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The Crystal Structure of 3-Methoxy-16-hydroxy-13α-estra-1,3,5(10),15-tetraen-17-one *p*-Bromobenzoate[1]

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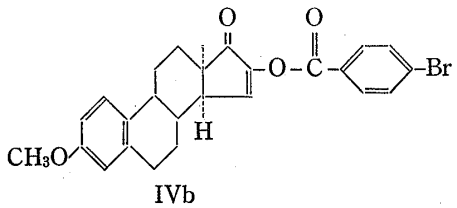
The crystal structure of the titled compound (IVb) has been determined by three-dimensional X-ray analysis from the diffractometer data. Crystals are monoclinic, $a=14.494$ (10), $b=6.586$ (3), $c=12.420$ (8) Å, $\beta=111.89$ (2)°, $U=1100.1$ Å^3, $Z=2$, space group $P2_1$. Conformation of ring C has proved to be somewhat distorted boat form. The relative ease with which 16,17-diketo-C/D-*cis* steroids do enolize has been interpreted in terms of conformational change.

In the preceding papers of this series the stereochemistry of ring D in C/D-*cis* steroids has been investigated. It was demonstrated that in the presence of oxygen and potassium *tert*-butoxide both 13α- and 14β-17-ketosteroids are readily transformed into the 16,17-oxygenated compounds, which exist in the diosphenol rather than in the diketo form as judged from the usual criteria.[3] In sharp contrast 16,17-diketo-C/D-*trans* steroids do not enolize at all.[4] The presence of an enolic system in ring D of C/D-*cis* steroids appears to be ascribable to the characteristic ring fusion, where conformational change of ring C may relieve its strain.[5] A particular interest in the flexibility of the C/D-*cis* fusion prompted us to determine the conformation of the 16-hydroxy-Δ^{15}-17-ketosteroid by three-dimensional X-ray analysis from the diffractometer data.

For this purpose an initial project was directed to the preparation of the *p*-bromobenzoates of 3β-methoxy-16-hydroxy-13α-androsta-5,15-dien-17-one and 3-methoxy-16-hydroxy-13α-estra-1,3,5(10),15-tetraen-17-one. The 13α-17-ketosteroids (I, III) were stirred with potassium *tert*-butoxide at room temperature to yield the 16-hydroxy-Δ^{15}-17-ketones (IIa, IVa), which on treatment with *p*-bromobenzoyl chloride and pyridine were led to the desired 16-*p*-bromobenzoates (IIb, IVb) in a satisfactory yield, respectively. Of these two IVb was obtained in a more suitable crystal form for X-ray analysis and therefore used as a model compound.



IVb

Chart 1

The crystals of IVb grown from an acetone solution were transparent colorless long plates elongated along the *b* axis. The lattice constants and intensity data were derived from the measurements using a Philips four-circle X-ray diffractometer with CuKα radiation. The

1) This paper constitutes Part LXXVII of the series entitled "Analytical Chemical Studies on Steroids"; Part LXXVI: T. Nambara, M. Kurata, and J.Goto, *Chem. Pharm. Bull.* (Tokyo), **22**, 3002 (1974).
2) Location: *a*) *Aobayama, Sendai*; *b*) *Hongo, 7-chome, Tokyo.*
3) *a*) T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.* (Tokyo), **17**, 947 (1969); *b*) T. Nambara, H. Hosoda, M. Usui, and T. Anjyo, *ibid.*, **19**, 612 (1971); *c*) T. Nambara and T. Kudo, *ibid.*, **20**, 2156 (1972).
4) M.N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947).
5) This assumption has been also presented by Chinn on the basis of nuclear magnetic resonance (NMR) spectral data (L.J. Chinn, *J. Org. Chem.*, **29**, 3304 (1964)).

radiation was monochromated by pyrolytic graphite. The intensity data were collected by the θ—2θ scan method with the scan speed of $\theta=4°$ min^{-1}. The background was counted at each end of the scan for half the scan time. The crystal data are as follows:

3-Methoxy-16-hydroxy-13α-estra-1,3,5(10),15-tetraen-17-one *p*-bromobenzoate, $C_{26}H_{25}O_4Br$, mol. wt.=481.4. Monoclinic, $a=14.494$ (10), $b=6.586$ (3), $c=12.420$ (8) Å, $\beta=111.89$ (2)°. $U=1100.1$ Å^3, $Z=2$. Space group $P2_1$.

The net intensities were then corrected for Lorentz and polarization factors but not for absorption factors. The size of the crystal used for the intensity measurement was about $0.1\times0.2\times0.35$ mm. The total number of independent observed reflections having net intensities greater than the 2σ level was 1408 out of 1507 theoretically possible reflections within $2\theta=156°$.

TABLE I. Atomic Parameters with Estimated Standard Deviations ($\times10^4$ for Br and $\times10^3$ for other atoms)[a)]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	−5348(3)	10000(14)	−8608(6)	59(2)	347(15)	79(7)	48(7)	16(3)	51(10)
C(1)	222(2)	83(6)	168(4)	3(2)	14(10)	6(5)	0(3)	1(2)	1(6)
C(2)	286(3)	143(7)	280(5)	5(2)	27(14)	7(6)	−2(5)	2(3)	0(7)
C(3)	335(2)	332(7)	294(4)	3(2)	29(13)	4(5)	−5(4)	1(2)	−3(7)
C(4)	327(3)	494(12)	202(4)	4(2)	53(19)	5(5)	10(7)	2(2)	8(10)
C(5)	264(2)	397(6)	88(4)	2(2)	10(8)	5(5)	0(3)	0(2)	3(5)
C(6)	256(2)	540(6)	−14(4)	4(2)	8(10)	8(6)	−1(3)	0(2)	2(5)
C(7)	210(2)	430(6)	−132(4)	3(2)	17(11)	6(5)	−2(3)	1(2)	1(5)
C(8)	119(2)	319(6)	−138(4)	4(2)	12(9)	5(5)	−3(3)	1(2)	5(5)
C(9)	145(2)	140(5)	−49(3)	3(2)	9(8)	1(3)	0(3)	1(2)	2(4)
C(10)	213(2)	215(6)	70(3)	2(1)	17(10)	1(3)	0(3)	0(2)	−4(5)
C(11)	48(2)	39(5)	−46(4)	3(2)	8(9)	5(5)	0(3)	1(2)	2(5)
C(12)	−47(3)	90(7)	−151(4)	5(2)	24(12)	3(4)	0(4)	1(2)	0(6)
C(13)	−26(2)	88(6)	−264(4)	3(2)	12(9)	5(5)	1(3)	0(2)	0(5)
C(14)	64(2)	218(5)	−261(4)	3(2)	9(8)	3(4)	0(3)	1(2)	1(5)
C(15)	25(3)	384(6)	−360(4)	7(3)	15(10)	1(3)	1(4)	2(2)	1(5)
C(16)	−72(3)	361(6)	−406(4)	4(2)	11(9)	6(5)	−1(4)	1(2)	−3(5)
C(17)	−114(2)	193(6)	−357(4)	4(2)	17(10)	2(3)	1(4)	2(2)	0(5)
C(21)	448(3)	571(10)	433(5)	3(2)	75(33)	8(7)	−14(7)	−1(3)	−3(11)
C(22)	−203(2)	413(5)	−587(4)	4(2)	11(8)	4(5)	0(3)	1(2)	−1(5)
C(23)	−19(4)	−127(7)	−306(5)	11(4)	17(12)	3(4)	−6(6)	3(3)	−6(6)
C(61)	−283(2)	547(5)	−655(4)	4(2)	13(11)	2(4)	−3(3)	0(2)	−4(5)
C(62)	−352(2)	488(8)	−759(4)	5(2)	24(11)	1(3)	−6(5)	0(2)	−2(7)
C(63)	−429(3)	632(6)	−821(5)	6(3)	11(10)	8(6)	−9(4)	4(3)	−4(6)
C(64)	−435(2)	810(7)	−779(4)	3(2)	33(14)	5(5)	−4(4)	1(2)	3(7)
C(65)	−363(3)	896(9)	−669(5)	4(2)	47(19)	5(5)	2(5)	3(3)	7(9)
C(66)	−284(3)	752(7)	−607(4)	7(3)	19(11)	2(4)	4(5)	1(3)	−2(6)
O(1)	−396(2)	390(6)	409(3)	6(2)	44(12)	1(3)	3(4)	0(2)	4(5)
O(2)	−202(2)	144(6)	−386(3)	5(2)	46(13)	4(4)	−7(4)	1(2)	5(6)
O(3)	−135(2)	491(5)	−489(2)	7(2)	12(6)	2(3)	1(3)	0(2)	0(4)
O(4)	−189(2)	251(5)	−622(3)	7(2)	21(8)	2(3)	1(3)	0(2)	−4(4)

a) Temperature factors are of the form: $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$. The absolute configuration is represented by taking a right-hand coordinate system.

The structure was solved by the heavy atom method and refined by several cycles of block-diagonal least-squares calculations[6)] in which unit weight was assigned for each reflection. The final difference electron density map showed no anomalous features except for those around the bromine atom where a peak of about 1.5 e.Å^{-3} in height was still observed. Since the

6) Calculated by HBLS Program of T. Ashida (The Universal Crystallographic Computing System (I), The Crystallographic Society of Japan, 1967, p. 65).

purpose of the present structure determination was to elucidate the molecular conformation, no further refinement was contemplated. The final R value was 0.106 for 1408 observed structure factors. The atomic scattering factors of C, O and Br atoms were those given in

TABLE II. Comparison of Observed and Calculated Structure Factors

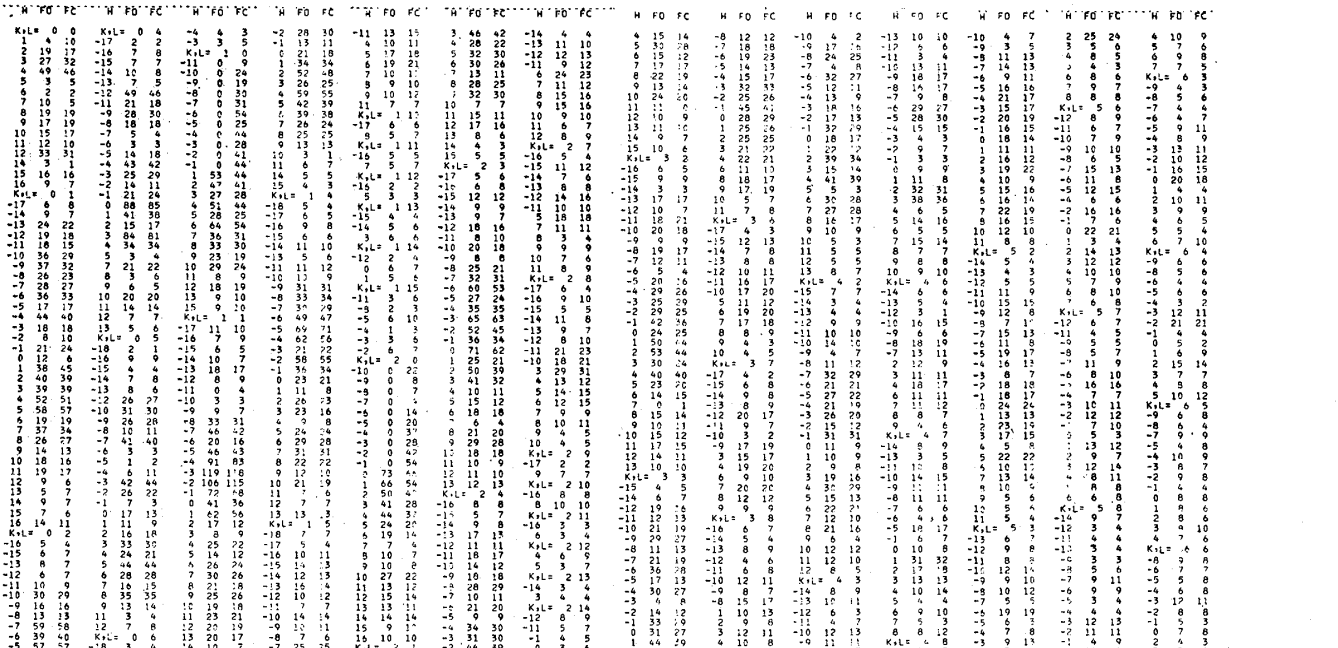


TABLE III. Comparison of Observed and Calculated Structure Factor Ratios between hkl and $\overline{hkl}$ Reflections

k	k	l	$\frac{\text{Fobs}(hkl)}{\text{Fobs}(\overline{hkl})}$	$\frac{\text{Fcal}(hkl)}{\text{Fcal}(\overline{hkl})}$	h	h	l	$\frac{\text{Fobs}(hkl)}{\text{Fobs}(\overline{hkl})}$	$\frac{\text{Fcal}(hkl)}{\text{Fcal}(\overline{hkl})}$
−4	2	1	1.15	1.03	−6	1	1	1.25	1.28
−2	2	1	1.17	1.03	2	1	1	1.22	1.16
8	2	1	1.24	1.18	−11	1	2	0.93	0.95
7	2	2	0.94	0.82	−10	1	3	0.94	0.93
−11	2	3	0.87	0.92	−7	1	3	0.88	0.85
−4	2	3	1.12	1.08	−11	1	5	0.83	0.89
−10	2	4	0.94	0.90	−5	1	5	0.77	0.58
−7	2	4	1.16	1.09	3	2	0	1.24	1.13

International Tables for X-ray Crystallography.[7] No correction was applied for the anomalous dispersion effect during the refinement. The final atomic parameters are given in Table I along with their standard deviations and the observed and calculated structure factors are listed in Table II. The absolute configuration was determined by the anomalous dispersion method. The $\Delta f'$ and $\Delta f''$ values of the bromine scattering factor for CuKα radiation were assumed to be -0.9 and 1.5, respectively.[8] Comparison of observed and calculated $F(hkl)/F(\bar{h}\bar{k}\bar{l})$ values (Table III) established the absolute configuration as shown in Fig. 1.

Bond lengths and angles are shown in Fig. 1 which also shows the intermolecular close approaches of atoms of the distances shorter than 3.6 Å. The estimated standard deviations of the bond lengths range from 0.05 Å for C-O and C-Br to 0.07 Å for most of the C-C bonds. Those of the bond angles are 4°. The lengths and angles agree generally with those expected from the chemical structure. A few of them differ considerably from the standard values but in view of the rather large standard deviations little significance may be attached to the differences.

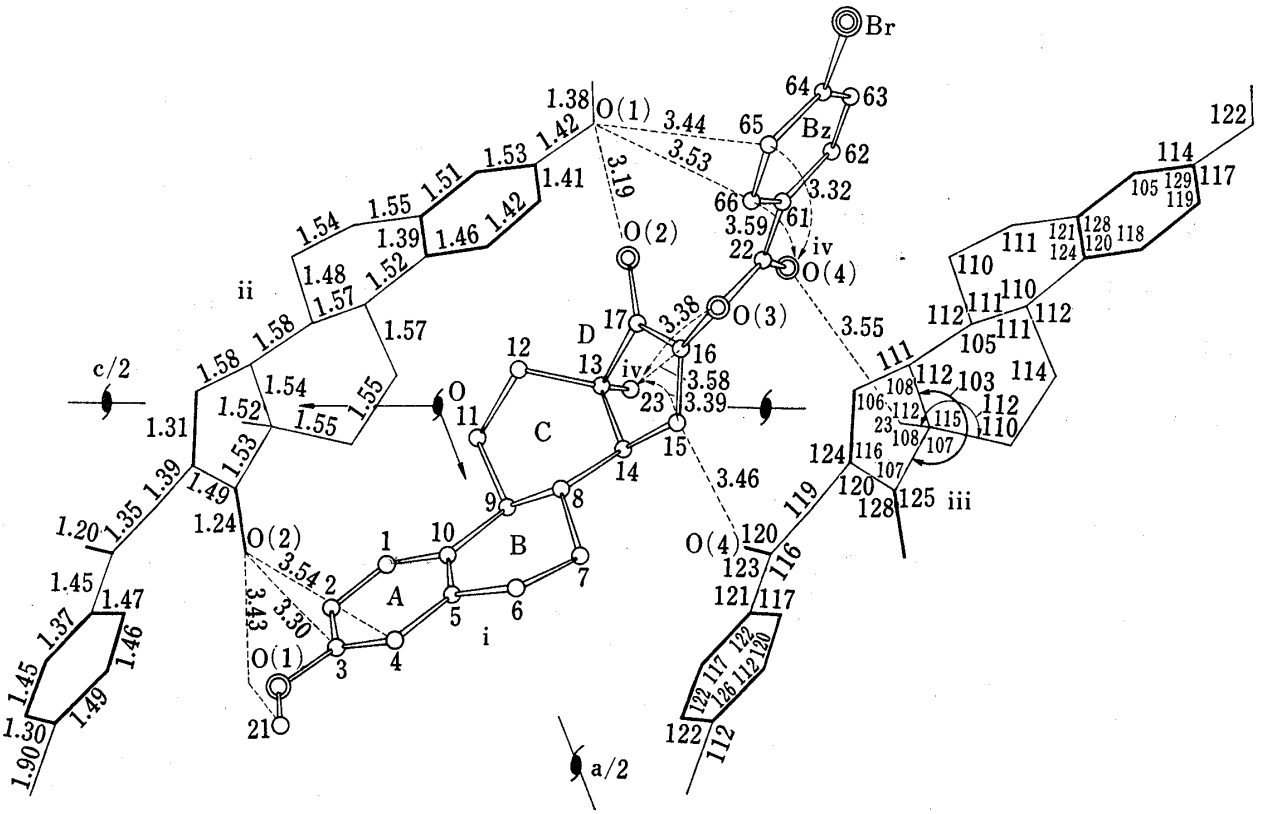


Fig. 1. Molecular and Crystal Structure

Interatomic distances are in Å unit and bond angles are in degrees. Short intermolecular interatomic distances less than 3.6 Å are also shown. Symmetry operations are: i at x, y, z; ii at $-x, 1/2+y, -z$; iii at $-x, 1/2+y, -1-z$; iv at $x, 1+y, z$.

The configuration and conformation of the molecule are shown in Fig. 1. It may be clearly seen that the junctures of the rings B/C and C/D are *trans* and *cis*, respectively. Fig. 2 shows the torsion angles along the bonds involved in each ring. An approximate symmetry of each ring is also illustrated in the Figure. As is clearly seen from Figs. 1 and 2, the conformations of B and C rings are half-chair and somewhat distorted boat form respectively. Each of the rings A, D and Bz is almost planar. The planarity of the ring can also be judged from the displacements of atoms from the least-squares plane which are shown in Table IV.

7) "International Table for X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, 1962.
8) C.H. Dauben and D.H. Templeton, *Acta Cryst.*, **8**, 841 (1955).

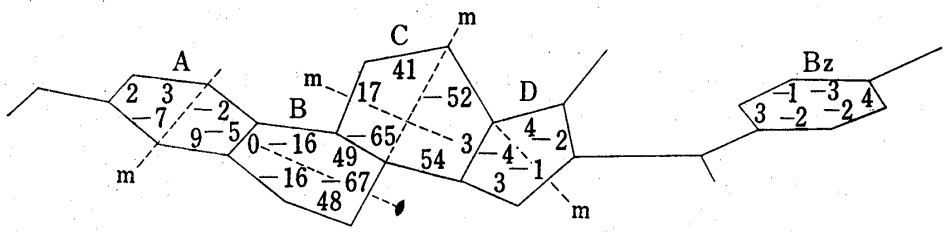


Fig. 2. Endocyclic Torsion Angles (°)
Approximate symmetry of each ring is also shown.

TABLE IV. Deviations of Atoms from the Least-squares Planes

A ring Atom	Deviation (Å)	D ring Atom	Deviation (Å)	Bz ring Atom	Deviation (Å)
C(1)	0.03	C (13)	−0.03	C (61)	−0.02
C(2)	−0.02	C (14)	0.02	C (62)	0.00
C(3)	−0.03	C (15)	−0.01	C (63)	0.02
C(4)	0.05	C (16)	0.00	C (64)	−0.02
C(5)	−0.04	C (17)	0.02	C (65)	0.00
C (10)	0.00			C (66)	0.01

TABLE V. Torsion Angles (°)

C(4)-C(3)-O(1)-C (21)	−5	C (17)-C (16)-O(3)-C (22)	−55
O(2)-C (17)-C (16)-O(3)	4	C (16)-O(3)-C (22)-C (61)	164
O(2)-C (17)-C (16)-C (15)	179	C (62)-C (61)-C (22)-O(4)	5
O(3)-C (16)-C (15)-C (14)	174		

The two exocyclic oxygen atoms O(2) and O(3) bonded to D ring are almost coplanar with D ring. The torsion angles involving O(2) and O(3) are listed in Table V along with other torsion angles.

It is evident from these results that in 13α steroids the diosphenol system with distorted boat conformation in ring C is thermodynamically more stable than the 16,17-diketo system. It has already been pointed out that a five-membered ring α-diketone is considerably strained due to the repulsive interaction of the two dipoles and hence does readily enolize.[9] In C/D-*cis* steroids with the flexible ring fusion the conformational change into the ring C boat form enables the ring D diketone to undergo facile enolization.

Experimental

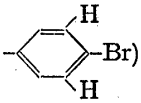
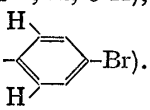
Syntheses of Samples[10]

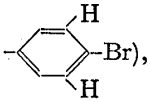
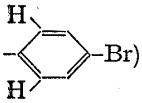
3β-Methoxy-13α-androst-5-en-17-one (I)——A solution of 3β-methoxyandrost-5-en-17-one (10 g) in EtOH (200 ml) was placed in an irradiation vessel and irradiated with light of $\lambda>280$ nm using a 450 W mercury lamp UM-452 in an atmosphere of N_2 under stirring for 2.5 hr. After evaporation of solvent the residue obtained was dissolved in EtOH (150 ml) and refluxed with Girard T (10 g) and AcOH (7.5 ml) for 2 hr. The resulting solution was poured into K_2CO_3 solution and extracted with AcOEt. The organic phase was washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crude product obtained was chromatographed on Al_2O_3 (60 g). Elution with hexane–AcOEt (3: 1) and recrystallization of the eluate from dil. MeOH gave I (1.92 g) as colorless leaflets. mp 118—119°. $[\alpha]_D^{25}$ −133.0° (c=0.11).

9) G. Shcwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 663 (1947).
10) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$. NMR spectra were obtained on a Hitachi Model R-20 spectrometer at 60 MHz employing tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, and m=multiplet. For preparative thin-layer chromatography (TLC) silica gel G (E. Merck AG, Darmstadt) was used as an adsorbent.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.40; H, 10.30. NMR (5% solution in $CDCl_3$) δ: 0.83 (3H, s, 19-CH_3), 0.98 (3H, s, 18-CH_3), 3.32 (3H, s, 3β-OCH_3), 5.35 (1H, m, 6-H).

3β-Methoxy-16-hydroxy-13α-androsta-5,15-dien-17-one (IIa)——To a solution of *tert*-BuOK prepared from metal K (1 g) and *tert*-BuOH (150 ml) was added I (1 g) in *tert*-BuOH (100 ml) and stirred at room temperature for 50 hr. The reaction mixture was neutralized with 5% HCl and concentrated *in vacuo*. The residue was diluted with AcOEt, washed with H_2O, and dried over anhydrous Na_2SO_4. After usual work-up the crude product obtained was submitted to preparative TLC using hexane–AcOEt (3:1) as developing solvent. Elution of the adsorbent corresponding to *Rf* 0.38 and recrystallization of the eluate from acetone-hexane gave IIa (640 mg) as colorless needles. mp 147—148°. $[\alpha]_D^{25}$ −203.7° (c=0.11). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.64; H, 9.01. NMR (5% solution in $CDCl_3$) δ: 0.92 (3H, s, 19-CH_3), 1.18 (3H, s, 18-CH_3), 3.37 (3H, s, 3β-OCH_3), 5.35 (1H, m, 6-H), 6.60 (1H, d, J=3 Hz, 15-H).

3β-Methoxy-16-hydroxy-13α-androsta-5,15-dien-17-one *p*-Bromobenzoate (IIb)——To a solution of IIa (300 mg) in pyridine (6 ml)–benzene (10 ml) was added *p*-BrC_6H_4COCl (300 mg) in benzene (10 ml) and refluxed for 1 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, and dried over anhydrous Na_2SO_4. After usual work-up the crude product obtained was submitted to preparative TLC using hexane–AcOEt (3:1) as developing solvent. Elution of the adsorbent corresponding to *Rf* 0.66 and recrystallization of the eluate from acetone gave IIb (200 mg) as colorless prisms. mp 168—169°. $[\alpha]_D^{25}$ −94.9° (c=0.33). *Anal.* Calcd. for $C_{27}H_{31}O_4Br$: C, 64.93; H, 6.26. Found: C, 65.21; H, 6.26. NMR (5% solution in $CDCl_3$) δ: 0.92 (3H, s, 19-CH_3), 1.24 (3H, s, 18-CH_3), 3.35 (3H, s, 3β-OCH_3), 5.35 (1H, m, 6-H), 7.55 (1H, d, J=2.4 Hz, 15-H), 7.60 (2H, d, J=7.2 Hz, ), 8.00 (2H, d, J=7.2 Hz, ).

3-Methoxy-16-hydroxy-13α-estra-1,3,5(10),15-tetraen-17-one *p*-Bromobenzoate (IVb)——To a solution of 3-methoxy-16-hydroxy-13α-estra-1,3,5(10),15-tetraen-17-one (IVa)[3c] (250 mg) in pyridine (6 ml)–benzene (10 ml) was added *p*-BrC_6H_4COCl (250 mg) in benzene (10 ml) and refluxed for 1 hr. The resulting solution was processed in the manner as described in IIb. The crude product obtained was submitted to preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to *Rf* 0.52 and recrystallization of the eluate from acetone gave IVb (185 mg) as colorless prisms. mp 177—178°. $[\alpha]_D^{25}$ −80.2° (c=0.12). *Anal.* Calcd. for $C_{26}H_{25}O_4Br$: C, 64.87; H, 5.24. Found: C, 64.99; H, 5.18. NMR (5% solution in $CDCl_3$) δ: 1.32 (3H, s, 18-CH_3), 3.75 (3H, s, 3-OCH_3), 6.60 (1H, m, 4-H), 6.80 (1H, m, 2-H), 7.06 (1H, m, 1-H), 7.50 (1H, d, J=2.4 Hz, 15-H), 7.60 (2H, d, J=7.2 Hz, ), 8.00 (2H, d, J=7.2 Hz, ).

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