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Studies on 1-Azabicyclo Compounds. XVIII.[1] Synthesis of Fourteen-membered Ring Diamine, 1,8-Dimethyl-1,8-diazacyclotetradecane, and Related Compounds from Perhydrodipyrido[1,2-*a*: 1′,2′-*d*]-pyrazine *via* Ten-membered Ring Diamine, 2-Methyl-perhydro-2*H*-pyrido[2,1-*c*]-2,9-diazecine[2]

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Oxidation of the *anti*- and *syn*-diamine (IX and X) with mercuric acetate gave the enaminolactam (XII). Treatment of the methiodides (XIII, XVIII, and XIX) with lithium in liquid ammonia afforded the ten-membered ring aminolactam (XX) in an excellent yield, which was reduced to the ten-membered ring diamine (XXI). Hofmann degradation of the carbamate (XXIII) derived from XXI provided the fourteen-membered ring aminocarbamate (XXVII) and the oxazolidone (XXVIII), which were converted to the fourteen-membered ring diamine (XXX) and the hydroxydiamine (XXXI), respectively.

In the previous papers of this series, we reported that the Birch reduction of 10-carbamoyl-5-methyloctahydroquinolizinium iodide[4] (I) and 5-methyl-1-oxoperhydropyrido[1,2-*a*]-pyrazinium iodide[5] (V), the latter of which has a 10-substituted carbamoyl group in the octahydroquinolizine ring in the former molecule, results in selective cleavage of the central C-N bond to afford 6-carbamoyl-1-methyldecahydroazecine[4] (II) and 1-methyldecahydro-1,4-diazecin-5-one[5] (VI), respectively, in an excellent yield. The latter methiodide (V) has been derived from the enaminolactam[5] (IV), obtained by oxidation of octahydropyrido-[1,2-*a*]pyrazine (III) with mercuric acetate. This paper describes further application of this method to the synthesis of a ten-membered ring diamine (XXI), and its transformation into a fourteen-membered ring diamine (XXX).

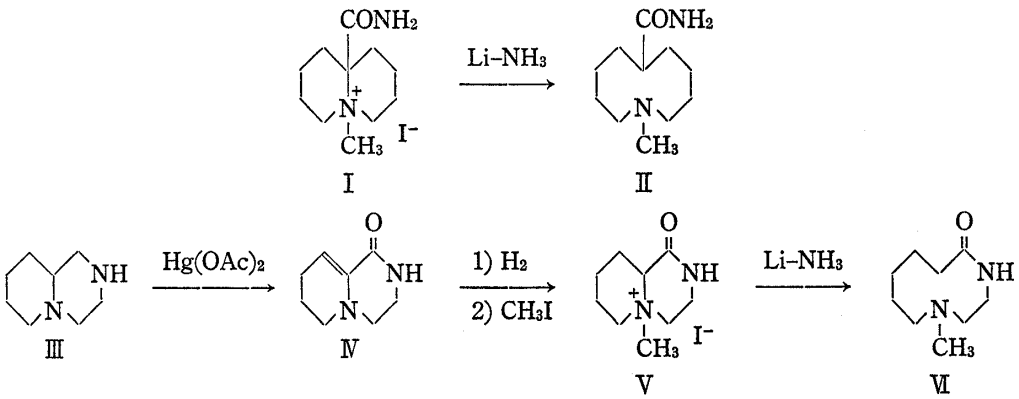

Chart 1

1) Part XVII: Y. Arata, Y. Oda, S. Yasuda, and M. Hanaoka, *Chem. Pharm. Bull.* (Tokyo), **21**, 2672 (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) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1363 (1969).
5) Y. Arata and Y. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 1248 (1973).

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According to the method of Winterfeld, *et al.*,[6] *anti*- and *syn*-perhydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazine (IX and X) were derived from ethyl 2-piperidinecarboxylate[7] *via anti*- and *syn*-perhydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazine-6,12-dione (VII and VIII), respectively. It has already been reported that oxidation of IX or X with mercuric acetate yields the enamine[6] (XI), but the enaminolactam (XII) might be produced by this oxidation, judging from the above-mentioned result with 2-azaoctahydroquinolizine[5] (III). Under the same condition as that reported, the *anti*-diamine (IX) was oxidized with mercuric acetate in 5% aqueous acetic acid to give in 37% yield an oily product (XII), which formed a crystalline methiodide (XIII), $C_{13}H_{21}ON_2I$, of mp 162—164°. The product showed bands at 1655 (enamine) and 1619 cm^{-1} (lactam) in its infrared (IR) spectrum, exhibited an olefinic signal at 3.95 τ (1H, t, J=5 Hz) in its nuclear magnetic resonance (NMR) spectrum, and featured a molecular ion peak at *m/e* 206 in its mass spectrum. Its perchlorate (XIV) (IR: 1665 cm^{-1} (lactam and iminium)) reacted with potassium cyanide to produce in 62% yield the nitrile (XV) (mp

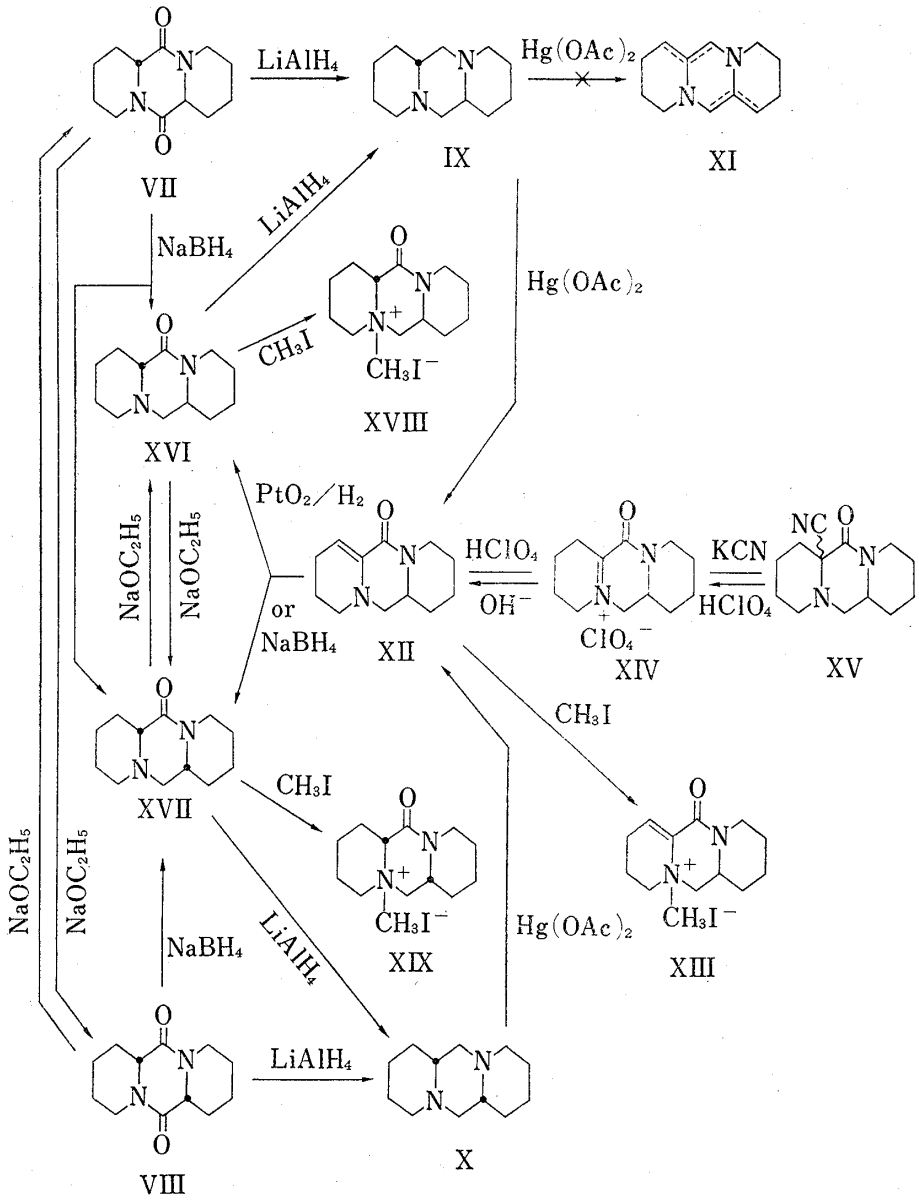

Chart 2

6) K. Winterfeld and H. Rath, *Arch. Pharm.*, **293**, 141 (1960).
7) R. Willstätter, *Ber.*, **29**, 389 (1896).

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146—148°, IR: 2210 cm^{-1} (CN)), which, on neutralization with perchloric acid, reverted to the perchlorate (XIV). Based on these evidences, the structure of the oxidation product (XII) was established as 1,2,3,4,6,8,9,10,12,12*a*-decahydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazin-6-one. In contrast with Winterfeld's result, the enamine (XI) could not be obtained from this reaction. Similar oxidation of the *syn*-diamine (X) with mercuric acetate also gave the same enaminolactam (XII) in 23% yield.

Catalytic reduction of XII over the Adams catalyst afforded two isomeric lactams (XVI and XVII) in 11% and 79% yield, which formed the methiodides (XVIII and XIX) of mp 248—249° and mp 240—241°, respectively. The lactam (XVII) would be predominantly obtained by the attack of hydrogen from the less hindered α-side in the conformation (XII′) of XII shown in Fig. 1. On the other hand, reduction of XII with sodium borohydride yielded quantitatively both lactams (XVI and XVII) in the 1:1 ratio. The lactam (XVI and XVII) were reduced with lithium aluminum hydride to the known *anti*- and *syn*-diamine (IX and X), respectively, in an excellent yield. Thus, configurations of XVI and XVII were confirmed unequivocally as depicted.

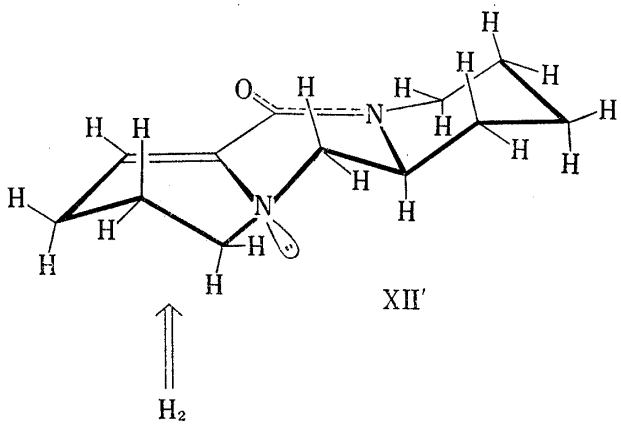

Fig. 1

The lactams (XVI and XVII) were also obtained by the following method. Sodium borohydride reduction of the *syn*-dilactam (VIII), readily soluble in ethanol, in ethanolic solution at room temperature gave the *syn*-lactam (XVII) in 68% yield, whereas the reduction of the *anti*-dilactam (VII), sparing soluble in ethanol, in boiling ethanol caused partial isomerization to give both *anti*- and *syn*-lactams (XVI and XVII) in 19% and 30% yield, respectively. Indeed, not only both *anti*- and *syn*-dilactams (VII and VIII) but also both *anti*- and *syn*-lactams (XVI and XVII) partially isomerized with each other into the corresponding isomers, on being heated in ethanolic solution containing sodium ethoxide.

Treatment of the enaminolactam methiodide (XIII) with lithium in liquid ammonia effected cleavage of the central C-N bond and hydrogenation of the double bond, giving the expected ten-membered ring aminolactam (XX), mp 154°, in 40% yield. Similar treatment of *anti*- and *syn*-aminolactam methiodide (XVIII and XIX) readily afforded the aminolactam (XX) in 89% and 90% yield, respectively. The IR spectrum of XX showed bands at 2800 (N-CH_3) and 1621 cm^{-1} (lactam) and its NMR spectrum exhibited an N-methyl signal at 7.78 τ as a singlet and no C-methyl signals. Thus, the structure of XX was assigned as 2-methylperhydro-2*H*-pyrido[2,1-*c*]-2,9-diazecin-8-one. The aminolactam (XX) was further reduced with lithium aluminum hydride to afford the ten-membered ring diamine (XXI) (dipicrate, mp 200—203°). When oxidized with mercuric acetate in aqueous acetic acid, XXI gave a complicated mixture, and not the expected enaminolactam (XXII).

Reaction of the diamine (XXI) with ethyl chloroformate[8] afforded three kinds of product (XXIII, XXIV, and XXV) in 58, 8, and 13% yield, respectively. The major product (XXIII) formed a crystalline methiodide (XXVI), $C_{16}H_{31}O_2N_2I$, of mp 174—175° and the indicated structure of XXIII was confirmed from spectral evidences; IR: 1695 cm^{-1} (carbamate), NMR τ: 8.75 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 5.90 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), Mass Spectrum *m/e*: 268 (M^+). The minor neutral products (XXIV and XXV) were identified as ethyl 2-(N-ethoxy carbonyl-N-methylaminomethyl)piperidine-1-carboxylate and ethyl 2-[N-ethoxy-

8) G. Krais and K. Nador, *Tetrahedron Letters*, **1971**, 57.

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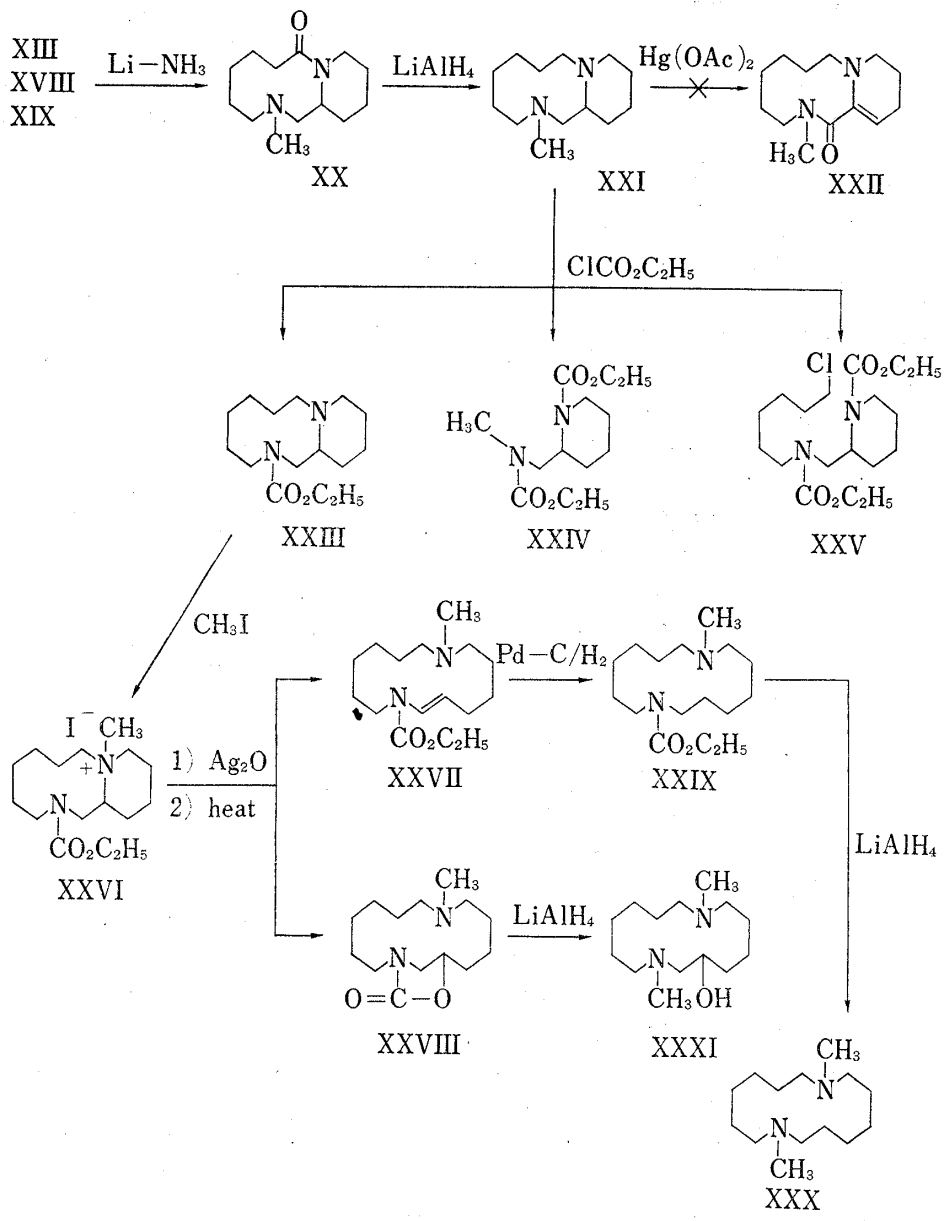

Chart 3

carbonyl-N-(6-chlorohexyl)aminomethyl]piperidine-1-carboxylate, respectively, from their spectral data (see Experimental).

Treatment of the methiodide (XXVI) with silver oxide and subsequent heating of the resulting methohydroxide at 160—170° provided the aminocarbamate (XXVII) and the amino-oxazolidone (XXVIII) in 33% and 32% yield, respectively. The former product (XXVII) showed bands at 2780 (N-CH_3), 1655 (C=C), and 1690 cm^{-1} (carbamate) in its IR spectrum, exhibited signals at 7.76 (3H, s, N-CH_3), 3.28 (1H, d, J=14 Hz, N-C<u>H</u>=CH), 5.10 (1H, d-t, J=14; 7 Hz, N-CH=C<u>H</u>CH_2), 8.73 (3H, t, J=7 Hz, CO_2CH_2C<u>H</u>$_3$), 5.83 τ (2H, q, J=7 Hz, CO_2C<u>H</u>$_2CH_3$), and no other C-methyl signals in its NMR spectrum, and featured a molecular ion peak at m/e 282 in its mass spectrum. Thus, the product (XXVII) was found to be the fourteen-membered ring amine, ethyl 8-methyl-1,8-diazacyclo-2-tetradecene-1-carboxylate.

The oxazolidone structure of the latter product (XXVIII) was determined from the evidences that it showed bands at 2800 (N-CH_3) and 1735 cm^{-1} (oxazolidone) in its IR spectrum and exhibited signals at 7.95 (3H, s, N-CH_3), 6.58 (2H, d, J=5 Hz, N-C<u>H</u>$_2$CH-O), and

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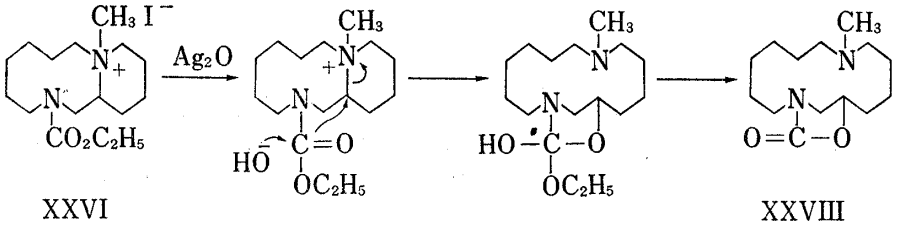
5.45 τ (1H, m, $NCH_2C\underline{H}$-O) in its NMR spectrum. The presence of an oxazolidone ring was further confirmed by the decoupling experiment; a doublet at 6.58 τ collapsed to a singlet on double irradiation at 5.45 τ. As the amine (XXVII) failed to be converted to XXVIII on treatment with alkali or under the Hofmann degradation condition, the formation of XXVIII probably proceeded through the displacement of the quaternary base by the carbamate group, as illustrated in Chart 4.



XXVI XXVIII

Chart 4

The fourteen-membered ring amine (XXVII) was reduced over palladium on charcoal to afford in 73% yield the dihydro derivative (XXIX) (picrolonate, mp 162.5—163.5°), which, on further reduction with lithium aluminum hydride, provided the fourteen-membered ring diamine, 1,8-dimethyl-1,8-diazacyclotetradecane (XXX), mp 42—45°, (dipicrate, mp 249—251°) in a quantitative yield. In agreement with the structure XXX, the product showed a signal due to two methyls at 7.89 τ as a singlet and that due to four N-methylenes at 7.73 τ as a triplet-like in its NMR spectrum, and exhibited a molecular ion peak at *m/e* 226 in its mass spectrum.

The oxazolidone (XXVIII) was reduced with lithium aluminum hydride to afford the fourteen-membered ring hydroxydiamine, 3-hydroxy-1,8-dimethyl-1,8-diazacyclotetradecane (XXXI), mp 75—76°, in a quantitative yield. Its structure was verified from spectral evidences: IR: 3270 cm^{-1} (OH), NMR τ: 7.83, 7.75 (each 3H, s, $N\text{-}CH_3 \times 2$), Mass Spectrum *m/e*: 242 (M^+). The hydroxydiamine (XXXI) formed a normal dipicrate of mp 241—243° (decomp). instead of the transannular cyclization product as seen in the picrate of 6-hydroxy-1-methyl-decahydroazecine.[9]

Thus, the fourteen-membered ring diamine (XXX) was successfully synthesized from the tricyclic diamine (IX or X) *via* the ten-membered ring diamine (XXI).

Experimental[10]

***anti*-Perhydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazine (IX)**——1) From VII: According to the method of Winterfeld, *et al.*,[6] IX was obtained from VII as colorless scales, mp 97° (acetone, lit.[6] mp 96.5°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2780, 2750, 2670 (Bohlmann bands).

2) From XVI: To a suspension of $LiAlH_4$ (700 mg) in anhyd. ether (40 ml) was added dropwise a solution of XVI (300 mg) in anhyd. ether (10 ml) with stirring. The reaction mixture was refluxed for 4 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 recrystallized from acetone to give IX (260 mg (quantitative)) as colorless scales, mp 97°, which was identified with IX obtained in 1) by IR spectra and mixed mp.

9) The picrate of this compound was found to be 5-methyloctahydroquinolizinium picrate (A.J. Sisti and D.L. Lohner, *J. Org. Chem.*, **32**, 2026 (1967); Y. Arata and T. Shioda, *Chem. Pharm. Bull.* (Tokyo), **20**, 783 (1972)).

10) All melthing points were measured with a Yanagimoto Micro Melthing 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. Kieselgel GF_{254} (Merck) or Aluminiumoxid GF_{254} (Merck) was used for thin-layer chromatography (TLC). Gas-liquid chromatography (GC) was carried on GC-3AH, Shimadzu Co., employing SE-30 column (column temp. 160°).

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***syn*-Perhydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazine (X)**——1) From VIII: According to the method of Winterfeld, *et al.*,[6] X was obtained from VIII as colorless needles, mp 56—57° (acetone, lit.[6] mp 57°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2760, 2670 (Bohlmann bands).

2) From XVII: To a suspension of $LiAlH_4$ (650 mg) in anhyd. ether (10 ml) was added dropwise a solution of XVII (250 mg) in anhyd. ether (10 ml) with stirring. The reaction mixture was refluxed for 4 hr and treated in the same procedure as that for IX from XVI to give X (192 mg (84%)) as a colorless oil, bp 125—130° (bath temp.)/3 mmHg, which soon solidified and was recrystallized from acetone to give colorless needles, mp 56—57°. The product was identified with X obtained in 1) by IR spectra and mixed mp.

1,2,3,4,6,8,9,10,12,12*a*-Decahydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazin-6-one (XII)——1) From IX: To a solution of $Hg(OAc)_2$ (30 g) in 5% aq. AcOH (300 ml) was added IX (2.3 g) with stirring in a stream of N_2 at 60°. After the reaction mixture was stirred at 60° for 7 hr, the precipitated $Hg_2(OAc)_2$ was filtered and washed with 5% aq. AcOH. H_2S was bubbled into the combined filtrate and washings. The precipitated HgS was separated by the centrifuge. The supernatant liquid was evaporated under 60°, and the residue was made alkaline with 10% NaOH and extracted with ether. The extract was dried and evaporated, and the residue was distilled to give XII (0.9 g (37%)) as a pale yellow oil, bp 150—160° (bath temp.)/0.1 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1655 (C=C), 1619 (lactam). NMR (7% $CDCl_3$) τ: 5.30 (1H, br-d, J=12 Hz, C_4-H_{eq}), 3.95 (1H, t, J=5 Hz, CH=C-). Mass Spectrum *m/e*: 206 (M^+).

Methiodide (XIII): colorless scales, mp 162—164° (EtOH). *Anal.* Calcd. for $C_{13}H_{21}ON_2I$: C, 44.83; H, 6.09; N, 8.05. Found: C, 44.83; H, 6.14; N, 7.69.

Perchlorate (XIV): colorless needles, mp 116—117.5° (AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1665 (iminium and lactam). *Anal.* Calcd. for $C_{12}H_{19}O_5N_2Cl$: C, 46.96; H, 6.24; N, 9.13. Found: 47.06; H, 6.23; N, 9.05.

Picrate: yellow needles, mp 175—178° (EtOH). *Anal.* Calcd. for $C_{18}H_{21}O_8N_5$: C, 49.65; H, 4.86; N, 16.09. Found: C, 49.26; H, 4.83; N, 15.46.

2) From X: To a solution of $Hg(OAc)_2$ (30 g) in 5% aq. AcOH (300 ml) was added X (2.0 g) with stirring in a stream of N_2 at 60°. The reaction mixture was treated in the same procedure as that described in 1) to give XII (0.5 g (23%)) as a pale yellow oil, which was identified with XII obtained in 1) by IR spectra.

6*a*-Cyanoperhydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazin-6-one (XV)——A solution of XIV (150 mg) and KCN (100 mg) in MeOH (10 ml) was refluxed for 8 hr and then evaporated. To the residue was added H_2O and the mixture was extracted with benzene. The extract was dried and evaporated. The residue was recrystallized from *n*-hexane–benzene to give XV (70 mg (62%)) as colorless needles, mp 146—148°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (CN), 1658 (lactam). *Anal.* Calcd. for $C_{13}H_{19}ON_3$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.95; H, 8.12; N, 18.29.

***anti*-and *syn*-Perhydrodipyrido[1,2-*a*: 1′,2′-*d*]pyrazin-6-one (XVI and XVII)**——1) Catalytic Reduction of XII: Compound (XII, 1.1 g) was hydrogenated in EtOH (20 ml) over PtO_2 (200 mg) at atmospheric pressure and room temp. After the theoretical amount of H_2 was uptaken during 1 hr, the catalyst was filtered off and the filtrate was evaporated. The residue was distilled to give a colorless oil (1.1 g), bp 155° (bath temp.)/3 mmHg, which showed two spots (Rf=0.50 and 0.38) on TLC using silica gel and acetone–*n*-hexane (1:2) as solvent. The product was chromatographed on silica gel (55 g) with acetone–*n*-hexane (1:2) as eluent. The first fraction was distilled to give XVII (880 mg (79%)) as a colorless oil, bp 155° (bath temp.)/3 mmHg, which was homogeneous in TLC (Rf=0.50) and GC (retention time=6.6 min). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2750 (Bohlmann bands), 1625 (lactam).

Methiodide (XIX): colorless needles, mp 240—241° (EtOH). *Anal.* Calcd. for $C_{13}H_{23}ON_2I$: C, 44.58; H, 6.62; N, 8.00. Found: C, 44.51; H, 6.75; N, 8.16.

The second fraction was distilled to give XVI (120 mg (11%)) as a colorless oil, bp 155° (bath temp.)/3 mmHg, which solidified on standing. The product was recrystallized from *n*-hexane to give colorless prisms, which were homogeneous in TLC (Rf=0.38) and GC (retention time=7.6 min). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2750 (Bohlmann bands), 1630 (lactam). *Anal.* Calcd. for $C_{12}H_{20}ON_2$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.43; H, 9.70; N, 13.12.

Methiodide (XVIII): colorless needles, mp 248—249° (EtOH). *Anal.* Calcd. for $C_{13}H_{23}ON_2I$: C, 44.58; H, 6.62; N, 8.00. Found: C, 44.34; H, 6.62; N, 8.30.

2) Reduction of XII with $NaBH_4$: To a solution of the hydrochloride prepared from XII (0.36 g) in MeOH (12 ml) was added $NaBH_4$ (1 g) in small portions. The reaction mixture was stirred at room temp. for 20 hr. The precipitate was filtered and washed with ether. The filtrate and washings were combined and evaporated. To the residue was added H_2O and the mixture was extracted with ether. The extract was dried and evaporated to give an oil, which was chromatographed on silica gel and treated in the same procedure as that described in 1) to give XVI (180 mg (quantitative)) and XVII (180 mg (quantitative)). These products were identified with the corresponding lactams (XVI and XVII) obtained in 1) by IR spectra and TLC.

3) Reduction of VII with $NaBH_4$: To a suspension of VII (10 g) in EtOH (250 ml) was added with stirring $NaBH_4$ (7.5 g) in small portions. The reaction mixture was refluxed for 5 days, acidified with 5% HCl and evaporated. To the residue was added H_2O and the mixture was extracted with ether. The extract was dried and evaporated to give the starting material (VII, 1.0 g), which was identified with the authentic specimen by IR spectra. The aq. layer was made alkaline with 10% NaOH and extracted with

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ether. The extract was dried and evaporated. The residue was distilled to give a colorless oil (4.2 g), bp 155—160° (bath temp.)/3 mmHg, which was chromatographed on silica gel and treated in the same procedure as that described in 1) to give XVI (1.6 g (19% based on consumed VII)) and XVII (2.5 g (30% based on consumed VII)). These products were identified with the corresponding lactams (XVI and XVII) obtained in 1) by IR spectra and TLC.

4) Reduction of VIII with $NaBH_4$: To a solution of VIII (1.1 g) in EtOH (30 ml) was added with stirring $NaBH_4$ (600 mg) in small portions. The reaction mixture was stirred for 8 hr at room temp., acidified with 5% HCl, and evaporated. The residue was made alkaline with 10% NaOH and extracted with ether. The extract was dried and evaporated. The residue was distilled to give XVII (700 mg (68%)) as a colorless oil, bp 155° (bath temp.)/3 mmHg, which was identified with XVII obtained in 1) by IR spectra and TLC.

Isomerization of VII and VIII——1) From VII: To a solution of Na (150 mg) in abs. EtOH (20 ml) was added VII (1.0 g) and the reaction mixture was refluxed for 40 hr. After the mixture was cooled and the precipitated crystals were collected by filtration to give VII (355 mg (36%)), which was identified with that obtained above by IR spectra and TLC. The filtrate was evaporated and H_2O was added to the residue. The mixture was extracted with $CHCl_3$. The extract was dried and evaporated to give a mixture of VII and VIII (440 mg) which was fractionally recrystallized several times from EtOH to give VIII (25 mg (3%)), identified with that obtained above by IR spectra and TLC.

2) From VIII: To a solution of Na (150 mg) in abs. EtOH (20 ml) was added VIII (1.0 g), and the reaction mixture was refluxed for 40 hr and treated in the same procedure as that described in 1) to give VII (375 mg (38%)), VIII (38 mg (4%)), and a mixture of VII and VIII (420 mg (42%)).

Isomerization of XVI and XVII——1) From XVI: A solution of Na (90 mg) in abs. EtOH (5 ml) was added XVI (80 mg) and the reaction mixture was refluxed for 40 hr. The mixture was acidified with 5% HCl and evaporated. The residue was made alkaline with 10% NaOH and extracted with ether. The extract was dried and evaporated. The residue was distilled to give a mixture of XVI and XVII (65 mg (81%)) as a colorless oil, bp 155° (bath temp.)/3 mmHg, in the ratio of 5:2 by GC.

2) From XVII: Compound (XVII, 80 mg) was treated in the same procedure as that described in 1) to give a mixture of XVI and XVII (65 mg (81%)) in the ratio of 2:1 by GC.

2-Methylperhydro-2*H*-pyrido[2,1-*c*]-2,9-diazecin-8-one (XX)——1) From XIII: To a solution of XIII (295 mg) in liq. NH_3 (200 ml) was added Li (80 mg) in small portions. The reaction mixture was stirred for 10 min and then evaporated. To the residue was added H_2O and the mixture was extracted with ether. The extract was dried and evaporated. The residue was recrystallized from *n*-hexane to give XX (76 mg (40%)) as colorless needles, mp 154°. IR ν_{max}^{KBr} cm^{-1}: 2800 (NCH_3), 1621 (lactam). NMR (6% $CDCl_3$) τ: 7.78 (3H, s, NCH_3). Mass Spectrum *m/e*: 224 (M^+). *Anal.* Calcd. for $C_{13}H_{24}ON_2$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.80; H, 10.84; N, 12.50.

2) From XVIII: To a solution of XVIII (319 mg) in liq. NH_3 (200 ml) was added Li (80 mg) in small portions. The reaction mixture was treated in the same procedure as that described in 1) to give XX (184 mg (89%)), which was identified with XX obtained in 1) by IR spectra and mixed mp.

3) From XIX: To a solution of XIX (500 mg) in liq. NH_3 (300 ml) was added Li (200 mg) in small portions. The reaction mixture was treated in the same procedure as that described in 1) to give XX (300 mg (90%)), which was identified with XX obtained in 1) by IR spectra and mixed mp.

2-Methylperhydro-2*H*-pyrido[2,1-*c*]-2,9-diazecine (XXI)——To a suspension of $LiAlH_4$ (6.5 g) in anhyd. ether (100 ml) was added with stirring XVII (3.0 g) in small portions. The reaction mixture was refluxed 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 XXI (2.4 g (86%)) as a colorless oil, bp 124° (bath temp.)/3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 2800 (NCH_3).

Dipicrate: yellow fine crystals, mp 200—203° (MeOH). *Anal.* Calcd. for $C_{25}H_{32}O_{14}N_8$: C, 44.91; H, 4.82; N, 16.72. Found: C, 44.57; H, 5.13; N, 16.71.

Reaction of XXI with Ethyl Chloroformate (Formation of XXIII, XXIV, and XXV)——To a solution of XXI (1.95 g) in abs. benzene (60 ml) was added ethyl chloroformate (4.1 g). The reaction mixture was refluxed for 5 hr and evaporated. To the residue was added 5% HCl and the mixture was extracted with ether. The extract was dried and evaporated. The residue showed two spots (Rf=0.91 and 0.87) on TLC using silica gel and $CHCl_3$–ether (2:1) as solvent and was fractionally distilled to give two products. The lower boiling fraction was ethyl 2-(N-ethoxycarbonyl-N-methylaminomethyl)piperidine-1-carboxylate (XXIV, 200 mg (8%)) as a colorless oil, bp 130—140° (bath temp.)/0.1 mmHg, which was homogeneous in TLC (Rf=0.87) and showed a negative Beilstein test. IR $\nu_{max}^{liq.}$ cm^{-1}: 1695 (carbamate). NMR (7% $CDCl_3$) τ: 8.80 (6H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3\times2$), 7.12 (3H, s, NCH_3), 5.90 (4H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3\times2$). Mass Spectrum *m/e*: 272 (M^+), 156 (base peak).

The higher boiling fraction was ethyl 2-[N-ethoxycarbonyl-N-(6-chlorohexyl)aminomethyl]piperidine-1-carboxylate (XXV, 440 mg (13%)) as a colorless oil, bp 180—190° (bath temp.)/0.1 mmHg, which was homogeneous in TLC (Rf=0.91) and showed a positive Beilstein test. IR $\nu_{max}^{liq.}$ cm^{-1}: 1695 (carbamate). NMR (7% $CDCl_3$) τ: 8.80 (6H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3\times2$), 6.50 (2H, t, J=6 Hz, CH_2Cl), 5.93 (4H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3\times2$). Mass Spectrum *m/e*: 378, 376 (M^+, 1:3), 156 (base peak).

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The above HCl-layer was made alkaline with 10% NaOH and extracted with ether. The extract was dried and evaporated. The residue was distilled to give ethyl perhydro-2*H*-pyrido[2,1-*c*]-2,9-diazecine-2-carboxylate (XXIII, 1.44 g (58%)) as a colorless oil, bp 160—165° (bath temp.)/3 mmHg, which showed a negative Beilstein test. IR $\nu_{max}^{liq.}$ cm^{-1}: 1695 (carbamate). NMR (7% $CDCl_3$) τ: 8.75 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 6.60 (4H, br, $CH_2NCO_2\times2$), 5.90 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$). Mass Spectrum *m/e*: 268 (M^+).

Methiodide (XXVI): colorless leaflets, mp 174—175° (EtOH). *Anal.* Calcd. for $C_{16}H_{31}O_2N_2I$: C, 46.83; H, 7.62; N, 6.83. Found: C, 46.64; H, 7.77; N, 6.62.

Hofmann Degradation of XXVI (Formation of XXVII and XXVIII)——To a solution of XXVI (2.0 g) in H_2O (50 ml) was added Ag_2O (10 g) and the mixture was stirred at room temp. for 6 hr. The precipitate was filtered off and the filtrate was evaporated. The residue was pyrolyzed at 170—180° for 1 hr. To the reaction mixture was added H_2O and extracted with ether. The extract was dried and evaporated. The residue was distilled to give a colorless oil (950 mg), bp 160—170° (bath temp.)/3 mmHg, which showed two spots (Rf=0.80 and 0.28) on TLC using alumina and ether–*n*-hexane (1: 1) as solvent. The mixture was chromatographed on alumina with ether–*n*-hexane (1: 1) as eluent.

The first fraction was distilled to give ethyl 8-methyl-1,8-diazacyclo-2-tetradecene-1-carboxylate (XXVII, 450 mg (33%)) as a colorless oil, bp 165—170° (bath temp.)/3 mmHg, which was homogeneous in TLC (Rf=0.80). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780 (NCH_3), 1690 (carbamate), 1655 (C=C). NMR (8% $CDCl_3$) τ: 8.73 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 7.76 (3H, s, NCH_3), 5.83 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.10 (1H, d-t, J=14; 7 Hz, NCH=C$\underline{H}$), 3.28 (1H, br-d, J=14 Hz, NC$\underline{H}$=CH). Mass Spectrum *m/e*: 282 (M^+).

The second fraction was recrystallized from *n*-hexane to give 8-methyl-1,8-diaza-14-oxabicyclo[11.2.1]-hexadecan-15-one (XXVIII, 400 mg (32%)) as colorless leaflets, mp 70—71°, which was homogeneous in TLC (Rf=0.28). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 (NCH_3), 1735 (oxazolidone). NMR (6% $CDCl_3$) τ: 7.95 (3H, s, NCH_3), 6.58 (2H, d, J=5 Hz, $NC\underline{H}_2CHO$), 5.45 (1H, m, $NCH_2C\underline{H}O$). Decoupling: Irradiate at 5.45→6.58 (s). Mass Spectrum *m/e*: 254 (M^+). *Anal.* Calcd. for $C_{14}H_{26}O_2N_2$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.31; H, 10.30; N, 10.93.

Ethyl 8-Methyl-1,8-diazacyclotetradecane-1-carboxylate (XXIX)——Compound (XXVII, 300 mg) was hydrogenated in EtOH (10 ml) over 3% Pd-C (200 mg) at atmospheric pressure and room temp. After the theoretical amount of H_2 was uptaken during 4 hr, the catalyst was filtered off and the filtrate was evaporated. The residue was distilled to give XXIX (220 mg (73%)) as a colorless oil, bp 165—170° (bath temp.)/3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 2800 (NCH_3), 1698 (carbamate). NMR (4% $CDCl_3$) τ: 8.68 (3H, t, J= 7 Hz, $CO_2CH_2C\underline{H}_3$), 7.77 (3H, s, NCH_3), 6.65 (4H, t-like, J=6 Hz, $CH_2NCO_2\times2$), 5.83 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$). Mass Spectrum *m/e*: 284 (M^+).

Picrolonate: yellow leaflets, mp 162.5—163.5° (EtOH). *Anal.* Calcd. for $C_{26}H_{40}O_7N_6$: C, 56.92; H, 7.35; N, 15.32. Found: C, 57.12; H, 7.51; N, 15.47.

1,8-Dimethyl-1,8-diazacyclotetradecane (XXX)——To a suspension of $LiAlH_4$ (300 mg) in anhyd. ether (20 ml) was added dropwise a solution of XXIX (220 mg) in anhyd. ether (5 ml) with stirring. The reaction mixture was stirred at room temp. 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 XXX (170 mg (quantitative)) as a colorless oil, bp 125—130° (bath temp.)/ 3 mmHg, which solidified on standing, mp 42—45°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780 (NCH_3). NMR (7% $CDCl_3$) τ: 8.62 (16H, br, $CH_2\times8$), 7.89 (6H, s, $NCH_3\times2$), 7.73 (8H, t-like, J=5 Hz, $NCH_2\times4$). Mass Spectrum *m/e*: 226 (M^+). *Anal.* Calcd. for $C_{14}H_{30}N_2$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.57; H, 13.44; N, 12.33.

Dipicrate: yellow scales, mp 249—251° (decomp.) (70% EtOH). *Anal.* Calcd. for $C_{26}H_{36}O_{14}N_8$: C, 45.61; H, 5.30; N, 16.37. Found: C, 45.96; H, 5.71; N, 16.22.

3-Hydroxy-1,8-dimethyl-1,8-diazacyclotetradecane (XXXI)——To a suspension of $LiAlH_4$ (300 mg) in anhyd. ether (20 ml) was added dropwise a solution of XXVIII (210 mg) in anhyd. ether (5 ml) with stirring. The reaction mixture was stirred at room temp. for 5 hr, and treated in the same procedure as that described for XXX. The crude product was recrystallized from petr. ether to give XXXI (200 mg (quantitative)) as colorless leaflets, mp 75—76°. IR ν_{max}^{KBr} cm^{-1}: 3270 (OH), 2780 (NCH_3). NMR (6% $CDCl_3$) τ: 7.83 (3H, s, NCH_3), 7.75 (3H, s, NCH_3), 7.25 (1H, s, OH, disappeared by addition of D_2O), 6.15 (1H, m, C$\underline{H}$OH). Mass Spectrum *m/e*: 242 (M^+). *Anal.* Calcd. for $C_{13}H_{30}ON_2$: C, 69.36; H, 12.48; N, 11.56. Found: C, 69.66; H, 12.32; N, 11.76.

Dipicrate: yellow leaflets, mp 241—243° (decomp.) (70% EtOH). *Anal.* Calcd. for $C_{26}H_{36}O_{15}N_8$: C, 44.57; H, 5.18; N, 16.00. Found: C, 44.80; H, 5.18; N, 15.69.

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