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Synthesis in the Diazasteroid Group. IV.[1] A Synthesis of 2,3-Dimethoxy-8,14-diaza-15-oxo-gona-1,3,5(10)-triene

Masanori Nagata, Sumiko Miyakoshi, Hiroshi Takezawa, Katsuhide Matoba, and Takao Yamazaki

Faculty of Pharmaceutical Sciences, University of Toyama[2]

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3,4-Dimethoxyphenethyl hydrazine (III), reacting with ethyl γ-oxopimelate, was converted into the hydrazone (IV), which was reduced to the corresponding hydrazine (V). V was then subjected to the intramolecular ring closure to afford (VI), which showed dimorphism. VI was subjected to the Bischler-Napieralski reaction accompanied with the reduction to afford the titled compound (VIII), which was also obtained by the Bischler-Napieralski ring closure of V followed by the reduction and the ring closure to furnish the D-ring of the diazasteroid.

The stereochemistry of VIII was discussed based on its nuclear magnetic resonance data and its mercuric acetate oxidation.

Succeeding to the preceding paper,[3] we now report on a synthesis of the 8,14-diazasteroid system. Previously S. Sugasawa and K. Kohno,[4] starting with homopiperonyl hydrazine and ethyl 3-formylpropionate, established a method for the synthesis of 1,2,3,6,7,11b-hexahydro-4H-1,3-dioxolo[*j*]pyridazo[3,2-*a*]isoquinoline, a derivative of 4,5-diazabenzo[*a*]quinolizine. After the manner of their method, the equivalent moles of homoveratraldehyde and acetohydrazide in alcohol were heated on a water bath to furnish colorless crystals, mp 132—134°, in 95% yield. The product was consistent with the given structure, 1-acetyl-2-(3′,4′-dimethoxyphenethylidene)hydrazine (I), identified by the elementary analysis and the infrared (IR) absorptions at 3100 cm^{-1} and 1630 cm^{-1}. I was reduced over platinum oxide, absorbing one mole of hydrogen, to give the corresponding hydrazine (II), mp 106—108°, in quantitative yield. The elementary analysis and the IR spectrum supported the structure given to II. II was then hydrolysed with hydrochloric acid to furnish a colorless viscous oil (III), $bp_{1-1.5}$ 157—159° in 67.5% yield. III, exhibiting a positive Fehling's test in the warm, furnished the corresponding hydrochloride mp 100°, treated with hydrochloric acid in alcohol. The elementary analysis and the IR spectrum of the hydrochloride supported the structure, 3,4-dimethoxyphenethyl hydrazine, III. Next III was treated with the equivalent moles of ethyl γ-oxopimelate in alcohol for 5.5 hr under reflux in the presence of a catalytic amount of acetic acid, affording colorless crystals, mp 66—68°, in 80% yield. The IR spectrum of the product gave typical absorption bands at 1720 cm^{-1} associated with an ester carbonyl and at 1650 cm^{-1} (broad) associated with a six-membered lactam. The nuclear magnetic resonance spectrum (NMR) and the elementary analysis also together with the IR absorption bands supported the structure, 3-carboethoxyethyl-4,5-dihydro-1-(3′,4′-dimethoxyphenethyl)-6(2H)-pyridazone (IV). A solution of IV in alcohol was successively subjected to the catalytic hydrogenation over platinum oxide in the presence of the equivalent mole of hydrogen chloride to afford a faint yellow oil in quantitative yield after work-up in a usual manner. The oil here obtained was verified to be 3-carboethoxyethyl-2,3,4,5-tetrahydro-1-(3′,4′-dimethoxyphenethyl)-6(2H)-

1) A part of this work was presented at the annual Meeting of the Pharmaceutical Society of Japan, 1970, in Sapporo.
2) Location: *Gofuku-3190, Toyama.*
3) Synthesis of Diazasteroids Group. III, T. Yamazaki, K. Matoba, K. Isomura, M. Nazata, and R.N. Castle. *J. Heterocycl. Chem.*, **11**, 503 (1974).
4) S. Sugasawa and K. Kohno, *Pharm. Bull.* (Japan), **4**, 477 (1956).

pyridazone (V) based on its IR and NMR data. V was heated at 195—200° in ethylene glycol under gentle reflux for 18 hr. As described in the experimental, the rapid crystallization of the reaction product from acetone afforded colorless needles, mp 124—126°, while the gradual crystallization furnishing colorless plates, mp 147—149°, in 75% yield. The each IR spectrum of the both crystals on KBr disk differed from each other, while their solutions in chloroform affording one and the same absorption spectrum. Both the elementary analyses and the NMR spectra were also respectively identical with each other, suggesting their dimorphism. Moreover, the mass spectrum (MS) gave the base peak at *m/e* 167 basides the molecular ion peak at *m/e* 318 (Chart 2a).

All of these chemical and physical data are thus consistent with the structure, 1-(3′,4′-dimethoxyphenethyl)-2,7-dioxo-octahydropyrrolo1[1,2-*b*]pyridazine (VI), given to the reaction product from V. It is therefore concluded that the intermolecular condensation leading to the formation of the ten membered lactam ring compound (IX) was not effected. VI was then subjected to the Bischler-Napieralski ring closure, giving colorless crystals, mp 192—194°, in quantitative yield. The product was verified to be 2,3-dimethoxy-8,14-diaza-11-oxo-gona-1,3,5(10),9(11)-tetraene (VII), based on its elementary analysis, IR, NMR, and ultraviolet (UV) spectra, and its iodonium salt (VIIa), mp 204°, also supported the given structure. Though a seven membered ring compound (X) was also expected on the cyclization of VI, the physical data preferred the structure VII to X. Moreover, in the MS spectrum of VII (Chart 2b), the stable ion peak of 6,7-dimethoxy-3,4-dihydroisoquinoline, *m/e* 190, could be observed, supporting the isoquinoline ring closure. Both the catalytic reduction over platinum oxide and sodium borohydride reduction of VIIa afforded one and the same product (VIII), mp 126—129°, in quantitative yield. In addition, the Bischler-Napieralski ring closure of V, accompanied with the reduction and the successive cyclization leading to the C/D ring fusion, also furnished one and the same compound, VIII. All of these data support the given structures, VII and VIII, denying the formation of X.

trans-Benzo[*a*]quinolizidine in general exhibits a triplet NMR signal at a higher field[5] ($>6.2\tau$) associated with 11bH-proton and Bohlman bands at the Wenkert region.[6] Moreover, it is readily subjected to the mercuric acetate oxidation to furnish the corresponding dehydrobase. On the other hand, *cis*-benzo[*a*]quinolizidine exhibits a triplet or a quartet NMR signal of 11bH-proton at a lower field ($<6.2\tau$) and no Bohlmann bands. And the mercuric acetate oxidation is effected only under servere conditions.

In our case, VIII exhibited a quartet signal at 5.96τ associated with C-9 proton which couldn't be observed when VII or VIIa was reduced with sodium borodeuteride in deuterium methoxide, and its mercuric acetate oxidation was effected under drastic conditions described in the experimental. Thus the configuration of VIII was deduced to be of *cis*-benzo[*a*]quinolizidine type.

In addition, the quartet signal at 5.96τ made us conclude that C-9 proton was located non-equivalent to both the adjacent C-11 protons, thus suggesting VIIIa type benzoquinolizidine moiety, because if C-9 proton were located equivalent to both the C-11 protons, the NMR signal of C-9 proton should be observed as a triplet suggesting VIIIb type benzoquinolizidine moiety. Accordingly C-9 proton is located equatorial to the B ring and axial to the C ring.

5) M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3346 (1964); H. Bruderer, M. Baumann, M. Uskoković, and A. Brossi, *Helv. Chim. Acta.*, **47**, 1852 (1964); T.A. Crabb, R.F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971); R.E. Brown, D.M. Lustgarten, R.J. Stanaback, and R.I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966); A.I. Meyers, G.G Munoz, M. Sobotka, and K. Baburao, *Tetrahedron Letters*, **1965**, 255; C.M. Lee, W.F. Trager, and A.H. Backett, *Tetrahedron*, **23**, 375 (1967).

6) E. Wenkert and D.K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

7) Here *syn* and *anti* refer to the relative configurations of the angular hydrogen at C-9 and the hydrogen at C-13: R.E. Brown, D.M. Lustgaten, R.J. Stanaback, and R.I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966).

As regards the spacial orientation of C-13 proton, two conformations, *syn* or *anti*[7] to C-9 proton might be possible. However taking the Dreiding model into consideration, C-9 and C-13 protons should be *anti* to each other, otherwise the D ring cann't be fabricated. In the above statement we assumed the chair form of the C ring, thus deducing *anti-cis*-benzoquinolizidine configuration, VIIIa (Chart 3). However assuming the boat form of the C ring, the structure VIIId is also accepted, but VIIIe should be denied, because in the structure, VIIIe, C-9 proton should exhibit a triplet signal in NMR spectrum.

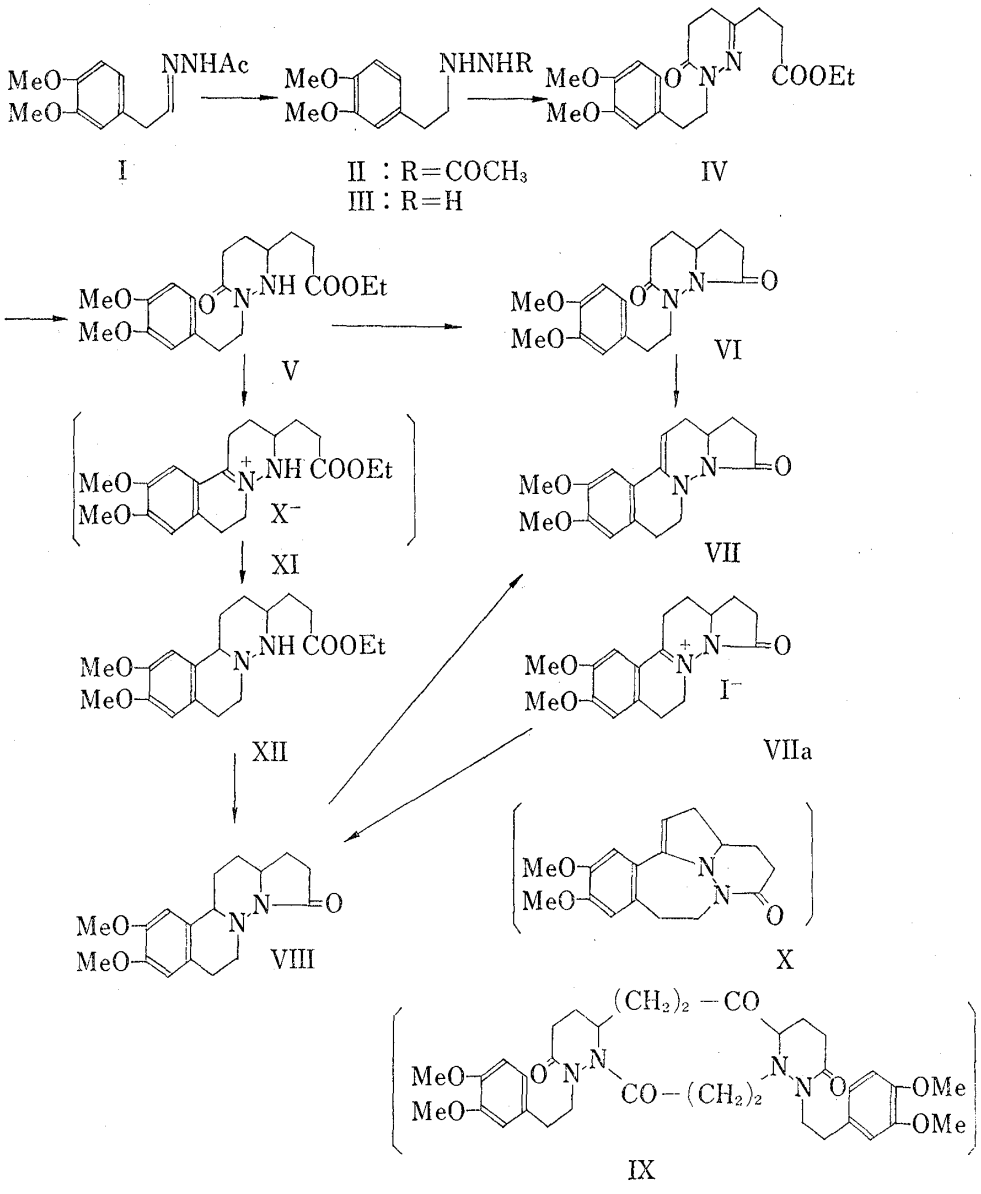


Chart 1. Synthesis of the 8,14-Diazasteroid System

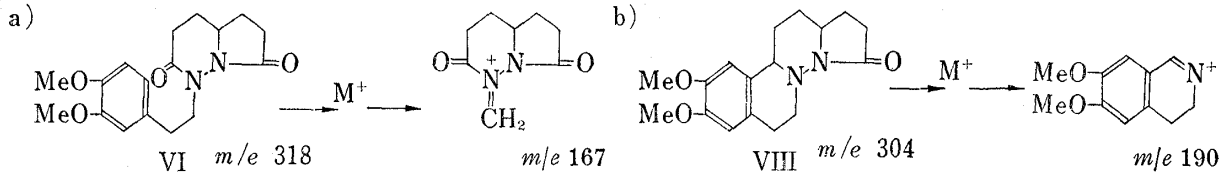
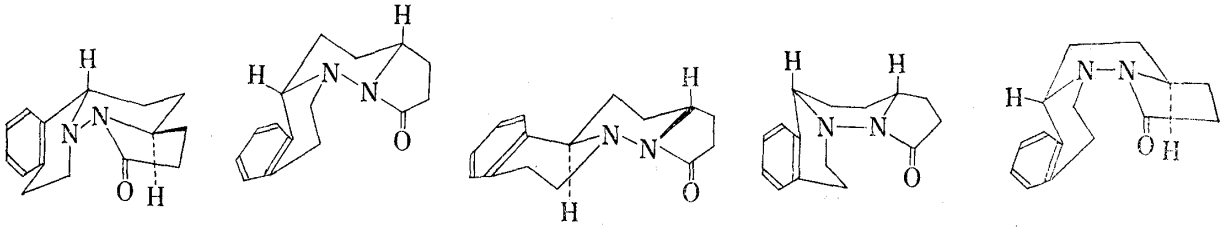


Chart 2. Principal Mass Spectral Cleavage

Finally we deduced that the retarted mercuric oxidation of VIII to VIIa should be ascribed to the slow conversion of VIIIa or VIIId into *anti-trans*-quinolizidine conformation VIIIc (Chart 3) even at an elevated temperature, followed by the successive dehydrogenation,[8] and the decisive conclusion on the structural determination of VIII, that is VIIIa or VIIId, wasn't obtained.



VIIIa	VIIIb	VIIIc	VIIId	VIIIe
anti-cis-quinolizidine	*syn-cis*-quinolizidine[a]	*anti-trans*-quinolizidine	*syn-cis*-quinolizidine	*anti-cis*-quinolizidine[b]

Chart 3

a) In this structure C-9 proton NMR signal should split into a triplet because two C-11 protons are equivalent to C-9 proton.
b) In this structure C-9 proton NMR signal should split into a triplet, because two C-11 protons are equivalent to C-9 proton.

Experimental

IR spectra were taken on a Hitachi Grating Infrared spectrophotometer 215, and UV spectra on a Hitachi 124 spectrophotometer. Gass–liquid chromatography (GLC) measurements were carried out by using a Shimazu GC-4A instrument (SE-30 as column material, hydrogen as the carrier gas). NMR spectra were taken on JEOL-C-60H and C-100 tetramethylsilane as internal standard). The wave length (λ) of the UV spectrum is represented by nm. Mass spectral data were taken on a Hitachi RMU-7L. All the melting points are uncorrected. Unless otherwise stated, all the solvents were distilled off under diminished pressure.

1-Acetyl-2-(3′,4′-dimethoxyphenethylidene)hydrazine (I)——To a solution of homoveratraldehyde (12 g, 0.067 mole) in EtOH (120 ml) was added acetohydrazide (5 g, 0.068 mole). The mixture was heated for 15 min on a water bath, and then concentrated until 40 ml. After cooling the solution gave crystals, which were recrystallized from EtOH to give (I) as white prisms. 15 g, (95%) mp 132—134°. IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1690 (CO), 1640 (C=N). *Anal.* Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.03; H, 6.94; N, 11.66.

1-Acetyl-2-(3′,4′-dimethoxyphenethyl)hydrazine (II)——Compound I (15.3 g, 0.065 mole) in EtOH (250 ml) added with AcOH (0.4 ml) was hydrogenated over PtO_2 (1.5 g) at 30—35° under atmospheric pressure. Hydrogen uptake ceased after absorption of one equivalent mole. The catalyst and the solvent were removed to give colorless crystals (15.4 g), which were recrystallized from EtOH to give II, as white prisms, mp 106—108°, IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1650 (CO). *Anal.* Calcd. for $C_{12}H_{18}O_3N_2$: C, 60.48; H, 7.61; N, 11.48. Found: C, 60.10; H, 7.96; N, 11.48.

3,4-Dimethoxyphenethylhydrazine (III)——Compound II (33.3 g, 0.14 mole) in 20% HCl (100 ml) was heated on a water bath for about 40 min. After the removal of the solvent, the reaction mixture was made basic with 20% KOH, saturated with K_2CO_3 and then extracted with *n*-BuOH. The *n*-BuOH extract, dried over K_2CO_3, was worked up in a usual fashion to give a viscous colorless oil III, (18.5 g, 67.5%) $bp_{1-1.5}$ 157—159°, which reduced Fehling solution in the warm. Hydrochloride: colorless plates (from EtOH) mp 100°. *Anal.* Calcd. for $C_{10}H_{16}O_2N_2 \cdot HCl$: C, 51.66; H, 7.37; N, 12.05. Found: C, 51.68; H, 7.53; N, 11.95.

3-Carboethoxyethyl-4,5-dihydro-1-(3′,4′-dimethoxyphenethyl)-6(2H)-pyridazinone (IV)——A solution of compound III (18.5 g, 0.094 mole) and diethyl γ-oxopimelate (21.7 g, 0.094 mole) in EtOH (185 ml) was refluxed for 5.5 hr in the presence of AcOH (0.5 ml), and then evaporated *in vacuo* almost to dryness. The residue was purified through alumina using benzene as an eluent, affording IV (27.3 g, 80%) as a solid mass. Recrystallization from ether–isopropylether (1:2) gave colorless plates, mp 66—68°. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO), 1650 (C=N). NMR ($CDCl_3$) τ: 3.2 (3H, m, arom.), 5.8 (2H, t, J=6 Hz, $-OC\underline{H}_2-CH_3$), 6.14, 6.16 (6H, s, di-OCH_3), 8.75 (3H, t, J=6 Hz, $-OCH_2-C\underline{H}_3$). *Anal.* Calcd. for $C_{19}H_{26}O_5N_2$: C, 62.96; H, 7.23; N, 7.73. Found: C, 62.90; H, 7.40; N, 7.49.

8) F. Bohlmann and C. Arndt, *Chem. Ber.*, **91**, 2167 (1958); E. Wenkert and D.K. Roychaudhuri, *J. Org. Chem.*, **21**, 1315 (1956); E. Farkas, E.R. Lavagnino, and R.T. Rapla, *J. Org. Chem.*, **22**, 1261 (1957).

3-Carboethoxyethyl-2,3,4,5-tetrahydro-1-(3′,4′-dimethoxyphenethyl)-6-(2H)-pyridazinone (V)——Compound IV (25.6 g, 0.071 mole) in EtOH (260 ml) added with 10% HCl–EtOH (25.8 g) was hydrogenated over PtO_2 (2.5 g) at room temperature under atmospheric pressure. Hydrogen uptake ceased after absorption of one equivalent mole. The catalyst and the solvent were removed to give a solid mass, which was neutralized with 10% Na_2CO_3 in the cold. The solution was extracted with $CHCl_3$, dried over anhydrous $CaSO_4$, and worked up in the usual fashion to give an oil. The brown oil was eluted with $CHCl_3$ from alumina column to give a yellow oil V (25.7 g, quantitative yield). IR ν_{max}^{Film} cm^{-1}: 1700 (CO), 1640 (CO, six membered lactam), 3300 (NH). NMR ($CDCl_3$) τ: 3.3 (3H, s, arom.), 6.2, 6.3 (6H, s, di-OCH_3).

1-(3′,4′-Dimethoxyphenethyl)-2,7-dioxo-octahydropyrrolo[1,2-*b*]pyridazine (VI)——Compound V (2 g, 5.5 mmole) in ethylene glycol (20 ml) was gently refluxed for 18 hr, and then the solvent was distilled off. After cooling the reaction mixture was saturated with NaCl, was extracted with $CHCl_3$. The $CHCl_3$ extract, dried over anhydrous $CaSO_4$, gave a brown oil after the removal of the solvent. The oil, purified through alumina using $CHCl_3$ as an eluent, afforded colorless crystals (1.5 g, 75%), which were recrystallized from acetone, giving colorless needles (A), mp 124—126° or colorless plates (B), mp 147—149°. The IR spectra of the $CHCl_3$ solutions of the both crystals were identical with each other. The rapid crystallization of B give A, while the gradual crystallization of A and B. Therefore A and B were dimorphous. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1700 (CO). Mass Spectrum: *m/e* 318 M^+; *m/e* 167 (M^+-151). *Anal.* Calcd. for $C_{17}H_{22}O_4N_2$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.20; H, 7.20; N, 8.63.

2,3-Dimethoxy-8,14-diaza-15-oxo-gona-1,3,5(10),9(11)-tetraene (VII)——To a solution of VI (2.2 g, 6.9 mmole) in benzene was added $POCl_3$ (11 ml) and the mixture was refluxed with stirring for 4 hr. The resultant orange yellow mixture after the trituration with petroleum-ether and the successive removal of the supernant layer, afforded a yellow semi solid mass, which was decomposed with 2% HCl (20 ml) to give a solution, which was treated with charcoal and filtered. The filtrate was neutralized with 10% Na_2CO_3 and extracted with $CHCl_3$. After drying over K_2CO_3, the solvent was evaporated to give crystals, which were recrystallized from EtOH to give VII as white prisms, (2 g, quantitative yield) mp 192—194°. IR ν_{max}^{Nujol} cm^{-1}: 1680 (five membered lactam CO), 1630 (C=C–N). UV λ_{max}^{EtOH} nm (log ε): 257 (3.90), 302 (3.54). NMR ($CDCl_3$) τ: 3.00 (1H, s, C_1–H), 3.45 (1H, s, C_4–H), 4.56 (1H, q, vinyl C_{11}–H), 6.15 (6H, s, $-OCH_3$). *Anal.* Calcd. for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.13; H, 6.79; N, 9.34.

2,3-Dimethoxy-8,14-diaza-15-oxo-gona-1,3,5(10),8-tetraenium Iodide (VIIa)——A solution of VII in 2% HCl was treated with KI afforded yellow crystals. But the reaction mixture was extracted with $CHCl_3$. The extract was dried over anhydrous $CaSO_4$, and worked up in the usual fashion to give yellow crystals, (2.9 g, quantitative yield), which were recrystallized from EtOH to afford yellow needles, mp 202—204°. UV λ_{max}^{EtOH} nm (log ε): 253 (3.96), 310 (3.64), 376 (3.48). *Anal.* Calcd. for $C_{17}H_{21}O_3N_2I$: C, 47.67; H, 4.95; N, 6.55. Found: C, 47.39; H, 4.82; N, 6.47.

2,3-Dimethoxy-8,14-diaza-15-oxo-gona-1,3,5(10)-triene (VIII)——a) Reduction over Platinum Oxide: A solution of compound VII (1 g, 2.3 mmole) in EtOH (10 ml) was reduced over PtO_2 (0.1 g) under atmospheric pressure in the presence of 0.1 g of HCl. After uptake of the calculated amount of hydrogen, the catalyst was removed by filtration, and the filtrate was neutralized with saturated Na_2CO_3 and extracted with $CHCl_3$. After drying, the solvent was evaporated to give crystals, which were recrystallized from EtOH to give VIII (0.9 g, 90%), as white prisms, mp 196—199°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO). NMR ($CDCl_3$) 100 Hz τ: 3.42 (1H, s, C_1–H), 3.50 (1H, s, C_4–H), 5.96 (1H, dd, $J_{ae}=5$ Hz, $J_{aa}=10$ Hz, C_9-H). *Anal.* Calcd. for $C_{17}H_{22}O_3N_2$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.76; H, 7.23; N, 9.31.

b) Reduction with Sodium Borohydride: To a solution of VIIa (1 g, 2.3 mmole) in 90% EtOH (10 ml) was added $NaBH_4$ (0.5 g, 13 mmole) in portions with ice cooling and stirring. The reaction mixture was then stirred at room temperature for 1 hr and acidified with AcOH. After the removal of EtOH, the residue was treated with a little H_2O and then extracted with $CHCl_3$ and the extract was dried over anhydrous $CaSO_4$. The solvent was distilled off to give colorless crystals, which were recrystallized from EtOH, mp 196—199°. The crystal was identical with the compound obtained by the previous method.

c) Another Method from Compound V: To a solution of V (2 g, 5.5 mmole) in dry benzene (30 ml) was added $POCl_3$ (10 ml) and the mixture was refluxed with stirring for 2 hr to separate a yellowish red layer. After cooling, the supernatant layer was decanted, and the residue was treated with petroleum-ether and then with 2% HCl, giving a reddish solution. This was treated with activated charcoal, and the resultant faint golden yellow filtrate was reduced catalytically over PtO_2 (1 g), absorbing one equivalent mole of hydrogen. Worked up as usual, the reaction mixture furnished a brown oil, which was eluted with $CHCl_3$ from alumina column to afford a brown oil XII (1.8 g, 94%), which reduced Fehling solution and exhibited a positive Liebermann test. Hydrazide of XII: Equimol amount of XII and hydrazine hydrate were refluxed for 2 hr in EtOH, and the reaction mixture was allowed to stand to separate the corresponding hydrazide, as white plates mp 175—177°. *Anal.* Calcd. for $C_{17}H_{26}O_3N_4$: C, 61.05; H, 7.84; N, 16.76. Found: C, 61.49; H, 7.41; N, 16.64. Compound XII (1.8 g, 5.2 mmole) in ethylene glycol (18 ml) was gently refluxed for 20 hr. After cooling, the reaction mixture was diluted with saturated NaCl (40 ml), and extracted with $CHCl_3$. The $CHCl_3$ extract, dried over anhydrous $CaSO_4$, gave a brown oil after the removal of the solvent which, when purified through an alumina column $CHCl_3$ as an eluent, afforded colorless crystals (1.1 g, 70%),

which were recrystallized from EtOH. The crystal was identical with the compound by the previous, a) and b).

Reduction of VIIa with Sodium Borodeuteride——A mixture of VIIa (300 mg, 0.7 mmole), $NaBD_4$ (60 mg, 1.5 mmole), and MeOD (50 ml) was stirred at 0° for 1 hr and then at 25° for 2 hr. The solution was diluted with D_2O and the MeOD was removed *in vacuo*. The residue was extracted with $CHCl_3$, was dried over anhydrous $CaSO_4$, and work up in the usual fashion to give colorless crystals, which were recrystallized from EtOH to afford colorless needles, VIII-d, mp 190—194°.

Dehydrogenation of VIII with Mercuric Acetate——A solution of compound VIII (1.2 g, 4.0 mmole) and mercuric acetate (5 g, 16 mmole) in 5% AcOH (25 ml) was heated at 95° for 4 hr with stirring. The first precipitation of mercurous acetate was forced to appear after 30 min. The reaction mixture was then cooled, and the precipitated mercurous acetate was collected by filtration and washed several times with 5% AcOH. The washings and filtrate were saturated with H_2S, and the HgS was filtered off. The filtrate was basified with 10% NaOH, and extracted with $CHCl_3$. After drying, the solvent was evaporated to give crystals, which were recrystallized from EtOH to afford white prisms of VII, which was identical with the compound obtained by the cyclization of VI, mp 192—194°.

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