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The Structure and Function of Oestrogens. IV* Synthesis of 17α-Ethynyloestradiol Specifically Polydeuterated in Ring C

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Abstract

Epoxidation of 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (5) by a two-phase procedure gave the labile 9α,11α-epoxide (11), treatment of which with lithium perchlorate in benzene gave 17,17-ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one (7). Deuteration of this by prolonged treatment with the monosodium salt of (*O*,*O*′-$^2H_2$)hydroquinone in dry (*O*-^{2}H)methanol gave mainly the 9β,12,12-trideutero ketone (24) (92% $^2H_3$). Reduction of this with lithium aluminium deuteride to a mixture of the 11-epimeric alcohols (27a) followed by dehydration gave 17,17-ethylenedioxy-3-methoxy(11,12,12-$^2H_3$)oestra-1,3,5(10),9(11)-tetraene (26) which upon reduction with lithium/ammonia gave 17,17-ethylenedioxy-3-methoxy(11ξ,12,12-$^2H_3$)oestra-1,3,5(10)-triene (25). Hydrolysis and demethylation of (25) followed by treatment with potassium acetylide in liquid ammonia yielded 3,17-dihydroxy-19-nor-17α-(11ξ,12,12-$^2H_3$)pregna-1,3,5(10)-trien-20-yne (29) ($^2H_4$, 9·2; $^2H_3$, 84·1; $^2H_2$, 3·1; $^2H_1$, 2·2; $^2H_0$, 1·3%).

Reduction of the trideutero 9(11)-ene (26) with hexadeuterodiborane followed by treatment with alkaline hydrogen peroxide afforded 17,17-ethylenedioxy-3-methoxy(9α,11β,12,12-$^2H_4$)oestra-1,3,5(10)-trien-11α-ol (30a). Reduction of the corresponding tosylate (30b) with lithium aluminium deuteride, then hydrolysis, demethylation and ethynylation gave 3,17-dihydroxy-19-nor-17α-(9,11,11,12,12-$^2H_5$)pregna-1,3,5(10)-trien-20-yne (35) ($^2H_5$, 84·5; $^2H_4$, 8·5; $^2H_3$, 4·4; $^2H_2$, 0·9; $^2H_1$, 0·8; $^2H_0$, 0·9%).

Introduction

Although some studies have been made of the degree to which contraceptive steroids, or their metabolites, are transferred into human milk,[1–8] precise data are still lacking in this area, and on the extent to which any such compounds present in breast milk affect the infant.[9,10] Analytical methods based on radioimmunoassay

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do not provide information about excretion of potentially active metabolites of the administered steroid, and their specificity is difficult to prove. The administration of radioactively labelled steroids, as in the early studies,[1–4] is no longer acceptable, especially since the advent of computerized g.l.c./m.s. simultaneously provides structural information as well as quantitative analysis of minute amounts of steroid hormones in biological fluids.[11–13] For such studies, polydeuterated compounds of high isotopic content and purity are required both for administration/recovery and as procedural reference standards. As part of a program sponsored by the World Health Organisation we undertook the synthesis of tri- and penta-deuterated forms of ethynyloestradiol, which is one of the two important oral contraceptive oestrogens. In addition to the requirement of material with high isotopic purity it was necessary to introduce the deuterium into metabolically stable positions of the steroid nucleus. Because human metabolism of 17α-ethynyloestradiol includes hydroxylation at C2, C4, C6, C7 and C16,[14–18] ring c is the most desirable, albeit not the most accessible location for polydeuteration of this molecule. This paper describes in detail the synthesis of 11ξ,12,12-tri- and 9α,11,11,12,12-penta-deutero ethynyloestradiol. Some of this work has been outlined previously.[19,20]

Preparation of 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one (7)

As the springboard for access to positions 9, 11 and 12, 9(11)-dehydrooestrone 3-methyl ether (3b) (see Scheme 1) was required in relatively large amounts. This compound has been prepared by total synthesis,[21,22] aromatization of suitable androstane derivatives,[23,24] and dehydrogenation of oestrone with the adamantanyl cation (60% yield),[25] or with 2,3-dichloro-5,6-dicyanoquinone (ddq) (62%):[26] but claims[27,28] for its preparation by direct dehydrogenation of oestrone 3-methyl ether (1b) with high potential quinones are misleading. In a patent[27] it was stated that (3b) was obtained by dehydrogenation of (1b) with chloranil in a mixture of dioxan and t-butyl alcohol, but no yield was given. Brown *et al.*[28] claimed 70%

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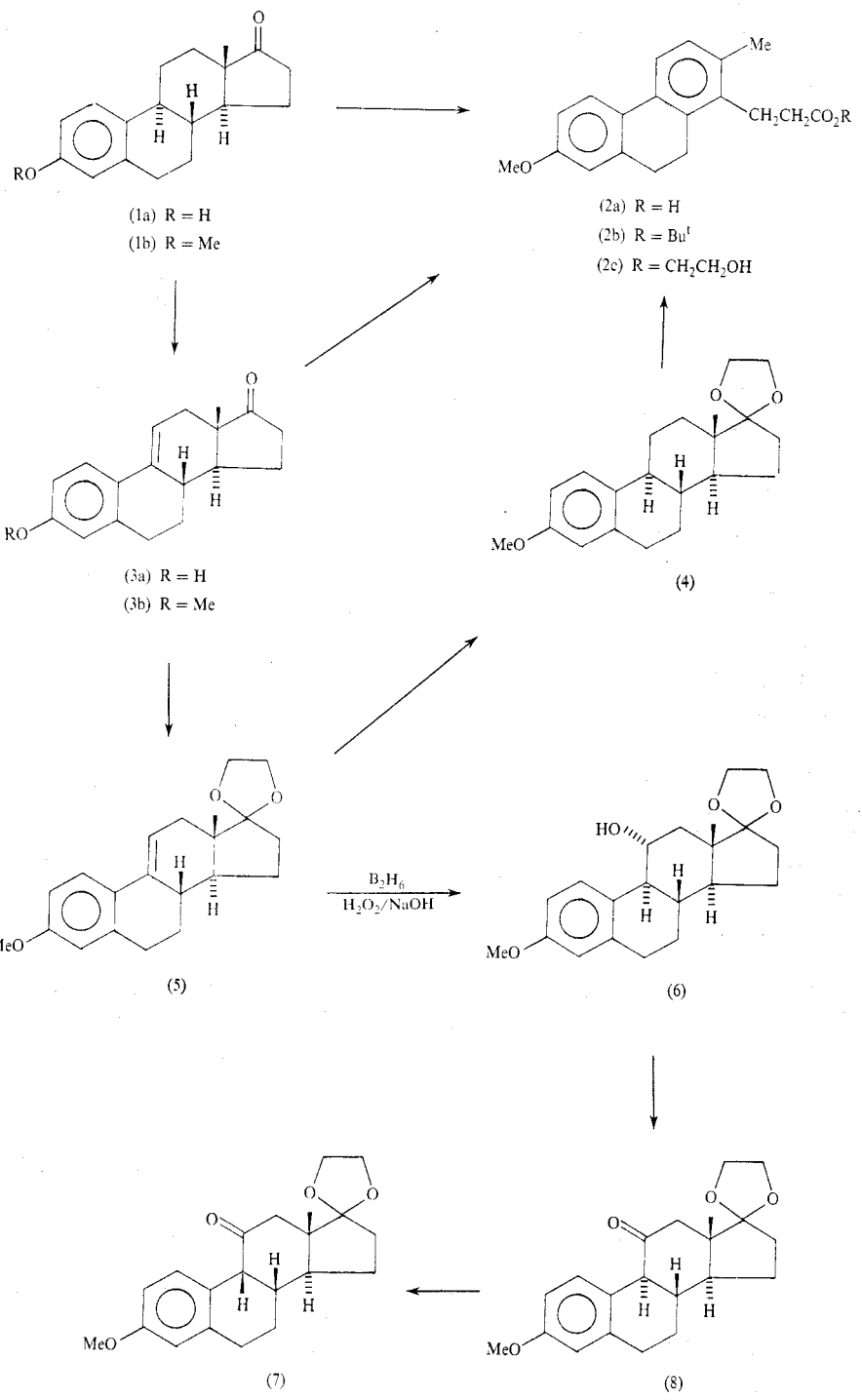
RO
(1a) R = H
(1b) R = Me
Me
CH2CH2CO2R
MeO
(2a) R = H
(2b) R = Bu^t
(2c) R = CH2CH2OH
RO
(3a) R = H
(3b) R = Me
MeO
(4)
MeO
(5)
B2H6
H2O2/NaOH
HO
MeO
(6)
MeO
(7)
MeO
(8)

Scheme 1

yield of (3b) by oxidation of (1b) with ddq in dioxan at 20°; numerous attempts to substantiate these claims failed. The nicely crystalline product from some runs appeared to have the correct melting point, but invariably it proved to be an approximately 1 : 1 mixture of (1b) and (3b), as shown by u.v. and g.l.c. analysis. Numerous reactions were tried in different solvents under various conditions with no significant improvement. Since chromatographic separation of (1b) and (3b) is difficult on a large scale, the direct oxidation of (1b) to (3b) with ddq is impractical. A reaction of (1b) with chloranil in refluxing t-butyl alcohol (cf.[27]) similarly gave an approximately 1 : 3 mixture of (3b) and (1b) as the neutral portion of the product. Apparently the 9(11)-dehydro compound (3b) suffers further dehydrogenation at a rate comparable with its formation; alkali washes of the crude product yielded acidic material which is probably mainly (2a). Such an aromatization–ring cleavage reaction was observed by Cross *et al.*[29] in the oxidation of (1b) with chloranil in refluxing t-butyl alcohol which gave the t-butyl ester (2b) in addition to (3b). Also, oxidation of the cyclic acetal (4) of oestrone 3-methyl ether with ddq for 5 min at 20° gave 77% of the ester (2c).[30] Cambie and Carlisle[26] found that 3-methoxyoestra-1,3,5(10)-triene could not be oxidized cleanly to the 9(11)-dehydro compound, but instead underwent aromatization in rings B and C with methyl migration. Clearly, the course of dehydrogenation of oestra-1,3,5(10)-triene derivatives by high potential quinones is very sensitive to the nature of the substituents at positions 3 and 17. Cambie and Carlisle[26] mentioned briefly that oestrone (1a) could be oxidized to (3a) in 62% yield with ddq in methanol, but no details were given; a patent[31] describes a similar reaction in dioxan. The reliable ddq/methanol procedure described below can be carried out conveniently on a 20-gram scale giving at least 70% of pure (3a). Methylation of this gave 87% of pure (3b).

Treatment of (3b) with ethylene glycol containing *p*-toluenesulfonic acid according to the Salmi procedure[21,32] gave 90% of the recrystallized cyclic ethylene acetal (5), m.p. 156–157°, $[\alpha]_D$ +90·7°, λ_{max} 263 nm (ε 19466). The corresponding values given in a patent[32] (146–147°, +63°, 18800) are appreciably lower, quite possibly because the 9(11)-dehydro ketone (3b) used was contaminated with oestrone methyl ether (1b). The physical constants of 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene (4) are consistent with this possibility (see Experimental). Hydroboration of (5) followed by alkaline peroxide oxidation gave the 11α-alcohol (6).[32] Oxidation of this with pyridinium chlorochromate afforded the non-crystalline 9αH 11-ketone (8) which had been obtained previously by Jones oxidation of the 11β-epimer of (6),[33–36] but the only physical data quoted for (8) was its i.r. absorption at 5·84 μm.[33] The 9αH 11-ketone (8) was quite unstable. Even rapid chromatography on basic alumina

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led to substantial epimerization to the more stable 9β-isomer (7); moreover, the total recovery of the epimers (7) and (8) was low due to alumina-catalysed hydroxylation at C9 (see below). Rapid chromatography on Florisil gave the pure 9αH 11-ketone (8) which has been fully characterized. The ease with which the 9αH 11-ketone (8) is epimerized to the 9β-isomer (7) is further illustrated by the fact that attempted reduction of (8) with lithium aluminium tri-t-butoxyhydride gave very little carbinol, presumably due to steric hindrance, but the recovered ketone was mainly the 9β-epimer (7). The greater stability of the 9β-epimers of oestra-1,3,5(10)-trien-11-ones has been observed previously,[37,38] and Liang *et al.*[38] have found that (19b) is more stable than (19a) by 1·47 kcal/mole.* The corresponding difference between (7) and (8) appears to be greater: whereas kinetically controlled protonation of the 9α-anion derived from the more stable 9βH 11-ketone (19b) gave mainly the 9α-epimer (19a),[38] similar treatment of (7) resulted in the recovery of almost pure (7). Possibly the buttressing effect of the 17α-pseudoaxial oxygen of the 17-cyclic acetal group on the 1,3-related 14α-axial hydrogen in the 9αH 11-ketone (8) is relayed to the 9α-proton, adding to the intrinsic configurational instability at C9 in the 11-oxo-9α-oestra-1,3,5(10)-triene system.

Since the 9αH 11-ketone (8) is stereochemically labile, direct preparation of the stable 9β-epimer (7) through rearrangement of the epoxide (11) was investigated (see Scheme 2). Initial attempts to epoxidize the 9(11)-ene (5) led only to yellow ketonic material which was mainly the 9βH 11-ketone (7). Epoxidation of (5) by the two-phase dichloromethane/aqueous potassium carbonate procedure of Anderson and Veysoglu[39] afforded the crystalline but extremely acid-sensitive epoxide (11). Even when its i.r. spectrum was measured immediately in freshly purified chloroform there was significant carbonyl absorption, and after a few hours none of the epoxide (11) remained; suitable precautions were necessary for its recrystallization and spectroscopic examination (see Experimental). Reduction of (11) with lithium aluminium hydride gave the 9α-alcohol (10) which was dehydrated with pyridinium chlorochromate to the 9(11)-ene (5) in high yield. The ^{1}H and ^{13}C n.m.r. spectra of (10) were consistent with its formulation as a tertiary alcohol. This indicates that the precursor epoxide is the 9α,11α-isomer (11) in which diaxial opening with hydride would be expected to give the 9α-alcohol (10), whereas reduction of the 9β,11β-epoxide (9) should afford the known[33] 11β-alcohol (12). A small amount of the 9β,11β-epoxide (9) was probably present in the mother liquor from crude (11) but it was not isolated. Preparation of the epimeric epoxides (9) and (11) was claimed in a patent[40] but no details or physical constants were given. Epoxidation of 9(11)-dehydrooestrone acetate was reported by Tsuda *et al.*[41] to give 76% of the 9α,11α-epoxide (16) and 1·2% of the 9β,11β-isomer. Upon reduction of the 9α,11α-epoxide (16) with lithium aluminium hydride they obtained a secondary alcohol which they formulated[37,41] as the 11α-alcohol (13) with 9α-stereochemistry, explaining the abnormal non-axial cleavage of the oxiran ring by intermediacy of a benzylic

* For SI units: 1 cal = 4·184 J.

[37] Hasegawa, H., Nozoe, S., and Tsuda, K., *Chem. Pharm. Bull.*, 1963, **11**, 1037.
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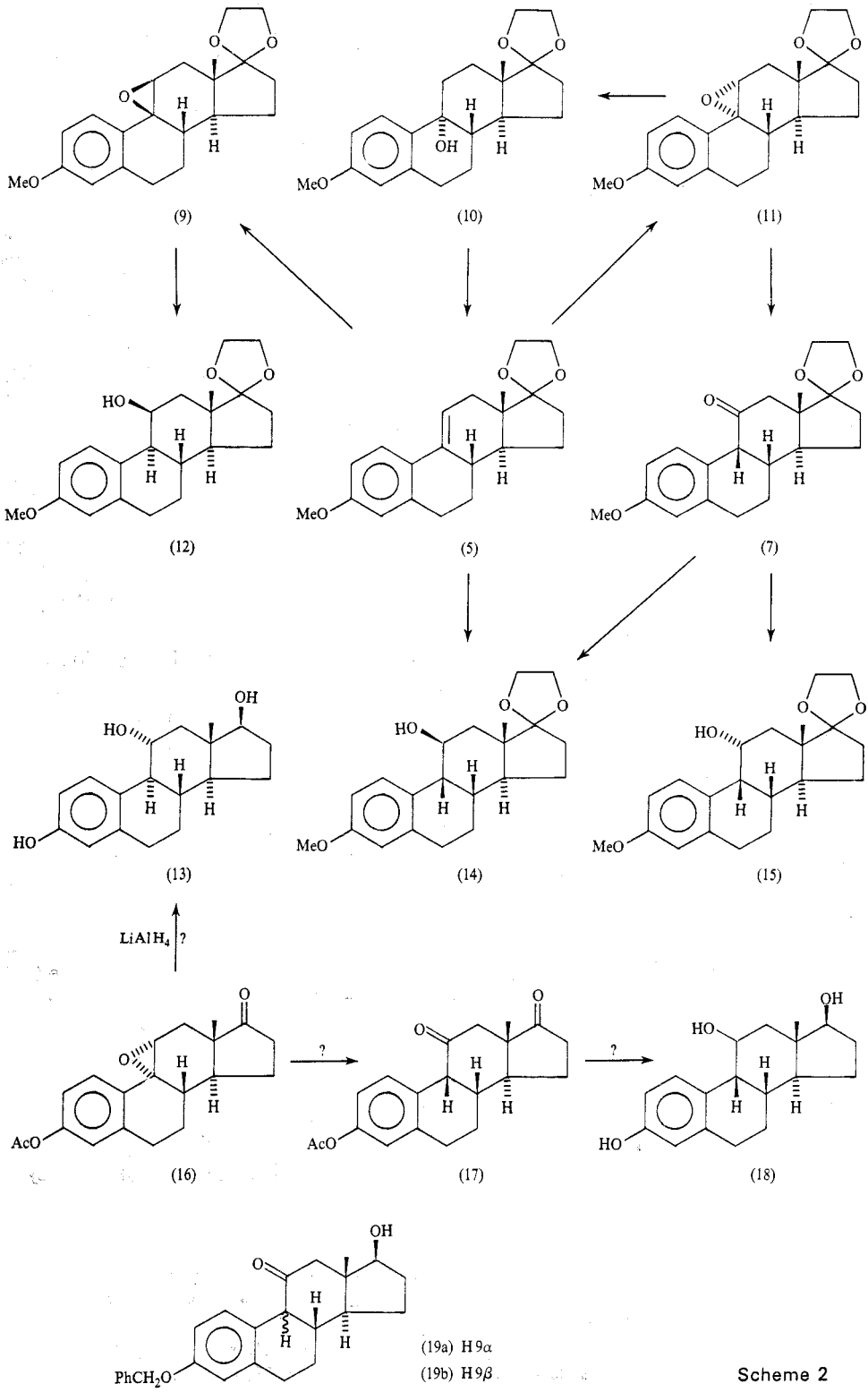

MeO
(9)
(10)
(11)
HO
(12)
(5)
O
(7)
OH
(13)
(14)
(15)
LiAlH4 ?
AcO
(16)
?
(17)
(18)
PhCH2O
(19a) H 9α
(19b) H 9β

Scheme 2

cation. This is surprising in view of our finding that the 9α,11α-epoxide (11) is reduced normally to give the tertiary alcohol (10) with the same reagent.*

Lithium perchlorate cleanly catalyses the rearrangement of certain cyclohexane-1,2-epoxides into the corresponding cyclohexanones.[42,43] When the epoxide (11) was heated under reflux for 2·5 h in dry benzene containing a small amount of lithium perchlorate the 9βH 11-ketone (7) was obtained almost quantitatively, and shown to be *c.* 97% pure by g.l.c. Reduction of the 9βH 11-ketone (7) with lithium aluminium hydride gave a non-crystalline product shown by g.l.c. to be a mixture of the epimeric carbinols (14) and (15) (17 and 81% respectively), together with about 2% of the 9(11)-ene (5). The last compound was presumably formed by dehydration of the sensitive 9α-alcohol (10) which could result from hydride reduction of a small amount of unrearranged epoxide present in the 11-ketone (7).

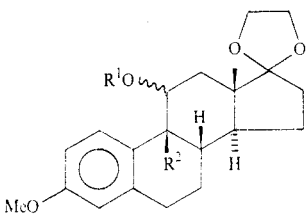
Preparative t.l.c. on alumina gave the major 11α-equatorial alcohol (15) as a gum, $[\alpha]_D$ +30·5° (H 11-axial δ 4·45, W_H 18 Hz), and the minor 11β-axial alcohol (14), m.p. 126–128°, $[\alpha]_D$ +102·6° (H 11-equatorial δ 4·76, W_H 5·6 Hz). The tentative configurational assignments of (14) and (15) are based on the assumption that ring C is in the chair form (cf.[38]), but the available evidence does not exclude the possibility that ring C is in a boat or twist boat conformation, in which case the assignments would be reversed. In the deuteration sequences described below the deuterated mixture of epimers corresponding to (14) and (15) was used directly without separation.

Deuteration Experiments (See Scheme 3)

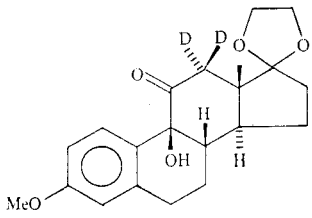
Attempted trideuteration of the 9βH 11-ketone (7) by phase-transfer catalysis with tetrabutylammonium bromide in dichloromethane/sodium deuteroxide/deuterium oxide (cf. Starks[44]) gave the 9β-monodeutero ketone (23). Direct g.l.c./m.s. analysis of the reaction mixture after 4 days showed the ketone (7) with *m/z* 342; this indicates apparent lack of deuteration. Evidently the 9β-deuterium of (23) being both benzylic to a *para*-methoxyl and adjacent to the 11-carbonyl group is labile in the g.l.c./m.s. system, and it was necessary to measure the deuterium content of (23) indirectly. Samples of the crude deuterated ketone worked up after 1–4 days reaction time were reduced with lithium aluminium hydride, and the mixture of 11-epimeric alcohols (20a) was trimethylsilylated to (20b), then analysed by g.l.c./m.s. This showed almost complete monodeuteration after 1 day, and little di- or tri-deuteration after even 4 days. Thus, the phase-transfer procedure could be used for selective 9β-monodeuteration of (7). That the deuterium atom was at C9 was indicated by the following observations. In addition to the expected epimeric trimethylsilyl ethers

* A possible alternative explanation for the formation of a secondary alcohol in the hydride reduction of (16) is that under the conditions used the epoxide (16) might have rearranged to the 9βH 11-ketone (17) prior to reduction. If so, the triol obtained would have been (18) with 9β-stereochemistry. If their evidence[37] for structure (13) with 9α-stereochemistry is sound, it is difficult to reconcile abnormal hydride attack at C9 in (16) with normal β-face attack of hydride at C11 in (11). Since the epoxide (16) was prepared by a normal perbenzoic acid/chloroform procedure and the Japanese authors made no mention of spontaneous rearrangement to (17) during normal handling,[41] it appears that (16) is more stable than (11) making it perhaps even more surprising that the reduction of (16) proceeds abnormally.

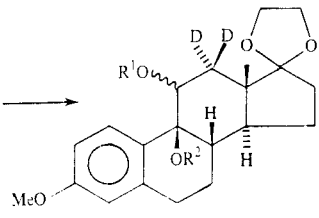
[42] Rickborn, B., and Gerkin, R. M., *J. Am. Chem. Soc.*, 1968, **90**, 4193.
[43] Rickborn, B., and Gerkin, R. M., *J. Am. Chem. Soc.*, 1971, **93**, 1693.
[44] Starks, C. M., *J. Am. Chem. Soc.*, 1971, **93**, 195.



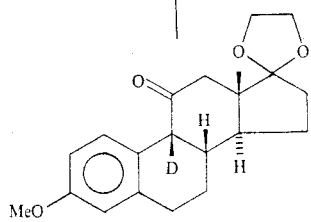
	R^1	R^2
(20a)	H	D
(20b)	Me_3Si	D
(20c)	Me_3Si	OH
(20d)	Me_3Si	$OSiMe_3$



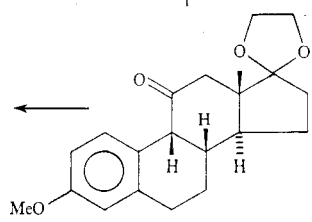
(21)



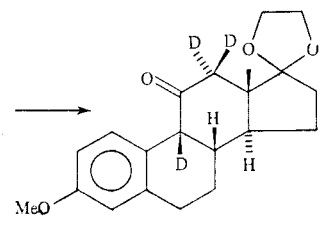
	R^1	R^2
(22a)	Me_3Si	H
(22b)	Me_3Si	Me_3Si



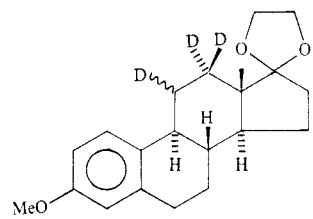
(23)



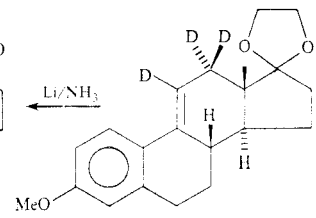
(7)



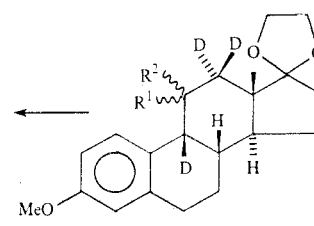
(24)



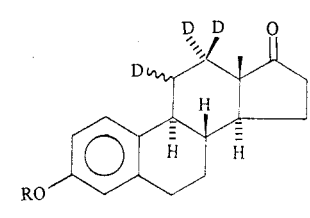
(25)



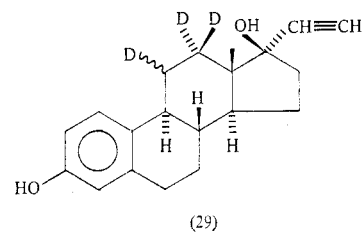
(26)



	R^1	R^2
(27a)	OH	D
(27b)	$OSiMe_3$	D
(27c)	$\alpha OSiMe_3$	βH
(27d)	$\beta OSiMe_3$	αH



(28a) R = Me
(28b) R = H



(29)

Scheme 3

(20b), g.l.c./m.s. analysis revealed higher molecular weight compounds with *m/z* 432 and 504, the amount of which increased with the reaction time. These derivatized by-products were formulated as (20c) and (20d) respectively, the tertiary 9β-hydroxyl being incompletely trimethylsilylated. Significantly, neither (20c) nor (20d) contained deuterium, the extra oxygen function having displaced the 9β-deuterium. Confirmation of structures (20c) and (20d) follows from the observation that the trideuteration of (7) described below correspondingly led to the formation of the dideutero hydroxy ketone (21); this was revealed after reduction and trimethylsilylation as a mixture of (22a) and (22b) with *m/z* respectively 434 and 506, each two mass units higher than the corresponding pair (20c) and (20d). The base-catalysed 9-hydroxylation of the 11-ketone (7) occurred in a nitrogen atmosphere with normal precautions for the exclusion of oxygen. It is very difficult to exclude oxygen completely, but the extent of hydroxylation appears to rule out atmospheric oxygen as the source of the 9-hydroxyl group, and reaction of a 9-anion radical with water is possibly involved.

Table 1. G.l.c. and g.l.c./m.s. analysis of products from deuteration of 17,17-ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one with NaOD/MeOD/D_2O, followed by hydride reduction and trimethylsilylation

Structure of product	Relative retention time[A]	Mol. wt[B]	Yield (%) after 24 h	48 h	72 h
(27c)	0·66	419	60	41	22
(27d)	0·91	419	13	<17[C]	<10[C]
(22b)	0·84	506	14	32	41
(22a)	1·04	434	7	5	10
Unidentified	1·14	—	2	3	5
Unidentified	1·21	—	4	3	13

[A] Relative to 5α-cholestane taken as 1·00.
[B] By mass spectrometry (*m/z*).
[C] These values are inflated by an unidentified overlapping impurity.

The revelation that the 9βH 11-ketone (7) undergoes base-catalysed hydroxylation at C9 explained the partial loss of (7), with concomitant formation of hydroxylic material during chromatography on alumina (see above), and also complicated the preparation of the fully trideuterated ketone (24). Thus, treatment of (7) with sodium deuteroxide in MeOD and D_2O under nitrogen in the usual way led to extensive formation of (21). For g.l.c./m.s. analysis the product, sampled at 24, 48 and 72 h, was reduced with lithium aluminium hydride then trimethylsilylated. As shown in Table 1, the yield of (24), analysed as a mixture of the 11-epimeric trimethylsilyl ethers (27c) and (27d), decreased with time, while there was a corresponding increase in formation of the 9-hydroxylated compound (21) [analysed a (22a) and (22b)], and of other unidentified by-products.

To prevent 9-hydroxylation during the deuteration of (7) a procedure was devised which essentially lacked OD^- while having the ability to exchange protons and deuterons. Fully *O*-deuterated hydroquinone was prepared by treatment of the disodium salt of hydroquinone with *O*-deuterated acetic acid, and recrystallization of the product from D_2O. A solution of this and the 11-ketone (7) in (*O*-^{2}H)methanol containing about 77% of the amount of sodium methoxide theoretically required

to form the dianion from the amount of (O,O'-$^2H_2$)hydroquinone used was stirred in a nitrogen atmosphere under gentle reflux for 10 days. Although the deuteration of (7) proceeded slowly owing to the weakly basic nature of the medium, g.l.c./m.s. analysis of the product showed only a negligible amount of hydroxylation at C9 and the ketone (24) [analysed as (27c) and (27d)], contained about 92% of the trideuterated species. This procedure could be useful in other cases where the ketone is unusually susceptible to hydroxylation in alkaline aqueous alcohol.

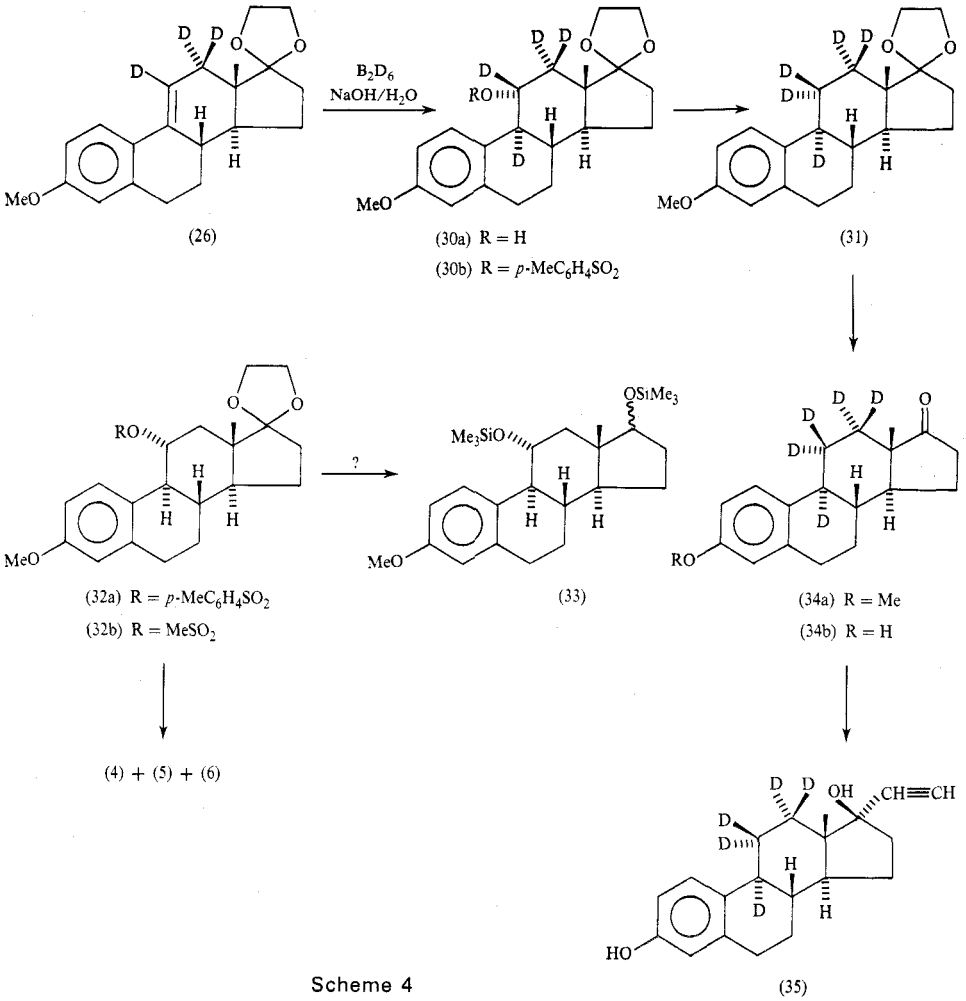
Reduction of the trideutero ketone (24) with lithium aluminium deuteride gave a mixture of the epimeric tetradeutero carbinols (27a) containing about 90% of the tetradeuterated species. Dehydration of this mixture (27a) with phosphoryl trichloride in pyridine gave the crystalline trideuterated olefin (26), g.l.c./m.s. of which showed about 90% trideuteration. Catalytic reduction of (26) to the required 9αH-trideuterated compound (25) was avoided because of the likelihood of partial isotopic scrambling and loss of deuterium, either of which could cause problems in the use of the derived compounds (28b) or (29) in quantitative metabolic studies. Reduction of the styrenoid double bond with lithium in liquid ammonia was therefore preferred. A trial reduction of the unlabelled 9(11)-dehydro compound (5) gave a crystalline product which was shown by g.l.c. to consist of at least 95% of the compound (4). If present, the 9β-isomer was there in negligible quantity, and one recrystallization gave analytically pure (4), identical with an authentic specimen prepared[45] from oestrone methyl ether (1b).

Lithium/ammonia reduction of the trideutero 9(11)-ene (26) afforded the corresponding 9αH compound (25). Surprisingly, g.l.c./m.s. analysis of this revealed appreciable isotope redistribution with 7·3% of tetradeuterated molecules, but overall retention of deuterium. The complete isotope distribution was: $^2H_4$, 7·3; $^2H_3$, 85·4; $^2H_2$, 3·0; $^2H_1$, 2·1; $^2H_0$, 2·2%. The 9(11)-ene precursor (26) showed: $^2H_3$, 89·9; $^2H_2$, 5·0; $^2H_1$, 2·3; $^2H_0$, 1·9%. There is no doubt about the accuracy of the computer analysis of the data, and all subsequent compounds in the reaction sequence showed a similar isotope distribution. The reason for this phenomenon is not clear. Studies of simple trideuterated styrenoid systems did not show this unusual behaviour.[46]

Acid-catalysed hydrolysis of (25) afforded trideuterated oestrone methyl ether (28a) which upon demethylation with hydrobromic acid/acetic acid gave the trideuterated oestrone (28b). Ethynylation of (28b) with potassium acetylide in anhydrous ammonia (cf.[47]) afforded the crude 17α-ethynyl compound (29) which was found to contain traces of the starting ketone (28b); this was removed by the use of Girard's reagent P (cf.[48]). Chromatography on Unisil (silicic acid) followed by crystallization then gave pure 3,17-dihydroxy-19-nor-17α-(11ξ,12,12-$^2H_3$)pregna-1,3,5(10)-trien-20-yne (29) which was shown by g.l.c./m.s. to have the isotopic composition $^2H_4$, 9·2; $^2H_3$, 84·1; $^2H_2$, 3·1; $^2H_1$, 2·2; $^2H_0$, 1·3%.

Ring C-pentadeuterated ethynyloestradiol (35) was prepared from the 11,12,12-trideutero-9(11)-dehydro compound (26) by the sequence shown in Scheme 4. Reaction of (26) with hexadeuterodiborane followed by alkaline peroxide oxidation afforded the tetradeutero carbinol (30a). Model experiments for the deuteride

[45] De Ruggieri, P., *Gazz. Chim. Ital.*, 1957, **87**, 795.
[46] Collins, D. J., Molinski, T. F., and Sjövall, J., *Aust. J. Chem.*, 1983, **36**, 361.
[47] Inhoffen, H. H., Logemann, W., Hohlweg, W., and Serini, A., *Ber. Dtsch. Chem. Ges.*, 1938, **71**, 1024.
[48] Colley, G., and Harris, I. A., *J. Labelled Compd.*, 1969, **5**, 8.



Scheme 4

displacement of a sulfonyloxy group from a sulfonate ester of (30a) were carried out on sulfonate esters of the undeuterated carbinol (6). The results are summarized in Table 2. Ether was much better than tetrahydrofuran as solvent for reduction of either the mesylate (32b) or the tosylate (32a) with lithium aluminium hydride. The amount of the β-elimination product (5) formed was comparable in both solvents, but hydride attack at sulfur in the sulfonyloxy group to give the carbinol (6) was much greater in tetrahydrofuran for the mesylate (32b) than for the tosylate (32a). Lithium triethylborohydride has been reported to be preferable to lithium aluminium hydride for the reductive displacement of sulfonyloxy groups from certain hindered sulfonate esters.[49,50] This was certainly not the case in the present instance. Lithium triethylborohydride gave no appreciable reaction with (32a) or (32b) at room temperature, and under reflux the tosylate (32a) underwent extensive 1,2-elimination to give 74% of (5), while the mesylate was mainly attacked at sulfur to give the 11α-alcohol (6).

[49] Krishnamurthy, S., and Brown, H. C., *J. Org. Chem.*, 1976, **41**, 3064.
[50] Holder, R. W., and Matturro, M. G., *J. Org. Chem.*, 1977, **42**, 2166.

Reduction of the tosylate (30b) with lithium aluminium deuteride in ether gave a mixture of (31), (26) and the carbinol (30a) (cf. Table 2) and the crude product was treated with hexadeuterodiborane and alkaline peroxide to convert the (26) into (30a); chromatography on alumina then readily gave the pure pentadeutero acetal (31), and the recovered 11α-alcohol (30a) was recycled through the tosylate (30b). Acid-catalysed hydrolysis of (31) to (34a), followed by demethylation, ethynylation, and the usual purification gave 3,17-dihydroxy-19-nor-17α-(9,11,11,12,12-$^2H_5$)pregna-1,3,5(10)-trien-20-yne (35) with the isotopic composition $^2H_5$, 84·5; $^2H_4$, 8·5; $^2H_3$, 4·4; $^2H_2$, 0·9; $^2H_1$, 0·8; $^2H_0$, 0·9%.

Table 2. Hydride reduction of sulfonate esters of 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol (6)

Samples of the crude reduction products were analysed by g.l.c. directly and also after trimethylsilylation which revealed the 11α-alcohol (6), and enabled its positive identification

Sulfonate ester	Reducing agent	Solvent	Products (%) 11-deoxy (4)	9(11)-ene (5)	11α-ol (6)	Unidentified
Tosylate (32a)	$LiAlH_4$	Et_2O	61	11	23	5
	$LiAlH_4$	thf	41	10	38	5
	$LiBEt_3H$	thf	3	74	21	2
Mesylate (32b)	$LiAlH_4$	Et_2O	28	15	51	6
	$LiAlH_4$	thf	2	3	25	70[A]
	$LiBEt_3H$	thf	6	11	65	18

[A] After trimethylsilylation, the major unidentified compound (43%, r.r.t. 0·76) was shown by g.l.c./m.s. to have mol. wt 446. This possibly corresponds to compound (33).

The polydeuterated ethynyloestradiols (29) and (35) have been used in the development of a new method for the quantitative analysis of isomeric ring-A and ring-D glucuronides of ethynyloestradiol.[51] Other metabolic studies involving the use of the polydeuterated ethynyloestradiols (29) and (35) are in progress.

Experimental

Melting points are uncorrected. Ultraviolet spectra were measured with a Zeiss DMR 21 recording spectrophotometer. Infrared spectra were measured with a Perkin–Elmer 257 grating infrared spectrophotometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. ^1H n.m.r. spectra were measured at 100 MHz with a Jeol FX100 spectrometer, or at 90 MHz with a Bruker WH-90 spectrometer. Chemical shifts are relative to internal $SiMe_4$. ^{13}C n.m.r. spectra were measured at 22·63 MHz with a Bruker WH-90 spectrometer, and chemical shifts are relative to internal $SiMe_4$. High-resolution mass spectra were obtained with a VG Micromass 7070F spectrometer. G.l.c./m.s. measurements were made with a modified LKB 9000 instrument equipped with a 2·8 m by 3·5 mm column of 1·5% SE-30 on Chromosorb WHP, 80–100 mesh. The temperatures of the column, separator and ion sources were 230°, 260° and 310°, respectively.[12] The electron energy was 22·5 eV, the ionizing current 60 μA, and the initial accelerating voltage 3·5 kV.

For the determination of isotope content and distribution, partial mass spectra for 6 to 8 values of *m/z* in the appropriate range were obtained by repetitive accelerating voltage scanning (2 s/scan), a data sampling rate of 10 kHz being used.[13] Intensity readings were bunched to give 11 values per mass spectrometric peak which were determined by comparison with the corresponding unlabelled reference compounds on an IBM 1800 computer. G.l.c. analyses were carried out by using a Pye 104 gas chromatograph equipped with a flame ionization detector and 2·5–3·5 m by 3 mm i.d. glass

[51] Sahlberg, B.-L., Axelson, M., Collins, D. J., and Sjövall, J., *J. Chromatogr.*, 1981, **217**, 453.

columns packed with 1·5% SE-30 on Chromosorb WHP. Nitrogen was used as carrier gas at a flow rate of approximately 30 ml/min. The oven temperature was about 220°. Relative retention times (r.r.t.) refer to 5α-cholestane as standard (1·0). Preparative thin-layer chromatography (t.l.c.) was carried out on plates (20 cm by 20 cm) coated with a 1·5-mm layer of Merck alumina F-254 type T. Microanalyses were carried out by Centrala Analys Laboratoriet, Department of Chemistry, University of Uppsala, Sweden, or the Australian Microanalytical Service, Melbourne.

(a) Treatment of 3-Methoxyoestra-1,3,5(10)-trien-17-one (1b) with 2,3-Dichloro-5,6-dicyanoquinone (ddq)

To a stirred solution of pure oestrone 3-methyl ether (132 mg, powdered and dried at 60°/1 mm for 2·5 h) in pure dry dioxan (5 ml), kept at 20°, was added recrystallized ddq (106 mg). The solution rapidly became green, then slowly faded during about 15 min while a greyish precipitate of 2,3-dichloro-5,6-dicyanohydroquinone ($ddqH_2$) separated. The mixture was stirred at 20° for a further 30 min by which time the supernatant had become pale lemon-coloured. The precipitate was collected and washed with dichloromethane (3 × 5 ml). The filtrate was washed successively with dilute sodium sulfite solution, 1% potassium hydroxide, and water, then dried (Na_2SO_4) and evaporated to give a solid (96 mg), λ_{max} (EtOH) 263 nm (ε 9022). T.l.c. indicated this to be an approximately 1 : 1 mixture of starting material and 3-methoxyoestra-1,3,5(10),9(11)-tetraen-17-one. The mixture readily crystallized from methanol or ether as prisms, m.p. 162–167°, $[\alpha]_D$ +191·4° (*c*, 0·49 in chloroform), λ_{max} 264 nm (ε 7270). G.l.c. showed this to be a mixture of oestrone methyl ether (1b) and the 9(11)-dehydro derivative (3b) in the ratio of 55 : 45. Separation of this mixture by column chromatography was difficult and not practicable.

Experiments in which the amount and the rate of addition of the reagent were varied, or t-butyl alcohol was used as a cosolvent, gave similar results. The product from an experiment carried out in 1,4-dioxan at 34° showed additional bands in the u.v. spectrum, and a reaction carried out in refluxing t-butyl alcohol gave a lower proportion of the 9(11)-ene.

(b) Oxidation of 3-Hydroxyoestra-1,3,5(10)-trien-17-one (1a) with 2,3-Dichloro-5,6-dicyanoquinone

A solution of oestrone (18·0 g, 0·067 mol) in dry methanol (2·9 l.) was stirred at 20° under nitrogen while a solution of ddq (15·9 g, 0·070 mol) in dry methanol (100 ml) was added during 2 min. The dark greenish brown solution quickly became orange, then pale yellow within 20 min. It was stirred for a further 40 min, then the methanol was evaporated under reduced pressure. The residue was triturated with hot chloroform (1·8 l.) and the mixture was allowed to stand overnight. Activated charcoal was added, and after brief stirring, this and the $ddqH_2$ were removed by filtration through Celite. The orange-yellow filtrate was evaporated and the residue was triturated with hot ethyl acetate (80 ml), then allowed to cool to room temperature. The solid was collected and washed with cold ethyl acetate (2 × 20 ml) to give crude 3-hydroxyoestra-1,3,5(10),9(11)-tetraen-17-one (3a) (14·8 g). Concentration of the filtrate gave additional, less pure material (1·7 g). Crystallization from ethyl acetate (charcoal) afforded plates (8·9 g), m.p. 258–263° (dec.); second crop (2·8 g), 255–262° (dec.), and third crop (1·1 g), 252–258° (dec.). The pure compound had m.p. 260–263° (dec.), $[\alpha]_D$ +301° (*c*, 0·44 in chloroform); λ_{max} (ethanol) 263·5 (18073), 298 (3138); λ_{min} 234·5 (2918); λ_{infl} 274 nm (ε 13994) [lit.[52] 248–254°, $[\alpha]_D$ +297·5°; lit.[23] 257–259°, λ_{max} 263 (18050), 298 (3125)]. ν_{max} (KBr) 3260, 1730, 1630 cm^{-1}.

(c) 3-Methoxyoestra-1,3,5(10),9(11)-tetraen-17-one (3b)

In an atmosphere of nitrogen 3-hydroxyoestra-1,3,5(10),9(11)-tetraen-17-one (3a) (26·8 g) was dissolved in methanol (800 ml) and water (100 ml) containing potassium hydroxide (7·0 g), then cooled to 0° and stirred rapidly while dimethyl sulfate (10 ml) was added dropwise. After the simultaneous dropwise addition of dimethyl sulfate (175 ml) and potassium hydroxide (115 g) in water (150 ml), the alkaline mixture was stirred for 10 min, then additional dimethyl sulfate (30 ml) and potassium hydroxide (30 g) in water (30 ml) were added. The stirred mixture was allowed to warm up to room temperature then heated under reflux for 1 h. Most of the methanol was removed by distillation and the cooled mixture was diluted with water (1 l.) and extracted with dichloromethane.

[52] Schering, A.-G., (by Wieske, R.), Ger. Offen. 1,177,636, 10 September 1964 (*Chem. Abstr.*, 1964, **61**, 14748h).

The extract was washed with Claisen's alkali (3 times) (methanol/40% aqueous potassium hydroxide, 1/1), then with water, and dried (Na_2SO_4). Charcoal (2 g) was added and the solution was filtered through Celite and evaporated. The pink crystalline residue (27·8 g, 98·7%) was dissolved in dichloromethane (50 ml) and adsorbed onto neutral alumina (Woelm, grade II, 300 g). Elution with benzene containing 10% dichloromethane gave a colourless solid (27·6 g), crystallization of which from methanol afforded pure 3-methoxyoestra-1,3,5(10),9(11)-tetraen-17-one (24·4 g), m.p. 147–149·5°, $[\alpha]_D$ +291·5 (*c*, 0·52 in chloroform) (lit.[21] 146–147°; lit.[27] 145–148°, +299°; lit.[22] 142·5–144°, +290·9°). λ_{max} (ethanol) 263 (18990), 298 (3193), λ_{min} 234 (2456); λ_{infl} 273 nm (ε 14984) [lit.[22] 263 (19300), 297 (3400)]. ν_{max} (Nujol) 1737, 1619 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$) δ 7·53, d, (*J* 8·6 Hz), H1; 6·52–6·83, m, H2,4; 6·14, m, H11; 3·79, s, OMe; 0·94, s, H18. ^{13}C n.m.r. δ 221·5, s, C17; 157·7, s, C3; 137·5, s, C5; 135·5, s, C10; 127·2, s, C9; 125·4, d, C1; 116·7, d, C11; 113·4, d, C4; 112·8, d, C2; 55·2, q, 3-OMe; 47·9, d, C14; 46·2, s, C13; 38·3, d, C8; 36·2, t, C16; 34·0, d, C12; 30·0, t, C6; 27·9, t, C7; 22·6, t, C15; 14·5, q, C18.

The assignments of C11 and C12 were confirmed by deuteration at these positions (see (*u*) below).

(d) 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (5)

A suspension of finely powdered 3-methoxyoestra-1,3,5(10),9(11)-tetraen-17-one (3b) (14·4 g) and *p*-toluenesulfonic acid (150 mg) in distilled ethylene glycol (500 ml) was stirred rapidly at reduced pressure (10–12 mm) under reflux for 5 h on an oil bath kept at 110–120°. The mixture soon became homogeneous then slowly deposited the crystalline product. The cooled mixture was poured into 1% sodium bicarbonate (1·5 l.) and allowed to stand overnight at room temperature. The precipitate was collected, washed several times with water, then dried (16·1 g). Crystallization from ethanol gave 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (14·6 g, 90%), m.p. 153·5–155·5°. The pure compound had m.p. 154·5–156·5°, $[\alpha]_D$ +90·7° (*c*, 0·98 in chloroform) (lit.[32] 146–147°, $[\alpha]_D$ +63°; lit.[21] m.p. 132–134°). λ_{max} (EtOH) 263 (19466), 298 (3135); λ_{min} 234 (2507); λ_{infl} 273 nm (14732). ^1H n.m.r. (90 MHz, $CDCl_3$) δ 7·47, d, H1; 6·48–6·70, m, H2, 4; 6·08, m, H11; 3·88, m, OCH_2CH_2; 3·76, s, OMe; 0·88, s, H18. ^{13}C n.m.r. δ 158·4, s, C3; 137·5, s, C5; 134·6, s, C10; 127·7, s, C9; 125·2, d, C1; 119·0, s, C17; 117·9, d, C11; 113·3, d, C4; 112·7, d, C2; 65·2, t and 64·6, t, OCH_2CH_2; 55·2, q, 3-OMe; 46·8, d, C14; 44·3, s, C13; 39·2, d, C8; 33·9, t, C16; 32·8, t, C12; 30·2, t, C6; 28·2, t, C7; 23·2, t, C15; 14·7, q, C18.

The assignments of C11 and C12 were confirmed by deuteration at these positions. See (*u*) below.

(e) 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol (6)

Diborane, prepared by the dropwise addition of a solution of sodium borohydride (2·65 g) in diglyme (40 ml) to a solution of boron trifluoride etherate (10·5 ml) in diglyme (10 ml), was introduced during 20 min with a slow stream of dry nitrogen into a cold (0°) solution of 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (2·05 g) in dry tetrahydrofuran (23 ml). The cold mixture was stirred for a further 60 min, then 2 N sodium hydroxide (50 ml) was added cautiously. After the addition of ethanol (20 ml) and hydrogen peroxide (20 ml of 30%), the mixture was heated under reflux for 1 h, then most of the volatiles were removed in vacuum. Water was added and the product was extracted with ether/benzene. Evaporation of the washed, dried (Na_2SO_4) extract gave a colourless gum (2·17 g) which was dissolved in benzene (20 ml) and adsorbed onto basic alumina (Woelm grade II, 65 g). Elution with benzene (300 ml) afforded the starting compound (80 mg), then elution with ether, and ether containing methanol (1%), yielded the crude alcohol (1·94 g). G.l.c. of the derived trimethylsilyl ether showed this material to be at least 88% pure. Preparative t.l.c. (Kieselgel 60 F_{254}) afforded non-crystalline 17,17-ethylenedioxy-3-methoxy-1,3,5(10)-trien-11α-ol, $[\alpha]_D$ −100·2° (*c*, 0·87 in chloroform) (lit.[32] m.p. 82°, $[\alpha]_D$ −107°). ^1H n.m.r. (100 MHz, $CDCl_3$) δ 7·80, d, H1; 6·56–6·74, m, H2, 4; 4·24, bm, H11; 3·88, m, OCH_2CH_2O; 3·75, s, OMe; 0·84, s, H18. ^{13}C n.m.r. δ 157·7, s, C3; 139·1, s, C5; 132·5, s, C10; 127·4, d, C1; 118·9, s, C17; 113·7, d, C4; 111·1, d, C2; 70·9, d, C11; 65·3 and 64·6, t, OCH_2CH_2O; 55·1, q, 3-OMe; 50·4, d, C9; 49·0, d, C14; 46·9, s, C13; 41·4, t, C12; 37·5, d, C8; 34·3, t, C16; 28·7, t, C6; 26·8, t, C7; 22·4, t, C15; 15·0, q, C18. (Very weak but completely resolved signals at δ 125·2, 117·9, 75·7, 70·4, 63·7, 49·9, 41·8, 36·7, 35·9, 26·3 and 21·7 are almost certainly due to the presence of a small amount of 17,17-ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11β-ol formed by *cis*-hydroboration of the β-face.) Mass spectrum: *m/z* 344 (17%), 326 (7), 282 (5), 265 (5), 225 (7), 211 (7), 160 (5), 100 (7), 99 (100).

(f) 9α,11α-Epoxy-17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene (11)

m-Chloroperoxybenzoic acid (1·93 g, 90% pure) was added in small portions with vigorous shaking to a two-phase mixture of 0·5 M sodium bicarbonate (120 ml) and a solution of 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (3·26 g) in dichloromethane (250 ml). After vigorous shaking for a total of 15 min, aqueous sodium sulfite solution (50 ml, 2%) was added and the mixture was again shaken. The organic layer was separated and washed with 0·5 M sodium bicarbonate (×3). A few drops of pyridine were added and the extract was washed with distilled water (×3), then dried over anhydrous potassium carbonate (one drop of pyridine was added at this stage). Evaporation in vacuum at < 30° gave a solid which was triturated with diethyl ether (15 ml), collected, and rinsed with two 5-ml portions of diethyl ether. The product (2·47 g, 72%) was sufficiently pure for the next step. Crystallization from dry ether containing a drop of pyridine gave pure *9α,11α-epoxy-17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene*, m.p. 160–163·5°, $[\alpha]_D$ +48·9° (*c*, 0·98 in dichloromethane containing a trace of pyridine) (Found: C, 73·5; H, 7·6. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·7%). This compound was extremely sensitive to traces of acid, and, for example, rapidly isomerized in chloroform solution. It was therefore always handled in solutions containing a small amount of pyridine. ν_{max} (Nujol) 1610s, 1583m, 1504s, 1437m, 1430m, 1420w, 1380m, 1342m, 1324s, 1316m, 1309s, 1283m, 1276m, 1250s, 1239s, 1225s, 1209m, 1194s, 1172s, 1143m, 1129s, 1101m, 1080m, 1060s, 1042s, 1038s, 1021m, 1004m, 992w, 968m, 956m, 945m, 930w, 910m, 886w, 871m, 850s, 840m, 834m, 798m, 784w, 750w, 740w, 731w, 718w, 682w, 663w cm^{-1}.

^1H n.m.r. [90 MHz, freshly alkali-washed $CDCl_3$ containing 1 drop of (D_5)pyridine] δ 7·09, complex d (major splitting 9·7 Hz), H1; 6·58–6·77, m, H2, 4; 4·05, d (*J* 5 Hz), H11; 3·90, m, OCH_2CH_2O; 3·77, s, OMe; 2·96, m, H6α,6β; 1·75, 1·59, AB part of ABX ($J_{11,12}$ 5 Hz); 0·90, s, H18. ^{13}C n.m.r. δ 159·5, s, C3; 141·5, s, C5; 127·6, s, C10; 126·3, d, C1; 118·5, s, C17; 113·7, d, C4; 112·4, d, C2; 65·2, t and 64·5, t, OCH_2CH_2O; 61·3, s, C9; 56·7, d, C11; 55·2, q, 3-OMe; 44·0, s, C13; 40·1, d, C8 or C14; 38·2, d, C14 or C8; 33·7, t, C16; 30·7, t, C6 or C12; 30·1, t, C12 or C6; 24·2, t, C7; 22·1, t, C15; 17·0, q, C18. Mass spectrum: *m/z* 342 (100%), 281 (10), 280 (11), 254 (16), 241 (20), 213 (13), 211 (11), 160 (24), 159 (17), 145 (12), 128 (10), 115 (16), 100 (24), 99 (67), 86 (33).

(g) Reduction of 9α,11α-Epoxy-17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene (11) with Lithium Aluminium Hydride

A solution of the epoxide (1·71 g) in dry tetrahydrofuran (20 ml) was added to a slurry of lithium aluminium hydride (740 mg) in the same solvent (10 ml) under nitrogen. The mixture was heated under reflux for 1 h, then cooled, and treated with water and 4 N sodium hydroxide. Extraction with ether/benzene gave a solid (1·70 g). Several recrystallizations from isopropyl alcohol, then from methanol, gave pure *17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-9α-ol* (10), m.p. 149–151°, $[\alpha]_D$ +39·6° (*c*, 0·86 in chloroform) (Found: C, 73·2; H, 8·3. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%). ν_{max} (Nujol) 3515 cm^{-1} (sharp). ^1H n.m.r. [90 MHz, freshly alkali-washed $CDCl_3$ containing 1 drop of (D_5)pyridine] δ 7·47, d (*J* 9 Hz), H1; 6·56–6·84, m, H2, 4; 3·91, m, OCH_2CH_2O; 3·78, s, OMe; 2·71–2·95, m, H6α,β; 1·65, s, OH (exch.); 0·89, s, H18. ^{13}C n.m.r. δ 158·7, s, C3; 138·4, s, C5; 134·8, s, C10; 126·7, d, C1; 119·3, s, C17; 113·8, d, C4; 112·3, d, C2; 69·8, s, C9; 65·2, t and 64·6, t, OCH_2CH_2O; 55·2, q, 3-OMe; 46·0, s, C13; 42·5, d and 42·1, d, C8, 14; 34·3, t, C16; 32·4, t, C11; 29·8, t, C6; 27·0, t, C12; 22·3, t, C15; 20·6, t, C7; 13·5, q, C18. Mass spectrum: *m/z* 344 (1·4%), 327 (11), 326 (44), 311 (16), 266 (24), 265 (100), 264 (28), 249 (9), 225 (23), 224 (23), 223 (10), 100 (8), 99 (34). This compound is very readily dehydrated. Even upon being kept overnight in chloroform solution, it was completely converted into 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (5). For this reason, the n.m.r. spectra were measured in deuterochloroform containing 1 drop of (D_5)pyridine.

(h) Treatment of 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-9α-ol (10) with Pyridinium Chlorochromate

To a slurry of pyridinium chlorochromate (323 mg) in dichloromethane (2·0 ml) was added, under nitrogen, a solution of the alcohol (344 mg) in dichloromethane (3·0 ml). The mixture was kept at room temperature for 2·5 h, then dry ether (5 ml) was added and the mixture was stirred. The supernatant was decanted and the residue was washed several times more with ether. The supernatant and washings (total volume of 60 ml) were combined, treated with charcoal, filtered

through Celite and evaporated. The i.r. spectrum of the crystalline residue (295 mg) showed it to be mainly 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (5). Recrystallization from ethanol yielded the pure compound, m.p. 155–157°, undepressed on admixture with authentic material.

(i) Conversion of 9α,11α-Epoxy-17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene (11) into 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one (7)

Pure dry benzene was filtered through grade I basic alumina directly into the reaction flask under nitrogen. In this solvent (15 ml) was dissolved the epoxide (1·59 g), and A.R. lithium perchlorate (46 mg) was added. The mixture was heated under reflux with stirring for 2·5 h, then cooled. More benzene was added and the solution was washed with water, dried (Na_2SO_4) and evaporated. The colourless viscous gum (1·59 g) was shown to be at least 97·5% pure by g.l.c. and was used directly in the next step. Chromatography of a portion on Florisil and elution with benzene gave pure *17,17-ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one* as a colourless gum, $[\alpha]_D$ +142·8° (*c*, 0·80 in chloroform) (Found: C, 73·5; H, 7·6. $C_{21}H_{26}O_4$ requires C, 73·6; H, 7·7%). ν_{max} (chloroform solution) 1690 cm^{-1}. ^1H n.m.r. (100 MHz, $CDCl_3$) δ 6·48–6·92, m, H1,2,4; 3·80, s, 3-OMe; 3·68–3·87, m, OCH_2CH_2O; 3·64, d, partly obscured by the previous signal, H9; 0·90, s, H18. ^{13}C n.m.r. δ 213·4, s, C11; 158·4, s, C3; 137·2, s, C5; 128·7, d, C1; 123·6, s, C10; 117·9, s, C17; 114·8, d, C4; 112·7, d, C2; 65·3, t, and 64·6, t, OCH_2CH_2O; 55·2, q, 3-OMe; 53·6, d, C9; 49·5, s, C13; 46·3, t, C12; 40·6, d, C14 or C8; 34·3, t, C16; 34·0, d, C8 or C14; 24·8, t, C6; 23·7, t, C17; 22·1, t, C15; 14·9, q, C18.

(j) Oxidation of 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol (6) with Pyridinium Chlorochromate

To a slurry of pyridinium chlorochromate (1·77 g) in pure dichloromethane (17 ml) was added a solution of the alcohol (1·88 g) in dichloromethane (15 ml). The mixture was stirred at room temperature for 17·5 h, then ether (35 ml) was added. Workup as in (*g*), and filtration through Florisil (20 g) in dichloromethane, gave an oil (1·59 g). The crude ketone, which showed $[\alpha]_D$ +183·6° (*c*, 1·13 in chloroform), was chromatographed on Florisil. The fractions eluted with benzene containing ether (4–8%), which showed a single spot upon t.l.c., were combined to give pure 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11-one (8) (497 mg) as a colourless oil, $[\alpha]_D$ +204·1° (*c*, 0·90 in chloroform), ν_{max} ($CHCl_3$) 1705 cm^{-1} (lit.[33] 5·84 μm). ^1H n.m.r. (100 MHz, $CDCl_3$) δ 7·20, d (*J* 16 Hz), H1; 6·68, apparent dd (major splitting 16 Hz), H2; 6·56, apparent d (splitting 5 Hz), H4; 4·87, m, OCH_2CH_2O; 3·75, s, OMe; 3·48, d (*J* 23 Hz), H9; 0·86, s, H18. ^{13}C n.m.r. δ 210·0, s, C11; 158·1, s, C3; 138·5, s, C5; 131·3, d, C1; 123·9, s, C10; 117·7, s, C17; 113·9, d, C4; 111·7, d, C2; 65·4, t, and 64·7, t, OCH_2CH_2O; 55·8, d, C9; 55·2, q, 3-OMe; 51·1, s, C13; 49·5, t, C12; 49·2, d, C14; 40·5, d, C8; 34·6, t, C16; 30·1, t, C6; 27·4, t, C7; 21·7, t, C15; 15·0, q, C18. Some additional, very low intensity signals corresponded to the 9β isomer present as a minor contaminant.

(k) Attempted Reduction of 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11-one (8) with Lithium Tri-t-butoxyaluminium Hydride

To a solution of lithium tri-t-butoxyaluminium hydride (157 mg) in dry tetrahydrofuran (3·0 ml) was added a solution of the ketone (8) (106 mg) in dry tetrahydrofuran (3·0 ml) and the solution was kept overnight at room temperature under nitrogen. After being heated at reflux for 30 min, the mixture was cooled, 4 N sodium hydroxide solution was added, and the product was extracted with ether/benzene. Evaporation of the dried (Na_2SO_4) extract gave a colourless gum (94 mg) whose i.r. spectrum showed only very weak hydroxyl absorption, strong carbonyl absorption at 1695 cm^{-1}, and was virtually identical with that of the 9βH 11-ketone (7).

(l) Reduction of 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one (7) with Lithium Aluminium Hydride

A solution of the ketone (342 mg) in dry ether (10 ml) was added to a slurry of lithium aluminium hydride (200 mg) in dry ether (5 ml) at 0°. The mixture was heated under reflux for 45 min then kept overnight at room temperature. The usual workup with 4 N sodium hydroxide, addition of benzene,

and washing gave a colourless gum (335 mg). G.l.c. of a trimethylsilylated sample showed the trimethylsilyl ether of (15) as the major component (81%, r.r.t. 0·66), together with that of (14) (17%, r.r.t. 0·91). A very minor component (2%, r.r.t. 0·82) was identified by g.l.c./m.s. as 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (5), formed by dehydration of the 9α-hydroxy compound (10) which would result from reduction of about 2% of unrearranged epoxide (11) present.

Preparative t.l.c. of 309 mg of the crude product on alumina (F254 Type T) gave the more polar, major product *17,17-ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11α-ol* (15) (173 mg) as a gum $[\alpha]_D$ +30·5° (*c*, 0·69 in chloroform) (Found: C, 73·4; H, 8·2. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%). ν_{max} ($CHCl_3$) 3600 sharp, 3470 cm^{-1} (broad). ^1H n.m.r. (100 MHz, $CDCl_3$) δ 7·76, d, (*J* 8·4 Hz), H1; 6·68, dd, H2; 6·65, bs, H4; 4·45, apparent quintet (W_H 18 Hz), H11; 3·86, 3·78, apparent s, OCH_2CH_2O; 1·74, OH (exch.); 1·02, s, H18. ^{13}C n.m.r. δ 157·3, s, C3; 140·5, s, C5; 130·0, d, C1; 128·9, s, C10; 118·6, s, C17; 113·7, d, C4; 112·0, d, C2; 73·2, d, C11; 65·1, t and 64·6, t, OCH_2CH_2O; 55·1, q, 3-OMe; 46·3, s, C13; 42·6, d, C9 or C14; 41·9, d, C14 or C9; 36·2, t, C12; 34·5, d, C8; 34·3, t, C16; 28·0, t, C6; 26·4, t, C7; 22·9, t, C15; 16·7, q, C18. Mass spectrum: *m/z* 344 (19%), 326 (3), 282 (3), 273 (6), 256 (3), 243 (3), 227 (3), 225 (4), 211 (3), 186 (3), 160 (11), 131 (4), 99 (100).

The minor, less polar product (58 mg) from preparative t.l.c. was a solid. Recrystallization from aqueous methanol gave *17,17-ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11β-ol* (14) as colourless needles, m.p. 126–128°, $[\alpha]_D$ +102·6° (*c*, 0·39 in chloroform) (Found: C, 73·2; H, 8·2. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%). ν_{max} 3575 cm^{-1}. ^1H n.m.r. (100 MHz, $CDCl_3$) δ 7·21, d, (*J* 8·6 Hz), H1; 6·74, dd, H2 overlapped by 6·68, bs, H4; 4·77, dd (W_H 5·6 Hz), H11; 3·92, 3·91, apparent s, OCH_2CH_2O; 3·78, s, OMe; 3·49, s, OH (exch.); 1·13, s, H18. ^{13}C n.m.r. δ 157·8, s, C3; 140·1, s, C5; 128·0, s, C10; 126·1, d, C1; 119·4, s, C17; 114·8, d, C4; 112·4, d, C2; 67·9, d, C11; 65·2 and 64·6, t, OCH_2CH_2O; 55·2, q, 3-OMe; 50·1, t, C9 or C14; 49·7, d, C14 or C9; 45·9, s, C13; 36·4, t, C12; 34·2, t, C16; 33·5, d, C8; 30·0, t, C6 or C7; 26·5, t, C7 or C6; 22·2, t, C15; 16·8, q, C18. Mass spectrum: *m/z* 344 (8%), 282 (10), 238 (4), 211 (6), 99 (100).

(*m*) *Dehydration of 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11α-ol* (*15*)

The alcohol (74 mg) in dry pyridine (1·0 ml) was treated with phosphoryl trichloride (0·3 ml) at 0–5°, then kept at room temperature for 2 days. The mixture was poured into ice-water and kept overnight at room temperature, then the solid was collected and dried. Crystallization from ethanol gave 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene, m.p. 155–156°, identical (i.r. and mixed m.p.) with authentic material.

(*n*) *Kinetic Protonation of the Anion from 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one* (*7*)

Sodium hydride (22 mg of 80% dispersion in oil) was rinsed twice with dry heptane, then twice with benzene under nitrogen. A solution of the ketone in dry benzene (10 ml) (228 mg) was added and the mixture was heated under reflux for 5 h. The cooled mixture (yellow supernatant and cream precipitate) was cooled in ice and glacial acetic acid (0·2 ml) was added dropwise with rapid stirring. The solution was washed with water until neutral, dried (Na_2SO_4) and evaporated to give an oil (205 mg). The specific rotation, +152·8° (*c*, 0·69 in chloroform), indicated a 9β/9α-ketone ratio of 84/16. The i.r. spectrum was consistent with this.

(*o*) *Epimerization of 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11-one* (*8*) *to the 9β-Isomer* (*7*)

A solution of the ketone (8) (307 mg) in 5% methanolic potassium hydroxide (20 ml) was heated under reflux in a nitrogen atmosphere for 8 h. The excess of methanol was evaporated, water was added and the product was extracted with dichloromethane. Evaporation of the washed, dried (Na_2SO_4) extract gave a yellow oil. A solution of this in benzene was treated with charcoal then filtered through Celite and evaporated to give a pale yellow oil (293 mg), $[\alpha]_D$ +145·6° (*c*, 0·86 in chloroform). Based on values of +204·1° and +142·8° for the pure 9α- and 9β-ketones, respectively, this corresponds to a 9α/9β ratio of approximately 5/95. The i.r. spectrum was typical of the 9β-ketone but in addition showed weak hydroxyl absorption at 3590 cm^{-1}, apparently due to base-catalysed hydroxylation. The extent of this was not determined.

(*p*) *Deuteration of 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one* (*7*) *by Phase-Transfer Catalysis*

To a solution of the ketone (53 mg) in dry dichloromethane (1·5 ml) under nitrogen was added tetrabutylammonium bromide (4 mg) and 5% sodium deuteroxide in deuterium oxide (0·8 ml). The mixture was sealed and stirred rapidly for 4 days at room temperature. Additional pure dichloromethane (5 ml) was added and the organic layer was separated and washed with three small portions of deuterium oxide, then dried briefly over sodium sulfate and evaporated. The oil (49 mg) showed $[\alpha]_D$ +138·8° (*c*, 0·43 in chloroform). The deuterium atom at C9 is labile in the g.l.c./m.s. system, and it was necessary to measure the deuterium content indirectly. Thus, the crude ketone (23) was reduced with lithium aluminium hydride in ether and the product was trimethylsilylated. G.l.c./m.s. showed the trimethylsilyl ethers of the 11-epimeric alcohols 11β-(20b) (r.r.t. 0·91) and 11α-(20b) (r.r.t. 0·66), each with the parent ion at *m/z* 417 corresponding to virtually complete monodeuteration. The amount of di- and tri-deuteration under these conditions was negligible.

There were small amounts of more polar compounds, r.r.t. 0·85 and 1·05, which had molecular weights of 504 and 432, corresponding to compounds (20d) and (20c), respectively.

(*q*) *Deuteration of 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one* (*7*) *with Sodium Deuteroxide in* (O-^2H)*Methanol*

To a solution of sodium (18 mg) in (*O*-^{2}H)methanol (2 ml) and deuterium oxide (0·12 ml) under nitrogen was added a solution of the ketone (85 mg) in (*O*-^{2}H)methanol (3 ml), and the mixture was heated under gentle reflux. Aliquots (1·0 ml) of the reaction mixture were withdrawn after 24, 48 and 72 h and were evaporated to dryness, dissolved in dichloromethane, washed with deuterium oxide (3 × 1·5 ml), dried (Na_2SO_4) and evaporated. Each residue was then reduced with lithium aluminium hydride in ether, trimethylsilylated and analysed by g.l.c. Although g.l.c./m.s. of the 24-h product showed approximately 85% trideuteration in (24), analysed as the epimeric 11-trimethylsilyl ethers (27c) and (27d), these totalled only 73% of the product; the two major by-products (22b) (r.r.t. 0·84, mol. wt 506, 14%), and (22a) (r.r.t. 1·04, mol. wt 434, 7%) correspond to dideuterated analogues of the impurities observed in (*p*). With longer equilibration times of 48 and 72 h deuteration was marginally improved but the by-products became predominant (see Table 1).

(*r*) *Deuteration of 17,17-Ethylenedioxy-3-methoxy-9β-oestra-1,3,5(10)-trien-11-one* (*7*) *with Sodium Methoxide/*(O,O′-$^2H_2$)*Hydroquinone/*(O-^2H)*Methanol*

Sodium hydride (19·6 g, from 24·5 g of 80% dispersion in oil) was suspended in sodium-dried ether (1 l.) under nitrogen and chilled to 0°. Dry hydroquinone (45·1 g) was added in portions with stirring during 50 min, then the mixture was allowed to warm up to room temperature and heated under reflux for 1 h. The mixture was again chilled in an ice bath and a solution of (*O*-^{2}H)acetic acid (50 g) in dry ether (50 ml) was added dropwise during 45 min to the well stirred suspension. The cooling bath was removed and the mixture was heated under reflux for 10 min. The cooled mixture was filtered rapidly and the filtrate, together with dry ether washings of the sodium acetate filter cake, was evaporated. The residue was crystallized from D_2O and dried in vacuum to give (*O*,*O*′-$^2H_2$)hydroquinone which was used directly in the next step.

Sodium (2·60 g, 0·113 mol) was dissolved in (*O*-^{2}H)methanol (100 g) under nitrogen, then (*O*,*O*′-$^2H_2$)hydroquinone (8·23 g, 0·073 mol) was added and dissolved with stirring. A solution of the ketone (12·25 g, 0·036 mol) in (*O*-^{2}H)methanol was added and the mixture was refluxed gently with stirring under nitrogen for 10 days. During this time additional (*O*-^{2}H)methanol (50 ml) was added. Most of the methanol was removed by distillation, and finally in vacuum. The residue was treated with deuterium oxide (80 ml) and 40% sodium deuteroxide/deuterium oxide (2·0 ml), then extracted with freshly dried dichloromethane (3 × 50 ml). The extract was washed with deuterium oxide until neutral (5 × 20 ml), dried (Na_2SO_4) and evaporated to give non-crystalline *17,17-ethylenedioxy-3-methoxy-9β-(9,12,12-*$^2H_3$*)oestra-1,3,5(10)-trien-11-one* (24) (12·2 g).

A small portion (56 mg) was reduced with lithium aluminium hydride in ether to give a mixture of 11-epimeric alcohols (50 mg), and a small sample (*c.* 50 μg) was trimethylsilylated. G.l.c./m.s. of this sample, (27c) and (27d), showed the isotope content: $^2H_3$, 91·6%; $^2H_2$, 4·3; $^2H_1$, 2·7; $^2H_0$, 1·5.

A set of small-scale exploratory experiments in which reaction mixtures were sampled between 1 to 5 days and analysed by g.l.c./m.s. after hydride reduction and trimethylsilylation showed that while deuteration proceeded much more slowly than with NaOD/MeOD [see (*q*) above], by-product formation was negligible: the percentage of 11-ketone present after 5 days was still at least 87%.

(*s*) *Reduction of 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (5) with Lithium in Anhydrous Ammonia*

To a solution of lithium (140 mg) in anhydrous re-distilled ammonia (120 ml) kept at −70° was added with stirring under nitrogen a solution of the 9(11)-ene (326 mg) in dry tetrahydrofuran (20 ml). The mixture was stirred for 45 min, then allowed to warm up to −35°. Ammonium chloride was added to destroy the excess of lithium, and the ammonia was evaporated. Extraction with ether/benzene gave a crystalline solid (310 mg) which was shown by g.l.c. to be at least 95% pure. Two recrystallizations from methanol gave analytically pure 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene (4), m.p. 103·5–104·5°, $[\alpha]_D$ +26·6° (lit.[45] 100–101·5°, +18·1°, measured in pyridine). This was identical (i.r. spectrum and mixed m.p.) with material prepared by treatment of 3-methoxyoestra-1,3,5(10)-trien-17-one (1b) with ethylene glycol and toluene-*p*-sulfonic acid in the usual way. ^{13}C n.m.r. δ 157·5, s, C3; 138·1, s, C5; 132·8, s, 10; 126·4, d, C1; 119·5, s, C17; 113·8, d, C4; 111·5, d, C2; 65·3, and 64·6 t, OCH_2CH_2O; 55·2, q, 3-OMe; 49·4, d, C14; 46·2, s, C13; 43·7, d, C9; 39·1, d, C8; 34·3, t, C16; 30·8,* t, C12; 29·8, t, C6; 27·0, t, C7; 26·2,* t, C11; 22·4, t, C15; 14·3, q, C18.

(*t*) *Preparation of the Epimeric Alcohols 17,17-Ethylenedioxy-3-methoxy-9β-(9,11,12,12-$^2H_4$)oestra-1,3,5(10)-trien-11-ol (27a)*

Reduction of the 9β,12,12-trideutero ketone (24) (10·8 g) from (*r*) with lithium aluminium deuteride (1·3 g) in dry ether in the usual way gave a crude mixture of the 11-epimers of *17,17-ethylenedioxy-3-methoxy-9β-(9,11,12,12-$^2H_4$)oestra-1,3,5(10)-trien-11-ol* (10·7 g). This was dissolved in benzene and adsorbed onto basic alumina (grade II, 300 g). Elution with benzene yielded crystalline 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (5) (206 mg), formed through (10) from unrearranged epoxide (11). Elution with ether, and ether containing methanol (1–2%), gave the tetradeutero 11-alcohols (27a) (8·31 g). G.l.c./m.s. of the trimethylsilylated product showed the isotopic composition: $^2H_4$, 89·6; $^2H_3$, 7·7; $^2H_2$, 1·4; $^2H_1$, 0·6; $^2H_0$, 0·8%.

(*u*) *17,17-Ethylenedioxy-3-methoxy(11ξ,12,12-$^2H_3$)oestra-1,3,5(10)-triene (25)*

Dehydration of the tetradeutero alcohols (27a) (8·26 g) by treatment with phosphoryl trichloride (25 ml) in dry pyridine (85 ml), as described in (*m*), gave a light buff-coloured solid (7·3 g). This was dissolved in benzene and filtered through basic alumina (grade II, 80 g). Elution with benzene (400 ml) gave *17,17-ethylenedioxy-3-methoxy(11,12,12-$^2H_3$)oestra-1,3,5(10),9(11)-tetraene* (26) as colourless crystals (6·93 g). Crystallization from ethanol gave the pure compound, m.p. 153–154·5°, the ^{13}C n.m.r. spectrum of which lacked the signals at δ 117·9 and 32·8 for C11 and C12 in (5), respectively [see (*d*) above]. G.l.c./m.s. established that it was pure, and gave the isotopic composition: $^2H_3$, 89·9; $^2H_2$, 5·0; $^2H_1$, 2·3; $^2H_0$, 1·9%.

Reduction of (26) (4·35 g) with lithium (2·15 g) in anhydrous ammonia (1·5 l.) and tetrahydrofuran (160 ml), as described in (*s*), gave a colourless solid (4·3 g) shown by g.l.c. to be at least 98% pure. Crystallization from methanol gave analytically pure *17,17-ethylenedioxy-3-methoxy-(11ξ,12,12-$^2H_3$)oestra-1,3,5(10)-triene* (25) (3·70 g), m.p. 103–104·5°. Chromatography of the second crop (3·21 mg), followed by crystallization from methanol, gave additional pure material (244 mg). The ^{13}C n.m.r. spectrum lacked the signals at 26·2 and 30·8 ppm for C11 and C12, respectively in (4) [see (*s*) above]. The isotopic composition was: $^2H_4$, 7·3; $^2H_3$, 85·4; $^2H_2$, 3·0; $^2H_1$, 2·1; $^2H_0$, 2·2%.

(*v*) *3-Hydroxy(11ξ,12,12-$^2H_3$)oestra-1,3,5(10)-trien-17-one (28b)*

A solution of pure 17,17-ethylenedioxy-3-methoxy(11ξ,12,12-$^2H_3$)oestra-1,3,5(10)-triene (25) in pure acetone (500 ml) containing 2 N sulfuric acid (50 ml) was stirred overnight at room temperature.

* These assignments were confirmed by deuterium labelling [see (*u*)].

Most of the acid was neutralized by the addition of 4 N sodium hydroxide (22 ml), then the solvent was removed. After addition of water, extraction with ether/benzene gave *3-methoxy(11ξ,12,12-$^2H_3$)-oestra-1,3,5(10)-trien-17-one* (28a) (3·16 g), m.p. 173–177°, most of which was used directly in the next step. Recrystallization of a portion from methanol gave the pure trideutero oestrone methyl ether (28a), m.p. 176–177°. ^{13}C n.m.r. δ 220·8, s, C17; 157·7, s, C3; 137·7, s, C5; 132·1, s, C10; 126·3, d, C1; 113·9, d, C4; 111·6, d, C2; 55·2, q, OMe; 50·4, d, C14; 47·9, s, C13; 43·9, d, C9; 38·4, d, C6; 35·8, t, C16; 29·7, t, C8; 26·6, t, C7; 21·6, t, C15; 13·8, q, C18 (See Blunt and Stothers[53] for assignment). This spectrum lacked the signals at δ 31·7, t, C12; and 26·0, t, C11, shown by the undeuterated compound (1b).

A mixture of the above compound (2·7 g), 48% hydrobromic acid (16 ml) and glacial acetic acid (27 ml) was heated under reflux with vigorous stirring in an atmosphere of nitrogen for 70 min. The cooled mixture was poured into ice-water and the product was collected (2·49 g). The pink solid was dissolved in chloroform and filtered through silicic acid ('Unisil', 140 g, 200–325 mesh, from Clarkson Chem. Co. Inc.). A fast-travelling yellow band was rejected and concentration of subsequent chloroform eluates, then addition of a small amount of methanol, gave colourless crystals of *3-hydroxy(11ξ,12,12-$^2H_3$)oestra-1,3,5(10)-trien-17-one* (28b), m.p. 265–269°. ν_{max} (KBr) 3320s, 2200w, 2180w, 2100w, 1715s, 1620s, 1582s, 1496s, 1460m, 1438m, 1397m, 1380m, 1356s, 1338w, 1320w, 1289s, 1250s, 1235s, 1226m, 1204m, 1185w, 1166m, 1157m, 1142w, 1124w, 1113w, 1102w, 1085w, 1071w, 1042w, 1018w, 1005m, 986w, 963w, 950w, 937m, 920m, 889w, 873m, 858w, 820s, 808m, 792w, 750w, 734w, 717w cm^{-1}. G.l.c./m.s. showed: $^2H_4$, 7·8; $^2H_3$, 86·2; $^2H_2$, 3·2; $^2H_1$, 1·7; $^2H_0$, 1·1%.

(*w*) *3,17-Dihydroxy-19-nor-17α-(11ξ,12,12-$^2H_3$)pregna-1,3,5(10)-trien-20-yne* (*29*)

To anhydrous ammonia (100 ml) (distilled from sodium) was added small pieces of clean potassium (2·0 g) at −78° under nitrogen. When all of the potassium had dissolved, pure dry acetylene [purified by passage through soda-lime, concentrated sulfuric acid and a cold trap (−78°)] was passed slowly through the solution with vigorous stirring until the blue colour was discharged. With continued slow passage of acetylene, a solution of 11ξ,12,12-trideuterated oestrone (28b) (0·75 g) in dry tetrahydrofuran (25 ml) was added dropwise during 10 min. Stirring and passage of acetylene was continued for 2 h, then the ammonia was allowed to evaporate. Ether (40 ml) was added and the mixture allowed to stand overnight under nitrogen, then 5% sulfuric acid (150 ml) and benzene (50 ml) were added. The organic layer was washed with water, 5% sodium bicarbonate, water (×3), dried (Na_2SO_4), and evaporated to give a frothy glass (820 mg). The i.r. spectrum showed weak carbonyl absorption, and g.l.c. revealed 1–2% of deuterated oestrone. This was removed by treatment of the crude product with a solution of Girard's reagent P (400 mg) in ethanol (10 ml) containing acetic acid (1·0 ml). The mixture was heated for 60 min under reflux, then cooled and poured into water (100 ml). The clear two-phase mixture was extracted with ether/benzene, and washed with water, 5% sodium bicarbonate (×2), water (×3), then dried (Na_2SO_4) and evaporated. The residue (800 mg) was dissolved in chloroform and filtered through silicic acid (Unisil, 40 g). The first eluate (200 ml) contained 21 mg of impure product which was discarded. The second fraction (150 ml) yielded the pure ethynyl derivative (770 mg) which was dissolved in hot methanol (8 ml), filtered, then treated with hot water (8 ml). The fluffy crystals (725 mg) were dried at 100°/1 mm for 24 h, then crystallized from benzene and again dried at 100°/1 mm for 20 h to give pure *3,17-dihydroxy-19-nor-17α-(11ξ,12,12-$^2H_3$)pregna-1,3,5(10)-trien-20-yne* (650 mg). G.l.c. showed this to be at least 99% pure, and g.l.c./m.s. revealed the isotopic composition: $^2H_4$, 9·2; $^2H_3$, 84·1; $^2H_2$, 3·1; $^2H_1$, 2·2; $^2H_0$, 1·3%.

(*x*) *Reduction of 17,17-Ethylenedioxy-3-methoxy(11,12,12-$^2H_3$)oestra-1,3,5(10),9(11)-tetraene* (*26*) *with Hexadeuterodiborane*

(D_6)Diborane, prepared by addition of sodium borodeuteride (1·21 g) in dry diglyme (18·2 ml) to redistilled boron trifluoride etherate (4·8 ml) and diglyme (4·6 ml), was flushed with nitrogen through a solution of the trideutero 9(11)-ene (933 mg) in dry tetrahydrofuran (10·5 ml), following the procedure described in (*e*). The usual workup and treatment with alkaline hydrogen peroxide gave the crude tetradeutero alcohol (938 mg). T.l.c. showed the presence of a small amount of

[53] Blunt, J. W., and Stothers, J. B., *Org. Magn. Reson.*, 1977, **9**, 439.

starting material. Chromatography on basic alumina grade II (30 g) gave crystalline 17,17-ethylenedioxy-3-methoxy(11,12,12-$^2H_3$)oestra-1,3,5(10),9(11)-tetraene (26) (90 mg) from the first benzene eluates (100 ml). Elution with ether, and ether containing 2% methanol, gave pure *17,17-ethylenedioxy-3-methoxy(9α,11β,12,12-$^2H_4$)oestra-1,3,5(10)-trien-11α-ol* (30a) (849 mg). G.l.c./m.s. showed: $^2H_4$, 89·6; $^2H_3$, 7·7; $^2H_2$, 1·4; $^2H_1$, 0·6; $^2H_0$, 0·8%.

(*y*) *Formation of Sulfonate Esters of 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol* (*6*)

(i) *The methanesulfonate* (*32b*).—A solution of the alcohol (344 mg) in dry dichloromethane (10 ml) containing trimethylamine (0·2 ml) was cooled to −10° and treated dropwise with methanesulfonyl chloride (0·08 ml), then the mixture was stirred at between −5 to −10° for 30 min. Ice and water were added and the mixture was shaken vigorously, then separated and extracted with additional dichloromethane. The extract was subjected to ice-cold washes of water (×2), aqueous oxalic acid (×2), 2% sodium bicarbonate (×2), sodium chloride solution (×2), then dried (Na_2SO_4) and evaporated at <30° to give a foamed solid (371 mg). The i.r. spectrum showed sulfonate absorption and complete lack of hydroxyl absorption. This material was used directly in the reactions described in (*z*).

(ii) *The* p-*toluenesulfonate* (*32a*).—A solution of the alcohol (845 mg) in dry pyridine (10 ml) was treated with *p*-toluenesulfonyl chloride (470 mg) and the mixture was kept at room temperature for 11 days. It was then poured into ice-water containing concentrated sulfuric acid (6·45 g) and the product was extracted with ether/benzene. The extract was washed successively with chilled sodium bicarbonate solution (×2), dilute copper sulfate solution, water (×3), dried (Na_2SO_4) and evaporated at <35° in vacuum to give the crude p-*toluenesulfonate* (1·15 g). The i.r. spectrum showed negligible hydroxyl absorption. Trial experiments showed that the reaction was incomplete after 4 days. The crude product was used directly as described in (*z*).

(*z*) *Hydride Reductions of the Sulfonate Esters* (*32a*) *and* (*32b*) *of 17,17-Ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol* (*6*)

(i) *With lithium aluminium hydride*.—Lithium aluminium hydride (50 mg) was added to a solution of the mesylate or tosylate ester of the 11α-alcohol (50 mg) in tetrahydrofuran (3 ml) and the mixture was heated under reflux in a nitrogen atmosphere for 24 h. The cooled mixture was treated with an excess of 4 N sodium hydroxide and the product was extracted with ether/benzene.

The crude products were analysed by g.l.c. directly, and again after trimethylsilylation to confirm identification of 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol (6). Relative retention times of the major components were: 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene (0·75); 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene (0·82); 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol (1·20) and its trimethylsilyl ether (1·00). The results are given in Table 2.

(ii) *With lithium triethylborohydride*.—To the mesylate or tosylate (53 mg) in dry tetrahydrofuran (0·5 ml) under nitrogen was added a 1 M solution of lithium triethylborohydride in tetrahydrofuran (1·06 ml) and the mixture was heated under reflux for 24 h. The cooled mixture was treated carefully with 4 N sodium hydroxide (0·4 ml) and 30% hydrogen peroxide (0·4 ml), then refluxed for 1 h. After being cooled and diluted with water, the mixture was extracted with ether/benzene and the washed, dried (Na_2SO_4) extract was analysed by g.l.c., as described above. The results are given in Table 2.

This reagent is normally used at room temperature but with (32a) and (32b) there was no apparent reaction during 2 days at *c.* 20°.

(*aa*) *Preparation of 17,17-Ethylenedioxy-3-methoxy(9,11,11,12,12-$^2H_5$)oestra-1,3,5(10)-triene* (*31*)

A solution of the 11α-tosylate (30b) (1·15 g), prepared from (30a) as described in (*y*)(ii), in dry ether (40 ml) was added to a slurry of lithium aluminium deuteride (300 mg) in dry ether (50 ml) and the mixture was heated under reflux for 24 h. The usual workup gave a gum (797 mg) which was treated with ($^2H_6$)diborane as in (*x*) in order to reconvert the contaminating trideutero 9(11)-ene (26), formed by elimination, into the tetradeutero 11α-alcohol (30a); this was isolated and recycled. The crude product (804 mg) from the deuteroboration–alkaline hydrogen peroxide sequence was adsorbed onto basic alumina grade II (24 g) in the minimum of benzene. Elution with heptane

containing 10% of benzene (100 ml) gave a gum (44 mg). Further elution with heptane containing 10–50% of benzene (total, 300 ml) gave a solid (360 mg) shown to be homogeneous by t.l.c. Crystallization from methanol gave pure *17,17-ethylenedioxy-3-methoxy(9,11,11,12,12-$^2H_5$)oestra-1,3,5(10)-triene* (31), m.p. 104·5–106°, undepressed on admixture with undeuterated material prepared as described in (*s*). G.l.c./m.s. showed: $^2H_6$, 0·8; $^2H_5$, 86·5; $^2H_4$, 8·7; $^2H_3$, 1·9; $^2H_2$, 1·1; $^2H_1$, 0·7; $^2H_0$, 0·3%.

(*bb*) *3-Hydroxy(9,11,11,12,12-$^2H_5$)oestra-1,3,5(10)-trien-17-one* (*34b*)

A solution of the pentadeutero acetal (31) (215 mg) in acetone (30 ml) containing 2 N sulfuric acid (3 ml) was stirred at room temperature for 24 h. The usual workup gave *3-methoxy(9,11,11,12,12-$^2H_5$)oestra-1,3,5(10)-trien-17-one* (34a) (183 mg), m.p. 172–176°, which was used without further purification.

The above methoxy ketone (34a) (179 mg) was suspended in a mixture of glacial acetic acid (1·8 ml) and 48% (w/v) hydrobromic acid (1·1 ml), and heated under reflux with rapid stirring under nitrogen for 1 h. The usual workup gave a pale pink solid (172 mg). This was dissolved in chloroform and filtered through silicic acid (Unisil, 9 g). The first fraction (35 ml) gave a gum, (4 mg) which was discarded. Subsequent chloroform eluates gave a solid (169 mg) which was triturated with acetone to give *3-hydroxy(9,11,11,12,12-$^2H_5$)oestra-1,3,5(10)-trien-17-one* (34b) as colourless crystals (122 mg), m.p. 264–267°. G.l.c. showed the compound to be pure.

(*cc*) *3,17-Dihydroxy-19-nor-17α-(9,11,11,12,12-$^2H_5$)pregna-1,3,5(10)-trien-20-yne* (*35*)

Ethynylation of the pentadeutero ketone (34b) (100 mg), as described in (*w*), gave the crude 17α-ethynyl derivative (108 mg) which was purified by treatment with Girard's reagent P, then chromatographed on silicic acid (Unisil, 4·3 g). Crystallization of the product (80 mg) from 50% aqueous methanol (1·7 ml), then from benzene and drying at 100°/< 1 mm for 24 h, gave *3,17-dihydroxy-19-nor-17α-(9,11,11,12,12-$^2H_5$)pregna-1,3,5(10)-trien-20-yne* (53 mg). G.l.c./m.s. showed: $^2H_5$, 84·5; $^2H_4$, 8·5; $^2H_3$, 4·4; $^2H_2$, 0·9; $^2H_1$, 0·8; $^2H_0$, 0·9%, and established its purity.

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