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### Syntheses of C<sub>20</sub> 13 $\alpha$ -Steroidal Progestagens<sup>1)</sup>

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In order to examine the physiological activity the preparation of 3,17-dihydroxy-19-nor-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one 17-acetates (III<sub>d</sub>, IX<sub>c</sub>) has been undertaken. The Grignard reaction of 13 $\alpha$ -estrone (I) with ethynylmagnesium bromide provided two epimeric 17-ethynyl-17-ols (II, VIII<sub>a</sub>), which on hydration were led to 3,17-dihydroxy-19-nor-13 $\alpha$ -pregnatrien-20-ones (III<sub>a</sub>, IX<sub>a</sub>). Elucidation of the stereochemistry at C-17 was attained by the degradative means. First, III<sub>a</sub> was submitted to metal hydride reduction, usual acetylation followed by Serini reaction to afford 19-nor-13 $\alpha$ -pregnatrien-20-one (V). Upon treatment with base V was readily transformed into the thermodynamically much more stable 17 $\alpha$ -epimer (VI<sub>b</sub>), whose structure was confirmed by leading to the known 13 $\alpha$ -estratriene-3,17 $\alpha$ -diol (VII<sub>a</sub>) employing Baeyer-Villiger reaction. The desired compounds were unequivocally obtained from the 3,17-diacetates (III<sub>c</sub>, IX<sub>b</sub>) by partial hydrolysis, respectively.

In a previous paper of this series we reported the syntheses of C-17 epimeric 5 $\alpha$ ,13 $\alpha$ -pregnane derivatives. Of these compounds 17 $\alpha$ -ethynyl-13 $\alpha$ -testosterone exhibited a progestational potency almost equivalent to that of progesterone.<sup>3)</sup> The result is of great theoretical interest since this is the first demonstration of a physiologically active steroid in the 13 $\alpha$ -series. Further interest in the structure-activity relationship of the 13 $\alpha$ -steroids prompted us to examine the 19-nor-13 $\alpha$ -pregnane derivatives having the aromatic ring A.

The preparation of the desired compounds was undertaken along the route previously established.<sup>3,4)</sup> 13 $\alpha$ -Estrone (I), readily obtainable from estrone by photochemical reaction,<sup>5)</sup> was first subjected to Grignard reaction with ethynylmagnesium bromide in tetrahydrofuran. The product could be efficiently separated by column chromatography on silica gel and then by preparative thin-layer chromatography (TLC) into two C-17 epimeric 17-ethynyl-17-ols (II and VIII<sub>a</sub>) in a ratio of *ca.* 5 to 1. When treated with mercury-resin used as a catalyst,<sup>6)</sup> the less polar epimer, II, was hydrated with ease to afford 3,17-dihydroxy-19-nor-13 $\alpha$ -pregnatrien-20-one (III<sub>a</sub>).

The stereochemistry at C-17 was elucidated by leading to the known compound employing Serini reaction<sup>7)</sup> followed by Baeyer-Villiger oxidation. Reduction of III<sub>a</sub> with lithium aluminum hydride and subsequent acetylation yielded the 17,20-glycol 20-acetate (IV), which in turn was subjected to further step without purification. When refluxed with granulated zinc in xylene, IV was led to 19-norpregnatrien-20-one (V) along the configurational inversion of the side chain. Upon brief exposure to methanolic alkali, V was easily transformed into the thermodynamically much more stable 17 $\alpha$ -epimer (VI<sub>a</sub>). Treatment of the 3-acetate

1) This paper constitutes Part XVII of the series entitled "Studies on Cardiotonic Steroid Analogs"; Part XVI: T. Nambara and J. Goto, *Chem. Pharm. Bull.* (Tokyo), **21**, 2209 (1973).

2) Location: Aobayama, Sendai.

3) T. Nambara, J. Goto, A. Sasaki, and K. Sudo, *Chem. Pharm. Bull.* (Tokyo), **21**, 565 (1973).

4) T. Nambara and J. Goto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1937 (1971).

5) T. Nambara, T. Kudo, H. Hosoda, K. Motojima, and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2366 (1969) and references quoted therein.

6) M.S. Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1953).

7) A. Serini, W. Logemann, and W. Hildebrand, *Ber.*, **72**, 391 (1939); L.F. Fieser and Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 1840 (1949).

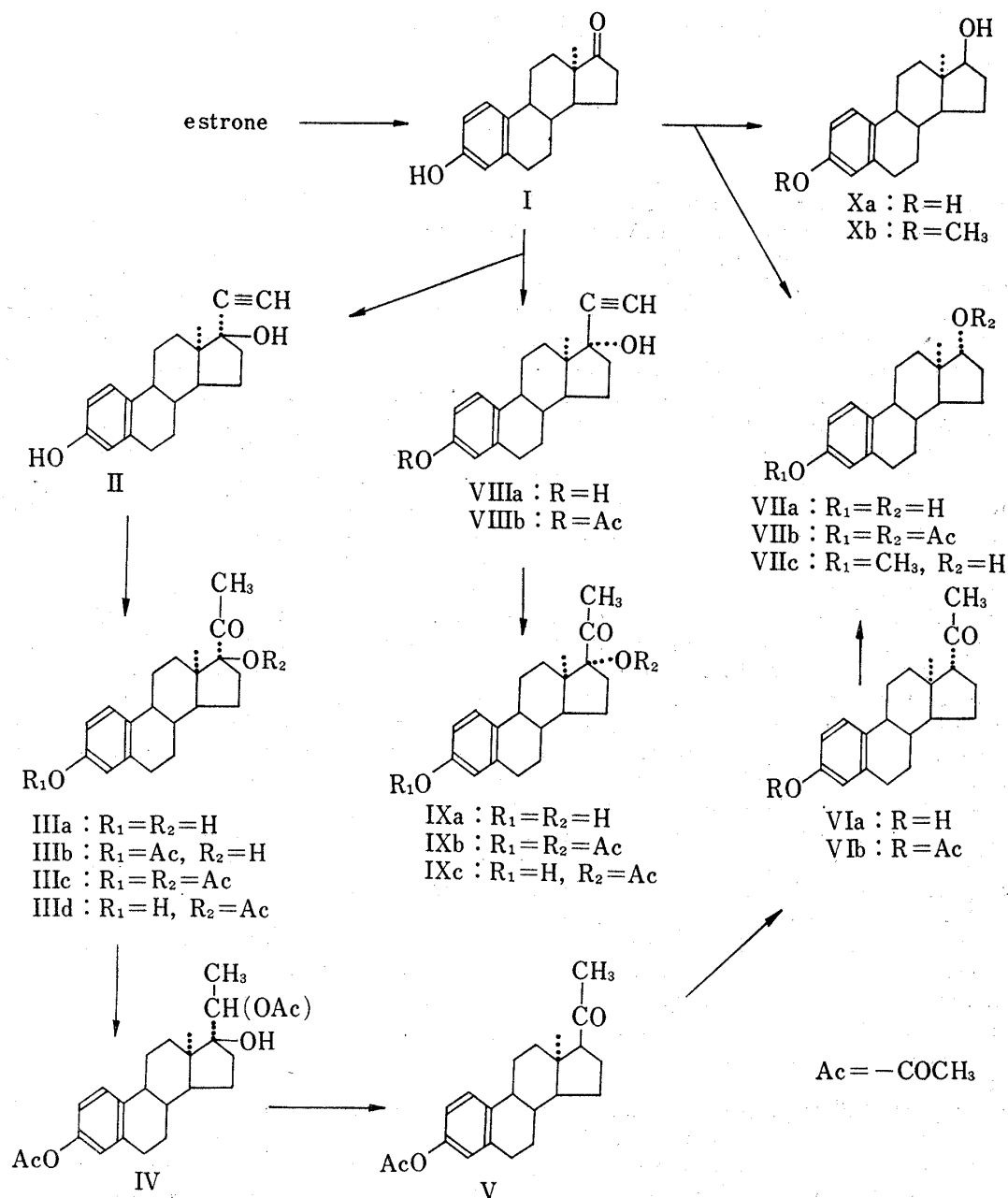


Chart 1

(VIb) with *m*-chloroperbenzoic acid furnished the 17-acetoxy derivative (VIIb) with retention of configuration at C-17.<sup>8)</sup> Hydrolytic cleavage of the 3,17-diacetate with alkali gave 13 $\alpha$ -estratriene-3,17 $\alpha$ -diol (VIIa), whose structure was unambiguously characterized by direct comparison with the authentic specimen. It is evident from these results that the C-17 acetyl group in VI and hence the ethynyl group in II should be both  $\alpha$ .

Similarly, hydration of the triple bond in VIIIa with mercury-resin resulted in formation of the corresponding 17 $\beta$ -acetyl derivative (IXa). Being treated with acetic anhydride in the presence of anhydrous *p*-toluenesulfonic acid, both IIIa and IXa were converted into the 3,17-diacetates (IIIc, IXb) in a satisfactory yield. Treatment of IIIc and IXb with potassium bicarbonate under the mild conditions effected the partial hydrolysis to provide the desired 17-monoacetates (IIId, IXc), respectively.

8) It is sufficiently substantiated that Baeyer-Villiger oxidation proceeds with retention of configuration.<sup>9)</sup>

9) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Co., New York, 1959, p. 338.

The details of bioassay results on these C<sub>20</sub> 13 $\alpha$ -steroids will be reported elsewhere in near future.

### Experimental<sup>10)</sup>

**Grignard Reaction of 3-Hydroxy-13 $\alpha$ -estra-1,3,5(10)-trien-17-one (13 $\alpha$ -Estrone) (I) with Ethynylmagnesium Bromide**—To a solution of CH<sub>3</sub>CMgBr<sup>11)</sup> in anhydrous tetrahydrofuran (THF) (0.5N, 200 ml) was added I (2 g) and refluxed for 6 hr. The resulting solution was poured into a cold saturated NH<sub>4</sub>Cl solution and extracted with AcOEt. The organic layer was washed with 5% HCl, H<sub>2</sub>O and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product was treated with Ac<sub>2</sub>O (12 ml) and pyridine (15 ml). On usual work-up the crude product obtained was submitted to chromatography on silica gel (40 g) and eluted with hexane–benzene (1:2 and 1:4 to 1:10). The more polar fraction was dissolved in 3% methanolic KOH (2 ml) and allowed to stand at room temperature overnight. The resulting solution was diluted with AcOEt, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product obtained was recrystallized from acetone–hexane to give 17 $\beta$ -ethynyl-13 $\alpha$ -estra-1,3,5(10)-triene-3,17-diol (VIIIa) (60 mg) as colorless needles. mp 184–185°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +142.5° (*c*=0.08, MeOH). *Anal.* Calcd. for C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>: C, 81.04; H, 8.16. Found: C, 80.87; H, 8.20. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 3270 (–C $\equiv$ CH), 1625, 1600, 1510 (C=C). NMR (4% solution in CD<sub>3</sub>OD)  $\delta$ : 1.11 (3H, s, 18-CH<sub>3</sub>), 2.72 (1H, s, –C $\equiv$ CH), 6.43 (1H, d, *J*=3 Hz, 4-H), 6.51 (1H, q, *J*=3 and 8 Hz, 2-H), 6.98 (1H, d, *J*=8 Hz, 1-H).

The less polar fraction was dissolved in 3% methanolic KOH (5 ml) and allowed to stand at room temperature overnight. The resulting solution was diluted with AcOEt, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product obtained was dissolved in THF (10 ml). To this solution was added NaBH<sub>4</sub> (100 mg) and allowed to stand at room temperature overnight. The resulting solution was extracted with AcOEt, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After usual work-up a crystalline product obtained was submitted to preparative TLC on Silica gel HF using benzene–AcOEt (15:1) as developing solvent. Elution of the adsorbent corresponding to the Spot (*R<sub>f</sub>* 0.10–0.25) with AcOEt and recrystallization of the eluate from acetone–hexane gave 17 $\alpha$ -ethyl-13 $\alpha$ -estra-1,3,5(10)-triene-3,17-diol (II) (295 mg) as colorless plates. mp 205–206°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +75.0° (*c*=0.06). *Anal.* Calcd. for C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>: C, 81.04; H, 8.16. Found: C, 80.99; H, 8.35. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 3300 (–C $\equiv$ CH), 1615, 1600, 1510 (C=C). NMR (4% solution in CD<sub>3</sub>OD)  $\delta$ : 1.05 (3H, s, 18-CH<sub>3</sub>), 2.72 (1H, s, –C $\equiv$ CH), 6.42 (1H, d, *J*=3 Hz, 4-H), 6.48 (1H, q, *J*=3 and 8 Hz, 2-H), 7.03 (1H, d, *J*=8 Hz, 1-H).

The adsorbent of the area corresponding to *R<sub>f</sub>* 0.05–0.10 was eluted with AcOEt. To a solution of the eluate (800 mg) in CH<sub>2</sub>Cl<sub>2</sub> (70 ml) was added pyridine (12.5 ml)–CrO<sub>3</sub> (1.7 g) complex at 0° and stirred at room temperature for 3 hr. The precipitate was removed by decantation and washed with ether. The supernatant and washings were combined and evaporated. The residue was taken up in ether, washed with 5% NaOH, 5% HCl, 5% NaHCO<sub>3</sub>, and H<sub>2</sub>O, successively, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crude product obtained was recrystallized from MeOH to give unchanged I (400 mg) as colorless prisms.

**3,17 $\beta$ -Dihydroxy-19-nor-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one (IIIa)**—To an ethanolic solution (6 ml) of II (190 mg) were added Hg-Dowex 50 (1.85 g) and H<sub>2</sub>O (0.6 ml) and refluxed for 1.5 hr. The reaction mixture was filtered and the filtrate was diluted with AcOEt, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product obtained was recrystallized from benzene to give IIIa (134 mg) as colorless needles. mp 194–196°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +123.1° (*c*=0.13). *Anal.* Calcd. for C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>: C, 76.40; H, 8.34. Found: C, 76.76; H, 8.48. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1705 (C=O), 1615, 1600, 1510 (C=C). NMR (4% solution in CDCl<sub>3</sub>)  $\delta$ : 0.98 (3H, s, 18-CH<sub>3</sub>), 2.29 (1H, s, 21-CH<sub>3</sub>), 6.52 (1H, d, *J*=3 Hz, 4-H), 6.58 (1H, q, *J*=3 and 8 Hz, 2-H), 7.10 (1H, d, *J*=8 Hz, 1-H).

**3,17 $\beta$ -Dihydroxy-19-nor-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one 3-Acetate (IIIb)**—Treatment of IIIa (30 mg) with Ac<sub>2</sub>O (0.5 ml) and pyridine (1 ml) in the usual manner followed by recrystallization from acetone–hexane gave IIIb (27 mg) as colorless plates. mp 101–103°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +103.3° (*c*=0.15). *Anal.* Calcd. for C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>: C, 74.13; H, 7.92. Found: C, 74.17; H, 7.84. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1770, 1710 (C=O), 1615, 1590, 1505 (C=C). NMR (4% solution in CDCl<sub>3</sub>)  $\delta$ : 0.97 (3H, s, 18-CH<sub>3</sub>), 2.25 (3H, s, 3-OCOCH<sub>3</sub>), 2.28 (3H, s, 21-CH<sub>3</sub>), 6.73 (1H, d, *J*=3 Hz, 4-H), 6.80 (1H, q, *J*=3 and 8 Hz, 2-H), 7.23 (1H, d, *J*=8 Hz, 1-H).

**3,17 $\beta$ -Dihydroxy-19-nor-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one Diacetate (IIIc)**—A solution of IIIa (170 mg) in Ac<sub>2</sub>O (8 ml) was stirred with anhydrous *p*-TsOH (170 mg) at room temperature for 2 hr. The

10) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in CHCl<sub>3</sub> unless otherwise specified. Infrared (IR) spectra were run on JASCO Model IRA-1 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on Hitachi Model R-20A spectrometer at 60 MHz using tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, q=quartet, and m=multiplet.

11) T. Nambara, J. Goto, Y. Fujimura, and Y. Kimura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1137 (1971).

reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with 5% NaHCO<sub>3</sub>, H<sub>2</sub>O and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product obtained was recrystallized from acetone-hexane to give IIIc (178 mg) as colorless needles. mp 125–126°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +95.5° (*c*=0.11). *Anal.* Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>5</sub>: C, 72.33; H, 7.59. Found: C, 72.41; H, 7.64. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1770, 1735, 1725 (C=O), 1610, 1590, 1500 (C=C). NMR (4% solution in CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, s, 18-CH<sub>3</sub>), 2.01 (3H, s, 17 $\beta$ -OCOCH<sub>3</sub>), 2.14 (3H, s, 21-CH<sub>3</sub>), 2.27 (3H, s, 3-OCOCH<sub>3</sub>), 6.76 (1H, d, *J*=3 Hz, 4-H), 6.83 (1H, q, *J*=3 and 8 Hz, 2-H), 7.27 (1H, d, *J*=8 Hz, 1-H).

**3,17 $\beta$ -Dihydroxy-19-nor-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one 17-Acetate (IIIId)**—A solution of IIIc (140 mg) in 1% KHCO<sub>3</sub>/aq. MeOH (25 ml) was allowed to stand at room temperature for 50 min. The resulting solution was diluted with AcOEt, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product was recrystallized from acetone-hexane to give IIIId (113 mg) as colorless prisms. mp 111–113°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +113.3° (*c*=0.15). *Anal.* Calcd. for C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>: C, 74.13; H, 7.92. Found: C, 74.62; H, 8.14. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1740, 1700 (C=O), 1623, 1590, 1510 (C=C). NMR (4% solution in CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, s, 18-CH<sub>3</sub>), 1.99 (3H, s, 21-CH<sub>3</sub>), 2.16 (3H, s, 17 $\beta$ -OCOCH<sub>3</sub>), 6.56 (1H, d, *J*=3 Hz, 4-H), 6.63 (1H, q, *J*=3 and 8 Hz, 2-H), 7.24 (1H, d, *J*=8 Hz, 1-H).

**3-Hydroxy-19-nor-13 $\alpha$ ,17 $\alpha$ -pregna-1,3,5(10)-trien-20-one (VIA)**—To a solution of IIIa (428 mg) in anhydrous THF (30 ml) was added LiAlH<sub>4</sub> (270 mg) and refluxed for 2.5 hr. To this solution was added moistened ether to decompose the excess reagent, diluted with AcOEt, and acidified with 5% HCl. The organic layer was separated, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent an oily residue was treated with Ac<sub>2</sub>O (2.5 ml) and pyridine (3 ml) in the usual manner. On usual work-up 19-nor-13 $\alpha$ ,17 $\alpha$ -pregna-1,3,5(10)-triene-3,17,20-triol 3,20-diacetate (IV) was obtained as an oily product. To a solution of IV in xylene (13 ml) was added granulated Zn (6.4 g) and refluxed under a stream of N<sub>2</sub> gas for 17 hr. The reaction mixture was filtered and the filtrate was evaporated. An oily residue obtained was submitted to preparative TLC on Silica gel HF using benzene-AcOEt (20:1) as developing solvent. The adsorbent of the area corresponding to *R*<sub>f</sub> 0.50–0.60 was eluted with AcOEt. On usual work-up 3-hydroxy-19-nor-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one acetate (V) (252 mg) was obtained as an oily product. NMR (4% solution in CD<sub>3</sub>OD)  $\delta$ : 1.33 (3H, s, 18-CH<sub>3</sub>), 2.16 (3H, s, 21-CH<sub>3</sub>), 2.21 (3H, s, 3-OCOCH<sub>3</sub>). A solution of V (250 mg) in 3% methanolic KOH (6 ml) was allowed to stand at room temperature for 6.5 hr. The resulting solution was diluted with AcOEt, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product was recrystallized from aq. MeOH to give VIA (148 mg) as colorless plates. mp 173–175°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> –34.6° (*c*=0.13, MeOH). *Anal.* Calcd. for C<sub>20</sub>H<sub>26</sub>O<sub>2</sub>: C, 80.49; H, 8.78. Found: C, 80.63; H, 8.90. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1685 (C=O), 1625, 1590, 1510 (C=C). NMR (4% solution in CD<sub>3</sub>OD)  $\delta$ : 0.86 (3H, s, 18-CH<sub>3</sub>), 2.11 (3H, s, 21-CH<sub>3</sub>), 6.46 (1H, d, *J*=3 Hz, 4-H), 6.53 (1H, q, *J*=3 and 8 Hz, 2-H), 7.11 (1H, d, *J*=8 Hz, 1-H).

**3-Hydroxy-19-nor-13 $\alpha$ ,17 $\alpha$ -pregna-1,3,5(10)-trien-20-one Acetate (VIB)**—Treatment of VIA (34 mg) with Ac<sub>2</sub>O (0.5 ml) and pyridine (1 ml) in the usual manner followed by recrystallization from acetone-hexane gave VIB (25 mg) as colorless plates. mp 102–103.5°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +50.0° (*c*=0.06). *Anal.* Calcd. for C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>: C, 77.61; H, 8.29. Found: C, 77.32; H, 8.39. NMR (4% solution in CD<sub>3</sub>OD)  $\delta$ : 0.87 (3H, s, 18-CH<sub>3</sub>), 2.11 (3H, s, 21-CH<sub>3</sub>), 2.22 (3H, s, 3-OCOCH<sub>3</sub>), 6.72 (1H, d, *J*=3 Hz, 4-H), 6.78 (1H, q, *J*=3 and 8 Hz, 2-H), 7.22 (1H, d, *J*=8 Hz, 1-H).

**Baeyer-Villiger Oxidation of VIB**—To a solution of VIB (30 mg) in CHCl<sub>3</sub> (3 ml) was added *m*-chloroperbenzoic acid (120 mg) and stirred at 35° for 30 hr. The reaction mixture was diluted with CHCl<sub>3</sub>, washed with 5% NaHSO<sub>3</sub>, 5% NaHCO<sub>3</sub>, and H<sub>2</sub>O, successively, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After usual work-up an oily residue obtained was submitted to preparative TLC on Silica gel HF using benzene-AcOEt (15:1) as developing solvent. The adsorbent of the area corresponding to *R*<sub>f</sub> 0.40–0.60 was eluted with AcOEt. Evaporation of solvent gave 13 $\alpha$ -estra-1,3,5(10)-triene-3,17 $\alpha$ -diol diacetate (VIIb) as an oily product, which in turn was treated with 3% methanolic KOH (2 ml) at room temperature overnight. The resulting solution was diluted with AcOEt, washed with H<sub>2</sub>O, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent a crystalline product obtained was recrystallized from acetone-hexane to give 13 $\alpha$ -estra-1,3,5(10)-triene-3,17 $\alpha$ -diol (VIIa) (10 mg) as colorless prisms. mp 197–200°. Mixed melting point on admixture with the authentic sample showed no depression and IR spectra of two samples were entirely identical in every respect.

**17 $\beta$ -Ethyne-13 $\alpha$ -estra-1,3,5(10)-triene-3,17-diol 3-Acetate (VIIIb)**—Treatment of VIIa (20 mg) with Ac<sub>2</sub>O (0.5 ml) and pyridine (1 ml) in the usual manner followed by recrystallization from acetone-hexane gave VIIIb (16 mg) as colorless plates. mp 119–120°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +123.3° (*c*=0.15). *Anal.* Calcd. for C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>: C, 78.07; H, 7.74. Found: C, 78.23; H, 7.93. NMR (4% solution in CDCl<sub>3</sub>)  $\delta$ : 1.16 (3H, s, 18-CH<sub>3</sub>), 2.26 (3H, s, 3-OCOCH<sub>3</sub>), 2.48 (1H, s, –C $\equiv$ CH), 6.76 (1H, d, *J*=3 Hz, 4-H), 6.82 (1H, q, *J*=3 and 8 Hz, 2-H), 7.21 (1H, d, *J*=8 Hz, 1-H).

**3,17 $\alpha$ -Dihydroxy-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one (IXa)**—To an ethanolic solution (5 ml) of VIIa (100 mg) were added Hg-Dowex 50 (1 g) and H<sub>2</sub>O (0.5 ml) and refluxed for 1 hr. The reaction mixture was processed in the manner as described in IIIa. A crystalline product obtained was recrystallized from acetone-hexane to give IXa (62 mg) as colorless plates. mp 205–208°. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +104.5° (*c*=0.11, MeOH). *Anal.* Calcd. for C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>: C, 76.40; H, 8.34. Found: C, 76.16; H, 8.49. IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 1700 (C=O), 1617, 1590, 1507

(C=C). NMR (4% solution in  $\text{CD}_3\text{OD}$ )  $\delta$ : 1.23 (3H, s, 18- $\text{CH}_3$ ), 2.21 (3H, s, 21- $\text{CH}_3$ ), 6.42 (1H, d,  $J=3$  Hz, 4-H), 6.50 (1H, q,  $J=3$  and 8 Hz, 2-H), 6.93 (1H, d,  $J=8$  Hz, 1-H).

**3,17 $\alpha$ -Dihydroxy-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one Diacetate (IXb)**—A solution of IXa (45 mg) in  $\text{Ac}_2\text{O}$  (2 ml) was stirred with anhydrous *p*-TsOH (45 mg) at room temperature for 2 hr. The reaction mixture was processed in the manner as described in IIIc to give IXb (48 mg) as an oily product. NMR (4% solution in  $\text{CDCl}_3$ )  $\delta$ : 1.30 (3H, s, 18- $\text{CH}_3$ ), 2.10 (6H, s, 17 $\alpha$ - $\text{OCOCH}_3$  and 21- $\text{CH}_3$ ), 2.24 (3H, s, 3- $\text{OCOCH}_3$ ).

**3,17 $\alpha$ -Dihydroxy-13 $\alpha$ -pregna-1,3,5(10)-trien-20-one 17-Acetate (IXc)**—A solution of IXb (45 mg) in 1%  $\text{KHCO}_3$ /aq. MeOH (2.5 ml) was allowed to stand at room temperature for 80 min. The resulting solution was diluted with AcOEt, washed with  $\text{H}_2\text{O}$ , and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After evaporation of solvent a crystalline product obtained was recrystallized from acetone-hexane to give IXc (30 mg) as colorless plates. mp 208–209°.  $[\alpha]_D^{25} + 75.0^\circ$  ( $c=0.10$ ). Anal. Calcd. for  $\text{C}_{22}\text{H}_{28}\text{O}_4$ : C, 74.13; H, 7.92. Found: C, 74.04; H, 8.01. IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1710, 1700 (C=O), 1614, 1594, 1505 (C=C). NMR (4% solution in  $\text{CDCl}_3$ )  $\delta$ : 1.39 (3H, s, 18- $\text{CH}_3$ ), 2.10 (6H, s, 21- $\text{CH}_3$  and 17 $\alpha$ - $\text{OCOCH}_3$ ), 6.45 (1H, d,  $J=3$  Hz, 4-H), 6.54 (1H, q,  $J=3$  and 8 Hz, 2-H), 6.96 (1H, d,  $J=8$  Hz, 1-H).

**Reduction of I with Sodium Borohydride**—To a stirred solution of I (118 mg) in THF (8 ml) was added  $\text{NaBH}_4$  (60 mg) at 0° and allowed to stand at room temperature for 1 hr. After decomposition of excess  $\text{NaBH}_4$  with AcOH (2 drops) the reaction mixture was diluted with AcOEt, washed with 5%  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ , and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After evaporation of solvent a crystalline product obtained was submitted to preparative TLC using benzene-AcOEt (2:1) as developing solvent. Elution of the adsorbent corresponding to the spot ( $R_f$  0.60–0.65) with AcOEt and recrystallization of the eluate from acetone-hexane gave 13 $\alpha$ -estra-1,3,5(10)-triene-3,17 $\alpha$ -diol (VIIa) (22 mg) as colorless prisms. mp 199–201°.  $[\alpha]_D^{25} - 34.6^\circ$  ( $c=0.13$ , MeOH). Anal. Calcd. for  $\text{C}_{18}\text{H}_{24}\text{O}_2$ : C, 79.37; H, 8.88. Found: C, 79.20; H, 9.01.

Elution of the adsorbent corresponding to the spot ( $R_f$  0.70–0.75) with AcOEt and recrystallization of the eluate from acetone-hexane gave 13 $\alpha$ -estra-1,3,5(10)-triene-3,17 $\beta$ -diol (Xa) (35 mg) as colorless needles. mp 190–192°.  $[\alpha]_D^{25} + 28.1^\circ$  ( $c=0.06$ , MeOH). Anal. Calcd. for  $\text{C}_{18}\text{H}_{24}\text{O}_2$ : C, 79.37; H, 8.88. Found: C, 79.54; H, 8.98.

**3-Methoxy-13 $\alpha$ -estra-1,3,5(10)-trien-17 $\alpha$ -ol (VIIC)**—Treatment of VIIa with  $\text{Me}_2\text{SO}_4$  and KOH in the usual manner followed by recrystallization from aq. MeOH gave VIIC as colorless needles. mp 132–136°. Mixed melting point on admixture with the authentic sample<sup>5)</sup> showed no depression and IR spectra of two samples were entirely identical in every respect.

**3-Methoxy-13 $\alpha$ -estra-1,3,5(10)-trien-17 $\beta$ -ol (Xb)**—Treatment of Xa with  $\text{Me}_2\text{SO}_4$  and KOH in the usual manner followed by recrystallization from aq. MeOH gave Xb as colorless needles. mp 75–78°. Mixed melting point on admixture with the authentic sample<sup>5)</sup> showed no depression and IR spectra of two samples were entirely identical in every respect.

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