Synthesis and Crystal and Molecular Structure of a 1,11-Methano-steroid, 3-Methoxy-1'β-methyl-1,11α-methano-9β-estra-1,3,5(10)-trien-17β-ol

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Treatment of 17,17-ethylenedioxy-3-methoxy-11α-vinylestra-1,3,5(10)-trien-11β-ol with various acids afforded 3-methoxy-1'β-methyl-1,11-methanoestra-1,3,5(10),9(11)-tetraen-17-one. and not the isomeric 1,11-ethano-steroid. Birch reduction of this pentacyclic product gave the title compound, the structure of which was established by X-ray single-crystal analysis. Crystals are orthorhombic, space group $P2_12_12_1$, with $a = 9.153(5)$, $b = 17.918(10)$, $c = 10.200(5)$ Å. $Z = 4$. The structure was solved by direct methods and refined by full-matrix least-squares calculations to R 0.046 over 1474 statistically significant reflections from diffractometer measurements. The steroid skeleton is folded severely to the α-side about the C(8)–C(9) bond. Ring B adopts a distorted half-chair conformation. ring C has a chair form significantly flattened around C(9). and ring D approximates to a C(13)-envelope.

INTRODUCTION of a methyl substituent at C(1) of the steroid skeleton is known to reduce hormonal activity.[1] This result may be attributed to the less effective binding to the hormonal receptor proteins as a consequence either of adverse methyl–receptor group interactions or of distortion of the steroid skeleton necessary to relieve the severe non-bonded interactions between the 11-methylene group and the C(1) substituent.

Because the skeletal distortion is largely eliminated if the C(1) substituent is part of a bridge to C(11), as in 1,11-methano- and -ethano-steroids, we have sought to synthesize and evaluate the biological activity of such derivatives.
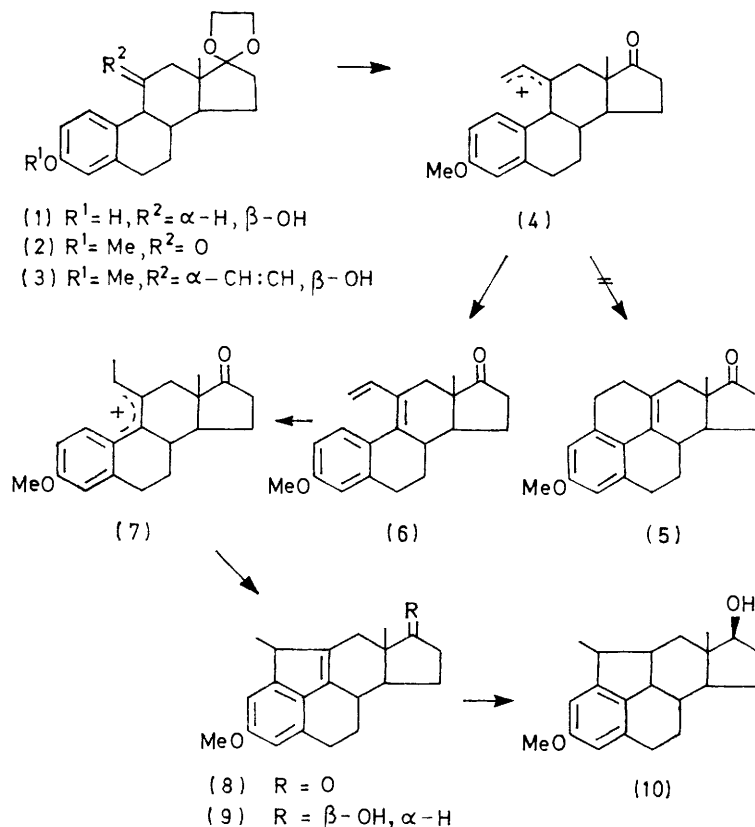
Our initial objective was the synthesis of an 1,11α-ethano-steroid. To this end, 17,17-ethylenedioxyestra-1,3,5(10)-triene-3,11β-diol (1) was converted into the known 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-11-one (2) by O-methylation, followed by oxidation.[2] The reaction of (2) with either vinyl-lithium or vinylmagnesium chloride afforded a single vinyl carbinol

[1] (a) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufman, and J. Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534; (b) H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *ibid.*, 1956, **78**, 2477; (c) C. Djerassi, A. E. Lippman, and J. Grossman, *ibid.*, 1956, **78**, 2479; (d) H. J. Ringold in ' Mechanism of Action of Steroid Hormones,' International Series of Monographs on Pure and Applied Chemistry, ed. C. Villee and L. L. Engel, vol. 1, Pergamon, New York, 1961.

[2] J. S. Baran, H. D. Lennon, S. E. Mares, and E. F. Nutting, *Experientia*, 1970, **26**, 762.

(3), most probably the 11α-vinyl isomer, in 71% yield. The product (3) was treated with toluene-*p*-sulphonic acid in benzene, in the expectation that the resulting tertiary allylic carbenium ion (4) would cyclize *via* an electrophilic aromatic substitution reaction. The [1]H n.m.r. spectrum of the major product (63%) showed the loss of the C(1) aromatic proton, but, in addition to the

(3) with other acids such as tin(IV) chloride, boron trifluoride–ether, and toluene-*p*-sulphonic acid in acetic acid–acetic anhydride, also gave (8) as the major product.

Reduction of compound (8) with sodium borohydride gave the 17β-ol (9) which, on further reduction with lithium in ammonia, gave the triene (10). *X*-Ray

(1) R¹= H, R²= α-H, β-OH
(2) R¹= Me, R²= O
(3) R¹= Me, R²= α-CH:CH, β-OH

(4)

(7)

(6)

(5)

(8) R = O
(9) R = β-OH, α-H

(10)

Scheme

18-methyl and methoxy singlets, a methyl doublet at δ 1.28 (*J* 7 Hz) was evident. The [13]C n.m.r. spectrum confirmed the presence of three methyl groups, and suggested the 1′-methyl-1,11-methano-structure (8). This was confirmed by single-crystal *X*-ray analysis of a transformation product of (8) (see later). The 9,11-position of the olefinic double bond of (8) was indicated by the absence of olefinic protons and by double resonance, which showed that the 1′-proton was coupled only to the three 1′-methyl protons.

The formation of compound (8) can be understood in terms of the mechanism shown in the Scheme, whereby deprotonation of the initially formed carbenium ion (4) gives the pentaene (6) to the exclusion of the cyclization product (5). Reprotonation of the diene system in (6) then produces a new, secondary but conjugated, carbenium ion (7), which cyclizes to (8). Apparently, this is the exclusive process, for the [1]H n.m.r. spectra of the two minor products of the cyclization reaction also showed the same CHMe part structure. Treatment of

[3] D. Caine, *Org. Reactions*, 1976, **23**, 1.

single-crystal analysis of (10) established that *cis*-reduction of the 9,11-double bond had occurred; this
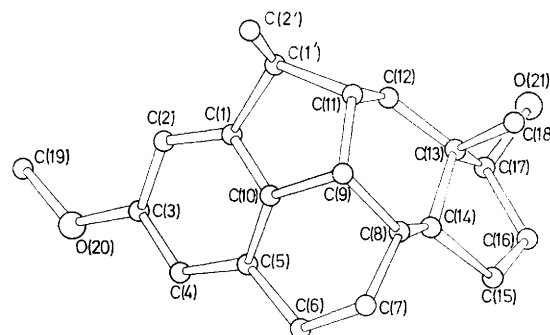
FIGURE 1 Atom numbering scheme and conformation of (10)

cis-reduction of a hydrindene part structure is not without precedent.[3] Figure 1 shows the molecular conformation and atom numbering scheme of the molecule (10). Final atomic co-ordinates are listed in Tables 1 and 2.

Interatomic distances and valency angles are in Table **3**, and torsion angles in Table **4**.

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$) for the non-hydrogen atoms, with estimated standard deviations in parentheses

Atom	x	y	z
C(1)	4 021(3)	−4 896(1)	4 959(2)
C(2)	4 842(3)	−4 325(2)	4 406(3)
C(3)	4 136(4)	−3 645(1)	4 184(3)
C(4)	2 660(3)	−3 551(1)	4 459(3)
C(5)	1 856(3)	−4 120(1)	5 033(3)
C(6)	220(3)	−4 074(2)	5 296(3)
C(7)	−357(3)	−4 734(2)	6 099(3)
C(8)	287(3)	−5 506(1)	5 740(3)
C(9)	1 942(3)	−5 468(1)	5 951(2)
C(10)	2 582(3)	−4 779(1)	5 322(2)
C(11)	2 944(3)	−6 086(1)	5 376(3)
C(12)	2 413(3)	−6 352(1)	4 023(3)
C(13)	76(3)	−6 494(1)	3 985(2)
C(14)	−29(3)	−5 764(1)	4 342(3)
C(15)	−1 619(3)	−5 900(2)	3 925(3)
C(16)	−1 514(3)	−6 428(2)	2 740(3)
C(17)	137(3)	−6 618(2)	2 605(3)
C(18)	359(3)	−7 147(1)	4 889(3)
C(19)	6 358(3)	−3 053(2)	3 494(4)
O(20)	4 825(3)	−3 027(1)	3 672(3)
O(21)	381(3)	−7 350(1)	2 106(2)
C(1′)	4 464(3)	−5 695(1)	5 262(3)
C(2′)	5 350(3)	−5 747(2)	6 532(3)

TABLE 2

Hydrogen atom fractional co-ordinates ($\times 10^3$), isotropic thermal parameters, and distances (d) to their bonded carbon or oxygen atoms; estimated standard deviations are in parentheses

Atom	x	y	z	$B/\text{Å}^2$	$d/\text{Å}$
H(2)	591(4)	−437(2)	414(3)	0.6(6)	1.02(3)
H(4)	214(5)	−308(2)	431(4)	3.3(9)	0.99(4)
H(6A)	−33(4)	−403(2)	437(3)	1.5(7)	1.07(3)
H(6B)	−3(4)	−357(2)	576(3)	2.0(8)	1.05(4)
H(7A)	−139(4)	−471(2)	599(4)	1.7(8)	0.96(4)
H(7B)	−20(3)	−460(2)	704(3)	0.5(6)	1.00(3)
H(8)	−14(4)	−586(2)	636(3)	0.8(7)	0.98(3)
H(9)	205(4)	−541(2)	687(4)	1.9(8)	0.94(4)
H(11)	302(4)	−653(2)	598(3)	1.1(7)	1.01(3)
H(12A)	269(3)	−599(2)	334(3)	0.5(6)	0.99(3)
H(12B)	304(4)	−681(2)	379(4)	0.9(6)	1.03(3)
H(14)	39(4)	−536(2)	374(3)	1.3(7)	1.03(3)
H(15A)	−208(5)	−538(2)	365(4)	2.9(9)	1.06(4)
H(15B)	−221(4)	−612(2)	471(4)	2.4(8)	1.05(4)
H(16A)	−190(5)	−619(2)	191(4)	3.1(10)	1.01(4)
H(16B)	−200(5)	−691(2)	286(4)	2.3(9)	0.98(4)
H(17)	59(3)	−625(2)	202(3)	0.2(6)	0.99(3)
H(18A)	−67(4)	−725(2)	490(4)	1.1(8)	0.96(4)
H(18B)	89(5)	−760(2)	463(4)	3.2(9)	0.98(4)
H(18C)	81(4)	−705(2)	580(4)	3.6(8)	1.03(4)
H(19A)	672(5)	−256(2)	312(4)	3.6(10)	1.02(4)
H(19B)	694(5)	−316(2)	445(4)	3.2(9)	1.13(4)
H(19C)	661(5)	−345(2)	286(4)	2.1(9)	0.98(4)
H(21)	58(5)	−747(2)	134(4)	8.5(15)	0.84(6)
H(1′)	504(4)	−594(2)	445(3)	3.3(6)	1.07(3)
H(2′A)	557(4)	−629(2)	672(4)	2.0(10)	1.02(4)
H(2′B)	633(5)	−546(2)	652(4)	3.1(10)	1.03(4)
H(2′C)	479(5)	−558(3)	721(4)	2.4(10)	0.92(4)

The BC *cis* ring fusion results in an overall steroid skeleton which is folded considerably to the α-side, as reflected in the torsion angle of 102.5° between the least-squares planes through C(1)–C(7), C(9), C(1′), O(22) and C(8), C(9), C(11)—C(17). A Dreiding model indicates that the presence of ring E introduces considerable strain, and this is revealed in the results of the crystallo-

graphic study by the elongation of two bonds in this ring, several highly significant valency angle deformations, and torsional strain in the rings. The C(9)–C(11), C(11)–C(1′), and C(16)–C(17) bonds [1.553(4), 1.562(4), and 1.555(4) Å] are all slightly longer than the mean of the remaining $C(sp^3)$–$C(sp^3)$ bond lengths (1.539 Å), which lies close to the standard value [4] [1.536(5) Å]. Of these, longer than normal C(16)–C(17) bonds appear to be a feature common to ring D of many steroids; the

TABLE 3

Interatomic distances (Å) and angles (deg.), with estimated standard deviations in parentheses

(a) Bond lengths

C(1)–C(2)	1.389(4)	C(9)–C(11)	1.553(4)
C(1)–C(10)	1.385(4)	C(11)–C(12)	1.538(4)
C(1)–C(1′)	1.519(4)	C(11)–C(1′)	1.562(4)
C(2)–C(3)	1.399(4)	C(12)–C(13)	1.532(4)
C(3)–C(4)	1.390(4)	C(13)–C(14)	1.538(4)
C(3)–O(20)	1.377(4)	C(13)–C(17)	1.536(4)
C(4)–C(5)	1.387(4)	C(13)–C(18)	1.536(4)
C(5)–C(6)	1.523(4)	C(14)–C(15)	1.536(4)
C(5)–C(10)	1.387(4)	C(15)–C(16)	1.538(5)
C(6)–C(7)	1.532(4)	C(16)–C(17)	1.555(4)
C(7)–C(8)	1.546(4)	C(17)–O(21)	1.426(3)
C(8)–C(9)	1.532(4)	C(19)–O(20)	1.416(4)
C(8)–C(14)	1.527(4)	C(1′)–C(2′)	1.531(4)
C(9)–C(10)	1.509(3)		

(b) Angles

C(2)–C(1)–C(10)	120.8(2)	C(9)–C(11)–C(12)	111.9(2)
C(2)–C(1)–C(1′)	129.2(2)	C(9)–C(11)–C(1′)	103.5(2)
C(10)–C(1)–C(1′)	110.0(2)	C(12)–C(11)–C(1′)	110.7(2)
C(1)–C(2)–C(3)	117.2(2)	C(11)–C(12)–C(13)	112.7(2)
C(2)–C(3)–C(4)	121.5(2)	C(12)–C(13)–C(14)	108.5(2)
C(2)–C(3)–O(20)	123.4(3)	C(12)–C(13)–C(17)	114.5(2)
C(4)–C(3)–O(20)	115.1(2)	C(12)–C(13)–C(18)	110.4(2)
C(3)–C(4)–C(5)	120.8(2)	C(14)–C(13)–C(17)	99.4(2)
C(4)–C(5)–C(6)	123.8(2)	C(14)–C(13)–C(18)	113.1(2)
C(4)–C(5)–C(10)	117.5(2)	C(17)–C(13)–C(18)	110.5(2)
C(6)–C(5)–C(10)	118.6(2)	C(8)–C(14)–C(13)	112.9(2)
C(5)–C(6)–C(7)	113.1(2)	C(8)–C(14)–C(15)	119.1(2)
C(6)–C(7)–C(8)	115.6(2)	C(13)–C(14)–C(15)	104.3(2)
C(7)–C(8)–C(9)	107.7(2)	C(14)–C(15)–C(16)	104.8(2)
C(7)–C(8)–C(14)	114.8(2)	C(15)–C(16)–C(17)	105.4(2)
C(9)–C(8)–C(14)	109.4(2)	C(13)–C(17)–C(16)	104.4(2)
C(8)–C(9)–C(10)	111.1(2)	C(13)–C(17)–O(21)	113.7(2)
C(8)–C(9)–C(11)	120.0(2)	C(16)–C(17)–O(21)	112.7(2)
C(10)–C(9)–C(11)	101.2(2)	C(3)–O(20)–C(19)	118.4(3)
C(1)–C(10)–C(5)	121.9(2)	C(1)–C(1′)–C(11)	101.5(2)
C(1)–C(10)–C(9)	111.0(2)	C(1)–C(1′)–C(2′)	111.8(2)
C(5)–C(10)–C(9)	127.0(2)	C(11)–C(1′)–C(2′)	112.4(2)

(c) Intermolecular distances <3.7 Å between non-hydrogen atoms

C(19) · · · O(21ᴵᴵ)	3.30	O(21) · · · C(4ᴵ)	3.62
O(21) · · · C(3ᴵ)	3.50	C(17) · · · C(2ᴵ)	3.67
O(21) · · · O(20ᴵ)	3.57	O(21) · · · C(2′ᴵᴵᴵ)	3.68
C(17) · · · C(3ᴵ)	3.58		

Roman numeral superscripts refer to the following transformations of the co-ordinates of the reference molecule at x, y, z:

I $\frac{1}{2} - x$, $-y$, $\frac{1}{2} + z$ III $-\frac{1}{2} + x$, $\frac{3}{2} - y$, $1 - z$
II $1 - x$, $\frac{1}{2} + y$, $\frac{1}{2} - z$

other two bonds are in ring E and their elongation provides an indication of the strain present. Valency angle deformation is especially apparent around C(5), C(7), C(9), and C(10), where the angles C(1)–C(10)–C(9) [111.0(2)°], C(10)–C(9)–C(11) [101.2(2)°], and C(6)–C(5)–C(10) [118.6(2)°] are all smaller than the corresponding

4 *Chem. Soc. Special Publ.*, No. 11, 1958; No. 18, 1965.

Table 4

Torsion angles (deg.); the angle A–B–C–D is defined as positive if, when viewed along the B–C bond, atom A must be rotated clockwise to eclipse atom D

C(10)–C(1)–C(2)–C(3)	−2.6
C(1′)–C(1)–C(2)–C(3)	177.4
C(2)–C(1)–C(10)–C(5)	6.6
C(2)–C(1)–C(10)–C(9)	−177.5
C(1′)–C(1)–C(10)–C(5)	−173.4
C(1′)–C(1)–C(10)–C(9)	2.5
C(2)–C(1)–C(1′)–C(11)	−160.5
C(2)–C(1)–C(1′)–C(2′)	79.4
C(10)–C(1)–C(1′)–C(11)	19.5
C(10)–C(1)–C(1′)–C(2′)	−100.6
C(1)–C(2)–C(3)–C(4)	−2.4
C(1)–C(2)–C(3)–O(20)	178.4
C(2)–C(3)–C(4)–C(5)	3.7
O(20)–C(3)–C(4)–C(5)	−177.1
C(2)–C(3)–O(20)–C(19)	−7.2
C(4)–C(3)–O(20)–C(19)	173.6
C(3)–C(4)–C(5)–C(6)	−176.6
C(3)–C(4)–C(5)–C(10)	0.2
C(4)–C(5)–C(6)–C(7)	−172.4
C(10)–C(5)–C(6)–C(7)	10.8
C(4)–C(5)–C(10)–C(1)	−5.3
C(4)–C(5)–C(10)–C(9)	179.6
C(6)–C(5)–C(10)–C(1)	171.7
C(6)–C(5)–C(10)–C(9)	−3.5
C(5)–C(6)–C(7)–C(8)	−40.3
C(6)–C(7)–C(8)–C(9)	59.8
C6)–C(7)–C(8)–C(14)	−62.3
C(7)–C(8)–C(9)–C(10)	−48.2
C(7)–C(8)–C(9)–C(11)	−165.8
C(14)–C(8)–C(9)–C(10)	77.2
C(14)–C(8)–C(9)–C(11)	−40.3
C(7)–C(8)–C(14)–C(13)	174.1
C(7)–C(8)–C(14)–C(15)	−63.1
C(9)–C(8)–C(14)–C(13)	52.9
C(9)–C(8)–C(14)–C(15)	175.7
C(8)–C(9)–C(10)–C(1)	−151.8
C(8)–C(9)–C(10)–C(5)	23.8
C(11)–C(9)–C(10)–C(1)	−23.4
C(11)–C(9)–C(10)–C(5)	152.2
C(8)–C(9)–C(11)–C(12)	37.4
C(8)–C(9)–C(11)–C(1′)	156.7
C(10)–C(9)–C(11)–C(12)	−85.1
C(10)–C(9)–C(11)–C(1′)	34.2
C(9)–C(11)–C(12)–C(13)	−45.7
C(1′)–C(11)–C(12)–C(13)	−160.6
C(9)–C(11)–C(1′)–C(1)	−32.9
C(9)–C(11)–C(1′)–C(2′)	86.7
C(12)–C(11)–C(1′)–C(1)	87.1
C(12)–C(11)–C(1′)–C(2′)	−153.3
C(11)–C(12)–C(13)–C(14)	59.2
C(11)–C(12)–C(13)–C(17)	169.2
C(11)–C(12)–C(13)–C(18)	−65.3
C(12)–C(13)–C(14)–C(8)	−63.9
C(12)–C(13)–C(14)–C(15)	165.4
C(17)–C(13)–C(14)–C(8)	176.2
C(17)–C(13)–C(14)–C(15)	45.5
C(18)–C(13)–C(14)–C(8)	59.0
C(18)–C(13)–C(14)–C(15)	−71.7
C(12)–C(13)–C(17)–C(16)	−157.8
C(12)–C(13)–C(17)–O(21)	79.0
C(14)–C(13)–C(17)–C(16)	−42.4
C(14)–C(13)–C(17)–O(21)	−165.6
C(18)–C(13)–C(17)–C(16)	76.7
C(18)–C(13)–C(17)–O(21)	−46.5
C(8)–C(14)–C(15)–C(16)	−158.2
C(13)–C(14)–C(15)–C(16)	−31.2
C(14)–C(15)–C(16)–C(17)	4.2
C(15)–C(16)–C(17)–C(13)	24.2
C(15)–C(16)–C(17)–O(21)	148.0

means in related compounds [5–9] (119.4, 113.0, and 122.0°), whereas the angles C(5)–C(10)–C(9) [127.0(2)°], C(4)–C(5)–C(6) [123.8(2)°], C(6)–C(7)–C(8) [115.6(2)°],

and C(8)–C(9)–C(11) [120.0(2)°] are all larger than their respective means in these same compounds.

Strain in the substituted phenyl ring A is indicated by the departure from ideal (0°) of the sum of the moduli of the endocyclic torsion angles, $\Sigma|\omega|$ 20.8°, which is a consequence of the mean deviation (0.020 Å) of the ring atoms from their least-squares plane. The largest torsion angle in ring A (6.6°) occurs around the C(1)–C(10) bond and there is a slight tendency toward a pyramidal geometry at C(10) which is displaced from the C(1), C(5), C(9) plane by 0.032 Å to the β-side. The geometry at the methoxy group is similar to that found in other compounds; [10] the methyl carbon C(19) lies close to the phenyl ring plane, Δ 0.267 Å, and the exocyclic valency angles at C(3) conform to the usual pattern.

Ring B, with $\Delta(C_2$-HC) * 24.4°, $\Delta(C_s$-E) 42.4°, adopts a distorted half-chair conformation in which C(7) and C(8) are displaced by 0.21 and 0.51 Å, respectively, to the β- and α-sides of the C(5), C(6), C(9), C(10) least-squares plane. This conformation differs from those encountered in ring B of estra-1,3,5(10)-trienes which lack ring E and where C(7) and C(8) are displaced to the α- and β-sides of the distorted half-chair or envelope forms.[11]

Ring C has a chair conformation which is significantly flattened around C(9) by the introduction of ring E. Ring D lies closer to a C(13)-envelope form † (ΔC_s = 14.3°) than to a C(16)-half-chair (ΔC_2 = 31.2°) and is characterized [12] by a maximum torsion angle ϕ_m = 46.1°, and phase angle of pseudorotation Δ = 25.2°, values which are typical of 17β-hydroxyestranes.[11] Ring E approximates to a C(11)-envelope form which is less puckered ($\Sigma|\omega|$ 112.5°, mean valency angle 105.4°) than that of ring D ($\Sigma|\omega|$ 147.5°, mean valency angle 103.7°).

The packing of molecules of (10) in the crystal is shown in Figure 2. Intermolecular distances <3.7 Å are included in Table 3; all of these are of the van der Waals type and thus, surprisingly, there are no intermolecular hydrogen bonds involving the hydroxy group.

A second method of synthesis of the 1,11α-methano-estra-1,3,5(10)-triene skeleton, also considered during these studies, was photolytic generation of the triplet

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* $\Delta(C_2$ − HC) and $\Delta(C_s$ − E) represent the sum of the deviations of the torsion angles from an ideal half-chair form, $\Delta(C_2$ − HC) = $|\omega_{5,10}| + |\omega_{5,6} - \omega_{9,10}| + |\omega_{6,7} - \omega_{8,9}|$ and an ideal envelope (semiplanar, 1,2-diplanar, sofa) form, $\Delta(C_s$ − E) = $|\omega_{5,10}| + |\omega_{5,6}| + |\omega_{6,7} + \omega_{9,10}| + |\omega_{7,8} + \omega_{8,9}|$.

† $\Delta(C_2) = |\omega_{14,15} - \omega_{13,17}| + |\omega_{15,16} - \omega_{16,17}|$; $\Delta(C_s) = |\omega_{15,16}| + |\omega_{14,15} + \omega_{16,17}| + |\omega_{13,14} + \omega_{13,17}|$.

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state of 1-formylestradiol. The formyl group is suitably positioned for insertion into the α-C(11)-H bond, and there is good precedent for such a cyclization.[13] Unfortunately, attempts to reproduce the reported synthesis of 1-formylestradiol from 1-methylestradiol were not successful.[14]
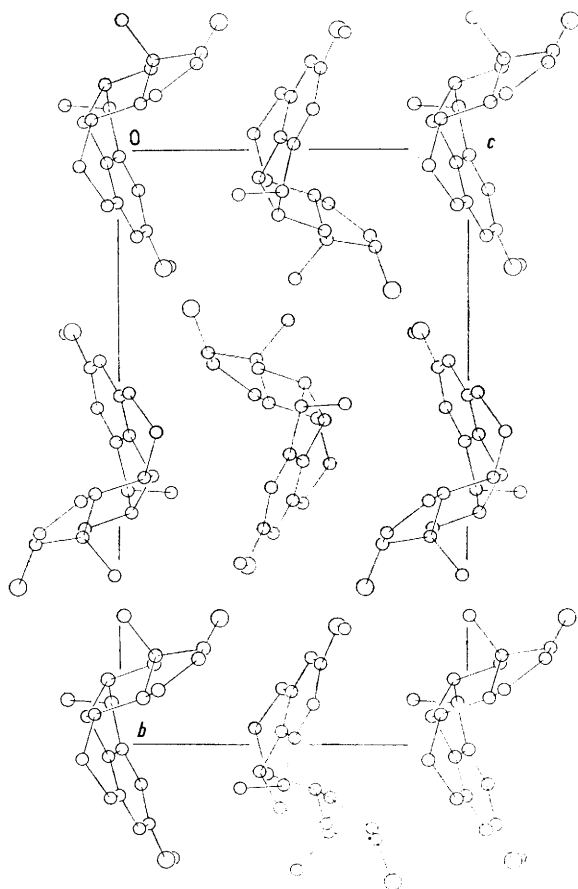

FIGURE 2   Molecular packing in crystals of (10), viewed in projection along the a-axis

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage microscope. I.r. spectra were measured with a Perkin-Elmer 267 spectrophotometer. Unless otherwise mentioned, n.m.r. spectra were recorded with a Varian HA-100 instrument (Me$_4$Si as internal standard). Mass spectra were determined with an A.E.I. MS902 instrument, and u.v. spectra with a Cary 14 spectrophotometer. G.l.c. analysis was carried out with a Varian 1400 instrument (column containing 3% SE-30 on Variport). Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois. Most reactions were carried out under dry, oxygen-free nitrogen.

17,17-Ethylenedioxy-3-methoxy-11α-vinylestra-1,3,5(10)-trien-11β-ol (3).—Vinylmagnesium chloride in tetrahydrofuran (16.1 ml; 2.2M) was added to a stirred solution of the ketone (2) (4.04 g, 11.8 mmol) in tetrahydrofuran (100 ml) at 0 °C. After 2 h at room temperature the mixture was poured into saturated aqueous ammonium chloride (400 ml). The aqueous phase was extracted with ether and the

combined extracts were washed with water and brine, and dried (Na$_2$SO$_4$). Concentration gave the crystalline product (3) (1.7 g, 40%). The mother liquor (4.26 g) was chromatographed on silica gel (200 g). Ether–hexane (2 : 8) eluted more product (3) (0.538 g; total yield 51%), m.p. 170—172° (from ether); [α]$_D^{24}$ + 45° (c 0.194 in CHCl$_3$); ν$_{max.}$ (CCl$_4$) 3 580 (OH) and 1 605 cm^{-1} (aromatic); δ(CDCl$_3$) 1.07 (3 H, s, C-18), 3.70 (3 H, s, OMe), 3.87br (4 H, s, O·CH$_2$·CH$_2$·O), 5.1 (1 H, dd, J 2 and 10 Hz, trans-CH:C·C), 5.4 (1 H, dd, J 2 and 17 Hz, cis-CH:C·C), 6.31 (1 H, dd, J 10 and 17 Hz, CH$_2$:CH), 6.67 (2 H, m, C-2 and C-4), and 7.85 (1 H, d, J 10 Hz, C-1) (Found: C, 74.45; H, 8.1. C$_{23}$H$_{30}$O$_4$ requires C, 74.55; H, 8.15%).

3-Methoxy-1'β-methyl-1,11-methanoestra-1,3,5(10),9(11)-tetraen-17-one (8).—A mixture of compound (3) (1.467 g), and toluene-p-sulphonic acid monohydrate (1.0 g) in benzene (100 ml) was refluxed for 1 h, with removal of water (Dean–Stark separator). Water (5 ml) was added and the mixture was stirred at room temperature until t.l.c. indicated acetal hydrolysis was complete (0.5 h). The mixture was diluted with ether, washed (sat. NaHCO$_3$, H$_2$O, and brine), dried (Na$_2$SO$_4$), and concentrated. The residue was chromatographed on silica gel (60 g). Ether–hexane (2 : 8) eluted the product (8) (0.500 g, 68%), m.p. 168—170°; [α]$_D^{24}$ + 220° (c 0.192 in CHCl$_3$), ν$_{max.}$ (CCl$_4$) 1 745 (CO) and 1 600 cm^{-1} (aromatic); λ$_{max.}$ (MeOH) 212 (ε 18 700), 267 (14 200), and 274 nm (13 300); δ(CDCl$_3$) 1.00 (3 H, s, C-18), 1.25 (3 H, d, J 7 Hz, 1'-Me), 3.17 (1 H, q, J 7 Hz, C-1'), 3.77 (3 H, OMe), 6.48 (1 H, d, J 2 Hz, C-2 or C-4), and 6.70 (1 H, d, J 2 Hz, C-2 or C-4) (Found: C, 81.85; H, 7.8%; M$^+$, 308.177. C$_{21}$H$_{24}$O$_2$ requires C, 81.8; H, 7.85%; M, 308.177).

3-Methoxy-1'-methyl-1,11-methanoestra-1,3,5(10),9(11)-tetraen-17β-ol (9).—Sodium borohydride (0.497 g, 10.3 mmol) was added to compound (8) (0.632 g, 2.07 mmol) in tetrahydrofuran (5 ml) and 95% ethanol (30 ml). After stirring for 1 h at room temperature, the mixture was diluted with ether, washed (aq. 10% HCl, sat. NaHCO$_3$, H$_2$O, and brine), dried (Na$_2$SO$_4$), and concentrated. The residual oil (9) (0.592 g, 92%) was homogeneous by t.l.c. and g.l.c. and was used without purification.

3-Methoxy-1'β-methyl-1,11α-methano-9β-estra-1,3,5(10)-trien-17β-ol (10).—Lithium (0.148 g, 0.021 0 g atom) was added to a stirred solution of compound (9) (0.656 g, 2.12 mmol) in dry tetrahydrofuran (5 ml) and ammonia (20 ml) at −78 °C. After 1 h, the deep blue colour of the mixture was discharged with saturated ammonium chloride and the ammonia was removed in a stream of nitrogen. Water (10 ml) was added and the mixture was extracted with ether. The extract was washed (H$_2$O and brine), dried (Na$_2$SO$_4$), and concentrated. The residue (0.618 g) was chromatographed on silica gel (EM prepacked column B). Elution with chloroform–hexane (4 : 6) gave two fractions, A (0.124 g, 19%) and B (0.282 g, 43%). Although homogeneous by t.l.c., and g.l.c., the n.m.r. spectrum of fraction A showed it to be a mixture. Crystallization of B from ether–hexane gave the product (10), m.p. 180—182°, [α]$_D^{24}$ −50° (c 0.101 in CHCl$_3$); ν$_{max.}$ (KBr) 3 610 and 3 450br (OH) and 1 610 and 1 600 cm^{-1} (aromatic); δ(CDCl$_3$) 0.76

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(3 H, s, C-18), 1.24 (3 H, d, J 8 Hz, 1'-Me), 3.74 (3 H, s, OMe), 6.42 (1 H, d, J 2 Hz, C-2 or C-4), and 6.58 (1 H, d, J 2 Hz, C-2 or C-4) (Found: M^+, 312.209 3. $C_{21}H_{28}O_2$ requires M, 312.208 9).

Crystal data. $C_{21}H_{28}O_2$, $M = 312.43$. Orthorhombic, $a = 9.153(5)$, $b = 17.918(10)$, $c = 10.200(5)$ Å, $U = 1\,672.8$ Å³, D_m(flotation) $= 1.25$, $Z = 4$, $D_c = 1.240$, g cm⁻³ $F(000) = 680$, Cu-K_α radiation, $\lambda = 1.5418$ Å; μ(Cu-K_α) $= 6.1$ cm⁻¹. Space group $P2_12_12_1(D_2^4)$ from the systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$.

Crystallographic Measurements.—A crystal of dimensions *ca.* $0.20 \times 0.30 \times 0.70$ mm was mounted on a glass fibre to rotate about the crystallographic c-axis. Preliminary unit-cell dimensions and space group information were obtained from oscillation and Weissenberg photographs. The crystal was then transferred to an Enraf-Nonius CAD 3 automated diffractometer (Ni-filtered Cu-K_α radiation; take-off angle 3°) and accurate unit-cell parameters were derived by least-squares treatment of the θ, χ, and φ angles for 40 high angle reflections widely separated in reciprocal space. One octant of intensity data up to θ 67° was collected by the θ—2θ scanning technique with scanwidths $(1.0 + 0.50 \tan θ)°$; automatic insertion of attenuators ensured that counting rates did not exceed 2 500 counts s⁻¹. Stationary background measurements were taken at each end of the scan range for a time equal to half the duration of the scan. The intensity of a strong standard reflection re-examined periodically showed no significant variation over the entire data collection period. From a total of 1 726 measurements, 1 474 reflections for which $I > 2.0\sigma(I)$ $[\sigma^2(I) = \text{scan count} + \text{total background count}]$ were used in the structure analysis. Absorption corrections, determined from the φ-dependence of the 006 reflection measured at χ 90°, were applied to these data, which were then corrected for the usual Lorentz and polarization effects.

Structure Analysis.—The structure was solved by direct non-centrosymmetric phase-determining methods using MULTAN [15] in conjunction with the 'Magic Integer' approach.[16] The primary set, consisting of 19 reflections,

was used to develop 51 secondary relationships, and a total of 70 phases constituted the starting set. An E-map calculated with the values of the phases produced by that set having the lowest residual and highest figure-of-merit led to complete definition of the molecular structure.

Atomic positional and isotropic thermal parameters were refined to R 0.114 by a number of full-matrix least-squares iterations. Hydrogen atom positions were then located in a difference-Fourier synthesis and their inclusion, with temperature-factors of their bonded carbon and oxygen atoms, into the next structure-factor calculation reduced R to 0.095. In subsequent least-squares cycles the carbon and oxygen atoms were allowed to assume anisotropic thermal parameters and the refinement converged at R 0.046 when no parameter shift exceeded 0.2 times its estimated standard deviation. Final atomic positional parameters are in Table 1. Anisotropic temperature factor parameters for the carbon and oxygen atoms are included with a Table of observed and calculated structure amplitudes in Supplementary Publication No. SUP 21831 (12 pp.).†

For all structure-factor calculations, scattering factors for carbon and oxygen were taken from ref. 17 and for hydrogen from ref. 18. In the least-squares calculations $\Sigma w\Delta^2$ was minimized, the weights w being given by $\sqrt{w} = 1$ for $|F_o| \leqslant 7.9$ and $\sqrt{w} = 7.9|F_o|$ for $|F_o| > 7.9$.

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

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