Synthesis of 9-Methyl-19-norsteroids

By **Robert V. Coombs,* Judit Koletar, Robert Danna, Henry Mah,** and **Eugene Galantay,** Sandoz–Wander, Inc., Research and Development Section, East Hanover, New Jersey, 07936, U.S.A.

Alkylation of an 11-oxoestrone derivative (I) has been shown to give a 9α-methyl product which could be further transformed into 9α-methyl-19-nor-compounds. A 9β-methyl-11-oxoestrone has been converted into 9β-methylestrone 3-methyl ether and a synthesis of 9β-methyl-19-norsteroids has been developed using as a key step the reaction of lithium dimethylcuprate with the secosteroid, 3,3-ethylenedioxy-17β-hydroxy-4,5-secoestr-9-en-5-one (XXXIV). Reaction of this same secosteroid with diethylaluminium cyanide led to the 9α-cyano-compound as the major product, as demonstrated by transformation of the cyano-group into a methyl substituent and comparison of the derived tetracyclic structure with 9-methyl steroids of proven stereochemistry.

THE interest in, and preparation of, potential steroidal hormones bearing additional nuclear methyl substituents continues.[1] Recent examples have included those involving a change of backbone stereochemistry,[2-4] which often seems essentially to eliminate biological activity, and those not affecting the skeletal framework,[5-7] which, in contrast, has sometimes led to very potent hormonal properties. We decided to initiate a programme to prepare 9-methyl-19-norsteroids including, if possible, the two series with 9α- and 9β-substituents, anticipating modified biological properties. These might arise in the latter case from the unnatural backbone and in the former from a divergence of the metabolic fate of the molecules in comparison with that of 'normal' 19-norsteroids. We now report our results.[8]

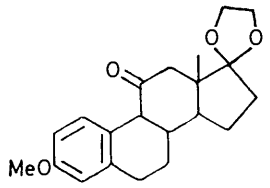
There are several reports of 9α-methylsteroids [9-11] prepared from various 11-oxo-derivatives, but all retain the 10-methyl group. It was this feature in fact which led to such a clear-cut stereochemical result on methylation of the respective intermediates. In the case of 9β-methyl compounds, the one reported example [4] does incorporate an aromatic ring A, which would readily lead to 19-nor-derivatives, but the low yield in its formation from the boron-trifluoride-catalysed rearrangement of a 9α,11α-epoxyandrostenone makes it an unsuitable starting material for further elaboration. One other report of a 9-methyl-19-norsteroid, of unknown stereochemistry, exists in the patent literature [12] but again its isolation as the minor product from a conjugate addition to a 4,9-dien-3-one leaves much to be desired.

The generation of the desired enolate from an 11-oxosteroid for alkylation at C-9 should be greatly favoured by the presence of an aromatic ring A, although the preference for selective attack of the entering methyl group would seem to be reduced. However, in practice this was not the case, complete stereoselectivity being maintained. The necessary 11-oxoestrone derivative (I) was prepared by the reported procedure [13] and reaction with potassium t-butoxide and methyl iodide gave, in high yield, a crystalline product (II). This contained an additional quaternary methyl signal in its n.m.r. spectrum, confirming the presence of the 9-methyl group.

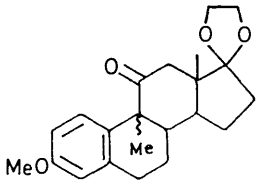
As a first attempt to obtain information about its stereochemistry, compound (II) was transformed by deacetalisation and methyl ether cleavage (pyridinium hydrochloride) into the phenol (III). The physical and spectral properties of this product (full details are given in the Experimental section) were different from those

[1] A. A. Akhrem, T. V. Ilyukhina, and Yu. A. Titov, *Russ. Chem. Rev.*, 1969, **38**, 850.
[2] W. G. Dauben and D. S. Fullerton, *J. Org. Chem.*, 1971, **36**, 3277.
[3] E. Galantay, N. Paolella, S. Barcza, R. V. Coombs, and H. P. Weber, *J. Amer. Chem. Soc.*, 1970, **92**, 5771.
[4] J. W. ApSimon, R. R. King, and J. J. Rosenfeld, *Canad. J. Chem.*, 1969, **47**, 1989.
[5] J. S. Baran, H. D. Lennon, S. E. Mares, and E. F. Nutting, *Experientia*, 1970, **26**, 762.
[6] J. A. Campbell, S. C. Lyster, G. W. Duncan, and J. C. Babcock, *Steroids*, 1963, **1**, 317.
[7] G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 1957, 4112.
[8] R. V. Coombs, presented in part at the Third International Congress on Hormonal Steroids, Hamburg, September 1970.
[9] E. R. H. Jones, G. D. Meakins, and J. S. Stephenson, *J. Chem. Soc.*, 1958, 2156.
[10] R. E. Beyler, Frances Hoffman, L. H. Sarett, and M. Tishler, *J. Org. Chem.*, 1961, **26**, 2426.
[11] Sir E. R. H. Jones and D. A. Wilson, *J. Chem. Soc.*, 1965, 2933.
[12] U.S.P. 3,418,327.
[13] J. S. Baran, *J. Medicin. Chem.*, 1967, **10**, 1188.

of the phenol (IIIb) of known 9β-stereochemistry,[4] strongly suggesting the structure of the initial alkylation

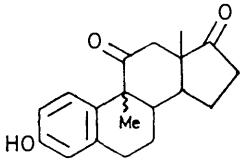


(I)



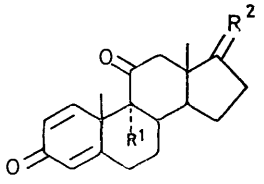
(II) a; 9α-Me
b; 9β-Me

product to be (IIa), *i.e.* 9α-methyl. To strengthen this conclusion, an alternative synthesis of a 9-methyl-11-oxoestrone was devised in which precedent would make the 9α-stereochemistry unequivocal.

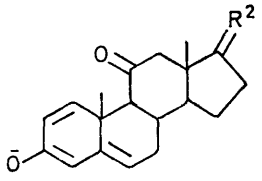


(III) a; 9α-Me
b; 9β-Me

The generation and subsequent trapping of the various possible enolates from the system exemplified in structure (IV) has been studied, as a function of the necessary base, in some detail.[14] Recent work [15] using the lithio- or sodio-derivative of bistrimethylsilylamine has demonstrated the selective formation of either the 3-enolate

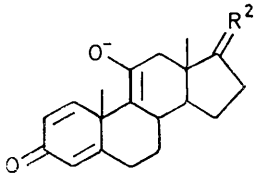


(IV) R^1=H, R^2=BMD
(VII) R^1=Me, R^2=BMD
(VIII) R^1=H, R^2=O·CH_2·CH_2·O
(X) R^1=Me, R^2=O·CH_2·CH_2·O



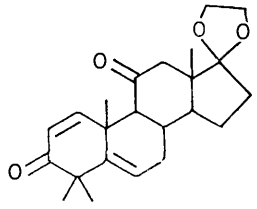
(V)

BMD =



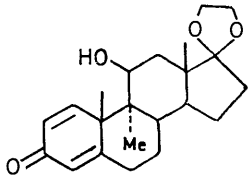
(VI)

(V) or the 11-enolate (VI). The latter could be trapped by reaction with methyl iodide to give the 9α-methyl product (VII). Application of these findings to compound (VIII) gave the expected products, *i.e.* the lithio-derivative and an excess of methyl iodide gave the 4,4-dialkyl product (IX), characterised by its n.m.r. and u.v. spectra [16] in particular, whereas the sodio-derivative and methyl iodide gave the 9α-alkyl product (X).

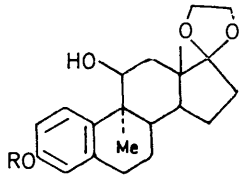


(IX)

The 9α-methyl compound (X) was then used as the starting material for an aromatisation sequence based on that used for the preparation of 11-oxoestrone. Treatment with lithium hydridotri-t-butoxyaluminate afforded the 11β-hydroxy-product (XI) which was aromatised by the lithium–biphenyl–diphenylmethane reagent. The resulting phenol (XII) was converted into the methyl ether (XIII) and then careful Jones oxidation [17] generated the 11-ketone (IIa); this was identical with our initial alkylation product (II). The stereochemistry of the original alkylation reaction is therefore established as α.



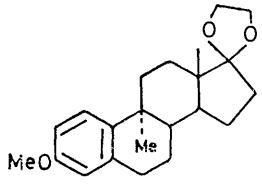
(XI)



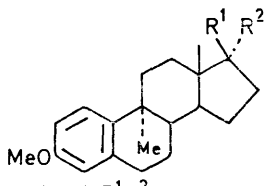
(XII) R = H
(XIII) R = Me

In practice, the first sequence involving alkylation as the final step led to higher overall yields and so was used for the larger scale preparations necessary for the further elaboration of the new skeleton.

Reduction of the 11-oxo-compound (IIa) under modified Wolff–Kishner conditions [18] [to (XIV)] and acidic deacetalisation led to 9α-methylestrone methyl ether (XV). Reduction with sodium borohydride gave the corresponding estradiol derivative (XVI).



(XIV)

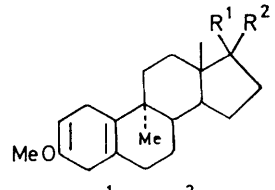


(XV) R^1R^2=O
(XVI) R^1 = OH, R^2=H

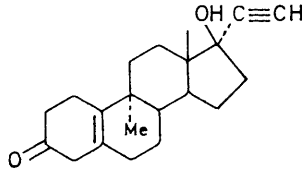
[14] M. Tanabe and D. F. Crowe, *Chem. Comm.*, 1969, 1498.
[15] D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Comm.*, 1969, 1497.
[16] W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and B. Sturgeon, *J. Chem. Soc.*, 1956, 4490.
[17] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2555.
[18] W. Nagata and H. Itazaki, *Chem. and Ind.*, 1964, 1194.

We were now in a position to pursue the preparation of derivatives for which hormonal or anti-hormonal properties could be anticipated,[19] and to this end the estradiol derivative (XVI) was subjected to the Birch reduction.[20] The resulting dihydro-compound (XVII) was oxidised under Oppenauer conditions [21] to the 17-ketone (XVIII). A 17α-ethynyl side-chain was introduced with the lithium acetylide–ethylenediamine complex,[22] and the crude product was divided into two parts. The first was dissolved in 80% aqueous acetic acid, yielding the 5(10)-en-3-one (XIX) on work-up; the second was dissolved in methanol containing *ca.* 2% concentrated hydrochloric acid, giving the 4-en-3-one (XX). The dihydro-derivative (XVIII) was treated with methyllithium followed by methanolic hydrogen chloride to provide the 9α,17α-dimethyl compound (XXI).*

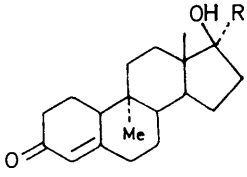
For the synthesis of 9α-methyl-19-norprogesterone the procedure used was modelled on the preparation of 19-norprogesterone from estrone 3-methyl ether.[23] The 9α-methylestrone derivative (XV) was treated with ethylidenetriphenylphosphorane to give a crude 17-ethylidene compound (XXII), from which the major isomer (XXIIa), presumably *cis* as in previous cases, could be isolated by crystallisation. The mixture of isomers was converted into the epimeric C-20 alcohols (XXIII) by treatment with diborane followed by base and hydrogen peroxide, and this crude product was reduced with lithium in liquid ammonia. Treatment of the crude residue, obtained after reisolation of the



(XVII) R^1= OH, R^2=H
(XVIII) R^1R^2 = O

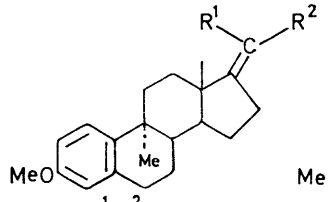


(XIX)

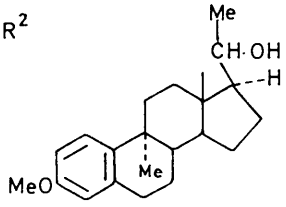


(XX) R = C≡CH
(XXI) R = Me

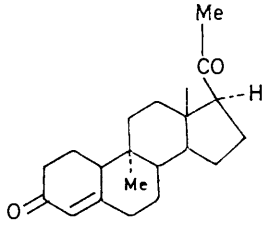
organic material, with methanolic hydrogen chloride generated the 4-en-3-one system, and the synthesis was completed by oxidation of the C-20 alcohols to the ketone with chromium trioxide. T.l.c. of the final product revealed the presence of a less polar impurity and so in the first instance column chromatography was necessary to isolate a pure sample of the desired product (XXIV). The impurity was also isolated, and characterised as the pregna-1,3,5(10)-trien-20-one (XXV), resulting from an incomplete Birch reduction.



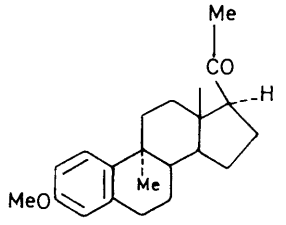
(XXII) R^1,R^2 = H, Me
(XXIIa) R^2=H, R^1 = Me



(XXIII)



(XXIV)



(XXV)

In the assignment of stereochemistry to the 19-norprogesterone (XXIV), the configuration of the C-10 hydrogen atom is a problem. In common with other 19-norstructures having 9α-stereochemistry it might be anticipated that the usual, more stable, 10β-configuration would predominate but it was felt necessary to confirm this. A total synthesis was therefore undertaken to provide a crystal of racemic (XXIV) for *X*-ray analysis.

A slight modification of the foregoing pathway was used in the racemic series, since estrone derivatives are readily available by total synthesis, thus making the lithium–biphenyl reaction step unnecessary. The known tetraene,[24] *rac*-(XXVI), was treated with diborane in the usual way to give a product formulated as the 11α-hydroxy-derivative, *rac*-(XXVII), on the basis of results in similar reactions.[25] This compound proved difficult to obtain in a satisfactory crystalline condition free from solvent, and after spectral characterisation it was therefore oxidised with dicyclohexylcarbodi-imide and dimethyl sulphoxide in the presence of dichloroacetic acid [26] to the 11-one, *rac*-(I). This was identical in spectral properties with the natural isomer and so, from this point on, the chemistry in the racemic series exactly paralleled that described for the optically active series.

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

[19] P. D. Klimstra and F. B. Colton in 'Contraception: the Chemical Control of Fertility,' ed. D. Ledincer, Marcel Dekker, New York, 1969.

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

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

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

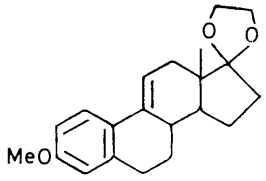
[23] A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, 1966, **31**, 24.

[24] 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.

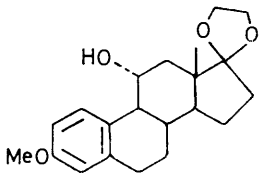
[25] A. Bowers, J. S. Mills, C. Casas-Campillo, and C. Djerassi, *J. Org. Chem.*, 1962, **27**, 361.

[26] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965, **87**, 5670; Neth.P. 6,703,618.

Full details are given in the Experimental section. A crystal of the final product, *rac*-(XXIV), was subjected to



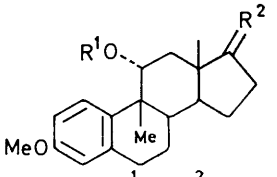
rac-(XXVI)



rac-(XXVII)

X-ray analysis, and the results * confirmed the 10β-stereochemistry.

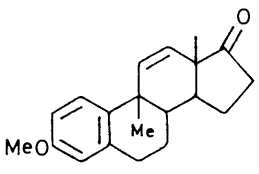
In the 9β-methyl series, our initial approach was to repeat the preparation of the known compound (XXVIII) until, despite the poor yield, sufficient material had been accumulated for further experiments. Protection of the 17-ketone by formation of the ethylene acetal and oxidation of the product (XXIX) with Jones reagent [17] gave



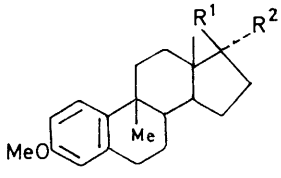
(XXVIII) R^1 = H, R^2 = O
(XXIX) R^1 = H, R^2 = O·CH_2·CH_2·O
(XXX) R^1 = COPh, R^2 = O

the 11-oxo-compound (IIb). In this series, however, despite the use of the severe conditions described for unreactive ketones,[18] attempts to perform a Wolff–Kishner reduction were unsuccessful. In one instance a low yield of a material, apparently the hydrazone, was isolated but, more usually, extensive decomposition was the only result.

To circumvent the need for this reaction, the benzoate (XXX) was prepared from the 11α-hydroxy-compound and pyrolysed at 350° and 100 mmHg. The olefin formed was shown by n.m.r. to be the expected 11-ene (XXXI), and hydrogenation of this material over palladium–carbon gave 9β-methylestrone 3-methyl ether (XXXII), markedly different from the 9α-methyl



(XXXI)

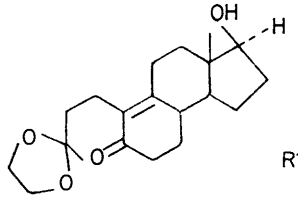


(XXXII) R^1R^2 = O
(XXXIII) R^1 = OH, R^2 = H

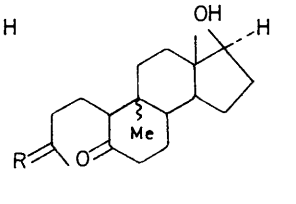
material. Reduction with sodium borohydride gave the estradiol derivative (XXXIII).

The synthesis of 9β-methyl-19-nor-steroids had meanwhile been achieved by an alternative approach and it became no longer necessary to pursue this original line beyond the ring-A-aromatic stage.

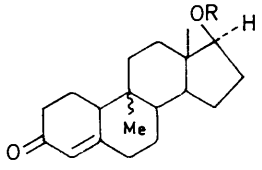
We had been interested in the possibility of conjugate addition reactions to the known [27] seco-steroid intermediate (XXXIV). In the first instance, the reaction with lithium dimethylcuprate [28] was investigated. Application of the described conditions led, in high yield, to a non-crystalline product whose spectral properties (in particular ν_{CO} 1705 cm^{-1}) suggested a single compound of overall structure (XXXV). Removal of the acetal group with aqueous acetic acid gave a crystalline diketone (XXXVI), which was cyclised with methanolic potassium hydroxide [29] to the 9-methyl-19-nortestosterone (XXXVII), further characterised as the crystalline 17-acetate (XXXVIII).



(XXXIV)



(XXXV) R = O·CH_2·CH_2·O
(XXXVI)a; R = O, 9α-Me
b; R = O, 9β-Me



(XXXVII)a; R = H, 9α-Me
b; R = H, 9β-Me
(XXXVIII)a; R = Ac, 9α-Me
b; R = Ac, 9β-Me

To solve the problem of stereochemistry we decided to compare directly the new compounds with those previously prepared by us and of now known structure. To this end, the 9α-methyldihydro-compound (XVII) was treated with methanolic hydrogen chloride to give the 9α-methyl-19-nortestosterone derivative (XXXVIIa). This product and its 17-acetate (XXXVIIa) were different from those prepared from the seco-steroid intermediate. Further, the new 9-methyl-19-nortestosterone derivative (XXXVII), now suspected of being the 9β-compound, was dehydrogenated with palladium–carbon [30] to the ring A phenol. This crude phenol was converted into the 3-methyl ether, which was identical with compound (XXXIII), thus confirming the structure of the seco-derived steroid as (XXXVIIb), *i.e.* 9β-methyl.

Two derivatives of potential pharmacological interest

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

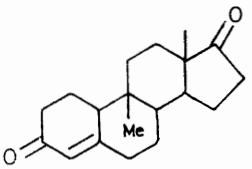
[27] L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède, *Compt. rend.*, 1963, **257**, 3086.

[28] H. O. House, W. L. Respress, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31**, 3128.

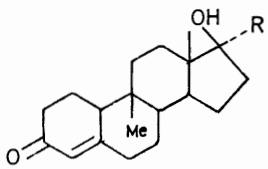
[29] A. L. Wilds and C. H. Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 471.

[30] R. B. Turner and J. A. Meschino, *J. Amer. Chem. Soc.*, 1958, **80**, 4862.

were prepared in the 9β-methyl series. The 19-nortestosterone compound (XXXVIIb), was oxidised with Jones reagent to the 3,17-diketone (XXXIX), which was



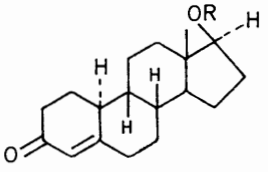
(XXXIX)

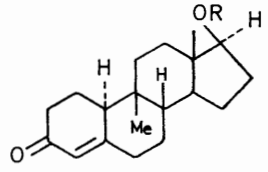


(XL) R = Me
(XLI) R = C≡CH

then treated with ethyl orthoformate in the presence of toluene-*p*-sulphonic acid to give a crude 3-enol ether. This, characterised only by t.l.c., was treated with the lithium acetylide–ethylenediamine complex in the usual way and, after acidic hydrolysis, the 17α-ethynyl derivative (XLI) was obtained. Alternatively, the crude enol ether was treated with ethereal methyl-lithium; after acidic hydrolysis to regenerate the 4-en-3-one system, the desired 9β,17α-dimethyl compound (XL) was obtained.

Acid-catalysed isomerisations in 9β*H*-estr-5-ene and 9β*H*-estra-2,5(10)-diene derivatives have been shown [31] to lead to 9β,10α-4-en-3-ones. It seems reasonable that introduction of the 9β-methyl group would not change



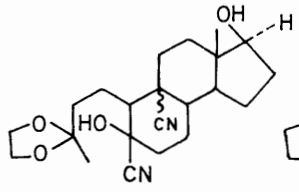


	R = H	R = Ac	(XXXVIIb) R = H	(XXXVIIIb) R = Ac
C-18 τ	9·20	9·13	9·16	9·10
C-17	6·21	5·21	6·22	5·24
Multiplicity	t	t	t	t

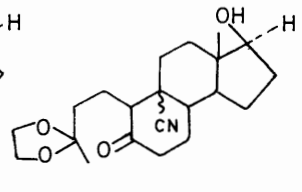
this conformational preference. Accordingly, our products are also assigned the 10α*H*-stereochemistry. Similarly, in considering the environment at C-17, the spectral data of compounds such as (XXXVIIb) and (XXXVIIIb) agree with the conclusions drawn [31] in the 9β*H*-series, *i.e.* the oxygen function having a β-orientation.

Attention was then turned to the conjugate addition of cyanide to the seco-steroid (XXXIV). Reaction with diethylaluminium cyanide in benzene [32] gave three products (t.l.c.). Direct crystallisation from the reaction mixture, after decomposition with sodium hydroxide solution, gave *ca.* 50% yield of the main product. Elemental analysis proved the presence of nitrogen and the i.r. spectrum indicated both a cyano-group and a six-membered ring ketone, confirming the material to be the product of conjugate addition. Chromatography of the non-crystalline residue gave more of the main product (*ca.* 15%) plus a minor one of similar polarity (*ca.* 10%), and a third (*ca.* 5%) of greater polarity. This third compound was assigned the structure (XLII) (the bis-adduct) on the basis of its spectral properties (no carbonyl absorption) and molecular weight. The second minor product was isomeric with the major one, suggesting that the two materials differed in the stereochemistry of the cyano-group (keeping in mind the basic nature of the reaction conditions). Indeed, attempted re-equilibration of the pure isomers led to their recovery unchanged. The stereochemistry of the cyano-group in the major isomer (XLIIIa) was proven to be α by the following series of transformations.

Reaction with ethylene glycol and acid gave the bis-acetal (XLIV); the cyano-substituent was then converted into a methyl group in an analogous fashion to



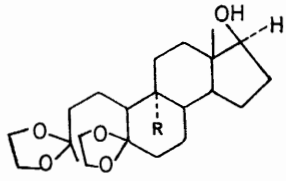
(XLII)



(XLIIIa; 9α-CN
b; 9β-CN

that reported for other cyano-steroids.[33] Reduction with di-isobutylaluminium hydride yielded the imino-methyl compound (XLV), which on further Wolff–Kishner reduction gave the crude methyl bis-acetal (XLVI). Hydrolysis with aqueous acetic acid then produced the crystalline seco-steroid (XXXVIa), which differed from the 9β-methyl diketone (XXXVIb) prepared from the lithium dimethylcuprate addition.

The α-stereochemistry was confirmed by cyclisation of the diketone (XXXVIa), as before, with methanolic potassium hydroxide, to a 9-methyl-17β-hydroxyestr-4-en-3-one, the crystalline 17-acetate of which was identical in all respects with the 9α-methyl compound (XXXVIIIa) already prepared. By exclusion, the cyano-group in the minor isomer (XLIIIb) is assigned the β-stereochemistry.



(XLIV) R = CN
(XLV) R = CH=NH
(XLVI) R = Me

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 instrument. Optical rotations refer to solutions in chloroform.

[31] J. M. H. Graves, G. A. Hughes, T. Y. Jen, and H. Smith, *J. Chem. Soc.*, 1964, 5488.
[32] W. Nagata and M. Yoshioka, *Tetrahedron Letters*, 1966, 1913.
[33] W. Nagata in 'Proceedings of the Symposium on Drug Research.' Montreal, Canada, June 1966.

17,17-*Ethylenedioxy*-3-*methoxy*-9α-*methylestra*-1,3,5(10)-*trien*-11-*one* (IIa).—To a solution of 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-11-one [13] (I) (13·2 g) in methyl iodide (150 ml) cooled in an ice-bath under nitrogen, a 1·1M-solution of potassium t-butoxide in t-butyl alcohol (150 ml) was added during 15 min. The resulting suspension was stirred at room temperature for 15 h, then poured on ice and extracted with methylene chloride (3 ×). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated and the residue was crystallised from ether, yielding the 9α-*methyl ketone* (IIa) (11·0 g), m.p. 143—145°, $[\alpha]_D$ +273° (*c* 1·2) (Found: C, 74·2; H, 8·2. $C_{22}H_{28}O_4$ requires C, 74·1; H, 7·9%); τ 9·6 [C(18)H_3] and 8·54 [C(9α)CH_3].

Application of this procedure to *rac*-(I) gave (±)-17,17-*ethylenedioxy*-3-*methoxy*-9α-*methylestra*-1,3,5(10)-*trien*-11-*one*, m.p. 124—125° (Found: C, 74·2; H, 7·9%).

3-*Hydroxy*-9α-*methylestra*-1,3,5(10)-*triene*-11,17-*dione* (IIIa).—To a warm solution of the 17,17-ethylenedioxy-derivative (IIa) (330 mg) in methanol (5 ml) was added 2N-hydrochloric acid (1·5 ml), and heating (steam-bath) was continued for 10 min. The solution was cooled and diluted with water. The resulting crystals were collected, dried, and recrystallised from methanol to give the 11,17-*dione* (270 mg), m.p. 288—290°, τ 9·16 [C(18)H_3] and 8·57 [C(9α)CH_3] (Found: C, 77·0; H, 7·4. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·8%). A mixture of this 3-methoxy-compound (270 mg) and pyridine hydrochloride (3 g) was maintained at 220° for 1 h with occasional stirring. The melt was then cooled and methylene chloride (50 ml) and water (50 ml) were added. The organic phase was evaporated and the residue was dissolved in 2N-sodium hydroxide solution. The filtered alkaline solution was acidified with 2N-hydrochloric acid and the crystalline precipitate was collected, dried, and recrystallised from ether to give the *phenol* (IIIa) (80 mg), m.p. 265—267°, too insoluble in chloroform for $[\alpha]_D$ measurement, τ 9·15 [C(18)H_3] and 8·59 [C(9α)CH_3] (Found: C, 76·6; H, 7·8. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

17,17-*Ethylenedioxy*-9α-*methylandrosta*-1,4-*diene*-3,11-*dione* (X).—To a stirred suspension of sodium hydride (55% dispersion in mineral oil; 1·6 g) in anhydrous tetrahydrofuran (200 ml) under nitrogen at room temperature, hexamethyldisilazane (12 ml) was added during 5 min. The mixture was heated under reflux for 4 h and then a solution of 17,17-ethylenedioxyandrosta-1,4-diene-3,11-dione [13] (VIII) (5·1 g) in tetrahydrofuran (100 ml) was rapidly added. After a further 1 h under reflux the mixture was cooled and methyl iodide (10 ml) was added. Stirring was continued at room temperature for a further 15 h, after which most of the solvent was removed under reduced pressure and water (250 ml) and methylene chloride (250 ml) were added. The organic layer was washed once with water, dried, and evaporated. The residue was crystallised from ether to give the 9α-*methyl ketone* (X) (2·4 g), m.p. 219—221°, $[\alpha]_D$ +157° (*c* 1·04), $\lambda_{max.}$ 240 nm (ε 15,200), τ 9·1 and 9·0 [C(18)H_3 and C(9α)CH_3], and 8·5 [C(19)H_3] (Found: C, 73·4; H, 7·9. $C_{22}H_{28}O_4$ requires C, 73·2; H, 8·2%).

17,17-*Ethylenedioxy*-4,4-*dimethylandrosta*-1,5-*diene*-3,11-*dione* (IX).—To a solution of hexamethyldisilazane (8 ml) in anhydrous tetrahydrofuran (100 ml) at room temperature under nitrogen was added a 1·6M-solution of n-butyllithium in hexane (22 ml). After 1 h a solution of 17,17-ethylenedioxyandrosta-1,4-diene-3,11-dione (VIII) (5·1 g) in tetrahydrofuran (100 ml) was added during 10 min and stirring was continued for a further 1 h. Methyl iodide (15 ml) was then added in one portion. After a further 2 h the mixture was concentrated and water (250 ml) and ether (250 ml) were added. The organic phase was washed with water, dried, and evaporated and the residue was crystallised from ether–hexane (1 : 1) to give the *dimethyl ketone* (IX) (2·6 g), m.p. 138—139°, $[\alpha]_D$ +35° (*c* 1·07), $\lambda_{max.}$ 224 nm (ε 10,770), τ 9·15 [C(18)H_3], and 8·74, 8·68, and 8·50 [C(19)H_3 and C(4)$(CH_3)_2$] (Found: C, 74·3; H, 8·0. $C_{23}H_{30}O_4$ requires C, 74·6; H, 8·1%).

17,17-*Ethylenedioxy*-11β-*hydroxy*-9α-*methylandrosta*-1,4-*dien*-3-*one* (XI).—To a suspension of lithium hydridotri-t-butoxyaluminate (3 g) in tetrahydrofuran (100 ml) was added the 11-oxo-compound (X) (2·1 g). The mixture was stirred at room temperature for 18 h and was then made neutral by careful addition of N-hydrochloric acid (*ca.* 1·5 ml). Most of the solvent was removed under reduced pressure and water (100 ml) and methylene chloride (100 ml) were added. The organic layer was separated, washed with water, dried, and evaporated. The residue was crystallised from ether to give the 11β-*hydroxy-compound* (XI) (1·4 g), m.p. 236—239°, $[\alpha]_D$ +8·3° (*c* 1·25), τ 9·3 [C(9α)CH_3], 8·8 [C(18)H_3], and 8·4 [C(19)H_3] (Found: C, 73·7; H, 8·5. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

17,17-*Ethylenedioxy*-11β-*hydroxy*-3-*methoxy*-9α-*methylestra*-1,3,5(10)-*triene* (XIII).—To a solution of biphenyl (8·5 g), diphenylmethane (4·5 g), and lithium (2·9 g of a 30% dispersion in wax) in tetrahydrofuran (100 ml) maintained at reflux was added dropwise a solution of the dienone (XI) (6·8 g) in tetrahydrofuran (100 ml) and heating under reflux was continued for a further 30 min. After cooling to *ca.* 40°, methanol (20 ml) was added and then water (50 ml). The solvent was removed *in vacuo* and the residue was extracted twice with methylene chloride (100 ml). The combined organic solutions were extracted with 2N-sodium hydroxide solution and the aqueous alkaline extracts were carefully neutralised by addition, with cooling, of glacial acetic acid. Extraction with methylene chloride, drying of the organic phase, and removal of the solvent gave a non-crystalline residue (2·3 g) of crude phenolic product (XII).

A mixture of the crude product (2·3 g), potassium carbonate (4 g), and methyl iodide (10 ml) in methanol (15 ml) was heated under reflux for 4 h. It was then concentrated and water (50 ml) and ether (50 ml) were added. The organic layer was washed with 2N-sodium hydroxide solution and then water, dried, and evaporated. The residue was crystallised from ether to give the 3-*methoxy-compound* (XIII) (1·7 g), m.p. 159—160°, $[\alpha]_D$ 100° (*c* 0·34), τ 8·9 [C(18)H_3 and C(9α)CH_3] and 6·23 [C(3)OCH_3] (Found: C, 73·5; H, 8·0. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

17,17-*Ethylenedioxy*-3-*methoxy*-9α-*methylestra*-1,3,5(10)-*trien*-11-*one* (IIa).—The 11β-hydroxy-compound (XIII) (250 mg) was oxidised with 8N-chromic acid in sulphuric acid [17] to give the 9α-methyl ketone (IIa) (165 mg), m.p. and mixed m.p. 142—145°, identical (i.r. and n.m.r. spectra) with material prepared by the alternative route.

17,17-*Ethylenedioxy*-3-*methoxy*-9α-*methylestra*-1,3,5(10)-*triene* (XIV).—A mixture of the 11-oxo-compound (IIa) (534 mg), hydrazine hydrate (5 g), and hydrazine dihydrochloride (1 g) in triethylene glycol (35 ml) was maintained at 130° for 2·5 h. To the resulting clear solution was added pelleted potassium hydroxide (1·8 g) and the temperature was raised to 210°, a distillate being collected. This temperature was maintained for 3 h. The solution was

then cooled and diluted with water; the precipitate was collected and dissolved in methylene chloride. The organic solution was washed with 2N-sodium hydroxide solution and water, dried, and evaporated. The residue was crystallised from hexane–ether (5 : 1) to give the *triene* (XIV) (270 mg), m.p. 114—115°, τ 9·14 [C(18)H_3], 8·93 [C(9α)CH_3], and 6·26 [C(3)OCH_3] (Found: C, 76·9; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%).

In some experiments a by-product, the free phenol, was obtained. This could be isolated from the sodium hydroxide washings in the work-up, and methylated again to give the desired product.

Application of the foregoing procedure to *rac*-(IIa) gave the *triene rac*-(XIV), m.p. 108—110° (Found: C, 77·2; H, 8·4%).

3-*Methoxy*-9α-*methylestra*-1,3,5(10)-*trien*-17-*one* (XV).—To a solution of the 17-acetal (XIV) (6·3 g) in methanol (100 ml) warmed on a steam-bath was added 2N-hydrochloric acid (5 ml). After warming for a further 5 min, the mixture was cooled and the precipitate isolated and dried to give the 17-*ketone* (XV) (5·6 g), m.p. 188—190°, $[\alpha]_D$ +141° (*c* 0·49), τ 9·12 and 8·96 [C(18)H_3 and C(9α)CH_3] and 6·25 [C(3)OCH_3] (Found: C, 80·3; H, 9·0. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·9%).

Application of the foregoing procedure to *rac*-(XIV) gave the 17-*ketone rac*-(XV), m.p. 147—148° (Found: C, 80·6; H, 8·7%).

3-*Methoxy*-9α-*methylestra*-1,3,5(10)-*trien*-17β-*ol* (XVI).—A mixture of the 17-oxo-compound (XV) (70 mg) and sodium borohydride (70 mg) in ethanol (10 ml) was stirred at room temperature for 2·5 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 methanol. The crystals were solvated; neither sublimation nor recrystallisation from other solvents gave a solvent-free sample. The methanol solvate (60 mg) had m.p. 70—75°, τ 9·24 and 8·98 [C(18)H_3 and C(9α)CH_3], 6·52 (MeOH), and 6·22 [C(3)OCH_3].

3-*Methoxy*-9α-*methylestra*-2,5(10)-*dien*-17β-*ol* (XVII).—The estratriene derivative (XVI) (6·0 g) was freed from methanol by dissolution in benzene and evaporation to dryness *in vacuo* (repeated twice). The non-crystalline residue was dissolved in tetrahydrofuran (90 ml) and t-butyl alcohol (90 ml) and added to freshly distilled liquid ammonia (200 ml). To this mixture was added lithium wire (2·8 g) in several portions during 15 min. The blue solution was stirred under reflux for 6 h, then methanol (50 ml) was added carefully. The solution was then left for 15 h during which time most of the ammonia evaporated. To the residue were added brine (300 ml) and benzene (200 ml), and the organic layer was then washed once more with brine before being dried and evaporated. The residue was crystallised from methanol to give the *dihydro-product* (XVII) (5·0 g), m.p. 115—120°, u.v. end absorption only (2·52 mg in 50 ml EtOH), τ 9·24 and 9·09 [C(18)H_3 and C(9α)CH_3], 6·44 [C(3)OCH_3], and 5·36 [C(2)H] (Found: C, 79·7; H, 10·2. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

3-*Methoxy*-9α-*methylestra*-2,5(10)-*dien*-17-*one* (XVIII).—A mixture of the 17β-hydroxy-compound (XVII) (5·0 g) and aluminium isopropoxide (4·5 g) in benzene (45 ml) and butan-2-one (45 ml) was stirred and heated under reflux for 22 h. It was then cooled and poured on ice and 2N-sodium hydroxide (5 ml). The organic layer was separated, washed with brine, dried, and evaporated. The residue was crystallised from ether–hexane (1 : 1) to give the 17-*ketone* (XVIII) (3·4 g), m.p. 175—177°, τ 9·10 and 9·06 [C(18)H_3 and C(9α)CH_3], 6·44 [C(3)OCH_3], and 5·34 [C(2)H] (Found: C, 80·3; H, 9·5. $C_{20}H_{28}O_2$ requires C, 79·9; H, 9·4%).

17α-*Ethynyl*-17β-*hydroxy*-9α-*methylestr*-5(10)-*en*-3-*one* (XIX).—A solution of 3-methoxy-9α-methylestra-2,5(10)-dien-17-one (XVIII) (1·9 g) in dimethyl sulphoxide (30 ml) was added to a stirred mixture of lithium acetylide–ethylenediamine complex (4 g) in dimethyl sulphoxide (30 ml) maintained under nitrogen at room temperature. After stirring for 2·5 h the brown mixture was poured on ice and the precipitate was filtered off. The solid was dissolved in benzene (50 ml) and the solution evaporated to dryness to give crude 17α-ethynyl-17β-hydroxy-3-methoxy-9α-methylestra-2,5(10)-diene (1·6 g) [$\nu_{max.}$ 1740 cm^{-1} (17-carbonyl, trace only)].

The crude product was dissolved in glacial acetic acid (30 ml) and water (4 ml) and left at room temperature for 1 h. The solution was poured on ice and extracted with ether. After the usual work-up the product was crystallised from acetone–hexane to give the non-conjugated *ketone* (XIX) (520 mg), m.p. 162—164°, $[\alpha]_D$ +92° (*c* 0·87), $\nu_{max.}$ 3590 (OH), 3300 (≡CH), and 1710 cm^{-1} (C=O); τ 9·12 and 9·03 [C(18)H_3 and C(9α)CH_3] and 7·39 [C(17α)C≡CH] (Found: C, 80·4; H, 9·1. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

17α-*Ethynyl*-17β-*hydroxy*-9α-*methylestr*-4-*en*-3-*one* (XX).—To a solution of crude 17α-ethynyl-17β-hydroxy-3-methoxy-9α-methylestra-2,5(10)-diene (1·0 g) [prepared as described for the 5(10)-en-3-one (XIX)] in methanol (10 ml) was added concentrated hydrochloric acid (5 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 acetone–hexane gave the conjugated *ketone* (XX) (360 mg), m.p. 197—200°, $[\alpha]_D$ −7° (*c* 0·79), $\lambda_{max.}$ 240 nm (ε 15,300), $\nu_{max.}$ 3590 (OH), 3300 (–C≡H), and 1660 cm^{-1} (C=O), τ 9·23 and 9·08 [C(18)H_3 and C(9α)CH_3] and 7·39 [C(17α)C≡CH] (Found: C, 80·6; H, 9·2. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

17β-*Hydroxy*-9α,17α-*dimethylestr*-4-*en*-3-*one* (XXI).—To a solution of the 17-ketone (XVIII) (4·5 g) in ether (120 ml) and tetrahydrofuran (50 ml), stirred under nitrogen, was slowly added a 1·6M-solution of methyl-lithium in ether (20 ml). The resulting solution was heated under reflux for 1 h, cooled, and poured on ice. Extraction with ether and work-up in the usual way gave a crude product which was dissolved in methanol (45 ml) and acidified with concentrated hydrochloric acid (2 drops). After 30 min at 60° the solution was cooled and again poured on ice and extracted with ether. Removal of the solvent left a residue which crystallised from methylene chloride–ether (1 : 1) to give the *dimethyl compound* (XXI) (2·7 g), m.p. 200—202°, $[\alpha]_D$ +28·6° (*c* 0·37), τ 9·27 and 9·06 [C(18)H_3 and C(9α)CH_3] and 8·73 [C(17α)CH_3] (Found: C, 79·2; H, 10·3. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

3-*Methoxy*-9α-*methyl*-19-*norpregna*-1,3,5(10),17(20)-*tetraene* (XXII).—A solution of ethylidenetriphenylphosphorane in dimethyl sulphoxide (250 ml) was prepared as reported [23] from sodium hydride (5·75 g of a 55% dispersion in mineral oil) and ethyltriphenylphosphonium iodide (48·7 g). To this solution was added a solution of the 17-oxo-compound (XV) (7·8 g) in dimethyl sulphoxide (150 ml) and the mixture was maintained at 100° for 20 h under nitrogen. It was then cooled, poured on ice, and extracted with ether. The extract was washed with brine and then water, dried,

and evaporated. The residue (*ca.* 15 g) was crystallised twice from methanol to give the *tetraene* (XXIIa) (1·8 g), m.p. 94—95°, τ 9·14 and 8·96 [C(18)H_3 and C(9α)CH_3], 8·32 [centre of multiplet, C(21)H_3], and 4·88 [centre of multiplet, C(20)H] (Found: C, 84·8; H, 9·8. $C_{22}H_{30}O$ requires C, 85·1; H, 9·7%).

The combined residues were dissolved in methylene chloride and filtered through silica gel (100 g) to give further product, as a mixture of *cis*- and *trans*-isomers (2·4 g), m.p. 75—80°.

Application of the foregoing procedure to *rac*-(XV) gave the racemic tetraene *rac*-(XXII), m.p. 85—95° (isomers).

9α-*Methyl*-19-*norpregn*-4-*ene*-3,20-*dione* (XXIV).—To a solution of the tetraene (XXII) (4·2 g) (mixture of *cis*- and *trans*-isomers) in tetrahydrofuran (200 ml) under nitrogen and cooled to 5° was added a 1M-solution of diborane in tetrahydrofuran (40 ml). After stirring at room temperature for 2·5 h the solution was again cooled to 5° and 2N-sodium hydroxide (120 ml) was added. This was followed after 15 min by 30% hydrogen peroxide (120 ml), added dropwise, and stirring at 5° was continued for 1·5 h. The mixture was then poured on ice and extracted with ethyl acetate. Drying and removal of the solvent gave a residue which was chromatographed on a column of silica gel (100 g). Fractions eluted with 2% methanol–chloroform gave the noncrystalline mixture of isomeric alcohols (3·2 g), τ (major isomer) 9·32 and 8·98 [C(18)H_3 and C(9α)CH_3] and 8·75 [d, C(21)H_3] (no olefinic proton signal).

A solution of the product in tetrahydrofuran (300 ml) and t-butyl alcohol (40 ml) was added to liquid ammonia (300 ml), followed in portions by lithium wire (3 g). The blue solution was stirred under reflux for 5 h, ethanol (40 ml) was added, and the ammonia was allowed to evaporate. To the residue were added water and benzene; the benzene layer gave a crude product (3·1 g) which was dissolved in methanol (30 ml) and treated with conc. hydrochloric acid (1 ml). After 30 min at 60° the solution was poured on ice–sodium hydrogen carbonate solution and extracted with ether in the usual way. The crude product showed $\lambda_{max.}$ 241 nm but t.l.c. indicated the presence of a minor, less polar component. This was not separated at this stage but oxidised along with the desired material.

To a solution of the crude material in dimethylformamide was added chromium trioxide (2·7 g), with slight cooling, followed by concentrated sulphuric acid (2 ml) in dimethylformamide (50 ml). After 2 h at room temperature the mixture was diluted with water and extracted with ether in the usual way. The residue remaining after removal of the ether was chromatographed on a column (15 × 2 cm) of silica gel. The initial fractions eluted with chloroform gave material which crystallised from ether to give 3-*methoxy*-9α-*methylpregna*-1,3,5(10)-*trien*-20-*one* (XXV) (120 mg), m.p. 115—116°, τ 9·38 and 8·94 [C(18)H_3 and C(9α)CH_3], 7·86 [C(21)H_3], and 6·24 [C(3)OCH_3] (Found: C, 81·3; H, 9·2. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

Subsequent fractions, also crystallised from ether, gave the 3,20-*dione* (XXIV) (660 mg), m.p. 152—155°, $[\alpha]_D$ 124° (*c* 0·75), $\lambda_{max.}$ 241 nm (ε 16,500), τ 9·31 and 9·22 [C(18)H_3 and C(9α)CH_3], 7·88 [C(21)H_3], and 4·08 [C(4)H] (Found: C, 80·4; H, 9·7. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

Application of the foregoing procedure to *rac*-(XXII) gave racemic 3,20-*dione* *rac*-(XXII), m.p. 162—165° (Found: C, 80·5; H, 9·7%).

17,17-*Ethylenedioxy*-11α-*hydroxy*-3-*methoxyestra*-1,3,5(10)-*triene* (XXVII).—The procedure just described was applied to (±)-17,17-ethylenedioxy-3-methoxyestra-1,3,5(10),9(11)-tetraene [24] *rac*-(XXVI) (11·0 g). Treatment with diborane gave a product, which, after filtration through a column of silica gel (20 g), crystallised from aqueous ethanol (4·1 g), m.p. 83—93° (presumably solvated). Attempts to recrystallise this material from alternative solvents and to improve the purity were unsuccessful; the product showed τ 9·14 [C(18)H_3], 6·22 [C(3)OCH_3], 6·08 [C(17)O·CH_2·CH_2·O], and 5·84 [m, C(11β)H].

(±)-17,17-*Ethylenedioxy*-3-*methoxyestra*-1,3,5(10)-*trien*-11-*one*, rac-(I) [*from* rac-(XXVII)].—To a solution of the 11α-hydroxy-compound *rac*-(XXVII) (13·5 g) in dimethyl sulphoxide (80 ml) were added benzene (80 ml) and pyridine (10 ml), followed by *NN*-dicyclohexylcarbodi-imide (24·8 g), and then (dropwise during 15 min) dichloroacetic acid (5·4 ml). After stirring at room temperature for 3 h, a white suspension resulted to which was added ether (400 ml), and then oxalic acid (13·5 g) in methanol (50 ml). After stirring for a further 40 min, the mixture was filtered and the filtrate was washed with sodium hydrogen carbonate solution and water (2 ×). The organic layer was dried, *etc.*, to give a residue which crystallised from ether (14 g), m.p. 135—145°.

This material was shown to contain non-steroidal impurities which proved difficult to remove completely. However, three recrystallisations from ether gave the 11-ketone *rac*-(I), m.p. 149—150°, whose spectral properties were identical with those of material prepared by the published procedure.[13]

17,17-*Ethylenedioxy*-11α-*hydroxy*-3-*methoxy*-9β-*methylestra*-1,3,5(10)-*triene* (XXIX).—A solution of the 17-ketone [4] (XXVIII) (700 mg) in benzene (20 ml) and ethylene glycol (0·5 ml) containing toluene-*p*-sulphonic acid (70 mg) was heated under reflux for 2 h, using a Dean–Stark trap. The cooled solution was worked up as usual to give a residue which crystallised from ether, yielding the 17-*acetal* (XXIX) (700 mg), m.p. 169—171°, $[\alpha]_D$ −40° (*c* 0·16), τ 9·01 [C(18)H_3], 8·61[C(9β)CH_3], 6·22 [C(3)OCH_3], and 1·78 [C(1)H] (Found: C, 73·4; H, 8·4. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

17,17-*Ethylenedioxy*-3-*methoxy*-9β-*methylestra*-1,3,5(10)-*trien*-11-*one* (IIb).—The 11α-hydroxy-compound (XXIX) (700 mg) was oxidised with 8N-chromic acid in sulphuric acid [17] to give the 11-ketone (IIb) (600 mg). This material could not be induced to crystallise; it showed $\nu_{max.}$ 1690 cm^{-1} (C=O), τ 9·13 [C(18)H_3], 8·62 [C(9β)CH_3], and 6·22 [C(3)OCH_3].

11α-*Benzoyloxy*-3-*methoxy*-9β-*methylestra*-1,3,5(10)-*trien*-17-*one* (XXX).—To a solution of the 11α-hydroxy-compound (XXVIII) (1·05 g) in dioxan (5 ml) and pyridine (2 ml) was added (at 0°) freshly distilled benzoyl chloride (1·0 ml). The mixture was left at 0° for 18 h, and then filtered. The filtrate was distributed between ether (100 ml) and cold N-hydrochloric acid (10 ml) and the organic phase was then further washed with water, 2N-sodium carbonate solution, and water again before being dried and evaporated. The residue crystallised from ether to give the 11α-*benzoate* (XXX) (1·0 g), m.p. 175—180°. Recrystallisation from ether gave a sample of m.p. 188—189°, $[\alpha]_D$ +67° (*c* 0·38), $\nu_{max.}$ 1735 [C(17)=O] and 1710 cm^{-1} (benzoate), τ 8·84 and 8·68 [C(18)H_3 and C(9β)CH_3], 6·22 [C(3)OCH_3], and 4·48 [q, C(11β)H] (Found: C, 77·8; H, 7·4. $C_{27}H_{30}O_4$ requires C, 77·5; H, 7·2%).

3-*Methoxy*-9β-*methylestra*-1,3,5(10),11-*tetraen*-17-*one* (XXXI).—The 11α-benzoate (XXX) (1·2 g) was heated in a kugelrohr apparatus at an oven temperature of 250° which

was slowly raised to 350°, the internal vacuum being maintained at *ca.* 100 mmHg. The more volatile material which collected in the second bulb proved to be benzoic acid (m.p. and mixed m.p.); the steroid slowly distilled into the first bulb. The non-crystalline contents of this bulb (800 mg) were dissolved in the minimum of methylene chloride and applied to six thick-layer chromatography plates (40 × 20 cm × 1 mm). After two developments with chloroform, two bands were apparent. The more polar (200 mg) was the starting benzoate (i.r.); the less polar (450 mg) was the desired tetraene (XXXI). This could not be obtained crystalline; it showed $\nu_{max.}$ 1740 cm^{-1} (C=O), τ 9·00 [C(18)H_3], 8·62 [C(9β)CH_3], 6·24 [C(3)OCH_3], and 4·04 [s, C(11)- and C(12)-H].

3-*Methoxy*-9β-*methylestra*-1,3,5(10)-*trien*-17-*one* (XXXII).—To a solution of the tetraene (XXXI) (450 mg) in methanol (25 ml) was added 10% palladium–carbon (100 mg) and the mixture was shaken under hydrogen. After 1 h (*ca.* 110% of the theoretical uptake) the mixture was filtered and evaporated; the residue crystallised from ether yielding the *triene* (XXXII) (420 mg), m.p. 124—125°, $[\alpha]_D$ +14° (*c* 0·98), τ 9·04 [C(18)H_3], 8·78 [C(9β)CH_3], and 6·22 [C(3)OCH_3] (Found: C, 80·3; H, 8·5. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

3-*Methoxy*-9β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* (XXXIII).—(a) The 17-ketone (XXXII) (90 mg) was reduced with sodium borohydride (100 mg) as described for the 9α-methyl compound (XVI) to give the 17β-*hydroxy-compound* (XXXIII) (70 mg), m.p. 117—118°, $[\alpha]_D$ −63° (*c* 0·26), τ 9·15 [C(18)H_3], 8·82 [C(9β)CH_3], 6·48 [t, C(17α)H], and 6·22 [C(3)OCH_3] (Found: C, 79·7; H, 9·3. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%).

(b) *From* 17β-*hydroxy*-9β-*methylestr*-4-*en*-3-*one* (XXXVIIb).—To a solution of the αβ-unsaturated ketone (XXXVIIb) (270 mg) in ethanol (5 ml) was added 5% palladium–carbon (270 mg). The suspension was refluxed under nitrogen for 20 h, cooled, and filtered and the filtrate was evaporated. The residue was applied to two thick-layer plates (40 × 20 cm × 1 mm) and after development in 5% methanol–chloroform the most polar band was isolated. This crude phenol (130 mg) was methylated (methyl iodide–potassium carbonate–methanol) to give the ring-A-aromatic compound (XXXIII) (110 mg), m.p. and mixed m.p. 115—118°, identical (spectra) with the product of method (*a*).

17β-*Hydroxy*-9β-*methyl*-4,5-*secoestrane*-3,5-*dione* (XXXVIb).—A solution of the αβ-unsaturated ketone [27] (XXXIV) (3·3 g) in ether (200 ml) was added during 15 min to a solution of lithium dimethylcuprate [28] in ether (200 ml) [from copper(I) iodide (19 g) and a 1·6M-solution of methyllithium in ether (125 ml)] cooled in ice, and stirring was continued at this temperature for 1·5 h. After stirring for a further 15 h, at room temperature, aqueous 10% ammonium chloride (200 ml) was added and the organic layer was separated, washed, dried, and evaporated to give crude 3,3-ethylenedioxy-17β-hydroxy-9β-methyl-4,5-secoestran-3-one (XXXV) (3·2 g) as an oil. A sample (100 mg) was purified by thick-layer chromatography; $\nu_{max.}$ 1705 cm^{-1} (C=O), τ 9·19 and 9·15 [C(18)H_3 and C(9β)CH_3], 8·67 [C(4)H_3], and 6·07 [C(3)O·CH_2·CH_2·O].

The crude acetal (XXXV) (2 g) was dissolved in glacial acetic acid (40 ml) and water (10 ml) and left at room temperature for 6 h. The solution was then carefully neutralised by pouring on ice and aqueous 10% sodium hydrogen carbonate and the mixture was extracted with ether (3 × 100 ml). The combined extracts were washed, dried, and evaporated; the residue crystallised from ether to give the 9β-*methyl dione* (XXXVIb) (690 mg), m.p. 118—120°, $[\alpha]_D$ −10° (*c* 0·45), $\nu_{max.}$ 1705 cm^{-1} (C=O), τ 9·17 and 9·15 [C(18)H_3 and C(9β)CH_3], 7·90 [C(4)H_3], and 6·2 [C(17α)H] (Found: C, 74·5; H, 10·0. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

17β-*Hydroxy*-9β-*methylestr*-4-*en*-3-*one* (XXXVIIb).—The dione (XXXVIb) (230 mg) dissolved in methanolic 5% potassium hydroxide (5 ml) was left at room temperature for 3 h. The solution was then concentrated *in vacuo* and water (20 ml) and methylene chloride (50 ml) were added. The organic phase was worked up as usual to give a non-crystalline residue (180 mg). This was applied to three thick-layer plates (silica gel, 40 × 20 cm × 1 mm) which were developed twice with 2% methanol–chloroform to give the αβ-unsaturated ketone (XXXVIIb) (130 mg), $\nu_{max.}$ 3620 (OH), 1660 (C=O), and 1610 cm^{-1} (C=C), τ 9·16 and 9·10 [C(18)H_3 and C(9β)CH_3], 6·22 [C(17α)H], and 4·04 [C(4)H].

This material could not be crystallised; it was characterised as the 17β-*acetate* (XXXVIIIb), m.p. 172—174°, $[\alpha]_D$ −91·5° (*c* 1·04), $\nu_{max.}$ 1725 (acetate), 1660 (C=O), and 1610 cm^{-1} (C=C), τ 9·10 [C(18)H_3 and C(9β)CH_3], 7·95 [C(17β)Ac], 5·24 [C(17α)H], and 4·05 [C(4)H] (Found: C, 76·1; H, 9·4. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·2%).

9β-*Methylestr*-4-*ene*-3,17-*dione* (XXXIX).—The 17β-hydroxy-compound (XXXVIIb) (3 g) was oxidised with 8N-chromic acid in sulphuric acid [17] to give the 9β-*methyl dione* (XXXIX) (1·85 g), m.p. 128—130°, $[\alpha]_D$ −20·6° (*c* 0·18), $\nu_{max.}$ 1735 [C(17)=O], 1660 [C(3)=O], and 1615 cm^{-1} (C=C), τ 9·05 [C(18)H_3 and C(9β)CH_3] and 4·04 [C(4)H] (Found: C, 79·8; H, 9·3. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·2%).

17β-*Hydroxy*-9β,17α-*dimethylestr*-4-*en*-3-*one* (XL).—To a solution of the diketone (XXXIX) (500 mg) in tetrahydrofuran (5 ml) and ethyl orthoformate (2 ml) under nitrogen, was added ethanol (0·5 ml) containing toluene-*p*-sulphonic acid (10 mg). After 1 h at room temperature, a few drops of pyridine were added, followed by ice–water, and the mixture was extracted with ether to give the crude 3-enol ether (500 mg) (t.l.c.). This was not characterised further but dissolved in tetrahydrofuran (10 ml) and treated at room temperature with 1·6M-methyl-lithium in ether (5 ml). After 3 h, brine was added, followed by ether, and the organic phase was separated. The residue (400 mg) remaining after removal of the solvent was dissolved in methanol (10 ml) and 2N-hydrochloric acid (0·5 ml) was added. After 1 h sufficient aqueous 10% sodium hydrogen carbonate was added to neutralise the acid and the mixture was concentrated *in vacuo*. To the residue were added water and methylene chloride and the organic phase was worked up as usual. The presence of two materials was shown by t.l.c. and the crude product (360 mg) was therefore applied to three thick-layer plates (SiO_2). Development in 2% methanol–chloroform (3 ×) gave a less polar material (50 mg) which proved (m.p. and mixed m.p.) to be the starting dione (XXXIX), and a more polar material which crystallised from ether to yield the *dimethyl ketone* (XL) (205 mg), m.p. 140—142°, $[\alpha]_D$ −110° (*c* 0·91), τ 9·10 and 9·05 [C(18)H_3 and C(9β)CH_3], 8·70 [C(17α)CH_3], and 4·04 [C(4)H] (Found: C, 78·9; H, 9·9. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

17α-*Ethynyl*-17β-*hydroxy*-9β-*methylestr*-4-*en*-3-*one* (XLI).—A solution of the crude enol ether (1·3 g) (see foregoing experiment) in dimethyl sulphoxide (10 ml) was added to a

stirred solution of lithium acetylide–ethylenediamine complex (3 g) in dimethyl sulphoxide (10 ml) and stirring was continued at room temperature for 2·5 h. The mixture was then poured on ice–water and extracted with methylene chloride. After work-up as usual, the organic phase gave a residue (1·2 g) which was dissolved in methanol (20 ml), and 2N-hydrochloride acid (1 ml) was added. After 3 h at room temperature the acid was neutralised with sodium hydrogen carbonate solution, as before, and work-up gave a residue (1 g) which was chromatographed on thick-layer plates (silica gel; 3% methanol–chloroform) to give a main fraction which crystallised from ether to afford the *ethynyl compound* (XLI) (600 mg), m.p. 192—194°, $[\alpha]_D$ −152° (*c* 0·41), τ 9·08 and 9·04 [C(18)H_3 and C(9β)CH_3], 7·38 [C(17α)C≡CH], and 4·03 [C(4)H] (Found: C, 80·6; H, 8·9. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

9α-*Cyano*-3,3-*ethylenedioxy*-17β-*hydroxy*-4,5-*secoestran*-5-*one* (XLIIIa).—To a solution of the αβ-unsaturated ketone[27] (XXXIV) (16·7 g) in benzene (250 ml) and toluene (150 ml), cooled to 0° under nitrogen, was added dropwise a 2M-solution of diethylaluminium cyanide[32] (50 ml), further diluted with benzene (50 ml). The mixture was stirred at 0° for 2 h and then poured with stirring into cold N-sodium hydroxide solution (800 ml). It was then extracted three times with ether and the combined extracts were washed, dried, and evaporated. The residue crystallised from ether to give the *cyano-seco-steroid* (XLIIIa) (9·5 g), m.p. 152—154°, $[\alpha]_D$ −24·5° (*c* 0·59), $\nu_{max.}$ 3620 (OH), 2230 (CN), and 1720 cm^{-1} (C=O), τ 9·14 [C(18)H_3], 8·68 [C(4)H_3], and 6·07 [C(3)O·CH_2·CH_2·O] (Found: C, 69·5; H, 8·8; N, 4·0. $C_{21}H_{31}NO_4$ requires C, 69·8; H, 8·7; N, 3·9%).

T.l.c. of the non-crystalline residue (6·5 g) indicated the presence of a mixture of the product (XLIIIa) and two others, besides some starting material. The second product was slightly more polar (silica gel; 5% methanol–chloroform) than the main product, whereas the third was considerably more polar. A portion (500 mg) of the oil was therefore applied to thick-layer plates (silica gel, 40 × 20 cm × 1 mm; 5% methanol–chloroform ×2) and the three products were isolated. After more 9α-isomer (XLIIIa) above, there was obtained the minor 9β-*cyano-isomer* (XLIIIb) (90 mg), m.p. 170—172°, $[\alpha]_D$ +15° (*c* 0·36), $\nu_{max.}$ 3610 (OH), 2230 (CN), and 1720 cm^{-1} (C=O), τ 9·10 [C(18)H_3], 8·70 [C(4)H_3], and 6·11 [C(3)O·CH_2·CH_2·O] (Found: C, 69·8; H, 8·7; N, 3·7%).

The third product, present in very minor amount, was probably the bis-adduct (XLII), m.p. 218—221° (from ether), $\nu_{max.}$ 3600 (OH) and 2230 cm^{-1} (CN) (no carbonyl), M^+ 388.

9α-*Cyano*-3,3;5,5-*bisethylenedioxy*-4,5-*secoestran*-17β-*ol* (XLIV).—A solution of the 5-oxo-compound (XLIIIa) (1·7 g) in benzene (45 ml) containing ethylene glycol (1·7 ml) and toluene-*p*-sulphonic acid (150 mg) was refluxed (Dean–Stark trap). After 1 h it was cooled, washed with aqueous 10% sodium hydrogen carbonate, dried, and evaporated. The residue was crystallised from di-isopropyl ether to give the *bis-acetal* (XLIV), m.p. 137—139°, $\nu_{max.}$ 3605 (OH) and 2225 cm^{-1} (CN), τ 9·22 [C(18)H_3], 8·69 [C(4)H_3], and 6·07 [C(3)- and C(5)-O·CH_2·CH_2·O] (Found: C, 68·6; H, 8·4. $C_{23}H_{35}NO_5$ requires C, 68·2; H, 8·7%).

17β-*Hydroxy*-9α-*methyl*-4,5-*secoestrane*-3,5-*dione* (XXXVIa).—To a stirred solution of the 9α-cyano-derivative (XLIV) (5·0 g) in ether (150 ml) was added dropwise at room temperature a solution of di-isobutylaluminium hydride in hexane (50 ml of a *ca.* 20% solution). The mixture was then heated under reflux for 3 h (>90% reaction by t.l.c.), cooled, and poured into ice-cold brine. The resulting emulsion was extracted several times with ethyl acetate and the combined extracts were washed with brine, dried, and evaporated to give the crude iminomethyl compound (XLV) (1·5 g), $\nu_{max.}$ 3600 (OH) and *ca.* 3450br cm^{-1} (NH) (no CN), τ 9·22 [C(18)H_3], 8·74 [C(4)H_3], 6·10 [C(3)- and C(5)-O·CH_2·CH_2·O], and 1·96 [C(9α)CH?].

A solution of this crude product (XLV) (3·0 g) in triethylene glycol (150 ml) containing hydrazine hydrate (24 g) and hydrazine dihydrochloride (3·94 g) was heated at 130° for 2·5 h. To this potassium hydroxide (9·1 g) was then added in portions and the temperature was slowly raised to 210° where it was held for 3 h. During this time a distillate was slowly collected. The solution was then cooled and poured into ice-cold brine (500 ml) before being extracted (3 ×) with ether. The combined extracts were washed, dried, and evaporated to give the crude product (2·5 g). This was chromatographed on a column of silica gel (3 × 25 cm). After elution of a small amount of by-product with methylene chloride, the main product was eluted with 2% methanol–methylene chloride to give the methyl bis-acetal (XLVI) (2·0 g), τ 9·24 and 9·20 [C(18)H_3 and C(9α)CH_3] and 6·08 [C(3)- and C(5)-O·CH_2·CH_2·O].

This material could not be crystallised; it was therefore dissolved in glacial acetic acid (40 ml) containing water (8 ml) and left at room temperature overnight. The solution was then concentrated *in vacuo* and the residue was dissolved in ether. After drying, the ether was removed to give a crystalline product which was recrystallised from ether, yielding the *methyl diketone* (XXXVIa) (860 mg), m.p. 164—165°, $[\alpha]_D$ −16·3° (*c* 0·39), $\nu_{max.}$ 3610 (OH) and 1710 cm^{-1} (C=O), τ 9·36 and 9·15 [C(18)H_3 and C(9α)CH_3], 7·89 [C(4)H_3], and 6·28 [C(17α)H] (Found: C, 74·8; H, 10·0. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

17β-*Hydroxy*-9α-*methylestr*-4-*en*-3-*one* (XXXVIIa).—(a) To a solution of the estradiene (XVII) (1·2 g) in methanol (20 ml) was added concentrated hydrochloric acid (2 drops) and after 2·5 h at room temperature the solution was neutralised with aqueous 10% sodium hydrogen carbonate and concentrated. The residue was extracted with methylene chloride and the organic solution was worked up in the usual way. The crude product (1 g) was chromatographed on silica gel (100 g) and after recovery of a small amount of starting material by elution with chloroform, elution with 5% methanol–chloroform gave the αβ-unsaturated ketone (XXXVIIa) (780 mg), τ 9·26 and 9·16 [C(18)H_3 and C(9α)CH_3], 6·24 [C(17α)H], and 4·05 [C(4)H].

This material could not be crystallised and was characterised as the 17β-*acetate* (XXXVIIIa), m.p. 143—145°, $[\alpha]_D$ +35° (*c* 1·01), τ 9·25 and 9·13 [C(18)H_3 and C(9α)CH_3], 7·94 [C(17β)OAc], 5·26 [C(17α)H], and 4·05 [C(4)H] (Found: C, 76·5; H, 9·3. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·2%).

(b) *From* 17β-*hydroxy*-9α-*methyl*-4,5-*secoestrane*-3,5-*dione* (XXXVIa).—The dione (XXXVIa) (250 mg) was dissolved in methanolic 5% potassium hydroxide (10 ml) and left at room temperature for 15 h. The solution was then concentrated *in vacuo* without heating, and water (10 ml) and ether (50 ml) were added to the residue. After drying, the ether was evaporated off to give the crude αβ-unsaturated ketone (XXXVIIa) (195 mg). This was acetylated as usual to give the 17β-acetate (XXXVIIIa), identical (m.p. and mixed m.p. 144—146°, i.r. and n.m.r. spectra) with the material from method (a).

[3/740 *Received*, 9*th April*, 1973]