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Synthesis in the Diazasteroid Group. XV.[1] Syntheses of the 5,9- and 8,13-Diazasteroids[2]

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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.

I II

Chart 1

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.

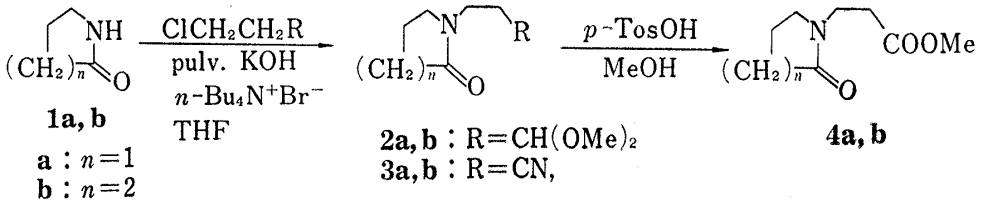
1) Part XIV: K. Matoba, T. Imai, Y. Nishino, H. Takahata, Y. Hirai, and T. Yamazaki, *Chem. Pharm. Bull.*, **28**, 1810 (1980).
2) Presented at the 99th Meeting of the Pharmaceutical Society of Japan, Sapporo, August, 1979, Abstracts p. 285.
3) Location: *2630, Sugitani, Toyama 930-01, Japan.*
4) I.Y.C. 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 105960*b* (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 E_2 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.



1a, b
a : $n=1$
b : $n=2$

2a, b : R=CH(OMe)$_2$
3a, b : R=CN,

4a, b

Chart 2

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	$C_9H_{17}NO_3$	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	$C_8H_{12}N_2O$	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	$C_9H_{15}NO_3$	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 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 D_2O. 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.

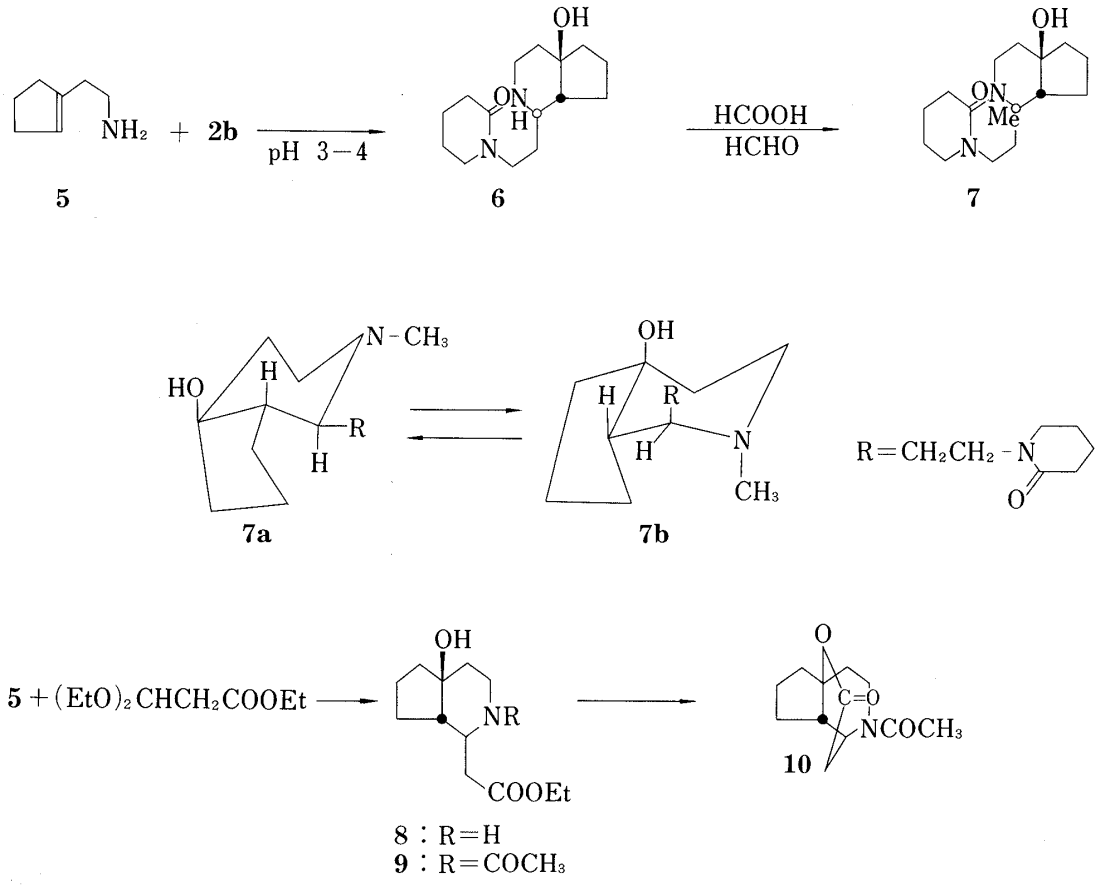


Chart 3

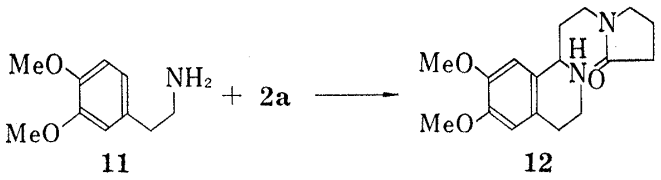
Similar annulation of homoveratrylamine (**11**) with the ester lactam (**2a**) afforded the 8,13-seco product (**12**) (mp 73°) in 35% yield; this compound was characterized by spectroscopic analysis and gave satisfactory elemental analysis data.

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

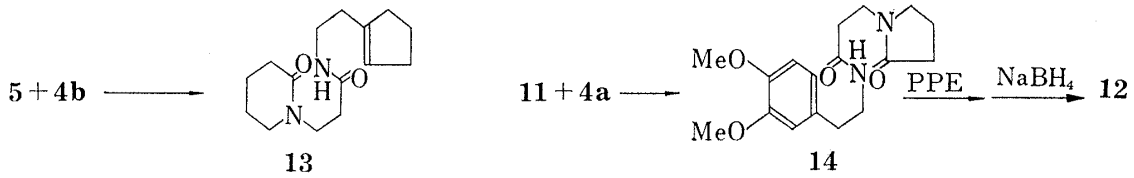
Reductive ring closure of the 5,9-seco compound (**6**) was carried out in dry THF with

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



11 12

Chart 4



13 14

Chart 5

$LiAlH_4$ to give the desired product (**15**) (mp 129—131°) 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 intrest, 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 $LiAlH[OCH(CH_3)Bu^t]_3$ (**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 equatorical 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 assignment were supported spectroscopically. The IR spectrum of **15** showed several intense bands in the 2810—2660 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.

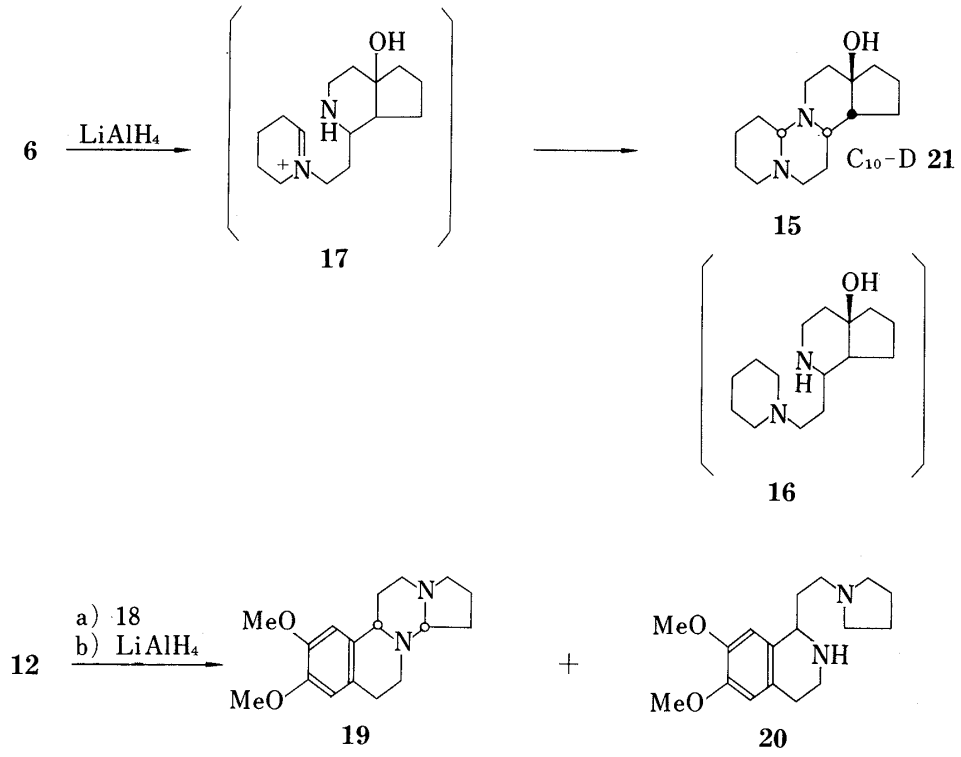


Chart 6

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

On the other hand, the IR spectrum of **19** showed intense Bohlmann bands in the 2800—2680 cm^{-1} region and the NMR spectrum exhibited no signals below δ 3.3 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-0ISG (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 ν_{max}^{film} cm^{-1}: 1640 (lactam C=O). NMR δ: 3.33 (6H, s, $2\times OCH_3$), 4.40 (1H, t, J=2.5, C<u>H</u>$(OCH_3)_2$). **2b**: IR ν_{max}^{film} cm^{-1}: 1640 (lactam C=O). NMR δ: 3.33 (6H, s, $2\times OCH_3$), 4.40 (1H, t, J=3.0, C<u>H</u> $(OCH_3)_2$), **3a**: IR ν_{max}^{film} cm^{-1}: 2250 (CN), 1640 (lactam C=O). **3b**: IR ν_{max}^{film} 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 *vs.* 2000 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. Wiewioroski, *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% Na_2CO_3 solution. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. $MgSO_4$, and concentrated *in vacuo* to give an oil (**4a**) (13 g, 70%). IR ν_{max}^{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 ν_{max}^{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 $CHCl_3$. The extract was dried over anhyd. Na_2CO_3, 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 ν_{max}^{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, C_8–H). MS: 266 (M^+), 248 140, 122. *Anal.* Calcd for $C_{15}H_{26}N_2O$: 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. Na_2CO_3, 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 ν_{max}^{film} cm^{-1}: 3400 (OH), 1620 (lactam C=O). NMR[18] δ: 2.33 (3H, s, half-width 1.5 Hz at 20°, 3 Hz at −20°, N–CH_3), 2.90 (1H, brs. OH). *Anal.* Calcd for $C_{16}H_{28}N_2O_2$: 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 ν_{max}^{Nujol} cm^{-1}: 3600, 3280, 1730 (ester C=O). NMR δ: 1.47 (3H, t, $J=7$, $COOCH_2\underline{CH_3}$), 2.33 (2H, s, NH, OH), 4.33 (2H, q, $J=7$, $COO\underline{CH_2}CH_3$). MS *m/e*: 227 (M^+), 140 (base peak). *Anal.* Calcd for $C_{12}H_{21}NO_3$: 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. $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$. The extract was dried over anhyd. $MgSO_4$, and concentrated *in vacuo* to give crude (**9**) (110 mg) as an oil. IR ν_{max}^{neat} cm^{-1}: 3380, 1720, 1610. NMR δ: 2.10 (3H, s, $COCH_3$). 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 CH_2Cl_2. The extract was dried over anhyd. $MgSO_4$, and concentrated *in vacuo* to leave an oil, which was purified by preparative chromatography (on silica gel) with CH_2Cl_2 as an eluant to afford **10** (26 mg, 27%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (lactone C=O), 1615 (amide C=O). NMR δ: 2.08 (3H, s, $NCOCH_3$). MS *m/e*: 223 (M^+), 180 (base peak). *Anal.* Calcd for $C_{12}H_{17}NO_3$: 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 ν_{max}^{Nujol} 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 $C_{15}H_{24}N_2O_2$: 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 $CHCl_3$ as an eluant to give **14** (5.1 g, 80%). IR ν_{max}^{film} cm^{-1} 1670 (C=O). NMR δ: 3.8 (6H, s, $2\times OCH_3$), 6.8 (1H, br.s, NHCO). MS *m/e*: 320 (M^+). *Anal.* Calcd for $C_{17}H_{24}N_2O_3$: 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 $CHCl_3$. 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** (2.1 g, 35%). mp 73° (recrystallization from ether-ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3550 (NH), 1670 (lactam C=O). NMR δ: 2.34 (1H, s, NH), 3.83 (6H, s, $2\times OCH_3$), 6.71 (2H, br.s, aromatic protons). MS *m/e*: 304 (M^+). *Anal.* Calcd for $C_{17}H_{24}N_2O_3$: 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—140° (recrystallization from ethyl acetate–ether). IR ν_{max}^{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, C_{10}–H), 3.1—3.3 (1H, m, C_8–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 $C_{15}H_{26}N_2O$: 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—137°. IR ν_{max}^{KBr} cm^{-1}: 2800, 2760, 2740 (Bohlmannn bands), 1920 (C_{10}–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—210° as the picrate (recrystallization from ethanol–acetone). IR ν_{max}^{neat} cm^{-1}: 2810, 2750, 2650, 2570 (Bohlmann bands). NMR δ: 3.83 (6H, s, $2\times OCH_3$). MS *m/e*: 288 (M^+), 218.70. *Anal.* Calcd for $C_{29}H_{26}N_8O_{16}$ (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—202° as the picrate (recrystallization from ethanol–acetone). IR ν_{max}^{neat} cm^{-1}: 3270 (NH). NMR δ: 2.35 (1H, s, NH), 3.83 (6H, s, $2\times OCH_3$), 6.72 (2H, brs. aromatic protons). MS *m/e*: 290 (M^+), 218. *Anal.* Calcd for $C_{29}H_{28}N_8O_{16}$ (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).