Synthesis in the Diazasteroid Group X (1). A Synthesis of 8,12-Diaza-D-homosteroid

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The condensation of 1-aminoethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1** with 1,2-cyclohexanedione **2** gave the 8,12-diaza-**D**-homosteroid system **3**, which was reduced with Adams' catalyst followed by acetic anhydride acetylation to afford the 8,12-diaza-**D**-homosteroids **4a,b**.

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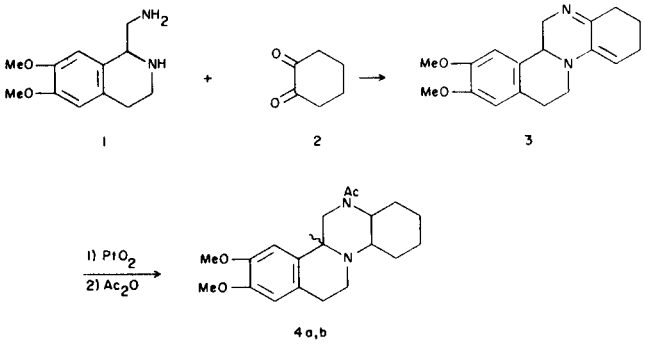
Following the preceding paper (1) and in view of potential biological activity (2), we now report the synthesis of the 8,12-diazasteroid ring system. The formation of the 8,12-diazasteroid system was accomplished by the condensation of compound **1** (3), employed as an A-B ring synthon, with the α-diketone **2**.

The reaction of **1** with **2** in ethanol at ambient temperature afforded the labile condensed-ring compound **3** in about 79% yield; the vinyl proton at C-15 in this compound appears at δ 5.3 in the nmr. However, on standing, compound **3** turned black-brown in color and decomposed giving a resinous substance. Therefore, the product **3** was reduced with Adams' catalyst in ethanol, furnishing an amber oil, which was subsequently acetylated without purification to give an oil, **4**, in about 65% yield. The acetylated product **4** proved to be a mixture of two components based on thin-layer chromatography. Separation was effected by silica gel column chromatography using ethyl acetate-chloroform as an eluent to afford the major product **4a** (m.p. 243-245° as its picrate) and the minor product **4b** (m.p. 228-231° as its picrate) in 22% and 9% overall yield, respectively, from **3**. Based on the elemental analyses of the picrates, and the ir, nmr and mass spectral data, both compounds **4a,b** were shown to be 8,12-diaza-**D**-homosteroids.

The isomer **4a** showed strong Bohlmann bands (2840 and 2760 cm^{-1}) in the ir spectrum and no signal at lower field than δ 3.8, except aromatic protons, in the nmr. Both observations are indicative of a *trans*-quinolizidine conformation with an axial C-9 hydrogen (4,5). On the other hand, the ir of **4b** exhibited no Bohlmann bands and its nmr spectrum indicated a down field signal for the C-9 proton at δ 4.2. These data support a *cis*-fusion of the B/C ring in **4b**. Furthermore, the stereochemistry of the B/C ring fusions in **4a,b** was substantiated experimentally. Mercuric acetate dehydrogenation of **4a** took place smoothly within 5 hours at room temperature, whereas **4b** was almost inert toward this reagent even at 70° after 5 hours.

Chart I



EXPERIMENTAL

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

Preparation of 2,3,6,7,11b,12-Hexahydro-9,10-dimethoxy-1*H*isoquino-[2,1-*a*]quinoxaline (**3**).

To a solution of 1-aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1** (3 g., 14 mmoles) in ethanol (6 ml.) was added 1,2-cyclohexanedione **2** (1.5 g., 14 mmoles) and the mixture was stirred for 15 minutes at ambient temperature. Evaporation of the solvent gave an oil, which was chromatographed on alumina using ether-methanol (10:1), affording a red-brown oil **3** (3.2 g., 79%). Compound **3** had b.p. (0.1 mm) 180° by employing a micro distillation; ir (film): 1620; nmr (deuteriochloroform): 5.3 (t, 1H, C_{15}-H); ms: m/e 298 (M^+).

Anal. Calcd. for $C_{18}H_{22}O_2N_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.28; H, 7.26; N, 9.13.

Preparation of 13-Acetyl-2,3,4,4a,6,7,11b,12,13,13a-decahydro-6,7-dimethoxy-1*H*-isoquino[2,1-*a*]quinoxaline (**4**).

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Compound **4** (980 mg., 3.3 mmoles) in ethanol (10 ml.) was hydrogenated over platinum oxide (150 mg.) at room temperature under atmospheric pressure. Hydrogenation uptake ceased after the absorption of an equivalent molar amount. After filtration, evaporation of the filtrate afforded a brown oil (950 mg.), which without purification was treated with acetic anhydride (1.5 ml.) in benzene (50 ml.) at 90° for 1 hour. Evaporation of the solvent gave an oil (740 mg.), which was chromatographed on silica gel using ethyl acetate-chloroform to afford **4a** (250 mg., 22%) and **4b** (100 mg., 9%). The picrate of **4a** had m.p. 243-245°; ir (film): 2840, 2750 and 1640; nmr (deuteriochloroform): 2.0 (s, 3H, N-Ac); ms: m/e 344 (M^+-$C_6H_9O_7N_3$).

Anal. Calcd. for $C_{26}H_{31}O_{10}N_5$: C, 54.44; H, 5.45; N, 12.21. Found: C, 54.71; H, 5.17; N, 12.06.

The picrate of **4b** had m.p. 228-231°; ir (film): 1640; nmr (deuteriochloroform): 1.95 (s, 3H, N-Ac), 4.2 (b-s, 1H, C_9-H); ms: m/e 344 (M^+-$C_6H_9O_7N_3$).

Anal. Calcd. for $C_{26}H_{31}O_{10}N_5$: C, 54.44; H, 5.45; N, 12.21. Found: C, 54.20; H, 5.32; N, 12.11.

Mercuric Acetate Dehydrogenation of **4a**.

Compound **4a** (100 mg., 0.29 mmole) was added to a mixture of mercuric acetate (500 mg.), 5% acetic acid (10 ml.) and ethanol (10 ml.), and the mixture was stirred for 5 hours at room temperature (no starting material on tlc).

REFERENCES AND NOTES

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