[Chem. Pharm. Bull. 21(3) 565—569 (1973)]

UDC 547.92.057 : 615.36.011.5

Syntheses of 13α-Progestagens[1]

Toshio Nambara, Junichi Goto, Akiko Sasaki, and Kenichi Sudo

Pharmaceutical Institute, Tohoku University[2]

(Received September 7, 1972)

In order to examine the structure-activity relationship the syntheses of some progestagens with the abnormal 13α-configuration have been undertaken. Epimeric 17-ethynyl-17-hydroxy derivatives (II and VII) having Δ^4-3-ketone system were prepared from the corresponding Δ^5-3β-ols (I and VI) by Oppenauer oxidation, respectively. 17-Acetoxy-13α-pregn-4-ene-3,20-diones (V and Xb) were prepared by Jones oxidation from 3β,17-dihydroxy-13α-pregn-5-en-20-one 17-acetates (IIIc and VIIIc) which were readily available from the 3,17-diacetates (IIIb and VIIIb) by partial hydrolysis. The occurrence of D-homo-annulation of 17-hydroxy-13α-pregnen-20-ones (IIIa and VIIIa) with aluminum isopropoxide has also been described.

In recent years considerable efforts have been made for the preparation of the modified steroids to obtain the more potent progestagens than the natural products. The discovery of orally active steroidal progestagens made possible the development of the drugs used for the control of human fertility.[3] In connection with these problems the structure-activity relationship has been investigated with a wide variety of compounds.[4] With regards to the C/D-ring fusion it was reported that 14β,17α-19-norpregn-4-ene-3,20-dione having the abnormal configuration at C-14 and C-17 is several times as active as progesterone.[5] However, the effects of stereochemistry at C-13 on the progestational activity have not yet been clarified. The progestagens, with few exceptions, fall into two classes, derivatives of progesterone, and of testosterone substituted at C-17 by saturated or unsaturated hydrocarbon group. A particular interest in these respects prompted us to synthesize some typical analogs in the 13α-series employing 13α-dehydroepiandrosterone[6] as a starting material.

An initial project was directed to the preparation of the desired compounds from 17β-ethynyl-13α-androst-5-ene-3β,17α-diol (I), obtainable from 13α-dehydroepiandrosterone together with the C-17 epimer (VI) by the Grignard reaction.[7] Oppenauer oxidation proceeded readily without exerting any disturbance on the substituents at C-17 to give the corresponding Δ^4-3-keto steroid (II). As previously reported I was led to 3β,17α-dihydroxy-13α-pregn-5-en-20-one (IIIa) by hydration with mercury-resin.[7] Oxidation of IIIa in the manner as mentioned above resulted in formation of the undesired product. Transformation into the Δ^4-3-keto structure was accompanied by D-homo-annulation, whose occurrence was verified by the usual criteria, *i.e.* elemental analyses, nuclear magnetic resonance (NMR), infrared (IR) and ultraviolet (UV) spectra. The ring D structure of the product, however, could not

1) This paper constitutes Part XIII of the series entitled "Studies on Cardiotonic Steroid Analogs"; Part XII: T. Nambara, K. Shimada, and Y. Fujii, *Chem. Pharm. Bull.* (Tokyo), **20**, 1424 (1972).
2) Location: *Aobayama, Sendai.*
3) V. Petrow, *Chem. Rev.*, **70**, 713 (1970).
4) H.J. Ringold, "Mechanism of Action of Steroid Hormones," ed. by C.A. Villee and L.L. Engel, Pergamon Press, New York, 1961, pp. 200—234.
5) G.W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957).
6) T. Nambara, T. Kudo, H. Hosoda, and S. Goya, *J. Chromatog.*, **31**, 210 (1967).
7) T. Nambara and J. Goto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1937 (1971).

definitely be determined and hence was tentatively assigned to be 17aα-hydroxy-17aβ-methyl-13α-D-homoandrost-4-ene-3,17-dione (IV) on the basis of the reaction mechanism.[8] Accordingly, the development of an alternative synthetic route was then undertaken. First, IIIa was converted into the 3,17-diacetate (IIIb) by acetylation with acetic anhydride and anhydrous *p*-toluenesulfonic acid. Treatment of IIIb with potassium bicarbonate under the mild conditions effected partial hydrolysis to yield the 17-monoacetate (IIIc). Subsequent oxidation with Jones reagent[9] was accompanied with migration of the Δ^5-double bond to give the desired 17α-acetoxy-13α-pregn-4-ene-3,20-dione (V) in overall yield of 38% from IIIa.

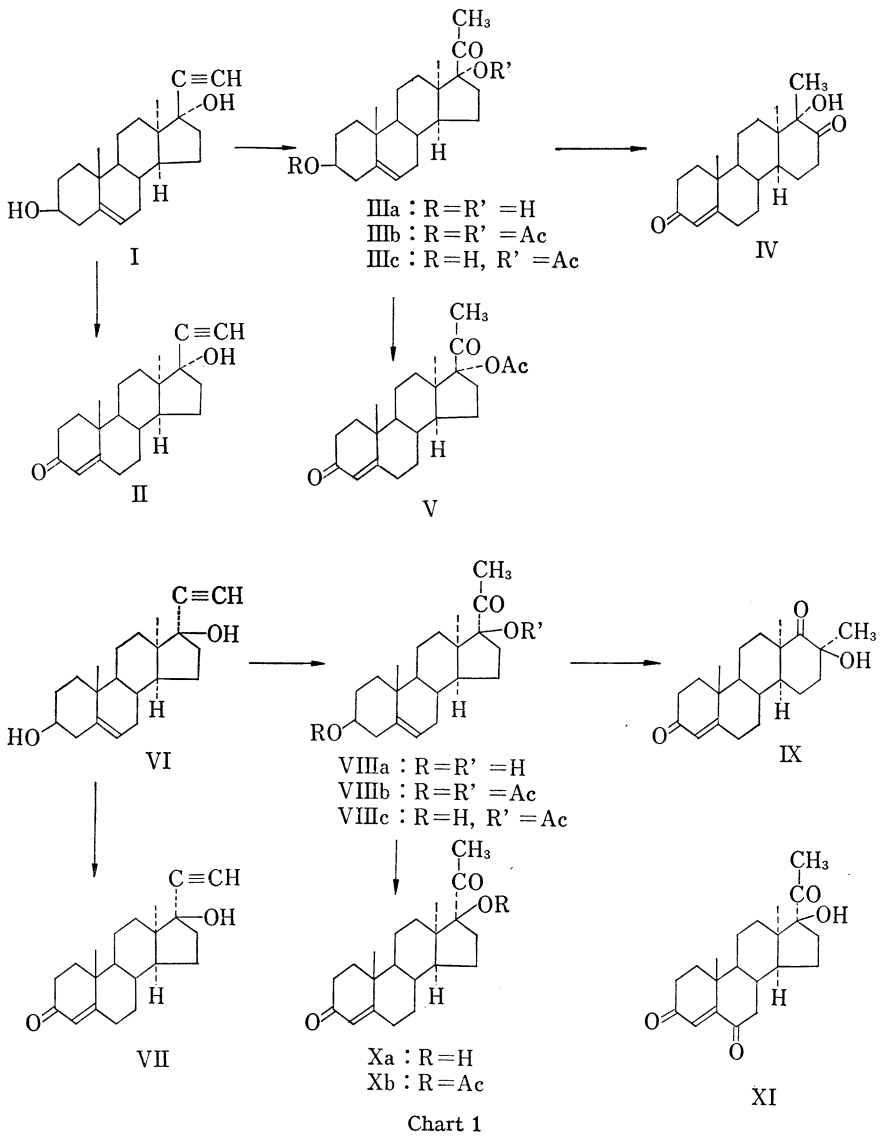

Chart 1

8) D.N. Kirk and M.P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier Publ. Co., Amsterdam, 1968, pp. 294—301.
9) K. Bowden, I.M. Heilbron, E.R.H. Jones, and B.C.L. Weedon, *J. Chem. Soc.*, **1946**, 39.

Next project was focused to the preparation of the C-17 epimeric progestagens. The 17α-ethynyl-17β-ol (VI) could be converted into the Δ^4-3-ketone (VII) in a reasonable yield by Oppenauer oxidation as was expected. Treatment of 3β,17β-dihydroxy-13α-pregen-5-en-20-one (VIIIa) which was derivable from VI,[7] with aluminum isopropoxide and cyclohexanone similarly gave rise to D-homo-rearrangement yielding the D-homosteroid. This product was also tentatively assigned to the structure 17β-hydroxy-17α-methyl-13α-D-homoandrost-4-ene-3,17a-dione (IX) from the spectroscopic data and the reaction mechanism. The synthesis of the desired compound was therefore carried out by the same reaction sequences as its C-17 epimer. Acetylation with acetic anhydride under the catalysis of *p*-toluenesulfonic acid gave the 3,17-diacetate (VIIIb), which on mild alkaline hydrolysis was led to the 17-monoacetate (VIIIc). Subsequent Jones oxidation gave 17β-acetoxy-13α-pregn-4-ene-3,20-dione (Xb) in a satisfactory yield. It is to be noted that oxidation of VIIIa with Jones reagent afforded 17β-hydroxy-13α-pregn-4-ene-3,20-dione (Xa) accompanied with the corresponding 6-keto derivative (XI).

The progestational activities of the 13α-steroids having Δ^4-3-keto structure were assayed by subcutaneous McPhail method.[10] Of these compounds the 17α-ethynyl-17β-ol (VI) exhibited the potency as much as progesterone. To the best our knowledges this is the first demonstration of the physiologically active steroid in the 13α-series. The present finding appears to be of great theoretical interest since it may provide the more precise information on the mode of interaction between progestagen and its receptor. The details of bioassay results will be reported elsewhere in the near future.

Experimental[11]

17β-Ethynyl-17α-hydroxy-13α-androst-4-en-3-one (II)——To a solution of 17β-ethynyl-13α-androst-5-ene-3β,17α-diol (I) (400 mg) in anhydrous toluene (30 ml) were added cyclohexanone (6.3 ml) and Al(iso-PrO)$_3$ (300 mg), and the resulting solution was concentrated to 25 ml and then refluxed for 9 hr. The resulting solution was diluted with benzene, washed with 2N H_2SO_4, 5% $NaHCO_3$ and H_2O, and then subjected to steam distillation. The residue was extracted with AcOEt, and the organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was recrystallized from acetone to give II (300 mg) as colorless prisms. mp 189.5—191°. $[\alpha]_D^{18}$ +125.0° (c=0.11). *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.88; H, 9.07. UV λ_{max}^{EtOH} mμ(ε): 243 (16100). IR ν_{max}^{KBr} cm^{-1}: 3170, 2130, 1660, 1612. NMR (4% solution in $CDCl_3$) δ: 1.01 (3H, s, 18-CH_3), 1.13 (3H, s, 19-CH_3), 2.58 (1H, s, -C≡CH), 5.72 (1H, s, 4-H).

3β,17α-Diacetoxy-13α-pregn-5-en-20-one (IIIb)——A solution of 3β,17α-dihydroxy-13α-pregn-5-en-20-one (IIIa) (90 mg) in Ac_2O (4 ml) was stirred with anhydrous *p*-TsOH (100 mg) at room temperature for 2 hr. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ and H_2O, and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was recrystallized from acetone–hexane to give IIIb (80 mg) as colorless needles. mp 142—144°. $[\alpha]_D^{29}$ −92.3° (c=0.13). *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.95; H, 8.67. NMR (4% solution in $CDCl_3$) δ: 0.95 (3H, s, 18-CH_3), 1.21 (3H, s, 19-CH_3), 2.03 (3H, s, 3β-OCOCH_3), 2.06 (3H, s, 17α-OCOCH_3), 2.12 (3H, s, 21-CH_3), 4.60 (1H, m, 3α-H), 5.40 (1H, m, 6-H).

17α-Acetoxy-13α-pregn-4-ene-3,20-dione (V)——A solution of IIIb (70 mg) in 2% $KHCO_3$/aq. MeOH was stirred overnight at 40°. The resulting solution was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of solvent gave 3β,17α-dihydroxy-13α-pregn-5-en-20-one 17-acetate (IIIc) (50 mg) as colorless oil. NMR (4% solution in $CDCl_3$) δ: 0.95 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 2.08 (3H, s, 17α-OCOCH_3), 2.12 (3H, s, 21-CH_3), 3.55 (1H, m, 3α-H), 5.35 (1H, m, 6-H). To a solution of IIIc (40 mg) in acetone (5 ml) was added 5 drops of Jones reagent at −15° and stirred for 5 min. The reaction mixture was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of solvent gave an oily residue, which in turn was submitted to preparative thin-layer chromatography

10) C.W. Emmens, "Hormone Assay," ed. by C.W. Emmens, Academic Press, New York, 1950, pp. 424—425.

11) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ solution. UV and IR spectra were run on Hitachi Model EPS-3 and JASCO Model IR-S spectrophotometers, respectively. NMR spectra were recorded on Hitachi Model R-20A spectrometer at 60 Mc using tetramethylsilane as an internal standard.

(TLC) using benzene–AcOEt (2: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.60) with AcOEt and recrystallization of the eluate from ether–hexane gave V (25 mg) as colorless plates. mp 152—153°. $[\alpha]_D^{27}$ +49.5° (c=0.09). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.08; H, 8.72. UV λ_{max}^{EtOH} mμ(ε): 242 (16000). IR ν_{max}^{KBr} cm^{-1}: 1740, 1710, 1675, 1620. NMR (4% solution in $CDCl_3$) δ: 1.12 (3H, s, 18-CH_3), 1.19 (3H, s, 19-CH_3), 2.10 (6H, s, 17α-OCOCH_3 and 21-CH_3), 5.70 (1H, s, 4-H).

17α-Ethynyl-17β-hydroxy-13α-androst-4-en-3-one (VII)——To a solution of VI (300 mg) in anhydrous toluene (30 ml) were added cyclohexanone (6.3 ml) and Al(iso-PrO)$_3$ (300 mg), and the resulting solution was concentrated to 25 ml and then refluxed for 7 hr. Similar treatment as described in II followed by recrystallization from acetone gave VII (260 mg) as colorless needles. mp 174—174.5°. $[\alpha]_D^{18}$ +65.2° (c=0.14). *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.78; H, 9.01. UV λ_{max}^{EtOH} mμ(ε): 244 (16200). IR ν_{max}^{KBr} cm^{-1}: 3190, 2130, 1650, 1612. NMR (4% solution in $CDCl_3$) δ: 0.99 (3H, s, 18-CH_3), 1.11 (3H, s, 19-CH_3), 2.51 (1H, s, –C≡CH), 5.75 (1H, s, 4-H).

3β,17β-Diacetoxy-13α-pregn-5-en-20-one (VIIIb)——A solution of 3β,17β-dihydroxy-13α-pregn-5-en-20-one (VIIIa) (200 mg) in Ac_2O (8 ml) was stirred with anhydrous p-TsOH (200 mg) at room temperature for 2 hr. Similar treatment as described in IIIb followed by recrystallization from acetone–hexane gave VIIIb (210 mg) as colorless plates. mp 140—141°. $[\alpha]_D^{28}$ −28.1° (c=0.09). *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.82; H, 8.78. NMR (4% solution in $CDCl_3$) δ: 0.85 (3H, s, 18-CH_3), 1.06 (3H, s, 19-CH_3), 2.05 (3H, s, 3β-OCOCH_3), 2.09 (3H, s, 17β-OCOCH_3), 2.13 (3H, s, 21-CH_3), 4.60 (1H, m, 3α-H), 5.04 (1H, m, 6-H).

3β,17β-Dihydroxy-13α-pregn-5-en-20-one 17-Acetate (VIIIc)——A solution of VIIIb (180 mg) in 2% $KHCO_3$/aq. MeOH (60 ml) was stirred overnight at 40°. The resulting solution was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was recrystallized from acetone–hexane to give VIIIc (113 mg) as colorless prisms. mp 149—151°. $[\alpha]_D^{28}$ −37.4° (c=0.11). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.37; H, 9.07. NMR (4% solution in $CDCl_3$) δ: 0.84 (3H, s, 18-CH_3), 1.05 (3H, s, 19-CH_3), 2.08 (3H, s, 17β-OCOCH_3), 2.13 (3H, s, 21-CH_3), 3.55 (1H, m, 3α-H), 5.35 (1H, m, 6-H).

17β-Acetoxy-13α-pregn-4-ene-3,20-dione (Xb)——To a solution of VIIIc (80 mg) in acetone (5 ml) was added 8 drops of Jones reagent at −15° and stirred for 5 min. Similar treatment as described in V gave an oily product, which in turn was submitted to preparative TLC using benzene–AcOEt (3: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.40) and recrystallization of the eluate from ether gave Xb (40 mg) as colorless plates. mp 140—142°. $[\alpha]_D^{28}$ +252.0° (c=0.10). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.94; H, 8.78. UV λ_{max}^{EtOH} mμ(ε): 243 (15000). IR ν_{max}^{KBr} cm^{-1}: 1738, 1710, 1675, 1620. NMR (4% solution in $CDCl_3$) δ: 0.88 (3H, s, 18-CH_3), 1.19 (3H, s, 19-CH_3), 2.12 (3H, s, 17β-OCOCH_3), 2.16 (3H, s, 21-CH_3), 5.73 (1H, s, 4-H).

17aα-Hydroxy-17aβ-methyl-13α-D-homoandrost-4-ene-3,17-dione (IV)——To a solution of IIIa (100 mg) in anhydrous toluene (30 ml) were added cyclohexanone (6.3 ml) and Al (iso-PrO)$_3$ (150 mg), and the resulting solution was concentrated to 25 ml and then refluxed for 4 hr. Similar treatment as described in II followed by recrystallization from acetone–hexane gave IV (70 mg) as colorless needles. mp 202.5—203°. $[\alpha]_D^{28}$ +85.1° (c=0.09). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.08; H, 9.20. UV λ_{max}^{EtOH} mμ(ε): 242 (15000). IR ν_{max}^{KBr} cm^{-1}: 1700, 1675, 1620. NMR (4% solution in $CDCl_3$) δ: 1.06 (3H, s, 18- or 19-CH_3), 1.32 (3H, s, 19- or 18-CH_3), 1.42 (3H, s, 17aβ-CH_3), 5.74 (1H, s, 4-H).

17β-Hydroxy-17α-methyl-13α-D-homoandrost-4-ene-3,17a-dione (IX)——To a solution of VIIIa (200 mg) in anhydrous toluene (30 ml) were added cyclohexanone (6.3 ml) and Al (iso-PrO)$_3$ (250 mg), and the resulting solution was concentrated to 25 ml and refluxed for 9 hr. Similar treatment as described in II gave an oily product, which in turn was submitted to preparative TLC using $CHCl_3$–AcOEt (3: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.50) with AcOEt and recrystallization of the eluate from ether–hexane gave IX (51 mg) as colorless prisms. mp 76—77.5°. $[\alpha]_D^{28}$ +60.0° (c=0.05). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.18. UV λ_{max}^{EtOH} mμ(ε): 242 (15500). IR ν_{max}^{KBr} cm^{-1}: 1695, 1670, 1615. NMR (4% solution in $CDCl_3$) δ: 1.08 (3H, s, 18- or 19-CH_3), 1.27 (3H, s, 19- or 18-CH_3), 1.43 (3H, s, 17α-CH_3), 5.73 (1H, s, 4-H).

Oxidation of VIIIa with Jones Reagent——To a solution of VIIIa (180 mg) in acetone (10 ml) was added dropwise Jones reagent (0.6 ml) at −2° and stirred for 10 min. The resulting solution was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of solvent gave an oily product, which in turn was submitted to preparative TLC using benzene–AcOEt (3: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.60) and recrystallization of the eluate from acetone–hexane gave 17β-hydroxy-13α-pregn-4-ene-3,20-dione (Xa) (81 mg) as colorless needles. mp 191—192°. $[\alpha]_D^{27}$ +239.3° (c=0.09). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.12; H, 9.00. UV λ_{max}^{EtOH} mμ(ε): 244 (15000). IR ν_{max}^{KBr} cm^{-1}: 1705, 1660, 1610. NMR (4% solution in $CDCl_3$) δ: 0.92 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 2.30 (3H, s, 21-CH_3), 5.71 (1H, s, 4-H).

Elution of the adsorbent corresponding to the spot (*Rf* 0.40) and recrystallization of the eluate from acetone–hexane gave 17β-hydroxy-13α-pregn-4-ene-3,6,20-trione (XI) (41 mg) as colorless needles. mp

178—179°. $[\alpha]_D^{29}$ +50.0° (c=0.02). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.22; H, 8.25. UV λ_{max}^{EtOH} mμ(ε): 252 (11000). IR ν_{max}^{KBr} cm^{-1}: 1705, 1685, 1660, 1608. NMR (4% solution in $CDCl_3$) δ: 0.97 (3H, s, 18-CH_3), 1.13 (3H, s, 19-CH_3), 2.29 (3H, s, 21-CH_3), 6.14 (1H, s, 4-H).

Acknowledgement The authors express their deep gratitudes to Dr. Hiromu Mori, Teikoku Hormone Mfg. Co., Ltd. for his support. They are also indebted to all the staffs of central analytical laboratory of this Institute for elemental analyses and spectral measurements.