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THE TOTAL SYNTHESIS OF (±)-2-AZAESTRADIOL-3-METHYL ETHER[1]

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In an earlier communication[2] we had described the syntheses of various series of 2-azasteroids Of particular interest in this work was the series of 19-nor-2-aza compounds which ultimately resulted in estradiol-3-methyl ether analogs While there have been reports[3] on the preparation of A-ring aza-aromatic steroids, the paucity of biological data on this type of compound prompted a thorough investigation of the biological profile of the newly synthesized 2-azaestratrienes and their precursors.

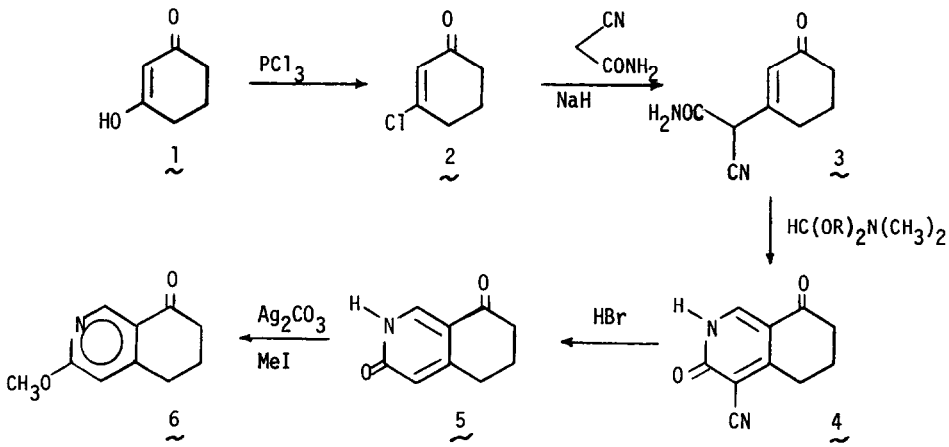
The 2-azaestratriene-3-methyl ether series showed little endocrine activity in a variety of assays used to determine anabolic, androgenic, estrogenic, progestational and anti-fertility properties.[4] Moreover, antagonistic hormonal activity was also absent However, this series was found to possess anti-viral properties in assays to determine anti-influenza activity in our laboratories [5] Even more interesting was the *in vivo* anti-leukemic activity disclosed to us by the National Cancer Institute when a representative of this series was submitted to their screening program.[6] Thus, these rather unique biological properties and the lengthy reaction sequence necessary from naturally occurring steroid starting material prompted our work on a total synthetic route to this series

The classic approach to the total synthesis of estrone derivatives appeared appropriate and a modified Torgov[7] sequence was proposed This made the 7-aza-analog of 6-methoxy-1-tetralone, a heretofore unknown compound, the key intermediate in the projected synthesis. Our approach to this azatetralone, produced in 25-30% overall yield from dihydroresorcinol (1), is shown in Scheme I

Chlorination of 1 with phosphorus trichloride gave 3-chlorocylohex-2-enone(2)[8] which, upon condensation with the sodium salt of cyanoacetamide in glyme, yielded 3-cyanoacetamido-cyclohex-2-enone (3) in 74% yield, mp 181-183°, λ_{max}^{KBr} 6 02, 4 55 and 2 97 μ, λ_{max}^{MeOH} 370 nm (21,900) Contacting 3 with dimethylformamide diethyl acetal in DMF gave rather auspiciously the desired cyanopyridone, 2,3,5,6,7,8-hexahydro-3,8-dioxo-4-isoquinolinecarbonitrile (4) in a single step

in 85% yield. mp >290°; λ_{max}^{MeOH} 227 nm (17,900), 232 nm (sh) (16,000), 279 nm (13,000), 324 nm (6800); δ ppm^{C_5D_5N} 1.93 (2H,m,3-CH_2), 2.57 (2H,brd t,2-CH_2), 2.93 (2H,brd t,4-CH_2), 8.67 (1H,s,8-H).

SCHEME I



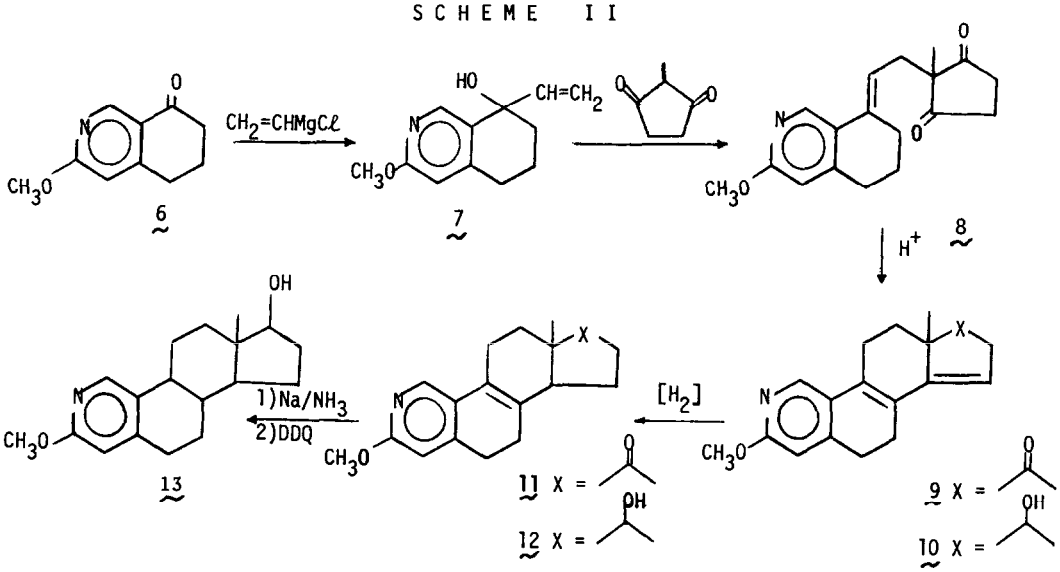
Removal of the nitrile group was achieved by treatment of 4 with aqueous hydrobromic acid affording 2,3,5,6,7,8-hexahydro-3,8-dioxo-isoquinoline (5) in 85% yield. mp 246-248°, λ_{max}^{MeOH} 221 nm (13,500), 279 nm (16,700), δ ppm$^{CDCl_3+CF_3CO_2D}$ 2.23 (2H,m,3-CH_2), 2.73 (2H,brd t,2-CH_2), 2.98 (2H,brd t, 4-CH_2). This sequence (1 to 5) constitutes a novel α-pyridone synthesis whose scope is currently under investigation. O-alkylation of the silver salt of 5 with methyl iodide in benzene yielded the desired 7-aza-6-methoxy-1-tetralone (6) in yields up to 70%: mp 55.5-57°, λ_{max}^{MeOH} 268 nm (13,100), $\lambda_{max}^{CHCl_3}$ 5.92, 6.23 and 7.80 μ, δ ppm^{CDCl_3} 2.14 (2H,m,3-CH_2), 2.64 (2H,brd t,2-CH_2), 2.91 (2H,brd t,4-CH_2), 3.97 (3H,s,-OCH_3), 6.56 (1H,brd s,5-H), 8.83 (1H,s,8-H).

The construction of the steroid ring system is shown in Scheme II. Reaction of 6 with excess vinyl magnesium chloride in xylene gave the vinyl carbinol (7) which was condensed with 2-methyl-cyclopenta-1,3-dione in refluxing xylene to afford 5,6,7,8 -tetrahydro-3-methoxy-8-[(2-methyl-1,3-dioxo-cylopent-2-yl) ethylidene] isoquinoline (8) in good overall yield mp 79-80 5°, λ_{max}^{MeOH} 262 nm (18,000), $\lambda_{max}^{CHCl_3}$ 5 78, 6.20, 6.73μ, δ ppm^{CDCl_3} 1.17 (3H,s,-CH_3), 2.73 (4H,brd s,cyclopentyl-CH_2's), 3 92 (3H,s,-OCH_3), 5.72(1H,brd t,vinyl-H), 6.44 (1H, brd s,5-H), 8.23 (1H,s,8-H).

Cyclization of 8 was sluggish, paralleling the reactivity of the 4-azaestratrienes and the 4,6-diazasteroids reported by Huisman et al.[9] and Bonet et al.,[10] respectively. However, by refluxing 8 in xylene-dioxane with two to three equivalents of tosyl acid the tetracyclic product 9 was obtained mp 167-169° (dec). λ_{max}^{MeOH} 298 nm (28,000); δ ppm^{CDCl_3} 1.14 (3H,s,18-CH_3), 3.93

(3H,s,-OCH_3), 5 89 (1H,t,J=3Hz,15-H), 6.55 (1H,brd s,4-H), 8.08 (1H,s,1-H). Sodium borohydride reduction of 9 in MeOH gave the 17-OH derivative, (±)-2-azaestra-1,3,5(10),8,14-pentaene-3,17-diol 3-methyl ether (10): mp 130-136°, λ_{max}^{MeOH} 300 nm (28,000). This compound underwent desired catalytic hydrogenation affording the 14α-H product (12) in 90% yield mp 155-157.5°, λ_{max}^{MeOH} 267 nm (18,000), δ ppm ^{CDCl_3} 0.79 (3H,s,18-CH_3), 3.93 (3H,s,-OCH_3), 6.52 (1H,brd s,4-H), 7.97 (1H,s,1-H). This assignment is based on the fact that this is the preponderant isomer of the hydrogenation and the relative position of its 18-CH_3 resonance is upfield (ca. 0.20 ppm) from the 18-CH_3 resonance of the other isomer.[11,12]

SCHEME II



Alternatively, 9 was hydrogenated to give 11 which upon sodium borohydride reduction also led to 12. However, the 14α/14β isomer ratio was greater when the hydrogenation was carried out on 10 rather than 9 (determined by nmr to be 9 1 vs. 8 2, respectively).[11,12]

The critical step in the synthesis of the estradiol-3-methyl ether analog was trans reduction of the 8,9-double bond. Earlier reports by Huisman[12] had indicated destruction of the A-ring aromatic nucleus during chemical reduction. We also observed this phenomenon when 12 was treated with sodium in liquid ammonia at -78°. However, rearomatization of the dihydropyridine produced by this reaction[13] could be achieved by subsequent dehydrogenation with DDQ which led to (±)-2-azaestradiol-3-methyl ether (13) in moderate yield mp 153-156°; λ_{max}^{MeOH} 276 nm (3700); δ ppm ^{CDCl_3} 0 78 (3H,s,18-CH_3), 3.90 (3H,s,-OCH_3), 6 44 (1H,brd s,4-H), 8.03 (1H,s,1-H).

Recent reports[14] also prompted investigation into the use of triethylsilane and trifluoracetic acid to steroespecifically reduce the 8,9-double bond. While this method appeared to be an attractive means of circumventing reduction of the A-ring, attempts thus far, have been unscuccessful in transforming 12 to 13 by this method.[15]

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REFERENCES

1. Presented at the IV International Congress on Hormonal Steroids, Mexico City, Sept., 1974 and abstracted in J. Steroid. Biochem., 5, 300 (1974).

2. R Pappo and R. J Chorvat, Tetrahedron Lett., 3237 (1972).

3. See for example H. O. Huisman, Angew. Chem , int ed., 10, 450 (1970) and references therein and P Morand and J Lyall, Chem. Revs., 68, 85 (1968) and references therein

4. These assays were carried out under the direction of Mr. Walter Pautsch, Head of Endocrinology Screening.

5. We are greatful to Dr N P Rapoza of our Virology Department for conducting these assays

6 2-Azaestradiol-3-methyl ether 17-acetate was active in the L1210 assay at 100 mpk when administered at 4 day intervals.

7. S. N Ananchenko and I.V. Torgov, Tetrahedron Lett , 1553 (1963).

8. Y. Tamura, Y. Yoshimoto, M. Suzuki and M. Terashima, Chem and Ind , 1410 (1970)

9. M A. T. Sluyter, U. K Pandit, W. N Speckamp and H O. Huisman, Tetrahedron Lett., 87 (1966)

10. J. J Artus, J J. Bonet and A. E Pena, Tetrahedron Lett., 3187 (1973)

11. J Steele, L. A Cohen and E Mosettig, J Am. Chem. Soc., 85, 1134 (1963). These relative positions have also been observed in our laboratories for the 18-CH_3 resonances of the 14α-and 14β-isomers of estra-1,3,5(10),8-tetraene-3,17-diol-3-methyl ether.

12 H. O Huisman, Bull. Soc , Chim. (Fr), 13 (1968)

13 Upon ammonium chloride quench, the predominant product of this reduction was the 2,5(10)-diene as indicated by nmr and uv spectroscopy

14. T. A Serebryakova, A. V Zakharychev, R N Chigir, S N Ananchenko, I V. Torgov and E. G Krjutchenko, U. S. Patent 3,712,910 (1973).

15. See also D N Kursanov, Z. N Parnes and N. M Loim, Synthesis (9), 633 (1974) and references therein for a more thorough review of this method.