Synthesis in the Diazasteroid Group VI. (1) A Synthesis of 2,3-Dimethoxy-15-methyl-8,15-diazaestra-1,3,5(10)triene

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Homoveratrylamine (II) was condensed with 3-(2-carbomethoxyethyl)-1,3-dimethyl-2-pyrrolidone (Ib) to furnish the corresponding amide (III), which was subjected to the Bischler-Napieralski reaction to afford the corresponding dihydroisoquinoline derivative (IV). Compound V was obtained by the reductive ring closure of VIIa which was obtained by the hydrogenation of IV. The stereochemistry of V is proposed to have the *anti-trans-trans* quinolizidine conformation.

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Following the preceding paper (1), we now report the synthesis of the 8,15-diazasteroid system. Previously, Oishi, *et al.*, (2) reported that 1-methyl-2-pyrrolidone dimethyl ether (IX), reacting with methyl acrylate, afforded 3-(2-carbomethoxyethyl)-1-methylpyrrolidone (Ia) in good yield, while 1-methyl-2-piperidone dimethyl ether (XIIIa) furnished 3,3-di(2-carbomethoxyethyl)-1-methyl-2-piperidone (XIVa). We attempted the condensation of homoveratrylamine with Ia leading to the 8,15-diazasteroid system as shown in Chart 1. Unfortunately, however, we found that the pyrrolidone gave 3,3-di-(2-carbomethoxyethyl)-1-methyl-2-pyrrolidone (X) as the sole product instead of Ia. Compound X, therefore, showed in the nmr spectrum characteristic signals at δ 3.55 associated with six protons due to the methyl ester functions and δ 2.75 associated with three protons due to *N*-methyl function. Compound X afforded, in addition, the corresponding dicarboxylic acid, m.p. 149-150° when hydrolyzed with alkali. The carboxylic acid was shown to be 3,3-di-(2-carboxyethyl)-1-methyl-2-pyrrolidone (XI) by elemental analysis. Moreover, IX (1 mole), when allowed to react with 1 mole of methyl acrylate, gave about 0.5 mole of X. A considerable amount of *N*-methyl-2-pyrrolidone was recovered. Thus we were unsuccessful in the synthesis of Ia as a starting material.

We then turned our attention to monomethylation of *N*-methyl-2-pyrrolidone at the 3-position followed by the subsequent introduction of the 2-carbomethoxyethyl function at the same position and succeeded in the synthesis of Ib in a fairly good yield, although Oishi emphasized (2) that the 3-monosubstituted pyrrolidone would not undergo further substitution. This was remarkably different from piperidone. The structure Ib was confirmed by ir spectrum [ν c=o 1735 cm^{-1} due to the ester moiety, ν c=o 1685 cm^{-1} due to the lactam function, and the nmr spectrum (δ 3.6 due to methyl ester group, δ 2.8 due to *N*-methyl group and δ 1.05 due to C-3 methyl group)]. These spectral data together with the elemental analysis provided the required evidence of structure Ib.

Compound Ib was treated with homoveratrylamine at 160-165° furnishing the corresponding amide (III) in quantative yield. The structure of III was established by ir and nmr spectral data. The Bischler-Napieralski ring closure of III with ethyl polyphosphate in chloroform furnished a pale yellow oil in 87% yield. The oil was shown to be the corresponding isoquinoline, 1-[2-(1,3-dimethyl-2-oxo-3-pyrrolidyl)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (IV) from the ir and nmr spectral data and from the elemental analysis of the picrolonate. Compound IV was successively subjected to the reductive cyclization with lithium aluminum hydride to afford the 8,15-diazasteroid ring system after the manner of Gribble (3) and Yamada (4); compound IV was treated with lithium aluminum hydride in absolute ether, and the product was purified through an alumina column using benzene and then chloroform-ethanol (1:1) as eluents. A colorless oil obtained in 24% yield after the evaporation of the benzene eluent, solidified in the cold and melted at 84-86°, however, it rapidly turned blood-red in color

Chart 1

Synthesis of the 8,15-Diazasteroid System

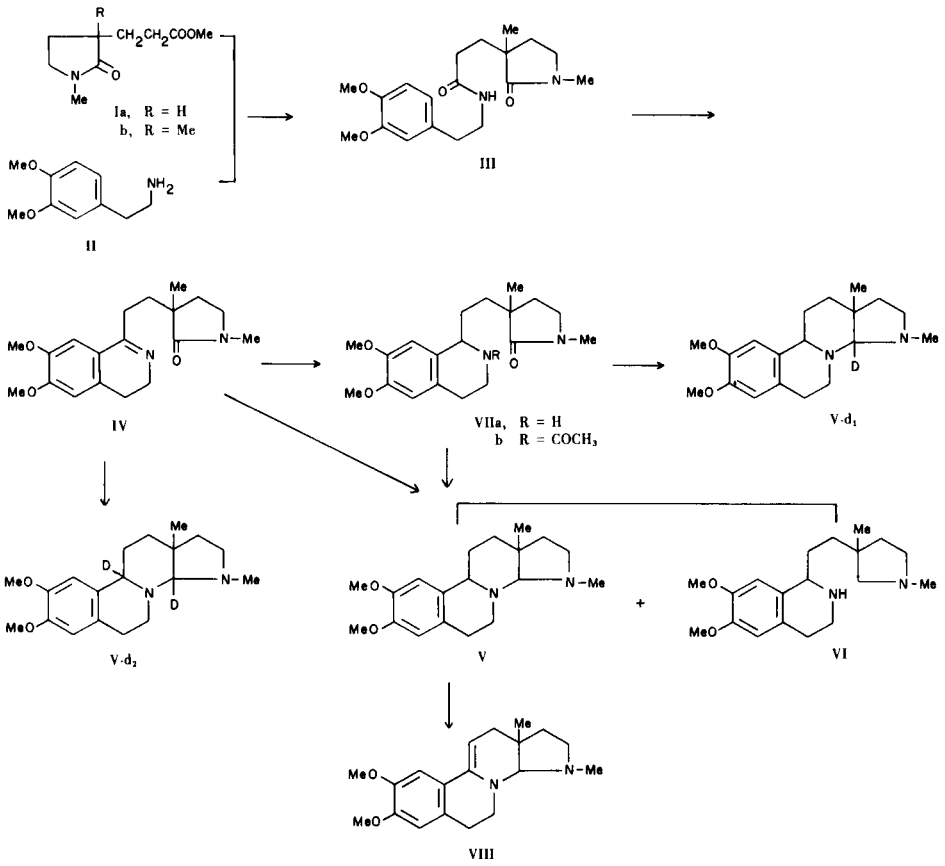
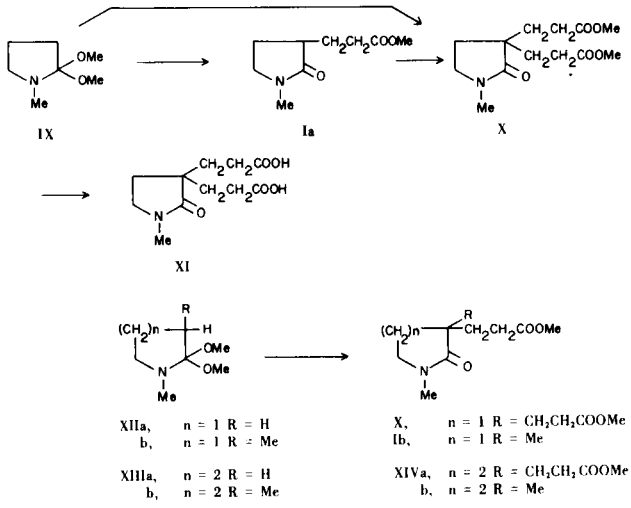


Chart 2



on exposure to air. This compound afforded a monopicrate, m.p. 108-111°, whose mass spectrum exhibited a parent ion peak at m/e 316 (M^+-$C_6H_3O_7N_3$), thus suggesting the formation of the expected 2,3-dimethoxy-15-methyl-8,15-diazaestra-1,3,5(10)triene (V).

On the other hand, the other oil obtained in 63% yield after the evaporation of the chloroform-ethanol eluent, afforded a dipicrate, m.p. 214-219°, whose mass spectrum exhibited a parent ion peak at m/e 318 (M^+-$2xC_6H_3O_7N_3$), thus supporting the formation of the undesired 1-[2-(1,3-dimethyl-3-pyrrolidyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI). Compound IV was hydrogenated over platinum oxide in ethanol, furnishing a colorless oil whose picrolonate melted at 222-227°. Based on the elemental analysis of the picrolonate, and the ir, nmr and mass spectral data of the *N*-acetyl derivative (VIIb), the oil was shown to be 1-[2-(1,3-dimethyl-2-oxo-3-pyrrolidyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIa). Compound VIIa was treated with lithium aluminum hydride to afford two different reduction products, V and VI, which were identical to those obtained by the lithium aluminum hydride reduction of IV.

With regard to the stereochemistry of V, nine conformers might be possible, according to the conformations of the C-9 proton, the C-13 methyl and the C-14 proton. However, we propose the steric structure as follows based on spectral data and the mercuric acetate oxidation.

At first, concerning C/D ring fusion, an nmr signal at δ 2.55 (singlet) could be assigned to the C-14 methine proton, which was supported by the fact that the product V-d_1 (5) obtained from lithium aluminum deuteride reduction of VIIa showed no signal at δ 2.55. Such a higher field shift of the C-14 proton suggests that the C-14 proton should be located *anti*-parallel to the lone pairs of both the adjacent nitrogens at the 8 and 15 positions (6) or at least situated *trans* diaxial to the lone pair on nitrogen at the 8 position. Thus the spatial orientation of the C-14 proton should be axial to the C-ring. On the other hand, the signal of the C-13 methyl appears at δ 0.94 (deuteriochloroform) or at δ 0.87 (hexadeuterobenzene) with a large half-width of 2~3 cps compared with that of TMS (1~2 cps), which suggests a long range spin-spin coupling (7) between the C-12 axial proton and the C-13 methyl, thus suggesting the axial orientation of the C-13 methyl to the C-ring.

trans-Quinolizidine, in general, is far more readily subjected to the mercuric acetate dehydrogenation than *cis*-quinolizidine. In our case, V was readily dehydrogenated to furnish the corresponding dehydrobase (VIII) under mild conditions (at 60° for 1.5 hours). The uv spectrum of VIII exhibited two absorption bands at 278 mμ and 310 mμ associated with the veratrol ring and with the 3,4-dimethoxystyrene moiety. The mass spectrum of the picrate (m.p. 144-148°) showed a parent ion peak at m/e 315 (M^+-$C_6H_3O_7N_3$) corresponding to VIII. The nmr spectrum of V in hexadeuteriobenzene exhibited no signal at lower field than δ 3.8 except aromatic protons, but a signal at δ 3.76 (< δ 3.8) associated with the C-9 methine proton was given as a quartet (8), while the product V-d_2 (5) obtained from lithium aluminum deuteride reduction of IV gave no signal at δ 3.76. The ir spectrum of V-d_1 showed several bands in the 2845-2600 region commonly known as Bohlmann bands (9) and those of V indicated broad bands in the same region. These facts supported the *trans* fusion of the B/C ring, though in the nmr spectrum a signal of the C-9 methine proton was exhibited at a little lower field.

Finally, we conclude from the above discussions that the structure of V is the *anti-trans-trans* quinolizidine conformation (10) with B/C-*trans* and the C-9 proton/C-13 methyl is in the *anti* conformation.

EXPERIMENTAL

All melting points were taken with a Yanaco micro melting point apparatus and are uncorrected. Infrared (ir) spectra were determined using a Hitachi Grating Infrared 215 spectrophotometer with absorptions given in cm^{-1}. Nmr spectra were recorded on JEOL C-60H and Varian HR-100 spectrometers using TMS as the internal standard. The chemical shifts and coupling constants (J) are described in δ and Hz respectively. Mass spectra were measured with a JEOL TMS-01SG (75 ev, direct inlet system) spectrometer. Uv spectra were obtained in ethanol by using a Hitachi Model EPS-2T spectrometer.

3,3-Di-(2-carbomethoxyethyl)-1-methyl-2-pyrrolidone (X) and 3,3-Di-(2-carboxyethyl)-1-methyl-2-pyrrolidone (XI).

A mixture of 2,2-dimethoxy-1-methylpyrrolidine (IX) (1.3 g., 8.9 mmoles) prepared by Bredereck's method (11) and methyl acrylate (1.5 g., 18 mmoles) was kept in a sealed tube at 100° for 17 hours. Evaporation of the reaction mixture left a pale brown oil, which was purified by chromatography on silica gel to afford a pale yellow oil (X) (1.7 g., 72%); ir (film): 1730, 1685; nmr (deuteriochloroform): 3.65 (s, 6H, $-COOCH_3$), 3.27 (t, J = 7, 2H, $-CH_2N<$), 2.75 (s, 3H, $CH_3N<$). A solution of X (1.0 g., 3.9 mmoles) in 10% sodium hydroxide solution (20 ml.) and methanol (15 ml.) was refluxed for 1 hour and then acidified with 20% hydrochloric acid. The solution was concentrated to one-third of its original volume, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and evaporation of the extract afforded a solid product followed by recrystallization from ethyl acetate:acetone (1:1) to give colorless crystals (0.6 g., 63%), m.p. 149-150°; ir (nujol): 3150, 1735, 1690.

Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.02; H, 6.84; N, 5.43.

3-(2-Carbomethoxyethyl)-1,3-dimethyl-2-pyrrolidone (Ib).

A mixture of 2,2-dimethoxy-1,3-dimethylpyrrolidine XIIb (2) (1.5 g., 9.3 mmoles) and methyl acrylate (1.7 g., 19 mmoles) was heated at 100° for 17 hours to give Ib (1.2 g., 65%), in a similar manner as described above. Compound Ib had b.p. (2.5 mm) 124°; ir (film): 1730, 1685; nmr (carbon tetrachloride): 3.6 (s, 3H, CH_3COO-), 3.27 (t, J = 7, 2H, $-CH_2N<$), 2.8 (s, 3H, $CH_3N<$), 1.05 (s, 3H, $-CH_3$).

Anal. Calcd. for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.99; H, 8.71; N, 7.10.

N-Homoveratryl-β-(2-oxo-1,3-dimethyl-3-pyrrolidyl)propionamide (III).

A mixture of Ib (12.3 g., 61.3 mmoles) and homoveratrylamine (13 g., 71.8 mmoles) was kept in a sealed tube at 160-165° for 6 hours. The reaction mixture was purified by chromatography on alumina using ether as an eluent to afford a colorless oil III (19.2 g., 94%); ir (film): 3300, 1680; nmr (deuteriochloroform): 6.8 (m, 3H, aromatic H), 3.85 (s, 6H, $2xCH_3O-$), 2.8 (s, 3H, $CH_3N<$) 2.45 (s, 1H, disappeared by treatment with deuterium oxide).

1-[2-(2-Oxo-1,3-dimethyl-3-pyrrolidyl)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (IV).

A solution of III (3.7 g., 10.6 mmoles) in dry chloroform (100 ml.) was treated with ethyl polyphosphate (19 g.) and heated under reflux for 4 hours. The reaction solution was poured into ice-water and the mixture was made basic with 20% potassium carbonate and extracted with chloroform three times. The extracts were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to leave an oil, which was purified through an alumina column using ether as an eluent to give an oil (3.05 g., 87%); ir (film): 1670, 1620; nmr (deuteriochloroform): 7.1 (s, 1H, aromatic H), 6.65 (s, 1H, aromatic H), 3.9 (s, 3H, $-OCH_3$), 3.8 (s, 3H, $-OCH_3$), 2.8 (s, 3H, $CH_3N<$), 1.15 (s, 3H, $-CH_3$). The picrolonate of IV had m.p. 215-217°.

Anal. Calcd. for $C_{29}H_{34}O_8N_6$: C, 58.57; H, 5.76; N, 14.13. Found: C, 58.53; H, 5.49; N, 14.09.

1-[2-(2-Oxo-1,3-dimethyl-3-pyrrolidyl)ethyl]-6,7-dimethoxy-1,2,-3,4-tetrahydroisoquinoline (VIIa) and 1-[2-(2-Oxo-1,3-dimethyl-3-pyrrolidyl)ethyl]-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydro-

isoquinoline (VIIb).

Compound IV (1.0 g., 3 mmoles) in ethanol (30 ml.) was hydrogenated over platinum oxide (70 mg.) at room temperature under atmospheric pressure. Hydrogen uptake ceased after the absorption of the equivalent molar amount. After filtration, evaporation of the filtrate afforded a brown oil, which was purified by chromatography through an alumina column using ether to give a colorless oil VIIa (0.7 g., 70%). The picrolonate of VIIa (yellow needles) had m.p. 222-224°.

Anal. Calcd. for $C_{29}H_{36}O_8N_6$: C, 58.38; H, 6.08; N, 14.09. Found: C, 58.15; H, 5.81; N, 13.96.

A solution of VIIa in acetic anhydride was heated on a boiling water bath for 3 hours. Evaporation of the solvent gave an oil, which was neutralized with 10% sodium carbonate solution. The mixture was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to leave an oil, which was purified by chromatography on an alumina column using benzene to afford VIIb; ir (neat): 1660, 1620; nmr (deuteriochloroform): 3.4 (m, 2H, aromatic H), 3.8 (s, 3H, $-OCH_3$), 2.8 (s, 3H, $CH_3N<$), 2.15 (s, 3H, CH_3CO-), 1.1 (s, 3H, CH_3-).

2,3-Dimethoxy-15-methyl-8,15-diazaestra-1,3,5(10)triene (V) and 1-[2-(1,3-dimethyl-3-pyrrolidyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI).

i) From IV.

A solution of lithium aluminum hydride (0.5 g., 10.6 mmoles) in dry ether (100 ml.) was added dropwise with stirring to a solution of IV (3.5 g., 10.6 mmoles) in dry ether (100 ml.) over 30 minutes under dry agron at 0° and then the mixture was refluxed for 5 hours. To the reaction mixture were added successively, water (0.5 ml.), 15% sodium hydroxide solution (0.5 ml.) and water (1.0 ml.) with ice cooling. The yellow precipitate was removed by filtration, followed by washing with ether. The combined solution of the filtrate and the ether was dried over anhydrous potassium carbonate and evaporated *in vacuo* to leave a pale yellow oil, which was chromatographed on alumina using benzene as an eluent to give V (0.8 g., 24%) as white needles and using chloroform-ethanol (1:1) as a successive eluent to afford VI (2.1 g., 63%) as a pale yellow oil. Compound V had m.p. 84-86°; ir (film): 1610; nmr (hexadeuterobenzene): 6.63-6.53 (m, 2H, aromatic H), 3.76 (q, J = 2.5, 1H, C_9-H) 3.58 (s, 3H, CH_3O-), 3.52 (s, 3H, CH_3O-), 2.62 (s, 3H, $CH_3N<$), 2.55 (s, 1H, C_{14}-H), 0.87 (s, 3H, $-CH_3$). The picrate of V had m.p. 108-111°; mass spectrum: m/e 316 (M^+-$C_6H_3O_7N_3$).

Anal. Calcd. for $C_{25}H_{31}O_9N_5$: C, 55.04; H, 5.73; N, 12.84. Found: C, 54.82; H, 5.63; N, 12.92.

Compound VI had ir (film): 3300, 1620; nmr (deuteriochloroform): 6.65 (s, 1H, aromatic H), 6.55 (s, 1H, aromatic H), 3.8 (s, 6H, 2x-OCH_3), 0.9 (s, 3H, $-CH_3$). The di-picrate of VI had mass spectrum: m/e 318 (M^+-2x$C_6H_3O_7N_3$).

Anal. Calcd. for $C_{31}H_{36}O_{16}N_8$: C, 47.95; H, 4.68; N, 14.46. Found: C, 48.49; H, 4.48; N, 14.19.

ii) From VIIa.

Analogous to the method described under (i), VIIa (450 mg., 1.5 mmoles) was treated with lithium aluminum hydride (57 mg., 1.5 mmoles) to afford V (90 mg., 21%) and VI (190 mg., 45%). The mixed melting points of the picrates of V prepared by both methods were not depressed. The mixed melting points of the picrates of VI prepared by both methods were also undepressed.

Dehydrogenation of V with Mercuric Acetate.

A solution of V (320 mg., 1.0 mmole) and mercuric acetate (805 mg., 2.5 mmoles) in 5% acetic acid was heated with stirring at 60° for 1 hour. The precipitated mercurous acetate was filtered after cooling and hydrogen sulfide was passed into the filtrate and the mercuric sulfide which separated was filtered. The filtrate was made basic with 10% sodium hydroxide solution and extracted with ether and the extract was dried over anhydrous potassium carbonate and evaporated to give a colorless oil VIII (100 mg.); uv: 278 mμ, 318 mμ. The picrate had m.p. 144-148°; mass spectrum: m/e 315 (M^+-$C_6H_3O_7N_3$).

Formation of V-d_2 and V-d_1 with Lithium Aluminum Deuteride.

According to the procedure described for V and VI, IV and VIIa were treated with lithium aluminum deuteride to give V-d_2 and V-d_1, respectively. Compound V-d_2 had ir (chloroform): 2060, 2040. The picrate of V-d_2 had m.p. 125-126°; mass spectrum: m/e 318 (M^+-$C_6H_3O_7N_3$). Compound V-d_1 had ir (chloroform): 2845, 2795, 2740 (weak), 2720 (weak), 2600, 2050. The picrate of V-d_1 had m.p. 158-160°; mass spectrum: m/e 317 (M^+-$C_6H_3O_7N_3$).

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(5) Compound V-d_2 showed two bands, at 2060 and 2040 cm^{-1}, and V-d_1 showed a band 2050 cm^{-1} in the C-D stretching region. It has been 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 groups), which suggests the *trans*-diaxial orientation of C-9 proton and C-14 proton to the nitrogen lone pair (at 8 position), see J. Skolik, P. J. Krueger, and M. Wiewiorowski *Tetrahedron.*, **24**, 5439 (1968), and references therein.

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