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THE SYNTHESIS OF STEROIDAL 1β,2β-METHYLENE DERIVATIVES

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Abstract—The synthesis of 1β,2β-methylene derivatives of a cortical steroid hormone and an androgen analog are described. The 1β,2β-methylene group was introduced stereospecifically by a Simmons-Smith reaction on Δ¹-3β-ols. The properties of the cyclopropyl steroids are discussed, including some anomalous molecular rotation shifts.

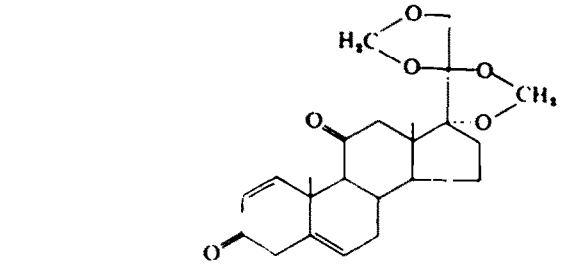
THE introduction of a variety of substituents into various positions on the steroid nucleus has been the subject of much recent research. The goal of the present investigation was to introduce the 1β,2β-methylene function into a cortical hormone, hydrocortisone, to obtain 1β,2β-methylenehydrocortisone acetate (VII); and into a typical androgen 17α-methyltestosterone, to obtain 1β,2β-methylene-17α-methyltestosterone (VIII). Similar structural variations steroids containing 1α,2α-methylene substituents have been previously described.[1] Since the completion of our work, Wiechert[2] has also described the synthesis and properties of 1β,2β-methylene steroids.

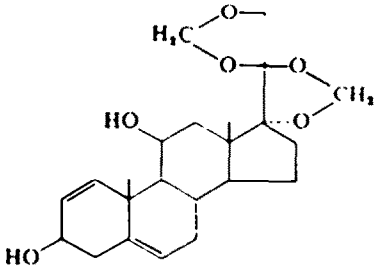
Our synthetic sequence commenced with the very versatile intermediates, the Δ¹·⁵-3-ketones I and VIII in the corticoid and androgen series. The preparation of these intermediates from the corresponding Δ¹·⁴-3-ketones was recently described.[3] These deconjugated ketones are extremely useful starting materials for our synthetic objectives since the 1β,2β-methylene function can in principle be selectively introduced at the Δ¹ double bond. Facile reconjugation of the βγ-unsaturated ketone to the Δ⁴-α,β-unsaturated ketone is expected.

In the corticosteroid series, LAH reduction of 17α,20;20,21-bismethylenedioxy-1,5-pregnadiene-3,11-dione (I) in tetrahydrofuran yielded a mixture of diols as determined by TLC. Direct crystallization of the products of the reaction mixture from acetone yielded the predominant isomer, the 3β,11β-diol II. The minor isomer, the 3α,11β-diol IIa, was obtained from the reduction mixture by extensive chromatography of the mother liquors of the crystallization. That the isomers differed only in configuration at C-3 was demonstrated by selective oxidation of the allylic C-3 alcohols with manganese dioxide, followed by base catalyzed conjugation of the intermediate 11β-hydroxy-Δ¹·⁵-3-ketone to the known prednisolone BMD.[4]

Reaction of the 3β-allylic alcohol II with the iodomethylzinc iodide reagent of Simmons and Smith[5] should serve to introduce the 1,2-methylene function onto the

[1] R. Wiechert and E. Kaspar, *Chem. Ber.* **93**, 1710 (1960).
[2] R. Wiechert, D. Engelfried, U. Kerb, H. Laurent, H. Miller and G. Schulz, *Chem. Ber.* 1118 (1966); G. Schulz and R. Wiechert, *Ibid.* **99**, 1128 (1966).
[3] E. L. Shapiro, T. Legatt, L. Weber, E. P. Oliveto, M. Tanabe and D. F. Crowe, *Steroids* **3**, 183 (1964).
[4] R. E. Beyler, Frances Hoffman, R. M. Moriarty and L. H. Sarett, *J. Org. Chem.* **26**, 2421 (1961).
[5] H. W. Simmons and R. D. Smith, *J. Am. Chem. Soc.* **80**, 5323 (1959); **81**, 4256 (1959).





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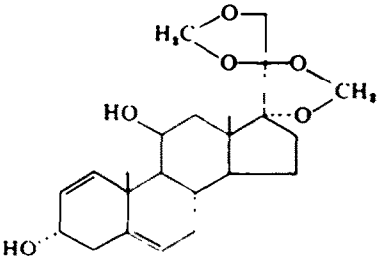

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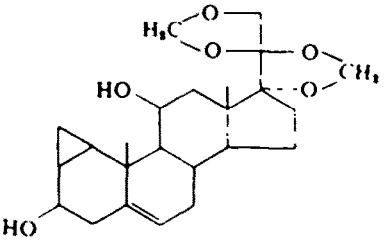

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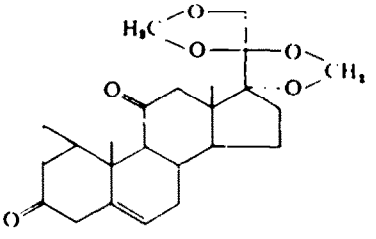

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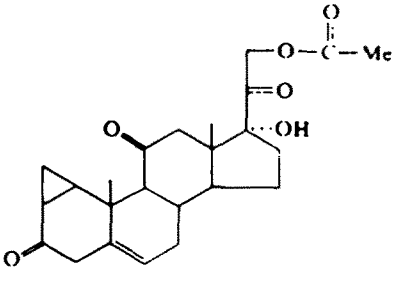

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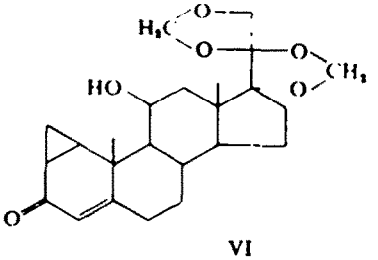


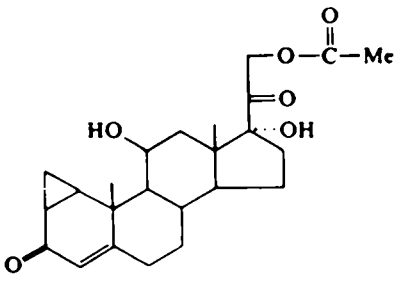
VI

Δ^1 double bond in the desired manner. Since stereospecific Simmons-Smith reactions have been observed previously with other allylic alcohols,[6-8] delivery of the methylene

[6] S. Winstein, J. Sonnenberg and L. DeVries, *J. Am. Chem. Soc.* **81**, 6523 (1959); S. Winstein and J. Sonnenberg, *Ibid.* **83**, 3235 (1961); P. Radlick and S. Winstein, *Ibid.* **86**, 1866 (1964).

[7] W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.* **85**, 468 (1963); W. G. Dauben and A. C. Ashcraft, *Ibid.* **85**, 3673 (1963).

[8] R. Ginsig and A. D. Cross, *J. Am. Chem. Soc.* **87**, 4629 (1965).



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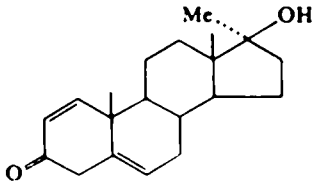

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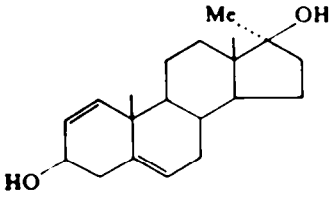

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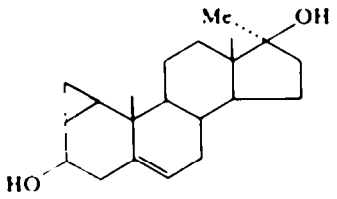

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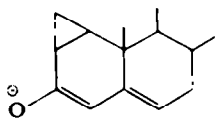

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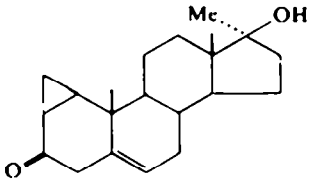

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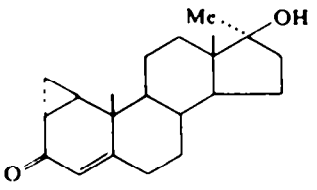

XIII

function of the Δ^1 double bond was anticipated to occur from the β side due to the directive influence of the allylic 3β-ol. Minimum interference from reaction of the iodomethylzinc iodide reagent at the Δ^5 double bond was expected because of the steric requirements of the reagent in the methylene transfer step.[9]

When the 3β-allylic alcohol II was allowed to react with iodomethylzinc iodide in boiling tetrahydrofuran for 24 hr, a 40% yield of the 1β,2β-methylene adduct III was isolated. The 1β,2β-methylene carbinol III displayed in the NMR spectrum high-field bands characteristic of cyclopropane hydrogens. The signals appeared as a multiplet in the 9·5 τ region of the spectrum.

To obtain the 1β,2β-methylene product in the androgen series, the identical reactions were employed. Reduction of 17β-hydroxy-17α-methyl-1,5-androstadien-3-one (VIII) with sodium borohydride in methanol yielded the 3β-ol IX.[10] Reaction of this allylic alcohol with the Simmons-Smith reagent, under identical reaction conditions with the corticoid II, afforded 17α-methyl-1β,2β-methylene-5-androstene-3β,17β-diol (X) in 52% yield obtained by direct crystallization from the reaction mixture. TLC

[9] H. E. Simmons, E. P. Blanchard and R. D. Smith, *J. Am. Chem. Soc.* **86**, 1347 (1964); E. P. Blanchard and H. E. Simmons, *Ibid.* **86**, 1327 (1964).

[10] 3β-Hydroxy-1,5-bisdehydrosteroids will be the subject of a forthcoming paper by E. L. Shapiro, L. Weber, E. P. Oliveto, H. L. Herzog, R. Nervi, M. Tanabe and D. F. Crowe. We thank E. L. Shapiro of the Schering Corporation, Bloomfield, New Jersey, for furnishing us samples and the physical constants of 17α-methyl-1,5-androstadiene-3β,17β-diol.

analysis of the mother liquor from the crystallization indicated the absence of any other products other than unreacted starting material. The absence of a 1α,2α-methylene adduct corroborates the importance of the allylic alcohol function in the stereospecific delivery of the methylene group from iodomethylzinc iodide. The lack of products attributable to addition at the Δ^5-double bond is in accord with the reported bulkiness of the mildly electrophilic iodomethylzinc iodide reagent towards multiple substituted double bonds.[9]

Oxidation of the 1β,2β-methylene alcohols II and X to the corresponding C-3 ketones was accomplished with the Jones[11] reagent. In the corticoid series simultaneous oxidation at C-11 occurred to give IV. It was observed that both βγ-unsaturated ketones IV and XII were extremely resistant to conjugation to α,β-unsaturated isomers. This conversion is usually effected with mild acidic or basic conditions such as dilute ammonium hydroxide at room temperature.[11] Conversion of the 3β-hydroxy-Δ^5-1β,2β-methylene derivatives to the 3-keto-Δ^4-system, VI and XIII, could be effected by aluminum isopropoxide and cyclohexanone in boiling toluene for 84 hr. This is to be contrasted with the faster rate (11 to 18 hr) of Oppenauer oxidation accompanied by conjugation to the 3-keto-Δ^4-system with other 3β-hydroxy-Δ^5-steroids.[12]

The base catalyzed conjugation of the intermediate, 3-keto-Δ^5 system to the conjugated isomer proceeds via the enolate ion XI. Inspection of Dreiding models of this enol shows that ring A is completely coplanar, resulting in considerable nonbonded 1,3 interaction between the C-19 angular Me group and the 1β,2β-methylene substituent. This interaction is reflected in the higher transition state energy to effect the over-all βγ to αβ unsaturated ketone transformation.

The molecular rotation shifts observed in the conversion of the 3β-hydroxy-Δ^5-1β,2β-methylene alcohols III and X to their respective 3-keto-Δ^4-systems, VI and XIII exhibit a large negative change. This molecular rotation shift with other steroids is usually associated with a large positive shift value,[13] as noted in Table 1.

TABLE 1. MOLECULAR ROTATION SHIFTS AT 589 mμ

	Δ
3β-hydroxy-Δ^5- → 3-keto-Δ^4-	+124
III → VI	−982
X → XIII	−428

It is of interest to note that in a recent report the ORD curves at 290 mμ of ketones conjugated to cyclopropanes do not follow the normal octant rule.[14] A reversed octant rule has been proposed instead to account for the Cotton effect of cyclopropyl and epoxy-ketones.

The synthesis in the corticosteroid series was completed by removing the protective bismethylenedioxy group from the dihydroxy-acetone side chain and isolating VII as the corresponding 21-acetate derivative. Removal of the bismethylenedioxy group from the Δ^5 isomer yielded V. The acidic conditions employed for this transformation

[11] C. Djerassi, R. R. Engle and A. J. Bowers, *J. Org. Chem.* **21**, 1547 (1956).
[12] C. Djerassi, *Steroid Reactions* p. 92. Holden-Day, San Francisco, California (1963).
[13] L. F. Fieser and M. Fieser, *Steroids* p. 180. Reinhold, New York (1959).
[14] C. Djerassi, W. Klyne, T. Norin, G. Ohloff and E. Klein, *Tetrahedron* **21**, 163 (1965).

are not rigorous enough to effect enolization and conjugation of the Δ^5 double bond to yield the 3-keto-Δ^4 system.

In the NMR spectra of the cyclopropyl compounds prepared in this study, a downfield shift of the cyclopropyl protons on conversion to the 3-ketones from the 3β-ols was observed. These protons are now obscured by the broad proton absorption of the steroid envelope.

The introduction of substituents 1,3-diaxial to the angular Me groups usually results in a downfield shift of the angular Me resonances and follows a frequency additivity principle for the position of specific substituents as described.[15,16] The chemical shift data for the C-19 angular Me group of some of the compounds prepared in this study are presented in Table 2.

TABLE 2. C-19 NUCLEAR MAGNETIC RESONANCE VALUES (τ)

Compound	C-19	Δ(τ)
3β-hydroxy-Δ^5-	9·2	−0·17
X	9·03	
3β-acetoxy-Δ^5-	9·19	−0·16
3β-acetate of X	9·03	
3-keto-Δ^5-	8·82	0
XII	8·82	
3-keto-Δ^4	8·80	−0·07
XIII	8·73	

Since the molecular rotational shift data indicate a conformational abnormality in ring A for the 1β,2β-methylene compounds, caution must be exercised in the use of the incremental NMR chemical shift data for the C-19 Me resonances of the 1β,2β-methylene substituent. The incremental shift for the C-19 Me group changes with the nature of the oxygen substituent at C-3 and the conformational nature of ring A in these derivatives. Preferential shielding effects from the cyclopropyl ring must also be taken into account[17] when considering the C-19 Me resonances for the compounds prepared in this study.

EXPERIMENTAL[18]

17α,20;20,21-*Bismethylenedioxy*-1,5-*pregnadiene*-3,11-*dione* (I). To a stirred slurry of 1·5 g $NaNH_2$ in 120 ml dry THF under a N atm, a soln of 5·8 g prednisone BMD[4] in 60 ml THF was added dropwise. The reaction mixture was boiled for 20 hr and then cooled to room temp and poured into 400 ml sat boric acid soln that was overlaid with 300 ml ether. The ethereal soln was washed with water and dried over Na_2SO_4. The solvent was removed at reduced press and the residue chromatographed on Florisil. Elution with benzene gave 3·1 g of I. An analytical sample was prepared by recrystallization from acetone; m.p. 203–205°; $[\alpha]_D$ −5°; λ_{max}^{Nujol} 5·87 and 5·93 μ; λ_{max}^{MeOH} 225 mμ (ε 11,000). (Found: C, 69·80; H, 7·25. $C_{28}H_{36}O_6$ requires: C, 69·98; H, 7·05%.)

17α,20;20,21-*Bismethylenedioxy*-1,5-*pregnadiene*-3β,11β-diol (II). To a slurry of 9 g LAH in 900 ml ether cooled to 0–10°, a soln of 9 g of I in 900 ml THF was added dropwise with stirring under a N atm. The reaction mixture was stirred for an additional 16 hr at room temp and the excess LAH

[15] R. F. Zürcher, *Helv. Chim. Acta* **44**, 1380 (1961); *Ibid.* **46**, 2054 (1963).
[16] A. I. Cohen and S. Rock Jr., *Steroids* **3**, 243 (1965).
[17] J. Tandler and W. J. Cole, *J. Org. Chem.* **27**, 4611 (1962).
[18] Melting points were taken on a Fisher-Johns apparatus. A Perkin–Elmer infracord was used to obtain IR spectra. Rotations were determined in chf at 1% concns at 23° unless otherwise stated. TLC data were obtained on Merck silica gel G. The NMR spectra were obtained with 10% solns in $CDCl_3$ on a Varian A-60 spectrometer.

was decomposed by dropwise addition of a sat Na_2SO_4aq. The soln was filtered and dried over Na_2SO_4 and the solvents were removed at reduced press. Crystallization of the residue from acetone gave 6·5 g of II. An analytical sample was prepared by recrystallization from acetone; m.p. 223–224°; $[\alpha]_D$ −125°; λ_{max}^{Nujol} 2·8 mμ. (Found: C, 68·40; H, 7·90. $C_{23}H_{32}O_6$ requires: C, 68·29; H, 7·97%.)

Chromatography of the mother liquor from the crystallization of II on Florisil afforded IIa. An analytical sample was prepared by crystallization from acetone, m.p. 198–200°; $[\alpha]_D$ +8°; λ_{max}^{Nujol} 2·9 mμ. (Found: C, 68·17; H, 8·12. $C_{23}H_{32}O_6$ requires: C, 68·29; H, 7·97%.)

A mixture of 100 mg of II and IIa and 1 g activated M_4O_9 in 50 ml chf was stirred at room temp for 16 hr. The mixture was filtered and the residue remaining after removal of the chf was dissolved in 10 ml MeOH and 1 ml 1N NaOH. The MeOH soln was heated on a steam bath for 10 min to effect conjugation of the intermediate 11β-hydroxy-17α,20;20,21-bismethylenedioxy-1,5-pregnadien-3-one to prednisolone BMD. The prednisolone BMD isolated from this reaction was identical in all respects with an authentic sample.[4]

1β,2β-Methylene-17α,20;20,21-bismethylenedioxy-5-pregnene-3β,11β-diol (III). To a vigorously stirred mixture of 7·2 g of the Zn–Cu couple[5] and 0·06 g I_2 in 100 ml ether, 15 ml CH_2I_2 was added. The reaction mixture was heated under a N atm for 3·0 hr with an IR lamp, cooled to room temp and a soln of 6·0 g of II in 20 ml THF was added. The reaction mixture was heated at 60° for an additional 24 hr, cooled to room temp and 5 ml sat NH_4Claq was added to decompose any unreacted complex. The ether soln was decanted, extracted with sat Na_2CO_3aq and washed with sat NaClaq and water. The ether soln was dried over Na_2SO_4 and the solvents were removed at reduced press. Trituration of the residue with ether gave 1·4 g of III. The mother liquor from the trituration was chromatographed on Merck acid washed alumina and elution with AcOEt gave an additional 1·0 g of III. An analytical sample was prepared by crystallization from acetone: m.p. 242–244°; $[\alpha]_D$ −62° (MeOH); λ_{max}^{Nujol} 2·9 mμ. (Found: C, 69·12; H, 7·97. $C_{24}H_{34}O_6$ requires: C, 68·87; H, 8·19%.)

1β,2β-Methylene-17α,20;20,21-bismethylenedioxy-5-pregnene-3,11-dione (IV). To a soln of 0·5 g of III in 100 ml acetone, Jones[11] reagent was added dropwise until a slight excess was present. The soln was filtered through Celite and 500 ml chf was added. The chf soln was washed with 10% $NaHSO_3$aq and 3 times with water and dried over Na_2SO_4. The solvent was removed at reduced press and crystallization of the residue from CH_2Cl_2–ether gave 0·175 g of IV. An analytical sample was prepared by recrystallizing twice from CH_2Cl_2–ether: m.p. 224–226°; $[\alpha]_D$ +35°; λ_{max}^{Nujol} 5·87 mμ. (Found: C, 69·31; H, 7·48. $C_{24}H_{30}O_6$ requires: C, 69·54; H, 7·30%.)

21-Acetoxy-17α-hydroxy-1β,2β-methylene-5-pregnene-3,11,20-trione (V). A soln of 0·1 g of IV in 6 ml formic acid was heated on a steam bath under a N atm for 1 min and then 4 ml water was added and the heating continued for an additional 0·5 hr. The formic acid and water were removed at reduced press and the residue was dissolved in 20 ml chf. The chf soln was washed with water and dried over Na_2SO_4 and the chf was removed at reduced press. The residue was dissolved in 2 ml pyridine and 2 ml Ac_2O was added. The reaction mixture stood for 60 hr under a N atm and then the pyridine and Ac_2O were removed at reduced press. Crystallization from acetone–hexane gave 16 mg of V. An analytical sample was prepared by recrystallization from acetone–ether: m.p. 235–237°; λ_{max}^{Nujol} 3·0, 5·7, 5·77, 5·87 and 5·98 mμ. (Found: C, 69·31; H, 7·48. $C_{24}H_{30}O_6$ requires: C, 69·54; H, 7·30%.)

11β-Hydroxy-1β,2β-methylene-17α,20;20,21-bismethylenedioxy-4-pregnen-3-one (VI). To a soln of 0·6 g of III in 24 ml cyclohexanone was added 120 ml toluene and 1·8 g aluminum isopropoxide. The reaction mixture was heated at 130° under a N atm for 84 hr, cooled to room temp, poured over ice-water and extracted with chf. The chf extract was washed with water and dried over Na_2SO_4. The solvent was removed at reduced press and the residue was chromatographed on Merck acid washed alumina. Elution with ether gave 0·3 g of VI. An analytical sample was prepared by crystallizing twice from CH_2Cl_2–ether: m.p. 281–284°; $[\alpha]_D$ −271°; λ_{max}^{Nujol} 2·93 and 6·13 μ; λ_{max}^{MeOH} 247 mμ (ε 10,000). (Found: C, 69·12; H, 7·51. $C_{24}H_{32}O_6$ requires: C, 69·21; H, 7·74%.)

21-Acetoxy-11β,17α-dihydroxy-1β,2β-methylene-4-pregnene-3,20-dione (VII). A soln of 0·26 g of VI in 25 ml 60% formic acid was heated on a steam bath under a N atm for 0·5 hr. The soln was cooled to room temp and the formic acid and water were removed at reduced press. The residue was dissolved in 50 ml chf. The chf was removed at reduced press and the residue was dissolved in 15 ml MeOH and 15 ml chf was added. This soln was cooled in an ice bath and 1 ml of 1N NaOH was added. The reaction mixture was stirred at ice bath temp for 0·5 hr under a N atm and then 30 ml chf and 30 ml water were added. The chf soln was washed with water and dried over Na_2SO_4. The

chf was removed at reduced press and the residue was dissolved in 5 ml pyridine and 5 ml Ac_2O. After 16 hr at room temp under a N atm the pyridine and Ac_2O were removed at reduced press and the residue was chromatographed on Merck acid washed alumina. Elution with chf and AcOEt gave 0·1 g of VII. An analytical sample was prepared by crystallization from benzene: m.p. 218–220°; $[\alpha]_D$ −118°; λ_{max}^{Nujol} 2·92, 3·0, 5·7, 5·77 and 6·2 mμ; λ_{max}^{MeOH} 246 mμ (ε 10,700). (Found: C, 68·89; H, 7·80. $C_{24}H_{32}O_4$ requires: C, 69·21; H, 7·74%.)

17α-*Methyl*-1,5-*androstadiene*-3β,17β-*diol* (IX).[10] A soln of 23·4 g 17β-hydroxy-17α-methyl-1,5-androstadiene-3-one[9] in 1·89 l. MeOH was cooled to 2° with stirring. To this was added 11·7 g $NaBH_4$ dissolved in 470 ml water, with the reaction temp maintained below 15°. After stirring at approximately 5° for 45 min, 1 l. of 50% aqueous acetone was added. The organic solvents were removed by distillation and the resulting ppt was collected by filtration to give a crude product of 22·4 g. Two crystallizations from MeOH afforded 16·10 g of IX: m.p. 188–190°; $[\alpha]_D$ −41° (dioxan); λ_{max}^{Nujol} 3·05 mμ. (Found: C, 79·30; H, 10·29. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%.)

17α-*Methyl*-1β,2β-*methylene*-5-*androstene*-3β,17β-*diol* (X). To a vigorously stirred mixture of 12·0 g Zn–Cu couple and 0·072 g I_2 in 100 ml anhyd ether under a N atm, 7·6 ml CH_2I_2 was added. The reaction mixture was heated with an IR lamp and then cooled to room temp and a soln of 1·0 g of IX in 40 ml anhyd THF was added. The reaction mixture was heated at 60° for an additional 24 hr. The mixture was cooled to room temp and 5 ml sat NH_4Claq was added to decompose any unreacted complex. The soln was decanted, extracted with Na_2CO_3aq and washed with sat NaClaq and water. The ether soln was dried over Na_2SO_4 and the solvent was removed at reduced press. Crystallization from acetone afforded 0·54 g of X. TLC of the mother liquor on silica gel G plates only indicated the presence of X and unreacted IX. An analytical sample was prepared by recrystallization from acetone: m.p. 211–213°; $[\alpha]_D$ +148° (dioxan); λ_{max}^{Nujol} 2·85 and 3·1 mμ; NMR τ 4·8 (C-6 H), 8·72 (C-17, 3H), 9·03 (C-18 3H and C-19 3H) and 9·4 (C-1, 2-methylene). (Found: C, 79·47; H, 9·96. $C_{21}H_{30}O_2$ requires: C, 79·70; H, 10·19%.)

17β-*Hydroxy*-17α-*methyl*-1β,2β-*methylene*-5-*androsten*-3-*one* (XII). To a soln of 0·05 g of X in 10 ml acetone, Jones[11] reagent was added dropwise until a slight excess was present. The soln was filtered through Celite and 50 ml chf was added. The chf soln was washed with 10% $NaHSO_3$aq and 3 times with water and dried over Na_2SO_4. The solvent was removed at reduced press and the residue was crystallized from CH_2Cl_2–ether. An analytical sample was prepared by recrystallization from CH_2Cl_2–ether: m.p. 220–222°; $[\alpha]_D$ +108°; λ_{max}^{Nujol} 2·85 and 5·9 mμ; NMR τ 4·73 (C-6 H) 8·75 (C-17 3H) 8·82 (C-19 3H) and 9·07 (C-18 3H). (Found: C, 80·55; H, 9·69. $C_{21}H_{30}O_2$ requires: C, 80·21; H, 9·62%.)

17β-*Hydroxy*-17α-*methyl*-1β,2β-*methylene*-4-*androsten*-3-*one* (XIII). To a soln of 1·2 g of X in 96 ml cyclohexanone was added 240 ml toluene and 3·6 g aluminum isopropoxide. The reaction mixture was heated at 120° with stirring and under a N atm for 84 hr. After cooling to room temp the reaction mixture was poured over ice-water and extracted with chf. The chf soln was washed with water and then dried with Na_2SO_4. The solvent was removed at reduced press. Trituration of the residue with hexane afforded 400 mg of XII. TLC analysis of the mother liquor from the trituration on silica gel GF using a chf–AcOEt solvent system showed it to be a mixture containing mostly XII and a small amount of XIII.

The 400 mg of pure XII obtained from the previous sequence was dissolved in 80 ml toluene and 1·2 g aluminum isopropoxide was added. The reaction mixture was stirred at reflux for 20 hr under a N atm, cooled to room temp and worked up as above. Removal of the solvent at reduced press afforded 0·4 g crude XIII. An analytical sample was prepared by repeated crystallization from CH_2Cl_2–ether: m.p. 190–192°; $[\alpha]_D$ −286°; λ_{max}^{Nujol} 2·9, 6·08 mμ; λ_{max}^{MeOH} 246 mμ (ε 11,200); NMR τ 4·42 (C-4 H); 8·80 (C-17 3H) 8·73 (C-19 3H), 9·08 (C-18 3H). (Found: C, 80·02; H, 9·60. $C_{21}H_{30}O_2$ requires: C, 80·21; H, 9·62%.)

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