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Synthesis of C-17 Epimeric 5α,13α-Pregnan-20-ones[1]

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The titled compounds have been synthesized from 13α-dehydroepiandrosterone (I) as outlined in Chart 1. The Grignard reaction of I with ethynylmagnesium bromide gave two epimeric 17-ethynyl-17-ols (IIa, VIIa), which on hydration were led to 17-hydroxy-13α-pregn-5-en-20-ones (IIIa, VIIIa), respectively. On catalytic hydrogenation these 5-dehydro compounds were transformed into the 5α-saturated derivatives (IIIc, VIIIc). The metal hydride reduction, usual acetylation followed by the Serini reaction afforded C-17 epimeric 3β-acetoxy-5α, 13α-pregnan-20-ones (Vb, Xb), whose structures were elucidated by leading to the known 5α,13α-androstane-3β,17-diol diacetates (VI, XIb) employing the Baeyer–Villiger reaction. In the analogous manner IIIa and VIIIa were converted into the corresponding 13α-pregn-5-en-20-ones (Va, Xa).

It has generally been accepted that the molecular structure having β-configuration at both C-14 and C-17 is essential for the physiological activity of cardenolides and bufadienolides. A particular interest in the feature of C/D-ring fusion of the cardiac aglycone prompted us to prepare the 13α-cardenolides. The present paper deals with the synthesis of the titled compounds which will serve as the key intermediate leading to the desired C/D-*cis*-α-steroids.

For this purpose an initial project was directed to the preparation of 17-hydroxy-13α-pregnan-20-one *via* the ethynyl derivative starting from 13α-dehydroepiandrosterone (I).[3] The Grignard reaction of I with ethynylmagnesium bromide in tetrahydrofuran and subsequent acetylation gave two epimeric 17-ethynyl-17-hydroxyl derivatives (IIb, VIIb) in a ratio of *ca.* 2 to 1, whose separation could efficiently be achieved by column chromatography on alumina.[4]

Upon hydration with use of mercury–resin[6] the more polar epimer (IIa) was converted into 17α-hydroxy-13α-pregn-5-en-20-one (IIIa) in 45% yield. The Δ^5-unsaturated product was then led to the 5α-pregnane derivative (IIIc) by catalytic hydrogenation over palladium-on-charcoal. Reduction with lithium aluminum hydride followed by usual acetylation gave 5α,13α-pregnane-3β,17α,20-triol 3,20-diacetate (IVb), which was subjected to further step without purification. When refluxed with granulated zinc in xylene,[7] IVb was readily transformed into 5α,13α,17α-pregnan-20-one (Vb) along with configurational inversion of the side chain. The stereochemistry at C-17 was elucidated by leading to the known 5α,13α-androstan-17-ol derivative by treatment with the peracid, since the Baeyer–Villiger oxida-

1) This paper constitutes Part XI of the series entitled "Studies on Cardiotonic Steroid Analogs"; Part X: T. Nambara, J. Goto, Y. Fujimura, and Y. Kimura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1137 (1971).
2) Location: *Aobayama, Sendai.*
3) J.P.L. Bots, *Rec. Trav. Chim.*, **77**, 1010 (1958); T. Nambara, T. Kudo, H. Hosoda, and S. Goya, *J. Chromatog.*, **31**, 210 (1967).
4) Crabbé, *et al.* carried out similarly the Grignard reaction with 13α-dehydroepiandrosterone 3-pyranyl ether. Of two possible 17-epimers, however, only 17α-hydroxy-17β-ethynyl derivative was obtained, and no definite evidence for the configurational assignment was presented.[5]
5) P. Crabbé, A. Cruz, and J. Iriarte, *Can. J. Chem.*, **46**, 349 (1968).
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).

tion is well known to proceed with retention of configuration.[8] Treatment with *m*-chloroperbenzoic acid converted the 17α-acetyl derivative into 5α,13α-androstane-3β,17α-diol diacetate (VI), whose structure was characterized by direct comparison with the authentic sample.[9] In a similar fashion 3β,17α-dihydroxy-13α-pregn-5-en-20-one (IIIa) was led to the corresponding 17α-acetyl derivative (Va) by way of the 17,20-glycol 20-acetate (IVa).

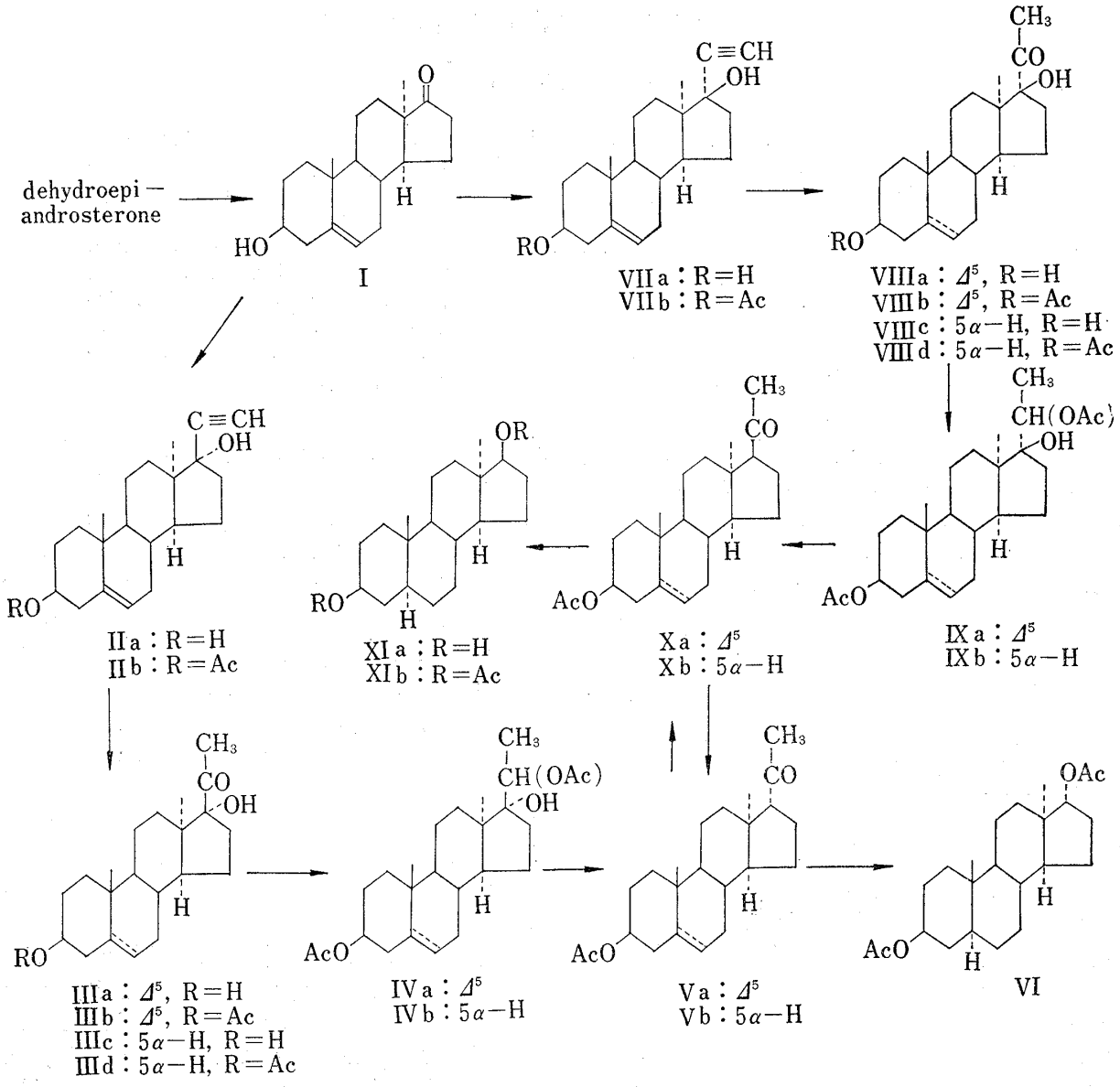

Chart 1

The next project was focused to the elaboration of the less polar product (VIIa) obtained by the Grignard reaction. Transformation into the epimeric 13α-pregnan-20-one (X) was performed by the above-mentioned reaction sequence. Hydration of the triple bond in VIIa with mercury–resin resulted in formation of 13α,17α-pregn-5-en-17β-ol (VIIIa), which in turn was led to the saturated compound (VIIIc) by catalytic hydrogenation. Reduction with metal hydride followed by acetylation gave the 20-ol acetate (IXb), which on the Serini reaction was readily transformed into the desired 5α,13α-pregnan-20-one (Xb). As was expected the Baeyer–Villiger reaction and subsequent alkaline hydrolysis provided

8) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Co., New York, 1959, p. 338.
9) T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.* (Tokyo), **17**, 1687 (1969).

5α,13α-androstane-3β,17β-diol (XIa), which was identified by comparison with the authentic sample.[10] Similarly the above-mentioned hydration product (VIIIa) was led to 3β-acetoxy-13α-pregn-5-en-20-one (Xa) through the 17β,20-glycol 20-acetate (IXa) in a reasonable yield.

It is to be noted that the attack of the Grignard reagent toward the 17-oxo group did take place from the both sides of the molecule. This result is fairly consistent with the previous finding on the metal hydride reduction and may be attributable to the characteristic C/D-*cis* linkage, where the β-side is crowded due to the cage-like structure and the rear side is also sterically hindered by the 18-methyl group.[10,11]

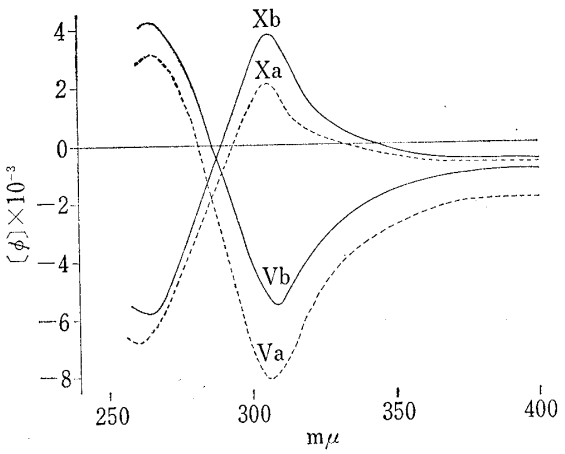

Fig. 1. Optical Rotatory Dispersion Curves of Va, Vb, Xa and Xb in Methanol

Both 5α,13α-pregnan-20-ones (Vb, Xb) were readily epimerized with base or acid to yield an equilibrium mixture, whose composition could be estimated by the optical rotation. The results on the equilibrium mixture obtained from either one of two epimers agreed well and gave an equilibrium value corresponding to 92% 17α and 8% 17β. It is of interest that the 17α-pregnan-20-one is thermodynamically more stable than the 17β-epimer in the 13α-steroids.

As to the results of optical rotatory dispersion the 17β-pregnan-20-ones (Xa, Xb) exhibit the positive Cotton effect whereas the 17α-epimers (Va, Vb) showed the negative one (see Fig. 1). These properties are consistent with those of C/D-*trans* and 14β-pregnan-20-ones.[12]

It is hoped that C-17 epimeric 5α,13α-pregnan-20-ones thus obtained will serve as the key intermediate for the preparation of the 13α-cardenolides.

Experimental[13]

The Grignard Reaction of 3β-Hydroxy-13α-androst-5-en-17-one (13α-Dehydroepiandrosterone) (I) with Ethynylmagnesium Bromide——To a solution of CH≡CMgBr[1] in anhydrous tetrahydrofuran (THF) (0.5N, 200 ml) was added I (2 g) and refluxed for 4.5 hr. The resulting solution was poured into a cold saturated NH_4Cl solution, extracted with AcOEt, washed with 5% H_2SO_4, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent a pale yellow crystalline product obtained was treated with Ac_2O (10 ml) and pyridine (15 ml). On usual work-up the crude product was chromatographed on Al_2O_3 (60 g). Elution with hexane–benzene (5:1 to 3:1) provided a crystalline product (1.6 g), which in turn was dissolved in 3% methanolic KOH (20 ml) and allowed to stand at room temperature overnight. The crystlline product thus obtained was recrystallized from acetone to give the unchanged I (1.45 g) as colorless needles. Elution with hexane–benzene (1:1) provided 17α-ethynyl-13α-androst-5-ene-3β,17β-diol 3-acetate (VIIb) (200 mg) as a colorless oil. This substance appeared to be homogeneous and therefore was submitted to further step without purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3265 (–C≡CH), 1725 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.96 (3H, s, 18- or 19-CH_3), 1.01 (3H, s, 19- or 18-CH_3), 2.00 (3H, s, 3β-$OCOCH_3$), 2.47 (1H, s, –C≡CH), 4.60 (1H, m, 3α-H), 5.32 (1H, m, 6-H). Elution with hexane–benzene (1:2) and recrystallization of the eluate from acetone–hexane gave 17β-ethynyl-13α-androst-5-ene-3β,17α-diol 3-acetate (IIb) (400 mg) as colorless

10) T. Nambara, H. Hosoda, and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1266 (1968).
11) L.J. Chinn, *J. Org. Chem.*, **30**, 4165 (1965).
12) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, 1960, p. 51; H. Mitsuhashi, T. Nomura, and M. Fukuoka, *Steroids*, **4**, 483 (1964).
13) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ solution unless otherwise specified. Rotatory dispersion (ORD) curves were obtained on JASCO Model ORD/UV-5 rotatory dispersion recorder. Infrared (IR) spectral measurements were run on IR-S spectrometer. Nuclear magnetic resonance (NMR) spectra were measured on Hitachi Model H-60 spectrometer at 60 Mc using tetramethylsilane as an internal standard. Abbreviation used s=singlet, t=triplet, and m=multiplet.

needles. mp 133—134°. $[\alpha]_D^{17}$ −92.6° (c=0.14). *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.67; H, 9.12. NMR (4% solution in $CDCl_3$) δ: 1.00 (6H, s, 18- and 19-CH_3), 2.01 (3H, s, 3β-OCOCH_3), 2.53 (1H, s, –C≡CH), 4.60 (1H, m, 3α-H), 5.32 (1H, m, 6-H).

17β-Ethynyl-13α-androst-5-ene-3β,17α-diol (IIa)——To a solution of IIb (400 mg) in MeOH (16 ml) was added an aqueous solution of K_2CO_3 (600 mg in 4 ml) and stirred at room temperature overnight. The reaction mixture was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. Upon evaporation of the solvent a crystalline product was obtained. Recrystallization from acetone–hexane gave IIa (330 mg) as colorless needles. mp 122—124°. $[\alpha]_D^{17}$ −77.8° (c=0.09). *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.96; H, 9.75. IR ν_{max}^{KBr} cm^{-1}: 3250 (–C≡CH). NMR (4% solution in $CDCl_3$) δ: 1.00 (6H, s, 18- and 19-CH_3), 2.53 (1H, s, –C≡CH), 3.55 (1H, m, 3α-H), 5.32 (1H, m, 6-H).

3β,17α-Dihydroxy-13α-pregn-5-en-20-one (IIIa)——To a ethanolic solution (6 ml) of IIa (200 mg) were added Hg-Dowex 50 (1.2 g) and H_2O (0.6 ml) and refluxed for 7 hr. The reaction mixture was filtered and the filtrate was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up an oily residue obtained was subjected to the preparative TLC on Silica gel G using benzene–AcOEt (5:1) as developing solvent. The adsorbent of the zone corresponding to *Rf* 0.40 was eluted with AcOEt and recrystallization of the eluate from acetone–hexane gave IIIa (100 mg) as colorless needles. mp 188—189°. $[\alpha]_D^{18}$ −154.8° (c=0.04). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.53; H, 9.53. IR ν_{max}^{KBr} cm^{-1}: 1698 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.96 (3H, s, 19-CH_3), 1.08 (3H, s, 18-CH_3), 2.23 (3H, s, 21-CH_3), 3.55 (1H, m, 3α-H), 5.30 (1H, m, 6-H).

3β,17α-Dihydroxy-13α-pregn-5-en-20-one 3-Acetate (IIIb)——Treatment of IIIa with Ac_2O and pyridine in the usual manner and recrystallization from acetone–hexane gave IIIb as colorless leaflets. mp 98—100°. $[\alpha]_D^{19}$ −122.8° (c=0.11). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.81; H, 9.20. NMR (4% solution in $CDCl_3$) δ: 0.96 (3H, s, 19-CH_3), 1.09 (3H, s, 18-CH_3), 2.00 (3H, s, 3β-OCOCH_3), 2.23 (3H, s, 21-CH_3), 4.60 (1H, m, 3α-H), 5.31 (1H, m, 6-H).

3β,17α-Dihydroxy-5α,13α-pregnan-20-one (IIIc)——A solution of IIIa (100 mg) in AcOEt (14 ml) was shaken with 10% Pd/C (30 mg) under a stream of H_2 at room temperature for 12 hr. After removal of the catalyst by filtration the filtrate was concentrated to give a crystalline product. Recrystallization from acetone gave IIIc (89 mg) as colorless plates. mp 214—216°. $[\alpha]_D^{21}$ −60.6° (c=0.10). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.61; H, 10.30. NMR (4% solution in $CDCl_3$) δ: 0.74 (3H, s, 19-CH_3), 1.03 (3H, s, 18-CH_3), 2.21 (3H, s, 21-CH_3), 3.55 (1H, m, 3α-H).

3β,17α-Dihydroxy-5α,13α-pregnan-20-one 3-Acetate (IIId)——Treatment of IIIc with Ac_2O and pyridine in the usual manner and recrystallization from acetone–hexane gave IIId as colorless needles. mp 118—120°. $[\alpha]_D^{20}$ −59.1° (c=0.11). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.44; H, 9.70. NMR (4% solution in $CDCl_3$) δ: 0.75 (3H, s, 19-CH_3), 1.02 (3H, s, 18-CH_3), 1.98 (3H, s, 3β-OCOCH_3), 2.19 (3H, s, 21-CH_3), 4.60 (1H, m, 3α-H).

3β-Acetoxy-13α,17α-pregn-5-en-20-one (Va)——To a solution of IIIa (80 mg) in anhydrous THF (5 ml) was added $LiAlH_4$ (40 mg) and refluxed for 2 hr. To this solution was added moistened ether to decompose the excess reagent and acidified with 10% HCl. The organic phase was separated, washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent a crystalline product obtained was treated with Ac_2O and pyridine. On usual work-up 13α-pregn-5-ene-3β,17α,20-triol 3,20-diacetate (IVa) was obtained in the crystalline state. To a solution of IVa in xylene (7 ml) was added granulated Zn (1.4 g) and refluxed under a stream of N_2 for 10 hr. The reaction mixture was filtered and the filtrate was evaporated. An oily residue was subjected to the preparative TLC on Silica gel H using benzene–AcOEt (100:1) as developing solvent. The adsorbent of the zone corresponding to *Rf* 0.60 was eluted with AcOEt and recrystallization of the eluate from acetone–hexane gave Va as colorless needles. mp 116—117°. $[\alpha]_D^{19}$ −115.0° (c=0.10). *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.19; H, 9.59. IR ν_{max}^{KBr} cm^{-1}: 1735, 1705 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.80 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 2.01 (3H, s, 3β-OCOCH_3), 2.10 (3H, s, 21-CH_3), 3.04 (1H, t, J=8 cps, 17β-H), 4.60 (1H, m, 3α-H), 5.34 (1H, m, 6-H). ORD (c=0.09, MeOH) $[\alpha]^{14}$ (mμ): −541.2° (400), −2258.8° (308) (trough), 0° (282), +870.6° (266) (peak), 0° (244).

3β-Acetoxy-5α,13α,17α-pregnan-20-one (Vb)——To a solution of IIIc (140 mg) in anhydrous THF (8 ml) was added $LiAlH_4$ (70 mg) and refluxed for 2 hr. When the reaction mixture was processed in the same manner as described in Va, 5α,13α-pregnane-3β,17α, 20-triol 3,20-diacetate (IVb) was obtained in the crystalline state. To a solution of IVb in xylene (12 ml) was added granulated Zn (2.4 g) and refluxed under a stream of N_2 for 43 hr. The reaction mixture was filtered and the filtrate was evaporated. The oily residue was subjected to the preparative TLC on Silica gel H using benzene–AcOEt (100:1) as developing solvent. The adsorbent of the zone corresponding to *Rf* 0.50 was eluted with AcOEt and recrystallization of the eluate from acetone–hexane gave Vb (90 mg) as colorless plates. mp 144—146°. $[\alpha]_D^{20}$ −67.8° (c=0.12). *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.71; H, 10.00. IR ν_{max}^{KBr} cm^{-1}: 1735, 1702 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.79 (6H, s, 18- and 19-CH_3), 2.00 (3H, s, 3β-OCOCH_3), 2.09 (3H, s, 21-CH_3), 2.98 (1H, t, J=8 cps, 17β-H), 4.60 (1H, m, 3α-H). ORD (c=0.19, MeOH) $[\alpha]^{19}$ (mμ): −259.5° (400), −1535.1° (309) (trough), 0° (287), +1167.6° (266) (peak), 0° (224).

5α,13α-Androstane-3β,17α-diol Diacetate (VI)——To a solution of Vb (15 mg) in $CHCl_3$ (3 ml) was added *m*-chloroperbenzoic acid (20 mg) and allowed to stand at 35° for 30 hr. The reaction mixture was diluted with $CHCl_3$, washed with cold 5% KOH, H_2O and dried over anhydrous Na_2SO_4. On usual work-up a crystalline product was obtained. Recrystallization from acetone–hexane gave VI (10 mg) as colorless plates. mp 129—131°. Mixed melting point on admixture with the authentic sample[9] showed no depression and IR spectra of two samples were identical in every respect.

17α-Ethynyl-13α-androst-5-ene-3β,17β-diol (VIIa)——To a solution of VIIb (200 mg) in MeOH (8 ml) was added an aqueous solution of K_2CO_3 (300 mg in 2 ml) and stirred at room temperature overnight. The reaction mixture was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. Upon evaporation of solvent a crystalline product was obtained. Recrystallization from acetone–hexane gave VIIa (160 mg) as colorless needles. mp 130—130.5°. $[\alpha]_D^{17}$ −129.8° (c=0.10). *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.16; H, 9.72. IR ν_{max}^{KBr} cm^{-1}: 3265 (-C≡CH). NMR (4% solution in $CDCl_3$) δ: 0.95 (3H, s, 18- or 19-CH_3), 1.01 (3H, s, 19- or 18-CH_3), 2.47 (1H, s, -C≡CH), 3.55 (1H, m, 3α-H), 5.32 (1H, m, 6-H).

3β,17β-Dihydroxy-13α,17α-pregn-5-en-20-one (VIIIa)——To an ethanolic solution (6 ml) of VIIa (120 mg) were added Hg-Dowex 50 (1.2 g) and H_2O (0.6 ml) and refluxed for 6 hr. The reaction mixture was filtered and the filtrate was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up a crystalline residue obtained was subjected to the preparative TLC on Silica gel G using benzene–AcOEt (5:1) as developing solvent. The adsorbent of the zone corresponding to *Rf* 0.50 was eluted with AcOEt and recrystallization of the eluate from acetone gave VIIIa (70 mg) as colorless needles. mp 199—201°. $[\alpha]_D^{19}$ −72.9° (c=0.10). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.32; H, 9.81. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 0.99 (3H, s, 19-CH_3), 2.23 (3H, s, 21-CH_3), 3.55 (1H, m, 3α-H), 5.30 (1H, m, 6-H).

3β,17β-Dihydroxy-13α,17α-pregn-5-en-20-one 3-Acetate (VIIIb)——Treatment of VIIIa with Ac_2O and pyridine in the usual manner and recrystallization from acetone–hexane gave VIIIb as colorless plates. mp 190—192°. $[\alpha]_D^{19}$ −89.3° (c=0.14). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.69; H, 9.10. NMR (4% solution in $CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 2.00 (3H, s, 3β-$OCOCH_3$), 2.24 (3H, s, 21-CH_3), 4.60 (1H, m, 3α-H), 5.32 (1H, m, 6-H).

3β,17β-Dihydroxy-5α,13α,17α-pregnan-20-one (VIIIc)——A solution of VIIIa (100 mg) in AcOEt (14 ml) was shaken with 10% Pd/C (30 mg) under a stream of H_2 at room temperature for 12 hr. After removal of the catalyst by filtration the filtrate was concentrated to give a crystalline product. Recrystallization from acetone gave VIIIc (90 mg) as colorless needles. mp 188—190°. $[\alpha]_D^{19}$ −13.9° (c=0.11). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.68; H, 10.34. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.76 (3H, s, 19-CH_3), 0.88 (3H, s, 18-CH_3), 2.27 (3H, s, 21-CH_3), 3.55 (1H, m, 3α-H).

3β,17β-Dihydroxy-5α,13α,17α-pregnan-20-one 3-Acetate (VIIId)——Treatment of VIIIc with Ac_2O and pyridine in the usual manner and recrystallization from acetone–hexane gave VIIId as colorless plates. mp 172—174°. $[\alpha]_D^{19}$ −15.6° (c=0.06). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.22; H, 9.65. NMR (4% solution in $CDCl_3$) δ: 0.76 (3H, s, 19-CH_3), 0.88 (3H, s, 18-CH_3), 2.02 (3H, s, 3β-$OCOCH_3$), 2.26 (3H, s, 21-CH_3), 4.60 (1H, m, 3α-H).

3β-Acetoxy-13α-pregn-5-en-20-one (Xa)——To a solution of VIIIa (40 mg) in anhydrous THF (2 ml) was added $LiAlH_4$ (20 mg) and refluxed for 2 hr. When the reaction mixture was processed in the same manner as described in Va, 13α,17α-pregn-5-ene-3β,17β,20-triol 3,20-diacetate (IXa) was obtained in the crystalline state. To a solution of IXa in xylene (4 ml) was added granulated Zn (800 mg) and refluxed under a stream of N_2 for 10 hr. The reaction mixture was filtered and the filtrate was evaporated. An oily residue was subjected to the preparative TLC on Silica gel H using benzene–AcOEt (100:1) as developing solvent. The adsorbent of the zone corresponding to *Rf* 0.65 was eluted with AcOEt and recrystallization of the eluate from acetone–hexane gave Xa (20 mg) as colorless needles. mp 87—89°. $[\alpha]_D^{18}$ −45.5° (c=0.09). *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.29; H, 9.61. NMR (4% solution in $CDCl_3$) δ: 0.92 (3H, s, 19-CH_3), 1.21 (3H, s, 18-CH_3), 2.02 (3H, s, 3β-$OCOCH_3$), 2.15 (3H, s, 21-CH_3), 2.69 (1H, m, 17α-H), 4.60 (1H, m, 3α-H), 5.34 (1H, m, 6-H). ORD (c=0.14, MeOH) $[\alpha]^{17}$ (mμ): −200.0° (400), 0° (334), +600.0° (306) (peak), 0° (294), −1907.1° (260)(trough).

3β-Acetoxy-5α,13α-pregnan-20-one (Xb)——To a solution of VIIIc (50 mg) in anhydrous THF (3 ml) was added $LiAlH_4$ (25 mg) and refluxed for 2 hr. When the reaction mixture was processed in the same manner as described in Va, 5α,13α,17α-pregnane-3β,17β,20-triol 3,20-diacetate (IXb) was obtained in the crystalline state. To a solution of IXb in xylene (5 ml) was added granulated Zn (900 mg) and refluxed under a stream of N_2 for 35 hr. The reaction mixture was filtered and the filtrate was evaporated. An oily residue was subjected to the preparative TLC on Silica gel H using benzene as developing solvent. After multiple development the adsorbent of the zone corresponding to *Rf* 0.50 was eluted with AcOEt and recrystallization of the eluate from acetone–hexane gave Xb (30 mg) as colorless plates. mp 110—112°. $[\alpha]_D^{19}$ +20.0° (c=0.10). *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.54; H, 10.01. IR ν_{max}^{KBr} cm^{-1}: 1728, 1708 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.72 (3H, s, 19-CH_3), 1.19 (3H, s, 18-CH_3), 2.00 (3H, s, 3β-$OCOCH_3$), 2.13 (3H, s, 21-CH_3), 2.61 (1H, m, 17α-H), 4.60 (1H, m, 3α-H). ORD (c=0.13, MeOH) $[\alpha]^{19}$ (mμ): −192.0° (400), 0°(345), +1056.0° (308)(peak), 0° (290), −1608.0° (265)(trough), 0° (223).

5α,13α-Androstane-3β,17β-diol (XIa)——To a solution of Xb (15 mg) in $CHCl_3$ (3 ml) was added *m*-chloroperbenzoic acid (20 mg) and allowed to stand at 35° for 25 hr. The reaction mixture was diluted with $CHCl_3$, washed with cold 5% KOH, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent 5α,13α-androstane-3β,17β-diol diacetate (XIb) was obtained as an oily product. XIb was dissolved in 3% methanolic KOH (3 ml) and allowed to stand at room temperature overnight. After usual work-up an oily residue obtained was subjected to the preparative TLC on Silica gel H using benzene–AcOEt (2:1) as developing solvent. The adsorbent of the zone corresponding to *Rf* 0.50 was eluted with AcOEt and recrystallization of the eluate from acetone–hexane gave XIa (6 mg) as colorless plates. mp 170—172°. Mixed melting point on admixture with the authentic sample[10] showed no depression and IR spectra of two samples were identical in every respect.

Epimerization of Vb and Xb with Alkali——i) Vb (6 mg) was dissolved in 2% methanolic KOH (2 ml) and allowed to stand at room temperature for 3 hr. The reaction mixture was diluted with $CHCl_3$, washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of solvent gave an oily residue, which in turn was treated with Ac_2O and pyridine. After usual work-up an oily product was subjected to the preparative TLC on Silica gel H using benzene–AcOEt (100:1) as developing solvent. The adsorbent of the zone corresponding to *Rf* 0.35—0.65 was eluted with AcOEt. The specific rotation of the eluate was found to be −61.6°. ii) Xb (5 mg) was epimerized with alkali in the manner as described in i). The specific rotation of the equilibrated mixture showed −60.1°. Epimerization of either one of two epimers with acid gave the same results.

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