SELECTIVE SYNTHESIS OF 14-DEHYDROESTRANES

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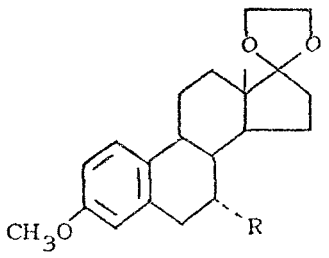
The report of the preparation and high androgenic activity of Δ^{14}-19-nortestosterone and its 7α-methyl derivative[1] prompts us to disclose an alternate synthesis of these compounds. The introduction of the double bond into the 14-position of estranes has been accomplished by acid or base equilibration of an initially formed Δ^{15} isomer.[1-4] The difficulty associated with such a preparation is that a thermodynamic mixture is usually obtained which contains appreciable amounts of other isomers. The presence of these isomers at the same time lowers the yield of the desired product and makes its isolation more difficult.

We have found that the sodium borohydride reduction of the enol acetate 5 derived from the parent estra-1,3,5(10)15-tetraen-17-one 4 affords the corresponding Δ^{14}-17β-ol 6 in good yield. In this approach the formation of double bond isomers is not observed and the overall synthesis can be accomplished without chromatography.

The intermediate Δ^{15}-17-ketones were prepared in three steps from the 3-methyl ethers of estrone and 7α-methyl estrone ketals 1 by a minor modification of a procedure used by Shoppee and Newman for the preparation of 5β-androst-15-en-17-one.[5] Bromination of the ketal 1 with pyridinium bromide perbromide in tetrahydrofuran gave the 16-bromo derivative 2 which was dehydrohalogenated in refluxing xylene

with potassium t-butoxide. The α,β-unsaturated ketone 4 was obtained by mild acid hydrolysis in acetone. The enol acetate 5 was formed by reacting the ketone with acetic anhydride in the presence of p-toluene sulfonic acid. Subsequent reduction of the enol acetate with aqueous sodium borohydride gave the desired Δ^{14}-estradiol derivatives 6. Birch reduction followed by acid hydrolysis then afforded the corresponding Δ^{14}-19-nortestosterone analogs 7 as crystalline, well-defined materials.



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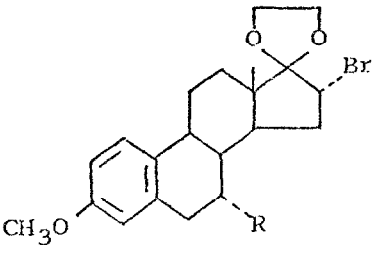

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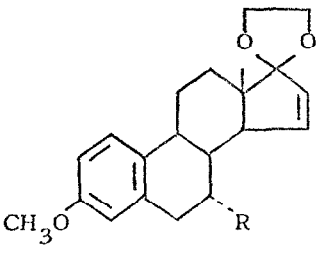

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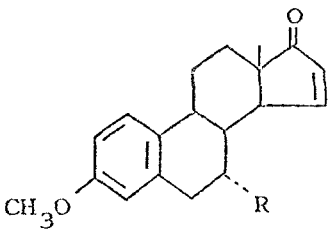

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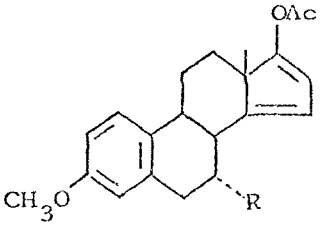

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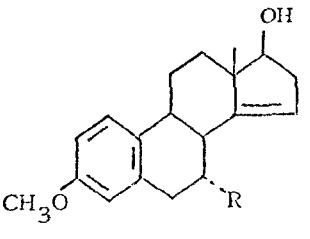

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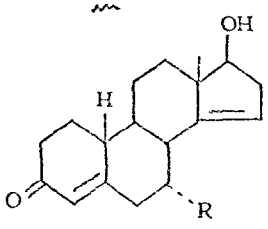

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a R = H

b R = CH_3

EXPERIMENTAL[6]

16-Bromo-17-ethylenedioxy-3-methoxy-7α-methylestra-1,3,5(10)-triene 2b. To an ice-cooled solution of the ketal 1b[7] (3.00 g, 8.77 mmoles) in 100 ml of tetrahydrofuran was added portionwise with stirring 3.00 g (9.37 mmoles) of pyridinium bromide perbromide. After stirring at 0° for 1.5 hr the mixture was filtered. The filtrate was concentrated to near dryness and then was treated with saturated $NaHCO_3$ solution. The product was extracted into ethyl acetate, washed well with water and then dried ($CaSO_4$). Concentration afforded a crystalline residue. Recrystallization from isopropanol gave 2.685 g of the brominated ketal 2b as plates, mp 128-130. Anal C, H, Br.

17-Ethylenedioxy-3-methoxy-7α-methylestra-1,3,5(10),15-tetraene 3b. Xylene (150 ml) containing 10 g of freshly prepared potassium t-butoxide was heated until about 25 ml of solvent had been removed. The bromoketal 2b (2.600 g, 6.17 mmoles) was added and the mixture was heated at reflux for 16 hr. Ice (50 g) was added to the cooled mixture. The organic layer was separated and washed with water. The solution was dried ($CaSO_4$) and concentrated. The residue was recrystallized from heptane to give 1.742 g of the Δ^{15}-ketal 3b, mp 125-126. Anal. C, H.

3-Methoxy-7α-methylestra-1,3,5(10),15-tetraen-17-one 4b. The unsaturated ketal 3b (1.70 g, 5.0 mmoles) was dissolved in 120 ml of acetone containing 20 ml of water and 85 mg of p-toluenesulfonic acid. After 4 hr at 26°C the acid was neutralized with solid sodium bicarbonate. The solution was concentrated to about 40cc and then was diluted with saturated sodium chloride solution. The product was extracted into ethyl acetate. After washing, drying ($CaSO_4$) and concentration the crystalline residue of 4b amounted to 1.295 g. A portion of 4b recrystallized from hexane-ether had mp 191-194° $[\alpha]_D$ -30.8 λ_{max} 224 (ε12,600), 272 (ε2100) and 287 nm (ε2000). Anal. C, H.

3-Methoxy-7α-methylestra-1,3,5(10),14-tetraene-17β-ol 5b. A solution of 1.28 g (4.32 mmoles) of the ketone 4b in 60 ml of acetic anhydride was treated with 360 mg of p-toluenesulfonic acid. After stirring at 26°C for 24 hr pyridine was added to the dark solution to neutralize the acid. The solution was then concentrated under reduced pressure at 25-30° to a small volume. Saturated sodium bicarbonate solution was added. When the anhydride was decomposed, the product was extracted into ether. The solution was washed with water and saturated sodium chloride solution, then dried and concentrated to 1.35 g of a yellow oil, 5b, which would not crystallize but which moved as a single spot on thin layer chromatography.

To a solution of this enol acetate in 75 ml of ethanol was added at 0° a solution of 800 mg of sodium borohydride in 75 ml of ethanol:water (10:3). This solution was kept at 5-10°C for 16 hr and then was neutralized with glacial acetic acid. The organic solvent was largely removed under reduced pressure and the crude product was precipitated by addition of water to the residue. The product after separation by filtration was washed with water and was dried in vacuo to afford 5b, 1.127 g, mp 155-159°. A portion from acetonitrile had mp 161-162°, $[\alpha]_D$ +103.7°. Anal. C, H.

3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate 5a. 3-Methoxyestra-1,3,5(10),15-tetraen-17-one 4a was prepared essentially as described above for the 7α-methyl derivative starting with estrone methyl ether 17-ethylene ketal. A solution of 3.00 g (10.06 mmoles) of the enone 4a in 100 ml of acetic anhydride containing 500 mg of p-toluene sulfonic acid was heated at 100° for 2 hr. Potassium bicarbonate (500 mg) was added to the cooled mixture which was then concentrated under reduced pressure to a dark semicrystalline mass. Saturated sodium bicarbonate solution was added and the product was extracted into ether. The ether layer was washed with water and dried. Concentration afforded 3.2 g of a reddish crystalline residue. Recrystallization from methanol gave 1.13 g of 5a, mp 122.5-124.5. An additional 536 mg was obtained by chromatography of the mother liquors on silica gel. Another recrystallization from hexane gave material mp 123-125° $[\alpha]_D$ +290.7°; nmr ($CDCl_3$) 3.02 m (arom. CH), 3.83 d (J=2.5 Hz, 16-CH), 4.14 narrow multiplet (15-CH), 6.23 s (CH_3O), 7.80 s (CH_3CO_2) and 8.90τ (18-CH_3). Anal. C, H.

3-Methoxyestra-1,3,5(10),14-tetraen-17β-ol 6a. A sample of the enol acetate 5a (1.367 g) was reacted with aqueous sodium borohydride as described above for the corresponding 7α-methyl compound to give 982 mg of the Δ^{14}-17β-hydroxy compound 6a, mp 112-114° $[\alpha]_D$ +149.6°, nmr ($CDCl_3$) 3.02 m (arom. CH), 4.79 narrow multiplet (15-CH), 6.24 s (CH_3O), and 9.00τ (18-CH_3). Anal. C, H.

17β-Hydroxyestra-4,14-dien-3-one 7a. To a solution of 1.00 g (3.52 mmoles) of the estratetraenol 6a in a mixture of 75 ml of ether, 25 ml of t-butanol and 300 ml of anhydrous liquid ammonia was added portionwise 90 mm of lithium wire. The blue solution was stirred under nitrogen for 3 hr. Methanol was added slowly until the blue color was quenched. The ammonia was allowed to evaporate and the product solution was diluted with ether. The organic layer was washed with water and then dried ($CaSO_4$). Concentration left a crystalline residue of the intermediate dihydroaromatic which was carried on directly to the next step. To a solution of the material in 30 ml of ethanol was added 5 ml of 2.5 N hydrochloric acid. The solution was refluxed for 15 min and then was cooled and neutralized with sodium bicarbonate solution. The mixture was partially concentrated under reduced pressure. The product was extracted into ethyl acetate. After washing with water and drying ($CaSO_4$) the solution was concentrated to a pale yellow crystalline residue. Recrystallization from acetonitrile gave 520 mg of 7a, mp 168-172. An analytical sample had mp 171-173°. Anal. C, H.

17β-Hydroxy-7α-methylestra-4,14-dien-3-one 7b. The 7α-methylestratetraenol (1.00 g, 3.36 mmoles) was converted to the corresponding 19-nortestosterone 7b as described above. The initially oily product could be crystallized (736 mg) from aqueous acetonitrile as needles with a double melting point of 62-65° and 124-126°, $[\alpha]_D$ +40.2, λ_{max} 240 nm (ε 18,100); nmr ($CDCl_3$) 4.12 m (4-CH), 4.85 m (14-CH), 6.00 dd (17-CH), 8.98 s (18-CH_3) and 9.15τ (d, J=7Hz, 7-C-CH_3). Anal. C, H.

The benzoate[8] of 7b had mp 167-169, $[\alpha]_D$ +94, λ_{max} 253 nm (ε29,500). The 17-pivalate[8] of 7b had mp 136-138, $[\alpha]_D$ +57.3, λ_{max} 241 nm (ε17,300)

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6. Melting points were determined on a Kofler Micro hotstage and are uncorrected. Rotations were determined as chloroform solutions (c 1.00) at 25°. NMR data were obtained on a Varian A60A spectrometer with tetramethylsilane as an internal standard. The infrared spectra of all the reported compounds are in agreement with the proposed structures.

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8. Prepared in these laboratories by G. F. Reynolds.