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Studies on 1-Azabicyclo Compounds. XVII.[1] Transannular Reaction of *cis*- and *trans*-1,2,3,4,7,8,9,10-Octahydroazecine and Their Derivatives[2]

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1-Methyl- and 1-ethyl-*cis*-octahydroazecine (I and X) were synthesized stereoselectively. Transannular reaction of the *trans*-N-oxide (VII) leading to decahydro-1-methylazecin-6-one (XI) proceeded more smoothly than that of the *cis*-N-oxide (VI). However, transannular cyclization between the nitrogen and the double bond of N-acetyl- and N-ethoxycarbonyl-*cis*-octahydroazecine (VIII and XII) producing 1-azabicyclodecane (XVI) proceeded much more easily than that of the corresponding *trans* derivatives (IX and XIII).

Transannular reactions between the nitrogen and the double bond of the medium-sized ring amines have appeared so far in a few reports,[4–6] in which stereochemical effect of the double bond was not elucidated. It would be of additional interest to study such transannular reactions of *cis*-1,2,3,4,7,8,9,10-octahydro-1-methylazecine[7,8] (I) by comparison with those of the corresponding *trans* isomer[4,7] (II). The latter olefin has already been synthesized by the Hofmann degradation of 5-methyl-octahydroquinolizinium iodide[4] or by fragmentation of 1-methyl-5α-tosyloxy-*trans*-decahydroquinoline,[7] while the former was obtained by fragmentation of 1-methyl-5α-tosyloxy-*cis*-decahydroquinoline[7] or by the Birch reduction of 10-methoxy-5-methyl-octahydroquinolizinium iodide[8] (III) but both syntheses required complicated routes.

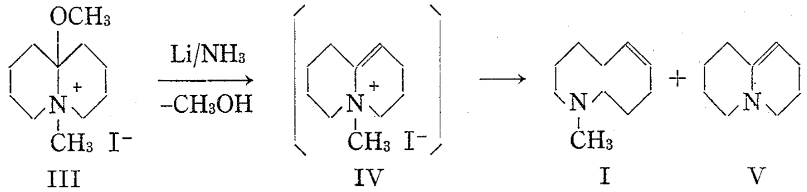

Chart 1

The fact that the above-mentioned reduction of III yielded hexahydroquinolizine (V) as a by-product in addition to I suggests the preceding formation of IV as an intermediate in this reaction. On the basis of this inference, the reduction of readily available 5-methyl-hexahydroquinolizinium iodide[9] (IV) with lithium in liquid ammonia was carried out and the expected *cis*-octahydroazecine (I) was obtained stereoselectively in 70% yield, together with the demethylated product (V) in 5% yield. The major product (I) showed the characteristic bands for *cis*-olefin at 1650 and 700 cm^{-1} in its infrared (IR) spectrum and was identical with the authentic specimen[8] in all respects. In the nuclear magnetic resonance (NMR)

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[1] Part XVI: H. Kato, E. Koshinaka, Y. Arata, and M. Hanaoka, *Chem. Pharm. Bull.* (Tokyo), **21**, 2661 (1973).
[2] Reported at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973.
[3] Location: *Takara-machi, Kanazawa 920, Japan.*
[4] K. Schofield and R.J. Wells, *Aust. J. Chem.*, **18**, 1423 (1965).
[5] A.R. Margni, D. Giacopello, and V. Deulofeu, *J. Chem. Soc.* (*C*), **1970**, 2578.
[6] R.A. Johnson, *J. Org. Chem.*, **17**, 312 (1972).
[7] C.A. Grob, H.R. Kiefer, H.J. Lutz, and H.J. Wilkens, *Helv. Chim. Acta*, **50**, 416 (1967).
[8] Y. Arata and T. Shioda, *Chem. Pharm. Bull.* (Tokyo), **20**, 783 (1972).
[9] N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, **77**, 439 (1955).

spectrum of I, two olefinic protons appeared at 4.69 τ as a multiplet. The splitting pattern of this signal is almost the same as that reported for olefinic protons of *cis*-cyclooctene,[10] whereas two olefinic protons of *trans*-octahydroazecine (II) appeared at 4.40 (doublets of triplet, J=15.5; 6.0 Hz) and 4.58 τ (doublets of triplet, J=15.5; 6.0 Hz).

Both I and II were oxidized with hydrogen peroxide in acetone giving the hygroscopic N-oxides (VI and VII), which formed the corresponding picrates of mp 170—171° and mp 187—188°, in 76% and 50% yield, respectively. The IR spectrum of VI showed bands at 950 (N-oxide), 1650 and 700 cm^{-1} (*cis*-olefin), while that of VII indicated bands at 1650, 980, and 960 cm^{-1} (*trans*-olefin and N-oxide). Both N-oxides were treated with an aqueous solution saturated with sulfur dioxide but only the starting materials were recovered. The Polonovski reaction[11] of both VI and VII with acetic anhydride gave the N-acetyl-amines (VIII and IX) in 54% and 33% yield, respectively. Reduction of VIII with lithium aluminum hydride afforded the N-ethyl-amine (X) (picrate, mp 128—129°), the IR spectrum of which showed bands at 1650 and 700 cm^{-1} (*cis*-olefin). The product (X) was identical with the authentic *cis*-1-ethyl-1,2,3,4,7,8,9,10-octahydroazecine in the IR spectra and the mixed melting point of both picrates. The authentic sample was stereoselectively prepared by quaternization of hexahydroquinolizine (V) with ethyl iodide, followed by treatment with lithium in liquid ammonia. Thus, the indicated structures of VI and VII were confirmed to be correct.

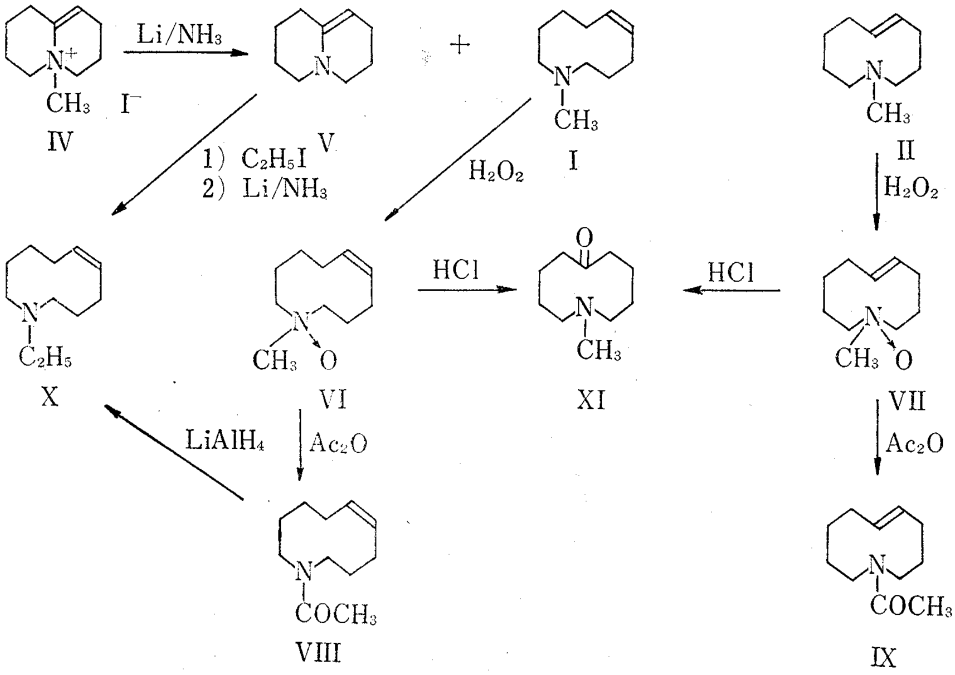

Chart 2

Heating of VI and VII with hydrochloric acid in acetic acid gave only the starting materials under the same condition as that reported for the conversion of anhydrotetrahydromethylberberine N-oxide into β-homochellidonine (α-allocryptopine).[12] On being heated in concentrated hydrochloric acid, however, both N-oxides (VI and VII) afforded the aminoketone (XI) in 5% and 20% yield, respectively, accompanied with an appreciable amount of the starting materials. This reaction was also carried out in a sealed tube at 160—170°

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[10] G.V. Smith and H. Kriloff, *J. Am. Chem. Soc.*, **85**, 2016 (1963).

[11] M. Polonovski and M. Polonovski, *Bull. Soc. Chim. France*, **41**, 1190 (1927); S. Oae, T. Kitao, and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3366 (1962).

[12] R.D. Haworth and W.H. Perkin, *J. Chem. Soc.*, **1926**, 445.

and afforded the aminoketone (XI) in 50% and 70% yield from VI and VII, respectively. The IR spectrum of XI showed a band at 1693 cm^{-1} attributable to the carbonyl group interacting transannularly with the nitrogen.[13] The aminoketone (XI) was identified with the authentic decahydro-1-methyl-6-azecinone[14] (XI) by the IR spectral comparison and mixed melting point determination of their picrates. Thus, the transannular reaction of the *trans*-N-oxide (VII) leading to XI proceeded more smoothly than that of the *cis*-N-oxide (VI).

Reaction of *cis*-octahydroazecine (I) with ethyl chloroformate[15] produced the *cis*-N-ethoxycarbonyl-amine (XII) in 88% yield, the IR spectrum of which showed a band at 1700 cm^{-1} (carbamate). Similar treatment of *trans* isomer (II) with ethyl chloroformate gave *trans*-N-ethoxycarbonyl-amine (XIII) (IR: 1690 cm^{-1} (carbamate)) only in 7.4% yield, along with a preponderance of the chloride (XIV). When treated with lithium aluminum hydride, XII and XIII afforded the N-methyl derivatives (I and II, respectively) in an excellent yield, and the structures of XII and XIII were now postulated as ethyl *cis*-1,2,3,4,7,8,9,10-octahydroazecine-1-carboxylate and the corresponding *trans* isomer, respectively. The structure of XIV was assigned from the following spectral data: IR: 1695 cm^{-1} (carbamate), NMR τ: 7.14 (singlet, N–CH$_3$), 6.76 (triplet, N–CH$_2$–), 6.50 (triplet, –CH$_2$Cl), mass *m/e*: 263, 261 (1: 3, M$^+$).

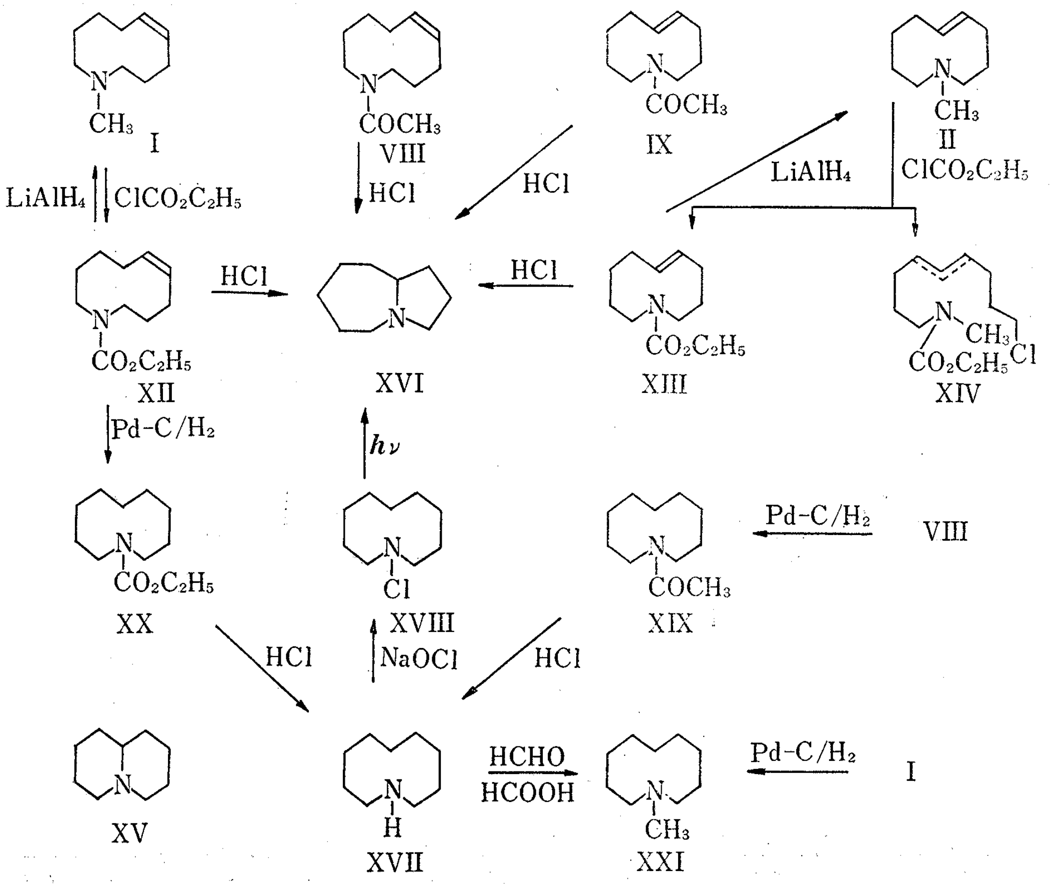

Chart 3

Next, the transannular cyclization of VIII, IX, XII, and XIII were tried. Schofield, *et al.*[4] have already reported that heating of II in acetic acid, followed by pyrolysis afforded octahydroquinolizine (XV) and 1-azabicyclo[5.3.0]decane[16] (XVI) in the ratio of 1: 1. Hy-

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13) N.J. Leonard, *Rec. Chem. Prog.*, **17**, 243 (1956).
14) Y. Arata and Y. Oda, *Chem. Pharm. Bull.* (Tokyo), **21**, 752 (1973).
15) G. Kraiss and K. Nador, *Tetrahedron Letters*, **1971**, 57.
16) L.A. Cohen and B. Witkop, *J. Am. Chem. Soc.*, **77**, 6595 (1955).

drolysis of both *cis*- and *trans*-N-acetyl-amines (VIII and IX) with 10% hydrochloric acid gave 1-azabicyclodecane (XVI) in 73% and 31% yield, respectively. In contrast with Schofield's result, octahydroquinolizine could not be obtained at all from these reactions. Similar treatment of *cis*- and *trans*-N-ethoxycarbonyl-amines (XII and XIII) with hydrochloric acid also produced XVI in 82% and 26% yield, respectively. It is quite interesting that the transannular cyclization between the nitrogen and the double bond of *cis* derivatives (VIII and XII) producing XVI proceeded much more smoothly than that of *trans* derivatives (IX and XIII), contrary to the transannular reaction of the N-oxides (VI and VII). These results suggest that the nitrogen is properly situated nearer to C-6 in the conformation of *cis* derivatives than that of *trans* derivatives.

1-Azabicyclodecane (XVI) was also obtained by the Hofmann-Löffler reaction17) of the amine (XVII). The amine (XVII) was treated with 10% aqueous sodium hypochlorite and the resulting N-chloroamine (XVIII) in concentrated sulfuric acid was irradiated with ultraviolet ray for 10 hr and subsequent treatment with sodium hydroxide gave XVI in 30% yield. This product (XVI) was identified with XVI derived from VIII by direct comparison. Decahydroazecine (XVII) (picrate, mp 192—193°) was synthesized in overall 73% yield from VIII by catalytic hydrogenation and subsequent hydrolysis of the resulting dihydro derivative (XIX). Alternatively, catalytic hydrogenation of XII, followed by acidic hydrolysis gave the amine (XVII) which, on treatment with formaldehyde solution and formic acid, afforded the N-methyl-amine18) (XXI). This product (XXI) was identified with the dihydro derivative of I by IR spectra and mixed melting point of the picrates.

Experimental19)

***cis*-1,2,3,4,7,8,9,10-Octahydro-1-methylazecine (I)**——1) From IV: To a solution of IV (2.0 g) in liq. NH_3 (500 ml) was added Li (0.6 g) in small portions with stirring. The reaction mixture was stirred vigorously for 5 min and evaporated at room temperature. To the residue was added H_2O, and the mixture was extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was distilled to give a colorless oil, bp 90—95° (bath temp.)/18 mmHg, which was converted to the picrates. Recrystallization of the crude picrates from EtOH to give the picrate of I (1.92 g (70%)) as yellow needles, mp 179° (lit.8) mp 180—181°). *Anal.* Calcd. for $C_{16}H_{22}O_7N_4$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.48; H, 5.83; N, 14.61. The free base was obtained as a colorless oil, bp 90—95° (bath temp.)/18 mmHg. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 2800 (N-CH_3), 3010, 1650, 700 (*cis*-olefin). NMR (10% $CDCl_3$) τ: 7.90 (3H, s, N-CH_3), 4.69 (2H, m, -CH=CH-).

The mother liquor of the recrystallization was evaporated and the residue was recrystallized from EtOH to give the picrate of V (0.13 g (5%)) as yellow needles, mp 108—109° (lit.8) 108—109°), which was identical with the authentic specimen8) in mixed mp.

2) From XII: To a suspension of $LiAlH_4$ (80 mg) in anhyd. ether (40 ml) was added dropwise a solution of XII (270 mg) in anhyd. ether (10 ml). The reaction mixture was stirred at room temperature for 5 hr. The excess hydride was decomposed with H_2O, and inorganic material was filtered and washed with ether. The filtrate and washings were combined, dried and evaporated. The residue was distilled to give I (160 mg (82%)) as a colorless oil, bp 90—95° (bath temp.)/18 mmHg, which was identical with I obtained in 1) in IR spectra and mixed mp of their picrates.

***trans*-1,2,3,4,7,8,9,10-Octahydro-1-methylazecine (II)**——1) From Quinolizidine Methiodide: According to the method by Schofield, *et al.*,4) II was obtained as a colorless oil, bp 90—95° (bath temp.)/18 mmHg. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 2790 (N-CH_3), 3025, 1655, 955 (*trans*-olefin). NMR (10% $CDCl_3$) τ: 7.86 (3H, s, N-CH_3), 4.58 (1H, d-t, J=15.5 Hz, 6.0 Hz, $CH_2\underline{CH}$=$CHCH_2$), 4.40 (1H, d-t, J=15.5 Hz, 6.0 Hz, CH_2CH=$\underline{CH}CH_2$). Decoupling: Irradiate at 7.99 ($\underline{CH_2}$CH=)$\longrightarrow$4.58, 4.40 (AB-q, J=15.5 Hz).

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17) M.E. Wolff, *Chem. Revs.*, **63**, 55 (1963).

18) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1363 (1969).

19) All melting points were measured with a Yanagimoto Micro Melting Point Apparatus. Melting points and boiling points are uncorrected. Organic extracts were dried over anhyd. Na_2SO_4. IR spectra were measured with a Spectrophotometer IR-G, Japan Spectroscopic Co., NMR spectra with H-60-C, Japan Electron Lab. Co., using $(CH_3)_4Si$ as an internal standard, and mass spectra with JMS-01SG, Japan Electron Lab. Co. Irradiation of ultraviolet ray was conducted with 100-watt lump Halos PIH-100, Eikosha.

Picrate: Yellow needles, mp 153—154° (MeOH) (lit.4) 153—154°).

2) From XIII: To a suspension of $LiAlH_4$ (50 mg) in anhyd. ether (20 ml) was added dropwise a solution of XIII (130 mg) in anhyd. ether (5 ml). The reaction mixture was treated in the same procedure as that for I from XII to give II (67 mg (71%)) as a colorless oil, bp 90—95° (bath temp.)/18 mmHg, which was identical with II obtained in 1) in IR spectra and mixed mp of their picrates.

***cis*-1,2,3,4,7,8,9,10-Octahydro-1-methylazecine N-Oxide (VI)**——To a solution of I (500 mg) in acetone (8 ml) was added a solution of 30% H_2O_2 (3 ml) in acetone (7 ml) under cooling. The reaction mixture was kept standing at room temperature for 5 days and then evaporated *in vacuo*. To the residue was added 10% NaOH and the mixture was washed with ether. The aq. layer was extracted thoroughly with $CHCl_3$. The extract was dried and evaporated to give VI (420 mg (76%)) as hygroscopic crystals. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2850 ($N-CH_3$), 1650, 700 (*cis*-olefin), 950 (N-oxide).

Picrate: Yellow needles, mp 170—171° (EtOH). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 14.07. Found: C, 47.96; H, 5.49; N, 13.90.

***trans*-1,2,3,4,7,8,9,10-Octahydro-1-methylazecine N-Oxide (VII)**——To a solution of II (680 mg) in acetone (10 ml) was added a solution of 30% H_2O_2 (4.2 ml) in acetone (10 ml) under cooling. The reaction mixture was treated in the same procedure as that for VI to give VII (350 mg (50%)) as hydroscopic crystals. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2850 ($N-CH_3$), 1650, 980, 960 (*trans*-olefin and N-oxide).

Picrate: Yellow needles, mp 187—188° (EtOH). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.44; H, 5.68; N, 14.14.

***cis*-1-Acetyl-1,2,3,4,7,8,9,10-octahydroazecine (VIII)**——A solution of VI (330 mg) in Ac_2O (3.5 ml) was heated at 60—65° for 4 hr and then evaporated. The residue was made alkaline with 10% NaOH and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was distilled to give VIII (180 mg (54%)) as a colorless oil, bp 120—130° (bath temp.)/3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1645 (amide), 720 (*cis*-olefin).

***trans*-1-Acetyl-1,2,3,4,7,8,9,10-octahydroazecine (IX)**——A solution of VII (510 mg) in Ac_2O (5.5 ml) was heated at 60—65° for 4 hr. The reaction mixture was treated in the same procedure as that for VIII to give IX (170 mg (33%)) as a colorless oil, bp 120—130° (bath temp.)/3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1635 (amide), 992 (*trans*-olefin).

***cis*-1-Ethyl-1,2,3,4,7,8,9,10-octahydroazecine (X)**——1) From V: A solution of V (2.1 g) and EtI (4.0 g) in EtOH (10 ml) was heated at 85—90° for 3 hr and then evaporated. The residue was recrystallized from EtOH–iso-Pr_2O (3:1) to give 5-ethyl-3,4,6,7,8,9-hexahydro-2*H*-quinolizinium iodide (2.2 g (52%)) as colorless scales, mp 227—230° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3010, 1630 (C=C). NMR (10%, $CDCl_3$) τ: 8.60 (3H, t, $J=7$ Hz, $NCH_2C\underline{H}_3$), 6.15 (2H, q, $J=7$ Hz, $NC\underline{H}_2CH_3$), 4.10 (1H, m, =CH). *Anal.* Calcd. for $C_{11}H_{20}NI$: C, 45.06; H, 6.87; N, 4.78. Found: C, 45.18; H, 6.89; N, 5.42.

To a solution of the above quaternary base (600 mg) in liq. NH_3 (200 ml) was added Li (300 mg) in small portions. The reaction mixture was treated in the same procedure as that for I from IV to give X (210 mg (60%)) as a colorless oil, bp 110—120° (bath temp.)/18 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3010, 1650, 700 (*cis*-olefin), NMR (10% in CCl_4) τ: 8.97 (3H, t, $J=7.2$ Hz, $NCH_2C\underline{H}_3$), 7.82 (2H, q, $J=7.2$ Hz, $NC\underline{H}_2CH_3$), 4.70 (2H, m, CH=CH).

Picrate: Yellow needles, mp 128—129° (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, 6.09; N, 14.40.

2) From VIII: To a suspension of $LiAlH_4$ (65 mg) in anhyd. ether (20 ml) was added dropwise a solution of VIII (200 mg) in anhyd. ether (10 ml). The reaction mixture was stirred at room temperature for 4 hr and treated in the same procedure as that for I from XII to give X (145 mg (79%)) as a colorless oil, bp 110—120° (bath temp.)/18 mmHg, which was identical with X obtained in 1) in IR spectra and mixed mp of their picrates.

1,2,3,4,5,6,7,8,9,10-Decahydro-1-methylazecin-6-one (XI)——1) From VI: a) A solution of VI (600 mg) in conc. HCl (6 ml) was refluxed for 10 hr and then evaporated. The residue was made alkaline with 10% NaOH and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was distilled to give XI (32 mg (5%)) as a colorless oil, bp 115—120° (bath temp.)/18 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 2800 ($N-CH_3$), 1693 (C=O).

Picrate: Yellow needles, mp 260—262° (decomp.) (EtOH) (lit.14) 260—262°). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 13.72. Found: C, 48.43; H, 5.74; N, 13.89.

The H_2O layer was thoroughly extracted with $CHCl_3$. The extract was dried and evaporated to give the starting material (VI, 400 mg (67%)).

b) A solution of VI (103 mg) in conc. HCl (7 ml) was heated at 160—170° in a sealed tube for 10 hr. The reaction mixture was treated in the same procedure as that described in a) to give XI (50 mg (50%)) as a colorless oil, bp 115—120° (bath temp.)/18 mmHg, which was identical with XI obtained above in IR spectra and mixed mp of their picrates.

2) From VII: a) A solution of VII (800 mg) in conc. HCl (8 ml) was refluxed for 10 hr. The reaction mixture was treated in the same procedure as that described in 1) to give XI (80 mg (20%)) as a colorless oil, bp 115—120° (bath temp.)/18 mmHg, which was identical with XI obtained in 1) in IR spectra and mixed mp of their picrates, and VII (350 mg (44%)).

b) A solution of VII (110 mg) was heated at 160—170° in a sealed tube for 10 hr. The reaction mixture was treated in the same procedure as that described in 1) to give XI (64 mg (70%)) as a colorless oil, bp 115—120° (bath temp.)/18 mmHg, which was identical with XI obtained in 1) in IR spectra and mixed mp of their picrates.

Ethyl *cis*-1,2,3,4,7,8,9,10-Octahydroazecine-1-carboxylate (XII)——A solution of I (1.0 g) and $ClCO_2Et$ (2.0 g) in C_6H_6 (4 ml) was refluxed for 5 hr and then evaporated. To the residue was added 10% NaOH and the mixture was extracted with ether. The extract was washed with 5% HCl and H_2O, dried and evaporated. The residue was distilled to give XII (1.2 g (88%)) as a colorless oil, bp 110—120° (bath temp.)/3 mmHg. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 1700 (carbamate), 1650, 710 (*cis*-olefin).

Ethyl *trans*-1,2,3,4,7,8,9,10-Octahydroazecine-1-carboxylate (XIII)——A solution of II (4.2 g) and $ClCO_2Et$ (8.0 g) in C_6H_6 (70 ml) was refluxed for 5 hr. The reaction mixture was treated in a same procedure as that for XII to give an oil, which was separated into two products by fractional distillation.

Lower boiling point product (XIII, 0.43 g (7.4%)) was obtained as a colorless oil, bp 110—120° (bath temp.)/4 mmHg. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 1690 (carbamate), 1650 (sh), 985 (*trans*-olefin). NMR (7% $CDCl_3$) τ: 8.76 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 6.93 (4H, br, $-C\underline{H}_2-N-C\underline{H}_2$), 5.91 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 4.48 (2H, m, -CH=CH-).

Higher boiling point product (XIV, 5.4 g (76%)) was obtained as a colorless oil, bp 145—150° (bath temp.)/4 mmHg. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 1695 (carbamate), 1650 (sh), 970 (*trans*-olefin). NMR (8% $CDCl_3$) τ: 8.74 (3H, t, $J=7.5$ Hz, $OCH_2C\underline{H}_3$), 7.14 (3H, s, $N-CH_3$), 6.76 (2H, t, $J=6.8$ Hz, $-CH_2N\langle$), 6.50 (2H, t, $J=5.6$ Hz, $-CH_2Cl$), 5.92 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 4.66 (2H, m, -CH=CH-). Mass Spectrum *m/e*: 263, 261 (M^+) (1:3). *Anal.* Calcd. for $C_{13}H_{24}O_2NCl$: C, 59.64; H, 9.24; N, 5.35. Found: C, 59.31; H, 9.08; N, 5.02.

Transannular Cyclization of VIII, IX, XII, XIII, XVII (Formation of 1-Azabicyclo[5.3.0]decane (XVI))——1) From VIII: A solution of VIII (220 mg) in 10% HCl (7 ml) was refluxed for 10 hr and then evaporated. The residue was made alkaline with 10% NaOH and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was distilled to give XVI (125 mg (73%)) as a colorless oil, bp 95—100° (bath temp.)/18 mmHg.

Picrate: Yellow needles, mp 216—217° (EtOH) (lit.[16] 215—216°). *Anal.* Calcd. for $C_{15}H_{20}O_7N_4$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.64; H, 5.44; N, 15.23.

2) From IX: A solution of IX (170 mg) in 10% HCl (5 ml) was refluxed for 10 hr. The reaction mixture was treated in the same procedure as that described in 1) to give XVI (41 mg (31%)) as a colorless oil, bp 95—100° (bath temp.)/18 mmHg, which was identical with XVI obtained in 1) in IR spectra and mixed mp of their picrates.

3) From XII: A solution of XII (180 mg) in conc. HCl (2.5 ml) and 60% AcOH (3 ml) was heated in a sealed tube at 150—160° for 10 hr. The reaction mixture was treated in the same procedure as that described in 1) to give XVI (98 mg (82%)) as a colorless oil, bp 95—100° (bath temp.)/18 mmHg, which was identical with XVI obtained in 1) in IR spectra and mixed mp of their picrates.

4) From XIII: A solution of XIII (447 mg) in conc. HCl (6 ml) and 60% AcOH (7.5 ml) was heated in a sealed tube at 150—160° for 10 hr. The reaction mixture was treated in the same procedure as that described in 1) to give XVI (77 mg (26%)) as a colorless oil, bp 95—100° (bath temp.)/18 mmHg, which was identical with XVI obtained in 1) in IR spectra and mixed mp of their picrates.

5) Hofmann–Löffler Reaction of XVII: To a solution of the hydrochloride (225 mg) of XVII in H_2O (1.5 ml) was added 10% NaOCl (0.9 ml) with stirring and under cooling. The reaction mixture was stirred for 1 hr and extracted with ether. The extract was dried and evaporated to give 1-chloro-1,2,3,4,5,6,7,8,9,10-decahydroazecine (XVIII, 170 mg), which was homogeneous in thin layer chromatography on silica gel. A solution of the crude N-chloride (XVIII, 170 mg) in conc. H_2SO_4 was irradiated with UV lamp in N_2 atmosphere for 10 hr below 10°. The reaction mixture was poured on ice and the solution was made alkaline with 10% NaOH and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was distilled to give XVI (50 mg (30%)) as colorless oil, bp 95—100° (bath temp.)/18 mmHg, which was identical with XVI obtained in 1) in IR spectra and mixed mp of their picrates.

1,2,3,4,5,6,7,8,9,10-Decahydroazecine (XVII)——1) From XIX: A solution of XIX (200 mg) in 10% HCl (7 ml) was heated in a sealed tube at 150—160° for 10 hr. The reaction mixture was evaporated and the residue was made alkaline with 10% NaOH and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was distilled to give XVII (130 mg (85%)) as a colorless oil, bp 90—100° (bath temp.)/18 mmHg. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 3300 (NH).

Picrate: Yellow needles, mp 192—193° (EtOH). *Anal.* Calcd. for $C_{15}H_{22}O_7N_4$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.68; H, 6.08; N, 14.80.

2) From XX: A solution of XX (220 mg) in conc. HCl (3 ml) and 60% AcOH (3 ml) was heated in a sealed tube at 150—160° for 10 hr. The reaction mixture was treated in the same procedure as that described above to give XVII (120 mg (81%)) as a colorless oil, bp 90—100° (bath temp.)/18 mmHg, which was identical with XVII obtained above in IR spectra and mixed mp of their picrates.

1-Acetyl-1,2,3,4,5,6,7,8,9,10-decahydroazecine (XIX)——Compound (VIII, 100 mg) was hydrogenated in EtOH (5 ml) over 5% Pd-C (200 mg) at atmospheric pressure and room temperature. After the theoretical amount of H_2 was uptaken during 3 hr, the catalyst was filtered off and the filtrate was evaporated. To the residue was added 10% NaOH and the mixture was extracted with ether. The extract was washed with

H_2O, dried and evaporated. The residue was distilled to give XIX (86 mg (86%)) as a colorless oil, bp 105—110° (bath temp.)/3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1640 (amide).

Ethyl 1,2,3,4,5,6,7,8,9,10-Decahydroazecine-1-carboxylate (XX)——Compound (XII, 750 mg) was hydrogenated in EtOH (25 ml) over 5% Pd-C (350 mg) at atmospheric pressure and room temperature. After the theoretical amount of H_2 was uptaken during 4 hr, the reaction mixture was treated in the same procedure as that for XIX to give XX (720 mg (95%)) as a colorless oil, bp 105—110° (bath temp.)/3 mmHg. IR $\nu_{max}^{liq.}$cm^{-1}: 1700 (carbamate).

1,2,3,4,5,6,7,8,9,10-Decahydro-1-methylazecine (XXI)——1) From XVII: A solution of XVII (130 mg), 37% HCHO (200 mg), and 80% HCO_2H (200 mg) was heated at 80—90° for 8 hr and then evaporated. The residue was made alkaline with 10% NaOH and extracted with ether. The extract was washed with H_2O, dried and evaporated. The residue was distilled to give XXI (105 mg (74%)) as a colorless oil, bp 80—90° (bath temp.)/18 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 2800 (N-CH_3).

Picrate: Yellow needles, mp 188—189° (lit.[18] 188—189°). The product (XXI) was identified with an authentic specimen[18] by IR spectra and mixed mp of their picrates.

2) From I: Compound (I, 100 mg) was hydrogenated in EtOH (5 ml) over 5% Pd-C (200 mg) at atmospheric pressure and room temperature. After the theoretical amount of H_2 was uptaken during 2 hr, the reaction mixture was treated in the same procedure as that for XIX to give XXI (80 mg (79%)) as a colorless oil, bp 80—90° (bath temp.)/18 mmHg, which was identical with XXI obtained above in IR spectra and mixed mp of their picrates.

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