Synthesis of 9,11-Disubstituted 19-Nor-steroids

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Reaction of a 9α-methyl-11-oxoestrone derivative (I) with methylmagnesium bromide gave the 11α-methyl-11β-hydroxy-compound (II). This could be dehydrated with acid to an olefin, shown to be an 11,11-dimethyl-$\Delta^{8,9}$-steroid, or converted into its acetate and pyrolysed to give a 9α-methyl-11-methylene derivative as the major product. Hydrogenation of this last material gave a 9α,11β-dimethyl derivative. All three substituted skeletons were converted into other 19-nor-compounds, in particular, the 17α-ethynyl-17β-hydroxy-4-en-3-ones (XVII), (XXV), and (XXXIX).

A CONTINUING interest in the pharmacological activities of potential steroid hormones bearing nuclear alkyl substituents encouraged us to investigate further the chemical transformations of the 9α-methyl-11-oxo-system, the preparation of which we have described earlier.[1]

The 11-oxoestrone derivative (I) reacted with methylmagnesium bromide to give as a single product in high yield the tertiary alcohol (II). The 11α-methyl-11β-hydroxy-configuration was assigned on the basis of a comparison of the n.m.r. spectra of compound (II) and the derived 17-ketone (III) with those of the corresponding known compounds [2] (IV) and (V), lacking the 9α-methyl group [Table 1; data for the isomeric 11β-methyl-11α-hydroxy-compound (see later) are also included]. Presumably the relatively low-field positions of the 11α-methyl signals reflect the fact that this group lies essentially in the plane of the aromatic ring in this orientation.

Treatment of the tertiary alcohol (III) with toluene-*p*-sulphonic acid in refluxing toluene led to the smooth elimination of water and the formation of two products in the ratio *ca.* 4 : 1. The major one could be isolated directly by crystallisation and its n.m.r. spectrum showed three singlet *C*-methyl signals. Furthermore, no olefinic proton signals could be seen, suggesting that the newly generated double bond must be fully substituted. A possible structure is thus (VII), incorporating the 11,11-dimethyl-$\Delta^{8,9}$-structure. This was substantiated by its u.v. spectrum which exhibited a maximum at 276 nm, in agreement with the value [3] for the corresponding 11-unsubstituted compound.

TABLE 1

Chemical shifts (τ values) for compounds (II)—(VI)

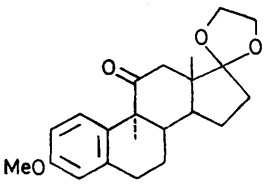
	C(18)H_3	11-CH_3	9α-CH_3
(II)	8·92	8·38	8·78
(III)	8·90	8·33	8·82
(IV)	8·90	8·36	
(V)	8·89	8·34	
(VI)	9·02	8·79	8·79

[1] R. V. Coombs, J. Koletar, R. Danna, H. Mah, and E. Galantay, *J.C.S. Perkin I*, 1973, 2095.

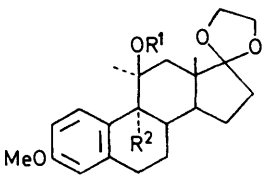
[2] J. S. Baran, H. D. Lennon, S. E. Mares, and E. F. Nutting, *Experientia*, 1970, **26**, 762.

[3] G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 1963, 5072.

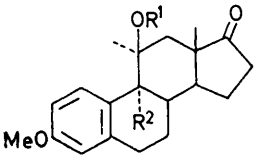
The minor product was not isolated in a pure state but since the n.m.r. spectrum of the product mixture showed



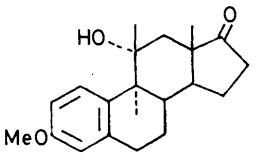
(I)



(II) R^1 = H, R^2 = Me
(IV) R^1 = H, R^2 = H
(XIX) R^1 = Ac, R^2 = Me



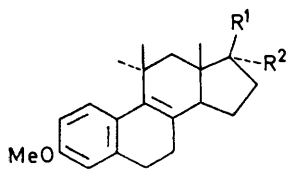
(III) R^1 = H, R^2 = Me
(V) R^1 = H, R^2 = H
(XVIII) R^1 = Ac, R^2 = Me



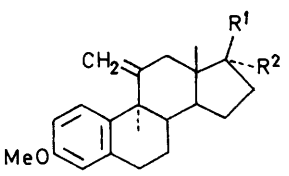
(VI)

a signal centred at τ 5·20, it was probably the 11-methylene compound (VIII). This was confirmed by comparison of the crude material with the pure compound prepared by a superior route (see later).

Reduction of the 17-oxo-steroid (VII) with sodium borohydride gave the 17-hydroxy-compound (IX), which was in turn reduced with sodium in liquid ammonia in the presence of aniline.[3] The product could not be obtained crystalline, but exhibited a u.v. spectrum typical of an estradiol derivative. However, the derived 17β-acetate could be crystallised and was fully characterised. The overall structure was readily confirmed as (XI), but the question of the stereochemistry



(VII) R^1R^2 = O
(IX) R^1 = OH, R^2 = H

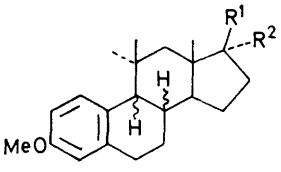


(VIII) R^1R^2 = O
(XX) R^1R^2 = O·CH_2·CH_2·O
(XXI) R^1 = OH, R^2 = H

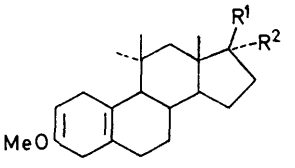
at C-8 and -9 remained unanswered. A possible solution would have involved the replacement of the 11-oxo-group in 17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-11-one by a *gem*-dimethyl group, and attempts were made to use a recently reported procedure [4] to effect such a change. Unfortunately, the 11-oxo-group proved extremely unreactive to most reagents and these efforts were not successful. Recourse was made, therefore, to an *X*-ray analysis of the acetate (XI) * and the results not only confirmed the overall structure but also indicated that the skeletal stereochemistry was 'normal,' *i.e.* 8β-H and 9α-H. For the purpose of biological comparison with estrone 3-methyl ether, the estradiol derivative (X) was oxidised with Jones reagent [5] to 11,11-dimethylestrone 3-methyl ether † (XII).

Pursuing the aim of synthesising derivatives for which hormonal properties might be anticipated, the estradiol derivative (IX) was subjected to the normal Birch reduction [6] to give the dihydro-compound (XIII), which was then oxidised under Oppenauer conditions [7] to the 17-ketone (XIV). In one instance the dihydro-compound (XIV) was treated directly with methanolic hydrogen chloride to give the required 4-ene-3,17-dione (XV), whereas in another it was first treated with the lithium acetylide–ethylenediamine complex,[8] giving the 17α-ethynyl derivative (XVI); this reacted with methanolic hydrogen chloride to afford the 4-en-3-one (XVII), the 11,11-dimethyl analogue of Norethindrone.

As an alternative to the acidic dehydration of the tertiary alcohol (III), it was decided to pyrolyse the



(X) R^1 = OH, R^2 = H
(XI) R^1 = OAc, R^2 = H
(XII) R^1R^2 = O



(XIII) R^1 = OH, R^2 = H
(XIV) R^1R^2 = O
(XVI) R^1 = OH, R^2 = C≡CH

derived acetate. The alcohol was therefore heated with calcium hydride in acetic anhydride under reflux [9] to give, on work-up, the crystalline acetate (XVIII), which was itself heated at 250° and 15 mmHg. The product was once more a mixture of the same two olefins as from the dehydration but although the ratio remained approximately the same, the previous minor product was now the major one. Thus the 11-methylene compound (VIII) could readily be isolated by crystallisation. Additionally, the 17-acetal (II) could be similarly acetylated and the acetate so formed (XIX) pyrolysed to afford the 11-methylene compound (XX).

The 9α-methyl-11-methylene-estrone (VIII) was subjected to the same sequence of reactions as used for the

* Performed by Dr. H. P. Weber, Sandoz, Basel. The analysis will be published in detail elsewhere.

† The pharmacological activities of these compounds will be reported elsewhere.

[4] F. E. Zielger and P. A. Wender, *J. Amer. Chem. Soc.*, 1971, **93**, 4318.

[5] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2555.

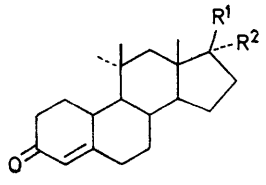
[6] H. F. Dryden, jun., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, 1961, **26**, 3237.

[7] C. Djerassi, *Org. Reactions*, 1951, **6**, 207.

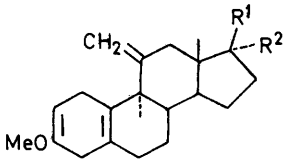
[8] O. F. Beumel, jun., and R. F. Harris, *J. Org. Chem.*, 1964, **29**, 1872.

[9] R. V. Oppenauer, *Monatsh.*, 1966, **97**, 62.

11,11-dimethyl skeleton, *i.e.* sodium borohydride reduction to (XXI), Birch reduction to (XXII), Oppenauer oxidation to (XXIII), reaction with lithium



(XV) $R^1R^2 = O$
(XVI) $R^1 = OH, R^2 = C{\equiv}CH$



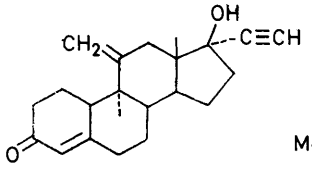
(XXII) $R^1 = OH, R^2 = H$
(XXIII) $R^1R^2 = O$
(XXIV) $R^1 = OH, R^2 = C{\equiv}CH$

acetylide to give (XXIV), and treatment with methanolic hydrogen chloride to yield the desired conjugated ketone (XXV).

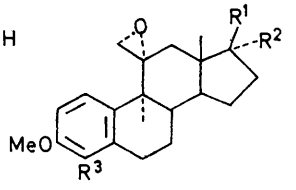
Treatment of the 11-methylene steroid (VIII) with *m*-chloroperbenzoic acid gave two products which could be separated by chromatography. The less polar, major component was shown from its elemental analysis to have incorporated a single additional oxygen atom and all spectral evidence was in agreement with the epoxide structure (XXVI). The α-stereochemistry is favoured since attack of reagents from this face is consistent with all reactions of 11-oxo- and 11-methylene-9α-methyl steroids studied in this series. The minor component gave a molecular ion indicating the incorporation of a second oxygen atom and from its n.m.r. spectrum it was seen that only two aromatic protons were present. These constituted an AX system with chemical shifts τ 3·36 and 2·60 and *J ca.* 8·5 Hz, characteristic of *ortho*-substitution on a benzene ring. A reasonable structure is, therefore, that of the epoxyphenol (XXVII).

From a similar epoxidation of the 11-methylene-17β-hydroxy-steroid (XXI), only the main product, the epoxide (XXVIII), was isolated.

Reductive cleavage of the epoxide ring in (XXVIII)



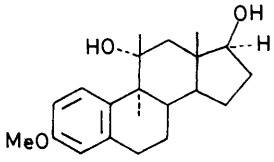
(XXV)



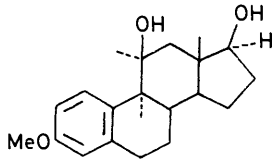
(XXVI) $R^1R^2 = O, R^3 = H$
(XXVII) $R^1R^2 = O, R^3 = OH$
(XXVIII) $R^1 = OH, R^2 = R^3 = H$

with lithium aluminium hydride led to the diol (XXIX). This could also be obtained by reduction of the epoxide (XXVI) with excess of the reagent. Two comparisons were now made between these tertiary alcohols resulting from the α-epoxides and those produced initially from the Grignard reaction of the 11-oxo-compounds. First, the 17-ketone (III) was reduced with sodium borohydride to the 11,17-diol (XXX), which was contrasted with diol (XXIX), and secondly the diol (XXIX) was oxidised under Oppenauer conditions to the 17-ketone (VI) which was contrasted, as already described, with the 17-ketone (III). These interconversions fully support the designation of the assigned isomeric structures and the secondary and tertiary nature of the 17- and 11-hydroxy-functions, respectively.

One further isomeric diol, the 17β-hydroxy-11β-hydroxymethyl steroid (XXXI), was prepared by treatment of the 11-methylene compound (XXI) with diborane followed by sodium hydroxide–hydrogen peroxide in the usual way. Its structure is assigned from spectral evidence and the known [10] mode of reaction of diborane with exocyclic olefins.

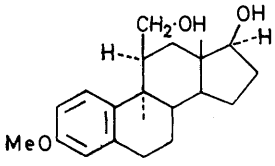


(XXIX)

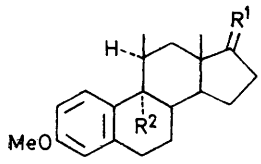


(XXX)

Finally, with the aim of producing the 9,11-dimethyl skeleton, the hydrogenation of the 11-methylene group was investigated. Reduction over palladium–carbon



(XXXI)



(XXXII) $R^1 = O, R^2 = Me$
(XXXIII) $R^1 = O{\cdot}CH_2{\cdot}CH_2{\cdot}O, R^2 = Me$
(XXXIV) $R^1 = O, R^2 = H$

proceeded rapidly with either the 11-methylene-17-oxo-compound (VIII) or the corresponding 17-acetal (XX) to give the dimethyl product (XXXII) or (XXXIII), which could be simply interconverted. In view of the previously described reactions of the 11-methylene group the products would be anticipated to have the 9α,11β-dimethyl stereochemistry and although no conclusive evidence is available on this point, strong support is lent once more by a spectral comparison with the known [2] 11β-methyl-9αH-compound (XXXIV) (Table 2). Further, as in the 11-hydroxy-11-methyl

TABLE 2

N.m.r. data (τ values) for compounds (XXXII) and (XXXIV)

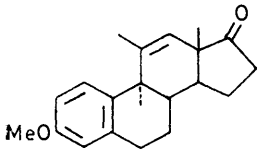
	$C(18)H_3$	11β-CH_3 (centre of d)	9α-CH_3
(XXXII)	8·99	9·10	8·82
(XXXIV)	8·97	9·11	

examples, the high τ value for the 11-methyl group in these two cases encourages the conclusion that it prob-

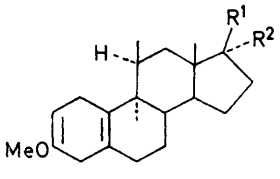
[10] H. C. Brown, ' Hydroboration,' Benjamin, New York, 1962, p. 115.

ably does *not* lie in the plane of the aromatic ring, *i.e.* it is β-oriented.

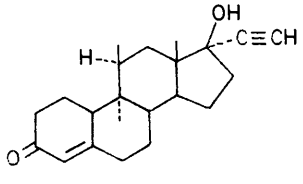
In one repetition of the hydrogenation of a rather impure, non-crystalline, sample of the 11-methylene compound (VIII) work-up gave a first crop of crystalline material in low yield which proved not to be the expected dimethyl product. In fact its mass spectrum indicated that it was not a dihydro-derivative, but rather an isomer of the 11-methylene starting material. The n.m.r. spectrum was especially revealing, showing in particular a *C*-methyl signal at τ 7·95 which was just resolved into a doublet, and a one-proton signal at τ 4·04 being almost a singlet. It seems, therefore, that this isomer is the 9α,11-dimethyl-$\Delta^{11,12}$-steroid (XXXV). Subsequent attempts to isolate further quantities from either the dehydration or the pyrolysis reactions were not successful.



(XXXV)



(XXXVI) R^1 = OH, R^2 = H
(XXXVII) R^1R^2 = O
(XXXVIII) R^1 = OH, R^2 = C≡CH



(XXXIX)

The 9α,11β-dimethylestrone derivative (XXXII) was put through the sequence of reactions: Birch reduction to (XXXVI), Oppenauer oxidation to (XXXVII), reaction with lithium acetylide to give (XXXVIII) and finally, immediate treatment of this crude product with methanolic hydrogen chloride. Thus was obtained the third potential progestational hormone, the conjugated ketone (XXXIX).

EXPERIMENTAL

M.p.s were determined on a Thomas–Hoover capillary apparatus. I.r. spectra were measured on a Perkin-Elmer 457 spectrophotometer and n.m.r. spectra for solutions in deuteriochloroform (tetramethylsilane as internal standard) on a Varian A-60 or T-60 instrument. Optical rotations refer to solutions in chloroform.

17,17-*Ethylenedioxy*-3-*methoxy*-9α,11α-*dimethylestra*-1,3,5(10)-*trien*-11β-*ol* (II).—To a solution of the 11-ketone [1] (I) (5·1 g) in tetrahydrofuran (50 ml), stirred under nitrogen, was slowly added 2·0M-methylmagnesium bromide in tetrahydrofuran (30 ml). The resulting solution was heated under reflux for 2 h, cooled, and poured on ice. It was then extracted with ether and the extract was washed with brine and water, dried, and evaporated. The residue was crystallised from methanol to give the *dimethyl compound* (II) (4·2 g), m.p. 108—110°, $[\alpha]_D$ +99·9° (*c* 0·90), τ 8·92 [C(18)H_3], 8·78 [C(9α)CH_3], 8·38 [C(11α)CH_3], 6·26 [C(3)-OCH_3], and 6·10 [C(17)O·CH_2·CH_2·O] (Found: C, 74·5; H, 8·3. $C_{22}H_{32}O_4$ requires C, 74·2; H, 8·1%).

11β-*Hydroxy*-3-*methoxy*-9α,11α-*dimethylestra*-1,3,5(10)-*trien*-17-*one* (III).—A solution of the 17,17-ethylenedioxy-derivative (II) (4·2 g) in aqueous 80% acetic acid (30 ml) was maintained at 60° for 30 min. It was then cooled, diluted with water (100 ml), and extracted with ether. The extract was washed with aqueous 10% sodium hydrogen carbonate and water, dried, and evaporated. The residue was crystallised from ether to give the 17-*ketone* (III) (3·1 g), m.p. 170—172°, $[\alpha]_D$ +214·6° (*c* 0·83), τ 8·90 and 8·82 [C(18)H_3 and C(9α)CH_3], 8·33 [C(11α)CH_3], and 6·23 [C(3)OCH_3] (Found: C, 77·0; H, 8·7. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

3-*Methoxy*-11,11-*dimethylestra*-1,3,5(10),8(9)-*tetraen*-17-*one* (VII).—To a solution of the hydroxy-compound (III) (3·3 g) in toluene (225 ml) was added toluene-*p*-sulphonic acid (580 mg), and the solution was heated under reflux in an atmosphere of nitrogen for 4 h (Dean–Stark trap). It was then cooled, washed with aqueous sodium hydrogen carbonate, and evaporated to give a crude crystalline residue (2·5 g), m.p. 140—180°. This was recrystallised from ether to give the *tetraene* (VII) (1·5 g), m.p. 186—188°, $[\alpha]_D$ +45·4° (*c* 1·28), $\lambda_{max.}$ 276 nm (ε 15,130), τ 9·08 [C(18)H_3], 8·57 [C(11α)CH_3 and C(11β)CH_3], and 6·23 [C(3)OCH_3] (Found: C, 81·5; H, 8·8. $C_{21}H_{26}O_2$ requires C, 81·2; H, 8·5%). The mother liquor deposited another crop of crystalline material (1·0 g), m.p. 145—170°, which was shown by n.m.r. to be a 1 : 1 mixture of the desired product (VII) and the isomeric 11-methylene compound (VIII).

3-*Methoxy*-11,11-*dimethylestra*-1,3,5(10),8(9)-*tetraen*-17β-*ol* (IX).—A mixture of the 17-oxo-compound (VII) (200 mg) and sodium borohydride (200 mg) in ethanol (10 ml) was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and water (25 ml) and ether (25 ml) were added. The organic phase was separated, dried, and evaporated; the residue was crystallised from ether–pentane (1 : 1) to give the 17β-*hydroxy-compound* (IX) (160 mg), m.p. 106—108°, $[\alpha]_D$ −25·6° (*c* 0·74), $\lambda_{max.}$ 275 nm (ε 15,200), τ 9·16 [C(18)H_3], 8·61 and 8·57 [C(11α)CH_3 and C(11β)CH_3], and 6·21 [C(3)OCH_3] (Found: C, 80·7; H, 9·4. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

3-*Methoxy*-11,11-*dimethylestra*-1,3,5(10)-*trien*-17β-*ol* (X).—A solution of the tetraene (IX) (1·5 g) in tetrahydrofuran (25 ml) was added to a mixture of freshly distilled liquid ammonia (50 ml) and aniline (4 ml). To this mixture was added sodium (800 mg) in several portions during 15 min. The blue solution was stirred under reflux for 5 h and then left for 15 h during which time most of the ammonia evaporated. To the residue were carefully added brine (50 ml) and ether (100 ml) and the organic layer was then washed twice more with brine before being dried and evaporated. Most of the remaining aniline was removed by evaporation under high vacuum leaving the crude product (X) (1·4 g) as a yellow oil, $\lambda_{max.}$ 280 and 287 nm (ε *ca.* 2300). This material could not be crystallised; it was characterised as the 17β-*acetate* (XI), m.p. 134—135°, $[\alpha]_D$ +89·2° (*c* 1·15), $\lambda_{max.}$ 277 and 286 nm (ε 1780), τ 9·07 and 9·02 [C(18)H_3 and C(11β)CH_3], 8·60 [C(11α)-CH_3], 7·97 [C(17β)Ac], 6·26 [C(3)OCH_3], and 5·40 [t,

C(17α)H] (Found: C, 77·8; H, 9·0. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·1%).

3-*Methoxy*-11,11-*dimethylestra*-1,3,5(10)-*trien*-17-*one* (XII).—The crude 17β-hydroxy-compound (X) (900 mg) was oxidised with 8N-chromic acid in sulphuric acid [5] to give the 17-*ketone* (XII) (670 mg), m.p. 155—157°, $[\alpha]_D$ +188·5° (*c* 0·85), τ 9·01 [C(18)H_3 and C(11β)CH_3], 8·56 [C(11α)CH_3], and 6·25 [C(3)OCH_3] (Found: C, 80·4; H, 9·3. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

3-*Methoxy*-11,11-*dimethylestra*-2,5(10)-*dien*-17β-*ol* (XIII).—A solution of the tetraene (IX) (500 mg) in tetrahydrofuran (11 ml) and t-butyl alcohol (6 ml) was added to freshly distilled liquid ammonia (20 ml). To this mixture was added lithium wire (250 mg) in several portions during 15 min. The blue solution was stirred under reflux for 21 h, then methanol (5 ml) was carefully added, followed by brine (50 ml) and ether (50 ml). The aqueous phase was separated and extracted three times with ether (50 ml). The combined organic extracts were washed with water, dried, and evaporated to give the crude diene (XIII) (500 mg) as an oil. This material showed u.v. end absorption only (4·60 mg in 50 ml of EtOH), τ 9·15 and 9·04 [C(18)H_3 and C(11β)CH_3], 8·80 [C(11α)CH_3], 6·47 [C(3)OCH_3], and 5·38 [t, C(2)H].

3-*Methoxy*-11,11-*dimethylestra*-2,5(10)-*dien*-17-*one* (XIV).—A mixture of the 17β-hydroxy-compound (XIII) (500 mg) and aluminium isopropoxide (500 mg) in benzene (17·0 ml) and butan-2-one (5·0 ml) was stirred and heated under reflux for 15 h. Further aluminium isopropoxide (250 mg), butan-2-one (2·5 ml), and benzene (10 ml) were then added and the heating was continued for 5 h. The mixture was cooled and poured on ice and 2N-sodium hydroxide (10 ml). The organic layer was separated, washed with brine, dried, and evaporated. The residue was crystallised from ether to give the 17-*ketone* (XIV) (300 mg), m.p. 177—180°, $[\alpha]_D$ +263° (*c* 0·81), τ 9·01 and 8·98 [C(18)H_3 and C(11β)CH_3], 8·75 [C(11α)CH_3], 6·45 [C(3)OCH_3], and 5·38 [t, C(2)H] (Found: C, 80·5; H, 9·8. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

11,11-*Dimethylestr*-4-*ene*-3,17-*dione* (XV).—To a solution of the diene (XIV) (230 mg) in methanol (10 ml) was added concentrated hydrochloric acid (2 drops). The solution was left at room temperature for 1·5 h and then poured on ice and extracted with ether. Work-up in the usual way and crystallisation of the product from ether–hexane (1 : 1) gave the conjugated *ketone* (XV) (180 mg), m.p. 143—146°, $[\alpha]_D$ +13·6° (*c* 0·73), τ 9·01 [C(18)H_3], 8·83 [C(11α)CH_3 and C(11β)CH_3], and 4·18 [C(4)H] (Found: C, 80·4; H, 9·6. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%).

17α-*Ethynyl*-17β-*hydroxy*-11,11-*dimethylestr*-4-*en*-3-*one* (XVII).—A solution of the 17-ketone (XIV) (630 mg) in dimethyl sulphoxide (10 ml) was added to a stirred mixture of lithium acetylide–ethylenediamine complex (1·05 g) in dimethyl sulphoxide (25 ml) maintained under nitrogen at room temperature. After stirring for 6 h the brown mixture was poured on ice and the gummy precipitate formed was extracted with ether (50 ml). The organic phase was washed with water (3 times), dried, and evaporated. The residue was crystallised from hexane to give 17α-ethynyl-17β-hydroxy-3-methoxy-11,11-dimethylestra-2,5(10)-diene (XVI) (307 mg), m.p. 102—106°, τ 9·01 and 8·96 [C(18)H_3 and C(11β)CH_3], 8·72 [C(11α)CH_3], 7·41 [C(17α)C≡CH], 6·46 [C(3)OCH_3], and 5·39 [t, C(2)H].

To a solution of the diene (XVI) (250 mg) in methanol (10 ml) was added concentrated hydrochloric acid (2 drops). The solution was left at room temperature for 1·5 h and then poured on ice and extracted with ether. Work-up in the usual way and crystallisation of the product from ether gave the conjugated *ketone* (XVII) (135 mg), m.p. 183—186°, $[\alpha]_D$ −105° (*c* 0·60), τ 9·02 [C(18)H_3], 8·83 [C(11α)CH_3 and C(11β)CH_3], 7·43 [C(17α)C≡CH], and 4·18 [C(4)H] (Found: C, 80·6; H, 9·1. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

11β-*Acetoxy*-3-*methoxy*-9α,11α-*dimethylestra*-1,3,5(10)-*trien*-17-*one* (XVIII).—A suspension of powdered calcium hydride (2·5 g) in acetic anhydride (250 ml) was heated under reflux for 1 h. The 11β-hydroxy-compound (III) (12·6 g) was added in one portion and the heating was continued for 48 h. The mixture was cooled and poured on ice and aqueous 2N-sodium carbonate before being extracted with ether. The extract was washed with water, dried, and evaporated. The residue was crystallised from ether to give the *acetate* (XVIII) (11·6 g), m.p. 182—185°, $[\alpha]_D$ +104° (*c* 0·80), τ 9·04 and 8·82 [C(18)H_3 and C(9α)CH_3], 8·23 and 7·99 [C(11α)CH_3 and C(11β)OAc], and 6·21 [C(3)OCH_3] (Found: C, 74·5; H, 7·8. $C_{23}H_{30}O_4$ requires C, 74·6; H, 8·2%).

3-*Methoxy*-9α-*methyl*-11-*methylene*-*estra*-1,3,5(10)-*trien*-17-*one* (VIII).—The 11β-acetate (XVIII) (2·5 g) was heated in a Kugelrohr apparatus at an oven temperature of 250°, the internal vacuum being maintained at *ca.* 15 mmHg. After 1 h the apparatus was cooled and the contents washed out with ether. The ether solution was concentrated to give the 11-methylene compound (VIII) (1·4 g), m.p. 190—192°, $[\alpha]_D$ +406° (*c* 1·41), τ 9·13 [C(18)H_3], 8·73 [C(9α)CH_3], 6·24 [C(3)OCH_3], and 5·12 [centre of m, C(11)CH_2] (Found: C, 81·0; H, 8·6. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%).

11β-*Acetoxy*-17,17-*ethylenedioxy*-3-*methoxy*-9α,11α-*dimethylestra*-1,3,5(10)-*triene* (XIX).—The 11β-hydroxy-compound (II) (1·0 g) was treated with calcium hydride (250 mg) and acetic anhydride (20 ml), as described for the hydroxy-compound (III), to give the *acetate* (XIX) (750 mg), m.p. 180—182°, $[\alpha]_D$ +27·0° (*c* 1·01), τ 9·09 and 8·82 [C(18)H_3 and C(9α)CH_3], 8·25 and 8·01 [C(11α)CH_3 and C(11β)OAc], 6·25 [C(3)OCH_3], and 6·13 [C(17)O·CH_2·CH_2·O] (Found: C, 72·5; H, 8·5. $C_{25}H_{34}O_5$ requires C, 72·4; H, 8·3%).

17,17-*Ethylenedioxy*-3-*methoxy*-9α-*methyl*-11-*methylene*-*estra*-1,3,5(10)-*triene* (XX).—The 11β-acetate (XIX) (300 mg) was pyrolysed as described for the corresponding 17-oxo-compound (XVIII), to give the 11-*methylene compound* (XX) (215 mg), m.p. 152—154°, $[\alpha]_D$ +267° (*c* 0·51), τ 9·17 [C(18)H_3], 8·68 [C(9α)CH_3], 6·24 [C(3)OCH_3], 6·09 [C(17)O·CH_2·CH_2·O], and 5·20 [centre of m, C(11)CH_2] (Found: C, 78·2; H, 8·4. $C_{23}H_{30}O_3$ requires C, 77·9; H, 8·5%).

3-*Methoxy*-9α-*methyl*-11-*methylene*-*estra*-1,3,5(10)-*trien*-17β-*ol* (XXI).—The 17-oxo-compound (VIII) (2·1 g) was reduced with sodium borohydride (1 g) as described for the analogous 17-ketone (VII), to give the 17β-*hydroxy-compound* (XXI) (1·9 g), m.p. 161—163°, $[\alpha]_D$ +339° (*c* 0·79), τ 9·08 [C(18)H_3], 8·76 [C(9α)CH_3], 6·24 [C(3)OCH_3], and 5·16 [centre of m, C(11)CH_2] (Found: C, 80·9; H, 9·3. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

3-*Methoxy*-9α-*methyl*-11-*methylene*-*estra*-2,5(10)-*dien*-17β-*ol* (XXII).—The triene (XXI) (420 mg) was reduced with lithium wire (210 mg) in liquid ammonia (20 ml) and t-butyl alcohol (5 ml) as described for the A-ring aromatic

steroid (IX), to give the *diene* (XXII) (400 mg), m.p. 153—154° [from hexane–ether (1 : 1)], $[\alpha]_D$ +238° (*c* 0·76), τ 9·27 [C(18)H_3], 8·92 [C(9α)CH_3], 6·45 [C(3)OCH_3], 6·17 [t, C(17α)H], and 5·32 [centre of m, C(11)CH_2 and C(2)H] (Found: C, 80·0; H, 9·8. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

3-*Methoxy*-9α-*methyl*-11-*methylene-estra*-2,5(10)-*dien*-17-*one* (XXIII).—The 17β-hydroxy-compound (XXII) (334 mg) was oxidised with aluminium isopropoxide (660 mg total) and butan-2-one (6·5 ml) in benzene (15 ml) as described for the analogous compound (XIII), to give the 17-*oxo-compound* (XXIII) (260 mg), m.p. 191—194° (from ether), $[\alpha]_D$ +389° (*c* 0·37), τ 9·14 [C(18)H_3], 8·90 [C(9α)CH_3], 6·45 [C(3)OCH_3], and 5·28 [centre of m, C(11)CH_2 and C(2)H] (Found: C, 80·8; H, 9·3. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

17α-*Ethynyl*-17β-*hydroxy*-9α-*methyl*-11-*methylene-estr*-4-*en*-3-*one* (XXV).—The 17-oxo-compound (XXIII) (228 mg) was treated with lithium acetylide–ethylenediamine complex (338 mg) in dimethyl sulphoxide (5 ml) as described for the analogous compound (XIV) to give the crude 17α-ethynyl derivative (XXIV). This product was immediately treated with concentrated hydrochloric acid (2 drops) in methanol (50 ml) to give the conjugated *ketone* (XXV) (140 mg), m.p. 208—211° (from ether), $[\alpha]_D$ +78° (*c* 0·18), τ 9·16 and 9·03 [C(18)H_3 and C(9α)CH_3], 7·38 [C(17α)C≡CH], 5·14 [C(11)CH_2], and 4·03 [C(4)H] (Found: C, 81·2; H, 9·0. $C_{22}H_{28}O_2$ requires C, 81·4; H, 8·7%).

(11R)-3-*Methoxy*-9α-*methylspiro*[*estra*-1,3,5(10)-*triene*-11-*oxiran*]-17-*one* (XXVI).—A solution of the 11-methylene compound (VIII) (1 g) and *m*-chloroperbenzoic acid (800 mg) in chloroform (30 ml) was kept at 0° for 48 h. Further *m*-chloroperbenzoic acid (400 mg) was then added and the solution was left at room temperature for 6 h. It was then poured on ice–sodium carbonate solution and extracted with methylene chloride. The organic phase was separated, washed with water, dried, and evaporated to give a residue which crystallised from ether. Both crystals and material in the mother liquor, however, were shown by t.l.c. to be essentially mixtures of two products. The total material was therefore applied to thick layer plates [silica gel (40 × 20 cm × 1 mm); chloroform × 3] and the two products were isolated. The less polar proved to be the *epoxide* (XXVI) (230 mg), m.p. 180—182° (from ether), $[\alpha]_D$ +229° (*c* 1·20), τ 9·02 [C(18)H_3], 8·68 [C(9α)CH_3], 6·25 [C(3)OCH_3], and 2·25 [centre of m, C(1)H] (Found: C, 76·9; H, 7·8. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%).

The more polar, isolated in much lower yield, was probably the result of further oxidation, (11*R*)-4-hydroxy-3-methoxy-9α-methylspiro[estra-1,3,5(10)-triene-11-oxiran]-17-one (XXVII), m.p. 240—245°, $[\alpha]_D$ +238° (*c* 1·0), τ 9·01 [C(18)H_3], 8·67 [C(9α)CH_3], 6·15 [C(3)OCH_3], and 2·97 [centre of dd, C(1)H and C(2)H], *m/e* 342 ($C_{21}H_{26}O_4$).

(11R)-3-*Methoxy*-9α-*methylspiro*[*estra*-1,3,5(10)-*triene*-11-*oxiran*]-17β-*ol* (XXVIII).—The 11-methylene compound (XXI) (500 mg) was treated with *m*-chloroperbenzoic acid (400 mg) as described for compound (VIII) and in this instance the major *product* (XXVIII) (280 mg) was isolated by direct crystallisation from ether; m.p. 177—178°, $[\alpha]_D$ +184° (*c* 0·25), τ 9·12 [C(18)H_3], 8·68 [C(9α)CH_3], 6·25 [C(3)OCH_3], and 2·26 [centre of m, C(1)H] (Found: C, 76·7; H, 8·6. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

3-*Methoxy*-9α,11β-*dimethylestra*-1,3,5(10)-*triene*-11α-17β-*diol* (XXIX).—To a solution of the α-epoxide (XXVIII) (150 mg) in tetrahydrofuran (5 ml) under nitrogen was added dropwise 1M-lithium aluminium hydride in ether (2 ml). The solution was left at room temperature for 3 h, then water (5 ml) was carefully added. Most of the solvent was removed under reduced pressure and water (50 ml) and methylene chloride (50 ml) were added. The organic layer was separated, washed with brine, dried, and evaporated. The residue was crystallised from ether to give the 11α,17β-*diol* (XXIX) (180 mg), m.p. 157—158°, $[\alpha]_D$ +157° (*c* 0·34), τ 9·12 [C(18)H_3], 8·76 [C(9α)CH_3 and C(11β)CH_3], 6·26 [C(3)OCH_3], and 1·88 [centre of m, C(1)H] (Found: C, 76·5; H, 9·0. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·2%).

11α-*Hydroxy*-3-*methoxy*-9α,11β-*dimethylestra*-1,3,5(10)-*trien*-17-*one* (VI).—The 17β-hydroxy-compound (XXIX) (150 mg) was oxidised with aluminium isopropoxide (150 mg) and butan-2-one (1 ml) in benzene (5 ml) as described for compound (XIII), to give the 17-*oxo-compound* (VI) (95 mg), m.p. 184—185°, $[\alpha]_D$ +190° (*c* 0·59), τ 9·02 [C(18)H_3], 8·79 [C(9α)CH_3 and C(11β)CH_3], 6·24 [C(3)OCH_3], and 1·84 [centre of m, C(1)H] (Found: C, 76·6; H, 8·7. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

3-*Methoxy*-9α,11α-*dimethylestra*-1,3,5(10)-*triene*-11β,17β-*diol* (XXX).—A mixture of the 17-oxo-compound (III) (200 mg) and sodium borohydride (200 mg) in ethanol (10 ml) was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and water (25 ml) and ether (25 ml) were added. The organic phase was separated, dried, and evaporated. The residue could not be induced to crystallise and was therefore chromatographed on thick-layer plates (silica gel; 2% methanol–chloroform). The main fraction (XXX) (130 mg), eluted with ethyl acetate, showed τ 9·00 and 8·83 [C(18)H_3 and C(9α)CH_3], 8·36 [C(11α)CH_3], and 6·23 [C(3)OCH_3].

11β-*Hydroxymethyl*-3-*methoxy*-9α-*methylestra*-1,3,5(10)-*trien*-17β-*ol* (XXXI).—To a solution of the 11-methylene compound (XXI) (312 mg) in tetrahydrofuran (15 ml) under nitrogen, cooled to 5°, was added 1M-diborane in tetrahydrofuran (3 ml). After being stirred at room temperature for 1 h the solution was again cooled to 5° and 2N-sodium hydroxide (10 ml) was added. This was followed after 15 min by 30% hydrogen peroxide (10 ml), added dropwise, and stirring at 5° was continued for 1 h. The mixture was then poured on ice and extracted with ethyl acetate. The organic extract was dried and evaporated. The residue was crystallised from ether–methylene chloride (2 : 1) to give the 11β-hydroxymethyl compound (XXXI) (290 mg), m.p. 174—175°, $[\alpha]_D$ +156° (*c* 0·55), τ 9·10 [C(18)H_3], 8·80 [C(9α)CH_3], 6·23 [C(3)OCH_3], and 2·77 [centre of m, C(1)H] (Found: C, 76·2; H, 9·3. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·2%).

3-*Methoxy*-9α,11β-*dimethylestra*-1,3,5(10)-*trien*-17-*one* (XXXII).—To a solution of the 11-methylene compound (VIII) (300 mg) in methanol (20 ml) was added 5% palladium–carbon (50 mg) and the mixture was shaken under hydrogen. After 6 h the uptake of hydrogen essentially stopped and the mixture was filtered and concentrated; the residue crystallised from methanol yielding the 9α,11β-*dimethyl compound* (XXXII) (220 mg), m.p. 128—129°, $[\alpha]_D$ +238° (*c* 0·47), τ 9·10 [d, C(11β)CH_3], 8·99 [C(18)H_3], 8·82 [C(9α)CH_3], 6·22 [C(3)OCH_3], and 2·94 [centre of m, C(1)H] (Found: C, 81·1; H, 9·2. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

In one repetition of this reaction a crude mother liquor from the preparation of the 11-methylene compound

(VIII) was used as a starting material. After the hydrogenation was complete and the catalyst had been removed, concentration of the methanolic solution gave a low yield of a crystalline material thought to be 3-methoxy-9α,11-dimethylestra-1,3,5(10),11-tetraen-17-one (XXXV), m.p. 162—165°, $[\alpha]_D$ −124° (*c* 0·55), τ 9·17 [C(18)H_3], 8·80 [C(9α)CH_3], 7·95 [d, C(11)CH_3], 6·25 [C(3)OCH_3], 4·04 [centre of m, C(12)H], and 2·88 [centre of m, C(1)H], *m/e* 310 (Found: C, 81·1; H, 8·4. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%).

17,17-*Ethylenedioxy*-3-*methoxy*-9α,11β-*dimethylestra*-1,3,5-(10)-*triene* (XXXIII).—The 11-methylene-17-acetal (XX) (1·6 g) was hydrogenated as described for the 11-methylene-17-oxo-compound (VIII) to give the *dimethyl product* (XXXIII) (1·35 g), m.p. 145—147°, $[\alpha]_D$ +141° (*c* 0·45), τ 9·11 [d, C(11β)CH_3], 9·02 [C(18)H_3], 8·82 [C(9α)CH_3], 6·24 [C(3)OCH_3], 6·10 [C(17)O·CH_2·CH_2·O], and 2·93 [centre of m, C(1)H] (Found: C, 77·1; H, 9·1. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·1%).

3-*Methoxy*-9α,11β-*dimethylestra*-2,5(10)-*dien*-17β-*ol* (XXXVI).—The estratriene (XXXII) (1·04 g) was reduced with lithium wire (2 g) in liquid ammonia (150 ml) and t-butyl alcohol (25 ml) as described for the A-ring aromatic compound (IX), to give the *diene* (XXXVI) (800 mg), m.p. 146—150°, u.v. end absorption only (4·1 mg in 50 ml of EtOH) (Found: C, 79·7; H, 10·6. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%).

3-*Methoxy*-9α,11β-*dimethylestra*-2,5(10)-*dien*-17-*one* (XXXVII).—The 17β-hydroxy-compound (XXXVI) (800 mg) was oxidised with aluminium isopropoxide (1 g) and butan-2-one (10 ml) in benzene (50 ml) as described for compound (XIII), to give the 17-*oxo-compound* (XXXVII) (550 mg), m.p. 158—160°, $[\alpha]_D$ +240° (*c* 0·22), τ 9·03 [d, C(11β)CH_3], 8·98 [C(18)H_3 and C(9α)CH_3], 6·47 [C(3)-OCH_3], and 5·36 [centre of m, C(2)H], *m/e* 314 ($C_{21}H_{30}O_2$).

17α-*Ethynyl*-17β-*hydroxy*-9α,11β-*dimethylestr*-4-*en*-3-*one* (XXXIX).—The 17-oxo-compound (XXXVII) (300 mg) was treated with lithium acetylide–ethylenediamine complex (1 g) in dimethyl sulphoxide (15 ml) as described for compound (XIV) to give the crude 17α-ethynyl derivative (XXXVIII). This product was immediately treated with concentrated hydrochloric acid (2 drops) in methanol (20 ml) to give the conjugated *ketone* (XXXIX) (110 mg), m.p. 168—170°, $[\alpha]_D$ +16·1° (*c* 0·81), τ 9·10 and 8·99 [C(18)H_3 and C(9α)CH_3], 8·84 [d, C(11β)CH_3], 7·39 [C(17)-C≡CH], and 4·07 [C(4)H] (Found: C, 80·6; H, 9·3. C_{22}-$H_{30}O_2$ requires C, 80·9; H, 9·3%).

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