11-Alkylidene steroids in the 19-nor series

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(Received June 27th, 1974)

Abstract. A number of 11-methylene-substituted estrenes and 19-nor-pregnenes have been synthesised. In addition, some 11-*(E)*-ethylidene estrenes have been prepared. Evidence is presented establishing the configuration of the ethylidene substituent.

Introduction

Since some 11-substituted 19-nor-steroids, particularly 11β-chloro[1]- and 11β-methyl[2] derivatives are biologically very active compounds it seemed to us of interest to synthesise some 11-alkylidene derivatives in this series.
Elks[3] and *Kirk* et al.[4], described the introduction of an 11-methylene group in the normal 5α-series by acidic dehydration of an 11β-hydroxy-11α-methyl-sapogenin leading to a mixture of the exocyclic olefin and the endocyclic olefin in a ratio of about 4 : 1. In the 5β-series *Buhler*[5] et al., found that the $\Delta^{9(11)}$ isomer is the major dehydration product when treating 11β-hydroxy-11α-methyl-5β-pregnane-3,20-dione 3,20-dioxime with hydrochloric acid in acetone.
In the 3-oxo-Δ^4 series *Beyler* et al.[6] reported the $\Delta^{9(11)}$ isomer as the main product of the alumina-catalysed dehydration of 11β,17α,21-trihydroxy-11α-methyl-Δ^4-pregnene-3,20-dione.
These examples show that small differences in the ring structure strongly influence the success or failure of this route to 11-methylene steroids. We could confirm this in our investigations.

Synthesis

Selective dithioacetalisation of Ia[7] (see Chart I) followed by protection of the 17-oxo function as the ethylene acetal, and reduction with sodium in liquid ammonia[8] gave on hydrolysis the 3-desoxo compound IIIb. Jones oxidation[9] of IIIb and re-acetalisation afforded IVb, which could also be obtained by Jones oxidation of IIIa.

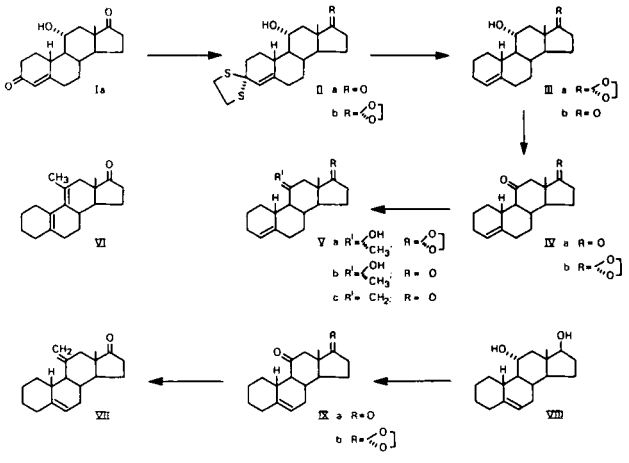

Chart I

Treatment of the 11-ketone IVb with either methylmagnesium iodide or methyllithium in diethyl ether and subsequent hydrolysis of the ethylene acetal group produced the 11α-methyl-11β-hydroxy derivative Vb. The configuration of the hydroxy group at C-11 was unequivocally established by NMR. Addition of $Eu(DPM)_3$ to Vb and to the model compound 11β-hydroxy-Δ^4-estren-17-one[10] induced a large downfield shift of the 13-CH_3 signal in both cases which was not observed with the 11α-hydroxy epimer IIIb[11].
Dehydration of Vb with formic acid gave a complex mixture from which only 11-methylene-Δ^5-estren-17-one (VII) could be isolated in a pure form in a yield of 5% by careful chromatography on silicagel impregnated with silver nitrate followed by crystallisation from acetonitrile. The structure of VII was assigned on NMR data (5.40 ppm, broad doublet, 6-H and 4.88 ppm, s, 11-CH_2) and unambiguously confirmed by a synthetical proof *(vide infra)*.
The NMR spectrum of the acetonitrile mother liquors revealed the presence of the desired 11-methylene-Δ^4-estren-17-one (Vc) next to VII in a ratio of 1 : 2.
In a preceding oily fraction the conjugated diene VI could be detected by spectral analyses (NMR and UV). Thus the introduction of the 11-methylene substituent by acidic dehydration of the alcohol Vb was accompanied by migration of the double bond from Δ^4 to Δ^5 or $\Delta^{5(10)}$, which suggests that better yields would be possible in the 3-oxo-Δ^4-estrene series. So 11α-hydroxy-Δ^4-estrene-3,17-dione (Ia) was converted to the diethylene acetal Xa (Chart II) by treatment with ethylene glycol/triethyl orthoformate/*p*-toluenesulfonic acid in methylene chloride at reflux temperature. Jones oxidation gave Δ^5-estrene-3,11,17-trione 3,17-diethylene acetal (Xb) in 60% yield. The reversed route, oxidation first and then acetalisation, gave Xb in comparable yield. In both acetalisation reactions the product was contaminated with less than 5% of the corresponding $\Delta^{5(10)}$ isomers as could be deduced from the integral curve of the NMR spectrum and from GLC analysis[12].

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[8] *M. S. de Winter, C. M. Siegmann* and *S. A. Szpilfogel*, Chem. Ind. London 905 (1959).
[9] *K. Bowden, I. M. Heilbron, E. R. H. Jones* and *B. C. L. Weedon*, J. Chem. Soc. 39 (1946).
[10] Prepared from IVb by reduction with $NaBH_4$ and hydrolysis of the ethylene acetal group.
[11] Determination of the configuration at C-11 in the model compounds IIIb and its 11β-hydroxy epimer is straightforward and based on the C-11 proton and 13-CH_3 signals in NMR (11βH: 3.80 ppm, multiplet; 13-CH_3: 0.88 ppm, s, for IIIb and 11α-H: 4.29 ppm, multiplet; 13-CH_3: 1.13 ppm, s, for the 11β-hydroxy epimer).
[12] In the 11-oxo series investigated by *K. Schönemann:* unpublished results.

This is in contrast to the acetalisation of the 11-non-substituted derivative[13], which, under the same reaction conditions, yields a far less favourable mixture of both isomers.

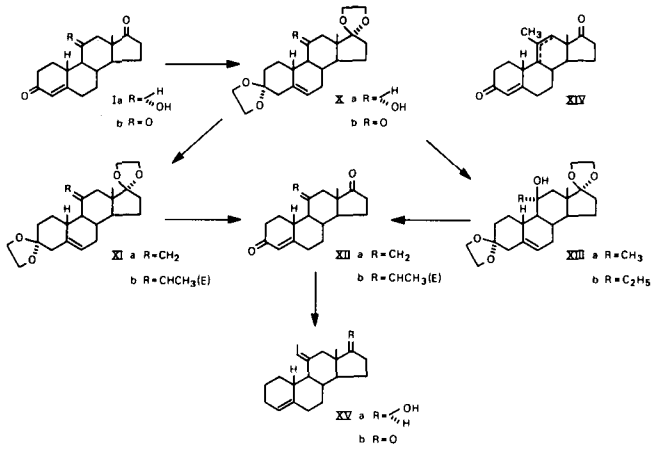

Chart 2

Acidic dehydration of the alcohol XIIIa, prepared from Xb with methyllithium, gave the 11-methyleneestrene XIIa in a yield of 64%. In the total reaction product only 5% of a possible mixture of the 11-methyl compounds XIV, not further identified, could be detected by NMR and GLC analyses. A similar composition of reaction products was observed when the acetal functions of XIIIa were hydrolysed first in acetone/hydrochloric acid prior to treatment with formic acid.

These investigations show that in the 3-oxo-Δ^4-19-nor series 11-methylene steroids can be prepared in good yields by acidic dehydration of 11β-hydroxy-11α-methyl steroids. For the other series another approach is needed. We found this in the Wittig reaction.

Wittig reaction

In contrast to the androstane and pregnane series[14] the Wittig reaction on an 11-oxo-19-nor-steroid, where the bulky angular 10-methyl substituent is lacking, proceeds in moderate to high yields when applying Corey's modification of the Wittig reaction[15]. Treatment of the 11-ketone IVb with methylenetriphenylphosphorane, prepared from methyltriphenylphosphonium bromide in dimethyl sulfoxide/benzene with sodium hydride as base, followed by hydrolysis of the ethylene acetal group gave the 11-methylene compound Vc in 60% yield. The same procedure applied to IXb, prepared from Δ^5-estrene-11α,17β-diol[16] (VIII) *via* Jones oxidation and selective acetalisation, gave, upon hydrolysis, 11-methylene-Δ^5-estren-17-one (VII), identical with the compound isolated from the dehydration reaction on Vb.

The modified Wittig reaction applied to Xb gave XIa in nearly quantitative yield.

When Xb was treated with ethylidenetriphenylphosphorane under similar reaction conditions a complex mixture was obtained. Resolution of this mixture by chromatography on silicagel afforded 30% of 11-*(E)*-ethylidene-Δ^5-estrene-3,17-dione 3,17-diethylene acetal XIb in addition to 36% of starting material Xb and polar material. None of the geometrical *(Z)*-isomer could be detected in the reaction mixture. Dreiding models showed that formation of the *(Z)*-isomer was not very likely owing to steric interference of the C-1-methylene with the methyl substituent in the four-centre Wittig intermediate[17] which should lead to the *(Z)*-isomer.

A similar steric hindrance applies to the *(Z)*-ethylidene substituent itself. Support for this explanation is the exclusive formation of the *(E)*-ethylidene isomer from the alcohol XIIIb upon treatment with formic acid.

Conclusive evidence for the *(E)*-configuration was obtained from a Nuclear Overhauser experiment[18] with XVa, which was prepared from XIIb by selective dithioacetalisation, reduction with $NaBH_4$, and reduction of the dithioacetal moiety with sodium in liquid ammonia. Compound XVa looked the most appropriate 11-ethylidene derivative since the 12β-H gives a doublet at 2.85 ppm (*J* 13 Hz) completely free for accurate integration when the vinylic CH_3 doublet (δ 1.67 ppm, *J* 7 Hz) is irradiated. In this way a reproducible Overhauser effect of about 13% was found, confirming the *(E)*-configuration.

In the ring A aromatic series dehydration of the alcohol XVII (Chart III) yields exclusively the endocyclic olefin XVIII[2]. Introduction of the 11-methylene substituent by the Wittig reaction failed in this series, which might be attributed to fast C-9 proton abstraction of the relatively acidic 11-ketone XVI by the Wittig carbanion, thus preventing addition of the Wittig reagent[19] to the carbonyl group. Evidence for this assumption is the presence of an appreciable amount of the 9β-isomer XXI[20] in the reaction product. Examination of Dreiding models showed no greater steric hindrance in the Wittig addition product than in the 19-nor steroids mentioned previously.

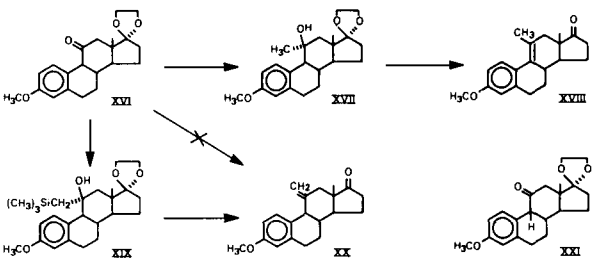

Chart 3

Peterson olefination reaction

A successful approach proved to be reaction of XVI with (trimethylsilyl)methylmagnesium chloride and decomposition of the product XIX into XX by a procedure described by Peterson[21]. The configuration at C-11 of XIX was assigned on the basis of the aromatic pattern and the position of the 13-CH_3 proton signal in the NMR spectrum (see Experimental Part). Moreover, attack of the bulky Grignard agent might be expected at the less hindered α-side. The most frequently used method in the literature to convert a β-silyl-alcohol to the olefin is treatment with base[21,22]. In the elimination reaction of XIX with NaH in tetrahydrofuran, however, only starting material was recovered. On the other hand, acid-catalysed elimination of XIX in acetone-HCl at

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[13] Ketalisation of Δ^4-estrene-3,17-dione under the same reaction conditions gave a mixture of $\Delta^{5(6)}$- and $\Delta^{5(10)}$-estrene-3,17-dione 3,17 diethylene acetal in a ratio 60:40 (NMR and GLC). See also: *N. N. Saha*, Steroids **12**, 735 (1968).

[14] Under the same reaction conditions 17β-hydroxy-Δ^5-androstene-3,11-dione 3-ethylene acetal and Δ^5-pregnene-3,11,20-trione 3,20-diethylene acetal failed to give the corresponding 11-methylene derivatives.

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[18] The NOE experiment was carried out by Mr. *Kruk* (Municipal University of Amsterdam) on a Varian HA-100 spectrometer.

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[20] An authentic sample of the 9β-isomer was made available by *M. van den Heuvel* of our laboratory.

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Table I Physical constants and analyses of compounds synthesised.

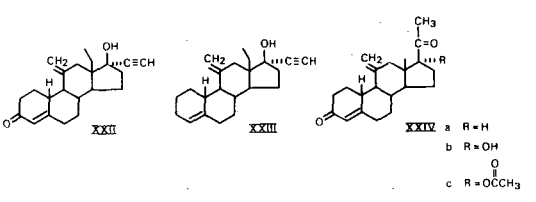
	Emperical formula	Mol weight	M.p.	$[\alpha]_D$	Analyses %					
					Found			Calc.		
Δ^5-estrene-3,11,17-trione, 3,17-diethylene acetal	$C_{22}H_{30}O_5$	374.46	189–190°C	+ 13°	C: 70.8	H: 8.1	O: 21.2	C: 70.56	H: 8.08	O: 21.36
11β-hydroxy-11α-methyl-Δ^4-estrene-3,17-dione	$C_{19}H_{26}O_3$	302.40	158–159°C	+ 88°	75.5	8.8	16.5	75.46	8.67	15.87
11-methylene-Δ^5-estrene-3,17-dione 3,17-diethylene acetal	$C_{23}H_{32}O_4$	372.49	206–209°C	+ 51°	73.9	8.6	17.6	74.16	8.66	17.18
11-methylene-Δ^4-estrene-3,17-dione[a]	$C_{19}H_{24}O_2$	284.38	200–202°C	+296°	80.1	8.6	10.9	80.24	8.52	11.25
17α-ethynyl-17β-hydroxy-11-methylene-Δ^4-estren-3-one[b]	$C_{21}H_{26}O_2$	310.42	212–213°C	+103°	81.3	8.5	10.5	81.25	8.44	10.31
11α-hydroxy-Δ^4-estren-17-one	$C_{18}H_{26}O_2$	274.39	130–131°C	+ 87°	79.0	9.5	11.3	78.79	9.55	11.66
Δ^4-estrene-11,17-dione	$C_{18}H_{24}O_2$	272.37	192–193°C	+288°	79.2	8.8	11.5	79.37	8.88	11.75
11β-hydroxy-11α-methyl-Δ^4-estren-17-one	$C_{19}H_{28}O_2$	288.41	161–163°C	+ 8°	79.3	9.6	11.0	79.12	9.79	11.10
11-methylene-Δ^5-estren-17-one	$C_{19}H_{26}O$	270.40	126–129°C	+170°	84.5	9.8	5.3	84.39	9.69	5.92
11-methylene-Δ^4-estren-17-one	$C_{19}H_{26}O$	270.40	140–143°C	+244°	84.2	9.7	5.8	84.39	9.69	5.92
11-methylene-Δ^4-estren-17β-ol	$C_{19}H_{28}O \cdot 1/3\ H_2O$[c]	278.41	144–145°C		82.2	10.4	7.8	81.95	10.38	7.66
17α-ethynyl-11-methylene-Δ^4-estren-17β-ol	$C_{21}H_{28}O$	296.44	143–145°C	+ 74°	85.1	9.7	5.8	85.08	9.52	5.40
17α-ethyl-11-methylene-Δ^4-estren-17β-ol	$C_{21}H_{32}O \cdot 1/2\ CH_3OH$[d]	316.49	83– 87°C	+126°	82.0	10.8	7.4	81.59	10.83	7.58
17β-hydroxy-11-methylene-Δ^4-estren-3-one 17β-phenylpropionate[e]	$C_{28}H_{34}O_3$	418.55	121–123°C	+138°	80.3	8.0	11.5	80.34	8.19	11.47
17α-ethynyl-11-methylene-Δ^5-estren-17β-ol	$C_{21}H_{28}O$	296.44	155–157°C	+ 1°	84.7	9.8	5.7	85.08	9.52	5.40
11-(E)-ethylidene-Δ^5-estrene-3,17-dione 3,17-diethylene acetal	$C_{24}H_{34}O_4$	386.51	172–175°C	+ 47°	74.7	8.9	16.7	74.57	8.87	16.56
11-(E)-ethylidene-Δ^4-estrene-3,17-dione[f]	$C_{20}H_{26}O_2$	298.41	191–193°C	+268°	79.8	8.8	10.9	80.49	8.78	10.72
11-(E)-ethylidene-Δ^4-estrene-3,17-dione 3-ethylene dithioacetal	$C_{22}H_{30}OS_2$	374.46	204–206°C	+234°	70.6	8.1	4.5	70.47	8.01	4.27
11-(E)-ethylidene-17β-hydroxy-Δ^4-estren-3-one 3-ethylene dithioacetal	$C_{22}H_{32}OS_2$	376.48	189–190°C	+187°	69.8	8.3	4.6	70.10	8.50	4.25
11-(E)-ethylidene-Δ^4-estren-17β-ol	$C_{20}H_{30}O$	286.44	139–141°C	+170°	83.8	10.8	5.7	83.86	10.56	5.59
11-(E)-ethylidene-Δ^4-estren-17-one	$C_{20}H_{28}O$	284.42	92– 93°C	+226°	84.6	10.1	5.5	84.45	9.92	5.63
11-(E)-ethylidene-17α-ethynyl-Δ^4-estren-17β-ol	$C_{22}H_{30}O$	310.46	oil	+ 54°						
11α-hydroxy-18-methyl-Δ^4-estrene-3,17-dione[g]	$C_{19}H_{26}O_3$	302.40	192–193°C	− 8°	75.6	8.7	16.0	75.46	8.67	15.87
18-methyl-11-methylene-Δ^5-estrene-3,17-dione 3,17-diethylene acetal	$C_{24}H_{34}O_4$	386.51	183–186°C	+ 36°	74.7	9.0	16.4	74.57	8.87	16.56
18-methyl-11-methylene-Δ^4-estrene-3,17-dione[h]	$C_{20}H_{26}O_2$	298.41	153–154°C	+223°	80.6	8.9	11.0	80.49	8.78	10.72
17α-ethynyl-17β-hydroxy-18-methyl-11-methylene-Δ^4-estren-3-one[i]	$C_{22}H_{28}O_2$	324.44	198–199°C	+ 84°	81.7	8.4	9.8	81.44	8.70	9.80
18-methyl-11-methylene-Δ^4-estrene-3,17-dione 3-ethylene dithioacetal	$C_{22}H_{30}OS_2$	374.46	185–187°C	+188°	70.3	8.2	4.6	70.56	8.08	4.27
18-methyl-11-methylene-Δ^4-estren-17-one	$C_{20}H_{28}O$	284.42	96– 99°C	+166°	84.5	10.1	5.4	84.45	9.92	5.63
17α-ethynyl-18-methyl-11-methylene-Δ^4-estren-17β-ol	$C_{22}H_{30}O$	310.46	109–110°C		85.2	9.8	4.9	85.11	9.74	5.15
3-hydroxy-$\Delta^{1,3,5(10)}$-estratriene-11,17-dione 3-methyl ether 17-ethylene acetal	$C_{21}H_{26}O_4$	342.42	106–110°C lit.[23] 122–123°C							
3-hydroxy-11-methylene-$\Delta^{1,3,5(10)}$-estratrien 17-one 3-methyl ether	$C_{20}H_{24}O_2$	296.39	173–179°C	+426°	81.1	8.4	10.5	81.04	8.16	10.80
17α-ethynyl-11-methylene-$\Delta^{1,3,5(10)}$-estratriene-3,17β-diol 3-methyl ether	$C_{22}H_{26}O_2$	322.43	194–198°C	+232°	81.8	8.4	10.1	81.95	8.13	9.92
Δ^4-19-nor-pregnene-3,11,20-trione	$C_{20}H_{26}O_3$	314.41	168–170°C lit.[24] 175–176°C	+283° +284°						
Δ^5-19-nor-pregnene-3,11,20-trione 3,20-diethylene acetal	$C_{24}H_{34}O_5$	402.51	153–155°C	+113°	71.7	8.5	20.2	71.61	8.51	19.88
11-methylene-Δ^4-19-nor-pregnene-3,20-dione[j]	$C_{21}H_{28}O_2$	312.44	167–169°C	+289°	80.6	9.0	10.5	80.73	9.03	10.24
17α-hydroxy-11-methylene-Δ^4-19-nor-pregnene-3,20-dione	$C_{21}H_{28}O_3$	328.44	188–190°C	+155°	76.7	8.6	14.3	76.79	8.59	14.61
17α-hydroxy-11-methylene-Δ^4-19-nor-pregnene-3,20-dione 17α-acetate[k]	$C_{23}H_{30}O_4$	370.47	195–197°C	+132°	74.7	8.2	17.2	74.56	8.16	17.28

[a] λ max 238 nm, ε 16400; [b] λ max 240 nm, ε 16200; [c] water content determined by Karl Fischer method 1.4%; [d] methanol content determined by glc 5.1%; [e] λ max 238 nm, ε 17000; [f] λ max 238 nm, ε 15600; [g] λ max 239 nm, ε 15820; [h] λ max 238 nm, ε 17200; [i] λ max 239 nm, ε 15600; [j] λ max 240 nm, ε 17200; [k] λ max 239 nm, ε 17300.

room temperature gave the 11-methylene compound XX in nearly quantitative yield without isomerisation to the more stable XVIII. Only 10% of isomerised product was detected by UV absorption when the 11-methylene compound XX was treated under the same dehydration conditions as the alcohol XVII in formic acid at room temperature, proving the direct formation of the $\Delta^{9(11)}$ compound XVIII in the dehydration reaction.

The compounds Vc, VII, XIIa, XIIb, XVb and XX were converted into several 17α-alkyl-substituted derivatives in good yields by the usual methods. In a similar way some 11-methylene derivatives in the 13-ethylestrene (XXII and XXIII) as well as in the 19-nor-pregnene series (XXIV) have been prepared.

Physical data of these compounds and of the intermediates from the syntheses are summarised in Table I.



[23] Dutch Patent Application 7,010,326.

[24] *A. Bowers, J. S. Mills, C. Casas-Campillo* and *C. Djerassi*, J. Org. Chem. **27**, 361 (1962).

Experimental part

In collaboration with Messrs. *H. M. van Alebeek, C. Bos, M. J. van den Heuvel.*
Elemental analyses were performed by Dr. *W. McMeekin*, Analytical Department Organon Labs, Newhouse, Scotland.
Melting points were taken in open capillaries on a Büchi-Tottoli apparatus and are uncorrected.
Optical rotations were measured at concentrations of about 1% in chloroform at 20°C.
U.V. spectra refer to solutions in 96% ethanol.
IR spectra (in cm^{-1}) were recorded in solutions (methylene dichloride or carbon tetrachloride) on a Perkin-Elmer Model 357 spectrophotometer, equipped with a grating.
NMR spectra were obtained with Varian A-60 or Bruker HX-90E spectrometer. Chemical shifts are reported in ppm relative to TMS as the internal standard and coupling constants in Hz. The analytical data are given in Table 1.

11α-Hydroxy-Δ⁴-estrene-3,17-dione 3-ethylene dithioacetal (IIa)

Ethanedithiol (40 ml) was added to a boiling solution of 100.0 g of 11α-hydroxy-Δ⁴-estrene-3,17-dione (Ia) in 100 ml of methanol and 15 ml of BF_3 etherate, refluxed for 30 minutes and cooled to 20°C. The precipitate was filtered off, washed with cold methanol and water, giving 111.0 g of IIa; m.p. 255–258°C; $[\alpha]_D$ +110°.
IR (CH_2Cl_2): 3623 (ν OH); 1739 (ν C(17)=O); 1404 (ν C(16)H_2); 999 (ν OH).

11α-Hydroxy-Δ⁴-estren-17-one (IIIb)

A mixture of 100.0 g of 11α-hydroxy-Δ⁴-estrene-3,17-dione 3-ethylene dithioacetal (IIa), 930 ml of toluene, 52 ml of ethylene glycol, 60 ml of ethyl orthoformate and 2.0 g of *p*-toluenesulfonic acid was refluxed for 3 hours, cooled to room temperature, made alkaline with aqueous $NaHCO_3$ solution, and the organic layer separated. The toluene extract was washed with water and evaporated *in vacuo* to yield 117.0 g of oily 11α-hydroxy-Δ⁴-estrene-3,17-dione 3-ethylene dithioacetal 17-ethylene acetal (IIb).
Without further purification, a solution of 117.0 g of IIb in 450 ml of tetrahydrofuran was added to a solution of 12.5 g of lithium in 1500 ml of liquid NH_3 over 1 hour. After stirring for another hour the excess of lithium was decomposed by a mixture of hexane and ethanol, ammonia was evaporated and the residue extracted into hexane, washed with water and evaporated to dryness.
The residue was dissolved in 370 ml of acetone and stirred with 125 ml of 2 *N* HCl for 3 hours at room temperature.
Extraction with methylene chloride and crystallisation from diethyl ether gave 62.0 g of IIIb; m.p. 130–131°C; $[\alpha]_D$ +87°.
NMR ($CDCl_3$): 5.48 ppm/broad singlet (4-H); 3.87 ppm/m (11β-H); 0.90 ppm/s (13-CH_3).

Δ⁴-Estrene-11,17-dione (IVa)

52 Ml of 8 *N* CrO_3 were added dropwise over 10 minutes to a solution of 45.0 g of 11α-hydroxy-Δ⁴-estren-17-one (IIIb) in 340 ml of acetone cooled to −10°C, stirred for another 20 minutes, methanol added and the reaction mixture concentrated to 500 ml. After dilution with water the crystals were collected and recrystallised from methylene chloride-ethanol giving 34.0 g of IVa; m.p. 192–193°C; $[\alpha]_D$ +288°.
IR (CH_2Cl_2): 1742 (ν C(17)=O); 1706 (ν C(11)=O); 1406 (ν C(16)H_2); (CS_2): 809 (ν Δ⁴).

Δ⁴-Estrene-11,17-dione 17-ethylene acetal (IVb)

A mixture of 10.0 g of Δ⁴-estrene-11,17-dione (IVa), 150 ml of methylene chloride, 7 ml of ethylene glycol, 8 ml of ethyl orthoformate and 0.3 g of *p*-toluenesulfonic acid was refluxed for 3 hours and gave in the usual way 11.5 g of Δ⁴-estrene-11,17-dione 17-ethylene acetal (IVb), satisfactorily pure for the next step.

11α-Methyl-11β-hydroxy-Δ⁴-estren-17-one (Vb)

A solution of 11.5 g of crude Δ⁴-estrene-11,17-dione 17-ethylene acetal (IVb) in 190 ml of dry benzene was added to a Grignard solution prepared from 14.3 g of magnesium turnings in 320 ml of diethyl ether to which 40 ml of methyl iodide were added drop by drop.
The reaction mixture was refluxed for 3 hours, cooled to room temperature and poured into an ice-cold aqueous ammonium chloride solution. Extraction with methylene chloride, washing with water and evaporation gave an oily residue of 11α-methyl-11β-hydroxy-Δ⁴-estren-17-one 17-ethylene acetal (Va).
Crude Va was dissolved in 250 ml of acetone and kept at room temperature with 4.0 ml of 2 *N* HCl for 2 hours.
Working up by extraction with methylene chloride and crystallisation from the same solvent gave 11.1 g of 11α-methyl-11β-hydroxy-Δ⁴-estren-17-one (Vb); m.p. 157–160°C; $[\alpha]_D$ +8°.
NMR ($CDCl_3$): 5.32 ppm/broad singlet (4-H); 1.44 ppm/s (11-CH_3); 1.09 ppm/s (13-CH_3).

Acidic dehydration of 11α-methyl-11β-hydroxy-Δ⁴-estren-17-one (Vb)

A solution of 10.0 g of 11α-methyl-11β-hydroxy-Δ⁴-estren-17-one (Vb) in 400 ml of formic acid was left at room temperature for 24 hours, then poured into ice-water and extracted with methylene chloride, washed with water, dried and evaporated to dryness.
The residue, dissolved in a mixture of toluene: ethyl acetate 97 : 3, was chromatographed on a column with 270 g of silicagel and eluted with the same solvent mixture. Fractions showing one spot on tlc in the system toluene/ethyl acetate 97 : 3 were combined. As the oily residue (5.3 g) could not be induced to crystallize it was dissolved again in toluene/ethyl acetate 97 : 3 and chromatographed on a column with 300 g of silicagel impregnated with 15% of silver nitrate. 25 × 50 ml fractions were collected and the crystalline fractions 14/16 (1.7 g) were purified further by crystallisation from acetonitrile giving 0.47 g of pure 11-methylene-Δ⁵-estren-17-one (VII); m.p. 126–129°C; $[\alpha]_D$ +170°.
The oily fraction 11 consisted mainly of the conjugated diene VI (UV and NMR).
VI NMR ($CDCl_3$): 1.77 ppm/broad singlet (11-CH_3); 0.84 ppm/s (13-CH_3). UV: Emol = 10400 at 242 nm (ethanol).
VII NMR ($CDCl_3$): 5.40 ppm/broad doublet (6-H); 4.88 ppm/s (11-CH_2); 0.79 ppm (13-CH_3).

11-Methylene-Δ⁴-estren-17-one (Vc)

In a nitrogen atmosphere a mixture of 4.1 g of NaH (50% oil dispersion) and 70 ml of dry dimethyl sulfoxide was heated at 70°C until evolution of hydrogen ceased. After cooling to room temperature a solution of 33.0 g of methyltriphenylphosphonium bromide in 120 ml of dry dimethyl sulfoxide was added followed by a solution of 5.0 g of Δ⁴-estrene-11,17-dione 17-ethylene acetal (IVb) in 35 ml of benzene. The reaction mixture was stirred at 60°C for 22 hours, cooled to room temperature, poured into ice-water and extracted with benzene. The benzene extract was washed with water and evaporated to dryness. To remove the triphenylphosphine oxide the residue was dissolved in a mixture of methanol/water/cyclohexane 13 : 7 : 20; the cyclohexane layer was separated and the aqueous methanol layer re-extracted 4 times with cyclohexane. The combined cyclohexane extracts were evaporated to dryness, the residue was hydrolysed in 100 ml of acetone with 2 ml of 2 *N* HCl at room temperature for 2 hours, the reaction mixture was poured into water and the precipitate was filtered off and recrystallised from diethyl ether giving 2.6 g of 11-methylene-Δ⁴-estren-17-one (Vc); m.p. 140–143°C; $[\alpha]_D$ +244°.
NMR ($CDCl_3$): 5.52 ppm/broad singlet (4-H); 4.90 ppm/broad singlet (11-CH_2); 0.84 ppm/s (13-CH_3).

11-Methylene-Δ⁵-estren-17-one (VII)

To a solution of 100 mg of Δ⁵-estrene-11α,17β-diol (VIII) in 4.0 ml of acetone was added dropwise 0.22 ml of 8 *N* CrO_3 at −10°C.
After stirring for 15 minutes the reaction mixture was diluted with water; the crystals were collected giving 80 mg of the diketone IXa.
Without further purification, 80 mg of the diketone IXa was refluxed in a mixture of 1 ml of methylene chloride, 0.1 ml of ethylene glycol, 0.1 ml of ethyl orthoformate and 3 mg of *p*-toluenesulfonic acid for 3 hours. Extraction gave an oily residue of 85 mg of Δ⁵-estrene-11,17-dione 17-ethylene acetal IXb.
A solution of 85 mg of the crude IXb in 1 ml of dry benzene was added to the Wittig reagent prepared from 620 mg of methyltriphenylphosphonium bromide in 4 ml of dry dimethyl sulfoxide and 80 mg of NaH (50% oil dispersion) in 1 ml of dimethyl sulfoxide. The reaction mixture was stirred at 60°C for 20 hours. Extraction with methylene chloride and treatment of the residue in acetone-HCl gave 60 mg of crude VII. This material was purified by thick layer chromatography giving 8 mg of pure VII with m.p. 126–128°C and spectroscopically fully identical with the compound isolated from the acidic dehydration of the alcohol Vb.

11α-Hydroxy-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (Xa)

A mixture of 50.0 g of 11α-hydroxy-Δ⁴-estrene-3,17-dione (Ia), 575 ml of methylene chloride, 375 ml of ethylene glycol, 170 ml of ethyl orthoformate and 0.5 g of *p*-toluenesulfonic acid was refluxed for 4 hours, cooled to room temperature, and washed with an aqueous K_2CO_3 solution and with water until neutral. The extract was dried over anhydrous Na_2SO_4, and evaporated to dryness, yielding 65.0 g of Xa, sufficiently pure for the oxidation step to Xb.

Δ⁴-Estrene-3,11,17-trione (Ib)

To a solution of 200.0 g of 11α-hydroxy-Δ⁴-estrene-3,17-dione (Ia) in 12 l of acetone, 216 ml of 8 *N* CrO_3 were added dropwise at −10°C over 10 minutes. Stirring was continued for 10 minutes at −10°C and the excess of CrO_3 was decomposed by addition of 50 ml of methanol. The reaction mixture was concentrated to 2 l, diluted with water and the resulting crystals were collected giving 163.0 g of Ib with m.p. 202–205°C; lit.[7]: m.p. 208–210°C.

Δ⁵-Estrene-3,11,17-trione 3,17-diethylene acetal (Xb)

a) 160.0 g of Δ⁴-estrene-3,11,17-trione (Ib) was acetalised in a similar way to that described for Ia to Xa. Triturating the crude diethylene acetal with diethyl ether gave 155.0 g of Xb; m.p. 187–188°C. An analytically pure sample melted at 189–190°C; $[\alpha]_D$ +13°. NMR (pyridine-d_5): 5.47 ppm/broad doublet (6-H); 3.88 ppm/s (3-ethylene acetal); 3.79 ppm/m (17-ethylene acetal); 2.52 ppm/AB, JAB 12 Hz ($C(12)H_2$); 0.87 ppm/s (13-CH_3).
b) To a solution of 65.0 g of the crude 11α-hydroxy-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (Xa) was added dropwise 54 ml of 8 *N* CrO_3 at −10°C over 10 minutes. Stirring for 10 minutes at this temperature and working up in the usual way gave, upon crystallisation from methylene chloride-diethyl ether (+drop of pyridine), 39.7 g of Xb; m.p. 182–186°C.

11-Methylene-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (XIa)

A solution of 18.0 g of Δ⁵-estrene-3,11,17-trione 3,17-diethylene acetal (Xb) in 180 ml of dry benzene was added to the Wittig reagent, prepared from 12.6 g of NaH (50% oil dispersion) in 216 ml of dry dimethyl sulfoxide and 105 g of methyltriphenylphosphonium bromide in 480 ml of dry dimethyl sulfoxide, and stirred for 3 hours at 70°C. The reaction mixture was poured into ice-water and the precipitate was filtered off. The wet precipitate was dissolved in a mixture of methanol/water/cyclohexane 13:17:20; the cyclohexane layer was separated and the aqueous methanol layer reëxtracted 4 times with cyclohexane. The cyclohexane extract was evaporated to dryness and the resulting residue was crystallised several times from methylene chloride-methanol (+drop of pyridine) yielding 15.9 g of XIa; m.p. 206–209°C; $[\alpha]_D$ +51°.
NMR ($CDCl_3$ + drop of pyridine-d_5): 5.48 ppm/broad doublet (6-H); 4.82 ppm/broad singlet (11-CH_2); 3.96 ppm/s (3-ethylene acetal); 3.90 ppm/broad singlet (17-ethylene acetal); 0.77 ppm/s (13-CH_3).

11β-Hydroxy-11α-methyl-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (XIIIa)

To a solution of 15.0 g of Δ⁵-estrene-3,11,17-trione 3,17-diethylene acetal (Xb) in 225 ml of benzene and 150 ml of diethyl ether was added dropwise 44 ml of a 2 *M* solution of CH_3Li in diethyl ether. After stirring for 3 hours at room temperature, the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed with water, evaporated to dryness, and the residue crystallised from methylene chloride-methanol yielding 13.1 g of the alcohol XIIIa: m.p. 182–190°C.

11-Methylene-Δ⁴-estrene-3,17-dione (XIIa)

a) A suspension of 15.0 g of 11-methylene-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (XIa) in 300 ml of acetone was treated with 1.6 ml of 36% HCl for 2 hours at room temperature. The reaction mixture was poured into 3 l of ice-water and the precipitate was filtered off. Crystallisation from diethyl ether gave 9.8 g of XIIa; m.p. 200–202°C; $[\alpha]_D$ +296°. NMR ($CDCl_3$): 5.88 ppm/broad singlet (4-H); 4.94 ppm/d, *J* 8 Hz (11-CH_2); 0.90 ppm/s (13-CH_3).
b) A solution of 10.0 g of 11β-hydroxy-11α-methyl-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal in 400 ml of formic acid was kept at 50°C for 24 hours. The reaction mixture was concentrated *in vacuo* to 80 ml and diluted with water. The crystals were collected and recrystallised from diethyl ether giving 4.7 g of XIIa; m.p. 200–202°C.

11(E)-Ethylidene-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (XIb)

To the ethylidenetriphenylphosphorane reagent obtained by reacting 180 g of ethyltriphenylphosphonium iodide in 800 ml of dimethyl sulfoxide with 21 g of NaH (50% oil dispersion) in 360 ml of dimethyl sulfoxide, were added 30 g of Δ⁵-estrene-3,11,17-trione 3,17-diethylene acetal (Xb) in 300 ml of benzene. After stirring for 22 hours at 60°C the reaction mixture was worked up by extraction with benzene. The benzene extract was evaporated and chromatographed on silicagel. Elution with toluene: ethyl acetate 8:2 and crystallisation from ethanol gave 8.4 g of XIb; m.p. 172–175°C; $[\alpha]_D$ +47°.
NMR ($CDCl_3$ + drop of pyridine-d_5): 5.47 ppm/broad doublet (6-H); 5.38 ppm/m (11 = CH−); 1.64 ppm/d, *J* 6 Hz (vinylic CH_3); 0.75 ppm/s (13-CH_3).

11(E)-Ethylidene-Δ⁴-estrene-3,17-dione (XIIb)

a) A suspension of 8.4 g of 11*(E)*-ethylidene-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (XIb) in 170 ml of acetone was stirred with 0.8 ml of 36% HCl for 2 hours.
Dilution with water, extraction with methylene chloride and crystallisation from methylene chloride-diethyl ether yielded 4.0 g of XIIb; m.p. 191–193°C; $[\alpha]_D$ +268°. NMR ($CDCl_3$): 5.93 ppm/broad singlet (4-H); 5.52 ppm/m (11 = CH−); 1.70 ppm/d, *J* 6.5 Hz (vinylic CH_3); 0.85 ppm/s (13-CH_3).
b) 30 ml of 1.68 M C_2H_5Li solution in diethyl ether were added dropwise to a solution of 8.0 g of Δ⁵-estrene-3,11,17-trione 3,17-diethylene acetal (Xb) in a mixture of 88 ml of dry benzene and 112 ml of dry diethyl ether cooled to −10°C. Stirring was continued for 30 minutes and the reaction mixture was then poured into ice-water. The organic layer was separated, washed with water, and evaporated giving a residue of 8.5 g of crude 11α-ethyl-11β-hydroxy-Δ⁵-estrene-3,17-dione 3,17-diethylene acetal (XIIIb).
Without further purification, 8.5 g of XIIIb were dissolved in 300 ml of formic acid and stirred for 6 hours at 50°C. The reaction mixture was poured into ice-water and the crystals were collected, giving 3.4 g of XIIb fully identical in NMR and IR analyses with the product obtained via the Wittig reaction.

3,11β-Dihydroxy-11α-(trimethylsilylmethyl)-Δ$^{1,3,5(10)}$-estratrien-17-one 3-methyl ether 17-ethylene acetal (XIX)

A solution of 31.5 ml of (chloromethyl)trimethylsilane in 80 ml of dry diethyl ether was added dropwise to a suspension of 5.8 g of magnesium turnings in 80 ml of dry diethyl ether over about 1 hour, keeping the reaction mixture just at reflux temperature without external heating. A solution of 10.0 g of 3-hydroxy-Δ$^{1,3,5(10)}$-estratriene-11,17-dione 3-methyl ether 17-ethylene acetal (XVI) in 500 ml of dry diethyl ether was added, and the reaction mixture was refluxed for 5 hours. After stirring overnight at room temperature the mixture was poured into ice-water containing 40 g of NH_4Cl. The product was extracted with methylene chloride, and the extract washed with water, dried, evaporated, and crystallised from methanol (+drop of pyridine) giving 7.1 g of XIX; m.p. 143–144°C; $[\alpha]_D$ −72°.
NMR ($CDCl_3$): 1.08 ppm/s (13-CH_3); 0.07 ppm/s ($(CH_3)_3SiCH_2$−); 3.89 ppm/broad singlet (ethylene acetal); 3.77 ppm/s (3-OCH_3); 7.83 ppm/m (1-H); 6.72 ppm/m (2-H and 4-H).

3-Hydroxy-11-methylene-Δ$^{1,3,5(10)}$-estratrien-17-one 3-methyl ether (XX)

7.0 g of 3,11β-dihydroxy-11α-(trimethylsilylmethyl)-Δ$^{1,3,5(10)}$-estratrien-17-one 3-methyl ether 17-ethylene acetal (XIX) was suspended in 140 ml of acetone and 0.4 ml of 36% HCl and stirred overnight at room temperature in a nitrogen atmosphere. The reaction mixture was neutralised with sodium acetate, concentrated *in vacuo* to 50 ml and diluted with water. The crystals were collected and recrystallised from acetone giving 4.8 g of XX; m.p. 173–179°C; $[\alpha]_D$ +426°.
NMR ($CDCl_3$): 7.27 ppm/d, *J* 9 Hz (1-H); 6.72 ppm/double doublet J_{12} 9 Hz, J_{24} 2.5 Hz (2-H); 6.65 ppm/d, J_{24} 2.5 Hz (4-H); 4.95 ppm/broad singlet (11-CH_2); 3.77 ppm/s (3-OCH_3); 0.89 ppm/s (13-CH_3).

Acknowledgement

Thanks are due to Mr. *W. A. M. de Groot*, Drs. *A. J. M. Weber* and Mr. *F. A. Nagel* for interpretation of the IR and NMR spectra. We are grateful to Dr. *F. J. Zeelen* and Prof. *Hewett* for constructive criticism during the preparation of the manuscript.