TOTAL SYNTHESIS OF 16-OXA-D-HOMOESTROGENS AND DETERMINATION OF THE RING STEREOCHEMISTRY

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As a part of our synthetic studies on novel heterocyclic steroids, we recently carried out the total synthesis of 16-oxa-D-homoestrogens. The key intermediate, 3-methoxy-16-oxa-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (1), was readily available starting from 2-methyl-5-oxacyclohexane-1,3-dione in good yield, as previously reported.

Catalytic hydrogenation of 1 over 5% Pd/C in ethanol-tetrahydrofuran allowed the stereoselective reduction of the 14,15-double bond, affording 3-methoxy-16-oxa-D-homoestra-1,3,5(10),8-tetraen-17a-one (2) in nearly quantitative yield. Attempted hydrogenation with 10% Pd/C failed to obtain 2, both tetrahydro isomers, 3-methoxy-16-oxa-8α- and -9β-D-homoestra-1,3,5(10)-trien-17a-ones (3 and 4) being isolated.

The dihydro ketone (2) was converted by hydride reduction to 3-methoxy-16-oxa-D-homoestra-1,3,5(10),8-tetraen-17aβ-ol (5). The 8,9-styrene double bond was then reduced stereospecifically with lithium in liquid ammonia and aniline to give the expected 16-oxa-D-homoestradiol 3-methyl ether (6). Conditions involving triethylsilane and trifluoroacetic acid yielded again the anti-trans compound as the major product. The B/C stereoisomers of 6 were also derived from 3 and 4. Finally, chromic acid oxidation of 6 smoothly led to 16-oxa-D-homoestrone 3-methyl ether (7).

The structures of the 16-oxasteroids thus synthesized were established on the basis of NMR data by application of Nagata's rule which involves in determination of the ring stereochemistry in an octahydrophenanthrene system.