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The Synthesis and Conformational Analysis of α-Bromo-16-ketones of 13α-Estratriene[1]

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Isomeric 15α- and 17α-bromo-13α-estratrien-16-ones (IX, X) were prepared from the parent 16-ketone (VII) by way of the enol acetate (VIII). The configuration of both bromine atoms introduced was determined by the standard method of Fieser and Ettorre. These positional isomers were readily distinguished by converting into the Δ^{15}- and Δ^{16}-unsaturated compounds (XIII, XIV), respectively. On the basis of the spectral data listed in Table I the nature of C-bromine bonds and the conformation of ring D have been discussed. Two synthetic routes leading to the 17α-acetoxy-16-ketone (V) have also been described.

As a series of our studies on the stereochemistry of 13α-androstanes the conformation of ring D having a ketone at C-16 has previously been investigated.[3] An alteration of the steroidal skeleton often exerts the significant influence on the chemistry of the remote site of a molecule and these phenomena are interpreted in terms of the long-range conformational effect.[4] A particular interest in these respects prompted us to explore the distant effect due to the aromatic ring A on the conformation of ring D. The present paper deals with the preparation of two isomeric 15- and 17-bromo-16-ketones and the conformational analysis of ring D on the basis of their physico-chemical data.

An initial effort was made on the synthesis of the parent 16-ketone starting from the Δ^{16}-enol acetate (II)[5] by the method worked out by Gallagher and his co-workers.[6] Treatment with *m*-chloroperbenzoic acid gave solely the α-epoxyacetate (III) whose configuration was deduced from the nature of the product obtained in the next step. When III was treated with sulfuric acid and then acetylated in the usual manner, the 16α-acetoxy-17-ketone (IV) was afforded in a reasonable yield. The stereochemistry of the acetoxyl group at C-16 was tentatively assigned to be α rather than β, because the splitting pattern of 16-proton signal in IV was similar to that in 16α-bromo-13α-estrone of two C-16 epimers.[5] Upon brief exposure to alkali IV underwent the rearrangement yielding the 17α-acetoxy-16-ketone (V), the most stable one of four possible 16,17-ketols.[7] It is to be noted that in the alkali treatment process IV was oxidized to the 16-hydroxy-Δ^{15}-17-ketone (VIa) to a considerable extent.

This synthetic route proved to be somewhat tedious and disadvantageous with respect to the yield. Accordingly the next project was directed to the development of an alternative route leading to V with the more ease. When 13α-estrone methyl ether (I) was stirred with

1) This paper constitutes Part LVIII of the series entitled "Analytical Chemical Studies on Steroids"; Part LVII: T. Nambara, Y. Kawarada, K. Shibata, and T. Abe, *Chem. Pharm. Bull.* (Tokyo), **20**, 1988 (1972).
2) Location: *Aobayama, Sendai.*
3) T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.* (Tokyo), **17**, 375 (1969).
4) D.H.R. Barton, F. McCapra, P.J. May, and J. Thudium, *J. Chem. Soc.*, **1960**, 1277 and references quoted therein.
5) T. Nambara, T. Kudo, H. Hosoda, K. Motojima, and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2366 (1969).
6) N.S. Leeds, D.K. Fukushima, and T.F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954); J. Fishman, *J. Am. Chem. Soc.*, **82**, 6143 (1960); T. Nambara and J. Fishman, *J. Org. Chem.*, **27**, 2131 (1962).
7) T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.* (Tokyo), **17**, 947 (1969).

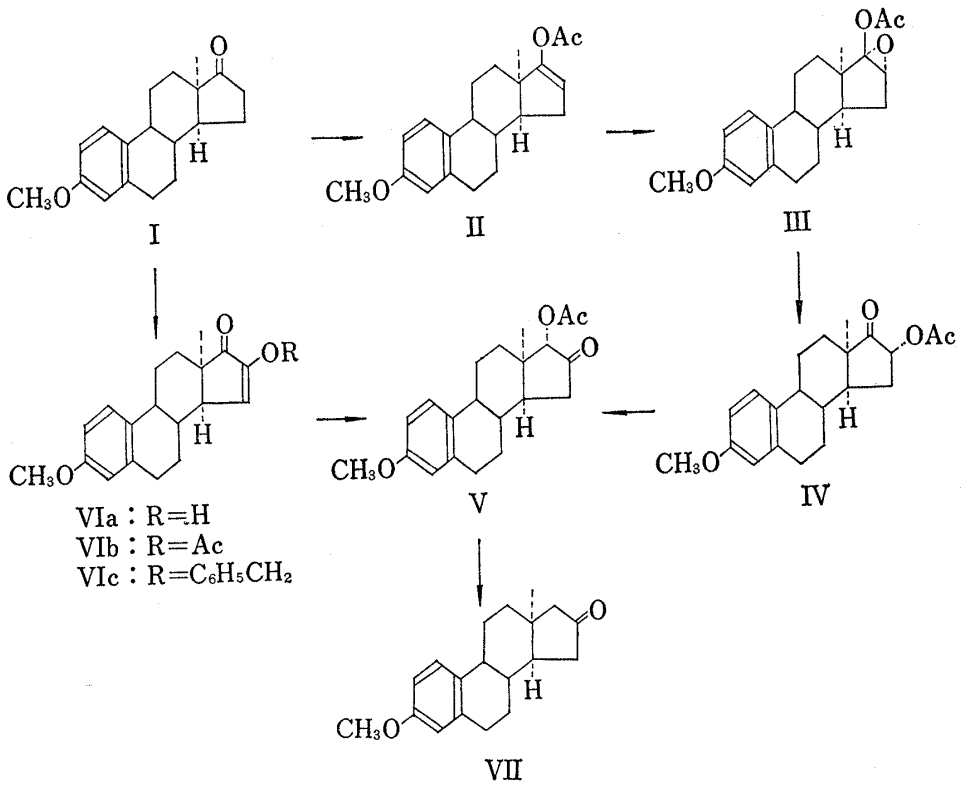

Chart 1

potassium *tert*-butoxide at room temperature, oxidation occurred at C-16 resulting in formation of VIa in a satisfactory yield. It is evident from the ferric chloride test and spectroscopic data that the 16-oxygenated product exists in the diosphenol form rather than in the diketo form. Subsequent treatment with benzyl chloride in the presence of potassium carbonate gave the 16-benzyloxy derivative (VIc), which on lithium aluminum hydride reduction was led to the corresponding 17-hydroxylic compound without affecting any disturbance on the Δ^{15}-double bond. Debenzylation with mineral acid followed by usual acetylation provided the desired 17α-acetoxy-16-ketone (V) in overall yield of 54% based upon the 17-ketone. Removal of the acetoxyl group in V was effected by reduction with zinc dust in acetic acid to provide the 16-ketosteroid (VII).

Treatment of VII with isopropenyl acetate and catalytic amount of anhydrous *p*-toluenesulfonic acid gave the enol acetate almost quantitatively, judged from the result of thin-layer chromatography (TLC). Inspection of the nuclear magnetic resonance (NMR) spectra, however, indicated that the product appeared to be a mixture of Δ^{15}- and Δ^{16}-enol acetates (VIIIa, VIIIb) in approximately equal amount, whose separation could not be attained. It is noteworthy that in the 13α-series enolization of the 16-ketone occurs in the both directions to almost the same degree, while in the C/D-*trans*- and 14β-steroids the 16-oxo function does enolize preferentially toward C-17.[8] Halogenation of the enol acetate with one equivalent amount of bromine under the non-enolizing conditions gave a mixture of two isomeric α-bromoketones, which were efficiently separated into the 15α-bromo- and 17α-bromo-16-ketones (IX, X) by the preparative TLC.

8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Co., New York, 1959, p. 282; J. Fajkoš and J. Joska, *Collection Czech. Chem. Commun.*, **25**, 2863 (1960); *idem*, *Chem. Ind.* (London), **1960**, 872; J. Fishman, *J. Org. Chem.*, **27**, 1745 (1962); T. Nambara, H. Hosoda, M. Usui, and T. Anjyo, *Chem. Pharm. Bull.* (Tokyo), **19**, 612 (1971).

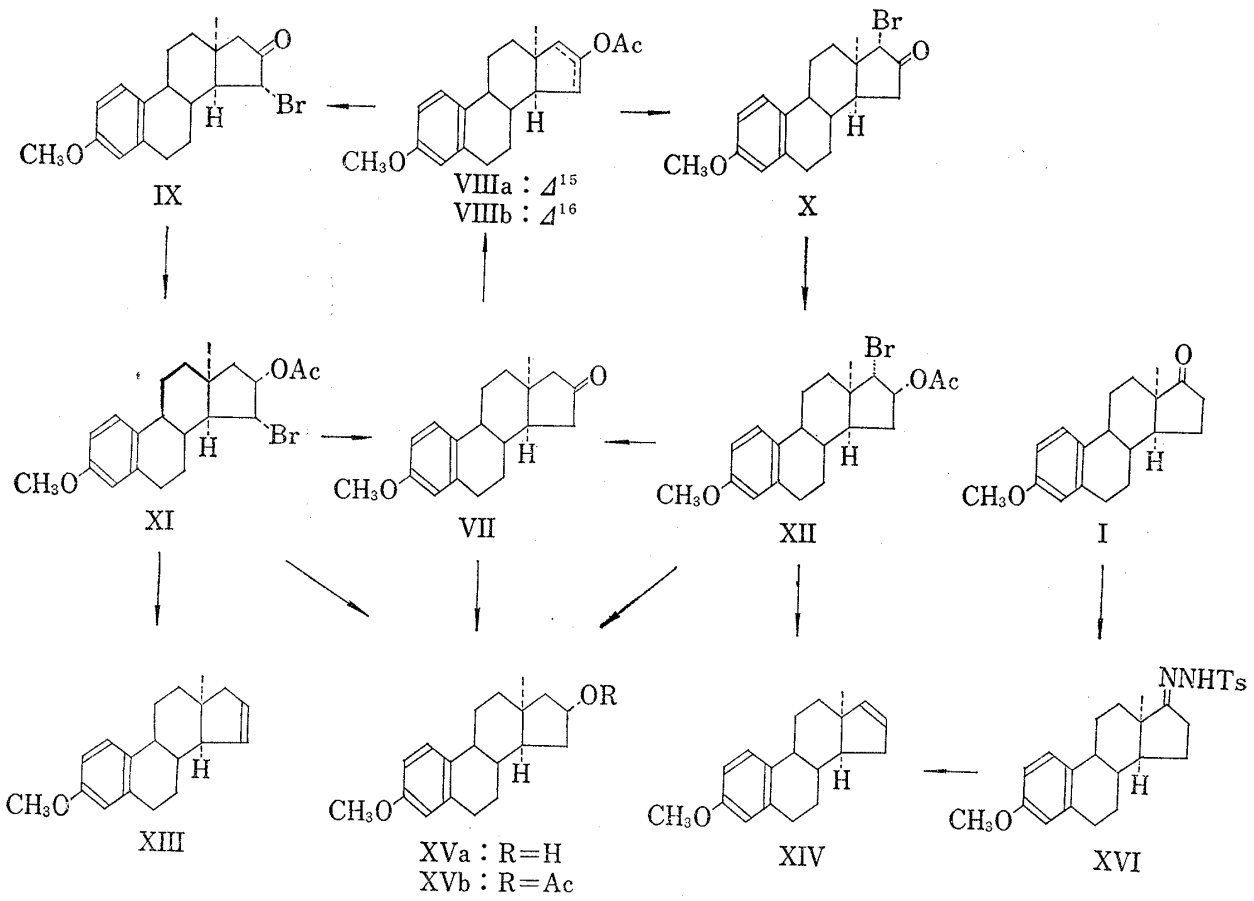

Chart 2

Structural elucidation of these two isomers was achieved by the method of Fieser and Ettorre.[9] Upon careful reduction with lithium aluminum hydride followed by usual acetylation the α-bromoketones were converted into the bromohydrin acetates (XI, XII), respectively. The *cis*-bromohydrin structure was rationalized by the formation of the same 16-ketone (VII), when refluxed with methanolic potassium hydroxide. On the other hand dehalogenation of both bromohydrins with hydrogen over palladium-on-barium carbonate gave the 16α-acetoxyl derivative (XVb), which proved to be identical with the product formed from VII by metal hydride reduction and subsequent acetylation. The configuration of the hydroxyl function at C-16 was evidently assigned on the basis of the chemical shift of 18-methyl proton. The use of pyridine instead of chloroform as solvent resulted in paramagnetic shift of 18-proton signal with 0.18 ppm and acetylation of the 16-hydroxylic compound (XVa) exerted the upfield shift of 0.04 ppm indicating the 1,3-diaxial relation of the 16-hydroxyl and 18-methyl groups.[10,11] The nature of the double bond in ring D produced from the bromohydrin served to distinguish these two positional isomers. For this purpose 3-methoxyestra-1,3,5(10),16-tetraene (XIV) was prepared as an authentic sample from the 17-ketone *p*-tosylhydrazone (XVI) with lithium aluminum hydride.[12] Reduction of XI with zinc dust in acetic acid yielded estra-1,3,5(10),15-tetraene derivative (XIII), which could be readily differentiated from the Δ^{16} isomer (XIV) by TLC employing silica gel plate impregnated

9) L.F. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, **75**, 1700 (1953).
10) P.V. Demarco, E. Farkas, D. Doddrell, B.L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90**, 5480 (1968); T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.* (Tokyo), **17**, 1687 (1969).
11) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).
12) L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963).

with silver nitrate.[13] Indeed, the similar treatment with the remaining 16,17-bromohydrin acetate (XII) gave the Δ^{16} compound (XIV) as was expected.

Table I. Spectral Data

Substance	IR		ORD			CD		
	$\nu_{max}^{CCl_4}$ cm^{-1}	$\Delta\gamma$	$\lambda_{1st\ extrem}^{MeOH}$ mμ	$\Delta\lambda$	$[\phi]$	λ_{max}^{MeOH} mμ	$\Delta\lambda$	$[\theta]$
16-Ketone (VII)	1745		312		+9120°	296		+9390
15α-Bromo-16-ketone (IX)	1759	+14	330	+18	+5980°	308	+12	+5480
17α-Bromo-16-ketone (X)	1763	+18	320	+ 8	+13230°	298	+ 2	+11580

The spectral data of the two isomeric α-bromo-16-ketones (IX, X) and the parent ketone (VII) are collected in Table I. The shift values in the infrared (IR) carbonyl abosorption are such as to assign to the 17α bond the quasi-equatorial and the 15α bond the bisectional character. The optical rotatory dispersion (ORD) and circular dichroism (CD) curves also support the conformational assignments of these α-bromoketones. As illustrated in Fig. 1, the 17α-bromo derivative exhibits the positive Cotton effect with a somewhat larger amplitude than the parent ketone in contrast to the 15α-bromo compound with a smaller amplitude. All the spectroscopic data together would support the half-chair conformation for ring D. There can be seen no substantial difference in the spectroscopic properties between the estratriene and 5α-androstane in the 13α-series. The influence of angular distortion due to the aromatic ring A on the remote site of a molecule would be of a subtle nature.

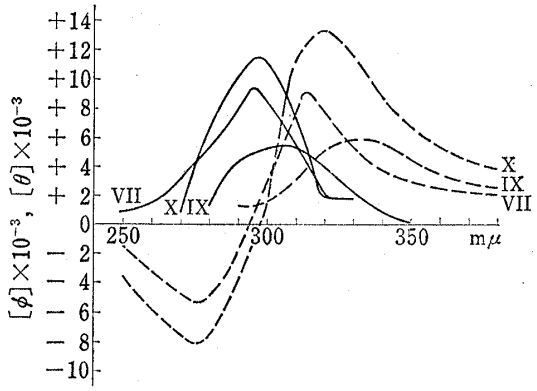

Fig. 1. ORD (---) and CD (—) Curves of VII, IX and X in Methanol

Experimental[14]

3-Methoxy-16α,17α-epoxy-13α-estra-1,3,5(10)-trien-17β-ol Acetate (III)——To a solution of 3-methoxy-13α-estra-1,3,5 (10), 16-tetraen-17-ol acetate (II)[5] (280 mg) in $CHCl_3$ (20 ml) was added *m*-chloroperbenzoic acid (150 mg) and allowed to stand at room temperature for 50 hr. The resulting solution was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.35) and recrystallization of the eluate from MeOH gave III (225 mg) as colorless prisms. mp 152—153°. $[\alpha]_D^{24}$ +56.0° (c=0.24). *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.99; H, 7.66. NMR (5% solution in $CDCl_3$) δ: 1.28 (3H, s, 18-CH_3), 2.06 (3H, s, 17β-OCOCH_3), 3.70 (3H, s, 3-OCH_3), 4.06 (1H, s, 16β-H).

3-Methoxy-16α-acetoxy-13α-estra-1,3,5(10)-trien-17-one (IV)——To a solution of III (115 mg) in acetone–MeOH (1:3) (10 ml) was added 6N H_2SO_4 (2 ml) and allowed to stand at room temperature for 2 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous

13) A.S. Gupta and S. Dev, *J. Chromatog.*, **12**, 189 (1963); R. Ikan, *ibid.*, **17**, 591 (1965); R. Ikan and M. Cudzinovski, *ibid.*, **18**, 422 (1965).

14) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise specified. IR spectra were run on JASCO Model DS-403G spectrophotometer. ORD and CD curves measurements were carried out on JASCO Model ORD/UV-5 recorder. Mass spectra were obtained by Hitachi Model RMU-7 spectrometer. NMR spectra were run on Hitachi Model R-20 spectrometer at 60 Mc in $CDCl_3$ using tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, t=triplet, and m=multiplet.

Na_2SO_4. After evaporation of solvent the residue was treated with Ac_2O and pyridine in the usual manner. The crude product was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.38) and recrystallization of the eluate from MeOH gave IV (75 mg) as colorless plates. mp 135—136°. $[\alpha]_D^{22}$ −142.9° (c=0.13). *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.32; H, 7.69. NMR (5% solution in $CDCl_3$) δ: 1.12 (3H, s, 18-CH_3), 2.08 (3H, s, 16α-$OCOCH_3$), 3.72 (3H, s, 3-OCH_3), 5.06 (1H, t, J=9 cps, 16β-H).

3-Methoxy-17α-acetoxy-13α-estra-1,3,5(10)-trien-16-one (V)——i) To a solution of IV (180 mg) in MeOH (70 ml) was added 0.2N KOH (15 ml) and refluxed for 30 min under a stream of N_2 gas. The resulting solution was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was treated with Ac_2O and pyridine in the usual manner. The crude product was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.32) and recrystallization of the eluate from MeOH gave V (45 mg) as colorless needles. mp 113—114°. $[\alpha]_D^{21}$ +74.4° (c=0.18). *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.32; H, 7.69. NMR (5% solution in $CDCl_3$) δ: 0.97 (3H, s, 18-CH_3), 2.12 (3H, s, 17α-$OCOCH_3$), 3.50 (1H, s, 17β-H), 3.72 (3H, s, 3-OCH_3). Elution of the adsorbent corresponding to the spot (*Rf* 0.27) and recrystallization of the eluate from MeOH gave VIb (106 mg). mp 152—153°. Mixed melting point on admixture with the sample obtained from I showed no depression.

ii) To a solution of VIa (650 mg) in EtOH (40 ml) were added $C_6H_5CH_2Cl$ (700 mg) and anhydrous K_2CO_3 (12 g) and refluxed for 20 hr. The resulting solution was diluted with H_2O and extracted with AcOEt. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.43) gave 3-methoxy-16-benzyloxy-13α-estra-1,3,5(10),15-tetraen-17-one (VIc) (600 mg) as colorless oil. NMR (5% solution in $CDCl_3$) δ: 1.16 (3H, s, 18-CH_3), 3.64 (3H, s, 3-OCH_3), 4.86 (2H, s, 16-$OC\underline{H}_2C_6H_5$), 7.19 (5H, s, 16-$OCH_2C_6\underline{H}_5$). To a solution of VIc (650 mg) in anhydrous ether was added $LiAlH_4$ (800 mg) at −5° and allowed to stand for 3 hr. The reaction mixture was decomposed with moist ether and acidified with 2N H_2SO_4. The organic layer was washed with 5% $NaHCO_3$, H_2O and then evaporated *in vacuo*. The residue was dissolved in MeOH (70 ml) and treated with 6N H_2SO_4 (2.8 ml) at room temperature for 2 hr. After usual work-up the crude product was treated with Ac_2O and pyridine in the usual manner and then submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.32) and recrystallization of the eluate from MeOH gave V (420 mg) as colorless needles. mp 113—114°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

3-Methoxy-16-hydroxy-13α-estra-1,3,5(10),15-tetraen-17-one (VIa)——To a solution of *tert*-BuOK prepared from metal K (150 mg) and *tert*-BuOH (10 ml) was added a solution of 13α-estrone methyl ether (I) (150 mg) in *tert*-BuOH (10 ml) and stirred at room temperature for 50 hr. The resulting solution was neutralized with dil. HCl and evaporated *in vacuo*. The residue was extracted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.23) and recrystallization of the eluate from acetone–hexane gave VIa (118 mg) as colorless needles. mp 122—122.5°. $[\alpha]_D^{23}$ −169.0° (c=0.15). *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.32; H, 7.51. NMR (5% solution in $CDCl_3$) δ: 1.22 (3H, s, 18-CH_3), 3.72 (3H, s, 3-OCH_3), 5.70 (1H, m, 16-OH).

3-Methoxy-16-acetoxy-13α-estra-1,3,5(10)-tetraen-17-one (VIb)——Treatment of VIa (45 mg) with Ac_2O (1 ml) and pyridine (2 ml) followed by recrystallization from MeOH gave VIb (32 mg) as colorless prisms. mp 152—153°. $[\alpha]_D^{24}$ −9.5° (c=0.21). *Anal.* Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.69; H, 7.16. NMR (5% solution in $CDCl_3$) δ: 1.25 (3H, s, 18-CH_3), 2.24 (3H, s, 16-$OCOCH_3$), 3.72 (3H, s, 3-OCH_3), 7.40 (1H, d, J=3 cps, 15-H).

3-Methoxy-13α-estra-1,3,5(10)-trien-16-one (VII)——To a stirred solution of V (280 mg) in AcOH (30 ml)–Ac_2O (3 ml) was added Zn dust (11 g) portionwise and refluxed for 50 hr. The cake was filtered off and washed with EtOH. The filtrate and washings were combined and concentrated *in vacuo*. The residue was extracted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was submitted to the preparative TLC using hexane–AcOEt (5:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.57) and recrystallization of the eluate from MeOH gave VII (180 mg) as colorless prisms. mp 104—105°. $[\alpha]_D^{22}$ +237.8° (c=0.15). *Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.03; H, 8.77. NMR (5% solution in $CDCl_3$) δ: 1.10 (3H, s, 18-CH_3), 3.75 (3H, s, 3-OCH_3).

3-Methoxy-13α-estra-1,3,5(10),15-tetraen-16-ol Acetate (VIIIa), 3-Methoxy-13α-estra-1,3,5(10),16-tetraen-16-ol Acetate (VIIIb)——To a solution of VII (184 mg) in isopropenyl acetate (8 ml) was added anhydrous *p*-TsOH (25 mg) and refluxed for 25 hr. The resulting solution was diluted with AcOEt, washed with cold 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was dissolved in hexane–benzene (2:1) and passed through a column of Al_2O_3 (3 g). The effluent was concentrated and submitted to the preparative TLC using hexane–AcOEt (6:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.75) with acetone gave a mixture of VIIIa and VIIIb as

amorphous substance. NMR (5% solution in $CDCl_3$) δ: 1.09 (1.4 H, s, 18-CH_3), 1.12 (1.6 H, s, 18-CH_3), 2.05, 2.06 (3H, s, 16-$OCOCH_3$), 3.70 (3H, s, 3-OCH_3), 5.20 (0.5 H, m, 15-H or 17-H), 5.65 (0.5 H, m, 17-H or 15-H).

3-Methoxy-15α-bromo-13α-estra-1,3,5(10)-trien-16-one (IX), 3-Methoxy-17α-bromo-13α-estra-1,3,5(10)-trien-16-one (X)——To a stirred solution of VIIIa and VIIIb (147 mg) in CCl_4 (20 ml) containing anhydrous K_2CO_3 (150 mg) was added a solution of the calculated amount of Br_2 in CCl_4 dropwise at 0°. The resulting solution was washed with 5% $NaHSO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was submitted to the preparative TLC using hexane–AcOEt (5:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.62) and recrystallization of the eluate from MeOH–acetone gave IX (23 mg) as colorless plates. mp 152—153°. $[\alpha]_D^{20}$ +63.4° (c=0.12). *Anal.* Calcd. for $C_{19}H_{23}O_2Br$: C, 62.81; H, 6.38. Found: C, 62.86; H, 6.61. NMR (5% solution in $CDCl_3$) δ: 1.36 (3H, s, 18-CH_3), 3.75 (3H, s, 3-OCH_3), 4.13 (1H, s, 15β-H). Elution of the adsorbent corresponding to the spot (*Rf* 0.53) and recrystallization of the eluate from MeOH–acetone gave X (40 mg) as colorless plates. mp 176—177°. $[\alpha]_D^{23}$ +119.4° (c=0.14). *Anal.* Calcd. for $C_{19}H_{23}O_2Br$: C, 62.81; H, 6.38. Found: C, 63.00; H, 6.55. NMR (5% solution in $CDCl_3$) δ: 1.06 (3H, s, 18-CH_3), 3.75 (3H, s, 3-OCH_3), 4.72 (1H, s, 17β-H).

3-Methoxy-15α-bromo-13α-estra-1,3,5(10)-trien-16α-ol Acetate (XI)——To a solution of XI (65 mg) in anhydrous ether (20 ml) was added $LiAlH_4$ (50 mg) portionwise at −15° and the resulting solution was allowed to stand for 5 min. The reaction mixture was decomposed with moist ether and acidified with 2N H_2SO_4. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was treated with Ac_2O and pyridine in the usual manner. The crude product was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.58) and recrystallization of the eluate from MeOH gave XI (43 mg) as colorless prisms. mp 88—88.5°. $[\alpha]_D^{13}$ +104.4° (c=0.15). *Anal.* Calcd. for $C_{21}H_{27}O_3Br$: C, 61.92; H, 6.68. Found: C, 61.70; H, 6.73. NMR (5% solution in $CDCl_3$) δ: 1.48 (3H, s, 18-CH_3), 2.16 (3H, s, 16α-$OCOCH_3$), 3.82 (3H, s, 3-OCH_3), 4.12 (1H, m, 15β-H), 5.06 (1H, m, 16β-H).

3-Methoxy-17α-bromo-13α-estra-1,3,5(10)-trien-16α-ol Acetate (XII)——X (50 mg) was submitted to reduction with $LiAlH_4$ (50 mg) followed by acetylation in the manner as described in XI. The crude product obtained was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.62) and recrystallization of the eluate from MeOH gave XII (45 mg) as colorless prisms. mp 137.5—138°. $[\alpha]_D^{14}$ +85.2° (c=0.15). *Anal.* Calcd. for $C_{21}H_{27}O_3Br$: C, 61.92; H, 6.68. Found: C, 61.53; H, 6.52. NMR (5% solution in $CDCl_3$) **δ: 1.19 (3H, s, 18-CH_3)**, 2.14 (3H, s, 16α-$OCOCH_3$), 3.80 (3H, s, 3-OCH_3), 4.45 (1H, d, J=6 cps, 17β-H), 5.47 (1H, m, 16β-H).

Transformation of XI and XII into VII with Alkali——i) A solution of XI (10 mg) in 5% methanolic KOH (8 ml) was refluxed for 1.5 hr. The resulting solution was diluted with AcOEt and washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was submitted to the preparative TLC using hexane–AcOEt (5:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.57) and recrystallization of the eluate from MeOH gave VII (5 mg) as colorless prisms. mp 104—105°. Mixed melting point on admixture with the authentic sample showed no depression.

ii) Similar treatment of XII (8 mg) with 5% methanolic KOH and recrystallization of the crude product from MeOH gave VII (4 mg) as colorless prisms. mp 104—105°. Mixed melting point on admixture with the authentic sample showed no depression.

Debromination of XI and XII——i) A solution of XI (20 mg) in EtOH (10 ml) was shaken with 5% Pd/$BaCO_3$ (110 mg) under a stream of H_2 for 70 hr. After removal of the catalyst by filtration the filtrate was concentrated *in vacuo*. The residue was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.70) was eluted with AcOEt to give XVb (10 mg) as colorless oil. Identity with the authentic sample was determined by chromatographic behaviors and IR and NMR spectra comparisons.

ii) Similar treatment of XII (20 mg) with 5% Pd/$BaCO_3$ (110 mg) under a stream of H_2 and purification by the preparative TLC gave XVb (10 mg) as colorless oil. Identity with the authentic sample was determined by chromatographic behaviours and IR and NMR spectra comparisons.

3-Methoxy-13α-estra-1,3,5(10),15-tetraene (XIII)——To a boiled solution of XI (30 mg) in AcOH (10 ml)–Ac_2O (1 ml) was added Zn dust (300 mg) portionwise and refluxed for 12 hr. After removal of the precipitate by filtration the filtrate was concentrated *in vacuo*. The residue was extracted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was submitted to the preparative TLC using hexane–AcOEt (20:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.50) gave XIII (11 mg) as colorless oil. NMR (5% solution in $CDCl_3$) δ: 1.02 (3H, s, 18-CH_3), 3.75 (3H, s, 3-OCH_3), 5.72—6.00 (2H, m, 15-H and 16-H). Mass Spectrum m/e: 268 (M^+). When developed on silica gel H impregnated with $AgNO_3$ using hexane–AcOEt (20:1) as solvent, XIII exhibited *Rf* 0.30, distinctly different from that of XIV (*Rf* 0.19).

3-Methoxy-13α-estra-1,3,5(10),16-tetraene (XIV)——i) Treatment of XII (22 mg) with Zn dust (200 mg) in AcOH (10 ml)–Ac_2O (1 ml) in the manner as described in XIII gave XIV (10 mg) as colorless oil. *Rf* 0.50 (hexane–AcOEt (20:1)). NMR (5% solution in $CDCl_3$) δ: 1.00 (3H, s, 18-CH_3), 3.73 (3H, s, 3-OCH_3),

5.50 (2H, s, 16-H and 17-H). Mass Spectrum *m/e*: 268 (M^+).

ii) To a solution of XVI (48 mg) in THF (10 ml) was added $LiAlH_4$ (50 mg) and refluxed for 20 hr. After usual work-up the crude product was submitted to the preparative TLC using hexane–AcOEt (20:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.50) gave XIV (21 mg) as colorless oil. NMR (5% solution in $CDCl_3$) δ: 1.00 (3H, s, 18-CH_3), 3.73 (3H, s, 3-OCH_3), 5.50 (2H, s, 16-H and 17-H). Identity with the sample obtained in i) was determined by chromatographic behaviors and IR and NMR spectra comparisons.

3-Methoxy-13α-estra-1,3,5(10)-trien-16α-ol (XVa)——To a solution of VII (21 mg) in MeOH (5 ml) was added $NaBH_4$ (10 mg) and allowed to stand at room temperature for 1 hr. After addition of AcOH to decompose the excess reagent, the resulting solution was extracted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the residue was submitted to the preparative TLC using benzene–ether (6:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.47) gave XVa as colorless oil. NMR (5% solution in $CDCl_3$) δ: 1.18 (3H, s, 18-CH_3), 3.75 (3H, s, 3-OCH_3), 3.75 (1H, m, 16β-H).

3-Methoxy-13α-estra-1,3,5(10)-trien-16α-ol Acetate (XVb)——XVa was treated with Ac_2O and pyridine in the usual manner and the crude product was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.70) was eluted with AcOEt to give XVb as colorless oil. NMR (5% solution in $CDCl_3$) δ: 1.14 (3H, s, 18-CH_3), 2.04 (3H, s, 16α-$OCOCH_3$), 3.75 (3H, s, 3-OCH_3), 5.20 (1H, m, 16β-H).

3-Methoxyestra-1,3,5(10)-trien-17-one *p*-Tosylhydrazone (XVI)——To a solution of I (105 mg) in MeOH (20 ml) were added *p*-$TsNHNH_2$ (105 mg) and a drop of AcOH, and refluxed for 80 hr. The resulting solution was diluted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.17) and recrystallization of the eluate from MeOH gave XVI (48 mg) as colorless prisms. mp 148—149°. $[\alpha]_D^{24}$ +33.1° (c=0.17). *Anal.* Calcd. for $C_{26}H_{32}O_3N_2S$: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.79; H, 7.24; N, 6.38. NMR (5% solution in $CDCl_3$) δ: 0.98 (3H, s, 18-CH_3), 1.16 (3H, s, *p*-$C\underline{H}_3C_6H_4$-), 3.75 (3H, s, 3-OCH_3).

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