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Synthesis in the Diazasteroid Group. XV.¹⁾ Syntheses of the 5,9- and 8,13-Diazasteroids²⁾

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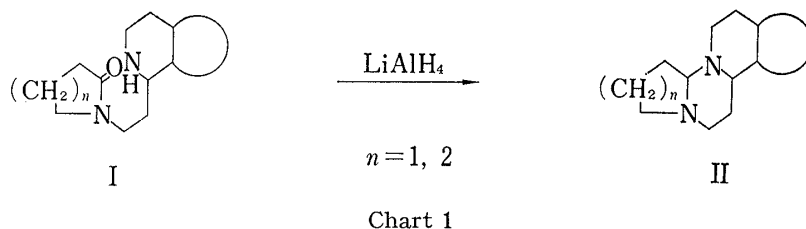
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Syntheses of 5,9- and 8,13-diazasteroids (**15**) and (**19**) employing reductive annulation with LiAlH_4 are described. The stereochemistry of **15** and **19** is discussed.

Keywords—5,9-diazasteroid; 8,13-diazasteroid; reductive annulation; phase transfer catalyst; N-alkylation of lactams; LiAlH_4 ; Pictet-Spengler reaction; Bischler-Napieralski reaction

We have had a continuing interest in the synthesis of diazasteroids with potential biological activities such as antitumor,⁴⁾ antiinflammatory,⁵⁾ and analgesic activities.⁶⁾ In particular, our attention has been devoted to syntheses of diazasteroids containing two nitrogens situated in a 1,3-relation and in a fused position. Three (8,10-,⁷⁾ 8,13-,⁸⁾ and 9,14-⁹⁾ diazasteroids (but not the 5,9-diazasteroid) have previously been synthesized by us, and the 8,13-diazasteroid exhibited antiinflammatory activity.¹⁰⁾ We now wish to report a convenient synthetic route to the 5,9- and 8,13-diazasteroids. Key features of our approach include the following.



a) Formation of the N–C–N bond was effected by reductive annulation of an intramolecular secondary amine-lactam (I) with LiAlH_4 .^{7,11)}

b) Seco-compounds (sec-amine lactam system) (I) were obtained by two routes. 1) Pictet-Spengler reaction of an amine with an acetal-lactam. 2) Bischler-Napieralski reaction of an amide prepared by the condensation of an amine with an ester-lactam.

- 1) Part XIV: K. Matoba, T. Imai, Y. Nishino, H. Takahata, Y. Hirai, and T. Yamazaki, *Chem. Pharm. Bull.*, **28**, 1810 (1980).
- 2) Presented at the 99th Meeting of the Pharmaceutical Society of Japan, Sapporo, August, 1979, Abstracts p. 285.
- 3) Location: 2630, Sugitani, Toyama 930-01, Japan.
- 4) I.Y.C. Tao and R.T. Blickenstaff, *J. Pharm. Sci.*, **67**, 283 (1978).
- 5) J.H. Burckhalter and H.N. Abramson, *J. C. S. Chem. Commun.*, **805** (1966).
- 6) U.K. Pandit, K. De Jonge, and H.O. Huisman, *Rev. Trav. Chim. Pays-Bas.*, **88**, 149 (1969).
- 7) H. Takahata, H. Okajima, M. Nagata, and T. Yamazaki, *Chem. Pharm. Bull.*, **28**, 984 (1980).
- 8) a) K. Matoba, K. Isomura, M. Nagata, T. Yamazaki, and R.N. Castle, *J. Heterocycl. Chem.*, **9**, 1359 (1972); b) T. Koizumi, Y. Yanagawa, E. Yoshii, and T. Yamazaki, *Chem. Pharm. Bull.*, **26**, 1308 (1978).
- 9) T. Yamazaki, K. Matoba, M. Yajima, M. Nagata, and R.N. Castle, *J. Heterocycl. Chem.*, **12**, 973 (1975).
- 10) K. Isomura, T. Yamazaki, M. Nagata, and K. Matoba, *Japan Kokai*, 7505400 (1975) [*C.A.*, **83**, p 105960b (1975)].
- 11) T. Yamazaki, M. Nagata, K. Matoba, H. Takahata, and R.N. Castle, *J. Heterocycl. Chem.*, **14**, 469 (1977).

c) Acetal- and ester-lactams were readily prepared by N-alkylation of lactams using a phase transfer catalyst exploited in our recent study.¹²⁾

Results and Discussion

N-Alkylation of Lactams

Mild syntheses of N-substituted lactams were readily performed by the use of a solid/liquid binary phase system containing pulverized KOH, with THF as a solvent, together with tetra-*n*-butylammonium bromide. The results are summarized in Table I. However, the reaction of the lactams (**1a, b**) with methyl β -bromopropionate proceeded in only low yield because of E₂ elimination of β -bromopropionate, and resulted in the recovery of **1a, b**. Therefore, the ester lactams (**4a, b**) were produced in moderate yields by esterification of the cyano lactams (**3a, b**) with *p*-TosOH–MeOH.

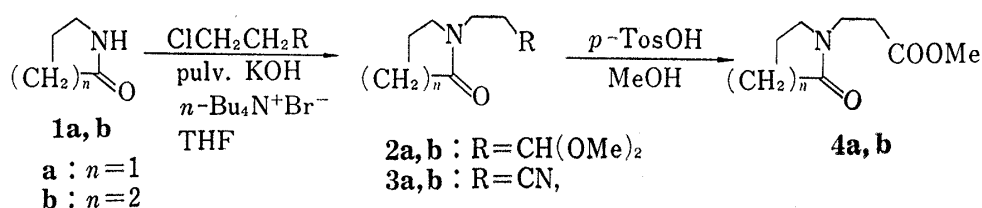


TABLE I. N-Substituted Lactams

Compd.	Yield (%)	bp (°C/mmHg)	Reaction conditions	Formula	Analysis (%)		
					Calcd (Found)	C	H M
2a	70	110/0.4	Reflux, 3 hr	C ₉ H ₁₇ NO ₃	57.73 (57.92)	9.15 (9.08)	7.48 (7.58)
2b	69	105/0.1	Reflux, 3 hr	C ₁₀ H ₁₉ NO ₃	59.67 (59.42)	9.52 (9.64)	6.96 (7.08)
3a	71	140/2 ^{a)}	Reflux, 3 hr	—	—	—	—
3b	70	147/2.5	Reflux, 3 hr	C ₈ H ₁₂ N ₂ O	63.13 (63.13)	7.95 (8.18)	8.41 (8.19)
4a	70	112/0.4 ^{b)}	Reflux, 20 hr	—	—	—	—
4b	70	125/1	Reflux, 20 hr	C ₉ H ₁₅ NO ₃	58.36 (58.50)	8.16 (8.22)	7.56 (7.29)

^{a)} Lit. bp. 120/0.1 (H. Oediger, H. J. Kabbe, F. Moeller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

^{b)} Lit.¹⁴⁾ bp. 104/0.2.

Syntheses of 5,9- and 8,13-seco-Diazasteroids

Pictet–Spengler reaction of 2-(cyclopenten-1-yl)ethylamine (**5**) with the acetal-lactam (**2b**) was carried out in HCl solution (pH 3–4) at 70–80° for 48 hr to provide the 5,9-seco product (**6**) (mp 122–3°) in 46% yield. The infrared (IR) spectrum of **6** showed NH and OH absorptions at 3320 and 3160 cm⁻¹, respectively, and the nuclear magnetic resonance (NMR) spectrum showed signals attributable to NH and OH protons at δ 2.3 (2H, broad singlet) which disappeared on treatment with D₂O. The structure of **6** was confirmed by satisfactory elemental analysis data together with its MS spectrum [m/e 266 (M⁺)].

The stereochemistry of **6** was deduced as follows. N-Methylation of **6** with HCOOH–HCHO afforded the N-methyl compound (**7**) in 71% yield, and its NMR spectrum exhibited a signal (half-width, 1.5 Hz) at δ 3.23 assigned to the N-methyl group. In the NMR spectrum, the half-width of the N-methyl signal of **7** increased at lower temperature, due to the two

12) H. Takahata, T. Hashizume, and T. Yamazaki, *Heterocycles*, **12**, 1449 (1979).

conformers (**7a**, **b**). Therefore, the ring junction of **6** was assigned as *cis*.¹³⁾ Pictet–Spengler reaction between **5** and ethyl 3,3-diethoxypropionate gave the annulated compound (**8**) (mp 98–9°). Acetylation of **8** followed by hydrolysis of the ester group with an alkali gave the lactone (**10**) as an oil. The IR spectrum of **10** showed the absorption of a 6-membered lactone group and an amide group at 1720 and 1615 cm^{-1} , respectively. The NMR spectrum exhibited the amide methyl proton at δ 2.00, and the MS spectrum had a peak at m/e 223 (M^+). These data suggested that the structure of **6** had the *cis* configuration.

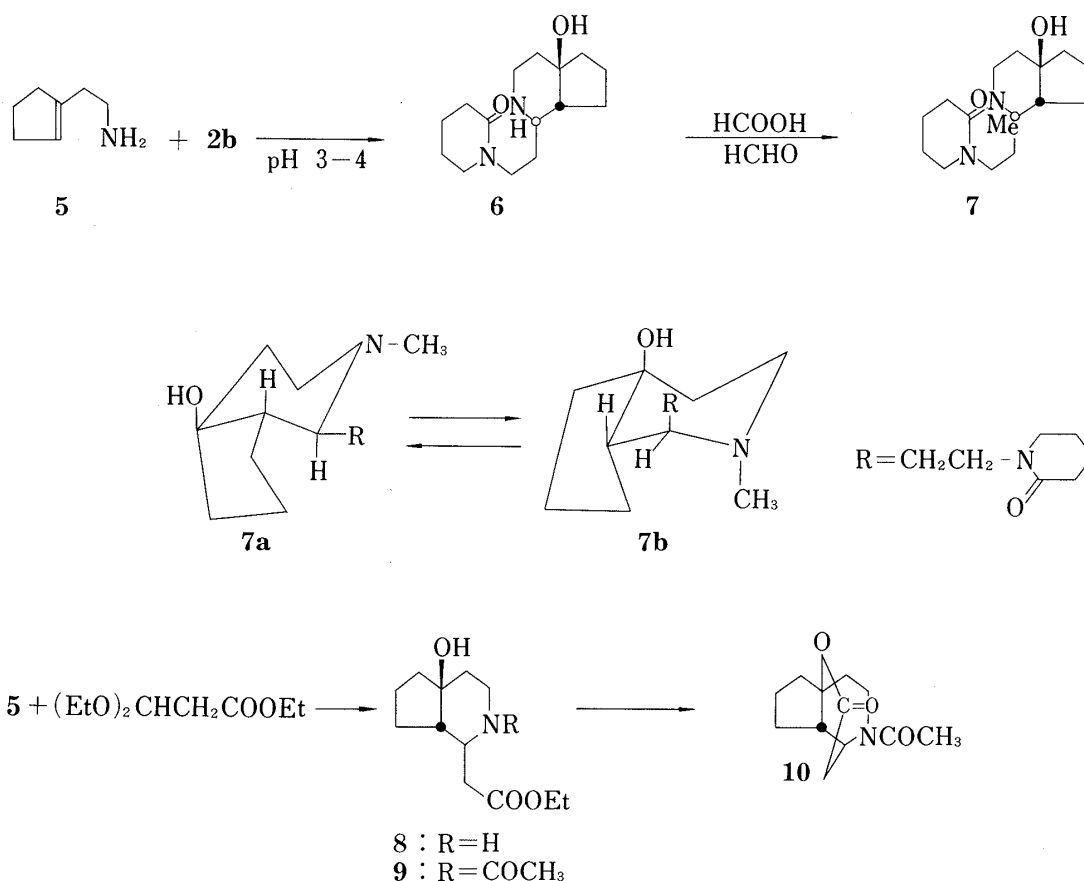


Chart 3

Similar annulation of homoveratrylamine (**11**) with the ester lactam (**2a**) afforded the 8,13-seco product (**12**) (mp 73°) in 35% yield; this compound was characterized by spectroscopic analysis and gave satisfactory elemental analysis data.

Condensation of the amine (**5**) with the ester lactam (**4b**) gave the diamide (**13**) (mp 35–36°) in 65% yield. Unfortunately, attempts to carry out the Bischler–Napieralski annulation of **13** with several condensing reagents (P_2O_5 , PPE, PPA, and POCl_3) under various conditions failed and resulted in the recovery of the starting material. On the other hand, the diamide (**14**) was produced in 80% yield by condensation of the amine (**11**) with the ester lactam (**4a**). The treatment of **14** with PPE as a condensing agent, following by reduction with NaBH_4 readily gave **12** in 60% yield; this product was identical with the sample prepared by means of the Pictet–Spengler reaction (IR and NMR data and chromatographic behavior.)

Syntheses of 5,9- and 9,13-Diazasteroids

Reductive ring closure of the 5,9-seco compound (**6**) was carried out in dry THF with

13) Similar considerations were applied to 10-hydroxydecahydroisoquinoline. C.A. Grob and R.A. Wohl, *Helv. Chim. Acta.*, **49**, 2175 (1966).

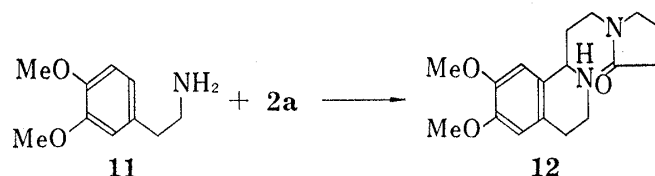


Chart 4

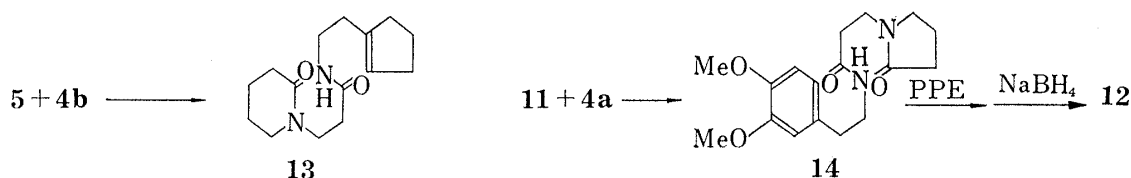


Chart 5

LiAlH_4 to give the desired product (**15**) (mp $129\text{--}131^\circ$) as white crystals on 80% yield. The elemental analysis and MS spectral data [m/e 248 (M^+)] were consistent with the 5,9-diazasteroid structure. In this reaction, the absence of formation of the dihydrogenated compound (**16**) was of interest, because reductive annulation of the 8,10-⁷⁾ and 8,15-¹¹⁾ compounds (sec-aminelactam system) invariably gave certain amounts of dihydrogenated compounds. This result can be explained as follows. Formation of the N-C-N bond could occur by an intramolecular attack of the secondary amine on the immonium intermediate, and overreduction by hydride would give the dihydrogenated products. In the case of **6**, LiAlH_4 would react first with the hydroxyl group of **6**, giving an aluminum alkoxide complex, which would act as a reducing agent. Therefore, overreduction of the immonium intermediate (**17**) would be very difficult due to steric bulkiness, and the intramolecular attack of the secondary amine would proceed exclusively to form the N-C-N bond. This explanation was confirmed by the use of $\text{LiAlH}[\text{OCH}(\text{CH}_3)\text{Bu}^t]_3$ (**18**) as a bulky reducing agent in the annulation of the 8,13-seco compound (**12**); that is, reaction of **12** was carried out with **18** to provide the 8,13-diazasteroid (**19**) in 40% yield (though it required a longer reaction time), and as expected, afforded no dihydro compound (**20**). On the other hand, annulation of **12** with LiAlH_4 gave **19** and **20** in 20% and 40% yields, respectively. The structure of **19** and **20** were assigned on the basis of their MS spectra and elemental analysis data.

Next, the stereochemistry of **15** and **19** was investigated. In the previous reports,^{7,11,14)} it was found that attack of the secondary amine occurred from the equatorial direction to result in *cis* arrangements of the C_8 and C_{10} protons in **15** as well as of the C_9 and C_{14} protons in **19**. These assignments were supported spectroscopically. The IR spectrum of **15** showed several intense bands in the $2810\text{--}2660\text{ cm}^{-1}$ region, commonly known as the Bohlmann bands, characteristic of the conformation of *trans* quinolizidine. In the NMR spectrum of **15**, the C_8 proton gave a signal at δ 3.1–3.3, and the C_{10} proton appeared at δ 2.87–2.91. These chemical shifts (above δ 3.8 ppm) support the view that both protons are oriented *trans* diaxial to the lone pairs of the neighboring nitrogen.¹⁵⁾ In particular, such as a high-field shift of the C_{10} proton suggests that the proton should be located *trans* diaxial to the lone pairs of both adjacent nitrogens at the 5 and 9 positions.¹⁶⁾ In addition, reaction of **6** with LiAlD_4

14) G.W. Gribble, *J. Org. Chem.*, **35**, 1944 (1970).

15) For the basis of this argument, see; a) T.A. Crabb, R.F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971); b) R.E. Brown, A.I. Meyers, L.M. Trefones, R.L.R. Towns, and J.N. Brown, *J. Heterocycl. Chem.*, **8**, 279 (1971); c) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).

16) a) R.O. Hutchins, L.D. Kopp, and E.L. Eliel, *J. Am. Chem. Soc.*, **90**, 7174 (1968); b) E.L. Eliel, E.D. Kopp, J.E. Dennis, and S.A. Evans, *Tetrahedron Lett.*, **1971**, 3409.

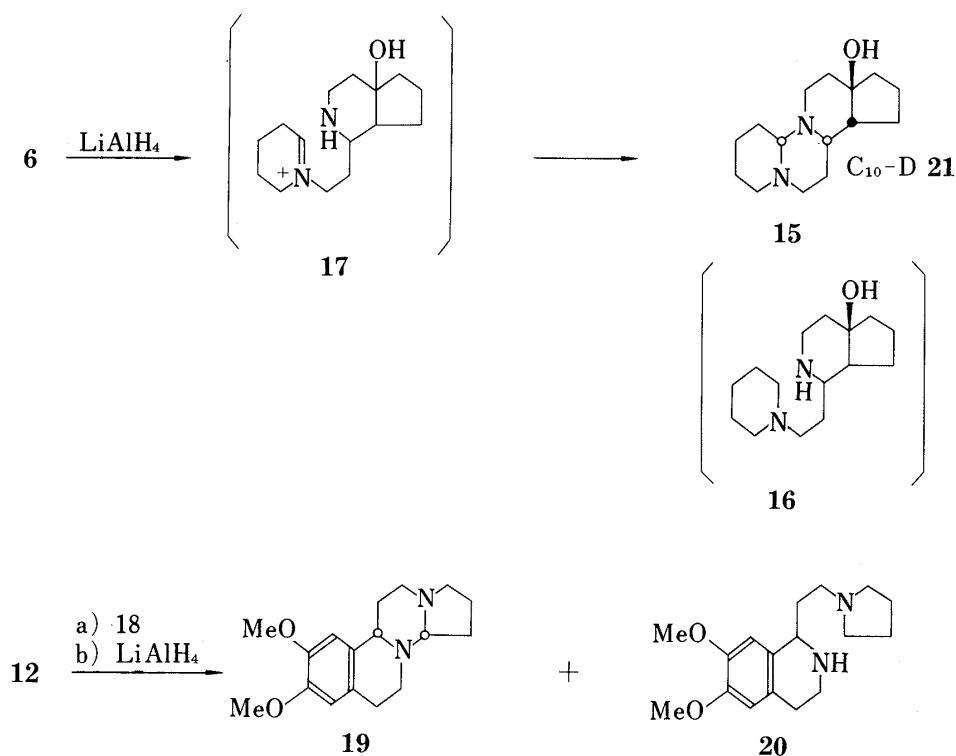


Chart 6

gave the 5,9-diazaasteroid deuterated at C_{10} (**21**), whose IR spectrum showed absorptions at 2800, 2760, 2740, (Bohlmann bands) and 1920 cm^{-1} ($\text{C}_{10}\text{C-D}$ stretching frequency).¹⁷⁾

On the other hand, the IR spectrum of **19** showed intense Bohlmann bands in the $2800\text{--}2680\text{ cm}^{-1}$ region and the NMR spectrum exhibited no signals below $\delta\ 3.3\text{ ppm}$ except for the methoxyl and aromatic protons.¹⁵⁾ These observations support a *cis* arrangement of the C_9 and C_{14} protons **19**. The biological activities of **15** and **19** are currently under investigation.

Experimental

All melting points were uncorrected. IR spectra were taken on a Hitachi grating infrared spectrophotometer. PMR spectra were measured in CDCl_3 solution with a JEOL C-60H spectrometer, with tetramethyl silane as an internal standard. The CMR spectrum was recorded with a Varian XL-200 machine. Coupling constants (J) are given in Hz and the following abbreviations are used: s=singlet, d=doublet, t=triplet, and m=multiplets. Mass spectra (MS) were taken on a JEOL TMS-01SG (75 eV, direct inlet system) spectrometer.

General Procedure for N-Alkylation (2a, b and 3a, b)—A solution of pyrrolidin-2-one (**1a**) or piperidin-2-one (**1b**) (0.05 mol) and β -chloropropionaldehyde dimethyl acetal or β -chloropropionitrile (0.05 mol) in 20 ml of dry THF was added to a suspension of pulverized KOH (0.055 mol) and tetra-*n*-butylammonium bromide (0.01 mol) in 50 ml of dry THF over a period of 1 hr at room temperature. On completion of the addition, the reaction mixture was stirred under reflux for 3 hr. The precipitate was filtered off and the filtrate was concentrated *in vacuo* to leave an oil, to which CH_2Cl_2 and H_2O were added. The organic phase was washed with brine, dried over anhyd. MgSO_4 , and concentrated *in vacuo* to leave an oil, which was distilled under reduced pressure to give 1-(3,3-dimethoxypropyl)-2-pyrrolidone (**2a**), 1-(3,3-dimethoxypropyl)-2-piperidone (**2b**), 3-(2-oxo-1-pyrrolidinyl)propionitrile (**3a**), or 3-(2-oxopiperidino)propionitrile (**3b**). **2a**: IR $\nu_{\text{max}}^{\text{film}}\text{ cm}^{-1}$: 1640 (lactam C=O). NMR δ : 3.33 (6H, s, $2 \times \text{OCH}_3$), 4.40 (1H, t, $J=2.5$, $\text{CH}(\text{OCH}_3)_2$). **2b**: IR $\nu_{\text{max}}^{\text{film}}\text{ cm}^{-1}$: 1640 (lactam C=O). NMR δ : 3.33 (6H, s, $2 \times \text{OCH}_3$), 4.40 (1H, t, $J=3.0$, $\text{CH}(\text{OCH}_3)_2$). **3a**: IR $\nu_{\text{max}}^{\text{film}}\text{ cm}^{-1}$: 2250 (CN), 1640 (lactam C=O). **3b**: IR $\nu_{\text{max}}^{\text{film}}\text{ cm}^{-1}$: 2250 (CN), 1630 (lactam C=O).

17) Since it is established that C-D bonds that are 1,2-*cis* to a nitrogen lone pair appear at higher frequency than those that are 1,2-*trans* diaxial ($2150\text{ vs. }2000\text{ cm}^{-1}$) for methylene and methine deuteriums, it is tempting to conclude that the low frequency value of 1920 cm^{-1} for **21** is consistent with the C_{10} (D) being *trans* diaxial to both nitrogen lone pairs. J. Skolik, P.J. Krueger, and M. Wiewiorski, *Tetrahedron*, **24**, 5439 (1968).

Methyl 3-(2-Oxo-1-pyrrolidinyl)propionate (4a)—A mixture of **3a** (15 g), *p*-toluene sulfonic acid monohydrate (21 g), and methanol (50 ml) was stirred under reflux for 20 hr. The precipitate was filtered off and the filtrate was concentrated *in vacuo* to leave an oil, which was made basic with 10% Na₂CO₃ solution. The mixture was extracted with CHCl₃. The extract was washed with water, dried over anhyd. MgSO₄, and concentrated *in vacuo* to give an oil (**4a**) (13 g, 70%). IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 1740 (ester C=O), 1640 (lactam C=O). NMR δ : 3.63 (3H, s, COOMe).

Methyl 3-(2-Oxopiperidino)propionate (4b)—Esterification of **3b** (8.4 g) with *p*-TosOH (10.5 g) in MeOH (50 ml) by the method described for **4a** gave **4b** (7.2 g, 70%) as an oil. IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 1740 (ester C=O), 1635 (lactam C=O). NMR δ : 3.63 (3H, s, COOMe).

Pictet-Spengler Reaction of 2b with 5—Conc. HCl solution was added to a solution of **5** (4.9 g) in water (200 ml), until the solution reached pH 3–4, and **3b** (9 g) was added to the acidified solution. The reaction mixture was stirred at 70–80° for 48 hr. The precipitate was filtered off. The filtrate was neutralized with 10% NaOH solution and extracted with CHCl₃. The extract was dried over anhyd. Na₂CO₃, and concentrated *in vacuo* to leave an oil, which was crystallized from isopropyl ether to give *cis*-10-oxo-13-hydroxy-5,9-diaza-9,10-seco-gonane (**6**) (3.2 g, 40%). mp 122–123° (recrystallization from ethyl acetate-isopropyl ether). IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3280 (NH), 3180 (OH), 1620 (lactam C=O). NMR δ : 2.3 (2H, s, NH and OH), 3.6–3.95 (1H, m, C₈-H). MS *m/e*: 266 (M⁺), 248 140, 122. Anal. Calcd for C₁₅H₂₆N₂O: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.37; H, 10.02; N, 10.37.

N-Methylation of 6—A mixture of **6** (500 mg), 86% HCOOH (10 ml), and 37% HCHO (0.5 ml) was stirred under reflux for 15 hr. The reaction mixture was concentrated *in vacuo* to leave an oil, which was neutralized with 10% NaOH solution. The mixture was extracted with ether. The extract was dried over anhyd. Na₂CO₃, and concentrated *in vacuo* to leave an oil, which was distilled under reduced pressure to give **7** (382 mg, 71%). bp 180–190° (0.04 mmHg). IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 3400 (OH), 1620 (lactam C=O). NMR¹⁸⁾ δ : 2.33 (3H, s, half-width 1.5 Hz at 20°, 3 Hz at -20°, N-CH₃), 2.90 (1H, brs. OH). Anal. Calcd for C₁₆H₂₈N₂O₂: C, 68.53; H, 10.07; N, 9.99. Found: C, 68.81; H, 9.95; N, 10.19.

cis-2-Ethoxycarbonylmethyl-6-hydroxy-3-azabicyclo[4.3.0]nonane (8)—By a procedure to that described for **6**, Pictet-Spengler reaction of **5** (2.52 g) with acetal (4.5 g) at 80° for 48 hr gave **8** (620 mg, 13%) as white crystals. mp 98–99° (recrystallization from isopropyl ether-ethyl acetate). IR $\nu_{\max}^{\text{NaCl}}$ cm⁻¹: 3600, 3280, 1730 (ester C=O). NMR δ : 1.47 (3H, t, *J*=7, COOCH₂CH₃), 2.33 (2H, s, NH, OH), 4.33 (2H, q, *J*=7, COOCH₂CH₃). MS *m/e*: 227 (M⁺), 140 (base peak). Anal. Calcd for C₁₂H₂₁NO₃: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.60; H, 9.53; N, 6.30.

The Lactone (10)—A mixture of **8** (100 mg), acetic anhydride (0.5 ml), and benzene (10 ml) was heated on a steam bath for 1.5 hr. The reaction mixture was concentrated *in vacuo* to leave an oil, which was neutralized with sat. NaHCO₃ solution. The mixture was extracted with CHCl₃. The extract was dried over anhyd. MgSO₄, and concentrated *in vacuo* to give crude (**9**) (110 mg) as an oil. IR $\nu_{\max}^{\text{NaCl}}$ cm⁻¹: 3380, 1720, 1610. NMR δ : 2.10 (3H, s, COCH₃). A mixture of **9** (110 mg), NaOH (40 mg), methanol (1 ml), and water (1 ml) was stirred for 6 hr at room temperature. The reaction mixture was slightly acidified with 5% HCl solution, and extracted with CH₂Cl₂. The extract was dried over anhyd. MgSO₄, and concentrated *in vacuo* to leave an oil, which was purified by preparative chromatography (on silica gel) with CH₂Cl₂ as an eluant to afford **10** (26 mg, 27%) as an oil. IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 1720 (lactone C=O), 1615 (amide C=O). NMR δ : 2.08 (3H, s, NCOCH₃). MS *m/e*: 223 (M⁺), 180 (base peak). Anal. Calcd for C₁₂H₁₇NO₃: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.96; H, 7.43; N, 6.58.

N-[2-(Cyclopenten-1-yl)ethyl]-3-(2-oxopiperidino)propionamide (13)—A mixture of **5** (4 g) and **4b** (3.4 g) was heated at 140–150° for 9 hr. The reaction mixture was distilled under reduced pressure (4 × 10⁻⁴ mmHg) at 160° (bath temp.) to give **13** (3.4 g, 65%) as white crystals. mp 35–36° (recrystallization from *n*-hexane-ether). IR $\nu_{\max}^{\text{NaCl}}$ cm⁻¹: 1675 (C=O). NMR δ : 5.25–5.30 (1H, m, vinyl proton), 6.10–6.65 (1H, br.s, NH). MS *m/e*: 264 (M⁺), 154, 112. Anal. Calcd for C₁₅H₂₄N₂O₂: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.30; H, 9.20; N, 10.76.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-(3-oxo-1-pyrrolidinyl)propionamide (14)—A mixture of **11** (4 g) and **4a** (3.5 g) was heated at 170–180° for 5 hr. The mixture was purified by alumina column chromatography with CHCl₃ as an eluant to give **14** (5.1 g, 80%). IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 1670 (C=O). NMR δ : 3.8 (6H, s, 2 × OCH₃), 6.8 (1H, br.s, NHCO). MS *m/e*: 320 (M⁺). Anal. Calcd for C₁₇H₂₄N₂O₃: C, 63.73; H, 7.55; N, 8.74. Found: C, 64.01; H, 7.32; N, 9.03.

6,7-Dimethoxy-1-[2-(3-oxo-1-pyrrolidinyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (12)—a) Conc. HCl solution was added to a mixture of **11** (4 g), **2a** (3.6 g), and water (150 ml) until the solution reached pH 1–2. The mixture was refluxed for 2 hr, made basic with 10% NaOH solution, and extracted with CHCl₃. The extract was dried over anhyd. K₂CO₃, and concentrated *in vacuo* to leave an oil, which was purified by alumina column chromatography with CHCl₃ as an eluant to give **12** (2.1 g, 35%). mp 73° (recrystallization from ether-ethyl acetate). IR $\nu_{\max}^{\text{NaCl}}$ cm⁻¹: 3550 (NH), 1670 (lactam C=O). NMR δ : 2.34 (1H, s, NH), 3.83 (6H, s, 2 × OCH₃), 6.71 (2H, br.s, aromatic protons). MS *m/e*: 304 (M⁺). Anal. Calcd for C₁₇H₂₄N₂O₃: C, 67.08;

18) The N-methyl signal of compound (**7**) was recorded with a Varian EM 390 machine (90 MHz).

H, 7.95; N, 9.20. Found: C, 66.89; H, 8.03; N, 9.21.

b) A mixture of **14** (3 g), polyphosphate ester (16 g), and dry CHCl_3 (100 ml) was stirred under reflux for 4.5 hr, and subsequently at room temperature for 8 hr. The reaction mixture was poured into ice-water (100 ml). The mixture was made basic with 10% Na_2CO_3 solution, and diluted with methanol (100 ml). Next, NaBH_4 (15 g) was added to the diluted mixture with ice-cooling. The reaction mixture was stirred at room temperature for 20 hr, then extracted with ether. The extract was dried over anhyd. K_2CO_3 , and concentrated *in vacuo* to leave an oil, which was purified by alumina column chromatography with CHCl_3 as an eluant to give **12** (1.1 g, 41%). This compound was identical with the sample prepared by means of the Pictet-Spengler reaction, with respect to IR and NMR data and chromatographic behavior.

cis-13-Hydroxy-5,9-diazagonane (15)—A solution of **6** (3 g) in dry THF (200 ml) was treated with a suspension of LiAlH_4 (500 mg) in dry THF (50 ml) under argon. The reaction mixture was heated at 50° for 24 hr. Water was added to the reaction mixture with ice-cooling. The precipitate was removed by filtration, then washed with ether. The filtrate and ether washing were combined, dried over anhyd. K_2CO_3 , and concentrated *in vacuo* to leave crystals of **15** (2.0 g, 75%). mp $139\text{--}140^\circ$ (recrystallization from ethyl acetate-ether). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450 (OH), 2800, 2780, 2700, 2650, 2595, 2545, (Bohlman bands). NMR δ : 1.88 (1H, s, OH), 2.87—2.91 (1H, m, $\text{C}_{10}\text{-H}$), 3.1—3.3 (1H, m, $\text{C}_8\text{-H}$). CMR δ : 35.5 (C_{14} , d), 45.5 (C_8 , d), 62.0 (C_{13} , s), 65.5 (C_{10} , d). MS m/e : 250 (M^+). Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}$: C, 71.93; H, 10.47; N, 11.19. Found: C, 71.96; H, 10.72; N, 11.40.

Preparation of 16—By a method to that described for **15**, **6** (1.5 g) was reacted with LiAlD_4 (250 mg) in dry THF (150 ml) to give **16** (700 mg, 58%). mp $135\text{--}137^\circ$. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2800, 2760, 2740 (Bohlmann bands), 1920 ($\text{C}_{10}\text{-D}$). MS m/e : 251 (M^+).

2,3-Dimethoxy-8,13-diaza-1,3,5(10)-gonatriene (19) and 6,7-Dimethoxy-1-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (20)—a) A solution of pinacolone (900 mg) in dry THF (10 ml) was added dropwise to a suspension of LiAlH_4 (114 mg) in dry THF (30 ml),¹⁹ and the mixture was stirred for 0.5 hr. Next, a solution of **12** (760 mg) in dry THF (150 ml) was slowly added and the mixture was heated with stirring under argon at 50° for 52 hr. Water (1 ml) was added to the mixture and the precipitate was filtered off. The filtrate was dried over anhyd. K_2CO_3 , and concentrated *in vacuo* to leave an oil, which was separated by alumina column chromatography with CHCl_3 as an eluant to give **19** (288 mg, 40%) and recovered starting material (**12**) (153 mg, 20%). mp $208\text{--}210^\circ$ as the picrate (recrystallization from ethanol-acetone). IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 2810, 2750, 2650, 2570 (Bohlmann bands). NMR δ : 3.83 (6H, s, $2 \times \text{OCH}_3$). MS m/e : 288 (M^+), 218.70. Anal. Calcd for $\text{C}_{29}\text{H}_{26}\text{N}_8\text{O}_{16}$ (dipicrate): C, 46.65; H, 4.05; N, 15.01. Found: C, 46.80; H, 4.20; N, 15.05.

b) A suspension of LiAlH_4 (400 mg) in dry THF (50 ml) was added dropwise with stirring to a solution of **12** (2 g) in dry THF (200 ml) over a period of 0.5 hr under argon and then the mixture was heated at 45° for 20 hr. Water (2.5 ml) was added to the reaction mixture with ice-cooling. The yellow precipitate was removed by filtration, followed by washing with THF. The combined filtrate and washing solution was dried over anhyd. K_2CO_3 , and concentrated *in vacuo* to leave an oil, which was separated by alumina column chromatography with ether- CHCl_3 (1:1) as an eluant to give **19** (380 mg, 20%) as an oil. Subsequent elution with CHCl_3 afforded **20** (900 mg, 48%) as an oil. **19** was identical with the sample prepared by method (a) with respect to IR and NMR data and chromatographic behavior. **20**: mp $198\text{--}202^\circ$ as the picrate (recrystallization from ethanol-acetone). IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3270 (NH). NMR δ : 2.35 (1H, s, NH), 3.83 (6H, s, $2 \times \text{OCH}_3$), 6.72 (2H, brs. aromatic protons). MS m/e : 290 (M^+), 218. Anal. Calcd for $\text{C}_{29}\text{H}_{28}\text{N}_8\text{O}_{16}$ (dipicrate): C, 46.78; H, 3.79; N, 15.05. Found: C, 46.52; H, 4.01; N, 15.29.

19) H. Haubenstock, *J. Org. Chem.*, **38**, 1765 (1973).