

Syntheses of D-Homo-14 β -pregnan-20-ones¹⁾

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In order to obtain the key intermediates leading to the D-homo cardenolide analogs, the preparation of the C-17a epimeric D-homo-5 α ,14 β -pregnan-20-ones (VIII, IX) has been undertaken. Upon catalytic hydrogenation the $\Delta^{14,16}$ -dien-17a-one (IV), derivable from D-homo-5 α -androstan-17a-one (I) by repeated unsaturation, provided the desired 14 β -steroid (V) as a main product. Introduction of a C₂ unit into C-17a was attained by the Grignard reaction with ethynylmagnesium bromide, followed by hydration with mercury resin to yield D-homo-5 α ,14 β ,17a-pregn-17-en-20-one (VII). Subsequent hydrogenation over palladium-on-charcoal afforded IX and VIII in a ratio of ca. 5 to 1. Configurational assignment of the side chain in IX was accomplished by transforming the 20-oxime (XIV) into the 17 α -acetamido derivative (XV) by the Beckmann rearrangement.

In view of the structure-activity relationship of the cardiotonic steroids,^{3,4)} the physiological activity of the D-homo cardenolide is of particular interest, although the preparation of the C-nor-D-homo analog has already been reported.⁵⁾ Of several synthetic routes leading to the formation of a butenolide ring, utilization of the acetyl group attached to ring D appears to be most feasible.^{6,7)} However, the chemistry of D-homo-14 β -pregnanes still remains unclear. The present paper deals with the preparation of two C-17a epimeric D-homo-5 α ,14 β -pregnan-20-ones.

For this purpose 3 β -hydroxy-D-homo-5 α -androstan-17a-one acetate (I), obtainable from isoandrosterone acetate in three steps, was taken as a starting material. Transformation into the Δ^{16} -17a-ketone (II) was easily attained by the method worked out by Zurflüh, *et al.*⁸⁾ Introduction of an additional double bond into the cyclohexenone structure was carried out in a similar fashion. Treatment of II with N-bromosuccinimide provided the 15 ξ -bromo compound (III), which on dehydrobromination with calcium carbonate in dimethylacetamide was led to the $\Delta^{14,16}$ -dien-17a-one (IV) in a satisfactory yield. Subsequent hydrogenation over palladium-on-charcoal proceeded on the expected side of the molecule resulting in the formation of 3 β -hydroxy-D-homo-5 α ,14 β -androstan-17a-one acetate (V) as a main product. The stereochemistry at C-14 was unambiguously assignable by comparison with the 14 α -epimer (I). It should be noted that the attack of hydrogen toward the Δ^{14} -double bond takes place preferentially from the β -side in this unsaturation system as observed in the fused cyclopentenone system.⁹⁾

- 1) This paper constitutes Part XVIII of the series entitled "Studies on Cardiotonic Steroid Analogs"; Part XVII: J. Goto, K. Sudo, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **22**, 1140 (1974).
- 2) Location: Aobayama, Sendai.
- 3) Ch. Tamm, "Proceedings of the 1st International Pharmacological Meeting," Vol. 3, ed. by W. Wilbrandt, Pergamon Press, Oxford, 1963, p. 11.
- 4) K. Meyer, *Planta Medica*, Suppl. **4**, 2 (1971).
- 5) Y. Shimizu and H. Mitsunashi, *Tetrahedron*, **24**, 4207 (1968).
- 6) L. Ruzicka, Pl. A. Plattner, and J. Pataki, *Helv. Chim. Acta*, **25**, 425 (1942).
- 7) N. Danieli, Y. Mazur, and F. Sondheimer, *J. Am. Chem. Soc.*, **84**, 875 (1962); *idem*, *Tetrahedron*, **22**, 3189 (1966).
- 8) R. Zurflüh and Ch. Tamm, *Helv. Chim. Acta*, **55**, 2495 (1972).
- 9) A.F. St. Andre, H.B. MacPhillamy, J.A. Nelson, A.C. Shabica, and C.R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

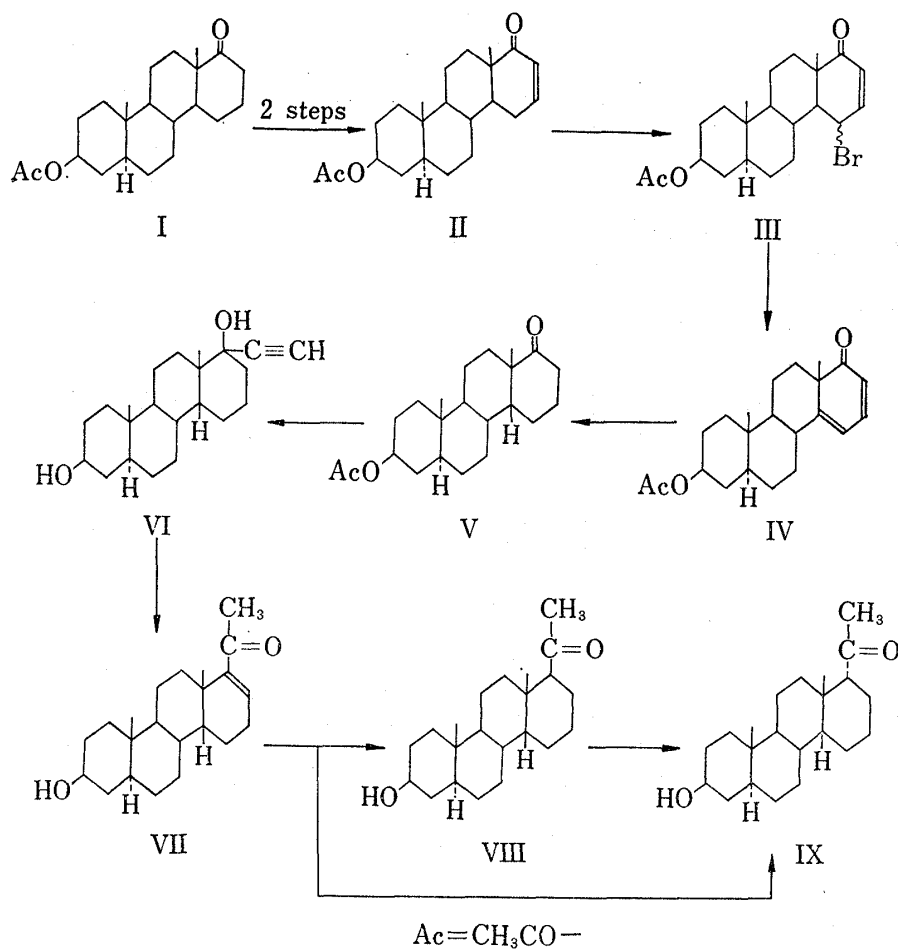


Chart 1

Introduction of a C₂ unit into C-17a was then undertaken utilizing the Grignard reaction.¹⁰⁾ Reaction of V with ethynylmagnesium bromide in tetrahydrofuran gave a mixture of the epimeric 17a-ethynyl-17a-hydroxyl derivatives (VI), whose separation could not readily be attained. However, their structures were deduced from the chromatographic behaviors and nuclear magnetic resonance (NMR) spectra, and hence the mixture was submitted to further elaboration without purification. Hydration with mercury resin¹⁰⁾ proceeded as was expected and the resultant 17a-hydroxy-20-ketones underwent dehydration spontaneously to yield the Δ^{17-20} -ketone (VII). Catalytic hydrogenation over palladium-on-charcoal afforded two C-17a epimeric D-homo-5 α ,14 β -pregnan-20-ones (IX, VIII) in a ratio of *ca.* 5 to 1, whose separation was attained by preparative thin-layer chromatography (TLC).

In order to elucidate the stereochemistry at C-17a of IX and VIII the preparation of C-17a epimeric 17a-hydroxy-D-homoandrostanes (X, XI) by the unequivocal route was then undertaken. Reduction of V with sodium borohydride under the mild conditions, followed by preparative TLC furnished the 3 β ,17 α -diol 3-monoacetate (Xb) together with a small amount of the C-17a epimer (XIb). Upon alkaline hydrolysis these monoacetates were led to the 3 β ,17 α -diols (Xa, XIa), respectively. Configuration of the hydroxyl group at C-17a was determined on the basis of the NMR spectral data. The 18-methyl protons of Xa and XIa experienced the paramagnetic effect of 0.24 ppm in pyridine relative to chloroform due to the formation of a collision complex with the hydroxyl function at C-17a¹¹⁾ and there was not seen any difference in the magnitude between these two epimers. These results suggested

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

11) P.V. Demarco, E. Farkas, D. Doddrell, B.L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90**, 5480 (1968).

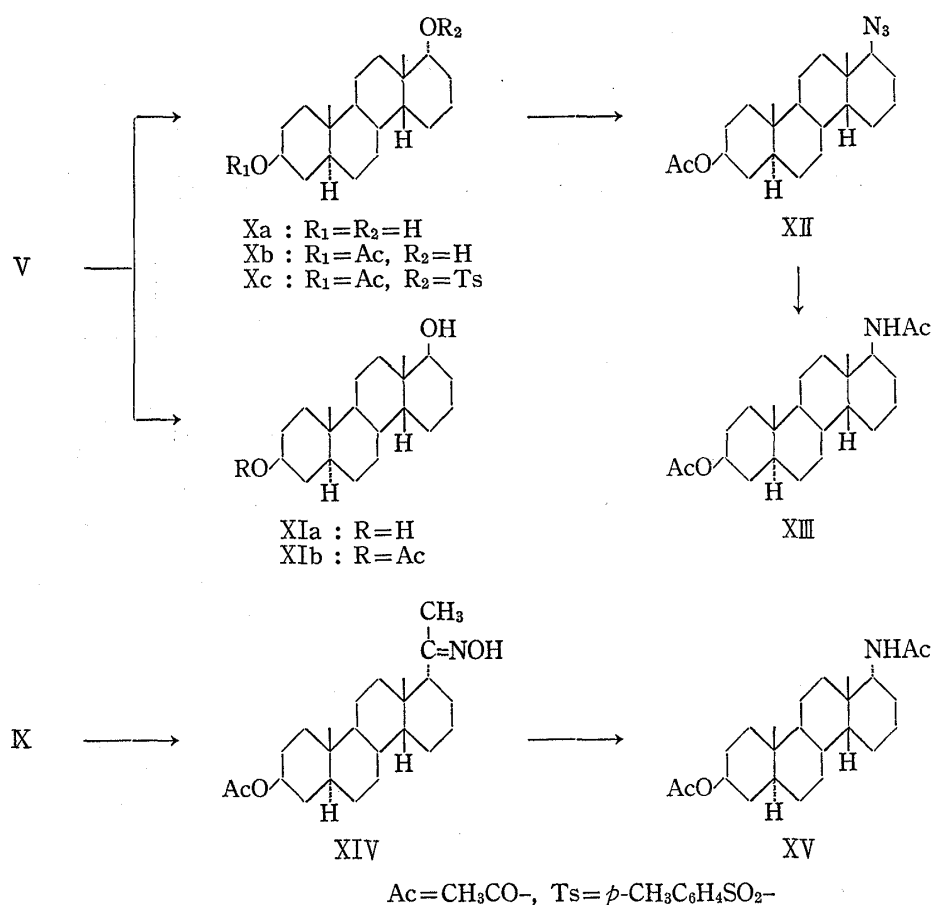


Chart 2

that ring D in the D-homo-14 β -androstan-17 α -ols would exist in the chair form, where the angles between the 18-methyl and C-17 α hydroxyl groups are substantially equivalent. In addition, inspection of the NMR spectra revealed that the half-band width of C-17 α proton of Xa was somewhat larger as compared with that of XIa. This result indicated the 17 α -hydroxyl group of Xa being of the equatorial nature. These evidences together led us to conclude that Xa should be the 17 $\alpha\alpha$ -ol and hence its epimer (XIa) the 17 $\alpha\beta$ -ol. It is to be noted that sodium borohydride attacks the ketone preferentially from the front side in the D-homo-14 β -androstan-17 α -one as observed in the 14 β -androstan-17-one.⁹⁾ Configurational assignment of the side chain in IX was attempted employing the Baeyer-Villiger oxidation and subsequent hydrolysis. Although difficulties were encountered with the less reactivity in the first step, the formation of a trace amount of the 3 β , 17 $\alpha\alpha$ -diol by these procedures could be ascertained by TLC.

In order to obtain further definite evidences for the stereochemical assignment, the Beckmann rearrangement of the 20-ketone oxime was undertaken. First, the synthesis of the 17 $\alpha\beta$ -acetamido derivative by the unequivocal route was carried out for the necessity of comparison with the rearrangement product. The 17 $\alpha\alpha$ -ol tosylate (Xc), easily prepared from Xb in the usual way, was treated with sodium azide to yield the 17 $\alpha\beta$ -azido derivative (XII) accompanying the Walden inversion.¹²⁾ Reduction with lithium aluminum hydride, followed by usual acetylation afforded 17 $\alpha\beta$ -acetamido-D-homo-5 α ,14 β -androstan-3 β -ol acetate (XIII) in a satisfactory yield.

On the other hand the major 17 α -acetyl derivative (IX) was transformed into the 20-ketone oxime (XIV) in the usual manner. Being treated with phosphorus oxychloride, the oxime

12) H.B. Henbest and W.R. Jackson, *J. Chem. Soc.*, 1962, 954.

underwent the Beckmann rearrangement with retention of the inherent configuration at asymmetric carbon¹³⁾ to yield the 17 α -acetamido compound (XV). It is evident from the NMR spectral data that the C-17 α substituent was assignable to the 17 α -acetamido, but not to the 17 α -N-methylcarbamoyl structure. In addition, XV was readily distinguishable from the 17 $\alpha\beta$ -acetamido compound (XIII), as judged from the usual criteria, *i.e.* spectral properties and chromatographic behaviors. Thus these two are obviously epimeric each other and hence the Beckmann rearrangement product should be the 17 $\alpha\alpha$ -acetamido derivative.

These evidences lent a support to assign the structure 17 $\alpha\alpha$ -pregnan-20-one (IX) to the main product obtained from VII by catalytic hydrogenation. Upon exposure to methanolic potassium hydroxide the 17 $\alpha\beta$ -pregnan-20-one (VIII) underwent epimerization to form IX, whereas IX did not epimerize to any appreciable extent even when treated with alkali for a prolonged period. The result indicates that the 17 $\alpha\alpha$ -pregnan-20-one is thermodynamically more stable than the 17 $\alpha\beta$ -epimer.

It is hoped that C-17 α epimeric 3 β -hydroxy-D-homo-5 α ,14 β -pregnan-20-ones obtained will serve as key intermediates for preparation of the D-homo cardenolide analogs.

Experimental¹⁴⁾

3 β -Hydroxy-D-homo-5 α -androst-16-en-17 α -one Acetate (II)—To a stirred solution of 3 β -hydroxy-D-homo-5 α -androst-17 α -one acetate (I) (40 g) in AcOH (135 ml) was added dropwise Br₂ (20.8 g) dissolved in AcOH (160 ml) for 50 min under ice-cooling and stirred for 2 hr. To the reaction mixture was added ether (300 ml) and the precipitated 17 ξ -bromo compound was collected by filtration and washed with ether-hexane (1:1). mp 239–241° (reported mp *ca.* 240°).¹⁵⁾ To a solution of the 17 ξ -bromo compound in dimethylacetamide (400 ml) was added CaCO₃ (150 g) and refluxed for 2 hr. The resulting solution was neutralized with 5% HCl and then extracted with ether. The organic layer was washed with 10% Na₂S₂O₃ and H₂O, dried over anhydrous Na₂SO₄, and evaporated. Recrystallization from MeOH gave II (30 g) as colorless needles. mp 161–161.5°. $[\alpha]_D^{25}$ –8.4° (*c*=0.19). UV λ_{max}^{MeOH} nm (ϵ): 224 (7100). *Anal.* Calcd. for C₂₂H₃₂O₃: C, 76.70; H, 9.36. Found: C, 76.43; H, 9.33. NMR (4.5% solution in CDCl₃) δ : 0.82 (3H, s, 19-CH₃), 1.01 (3H, s, 18-CH₃), 2.01 (3H, s, 3 β -OCOCH₃), 4.65 (1H, m, 3 α -H), 5.86 (1H, q, *J*=3, 10.5 Hz, 17-H), 6.80 (1H, m, *W*/2=20 Hz, 16-H). Johns, *et al.* prepared this compound by the different method (reported mp 148–151°).¹⁶⁾

3 β -Hydroxy-D-homo-5 α -androsta-14,16-dien-17 α -one Acetate (IV)—II (30 g) was dissolved in CCl₄ (450 ml) and the moisture was azeotropically removed by slow distillation. To this solution were added N-bromosuccinimide (22.5 g) and α,α' -azobisisobutyronitrile (5 mg) and the solution was irradiated with a tungsten lamp (350 W) under a stream of N₂ gas. After removal of the precipitate by filtration, the filtrate was concentrated to give the 15 ξ -bromo derivative (III) as an oily residue. To a solution of III in dimethylacetamide (300 ml) was added CaCO₃ (30 g) and refluxed for 1 hr. The resulting solution was neutralized with 5% HCl and then extracted with ether. The organic layer was washed with 10% Na₂S₂O₃ and H₂O, dried over anhydrous Na₂SO₄, and evaporated. The residue thus obtained was submitted to chromatography on silica gel. Elution with benzene-ether (50:1) and recrystallization of the eluate from MeOH gave IV (15 g) as pale yellow needles. mp 174–174.5°. UV λ_{max}^{MeOH} nm (ϵ): 321 (6500). $[\alpha]_D^{25}$ +33.3° (*c*=0.015). *Anal.* Calcd. for C₂₂H₃₀O₃: C, 77.15; H, 8.83. Found: C, 77.19; H, 8.83. NMR (3% solution in CCl₄) δ : 0.91 (3H, s, 19-CH₃), 1.18 (3H, s, 18-CH₃), 1.92 (3H, s, 3 β -OCOCH₃), 4.50 (1H, m, 3 α -H), 5.84 (1H, d, *J*=9 Hz, 17-H or 15-H), 5.87 (1H, d, *J*=6 Hz, 15-H or 17-H), 6.90 (1H, q, *J*=6, 9 Hz, 16-H).

3 β -Hydroxy-D-homo-5 α ,14 β -androstan-17 α -one Acetate (V)—A solution of IV (13.2 g) in EtOH (400 ml) was shaken with 5% Pd/C (20 g) under a stream of H₂ gas at room temperature for 1.5 hr. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. Recrystallization from MeOH gave V (10 g) as colorless leaflets. mp 175–176.5°. $[\alpha]_D^{25}$ +55.5° (*c*=0.06). *Anal.* Calcd. for C₂₂H₃₄O₃: C, 76.26;

13) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt & Co., New York, 1959, p. 620.

14) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in CHCl₃ unless otherwise specified. Ultraviolet and infrared spectra were run on Hitachi Model 124 and JASCO IRA-1 spectrometers, respectively. NMR spectra were recorded using tetramethylsilane as an internal standard on Hitachi Model R-20A and JEOL Model PS-100 spectrometers at 60 MHz and 100 MHz, respectively. Abbreviation used s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. For preparative TLC silica gel H (E. Merck AG, Darmstadt) was used as an adsorbent.

15) D.A. Prins and C.W. Shoppee, *J. Chem. Soc.*, **1946**, 494.

16) W.F. Johns and K.W. Salamon, *J. Org. Chem.*, **36**, 1952 (1971).

H, 9.89. Found: C, 76.43; H, 9.78. NMR (4% solution in CDCl_3) δ : 0.83 (3H, s, 19- CH_3), 1.19 (3H, s, 18- CH_3), 2.03 (3H, s, 3 β - OCOCH_3), 4.72 (1H, m, 3 α -H).

17 α -Ethyne- β -homo-5 α ,14 β -androstane-3 β ,17 α -diol (VI)—To a THF solution (1.5 liter) saturated with $\text{CH}\equiv\text{CH}$ was added EtMgBr dissolved in ether (2.2 mole, 400 ml) and $\text{CH}\equiv\text{CH}$ gas was passed for 3 hr at room temperature. To this solution was added V (10 g) and refluxed for 4 hr. The resulting solution was poured into a cold saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 5% HCl , 10% $\text{Na}_2\text{S}_2\text{O}_3$, and H_2O , successively and dried over anhydrous Na_2SO_4 . Evaporation of solvent gave VI as a yellow oil. NMR (4% solution in CDCl_3) δ : 0.81 (3H, s, 19- CH_3), 1.18 (1.2 H, s, 18- CH_3), 1.22 (1.8 H, s, 18- CH_3), 2.46 (0.6 H, s, $-\text{C}\equiv\text{CH}$), 2.55 (0.4 H, s, $-\text{C}\equiv\text{CH}$), 3.72 (1H, m, 3 α -H). TLC (Al_2O_3 Neutral Type T): R_f 0.36, 0.42 (CHCl_3 - AcOEt (10:3)). The crude product was subjected to further elaboration without purification.

3 β -Hydroxy- β -homo-5 α ,14 β ,17 α -pregn-17-en-20-one (VII)—To a solution of VI (11 g) in AcOH (300 ml) were added Hg-Dowex 50 (44 g) and H_2O (14 ml) and refluxed for 4.5 hr. After removal of the resin by filtration, the filtrate was extracted with ether. The organic layer was washed with 30% NaOH and H_2O , dried over anhydrous Na_2SO_4 , and evaporated. To an oily residue dissolved in MeOH (300 ml) was added 10% NaOH (30 ml) and refluxed for 20 min under a stream of N_2 gas. After evaporation of MeOH *in vacuo* the colorless precipitate was extracted with ether. The organic layer was washed with 5% HCl and H_2O , dried over anhydrous Na_2SO_4 , and evaporated. The residue thus obtained was submitted to chromatography on silica gel. Elution with benzene-ether (10:1) and recrystallization of the eluate from MeOH gave VII (1.7 g) as colorless leaflets. mp 193–196°. $[\alpha]_D^{25} -16.0^\circ$ ($c=0.125$). Anal. Calcd. for $\text{C}_{22}\text{H}_{34}\text{O}_2$: C, 79.95; H, 10.37. Found: C, 79.73; H, 10.47. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 234 (8600). NMR (4% solution in CDCl_3) δ : 0.81 (3H, s, 19- CH_3), 1.21 (3H, s, 18- CH_3), 2.25 (3H, s, 17 α - COCH_3), 3.54 (1H, m, 3 α -H), 6.70 (1H, t, $J=4.5$ Hz, 17-H).

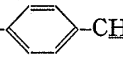
3 β -Hydroxy- β -homo-5 α ,14 β ,17 α -pregn-20-one (VIII), 3 β -Hydroxy- β -homo-5 α ,14 β ,17 α -pregn-20-one (IX)—A solution of VII (1 g) in EtOH (100 ml) was shaken with 5% Pd/C (5 g) at room temperature for 1 hr. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue thus obtained was submitted to preparative TLC employing benzene- AcOEt (10:1) as solvent. Elution of the area corresponding to the spot (R_f 0.44) with AcOEt and recrystallization of the eluate from CH_2Cl_2 -hexane gave VIII (154 mg) as colorless needles. mp 212–215°. $[\alpha]_D^{25} -71.9^\circ$ ($c=0.08$). Anal. Calcd. for $\text{C}_{22}\text{H}_{36}\text{O}_2$: C, 79.46; H, 10.92. Found: C, 79.27; H, 11.12. NMR (3.5% solution in CDCl_3) δ : 0.79 (3H, s, 19- CH_3), 0.97 (3H, s, 18- CH_3), 2.11 (3H, s, 17 α - COCH_3), 2.40 (1H, d, $J=5$ Hz, 17 α -H), 3.55 (1H, m, 3 α -H). Elution of the area corresponding to the spot (R_f 0.29) with AcOEt and recrystallization of the eluate from CH_2Cl_2 -hexane gave IX (729 mg) as colorless needles. mp 166–168°. $[\alpha]_D^{25} -20.6^\circ$ ($c=0.10$). Anal. Calcd. for $\text{C}_{22}\text{H}_{36}\text{O}_2$: C, 79.46; H, 10.92. Found: C, 79.19; H, 11.25. NMR (2% solution in CDCl_3) δ : 0.81 (3H, s, 19- CH_3), 1.09 (3H, s, 18- CH_3), 2.20 (3H, s, 17 α - COCH_3), 2.44 (1H, q, $J=4$, 12 Hz, 17 β -H), 3.75 (1H, m, 3 α -H).

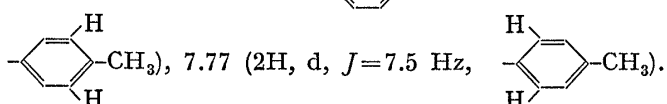
β -Homo-5 α ,14 β -androstane-3 β ,17 α -diol 3-Acetate (Xb), β -Homo-5 α ,14 β -androstane-3 β ,17 α -diol 3-Acetate (XIb)—To a stirred solution of V (228 mg) in MeOH (20 ml) was added NaBH_4 (48 mg) dissolved in H_2O under ice-cooling and stirred for 10 min. After addition of AcOH the resulting solution was concentrated *in vacuo* and extracted with AcOEt . The organic layer was washed with 5% NaHCO_3 and H_2O , dried over anhydrous Na_2SO_4 , and evaporated. The crude product thus obtained was submitted to preparative TLC employing benzene- AcOEt (10:1) as solvent. Elution of the area corresponding to the spot (R_f 0.23) with AcOEt gave Xb (194 mg) as colorless oil. NMR (6% solution in CDCl_3) δ : 0.82 (3H, s, 19- CH_3), 1.10 (3H, s, 18- CH_3), 2.01 (3H, s, 3 β - OCOCH_3), 3.30 (1H, m, $W1/2=20$ Hz, 17 α -H), 4.65 (1H, s, 3 α -H). Elution of the area corresponding to the spot (R_f 0.41) with AcOEt gave XIb (4 mg) as colorless oil. NMR (1% solution in CDCl_3) δ : 0.80 (3H, s, 19- CH_3), 1.02 (3H, s, 18- CH_3), 1.99 (3H, s, 3 β - OCOCH_3), 3.29 (1H, m, $W1/2=10$ Hz, 17 α -H), 4.62 (1H, m, 3 α -H).

β -Homo-5 α ,14 β -androstane-3 β ,17 α -diol (Xa)—To a solution of Xb (50 mg) in MeOH (20 ml) was added 10% K_2CO_3 (10 ml) and stirred at room temperature overnight. After removal of MeOH by evaporation the resulting solution was extracted with AcOEt . The organic layer was washed with H_2O , dried over anhydrous Na_2SO_4 , and evaporated. Recrystallization from CH_2Cl_2 -hexane gave Xa (46 mg) as colorless needles. mp 206–207°. $[\alpha]_D^{18} +43.5^\circ$ ($c=0.02$). Anal. Calcd. for $\text{C}_{26}\text{H}_{44}\text{O}_2$: C, 78.38; H, 11.18. Found: C, 78.23; H, 10.81. NMR (1% solution in CDCl_3) δ : 0.79 (3H, s, 19- CH_3), 1.08 (3H, s, 18- CH_3), 3.26 (1H, m, $W1/2=20$ Hz, 17 α -H), 3.55 (1H, m, 3 α -H); (1% solution in pyridine- d_5) δ : 0.83 (3H, s, 19- CH_3), 1.32 (3H, s, 18- CH_3), 3.48 (1H, m, $W1/2=20$ Hz, 17 α -H), 3.81 (1H, m, 3 α -H).

β -Homo-5 α ,14 β -androstane-3 β ,17 α -diol (XIa)—To a solution of XIb (9 mg) in MeOH (6 ml) was added 10% K_2CO_3 (3 ml) and stirred at room temperature overnight. After removal of MeOH by evaporation the resulting solution was extracted with AcOEt . The organic layer was washed with H_2O , dried over anhydrous Na_2SO_4 , and evaporated. Recrystallization from CH_2Cl_2 -hexane gave XIa (8 mg) as colorless needles. mp 157–158.5°. $[\alpha]_D^{19} +65.7^\circ$ ($c=0.03$). Anal. Calcd. for $\text{C}_{26}\text{H}_{44}\text{O}_2 \cdot 1/3\text{H}_2\text{O}$: C, 76.87; H, 11.18. Found: C, 76.84, 76.93; H, 11.12, 11.03. NMR (0.5% solution in CDCl_3) δ : 0.80 (3H, s, 19- CH_3), 1.04 (3H, s, 18- CH_3), 3.27 (1H, m, $W1/2=10$ Hz, 17 α -H), 3.50 (1H, m, 3 α -H); (0.5% solution in pyridine- d_5) δ : 0.83

(3H, s, 19-CH₃), 1.28 (3H, s, 18-CH₃), 3.48 (1H, m, $W_{1/2}=10$ Hz, 17 α -H), 3.75 (1H, m, 3 α -H). TLC (silica gel G): *R_f* 0.40 (benzene-AcOEt (3:1)), 0.19 (CHCl₃-AcOEt (5:1)), 0.35 (hexane-AcOEt (2:1)).

n-Homo-5 α ,14 β -androstane-3 β ,17 α -diol 3-Acetate 17 α -p-Toluenesulfonate (Xc)—To a solution of Xb (155 mg) in pyridine (5 ml) was added *p*-TsCl (1.6 g) and allowed to stand at room temperature for 10 days. The resulting solution was poured onto ice-water. The precipitate was collected by filtration, washed with H₂O, and dissolved in CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄ and evaporated. An oily product obtained was subjected to preparative TLC employing hexane-AcOEt (5:1). Elution of the adsorbent corresponding to the spot (*R_f* 0.35) and recrystallization from acetone gave Xc (121 mg) as colorless needles. mp 171–172°. $[\alpha]_D^{16.5} +17.7^\circ$ ($c=0.09$). *Anal.* Calcd. for C₂₉H₄₂O₂S: C, 69.29; H, 8.42. Found: C, 69.33; H, 8.26. NMR (5% solution in CDCl₃) δ : 0.79 (3H, s, 19-CH₃), 0.94 (3H, s, 18-CH₃), 2.01 (3H, s, 3 β -OCOCH₃), 2.43 (3H, s, , 4.32 (1H, m, 17 α -H), 4.64 (1H, m, 3 α -H), 7.29 (2H, d, $J=7.5$ Hz,



17 α -Acetamido-n-homo-5 α ,14 β -androstane-3 β -ol 3-Acetate (XIII)—To a solution of Xc (140 mg) in N-methylpyrrolidone (3 ml) was added NaN₃ (200 mg) and heated at 90° for 6.5 hr. The resulting solution was poured onto ice-water and extracted with ether. The organic layer was washed with H₂O, dried over anhydrous Na₂SO₄, and evaporated. An oily product obtained was subjected to preparative TLC employing hexane-AcOEt (6:1) as solvent. Elution of the adsorbent corresponding to the spot (*R_f* 0.60) with AcOEt gave 17 α -azido-n-homo-5 α ,14 β -androstane-3 β -ol acetate (XII) (68 mg) as pale yellow oil. To a solution of XII in anhydrous ether (15 ml) was added LiAlH₄ (130 mg) and stirred at room temperature for 6 hr. After addition of moist ether the organic layer was separated, washed with H₂O, dried over anhydrous Na₂SO₄, and evaporated. An oily residue obtained was treated with Ac₂O and pyridine in the usual manner. The crude product was subjected to preparative TLC employing hexane-AcOEt (1:1) as solvent. Elution of the adsorbent corresponding to the spot (*R_f* 0.30) with AcOEt and recrystallization of the eluate from CH₂Cl₂-hexane gave XIII (19 mg) as colorless needles. mp 214–216°. $[\alpha]_D^{18} -3.5^\circ$ ($c=0.14$). *Anal.* Calcd. for C₂₄H₃₉O₃N: C, 73.99; H, 10.09; N, 3.60. Found: C, 73.92; H, 10.29; N, 3.89. NMR (3% solution in CDCl₃) δ : 0.81 (3H, s, 19-CH₃), 0.95 (3H, s, 18-CH₃), 2.00 (6H, s, 3 β -OCOCH₃, -NHCOCH₃), 3.72 (1H, m, 17 α -H), 4.57 (1H, m, 3 α -H), 5.71 (1H, m, -NHAc). TLC (silica gel G): *R_f* 0.15 (hexane-AcOEt (1:1)). IR (KBr) cm⁻¹: 3280, 1645, 1560.

3 β -Hydroxy-D-homo-5 α ,14 β ,17 α -pregnan-20-one 3-Acetate 20-Oxime (XIV)—Treatment of IX (80 mg) with Ac₂O-pyridine in the usual manner gave the 3-acetate as colorless oil. To a solution of the acetate in pyridine (10 ml) was added NH₂OH·HCl (80 mg) dissolved in H₂O and refluxed for 4 hr. The resulting solution was neutralized with 5% HCl under ice-cooling and extracted with ether. The organic layer was washed with H₂O, dried over anhydrous Na₂SO₄, and evaporated. An oily product obtained was subjected to preparative TLC employing benzene-AcOEt (10:1) as solvent. Elution of the area corresponding to the spot (*R_f* 0.41) with AcOEt gave XIV (75 mg) as colorless oil. NMR (4% solution in CDCl₃) δ : 0.80 (3H, s, 19-CH₃), 1.00 (3H, s, 18-CH₃), 1.83 (3H, s, 21-CH₃), 2.00 (3H, s, 3 β -OCOCH₃), 4.70 (1H, m, 3 α -H).

17 α -Acetamido-D-homo-5 α ,14 β -androstane-3 β -ol 3-Acetate (XV)—To a stirred solution of XIV (75 mg) in pyridine (1 ml) was added dropwise POCl₃ (0.2 ml) under ice-cooling and stirred for 3 hr.¹⁷ To the resulting solution was added conc. HCl (1 ml) and extracted with ether. The organic layer was washed with H₂O, dried over anhydrous Na₂SO₄, and evaporated. An oily product obtained was submitted to preparative TLC employing benzene-ether (5:1). Elution of the adsorbent corresponding to the spot (*R_f* 0.10) with AcOEt and recrystallization of the eluate from CH₂Cl₂-hexane gave XV (18 mg) as colorless prisms. mp 203–204°. $[\alpha]_D^{17} +41.8^\circ$ ($c=0.14$). *Anal.* Calcd. for C₂₄H₃₉O₃N: C, 73.99; H, 10.09; N, 3.60. Found: C, 73.29; H, 10.35; N, 3.67. NMR (5% solution in CDCl₃) δ : 0.81 (3H, s, 19-CH₃), 1.00 (3H, s, 18-CH₃), 1.96 (3H, s, -NHCOCH₃), 2.01 (3H, s, 3 β -OCOCH₃), 3.74 (1H, m, 17 α -H), 4.65 (1H, m, 3 α -H), 5.46 (1H, m, -NHAc). TLC (silica gel G): *R_f* 0.10 (hexane-AcOEt (1:1)). IR (KBr) cm⁻¹: 3320, 1660, 1560. Mixed melting point on admixture with XIII showed depression.

Transformation of IX into Xa—Usual acetylation of IX (18 mg) with Ac₂O-pyridine gave the 3-acetate (11 mg), which in turn was treated with *m*-chloroperbenzoic acid (45 mg) in CHCl₃ (1 ml) at room temperature for 16 days. The resulting solution was diluted with ether, washed with 10% Na₂S₂O₃, 5% NaHCO₃, and H₂O, dried over anhydrous Na₂SO₄, and evaporated. The residue obtained was submitted to preparative TLC employing hexane-AcOEt (6:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*R_f* 0.67) gave an oily residue. The crude product was dissolved in 10% NaOH (0.1 ml)-MeOH (10 ml) and heated at 80° for 15 min. Usual work-up gave a colorless amorphous substance (0.7 mg). The product proved to be identical with Xa, but not with its C-17 α epimer (XIa) according to TLC employing benzene-AcOEt (3:1), CHCl₃-AcOEt (5:1), and hexane-AcOEt (2:1) as developing solvents.

17) J. Schmidt-Thomé, *Chem. Ber.*, **88**, 895 (1955).

Epimerization of VIII with Alkali—A solution of VIII (10 mg) dissolved in 3% methanolic KOH (2.5 ml) was refluxed for 1 hr. After usual work-up the crystalline product obtained was submitted to gas-liquid chromatography (GLC). It proved that the mixture consisted of IX (t_R 18.8 min) and unchanged VIII (t_R 16.9 min) in a ratio of *ca.* 1 to 6. The GLC conditions were as follows. The apparatus used for this work was a Shimadzu Model GC-3BF gas chromatograph equipped with a hydrogen flame ionization detector and a spiraled glass column (2.1 m \times 3 mm i.d.). The column was packed with 1.5% OV-1 on a support of Shimalite W (60–80 mesh). The detector and flash heater were kept at 250°, while the column was at 230°. N₂ was used as a carrier gas at a flow rate of 60 ml/min.

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