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH_3), 2240 (CN). NMR ($CDCl_3$) τ: 7.87 (3H, s, N-CH_3). Mass Spectrum *m/e*: 194 (M^+). The picrate: yellow plates, mp 137—140° (EtOH). *Anal.* Calcd. for $C_{18}H_{25}O_7N_5$: C, 51.06; H, 5.95; N, 16.54. Found: C, 51.18; H, 5.52; N, 16.40.

2) The methiodide (VIIa, 1.0 g) was treated with Li (150 mg) in liq. NH_3 (300 ml) in the same procedure as that described in 1) to give the residue (40 mg). The residue showed two spots (*Rf*: 0.87 and 0.70) on TLC (*n*-hexane), and two peaks on GC (retention time: 6.4 min (X) and 8.4 min (IX)) in the 1: 3 ratio. GC–mass Spectrum *m/e*: X, 169 (M^+), IX, 167 (M^+). The mass spectrum of IX was identical with that of IX obtained in 1).

Reduction of VIIa with Na/NH_3 (Formation of VII, IX, and X)——1) The methiodide (VIIa, 1.0 g) was treated with Na (200 mg) in liq. NH_3 (300 ml) in the same procedure as that described in the Li/NH_3 reduction to give IX (34 mg, 7%) and VIII (263 mg, 43%), which were identified with IX and VIII, respectively, obtained above by IR and NMR spectra and mixed mp of their picrates.

2) The methiodide (VIIa, 1.0 g) was treated with Na (1.0 g) in liq. NH_3 (300 ml) in the same procedure as that described in the Li/NH_3 reduction to give the product (60 mg), which showed two peaks on GC (retention time: 6.4 min (X) and 8.4 min (IX)) in the 3.5: 1 ratio. The product was identified with that obtained by the Li/NH_3 reduction by TLC and GC.

1,6-Dimethyldecahydroazecine (X)——The nitrile (VIII, 260 mg) was treated with Li (300 mg) in liquid NH_3 (100 ml) in the same procedure as that described in the reduction of VIIa. The product was chromatographed on alumina using *n*-hexane and benzene as eluents.

The fraction eluted with *n*-hexane gave X (19 mg, 11%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2790 (N-CH_3). NMR ($CDCl_3$) τ: 7.88 (3H, s, N-CH_3), 9.18 (3H, d, J=6 Hz, >CH$\underline{C}H_3$). Mass Spectrum *m/e*: 169 (M^+). The picrate: yellow needles, mp 158—160° (EtOH). *Anal.* Calcd. for $C_{17}H_{26}O_7N_4$: C, 51.25; H, 6.58; N, 14.06. Found: C, 51.42; H, 6.46; N, 14.18. The mass spectrum of X was identical with that of X obtained from VIIa.

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11) All melting points were measured with a Yanagimoto Micro Melting Point Apparatus. Melting points and boiling points are uncorrected. The extracts were dried over anhydrous Na_2SO_4. Alumina (Brockmann grade II—III, Merck) and silica gel (Wakogel C-200, Wako) were used for column chromatography. Alumina (Aluminiumoxid GF_{254} Typ E, Merck) was used for thin-layer chromatography (TLC). IR spectra were measured with Spectrophotometer IRA-2, Japan Spectroscopic Co., NMR spectra with R-20B, Hitachi, using TMS and DSS as internal standards in $CDCl_3$ and D_2O, respectively, ^{13}C-NMR spectra with PS-100-PF-100, Japan Electron Lab. Co., at 25.1 MHz using TMS as an internal standard in CF_3CO_2D, mass and GC–mass spectra with RMU-6M and RMU-7M, Hitachi, GC with Hitachi-063 employing SE-30 column (column temperature 60°).

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The fraction eluted with benzene gave VIII (55 mg, 21%).

9a-Ethoxycarbonylmethyloctahydroquinolizine (XI)——A solution of V (4.3 g) and monomethyl malonate (6.95 g) in dioxane (50 ml) was refluxed for 7 hr and evaporated *in vacuo*. The residue was distilled to give XI (6.24 g, 88%) as a colorless oil, bp 85—87°/15 mmHg. IR ν_{max}^{liq} cm^{-1}: 2800, 2760, 2680 (Bohlmann bands), 1720 (C=O). NMR ($CDCl_3$) τ: 5.86 (2H, q, J=7 Hz, C$\underline{H}_2$CH$_3$), 7.35 (2H, s, CH_2CO), 8.75 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$). The picrate: yellow prisms, mp 160—162° (EtOH). *Anal.* Calcd. for $C_{19}H_{26}O_9N_4$: C, 50.22; H, 5.77; N, 12.33. Found: C, 50.24; H, 5.86; N, 12.16.

The methiodides (XIIa and XIIb): A solution of XI (1.0 g) and CH_3I (1.9 g) in MeOH (10 ml) was kept standing at room temperature for 5 days, evaporated *in vacuo*, and washed with ether to give a mixture of XIIa and XIIb (1.53 g, 94%) in the 3: 2 ratio. NMR (D_2O) τ: 6.70 (6/5 H, s, N$^+$-CH$_3$), 6.92 (9/5 H, s, N$^+$-CH$_3$).

The mixture was recrystallized from EtOH to give XIIa (0.68 g) as colorless scales, mp 195—198°. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR (D_2O) τ: 6.92 (3H, s, N$^+$-CH$_3$). ^{13}C-NMR ppm: 173.59 (C=O), 71.90 (C_{10}), 65.89 ($\underline{C}H_2CH_3$), 63.89 (C_4 or C_6), 60.55 (C_6 or C_4), 48.84 (N$^+$-CH$_3$), 41.07 ($\underline{C}H_2CO$), 33.13 (C_1 or C_9), 28.21 (C_9 or C_1), 21.42 (C_3, C_7), 19.23 (C_2 or C_8), 18.75 (C_8 or C_2), 14.32 ($CH_2\underline{C}H_3$). *Anal.* Calcd. for $C_{14}H_{26}O_2NI$: C, 45.78; H, 7.14; N, 3.81. Found: C, 45.59; H, 7.21; N, 3.78.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized from EtOH. The mother liquor was evaporated *in vacuo* and the residue was recrystallized from EtOH twice to give XIIb as colorless needles, mp 212—214°. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR (D_2O) τ: 6.70 (3H, s, N$^+$-CH$_3$). ^{13}C-NMR ppm: 173.46 (C=O), 72.08 (C_{10}), 65.83 ($\underline{C}H_2CH_3$), 62.28 (C_4, C_6), 44.23 (N$^+$-CH$_3$), 35.37 ($\underline{C}H_2CO$), 30.03 (C_1, C_9), 20.32 (C_3, C_7), 18.14 (C_2, C_8), 14.32 ($CH_2\underline{C}H_3$). *Anal.* Calcd. for $C_{14}H_{26}O_2NI$: C, 45.78; H, 7.14; N, 3.81. Found: C, 45.54; H, 6.87; N, 3.60.

6-(2-Hydroxyethyl)-1-methyldecahydroazecine (XIII)——1) From XIIa: To a solution of XIIa (1.0 g) in liq. NH_3 (300 ml) was added Li (200 mg) in small portions with stirring. After evaporation of NH_3, the residue was shaken with H_2O and ether. The ether layer was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give XIII (320 mg, 59%) as a colorless oil, bp 165—170° (bath temp.)/20 mmHg. IR ν_{max}^{liq} cm^{-1}: 3330 (OH), 2800 (N-CH$_3$). NMR ($CDCl_3$) τ: 6.32 (2H, t, J=6.5 Hz, $CH_2C\underline{H}_2OH$), 7.68 (1H, s, OH, disappeared by addition of D_2O), 7.85 (3H, s, N-CH$_3$). Mass Spectrum *m/e*: 199 (M$^+$). The picrate: yellow scales, mp 103—104° (EtOH). *Anal.* Calcd. for $C_{18}H_{28}O_8N_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.37; H, 6.79; N, 12.83.

2) From XIV: To a suspension of LAH (270 mg) in anhyd. ether (40 ml) was added dropwise a solution of XIV (170 mg) in anhyd. ether (5 ml) with stirring, and the reaction mixture was stirred at room temperature for 20 hr. The excess hydride was decomposed with H_2O, and the inorganic material was filtered and washed with ether. The filtrate and washings were combined, dried, and evaporated *in vacuo*. The residue was distilled to give XIII (120 mg, 86%) as a colorless oil, bp 165—170° (bath temp.)/20 mmHg, which was identified with XIII obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

3) From XVIII: The ester (XVIII, 150 mg) was treated with Li (200 mg) in liq. NH_3 (200 ml) in the same procedure as that described in 1) to give XIII (80 mg, 65%), which was identified with XIII obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

6-Ethoxycarbonylmethyl-1-methyldecahydroazecine (XIV)——A solution of VIII (310 mg) in abs. EtOH (50 ml) was saturated with HCl gas, refluxed for 8 hr, and evaporated *in vacuo*. The residue was made alkaline with aq. K_2CO_3 solution and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give XIV (240 mg, 62%) as a colorless oil, bp 120—125° (bath temp.)/2 mmHg. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH$_3$), 1735 (C=O). NMR ($CDCl_3$) τ: 5.86 (2H, q, J=7 Hz, C$\underline{H}_2$-CH$_3$), 7.86 (3H, s, N-CH$_3$), 8.73 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$). Mass Spectrum *m/e*: 241 (M$^+$). The picrate: yellow needles, mp 98—100° (EtOH). *Anal.* Calcd. for $C_{20}H_{30}O_9N_4$: C, 51.06; H, 6.43; N, 11.91. Found: C, 50.94; H, 6.49; N, 11.80.

6-Cyanomethyl-1-methyl-1,2,3,4,7,8,9,10-octahydroazecine (XV)——1) From VIIa with NaOEt: To a solution of Na (760 mg) in abs. EtOH (20 ml) was added VIIa (960 mg), and the reaction mixture was refluxed for 4 hr in a stream of N_2 and evaporated *in vacuo*. The residue was purified with column chromatography (silica gel, ether) to give XV (460 mg, 80%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH$_3$), 2250 (CN). NMR ($CDCl_3$) τ: 4.45 (1H, t, J=8 Hz, >C=C$\underline{H}$CH$_2$), 6.96 (2H, s, CH_2CN), 7.86 (3H, s, N-CH$_3$). Mass Spectrum *m/e*: 192 (M$^+$). The picrate: yellow needles, mp 156—158° (EtOH). *Anal.* Calcd. for $C_{18}H_{23}O_7N_5$: C, 51.30; H, 5.50; N, 16.62. Found: C, 51.15; H, 5.59; N, 16.22.

2) From VIIa with Na-Hg: To a solution of VIIa (1.96 g) in 80% aq. EtOH (80 ml) was added 5% Na-Hg (10 g) in a small portions with stirring, and the reaction mixture was stirred at room temperature for 60 hr. The deposited Hg was filtered off and the filtrate was evaporated *in vacuo*. The residue was shaken with H_2O and ether. The ether layer was washed with H_2O, dried, and evaporated *in vacuo*. The residue was purified with column chromatography (silica gel, ether) to give XV (650 mg, 55%) as a colorless oil, which was identified with XV obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

3) From XVII with NaOEt: The nitrile (XVII, 100 mg) was treated with Na (100 mg) in abs. EtOH (10 ml) in the same procedure as that described in 1) to give XV (70 mg, 70%) as a colorless oil, which was identified with XV obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

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6-Ethoxycarbonylmethyl-1-methyl-1,2,3,4,7,8,9,10-octahydroazecine (XVI)——1) From XIIa: The methiodide (XIIa, 1.10 g) was treated with Na (760 mg) in abs. EtOH (20 ml) in the same procedure as that described for XV to give XVI (200 mg, 28%) as a colorless oil, bp 115—120° (bath temp.)/2 mmHg. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH_3), 1735 (C=O). NMR ($CDCl_3$) τ: 4.70 (1H, t, $J=8$ Hz, >C=C<u>H</u>CH_2), 5.86 (2H, q, $J=7$ Hz, C<u>H_2</u>CH_3), 7.00 (2H, s, CH_2CO), 7.85 (3H, s, N-CH_3), 8.73 (3H, t, $J=7$ Hz, CH_2C<u>H_3</u>). Mass Spectrum *m/e*: 239 (M^+). The picrate: yellow prisms, mp 122—123° (EtOH). *Anal.* Calcd. for $C_{20}H_{28}O_9N_4$: C, 51.28; H, 6.02; N, 11.96. Found: C, 51.26; H, 6.12; N, 11.74.

2) From XV: A solution of XV (430 mg) in abs. EtOH (80 ml) was saturated with HCl gas and treated in the same procedure as that described for XIV to give XVI (380 mg, 71%) as a colorless oil, bp 115—120° (bath temp.)/2 mmHg, which was identified with XVI obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

3) From XVIII: The ester (XVIII, 200 mg) was treated with Na (200 mg) in abs. EtOH (10 ml) in the same procedure as that described for XV to give XVI (80 mg, 40%) as a colorless oil, bp 120° (bath temp.)/2 mmHg, which was identified with XVI obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

6-Cyanomethylene-1-methyldecahydroazecine (XVII)——To a solution of VIIa (1.0 g) in liq. NH_3 (300 ml) was added $NaNH_2$ (500 mg) in small portions with stirring. After evaporation of NH_3, the residue was shaken with H_2O and ether. The ether layer was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give XVII (300 mg, 50%) as a colorless oil, bp 165—170° (bath temp.)/11 mmHg. IR ν_{max}^{liq} cm^{-1}: 2780 (N-CH_3), 2200 (CN), 1615 (C=C). NMR ($CDCl_3$) τ: 4.93 (1H, m, $W_H=3$ Hz, >C=CHCN), 7.93 (3H, s, N-CH_3). Mass Spectrum *m/e*: 192 (M^+). The picrate: yellow leaflets, mp 258—261° (decomp.) (EtOH). *Anal.* Calcd. for $C_{18}H_{23}O_7N_5$: C, 51.30; H, 5.50; N, 16.62. Found: C, 51.21; H, 5.54; N, 16.37.

6-Ethoxycarbonylmethylene-1-methyldecahydroazecine (XVIII)——The methiodide (XIIa, 500 mg) was treated with $NaNH_2$ (200 mg) in liq. NH_3 (200 ml) in the same procedure as that described for XVII to give XVIII (100 mg, 31%) as a colorless oil, bp 130° (bath temp.)/1 mmHg. IR ν_{max}^{liq} cm^{-1}: 2780 (N-CH_3), 1710 (C=O), 1630 (C=C). NMR ($CDCl_3$) τ: 4.35 (1H, m, $W_H=3$ Hz, >C=CHCO), 5.86 (2H, q, $J=7$ Hz, C<u>H_2</u>-CH_3), 7.95 (3H, s, N-CH_3), 8.73 (3H, t, $J=7$ Hz, CH_2C<u>H_3</u>). Mass Spectrum *m/e*: 239 (M^+). The picrate: yellow needles, mp 129—130° (EtOH). *Anal.* Calcd. for $C_{20}H_{28}O_9N_4$: C, 51.28; H, 6.02; N, 11.96. Found: C, 51.54; H, 6.13; N, 12.06.

6-(2-Hydroxyethyl)-1-methyl-1,2,3,4,7,8,9,10-octahydroazecine (XIX)——1) With LAH: The ester (XVI, 240 mg) was treated with LAH (400 mg) in anhyd. ether (20 ml) in the same procedure as that described for XIII to give XIX (150 mg, 76%) as a colorless oil, bp 110—115° (bath temp.)/2 mmHg. IR ν_{max}^{liq} cm^{-1}: 3300 (OH), 2800 (N-CH_3). NMR ($CDCl_3$) τ: 4.75 (1H, t, $J=8$ Hz, >C=C<u>H</u>CH_2), 6.34 (2H, t, $J=6.5$ Hz, CH_2C<u>H_2</u>OH), 7.86 (3H, s, N-CH_3), 8.35 (1H, s, OH, disappeared by addition of D_2O). Mass Spectrum *m/e*: 197 (M^+). The picrate: yellow prisms, mp 128—129° (EtOH). *Anal.* Calcd. for $C_{18}H_{26}O_8N_4$: C, 50.70; H, 6.15; N, 13.14. Found: C, 50.43; H, 6.16; N, 12.88.

2) With Li/NH_3: The ester (XVI, 130 mg) was treated with Li (200 mg) in liq. NH_3 (100 ml) in the same procedure as that described for XIII to give XIX (80 mg, 38%) as a colorless oil, bp 110° (bath temp.)/2 mmHg, which was identified with XIX obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

1,6-Dimethyl-1,2,3,4,7,8,9,10-octahydroazecine (XX)——The nitrile (XV, 350 mg) was treated with Li (300 mg) in liq. NH_3 (100 ml) in the same procedure as that described for XIII, followed by chromatography on alumina (*n*-hexane) to give XX (130 mg, 43%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH_3). NMR ($CDCl_3$) τ: 4.88 (1H, t, $J=8$ Hz, >C=C<u>H</u>CH_2), 7.87 (3H, s, N-CH_3), 8.34 (3H, s, C-CH_3). Mass Spectrum *m/e*: 167 (M^+). The picrate: yellow needles, mp 180—182° (EtOH). *Anal.* Calcd. for $C_{17}H_{24}O_7N_4$: C, 51.51; H, 6.10; N, 14.14. Found: C, 51.34; H, 6.19; N, 14.00.

1-Ethoxycarbonyl-$\Delta^{1,9a}$-hexahydroquinolizine (XXI)——1) From V: According to the method of Bohlmann *et al.*,[9] XXI was obtained from V. The perchlorate: colorless needles, mp 85—86° (EtOH). *Anal.* Calcd. for $C_{12}H_{20}O_6NCl$: C, 46.53; H, 6.51; N, 4.52. Found: C, 46.46; H, 6.75; N, 4.35.

2) From XXII: To a solution of $Hg(OAc)_2$ (26 g) in 5% aq. AcOH (80 ml) was added a solution of XXII (2.6 g) in 5% aq. AcOH (25 ml) with stirring, and the reaction mixture was heated at 65—70° for 40 hr. The deposited $Hg_2(OAc)_2$ was filtered and washed with 5% aq. AcOH. H_2S was bubbled into the combined filtrate and washings. The deposited HgS was separated by the centrifuge. The supernatant liquid was made alkaline with K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give XXI (1.18 g, 46%) as a colorless oil, bp 110—112°/1 mmHg, which was identified with XXI obtained in 1) by IR spectra and mixed mp of their perchlorates.

1-Ethoxycarbonyl(*a*)-*trans*-octahydroquinolizine (XXII) and 1-Ethoxycarbonyl(*e*)-*trans*-octahydroquinolizine (XXIII)——1) With $NaBH_4$: To a cooled solution of XXI (1.60 g) in EtOH (30 ml) was added $NaBH_4$ (1.0 g) in small portions, and the reaction mixture was stirred at room temperature for 20 hr and evaporated *in vacuo*. The residue was shaken with H_2O and ether. The ether layer was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give a colorless oil (1.13 g, 70%), bp 97—98°/1 mmHg, which was chromatographed on alumina using petr. ether–ether as eluents.

The fraction eluted with petr. ether–ether (7: 3) gave XXIII (0.1 g) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2760, 2680 (Bohlmann bands), 1730 (C=O). The picrate: yellow needles, mp 185—186° (EtOH). *Anal.* Calcd. for $C_{18}H_{24}O_9N_4$: C, 49.09; H, 5.45; N, 12.72. Found: C, 48.81; H, 5.37; N, 12.56.

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The fraction eluted with petr. ether–ether (1: 1) gave XXII (1.0 g) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2760, 2680 (Bohlmann bands), 1730 (C=O). The picrate: yellow needles, mp 133—135° (EtOH). *Anal.* Calcd. for $C_{18}H_{24}O_9N_4$: C, 49.09; H, 5.45; N, 12.72. Found: C, 48.93; H, 5.40; N, 12.43.

The methiodide (XXIV): colorless plates, mp 203—205° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). NMR (D_2O) τ: 6.75 (3H, s, N^+-CH_3). *Anal.* Calcd. for $C_{13}H_{24}O_2NI$: C, 44.20; H, 6.85; N, 3.97. Found: C, 44.03; H, 7.05; N, 3.81.

2) With H_2/PtO_2: The ester (XXI, 0.9 g) was hydrogenated in EtOH (20 ml) over PtO_2 (0.1 g) at atmospheric pressure and room temperature. After the theoretical ammount of H_2 (120 ml) was uptaken, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was distilled to give XXII (0.5 g, 56%) as a colorless oil, bp 97—98°/1 mmHg. The product was shown to be homogeneous on TLC and identified with XXII obtained in 1) by IR spectra and mixed mp of their picrates.

5-Hydroxymethyl-1-methyldecahydroazecine (XXV)——1) From XXIV: The methiodide (XXIV, 1.0 g) was treated with Li (300 mg) in liq. NH_3 (300 ml) in the same procedure as that described for XIII to give XXV (290 mg, 55%) as a colorless oil, bp 125—127°/14 mmHg. IR ν_{max}^{liq} cm^{-1}: 3300 (OH), 2800 (N-CH_3). NMR ($CDCl_3$) τ: 6.58 (2H, d, J=6 Hz, $CH_2C\underline{H}_2OH$), 7.75 (1H, s, OH, disappeared by addition of D_2O), 7.87 (3H, s, N-CH_3). Mass Spectrum *m/e*: 185 (M^+). The picrate: yellow needles, mp 143—145° (EtOH). *Anal.* Calcd. for $C_{17}H_{26}O_8N_4$: C, 49.27; H, 6.32; N, 13.52. Found: C, 49.06; H, 6.43; N, 13.45.

2) From XXX: The ester (XXX, 100 mg) was treated with Li (100 mg) in liq. NH_3 (50 ml) in the same procedure as that described for XIII to give XXV (52 mg, 63%) as a colorless oil, bp 150° (bath temp.)/14 mmHg, which was identified with XXV obtained in 1) by IR and NMR spectra and mixed mp of their picrates.

5-Ethoxycarbonyl-1-methyl-1,2,3,4,7,8,9,10-octahydroazecine (XXX)——The methiodide (XXIV, 1.0 g) was treated with $NaNH_2$ (400 mg) in liq. NH_3 (200 ml) in the same procedure as that described for XVII to give XXX (360 mg, 57%) as a colorless oil, bp 175—180° (bath temp.)/14 mmHg. IR ν_{max}^{liq} cm^{-1}: 2780 (N-CH_3), 1705 (C=O), 1640 (C=C). NMR ($CDCl_3$) τ: 3.22 (1H, t, J=8 Hz, >C=C$\underline{H}$$CH_2$), 5.84 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.88 (3H, s, N-CH_3), 8.71 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$). Mass Spectrum *m/e*: 225 (M^+). The picrate: yellow prisms, mp 104—106° (EtOH). *Anal.* Calcd. for $C_{19}H_{26}O_9N_4$: C, 50.21; H, 5.77; N, 12.33. Found: C, 50.20; H, 5.84; N, 12.20.

1-Ethoxycarbonyl-1-methyl-$\Delta^{9,9a}$-hexahydroquinolizine (XXVI)——A solution of XXI (2.45 g) and CH_3I (5.0 g) in acetone (40 ml) was kept standing at room temperature for 50 hr. The precipitate was collected by filtration and dissolved in H_2O. The solution was made alkaline with aq. K_2CO_3 solution and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give XXVI (1.13 g, 43%) as a colorless oil, bp 141—143°/16 mmHg. IR ν_{max}^{liq} cm^{-1}: 1720 (C=O), 1640 (enamine). NMR ($CDCl_3$) τ: 5.22 (1H, t, J=4 Hz, >C=C$\underline{H}$$CH_2$), 5.86 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.70 (3H, s, C-CH_3), 8.77 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$). The perchlorate: colorless plates, mp 138—139° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O), 1670 (iminium). *Anal.* Calcd. for $C_{13}H_{22}O_6NCl$: C, 48.22; H, 6.85; N, 4.33. Found: C, 48.03; H, 7.09; N, 4.18.

1-Ethoxycarbonyl(*a*)-1-methyl(*e*)-*trans*-octahydroquinolizine (XXVII)——The ester (XXVI, 4.92 g) was treated with $NaBH_4$ (4.28 g) in EtOH (80 ml) in the same procedure as that described for XXII to give XXVII (3.62 g, 73%) as a colorless oil, bp 138—142°/20 mmHg. The product was shown to be homogeneous on TLC. IR ν_{max}^{liq} cm^{-1}: 2760, 2680 (Bohlmann bands), 1725 (C=O). NMR ($CDCl_3$) τ: 5.82 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.76 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 8.83 (3H, s, C-CH_3). Mass Spectrum *m/e*: 229 (M^+). The picrate: yellow prisms, mp 148—149° (EtOH). *Anal.* Calcd. for $C_{19}H_{26}O_9N_4$: C, 50.21; H, 5.77; N, 12.33. Found: C, 50.44; H, 6.01; N, 12.15.

The methiodide (XXIX): colorless scales, mp 201—202° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). NMR (D_2O) τ: 7.10 (3H, s, N^+-CH_3), 8.70 (3H, s, C-CH_3). *Anal.* Calcd. for $C_{14}H_{22}O_2NI$: C, 45.78; H, 7.14; N, 3.81. Found: C, 45.69; H, 7.38; N, 3.57.

1-Hydroxymethyl(*a*)-1-methyl(*e*)-*trans*-octahydroquinolizine (XXVIII)——1) From XXVII: The ester (XXVII, 400 mg) was treated with LAH (300 mg) in anhyd. ether (20 ml) in the same procedure as that described for XIII to give XXVIII (300 mg, 92%) as a colorless oil, bp 160—165° (bath temp.)/20 mmHg, which solidified on standing and was recrystallized from *n*-hexane as colorless prisms, mp 89—90°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} molar solution): 3250 (bonded OH), 2760, 2680 (Bohlmann bands). NMR ($CDCl_3$) τ: 4.50 (1H, br, OH, disappeared by addition of D_2O), 9.29 (3H, s, C-CH_3). Mass Spectrum *m/e*: 183 (M^+). *Anal.* Calcd. for $C_{11}H_{21}ON$: C, 72.08; H, 11.25; N, 7.64. Found: C, 72.12; H, 10.93; N, 7.39.

2) From XXIX: The methiodide (XXIX, 500 mg) was treated with Li (300 mg) in liq. NH_3 (200 ml) in the same procedure as that described for XIII to give XXVIII (220 mg, 88%) as colorless prisms, mp 89—90°, which was identified with XXVIII obtained in 1) by IR and NMR spectra and mixed mp.

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