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# Reactions of Enolizable Steroidal 4-En-3-ones and 17-Ones with Hypervalent Iodine[1)]

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Reaction of the 3-oxo-4-androsten-derivative **1** or **4** with 1.2 eq of *o*-iodosylbenzoic acid in methanolic KOH gave the methoxy products, the 4-methoxide **2** or **5** and the 6β-methoxide **3** or **6**, along with the dehydrated compound, the 4,6-dienone **7** or **8**, respectively. Treatment of the 6-methoxide **3** or **6** with trimethylsilyl iodide yielded the 5α-androstane-3,6-dioxo derivative **11** or **12** in high yield. The same hypervalent oxidation of the 17-oxo steroid **15**, **18**, **21** or **24** using excess iodine and a longer reaction time produced the corresponding 16α-hydroxy-17,17-dimethylacetal **16**, **19**, **22** or **25**, which was converted into the 16α-hydroxy-17-one **17**, **20**, **23** or **26** by treatment with diluted HCl in every case.

**Keywords**——hypervalent iodine oxidation; *o*-iodosylbenzoic acid; 4-en-3-oxo steroid; 17-oxo steroid; methoxylation; dehydration; 16α-hydroxy-17,17-dimethoxy steroid; 16α-hydroxy-17-oxo steroid; 5α-saturated 3,6-dioxo steroid

Moriarty *et al.*[2)] have recently demonstrated the synthetic usefulness of hypervalent iodines, diacetoxyphenyliodine, iodosylbenzene and *o*-iodosylbenzoic acid, in methanolic KOH for the α-hydroxylation of enolizable ketones, esters and carboxylic acid. In the case of ketones the primary product is the α-hydroxydimethylacetal and iodobenzene. More recently it has been reported that hypervalent iodine and excess base, when reacted with a 5α-androstan-3-one derivative, gave a good yield of Favorskii acid.[3)] α,β-Unsaturated ketones, which cannot form anions by α-hydrogen abstraction, have been shown to react with hypervalent iodine, giving the α-hydroxy-β-methoxydimethylacetal derivatives.[4)] The hypervalent iodine oxidation of silyl enol ethers of aryl methyl ketones under Lewis acid conditions results in coupling to yield 1,4-diketones.[5)]

During the course of our chemical studies on steroidal α-ketols, we became interested in the hypervalent iodine oxidation of some steroidal ketones. We now report on the *o*-iodosylbenzoic acid–MeOH–KOH reaction applied to enolizable steroidal α,β-unsaturated ketones, the 3-oxo-4-androsten-derivatives **1** and **4**, and also report the reaction with enolizable 17-oxo steroids, **15**, **18**, **21** and **24**.

Treatment of 4-androstene-3,17-dione (**1**) with 1.2 eq of *o*-iodosylbenzoic acid and 3.3 eq of KOH in dry MeOH under a nitrogen atmosphere at 70 °C for 1 h afforded a mixture of the 4-methoxide **2**, the 6β-methoxide **3** and the dehydrogenated product, the 4,6-dienone **7**. Silica gel column chromatography of the crude product gave a 25% yield of the methoxide **2**, a 33% yield of the methoxide **3** and a 20% yield of the dienone **7**. 17β-Hydroxy-4-androsten-3-one (**4**) was similarly converted into the corresponding 4-methoxide **5** (23%), 6-methoxide **6** (47%) and dienone **8** (22%). The products were identical with the corresponding authentic samples. When the reactions were carried out at room temperature (36 h), essentially similar results were obtained. These products were not isolated in the reactions without KOH and/or the iodosyl compound, but the starting materials were quantitatively recovered in each case. It should be noted that no detectable amounts of the 16α-hydroxy-17,17-dimethoxy derivative

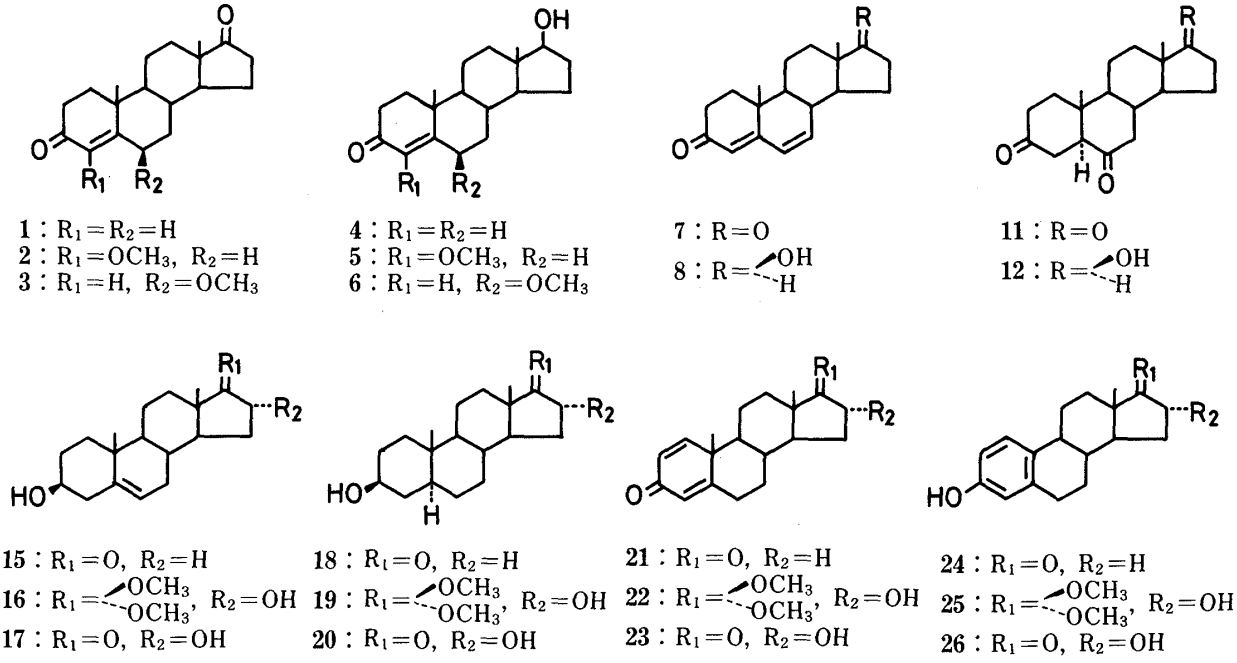


Chart 1

of compound **1** having a 17-carbonyl group were produced under the conditions employed.

Previously the iodosylbenzene-dependent alkene epoxidation[6] and the conversion of the 4,5-epoxide of compound **1** into the 4-methoxide **2** by treatment with methanolic NaOH[7] have been reported. These facts suggested that compounds **2** and **5** might be produced *via* the corresponding epoxides in this study. However, when the 4,5-epoxide of compound **1** was subjected to the above reaction with or without the iodosyl compound, compound **2** was not produced. Moreover, similar treatment of the dehydrated product **7** with the *o*-iodosylbenzoic acid–MeOH–KOH system gave neither compound **2** nor the 6-methoxide **3**. The reaction thus probably proceeds *via* the kinetically-preferred 2,4-dienolate, which is allowed to equilibrate in favor of the stable 3,5-isomer **9**[8] owing to the low reactivity of the iodosyl compound (Fig. 1); subsequent electrophilic addition to the C-4 position of the 3,5-isomer **9** through the less hindered α-face gives an adduct **10**. Finally, addition of $MeO^-$ at the C-4 and C-6 positions yields the 4-methoxide **2** with elimination of *o*-iodobenzoic acid followed by isomerization (path a) and the 6-methoxide **3** (path b), respectively. The β-face addition of $MeO^-$ in path b is predicted in view of the steric hindrance of the *o*-iodosylbenzoic acid substituent at C-4α, which is bulkier than the C-19 angular methyl group. Deprotonation at C-7 with the elimination of the iodo compound affords the dienone **7** (path c).

The above reaction conditions represent a striking way of functionalizing the C-4 and C-6 positions without affecting the C-17 carbonyl function. The methoxide **2** is an obvious precursor for the synthesis of 4-hydroxy-4-androstene-3,17-dione, a potent inhibitor of estrogen synthetase.

To obtain 6β-hydroxy steroids from the 6β-methoxides **3** and **6**, compounds **3** and **6** were subjected to reaction with trimethylsilyl iodide. However, the 5α-androstane-3,6-dioxo derivatives **11** and **12** were unexpectedly obtained in high yields, respectively. Compounds **11** and **12** were identical with the corresponding authentic samples. As shown in Fig. 2, the 6β-hydroxy compound **13** initially formed isomerizes to the thermodynamically stable 5α-steroid **11** *via* the enediol **14** in the presence of HI produced *in situ* in the reaction.

The enolizable 17-oxo steroid **15** or **18** having a 5-en-3β-ol system or 5α-3β-ol system was subjected to hypervalent iodine oxidation under more drastic conditions (2.4 eq of *o*-iodosylbenzoic acid, 6.6 eq of KOH, MeOH, nitrogen stream, 8 h at 70 °C or 15 d at room

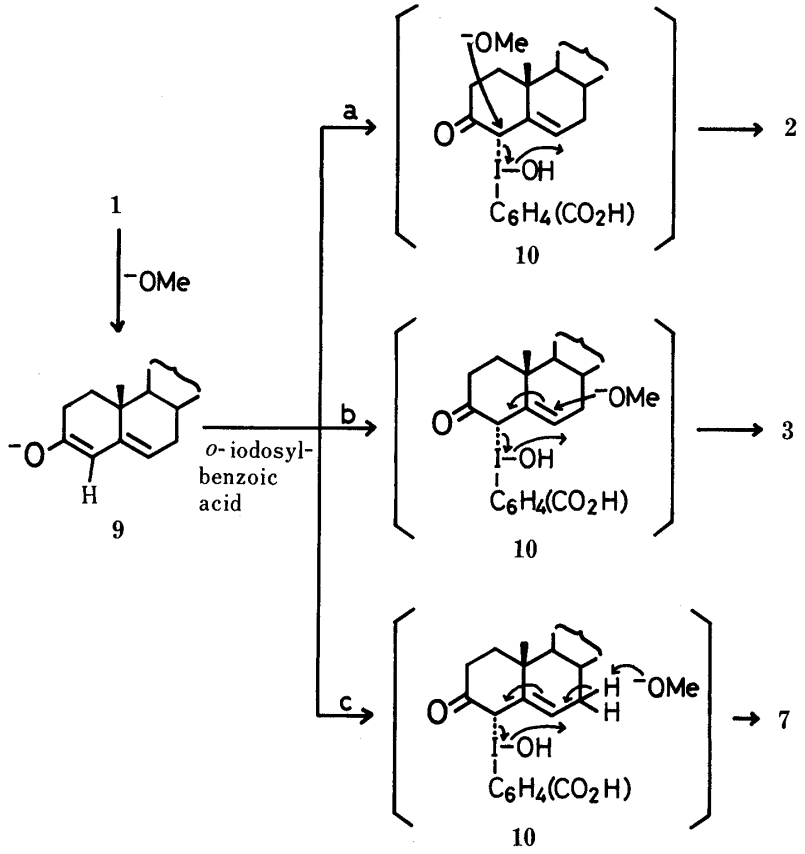


Fig. 1

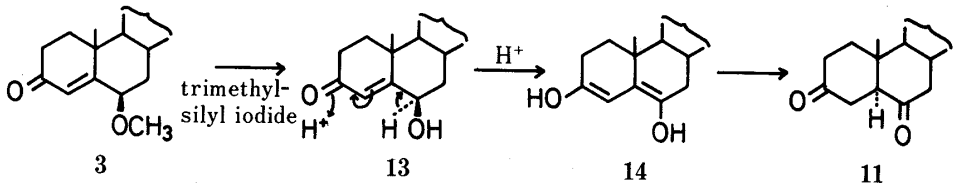


Fig. 2

temperature) compared with the above conditions. After separation of the product by silica gel column chromatography, the 16α-hydroxy-17,17-dimethylacetal **16** or **19** was isolated in *ca.* 20% yield in each case. The 17-oxo steroids **21** or **24** having a 1,4-dien-3-one system or phenolic ring A was similarly converted into the corresponding 16α-hydroxy acetal **22** (26%) or **25** (22%). The structures of the acetals were determined from the proton nuclear magnetic resonance ($^1$H-NMR) and infrared (IR) spectra and by elemental analysis.

The stereochemistry of the 16α-hydroxy derivatives may be predicted from its mechanism of formation, which is considered to involve (a) enolate anion formation, **15**→**27**, (b) addition of the enolate **27** to the iodosyl compound at the less hindered α-face, **27**→**28**, (c) isomerization of the adduct **28** to the more thermodynamically stable 16β-isomer **30**[9] through the enolate **29**, (d) addition of $MeO^-$ to the C-17 carbonyl group, **30**→**31** with intramolecular reductive elimination of *o*-iodobenzoic acid,[10] and finally, (e) ring-opening of the thus formed epoxide **31** by $MeO^-$, **31**→**16** (Fig. 3).

The requirement of more drastic conditions for the functionalization of the C-17 carbonyl group (five-membered ring ketone) may be explained as a consequence of the difference of thermodynamic stability between the 16-enolate **27** (Fig. 3) and the 3,5-dienolate **9** (Fig. 1).

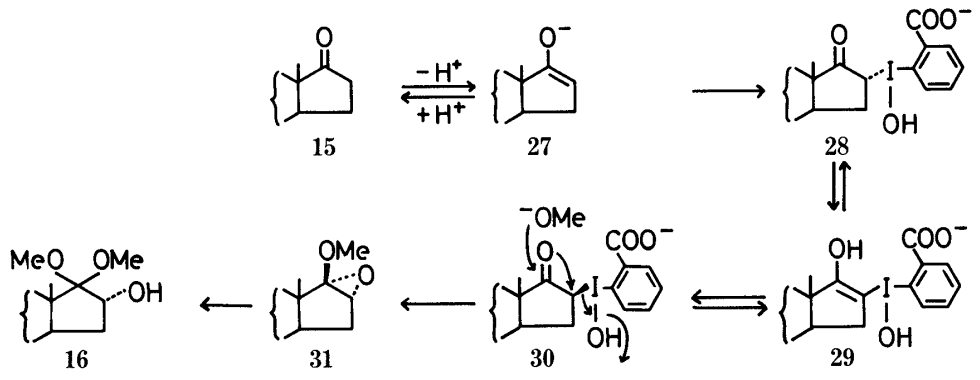


Fig. 3

Treatment of the acetals **16**, **19**, **22** and **25** with diluted HCl in MeOH afforded the corresponding 16α-hydroxy-17-ones **17**, **20**, **23** and **26** in good yields. The relative stability[11] of the steroidal ring D 16,17-ketols toward base and acid along with the fact that the thermodynamically most stable ketol, the 17β-hydroxy-16-one, which would be produced from the 16β-hydroxy-17-one under the above hydrolysis conditions, was not isolated also confirm the stereochemistry of the C-16α hydroxyl group of the acetals.

Steroidal ring D 16,17-ketols, especially 16α-hydroxy-17-ones, are major metabolites of C-18 and C-19 steroids and are also potentially useful intermediates in the sysnthesis of ring D 16,17-glycols. We[1,2] previously reported a generally applicable and simple synthesis for the 16α-hydroxy-17-ones employing a controlled alkaline hydrolysis, with pyridine, dimethylformamide or acetone as a solvent, of 16α-bromo-17-oxo steroids. The hypervalent iodine–MeOH–KOH system is an alternative to the method outlined above for the synthesis of steroid ring D α-ketols.

## Experimental

Melting points were measured on a Yanagimoto melting-point apparatus and are uncorrected. Ultraviolet (UV) spectra were measured on a Shimadzu UV 300 spectrometer. IR spectra were recorded on a Shimadzu IR 400 spectrometer as KBr pellets. $^1$H-NMR spectra were obtained with a JEOL PMX 60 spectrometer at 60 MHz with tetramethylsilane as an internal standard. Mass spectra (MS) were measured on a Hitachi RMU-7 spectrometer.

**Reaction of 3-Oxo-4-androsten Steroid 1 or 4 with *o*-Iodosylbenzoic Acid**——A solution of compound **1** or **4** (300 mg, 1.04 mmol), *o*-iodosylbenzoic acid (335 mg, 1.25 mmol) and KOH (192 mg, 3.44 mmol) in 12 ml of dry MeOH was heated with stirring at 70 °C for 1 h under a nitrogen stream. After this time, the reaction mixture was diluted with AcOEt (200 ml) and then washed with 5% $NaHCO_3$ solution and $H_2O$, and dried ($Na_2SO_4$). Evaporation of the solvent under reduced pressure gave an oily substance, which was then subjected to silica gel (25 g) column chromatography (hexane–AcOEt). The isolated crude products were recrystallized from an appropriate solvent to give pure products.

**4-Methoxy-4-androstene-3,17-dione (2)**——Yield: 25% (82 mg). mp 135—136 °C (ether, colorless prisms) (lit.[7] 136—138 °C). $^1$H-NMR ($CDCl_3$) $\delta$: 0.93 (3H, s, 18-Me), 1.22 (3H, s, 19-Me), 3.60 (3H, s, 4-OMe). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 248 ($1.27 \times 10^4$). IR (KBr): 1740, 1680 cm$^{-1}$.

**6β-Methoxy-4-androstene-3,17-dione (3)**——Yield: 33% (108 mg). mp 161—162 °C (acetone, colorless prisms) (lit.[13] 164—166 °C). $^1$H-NMR ($CDCl_3$) $\delta$: 0.93 (3H, s, 18-Me), 1.32 (3H, s, 19-Me), 3.21 (3H, s, 6β-OMe), 3.72 (1H, m, 6α-H), 5.80 (1H, br s, 4-H). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 232 ($1.23 \times 10^4$). IR (KBr): 1740 and 1680 cm$^{-1}$.

**4-Methoxy-17β-hydroxy-4-androsten-3-one (5)**——Yield: 23% (75 mg). mp 221—223 °C (acetone, colorless needles) (lit.[14] 160 °C). $^1$H-NMR ($CDCl_3$) $\delta$: 0.80 (3H, s, 18-Me), 1.02 (3H, s, 19-Me), 3.16 (1H, t, $J$ = 10 Hz, 17α-H), 3.90 (3H, s, 4-OMe). IR (KBr): 3450, 1657 cm$^{-1}$. MS $m/z$: 318 ($M^+$).

**6β-Methoxy-17β-hydroxy-4-androsten-3-one (6)**——Yield: 47% (154 mg). mp 215 °C (acetone, colorless plates) (lit.[13] 210—214 °C). $^1$H-NMR ($CDCl_3$) $\delta$: 0.81 (3H, s, 18-Me), 1.30 (3H, s, 19-Me), 3.18 (3H, s, 6β-OMe), 3.65 (2H, m, 6α-H and 17α-H), 5.78 (1H, br s, 4-H). IR (KBr): 3450, 1660 cm$^{-1}$. MS $m/z$: 318 ($M^+$).

**4,6-Androstadiene-3,17-dione (7)**——Yield: 20% (65 mg). mp 171—172 °C (acetone, colorless needles) (lit.[15] 170—172 °C). $^1$H-NMR ($CDCl_3$) $\delta$: 0.98 (3H, s, 18-Me), 1.16 (3H, s, 19-Me), 5.73 (1H, s, 4-H), 6.22 (2H, br s, 6-H

and 7-H). IR (KBr): 1740, 1660 $cm^{-1}$.

**17β-Hydroxy-4,6-androstadien-3-one (8)**——Yield: 22% (71 mg). mp 203—204 °C (acetone, colorless needles) (lit.[15] 208—210 °C). $^1$H-NMR ($CDCl_3$) δ: 0.83 (3H, s, 18-Me), 1.12 (3H, s, 19-Me), 3.68 (1H, m, 17α-H), 5.67 (1H, s, 4-H), 6.10 (2H, br s, 6-H and 7-H). IR (KBr): 3450, 1648 $cm^{-1}$. MS *m/z*: 286 ($M^+$).

**Reaction of the 6β-Methoxide 3 or 6 with Trimethylsilyl Iodide**——A mixture of compound **3** or **6** (100 mg, 0.32 mmol), the silyl iodide (140 mg, 0.68 mmol) and 10 ml of $CHCl_3$ was allowed to stand under a nitrogen stream for 4 h at room temperature. After this time, the mixture was diluted with $CHCl_3$ (20 ml) and washed with 5% $Na_2S_2O_3$ solution, 5% $NaHCO_3$ solution and $H_2O$. The organic phase was dried ($Na_2SO_4$) and evaporated under reduced pressure to afford the crude product which was recrystallized from an appropriate solvent.

**5α-Androstane-3,6,17-trione (11)**——Yield: 88% (85 mg). mp 196—197 °C (acetone, colorless plates) (lit.[16] 192—194.5 °C). $^1$H-NMR ($CDCl_3$) δ: 0.92 (3H, s, 18-Me), 1.00 (3H, s, 19-Me). IR (KBr): 1738, 1719, 1699 $cm^{-1}$.

**17β-Hydroxy-5α-androstane-3,6-dione (12)**——Yield: 83% (80 mg). mp 230—231 °C (acetone, colorless needles) (lit.[17] 218—221 °C). $^1$H-NMR ($CDCl_3$) δ: 0.78 (3H, s, 18-Me), 0.97 (3H, s, 19-Me), 3.70 (1H, t, $J$=10 Hz, 17α-H). IR (KBr): 3550, 1710 $cm^{-1}$.

**Reaction of 17-Oxo Steroid 15, 18, 21 or 24 with *o*-Iodosylbenzoic Acid**——A solution of a 17-oxo steroid **15**, **18**, **21** or **24** (1.86 mmol), KOH (700 mg, 12.4 mmol) and *o*-iodosylbenzoic acid (1.17 g, 4.44 mmol) in 22 ml of dry MeOH was heated with stirring under a nitrogen stream for 8 h at 70 °C or for 15 d at room temperature. After this time, the reaction mixture was diluted with AcOEt (200 ml) and washed with 5% $NaHCO_3$ solution and $H_2O$, and dried ($Na_2SO_4$). After evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (hexane–AcOEt), yielding the partially purified α-hydroxydimethylacetal, recrystallization of which from an appropriate solvent gave the pure product.

**17,17-Dimethoxy-5-androstene-3β,16α-diol (16)**——Yield: 19% (124 mg). mp 176—178 °C (acetone–hexane, colorless needles) (lit.[18] 177—179 °C). $^1$H-NMR ($CDCl_3$) δ: 0.80 (3H, s, 18-Me), 0.99 (3H, s, 19-Me), 3.37 and 3.46 (3H, s, 17-OMe), 3.50 (1H, m, 3α-H), 4.29 (1H, m, 16β-H), 5.37 (1H, m, 6-H). IR (KBr): 3400 $cm^{-1}$. MS *m/z*: 318 ($M^+ - 32$).

**17,17-Dimethoxy-5α-androstane-3β,16α-diol (19)**——Yield: 18% (118 mg). mp 178—180 °C (MeOH, colorless needles) (lit.[18] 179—180 °C). $^1$H-NMR ($CDCl_3$–$CD_3OD$) δ: 0.78 (6H, s, 18-Me and 19-Me), 3.35 and 3.45 (3H, s, 17-OMe), 4.23 (1H, m, 16β-H). IR (KBr): 3425 $cm^{-1}$.

**17,17-Dimethoxy-16α-hydroxy-1,4-androstadien-3-one (22)**——Yield: 26% (167 mg). mp 167.5—168 °C (acetone–hexane, colorless prisms). $^1$H-NMR ($CDCl_3$) δ: 0.86 (3H, s, 18-Me), 1.20 (3H, s, 19-Me), 3.37 and 3.43 (3H, s, 17-OMe), 4.32 (1H, m, 16β-H), 6.05 (1H, d, $J$=2 Hz, 4-H), 6.18 (1H, dd, $J$=12, 2 Hz, 2-H), 7.03 (1H, d, $J$=12 Hz, 1-H). IR (KBr): 3450, 1665 $cm^{-1}$. *Anal.* Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.64; H, 8.79.

**17,17-Dimethoxy-1,3,5 (10)-estratriene-3,16α-diol (25)**——Yield: 22% (133 mg). mp 124—126 °C (acetone–hexane, colorless needles). $^1$H-NMR ($CDCl_3$) δ: 0.82 (3H, s, 18-Me), 3.38 and 3.50 (3H, s, 17-OMe), 4.33 (1H, m, 16β-H), 6.52—7.73 (3H, m, aromatic protons). IR (KBr): 3420 $cm^{-1}$. *Anal.* Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.01; H, 8.29.

**Treatment of the 16α-Hydroxy-17,17-dimethylacetal 16, 19, 22 or 25 with Diluted HCl**——The acetal **16**, **19**, **22** or **25** (0.75 mmol) was dissolved in 30 ml of MeOH, 5% HCl (6 ml) was added, and the mixture was allowed to stand for 1 h at room temperature. The mixture was concentrated to *ca.* 10 ml under reduced pressure, and the residue was diluted with AcOEt (100 ml), then washed with 5% $NaHCO_3$ solution and $H_2O$, and dried ($Na_2SO_4$). After the usual work-up, the crude product obtained was purified by silica gel (10 g) column chromatography (hexane–AcOEt) followed by recrystallization from an appropriate solvent.

**3β,16α-Dihydroxy-5-androsten-17-one (17)**——Yield: 68% (155 mg). mp 188—190 °C (MeOH, colorless needles) (lit.[19] 187—189 °C). $^1$H-NMR ($CDCl_3$) δ: 0.98 (3H, s, 18-Me), 1.00 (3H, s, 18-Me), 3.45 (1H, br m, 3α-H), 4.40 (1H, m, 16β-H), 5.41 (1H, m, 6-H).

**3β,16α-Dihydroxy-5α-androstan-17-one (20)**——Yield: 74% (170 mg). mp 182—183 °C (MeOH, colorless needles) (lit.[19] 181—184 °C). $^1$H-NMR ($CDCl_3$) δ: 0.83 (3H, s, 19-Me), 0.90 (3H, s, 18-Me), 3.66 (1H, br m, 3α-H), 4.55 (1H, m, 16β-H).

**16α-Hydroxy-1,4-androstadiene-3,17-dione (23)**——Yield: 75% (169 mg). mp 161—162 °C (MeOH–$H_2O$, colorless needles). $^1$H-NMR ($CDCl_3$) δ: 1.03 (3H, s, 18-Me), 1.26 (3H, s, 19-Me), 4.40 (1H, m, 16β-H), 6.12 (1H, br s, 4-H), 6.23 (1H, dd, $J$=12, 2 Hz, 2-H), 7.05 (1H, d, $J$=12 Hz, 1-H). IR (KBr): 3410, 1746, 1658 $cm^{-1}$. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 244 ($1.32 \times 10^4$). *Anal.* Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.10; H, 8.01.

**3,16α-Dihydroxy-1,3,5(10)-estratrien-17-one (26)**——Yield: 83% (178 mg). mp 204—206 °C (MeOH, colorless plates) (lit.[20] 205—207 °C). $^1$H-NMR ($CDCl_3$) δ: 0.97 (3H, s, 18-Me), 4.40 (1H, m, 16β-H), 6.51—7.72 (3H, m, aromatic protons).

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