Total Synthesis of 12-Methyl-19-nor-steroids

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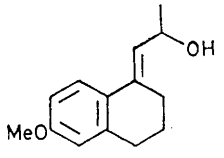
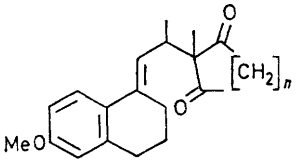
The reaction of 6-methoxy-1-tetralone with the Grignard reagent from 1-bromopropene gave a mixture of allylic alcohols which could be condensed with 2-methylcyclopentane-1,3-dione, in the presence of acetic acid, to yield two isomeric 12-methylestra-1,3,5(10),8,14-pentaenes (VIa) in the ratio *ca.* 5 : 1, albeit in a combined yield of less than 10%. Subsequent chemical transformations and an *X*-ray analysis of a derivative showed that the major isomer had the C-12 and -13 methyl groups in a *trans*-arrangement.

In pursuance of our programme on the synthesis of potential steroid hormones bearing nuclear alkyl groups,[1] we chose as the next goal 12-methyl-19-nor-steroids, a little studied class of compounds. In fact, although an extensive literature exists on 12-methyl-steroids, often derived from hecogenin or the like,[2] only one complete sequence has been described leading to a similarly substituted 19-nor-compound.[3] The key reaction in this is the introduction of the methyl group by 1,8-conjugate addition of an organometallic reagent to a 3-oxo-4,9,11-triene. However, the poor yields obtained in our hands, and the anticipated difficulties in the stereospecific reduction of such a system to the desired 12-methyl analogue of 19-nortestosterone, *etc.*, made it unattractive for our purposes. We, therefore, turned to total synthesis.[4]

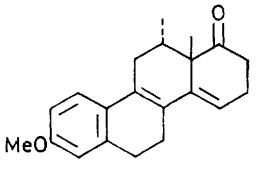
The utility of the Torgov approach to the synthesis of modified steroids has been well documented,[5] and the Russian workers themselves have reported [6] some initial



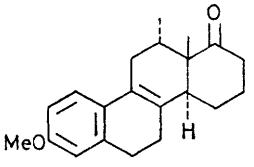
(I)



(II) a; *n* = 2
b; *n* = 3



(III)



(IV)

results on the synthesis of 12-methylestrogens. Condensation of the allylic alcohol (I) with cyclic 2-methyl-1,3-diones gave the tricyclic intermediates (IIa and b). No further work was reported with (IIa), cyclisation of which would have given the normal steroid skeleton, but the intermediate (IIb) was treated with toluene-*p*-sulphonic acid in benzene to yield the D-homo-estrapentaene (III), the C-12 methyl group being assigned the α-stereochemistry. Hydrogenation of this product was reported to give 3-methoxy-12α-methyl-D-homoestra-1,3,5(10),8-tetraen-17a-one (IV).

We treated the Grignard reagent prepared from a *cis–trans*-mixture of isomers of 1-bromopropene with 6-methoxy-1-tetralone, to give the mixed tetralols (V). The crude alcohol mixture was treated with 2-methylcyclopentane-1,3-dione in refluxing xylene in the presence of acetic acid, conditions known [7] to effect direct cyclisation to the tetracyclic structure. After work-up, *ca.* 80% of unchanged dione could be recovered by filtration, and chromatography of the residual oil gave at first a mixture of the diene and its dimers derived from the starting alcohols by dehydration, and subsequently a seemingly homogeneous material in 5—10% yield. More rigorous examination of this showed it to be a binary mixture (*ca.* 5 : 1), which could be separated by thick-layer chromatography. Both components gave satisfactory elemental analyses for the expected estrapentaenone (VIa), and although having very similar m.p.s showed markedly different n.m.r. spectra, one of the *C*-methyl signals appearing as a doublet at τ 9.24 in that of the major isomer and at τ 8.72 in that of the minor. The u.v. spectra were identical, each having a maximum at 312 nm as expected for estra-1,3,5(10),8,14-pentaenes.[8] The compounds, therefore, are isomeric, differing in the stereochemistries at C-12 and -13.

The structure of the major isomer A was established as (VIb) by an *X*-ray structure determination † of the 3-oxo-Δ^4-compound (VII) derived from the pentaenone by the reaction sequence shown in Scheme 1 (the C-13 methyl group being arbitrarily designated β, all compounds being racemic mixtures).

The presence of the C-12 methyl group on the α-side of the molecule results in the formation of a *cis*-CD ring fusion in the ketone (VIIIa), in contrast to the *trans*-fusion produced not only in the unsubstituted series [8]

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

[1] (*a*) R. V. Coombs, J. Koletar, R. Danna, H. Mah, and E. Galantay, *J.C.S. Perkin I*, 1973, 2095; (*b*) R. V. Coombs, J. Koletar, R. P. Danna, and H. Mah, *ibid.*, 1975, 792.

[2] *E.g.* J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Letters*, 1965, 4469.

[3] Fr. P. 01,653/1969.

[4] R. V. Coombs, presented at the Fourth International Congress on Hormonal Steroids, Mexico City, September 1974.

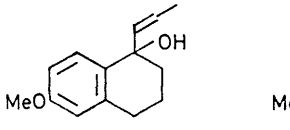
[5] J. Weill-Raynal, *Bull. Soc. chim. France*, 1969, 4561.

[6] (*a*) A. V. Zakharychev, D. R. Lagidze, and S. N. Ananchenko, *Tetrahedron Letters*, 1967, 803; (*b*) A. V. Zakharychev, D. R. Lagidze, S. N. Ananchenko, and I. V. Torgov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1968, 2332.

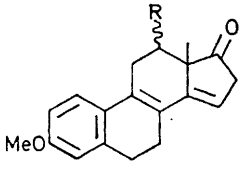
[7] C. H. Kuo, D. Taub, and N. L. Wendler, *J. Org. Chem.*, 1970, **33**, 3126.

[8] 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.

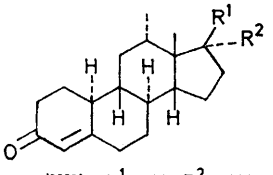
but also in the 12α-methyl-D-homo-example.[6] In agreement with the reported[9] formation of the 17α-hydroxy-compound (IXb) on reduction of the 17-ketone (VIIIb) by hydride ion, the 12α-methyl-17-hydroxy-steroid has structure (IXa). Reduction of the 8,9-double bond with sodium in liquid ammonia in the presence of aniline[8] yields a single isolated product (Xa) with the 8α,9β-geometry, whereas the tetraene (IXb) gives two isomeric trienes having the 8α,9β- and 8α,9α-stereochemistry, respectively.[9] Birch reduction[10] of (Xa) then leads to the diene (XI), and treatment of this with methanolic hydrogen chloride yields the 3-oxo-Δ^4-compound (VII) of known stereochemistry. The transformation of a 3-methoxy-1,3,5(10),8-tetraene into a 3-oxo-Δ^4-system has been described[11] in the unsubstituted 14βH-series, and a major product was deduced by further synthetic work and a comparison with known compounds to have the same arrangement as in the present instance, *i.e.* 8α-H,9β-H,10α-H.



(V)



(VI) a; R = Me
b; R = α-Me
c; R = β-Me



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

Oxidation of the 17α-hydroxy-compound (XI) under Oppenauer conditions[12] regenerated the 17-oxo-group but all attempts to bring about the reaction of this product (XII) with the lithium acetylide–ethylenediamine reagent[13] in dimethyl sulphoxide or to initiate the synthesis of the 17-(propa-1,2-dienyl) steroid by reaction with the lithium salt of 3-dimethylaminopropyne[14] were unsuccessful. The presence of a *cis*-fused CD ring juction can apparently cause the reactions of a 17-ketone to be modified; for example, the ketone (VIIIb) is reported[11] to give the 17β-ethynyl product in only 25% yield under the usual reaction conditions. It is concluded that the extra hindrance of the 12α-methyl substituent (even though molecular models predict this to be slight in most conformations) is sufficient to prevent reaction with these bulky, complexed reagents.

Isomer A —i→ 14,15-Dihydro (VIIIa) —ii→ 17-Hydroxy (IXa) —iii→ 8,9-Dihydro (Xa) —iv→ 1,4-Dihydro (XI) —v→ 3-Oxo (VII)
1,4-Dihydro (XI) —vi→ 17-Oxo (XII) —vii→ No reaction

SCHEME 1 Reagents: i, Pd–H_2; ii, $NaBH_4$; iii, Na–NH_3–$PhNH_2$; iv, Li–NH_3–Bu^tOH; v, H^+; vi, $Al(OPr^i)_3$–MeCOEt; vii, LiC≡CH

Reactions performed with the minor isomer B, which must have structure (VIc), are outlined in Scheme 2. Hydrogenation proved difficult to stop at the dihydro-stage, the main product being the 8,9,14,15-tetrahydro-compound. Since the presence of an additional substituent, the 12-methyl group, on the β-face should not hinder the normally preferred mode of hydrogenation from the α-side, these products can be assigned structures (XIV) and (XV), respectively. The ketone (XV) was available in sufficient quantity for one reaction to be attempted, and in this instance the 17-ethynyl product (XVI) was isolated in good yield without difficulty. The ethynyl group is assigned the α-orientation in consideration of the reported[9] reactions of 8α-estrone.

Isomer B —i→ 14,15-Dihydro (XIV) + 8,9,14,15-Tetrahydro (XV) —ii→ 17-Ethynyl-17-hydroxy (XVI)

SCHEME 2 Reagents: i, Pd–H_2; ii, LiC≡CH

The biological properties of several of these compounds will be reported elsewhere.

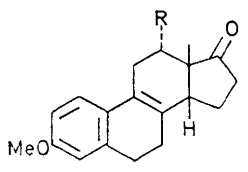
EXPERIMENTAL

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

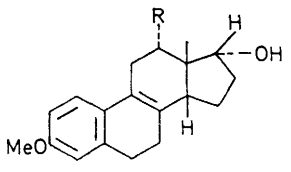
3-Methoxy-12-methylestra-1,3,5(10),8,14-pentaen-17-one (VIa).—To a mixture of magnesium (33.8 g) and tetrahydrofuran (50 ml), stirred under nitrogen, was slowly added a solution of 1-bromopropene (183.5 g) in tetrahydrofuran (130 ml), so as to maintain a steady reflux. When the addition was complete the mixture was heated under reflux for 1 h, and then cooled to room temperature. To this was added a solution of 6-methoxy-1-tetralone (132 g) in tetra-

[9] C. Rufer, E. Schröder, and H. Gibian, *Annalen*, 1967, **705**, 211.
[10] H. F. Dryden, jun., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, 1961, **26**, 3237.
[11] P. Crabbe, A. Cruz, and J. Iriarte, *Canad. J. Chem.*, 1968, **46**, 349.
[12] C. Djerassi, *Org. Reactions*, 1951, **6**, 207.
[13] O. F. Beumel, jun., and R. F. Harris, *J. Org. Chem.*, 1964, **29**, 1872.
[14] E. Galantay, I. Bacso, and R. V. Coombs, *Synthesis*, 1974, 344.

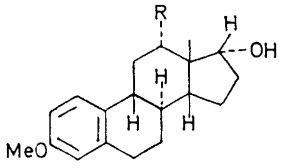
hydrofuran (600 ml) at such a rate as to maintain the reaction temperature between 35 and 40 °C. Stirring was continued at room temperature for 12 h. The mixture was diluted with ether (500 ml) and cooled to 10 °C. Brine (25 ml) was added and the precipitate was removed by filtration through



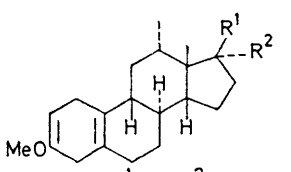
(VIII) a; R = Me
b; R = H



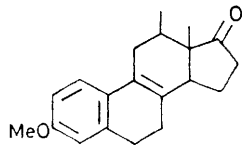
(IX) a; R = Me
b; R = H



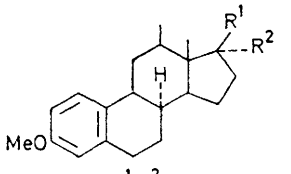
(X) a; R = Me
b; R = H



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



(XIV)



(XV) R^1 R^2 = O
(XVI) R^1 = OH, R^2 = C≡CH

Celite. The filtrate was further diluted with ether (500 ml) and washed with water (2 times) and brine. The organic layer was separated, dried, and evaporated to give the crude alcohols (V) (167 g), $\nu_{max.}$ 3 600 cm^{-1} (OH) (no carbonyl).

To a solution of this crude product (V) (164 g) in xylene (1 200 ml) and glacial acetic acid (525 ml) was added 2-methylcyclopentane-1,3-dione (97 g), and the mixture was heated under reflux when dissolution had occurred, for 48 h. It was then cooled and diluted with ether (1 000 ml), producing a precipitate of the starting dione (86.5 g), m.p. and mixed m.p. 111—112°. The filtrate was concentrated to a red oil (125 g), which was chromatographed on a column of silica gel (15 × 30 cm). Elution with benzene gave a yellow oil (42.5 g) from which, on dilution with ether–petroleum (1 : 1), crystals were obtained (7.5 g), m.p. 179—182°, τ 9.12 (d, CH_3), 8.85 (CH_3), and 6.22 (OCH_3), *m/e* 400 (Found: C, 84.4; H, 8.0. $C_{28}H_{32}O_2$ requires C, 84.0; H, 8.0%); the foregoing data suggest the overall composition to be that of a dimer of 3,4-dihydro-6-methoxy-1-(prop-1-enyl)naphthalene. The mother liquor was a mixture of monomers [g.l.c., and *m/e* 200 ($C_{14}H_{16}O$)]. Further elution with methylene chloride gave an oil (70 g) which t.l.c. showed to contain three components: more diene/monomer (the least polar), a more polar purple product, and thirdly a yet more polar material. This oil was then rechromatographed on a column of silica gel (8 × 40 cm). Elution was performed with methylene chloride containing a gradually increasing percentage (0—5%) of methanol. Fractions with a purple colouration were combined and evaporated yielding an oil (33 g) which still contained some non-polar material as the main contaminant. Moreover, t.l.c. showed there to be two purple coloured products of similar polarity. The oil (33 g) was therefore chromatographed a third time on silica gel (5 × 40 cm). Fractions (50 ml) were collected, with methylene chloride–methanol as eluant as before, and were examined by t.l.c. Thus were obtained two purple oils, one containing mostly the more polar product (12.6 g), and the other mostly the less polar (3.1 g). Crystallisation of the more polar material from ether–hexane (1 : 1) gave 3-*methoxy*-12α-*methylestra*-1,3,5(10),8,14-*pentaen*-17-*one* (VIb) (' isomer A ') (6.1 g), m.p. 109—111°, $\lambda_{max.}$ 312 nm (ε 29 500), τ 9.24 [d, C(12α)CH_3], 8.86 [C(18)H_3], 6.20 [C(3)OCH_3], and 4.01 [m, C(15)H] (Found: C, 81.3; H, 7.6. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.5%).

Treatment of the less polar material with ether yielded the 12β-methyl isomer (B) (VIc) (840 mg), m.p. 107—109°, mixed m.p. with isomer A 80—105°, $\lambda_{max.}$ 312 nm (ε 29 000), τ 8.96 [C(18)H_3], 8.72 [d, C(12β)CH_3], 6.18 [C(3)OCH_3], and 4.12 [t, C(15)H] (Found: C, 81.5; H, 7.5. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.5%).

A more complete separation, albeit of small amounts, was achieved by the use of thick-layer plates [silica gel (40 × 20 cm × 1 mm)] and development with benzene (3 ×).

3-*Methoxy*-12α-*methyl*-14β-*estra*-1,3,5(10),8-*tetraen*-17-*one* (VIIIa).—To a solution of the pentaene (VIb) (294 mg) in benzene (15 ml) was added 5% palladium–calcium carbonate (150 mg) and the mixture was shaken under hydrogen. After 4 h *ca.* 1 equiv. had been absorbed and the mixture was filtered and concentrated. The residue crystallised from methanol yielding the *tetraene* (VIIIa) (270 mg), m.p. 80—82°, $\lambda_{max.}$ 273 nm (ε 15 300), τ 8.80 [C(18)H_3], 8.76 [d, C(12α)CH_3], and 6.17 [C(3)OCH_3] (Found: C, 80.9; H, 8.4. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%).

3-*Methoxy*-12α-*methyl*-14β-*estra*-1,3,5(10),8-*tetraen*-17α-*ol* (IXa).—A mixture of the 17-oxo-compound (VIIIa) (205 mg) and sodium borohydride (80 mg) in ethanol (10 ml) was stirred at room temperature for 4 h. The solvent was then 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 × chloroform). The main fraction (IXa) (178 mg), eluted with ethyl acetate, showed τ 8.98 [C(18)H_3], 8.72 [d, C(12α)CH_3], 6.22 [C(3)OCH_3], and 5.97br [C(17β)].

3-*Methoxy*-12α-*methyl*-8α,9β,14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (Xa).—A solution of the tetraene (IXa) (600 mg) in tetrahydrofuran (10 ml) and aniline (3 ml) was added to freshly distilled liquid ammonia (20 ml). To this mixture were added sodium pellets (600 mg) in several portions during 30 min. The brown solution was stirred under reflux for 2 h and then aqueous ammonium chloride (125 ml; saturated solution) was added, followed by ether (50 ml). The aqueous phase was separated and extracted three times with ether (50 ml). The combined organic extracts were washed with water and brine, dried, and evaporated. The residue was crystallised from ether–petroleum (1 : 1) to give the *triene* (Xa) (230 mg), m.p. 122—124°, $\lambda_{max.}$ 287 nm (ε 1 850) and 278 (ε 1 960), τ 9.11 [C(18)H_3], 8.76 [d, C(12α)-CH_3], 6.22 [C(3)OCH_3], and 5.96br [C(17β)H] (Found: C, 80.0; H, 9.2. $C_{20}H_{28}O_2$ requires C, 79.9; H, 9.4%).

3-*Methoxy*-12α-*methyl*-8α,9β,14β-*estra*-2,5(10)-*dien*-17α-*ol* (XI).—A solution of the triene (Xa) (424 mg) in tetrahydrofuran (10 ml) and t-butyl alcohol (6 ml) was added to freshly distilled liquid ammonia (20 ml). To this mixture was added lithium wire (170 mg) in several portions during 15 min. The blue solution was stirred under reflux for 4 h then methanol (5 ml) was added and the ammonia was allowed to evaporate overnight. To the residue were added ether (50 ml) and water (50 ml) and the aqueous phase was separated and extracted three times with ether (50 ml). The combined organic extracts were washed with water, dried, and evaporated. The residue was crystallised from hexane yielding the *diene* (XI) (360 mg), m.p. 109—110°, u.v. end absorption only (4.7 mg in 50 ml of EtOH), τ 9.14 [C(18)H_3], 8.82 [d, C(12α)CH_3], 6.43 [C(3)OCH_3], 5.98 [d, C(17β)H], and 5.33 [t, C(2)H] (Found: C, 79.7; H, 9.9. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%).

3-*Methoxy*-12α-*methyl*-8α,9β,14β-*estra*-2,5(10)-*dien*-17-*one* (XII).—A mixture of the 17α-hydroxy-compound (XI) (600 mg) and aluminium isopropoxide (500 mg) in benzene (15 ml) and butan-2-one (4 ml) was stirred and heated under reflux for 16 h. Further aluminium isopropoxide (450 mg), butan-2-one (4 ml), and benzene (10 ml) were then added and the heating was continued for 17 h. The mixture was cooled and poured on ice and 2N-sodium hydroxide (15 ml). The organic layer was separated, washed with brine, dried, and evaporated. The residue was crystallised from methanol to give the 17-*ketone* (XII) (220 mg), m.p. 135—137°, τ 8.83 [C(18)H_3], 8.69 [d, C(12α)CH_3], 6.44 [C(3)OCH_3], and 5.35 [t, C(2)H] (Found: C, 79.6; H, 9.1. $C_{20}H_{28}O_2$ requires C, 79.9; H, 9.4%).

Attempted Preparation of 17β-*Ethynyl*-17α-*hydroxy*-3-*methoxy*-12α-*methyl*-8α,9β,14β-*estra*-2,5(10)-*diene*.—A solution of the 17-ketone (XII) (340 mg) in dimethyl sulphoxide (10 ml) was added to a stirred mixture of lithium acetylide–ethylenediamine complex (400 mg) in dimethyl sulphoxide (10 ml) maintained under nitrogen at room temperature. After stirring for 4 h the brown mixture was poured on ice and the precipitate was filtered off. It was dissolved in ether and the solution was washed with water, dried, and evaporated. The residue was crystallised from methanol to yield the starting 17-*ketone* (XII) (184 mg), m.p. 133—136°. The mother liquor contained a more polar material (t.l.c.) in addition to further starting material. This product, isolated on thick-layer plates [silica gel (40 × 20 cm × 1 mm); chloroform], was the 3,17-*diketone* (XIII) (67 mg), m.p. 194—196°, $\lambda_{max.}$ 237 nm (ε 14 900), τ 8.81 [C(18)H_3], 8.68 [d, C(12α)CH_3], and 4.13 [C(4)H] (Found: C, 79.3; H, 9.4. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.2%).

17α-*Hydroxy*-12α-*methyl*-8α,9β,10α,14β-*estr*-4-*en*-3-*one* (VII).—To a solution of the diene (XI) (470 mg) in methanol (25 ml) was added concentrated hydrochloric acid (2 drops). The solution was left at room temperature for 1 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* (VII) (240 mg), m.p. 159—161°, $\lambda_{max.}$ 241 nm (ε 15 200), τ 9.16 [C(18)H_3], 8.82 [d, C(12α)CH_3], 5.96 [d, C(17β)H], and 4.15 [C(4)H] (Found: C, 79.0; H, 10.1. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%).

3-*Methoxy*-12β-*methyl*-8α-*estra*-1,3,5(10)-*trien*-17-*one* (XV).—To a solution of the pentaene (VIc) (790 mg) in benzene (25 ml) was added 5% palladium–calcium carbonate (650 mg), and the mixture was shaken under hydrogen. After 5 h the uptake approached 1 equiv. and the mixture was filtered and evaporated. T.l.c. indicated the presence of some starting material, and essentially one more polar product. The crude residue could not be crystallised and was chromatographed on silica gel plates (40 × 20 cm × 1 mm), developed twice with benzene. The new material was eluted with ethyl acetate and crystallisation from ether–petroleum (1 : 1) gave the *triene* (XV) (275 mg), m.p. 126—127°, $\lambda_{max.}$ 287 (ε 2 500) and 278 nm (ε 2 670), τ 9.08 [C(18)H_3], 8.91 [d, C(12β)CH_3], and 6.22 [C(3)OCH_3], *m/e* 298 (Found: C, 80.4; H, 8.4. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%).

Successive fractions of crystalline material were obtained on concentration of the mother liquor, and recrystallisation from methanol of the combined later crops yielded 3-*methoxy*-12β-*methyl*-8α-*estra*-1,3,5(10),8-*tetraen*-17-*one* (XIV) (50 mg), m.p. 133—135°, $\lambda_{max.}$ 279 nm (ε 15 900), τ 9.20 [C(18)H_3], 8.73 [d, C(12β)CH_3], and 6.11 [C(3)OCH_3], *m/e* 296 (Found: C, 80.7; H, 8.5. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%).

17α-*Ethynyl*-17β-*hydroxy*-3-*methoxy*-12β-*methyl*-8α-*estra*-1,3,5(10)-*triene* (XVI).—The 17-ketone (XV) (225 mg) was treated with lithium acetylide–ethylenediamine complex (300 mg) in dimethyl sulphoxide (10 ml) as described for compound (XII). The crude product crystallised from hexane to give the 17α-*ethynyl compound* (XVI) (185 mg), m.p. 120—122°, τ 9.13 [C(18)H_3], 9.06 [d, C(12β)CH_3], 7.41 [C(17)C≡CH], and 6.26 [C(3)OCH_3] (Found: C, 81.1; H, 8.8. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%).

[5/2506 *Received*, 22*nd December*, 1975]