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Studies on Antiandrogenic Agents. Synthesis of 16β-Ethyl-19-nortestosterone

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The mixture of enol acetates (II and III) of 16-acetyl-estrone-3-methyl ether underwent hydrogenolysis under high pressure (100 kg/cm^2) of hydrogen in the presence of Raney Ni to form the 16β-ethyl-17β-ol compound (X) in high yield. The mechanism of hydrogenolysis was discussed. This facile and stereoselective introduction of 16β-ethyl and 17β-hydroxy groups was applied to the synthesis of 16β-ethyl-19-nortestosterone (TSAA-291, XIX), which shows strong antiandrogenic activity.

In the course of our investigation on the structure-activity relationships of 16β-substituted steroids with antiandrogenic activity,[2] we demonstrated previously that kinetically controlled vinyl dehydration of 16α-substituted-16β,17β-diols by acid treatment gave 16β-substituted-17-oxo steroids,[3] which could also be stereoselectively synthesized by the Serini reaction of 16α-substituted-16β,17β-diol 17-acetates.[4] Among the 16β-substituted testosterone and 19-nortestosterone derivatives thus obtained, we found that 16β-ethyl-19-nortestosterone (TSAA-291, XIX) showed the strongest antiandrogenic activity with the least side effects.[2] Other methods[5,6] of synthesizing 16-ethyl steroids were not stereoselective, giving a mixture of stereoisomers at C-16.

The present paper deals with the facile and stereoselective introduction of a 16β-ethyl group by catalytic hydrogenation of the 16-(1′-acetoxyethylidene)-17-oxo steroid (II) and its isomer (III). Although 16-(2′,2′,2′-trifluoro-1′-acetoxyethylidene)-17-oxo steroids are known to undergo hydrogenolysis to form 16ξ-trifluoroethyl-17-oxo steroids, the configuration at C-16 of the products has not been determined.[7]

The enol acetates (II and III) were readily prepared by acetylation of 16-acetyl-estrone-3-methyl ether (I), which was obtained by condensing ethyl acetate with estrone-3-methyl ether. The nuclear magnetic resonance (NMR) spectra showed that the 16-acetyl derivative (I) existed in a mixture of two enol forms as Ia and Ib in solution. Acetylation of I with acetic anhydride-pyridine afforded a mixture of II and III in a ratio of 4: 1, with acetic anhydride-*p*-TsOH a ratio of 1: 4, and with acetylchloride-pyridine or acetic anhydride-sodium acetate a mixture of almost equal quantities of II and III. The structures of II and III were confirmed by the NMR spectra; the methyl signal of II due to vinyl methyl was observed as a broad singlet at 2.31 ppm, while methyl signals of III due to methyl ketone and enol acetate were found as two singlets at 1.96 ppm and 2.20 ppm. The mixture was separated into pure II and III by recrystallization from ethanol.

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1) Location: *Juso-Honmachi, Yodogawa-ku, Osaka.*

2) *a*) M. Masuoka, T. Masaki, and R. Nakayama, *Folia Endocrinologica, Japonica*, **47**, 753 (1972); *b*) I. Yamazaki, T. Hori, Y. Kimura, and R. Nakayama, *ibid.*, **47**, 754 (1972).

3) G. Goto, K. Yoshioka, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 1393 (1973).

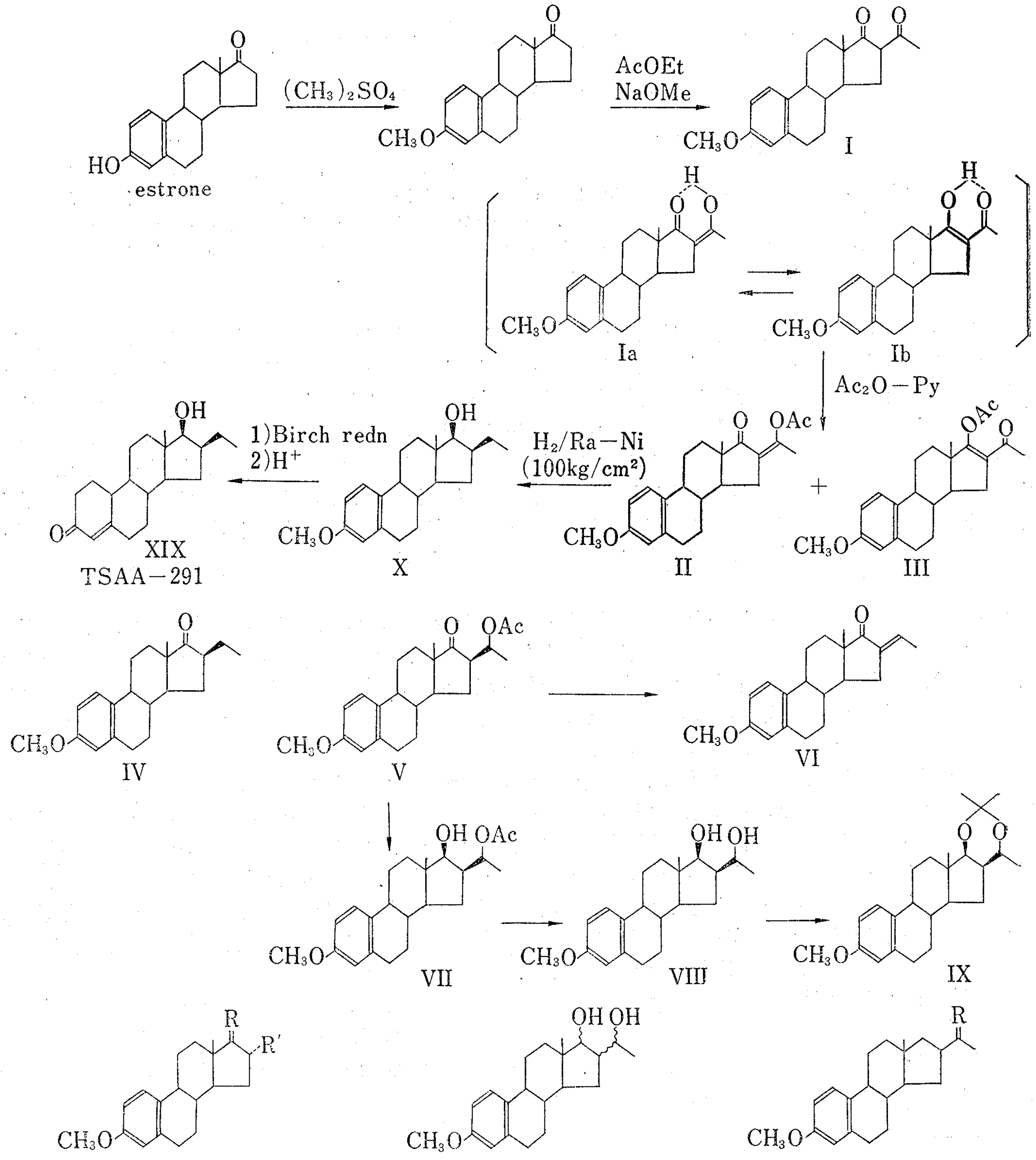
4) G. Goto, K. Yoshioka, and K. Hiraga, *Tetrahedron*, **30**, 2107 (1974).

5) J. Hooz, M. Gunn, and H. Kono, *Can. J. Chem.*, **49**, 2371 (1971).

6) N.V. Organon, Belg. Patent 660312 (1965) [*C.A.* **64**, 785 *c* (1966)].

7) M. Harnik, E. Hurzeler, and E.V. Jensen, *Tetrahedron*, **23**, 335 (1967). They reported that enol acetates of steroids trifluoroacetylated at the 2- or 21-positions did not undergo hydrogenolysis in the presence of Pd-C and only saturation of the double bond took place.

Reduction of II in the presence of Pd-C in ethanol under atmospheric pressure of hydrogen afforded the objective 16β-ethyl-17-one (IV)$^{4)}$ and 16β-(1′-acetoxyethyl)-17-one (V) in a ratio of 4: 5. The structure of V was confirmed by spectral data and the evidence of easy formation of the E-16-ethylidene-17-one (VI)$^{4)}$ on treatment with conc. sulfuric acid or potassium hydroxide in methanol. The β-orientation of the 16-(1′-acetoxyethyl) group was determined by converting V into the acetonide (IX) (Chart 1). A better products ratio was obtained when Raney



XI : $R{=}O$, $R'{=}CH_2CH_3$

XII : $R{=}\!<^{H}_{OH}$, $R'{=}CH_2CH_3$

XIII : $R{=}\!<^{OH}_{H}$, $R'{=}CH_2CH_3$

XVII : $R{=}O$, $R'{=}CH(OAc)CH_3$

XVIII : $R{=}\!<^{OH}_{H}$, $R'{=}CH(OH)CH_3$

XV : $R{=}O$

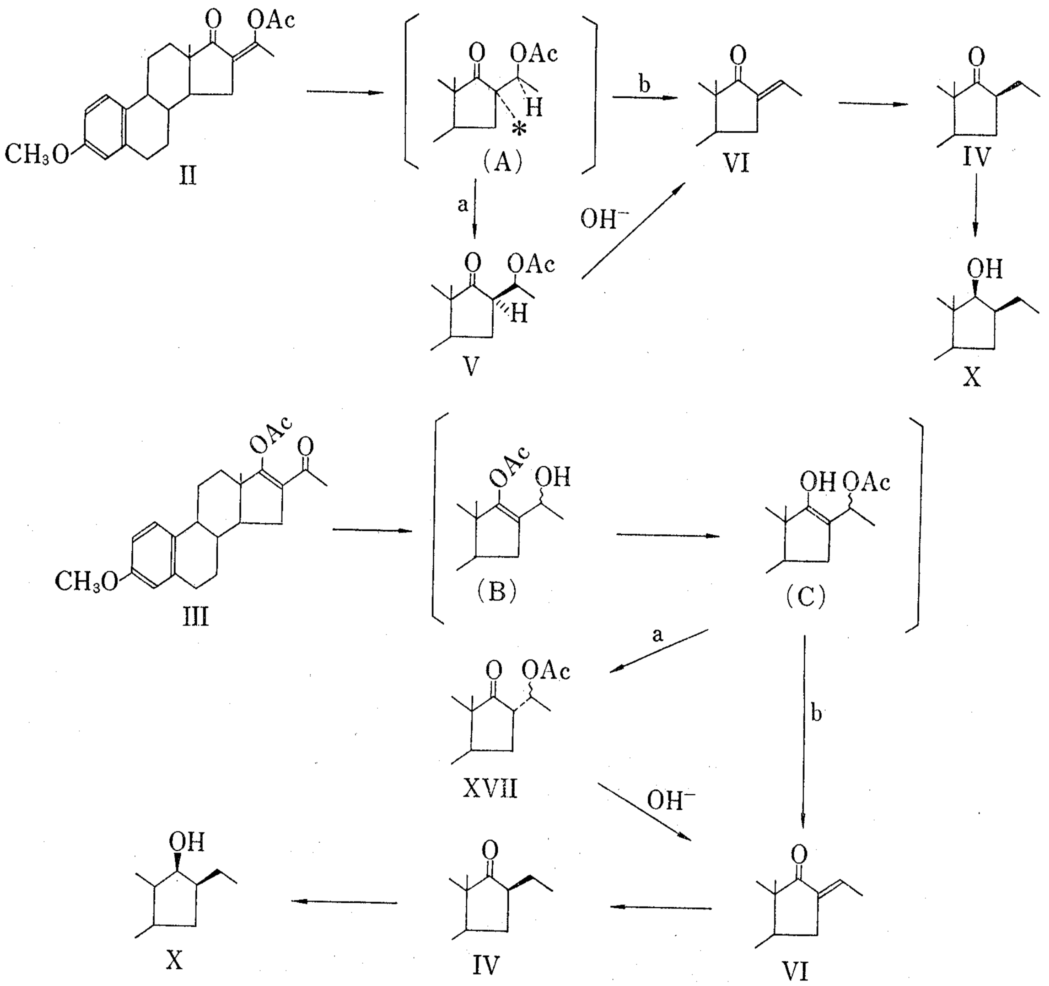
XVI : $R{=}\!<^{OH}_{H}$

Chart 1

Ni was used as a catalyst in dioxane, IV: V (4: 1); when methanol was used as a solvent 16β-ethyl-17-ol (X)[3] was formed in fair yield, IV: X: V (15: 4: a small amount). On the other hand, Pt catalyst decreased the stereoselectivity, giving a 9: 1 mixture of IV and 16α-ethyl-17-one (XI).

On the basis of these results an improved method was devised as follows. II dissolved in a mixture of dioxane and methanol was hydrogenated under 100 kg/cm^2 of hydrogen with Raney Ni in an autoclave to give X in 92% yield. In this procedure a solution of potassium hydroxide in methanol was added halfway during the reduction in order to neutralize the acidic solution due to acetic acid generated during the reaction and to eliminate the acetoxy group from V. Accompanying X, 16α-ethyl-17α-ol isomer (XII), 16α-ethyl-17β-ol isomer (XIII) and 16-(1′-hydroxyethyl)-17-ol derivatives (XIV, a mixture of four isomers) were isolated in yields of 1.8%, 2.1% and 3.4%, respectively.

When isomer III was subjected to similar hydrogenation (100 kg/cm^2) in the presence of Raney Ni, no trace of products like XV and XVI which were expected to arise from III could be detected but IV (14%) and X (78.5%) were obtained. In this reduction, a small amount of the acetyl-migrated compound (XVII) and VI were found when the reaction was monitored by thin-layer chromatography (TLC). When Pd-C was used as catalyst, compound XVII was isolated in fair yield (58%) along with IV (40%). The structure of XVII was confirmed by spectral data and the facts that it was readily converted into VI on treatment with potassium hydroxide in methanol and the diol (XVIII) obtained by NaBH$_4$ reduction of XVII, followed by hydrolysis did not form acetonide.



(where * represents an active center)

Chart 2

Formation of IV and V from II can be understood by assuming the existence of a half-hydrogenated intermediate A,[8] through which hydrogenation (a) and β-elimination[9] (b) occur competitively (Chart 2). On the other hand, the results of catalytic reduction of III may be rationalized by presuming that hydrogen preferentially attacks the carbonyl group situated outside the steroid nucleus, giving a 16-(1′-hydroxyethyl) compound (B) which, after acyl migration, is converted to XVII and VI according to routes a and b, respectively.

Thus the mixture of the enol acetates (II and III) was directly subjected to high pressure (100 kg/cm^2) hydrogenation in the presence of Raney Ni in dioxane and methanol, while potassium hydroxide dissolved in methanol was added to afford the 16β-ethyl-17β-ol compound (X) in high yield (92%).

Chart 1 shows our new synthetic route leading to TSAA-291 (XIX) from estrone.

Experimental[10]

16-Acetyl-estrone-3-methyl Ether (I)——This compound was prepared by Harnik, *et al.*[7] in rather low yield (35%). We reinvestigated this procedure and improved it as follows: MeONa (250 g) was added to a solution of estrone-3-methyl ether (350 g) in a mixture of benzene (5 liters), AcOEt (1.25 liter) and DMSO (1.25 liter) at 50°. The mixture was refluxed for 30 min, cooled and poured into ice water. Extraction twice with 5% NaOH aq and acidification of the extract with 5% H_2SO_4 gave crystals, yield 353 g (87.8%). NMR ($CDCl_3$) δ: 0.84, 0.97 (total 3H, 2 singlets), 1.98 (s), 2.36 (broad s) (total 3H).

Acetylation of the β-Diketone (I)——A solution of I (100 g) in Ac_2O (160 ml) and pyridine (80 ml) was heated for 2 hr at 65°. Evaporation *in vacuo* gave crystals which were washed well with water, yield 111 g (98.2%). These crystals consisted of the enol acetate of II and III in a ratio of 4 : 1 (determined by isolation by preparative TLC) and could be used for the following reduction. The crystals were recrystallized from EtOH, yielding 85 g (75.2%) of 16-(1′-acetoxyethylidene)-estrone-3-methyl ether (II), mp 125—126°. *Anal.* Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.96; H, 7.49. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1750, 1725 (C=O), 1660 (C=C), 1200, 1180. NMR ($CDCl_3$) δ: 0.90 (3H, s, C_{18}–CH_3), 2.17 (3H, s, $COCH_3$), 2.31 (3H, broad s, CH_2–C=C–CH_3), 3.90 (3H, s, OCH_3), 6.60—7.30 (3H, m, arom H).

Concentration of the mother liquor yielded an oil which was dissolved in 5% KOH–MeOH and refluxed for 30 min. Evaporation *in vacuo* gave a solid which was shaken with ether and water. The ether layer was extracted several times with 5% NaOH aq. and the combined aqueous extracts were acidified with 5% H_2SO_4 giving crystals which were collected and washed with water, yield 24.0 g. This compound was identical with I in all respects.

17-Acetoxy-16-acetyl-3-methoxyestra-1,3,5(10),16-tetraene (III) was prepared as follows: a mixture of I (100 g), p-TsOH (10 g) and Ac_2O (1 liter) was heated for 10 min at 80°. The cooled mixture was poured into water and the resulting solid was collected. Recrystallization thrice of the crude solid from EtOH gave the pure sample, yield 17 g, mp 135—136°. *Anal.* Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.99; H, 7.72. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1755, 1720 (C=O), 1655 (C=C), 1180. NMR ($CDCl_3$) δ: 0.88 (3H, s, C_{18}–CH_3), 1.96 (3H, s, $COCH_3$), 2.20 (3H, s, $COCH_3$), 3.76 (3H, s, OCH_3), 6.60—7.25 (3H, m, arom H). The crude solid consisted of II and III in a ratio of 1 : 4 (determined in the same manner as above).

Acetylation of I with acetylchloride and pyridine or Ac_2O and NaOAc gave a mixture of almost equal quantities of II and III.

Reduction of the Enol Acetate (II)——A) A solution of II (1.0 g) in EtOH (30 ml) was hydrogenated in the presence of 10% Pd-C (0.5 g) under atmospheric pressure of hydrogen. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (30 g) with benzene to give 0.4 g of 16β-ethyl-estrone-3-methyl ether (IV), mp 94°. The mixed mp and IR and NMR spectra were identical with those of a sample obtained previously.[4] Next, elution with benzene-AcOEt (10 : 1) gave 0.5 g of 16β-(1′-acetoxyethyl)estrone-3-methyl ether (V), mp 145—146°. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.66; H, 8.16. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1720 (C=O). NMR ($CDCl_3$) δ: 1.34 (3H, d, J=5 Hz, $CHCH_3$), 2.04 (3H, s, $OCOCH_3$), 3.75 (3H, s, OCH_3), 5.16 (1H, m, –CH–OAc), 6.62—7.20 (3H, m, arom H). Treatment of V with 5% KOH–MeOH for 10 min at room temperature or with conc. H_2SO_4 for 5 min at room temperature yielded 16-ethylidene-estrone-3-methyl ether (VI)[4] in quantitative yield.

B) A suspension of II (1.0 g) and Raney Ni (3.0 g) in dioxane (30 ml) was shaken under a stream of hydrogen until absorption of hydrogen stopped. The reaction mixture was worked up in a manner similar

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[8] J. Horiuti and M. Polanyi, *Trans. Faraday Soc.*, **30**, 1164 (1934).

[9] S. Mitsui, M. Fujimoto, Y. Nagahisa, and T. Sukegawa, *Chem. Ind.* (London), **1969**, 241.

[10] All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 215 spectophotometer. NMR spectra were determined on a Varian HA-100 spectrometer. The mass spectra were determined on a Hitachi RMU-6D mass spectrometer equipped with a direct inlet system.

to that described above to give IV (0.7 g) and V (0.16 g). When MeOH was used as a solvent, IV (0.66 g), 16β-ethyl-estradiol-3-methyl ether (X)[3] (0.17 g) and V (0.01 g) were obtained from II (1.00 g).

C) A solution of II (1.5 g) in a mixture of EtOH (50 ml) and AcOEt (10 ml) was hydrogenated in the presence of PtO_2 (100 mg) under atmospheric pressure of hydrogen. The reaction mixture was worked up in a manner similar to that described above to give IV (1.14 g) and 16α-ethyl-estrone-3-methyl ether (XI) (0.12 g), mp 73—74°. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.70; H, 9.05. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O). NMR ($CDCl_3$) δ: 0.85 (3H, s, C_{18}–CH_3), 0.98 (3H, t, J=7 Hz, CH_2CH_3), 3.75 (3H, s, OCH_3), 6.60—7.25 (3H, m, arom H). Mass Spectrum *m/e*: 312 (M^+), 283.

D) A suspension of II (100 g) and Raney Ni (300 g) in a mixture of dioxane (200 ml) and MeOH (700 ml) was shaken at 100 kg/cm^{-1} pressure of hydrogen for 2 hr in an autoclave. After addition of 5% KOH–MeOH soln (300 ml), hydrogenation (100 kg/cm^{-1}) was continued for a further 2 hr. The filtered solution was evaporated and the crude solid was chromatographed over silica gel (300 g). Elution with benzene–AcOEt (10:1) gave XII (1.53 g, 1.8%), with benzene–AcOEt (5:1) X(78.1 g, 91.7%), with benzene–AcOEt (3:1) XIII (1.78 g, 2.1%), and then with AcOEt–acetone (1:1) XIV (2.9 g, 3.2%).

XII: mp 98—100°. *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.25; H, 9.55. Found: C, 79.96; H, 9.68. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1040. NMR ($CDCl_3$) δ: 0.79 (3H, s, C_{18}–H), 0.97 (3H, t, J=7 Hz, CH_3CH_2), 3.68 (1H, d, J=5 Hz, $C_{17\beta}$–H), 3.76 (3H, s, OCH_3).

XIII: mp 74°. This was identical with the authentic sample[6] in all aspects.

XIV: XIV consisted of four components in almost equal quantities. Each component was separated by preparative TLC (benzene–ether=3:1). These spectral data were similar to each other: Mass Spectrum *m/e*: 330 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200—3500 (OH). NMR ($CDCl_3$) δ: 1.1—2.3 (3H, d, J=6 Hz, $CHCH_3$).

Oxidation of XII and XIII with Jones reagent gave the same product, mp 73—74°. IR ν_{max}^{KBr} cm^{-1}: 1730. The mixed mp and IR spectra were identical with those of the sample (XI) obtained by procedure C.

Reduction of the Enol Acetate (III)——A) A solution of III (10 g) with Raney Ni (30 g) was hydrogenated (100 kg/cm^2) in a manner similar to procedure D to give IV (1.2 g, 14.2%) and X (6.7 g, 78.6%).

B) A solution of III (1.0 g) in AcOEt (30 ml) was hydrogenated with 10% Pd-C (0.5 g) under atmospheric pressure of hydrogen. The reaction mixture was worked up in a manner similar to that described above to give IV (0.34 g, 40.1%) and XVII (0.58 g, 57.7%).

XVII: mp 129—130°. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.15. Found: C, 74.46; H, 8.32. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O), 1370, 1240, 1020. NMR ($CDCl_3$) δ: 0.90 (3H, s, C_{18}–CH_3), 1.33 (3H, d, J=6.5 Hz, $CHCH_3$), 1.97 (3H, s, $COCH_3$), 3.77 (3H, s, OCH_3), 5.30 (1H, m, $C_{1'}$–H). Mass Spectrum *m/e*: 370 (M^+), 310 (M^+–CH_3COOH). Treatment of XVII with 5% KOH–MeOH at room temperature yielded E-16-ethylidene-estrone-3-methyl ether (VI)[4] in quantitative yield. But the diol (XVIII) obtained by $NaBH_4$ reduction of XVII, followed by hydrolysis with 5% KOH–MeOH in the manner described for the formation of VIII from V, did not form acetonide.

Reduction of the Enol Acetates (II and III)——A mixture of the enol acetates (II and III, 100 g) was hydrogenated (100 kg/cm^{-1}) with Raney Ni (300 g) as described for the reduction of II (procedure D), to yield 78.0 g of X (91.5%).

Formation of the Acetonide (IX)——To a solution of V (500 mg) in methanol (10 ml), $NaBH_4$ was added at 0° with stirring. The crystals of VII (450 mg) were separated from the reaction mixture. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1700 (C=O), 1270, 1230, 1030. A solution of VII (450 mg) in 5% KOH–MeOH soln was heated for 5 min at 60°. The reaction mixture was poured into water and the resulting crystals of VIII (380 mg) were collected. IR ν_{max}^{KBr} cm^{-1}: 3200 (OH), 1030. Next, to a solution of VIII (350 mg) in acetone (5 ml), two drops of BF_3 etherate were added at room temperature with stirring. The mixture was poured into water and extracted with ether. Evaporation of the solvent gave a solid, which was purified by chromatography on silica gel, yield 370 mg, mp 162—164°. *Anal.* Calcd. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.99; H, 9.78. IR ν_{max}^{KBr} cm^{-1}: 1230, 1030. NMR ($CDCl_3$) δ: 0.84 (3H, s, C_{18}–CH_3), 1.11 (3H, d, J=6.5 Hz, CH_3CH), 1.35 (6H, s, $\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C\!<\!\begin{matrix}O\\O\end{matrix}$, 3.70 (1H, d, J=9.5 Hz, 17α-H), 3.74 (3H, s, OCH_3).

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