On the formation of allenes in the steroid series III. Synthesis and reactions of 3-methoxy-17α-hydroxy-17β-ethynyl-1,3,5(10)-estratriene ("epimestranol")

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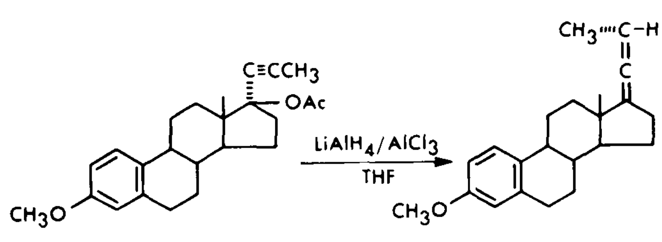
Abstract. "Epimestranol" (6) has been prepared from the 16α,17-epoxide **5** by reduction with $LiAlH_4$. The structures of several by-products have been elucidated and a mechanism for their formation is discussed. Both "mestranol" (3) and "epimestranol" failed to form *p*-tosylates and only "mestranol" could be converted into the *p*-toluenesulfinate which readily rearranged to the allenic sulfone **14**. "Epimestranol" was transformed into a mixture of the two epimeric 17-sulfones instead of the 17α-sulfinate.

1) Preparation of 3-methoxy-17α-hydroxy-17β-ethynyl-1,3,5(10)-oestratriene

The stereospecific formation of allenes by the reduction of 17β-hydroxy-17α-alkynyl steroids or their 17β-acetoxy derivatives[1] with $LiAlH_4/AlCl_3$, exemplified by the conversion of **1** into **2**, provoked the question whether the 17-epimers could also be converted into sterochemically pure allenes. To test this point 3-methoxy-17α-hydroxy-17β-ethynyl-1,3,5(10)-estratriene (**6**) had to be prepared; this compound was first mentioned by *Engelfried* et al.[2a] as a product isolated from the mother liquors of the epimer **3** ("mestranol"). The authors discuss only the NMR signals of the ethynylic proton in **3** and in **6** (see Table I) as significantly differing structural details but give neither preparative nor pharmacological data.

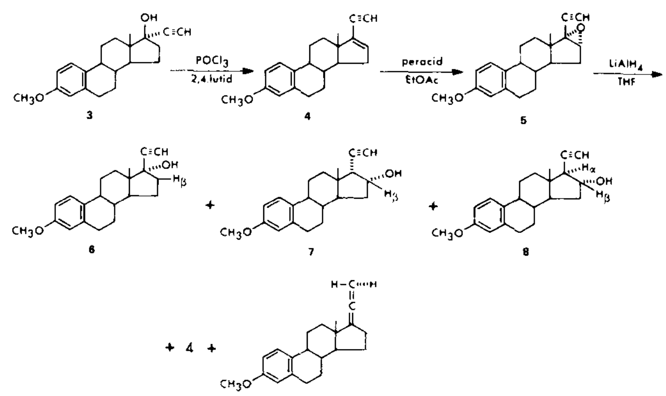


1 2

When, however, our paper was being written the short communication by *Kanojia*[2b] appeared, describing the epimerization of mestranol acetate on alumina and the preparation of "epimestranol" along similar lines as ours. Their results are essentially identical with ours, both from the chemical and from the spectroscopical point of view.

Starting from **3** we obtained the pure epimer **6** ("epimestranol") in 6% overall yield; the dehydration with $POCl_3$ in 2,4-lutidine[3] proceeded smoothly, rendering the enyne **4** in about 65% yield.

Oxidation of the enyne **4** with monoperphthalic acid in ethyl acetate[4] produced the epoxide **5** in ~ 40% yield. The 16β-H signal of this epoxide appears at 3.63 ppm as a slightly broadened singlet, not easily explained by simply assuming that the *Karplus* equation may not be applicable here for the calculation of the coupling constant between 16β-H and the two protons at position 15. A similar feature was observed by *Tori* et al.[5] for some 16α,17-epoxy steroids. The reduction of **5** with $LiAlH_4$ in dry tetrahydrofuran[4] produced a complicated reaction mixture, consisting of three identified hydroxylic products, *viz.* the desired epimer **6*** (isolated from the crude product by column chromatography and crystallisation from ethanol in about 25% yield) and the two 16α-hydroxy-17-ethynyl compounds **7** and **8**, along with the enyne **4**, being the persistent main product (about 50%) of the reduction mixture, and a few percent of the allenic product **9**, which we have already described[1].



The structure of the "epimestranol" **6** was unambiguously characterised by its physical constants: especially the optical rotation and the NMR shift for the ethynylic proton are remarkable when compared with other pairs of epimers bearing the same substituents at C-17 (see Table I). The increase in the specific rotation when the 17α-ethynyl-17β-hydroxy moiety is reversed can be expected from *Brewster*'s rules[9] assuming the polarisability sequence C≡C > CH_2 > C< > OH; a similar difference has already been observed by *Reichstein* and *Meystre* in 1939[10] for

* In a few batches of the crude "epimestranol" **6** an impurity could be detected by means of TLC (Silica gel, hexane/acetone 85 : 15) isolated and identified[17] as 3-methoxy-17α-hydroxy-17β-vinyl-1,3,5(10)-oestratriene. This may be due to slight differences in quality of the $LiAlH_4$ used, because this product, being less polar than **7** (R_f values 0.35 and 0.21, respectively) could not always be found in crude **6**.

1 *L. A. van Dijck et al.*, Recl. Trav. Chim. Pays-Bas **90**, 801 (1971).
2a *O. Engelfried, H. Gibian, F. Neumann, K. Prezewowsky, G. Schulz* and *R. Wiechert*, Arzneimittelforschung **16**, 1518 (1966).
2b *R. M. Kanojia, L. Yarmchuck* and *I. Scheer*, J. Org. Chem. **39**, 2304 (1974).
3 Belgian Patent 70,3564 *(Schering AG)*.
4 French Publications nos. 2,097,045 and 2,097,046 *(Roussel-Uclaf)*.
5 *K. Tori, T. Komeno* and *T. Nakagawa*, J. Org. Chem. **29**, 1136 (1964).
6 Own measurements.
7 *A. I. A. Broess, J. S. Favier, N. P. van Vliet* and *D. C. Warrell*, J. Labelled Comp. **11**, 223 (1975).
8 The Merck Index, 8th Edition 1968 Merck & Co Inc., Rahway, N.J., USA.
9 *J. H. Brewster*, J. Am. Chem. Soc. **81**, 5475 (1959); *E. Eliel*, Tetrahedron Letters no. 8, 17 (1960).
10 *T. Reichstein* and *C. Meystre*, Helv. Chim. Acta **22**, 728 (1939).

Table I Physical data of 17-hydroxy-17-ethynyl steroids; NMR data for $CDCl_3$ solutions (δ TMS = 0). The differences in rotation and chemical shift refer to those between the second and first member of each pair of epimers.

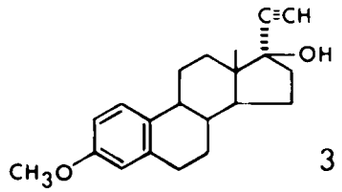
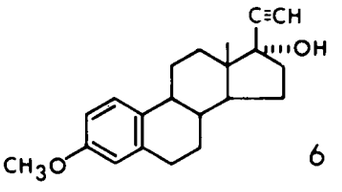
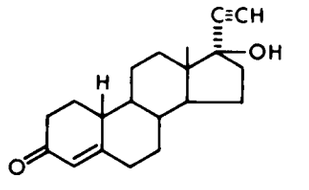
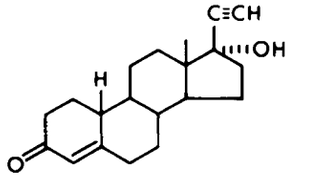
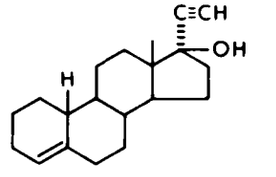
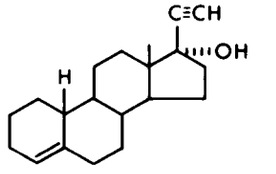
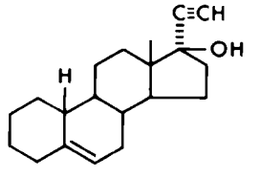
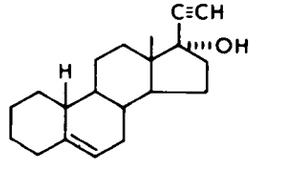
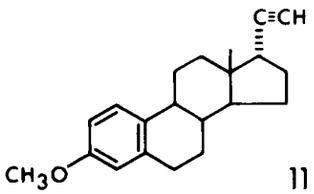
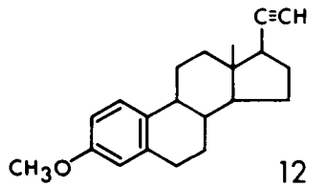
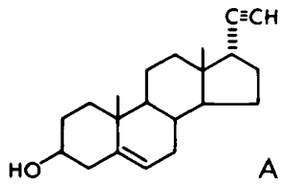
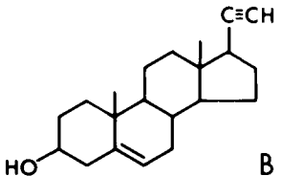
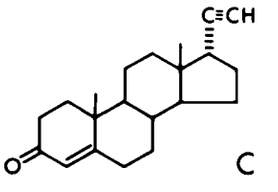
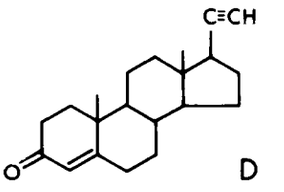
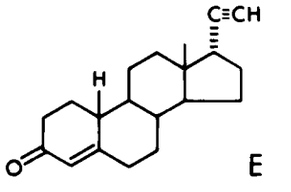
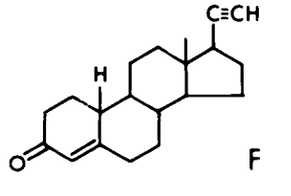
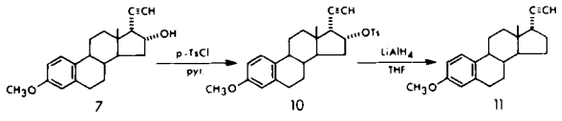
Compound	$[\alpha]_D$	NMR	$\Delta[\alpha]_D$	$\Delta\delta$ (≡CH)	M.p. °C	Ref.
 3	+6° (CH_2Cl_2) 20°C	0.88 (13-CH_3) 2.60 (≡CH) 3.76 (OCH_3)	+ 66°	−0.10 ppm	150–151	2, 6
 6	+71.7° (CH_2Cl_2) 20°C	0.92 (13-CH_3) 2.50 (≡CH) 3.76 (OCH_3)			135–136	2a, 2b, 6
	−31.7° ($CHCl_3$) 20°C	0.92 (13-CH_3) 2.59 (≡CH) 5.87 (4-H)	+115°	−0.10 ppm	203–204	6, 8
	+83.5° (C_2H_5OH) 20°C	0.94 (13-CH_3) 2.49 (≡CH) 5.87 (4-H)			223	4
	−13° ($CHCl_3$) 20°C	0.88 (13-CH_3) 2.55 (≡CH) 5.44 (4-H)	+100°	−0.09 ppm	158–160	6
	+87° ($CHCl_3$) 20°C	0.90 (13-CH_3) 2.46 (≡CH) 5.41 (4-H)			100–102	6, 7
	−81° ($CHCl_3$) 20°C	0.86 (13-CH_3) 2.55 (≡CH) 5.37 (6-H)	+ 93°	−0.08 ppm	130–132	6
	+11.8° (CH_2Cl_2) 20°C	0.88 (13-CH_3) 2.47 (≡CH) 5.40 (6-H)			173–175	6

Table II Physical dat of 17α/β-ethynyl steroids; NMR data for $CDCl_3$ solutions (δ TMS = 0 ppm). The differences in $[\alpha]_D$ and δ refer to those between the second and first member of each pair of epimers.

Compound	$[\alpha]_D$	NMR	$\Delta[\alpha]_D$	Δδ (≡CH)	M.p. °C	Ref.
 11	−5.8° (CH_2Cl_2) 20°C	0.80 (13-CH_3) 2.17 (≡CH) $J_{17,21}$ 2.5 Hz 3.77 (OCH_3)	+112°	−0.07 ppm	84–88	6
 12	+118° (CH_2Cl_2) 20°C	0.83 (13-CH_3) 2.10 (≡CH) $J_{17,21}$ 2.0 Hz 3.77 (OCH_3)			148–149	6, 12
 A	−153.4° ($CHCl_3$)	0.78 (13-CH_3) 1.02 (10-CH_3) 2.12 (≡CH) *J* not given	+138°	−0.07 ppm	201.5–202.5	12
 B	−14.6° ($CHCl_3$)	0.80 (13-CH_3) 1.01 (10-CH_3) 2.05 (≡CH) *J* not given			167–168.5	12
 C	+3.9° ($CHCl_3$)	0.98 (13-CH_3) printer's error? 1.17 (10-CH_3) 2.33 (≡CH) *J* not given	+ 71°	−0.19 ppm	213–214	12
 D	+51.0° ($CHCl_3$)	0.85 (13-CH_3) 1.20 (10-CH_3) 2.14 (≡CH) *J* not given			121–123	12
 E	−65.5° (ethanol)	no data	+189°		133	4
 F	+123° (ethanol)				212.5	4

the epimeric 17-ethynyl-17-hydroxy compounds in both the 5α and the 5β series. Their Δ $[\alpha]_D$ was ~ +75° for both pairs of compounds, whose plain rotation dispersion curves[11] also reveal the strong positive shift.

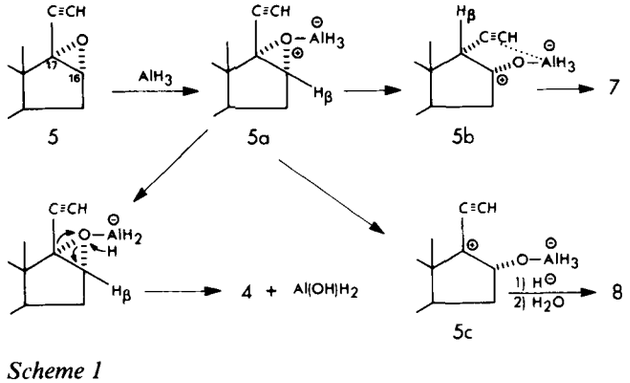
The (6 : 1) mixture of the two epimers **7** and **8** (total yield ~ 20%) could be separated by preparative thick-layer chromatography; the *cis* relationship between the hydroxylic and the ethynylic groups in the major product **7** followed from the characteristic IR absorption band at 3558 cm^{-1} in dilute CCl_4 solution (intramolecular hydrogen bond).



Moreover, **7** could be converted by reduction[4] of its tosylate **10** with $LiAlH_4$ in THF to the 17α-ethynyl compound **11**, significantly differing from the 17β-ethynyl epimer, described by *Krubiner* et al.[12]. In Table II several pairs of similar epimers, found in the literature are compared. The expected[9] positive difference in $[\alpha]_D$ and the observed negative shift difference Δδ (≡CH) clearly demonstrate the predominant role of the configuration at C-17. By comparing data of similar compounds in Tables I and II it appears that the ethynyl moiety exerts a stronger influence on the position of the 13-CH_3 signal and on the optical rotation than the hydroxyl group. In this respect the value of 0.98 ppm, reported for 17α-ethynyl-4-androsten-3-one (Table II, compound A) can only be attributed to a printer's error*. The couplings between the ethynylic proton and the proton at position 17 (mentioned in Table II) are of the order of magnitude given by *Dale*[13]; *Krubiner* et al.[12] did not mention this long range coupling for their compounds A–D.

2) Possible mechanism of formation of the reduction products

It seems unlikely that compound **7** has been formed by a direct hydride attack on the strongly hindered C-17β position of **5**. An alternative mechanism, starting with an attack on the epoxide oxygen[14a] by an electrophilic species like AlH_3 seems justified.

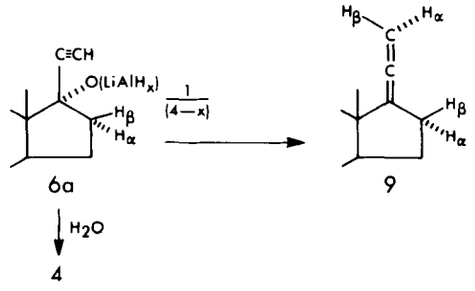


Scheme 1

The intermediate **5a** may eliminate its epoxide moiety mainly, thus forming the chief reaction product, the enyne **4**, and secondarily undergo either a hydride shift from C-16 to C-17 accompanied by a reduction of the short-lived complex **5b** leading to **7** or open to the relatively stable carbonium ion **5c**, which, after hydride attack from the α face, leads to the minor product **8** (Scheme 1).

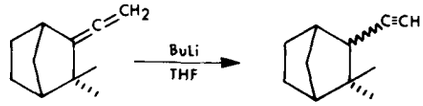
The structure of **8** follows from its IR and NMR spectra; the hydroxyl band shows no hydrogen bonding, the δ(CH_3) is found at 0.85 ppm (the corresponding value for the 16β-hydroxy-17α-ethynyl isomer should be expected at 0.80 + 0.25 ppm according to Table II – this work – and Table IV of *Bridgeman* et al.[15]) and the ethynylic proton signal is found at 2.22 ppm, a value being 0.21 ppm *lower* than that found for the 17α-ethynyl compound **8**. The influence of both substituents upon the position of the angular methyl signal is negligible (**7**: 0.84 ppm, **8**: 0.85 ppm). As a final proof **8** was converted into its tosylate which after reduction with $LiAlH_4$, completely analogous with the sequence **7** → **10** → **11**, rendered the β-ethynyl compound **12** (Table II).

The epimestranol **6** and the allenic by-product may have a common origin: the hydride attack on C-16 from the β-face[14b] gives rise to an intermediate, symbolised by **6a** which is fairly stable under the reaction conditions, but may be partly converted during that reaction by a second (intramolecular) hydride transfer into the allene **9** (Scheme 2).



Scheme 2

This allene[1] could be isomerised to a mixture of the 17β-ethynyl derivative **12** (85%) and the 17α isomer **11** (15%) by treatment with *n*-butyllithium in ether/THF at room temperature; *Mühlstädt* et al.[16] also found that this type of isomerisation afforded an epimeric mixture of ethynyl compounds (H) when applied to (+)-2,2-dimethyl-3-vinylidenenorbornane (G).



Supporting evidence for the proposed Schemes 1 and 2 could be drawn from the reduction of the epoxide **5** with $LiAlD_4$ in THF under the same conditions as used with

* In our previous paper[1] the chemical shift of the 21α-CH_3, given for compound **10** in Table II (p. 807) should be 95.5 + 102.5 Hz instead of 95.5 + 92.5 Hz; this error was overlooked in the proofreading.

[11] *L. Mamlok, A. M. Giroud* and *J. Jacques*, Bull. Soc. Chim. France 1806 (1961); *P. Crabbé*, Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry, Holden-Day, 1965, p. 57.

[12] *A. M. Krubiner, N. Gottfried* and *E. P. Oliveto*, J. Org. Chem. **34**, 3502 (1969).

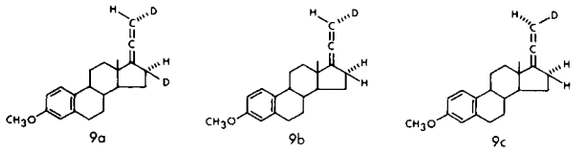
[13] *J. Dale* in *H. G. Viehe* (Editor), The Chemistry of Acetylenes, p. 44 ff., Marcel Dekker, New York 1969. See also *M. M. Kreevoy, H. B. Charman* and *D. R. Vinard*, J. Am. Chem. Soc. **83**, 1978 (1961).

[14] *D. N. Kirk* and *M. P. Hartshorn*, Steroid Reaction Mechanism, Elsevier Publ. Comp. Amsterdam/London/New York, 1968,
[a] Ch. 8, p. 353;
[b] Ch. 3, p. 115;
[c] *J. Fishman*, J. Am. Chem. Soc. **87**, 3455 (1965).

[15] *J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, E. R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards* and *P. D. Woodgate*, J. Chem. Soc. (C) 250 (1970).

[16] *M. Mühlstädt, L. Quang Thanh* and *J. Graefe*, Tetrahedron **28**, 4389 (1972).

$LiAlH_4$. The mixture showed a composition slightly different from that formed by $LiAlH_4$ reduction. The enyne **4**, isolated from it was completely deuterium-free according to mass spectral analysis. The "epimestranol", isolated in 10.5% yield, contained *one* deuterium (MS: 99% d., IR band at 2198 cm^{-1}) probably at position 16β (**6**, H_β = D) because of the generally assumed reaction mechanism[14b,14c]. The allene **9a** could be isolated by thick-layer chromatography and contained two deuteriums per mole; the IR spectrum showed one weak band for deuterium at saturated carbon (2178 cm^{-1} in CCl_4; cf. 2197 cm^{-1} for 2-deuteriocyclopentanone[18]) and a very weak band at 2258 cm^{-1} [ν(=C–D)]. The NMR spectrum of **9a** showed a *doublet* at 4.74 ppm (*J* 4 Hz) at the same position and with the same intensity as found for the *triplet* (*J* 4 Hz) of **9b**, prepared either from the side-chain deuterated "mestranol"[17] by $LiAlH_4/AlCl_3$ reduction or from "epimestranol" (**4**) by $LiAlD_4/AlCl_3$ reduction; the isomeric allene **9c**, prepared from "mestranol" (**3**) by reduction with $LiAlD_4/AlCl_3$, also showed a *triplet* (*J* 4 Hz) but at a higher field (4.70 ppm) than the epimeric **9b**. This remarkable difference (compare 4.73 ppm for the non-deuterated allene **9**) will be discussed in a subsequent paper[17].



9a 9b 9c

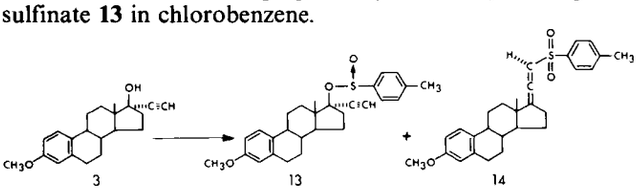
Finally, the 16β-deuterated analogue of **7** (H_β = D) and the 17α-deuterated analogue of **8** (H_α = D) could be isolated and characterised by IR, NMR and MS (see Experimental part), thus supporting the proposed mechanism of formation for the compounds **4**, **6**, **7**, **8** and **9** in Schemes 1 and 2.

3) Reactions of the "mestranols" 3 and 6

Because in the steroid series for the reduction or intramolecular rearrangements of this type of 2-propynols no types of leaving groups have been studied other than the unsubstituted hydroxyl group itself or its acetate[1], an attempt was made to prepare the *p*-tosylates[20] first. These tertiary tosylates might be useful to test the *trans* mechanism, reported by *Borden* and *Corey*[19] in allene-forming $LiAlH_4$ reductions of sulfonates of 2-propynols, not confirmed for other derivatives of alcohols or for 2-propynylamines as found by *Claesson* et al.[21], who found strong evidence for a suprafacial departure mechanism.

Attempts to prepare the *p*-tosylate from mestranol (**3**) failed [tosylation in pyridine under normal (room temperature) and forcing (boiling under reflux) conditions, heating with *p*-tosylic anhydride and pyridine].

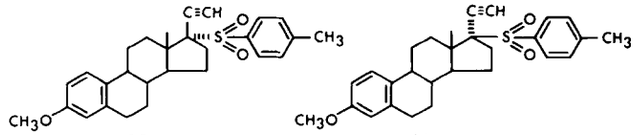
The *p*-toluenesulfinates **13**, epimeric at sulfur, could be prepared according to *Benn*[22]; a small amount of [2,3]-sigmatropic rearrangement[23] product **14** could also be isolated from the reaction mixture. This sulfone **14** proved to be identical with that prepared by *Benn*[22] by heating the sulfinate **13** in chlorobenzene.



3 13 14

The rather unstable, easily hydrolysed, glassy mixture **13**, could not be converted, however, into the *p*-tosylate by *m*-chloroperbenzoic acid in CH_2Cl_2 at low temperature, as successfully applied to the *p*-toluenesulfinate of longicamphenylol by *Coates* and *Chen*[24] or of 1-hydroxyadamantane by *Ree* and *Martin*[25]. Only complex mixtures were obtained at 0° and −20°C; oxidation by a stream of oxygen in CH_2Cl_2 or acetone solution with or without active carbon or cobalt(II) acetate added, proved to be unsuccessful as was activated manganese dioxide in carbon tetrachloride, preprepared as described by *Attenburrow* et al.[26]. Replacement of the tertiary hydroxyl group by chlorine or bromine, easily performed for 2-methyl-3-butyn-2-ol with concentrated hydrochloric acid and calcium chloride or 48% hydrobromic acid, copper, cuprous bromide and ammonium bromide[27] failed, only dehydration occurring.

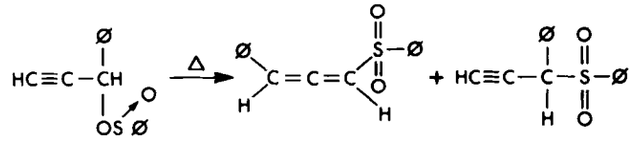
The preparation of the *p*-toluenesulfinate of the "epimestranol" **6** proved to be impossible; reactions carried out at the same time under the same mild conditions (−5°) for "mestranol" **3** and "epimestranol" **6** led in the case of **3** to mixtures of starting material, **13** and **14**, but, contrarily, in the case of **6**, to a mixture of the starting material and the *p*-toluenesulfones **15** and **16**.



15 16

These two sulfones, which surprisingly showed weak IR bands[28] in the antisymmetric SO_2 vibration region (1300–1350 cm^{-1}) but a strong symmetric SO_2 vibration (**15**: 1140 cm^{-1} in CCl_4; **16**: 1134 cm^{-1} in CH_2Cl_2) were formed in 16 and 28% yields, respectively and could be obtained pure but non-crystalline by careful column chromatography on Al_2O_3. The striking differences in the NMR spectra [δ(C≡CH) 2.87 for **15** and δ(C≡CH) 2.93 for **16**] and in the optical rotations ($[\alpha]_D^{22}$ +49.9° for **15** and $[\alpha]_D^{22}$ −64.8° for **16**) are sufficient evidence[9] for the stereochemistry at C-17. In the mass spectra loss of 155 a.m.u. ($CH_3C_6H_4SO_2$) caused the base peak (B 293.1) for both epimers.

No allenes or sulfinates could be isolated. *Braverman* and *Mechoulam*[23] found that the 1-phenyl-2-propynyl benzenesulfinate **17**, being the primary reaction product of 1-phenyl-2-propynol with benzenesulfinyl chloride, could be rearranged to a mixture of the 3-phenylallenyl phenyl sulphone (**18**) and a small amount of the 1-phenyl-2-propynyl phenyl sulphone (**19**) by heating **17** in acetonitrile at 80°.



17 18 19

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In our case the stability of the sulfones **15** and **16** is apparently much higher than that of the sulfinate esters; more profound study of this reaction under different conditions needs to be carried out.

Experimental section

Melting points were taken in open capillaries on a Büchi-Tottoli apparatus. Optical rotations were measured at 20° in methylene dichloride solution ($c = 1$), unless otherwise stated, with a Perkin-Elmer model 141 polarimeter. Infrared spectra (in cm^{-1}) were recorded in solution or in KBr pellets on a Perkin-Elmer model 21 spectrophotometer, equipped with a NaCl prism or a Perkin-Elmer model 357 grating spectrophotometer. NMR spectra were obtained with Varian A-60 D or Bruker HX-90E spectrometers in deuteriochloroform containing a trace of deuteriopyridine if allenes had to be scanned. Chemical shifts are reported in ppm relative to TMS as the internal standard and coupling constants in Hz.

Elemental analyses were kindly performed by Dr. *W. McMeekin* (Organon Labs., Newhouse, Scotland) on a Perkin-Elmer Model 240 Analyzer. Mass spectra were provided by Dr. *P. Bladon* (University of Strathclyde, Glasgow, Scotland) run on a AEI Model 902 spectrometer and by Dr. *J. J. de Ridder* (Drug Metabolism R & D Labs., Organon, Oss) run on a Varian MAT Model CH-7-SS 100-MS combination. Thin-layer chromatograms were obtained using silicagel G spread 250 μm thick on glass plates or on DC Fertigplatten Kieselgel F_{254}, Merck, Darmstadt, West-Germany; visualisation was effected by means of sulfuric acid, column chromatography was performed on silicagel (0.02–0.5 mm diameter, Merck, Darmstadt, West-Germany), unless otherwise stated, and on alumina (W 200, neutral, activity II, Woelm, Eschwege, West-Germany).

3-Methoxy-17-ethynyl-1,3,5(10),16-oestratetraene (**4**)

A solution of 10 g of **3** and 17 g of $POCl_3$ in 60 ml of 2,4-lutidine (Merck, zur Synthese) was stirred at room temperature for 16 hours in a nitrogen atmosphere. The brown-coloured reaction mixture was poured on to crushed ice and slightly acidified with H_2SO_4. After working up by extraction with ether and washing with aqueous $NaHCO_3$ solution followed by water until neutral, the ethereal solution was dried over anhydrous Na_2SO_4. After filtration and evaporation *in vacuo*, the crude residue (9.5 g) was chromatogaphed on silicagel with toluene. The main fraction (6.2 g) was crystallised from acetone/methanol, giving 6.0 g of **4** (64% yield). M.p. 148–150 °C, $[\alpha]_D^{20}$ +68.6°. Exact mass determination 292.1834 calcd. 292.1827 for $C_{21}H_{24}O$). IR bands (CS_2) at 3300 [ν(≡CH)], 2105 [ν(C≡C)] and 817 [δ(=CH)], UV maximum in ethanol at 225 nm (ε 19,300). NMR: 0.88 (13-CH_3), 3.08 (≡CH), 3.77 (OCH_3) 6.13 (broadened triplet, $J \simeq 2.5$ Hz) and the ring A aromatic multiplet between 6.5 and 7.3.

3-Methoxy-16α17-epoxy-17β-ethynyl-1,3,5(10)-oestratriene (**5**)

An amount of 5 g of **4** was dissolved in 250 ml of dry ethyl acetate and 35 ml of a 1 *M* solution of monoperphthalic acid in ethyl acetate was added under stirring in a nitrogen atmosphere. After 16 h at room temperature the reaction was terminated by adding aqueous 2N NaOH solution to the reaction mixture to pH 8 and after 10 minutes stirring the mixture was neutralised with 50% acetic acid. The organic layer was separated, washed till neutral with distilled water and dried over anhydrous Na_2SO_4. The crude product, obtained after evaporation of the solvent, was chromatographed on SiO_2 (Woelm, 0.63–0.2 mm) with toluene; the main fraction afforded, after crystallisation from acetone, 2.0 g of the epoxide **5** (38% yield). M.p. 195–196 °C, $[\alpha]_D^{20}$ +104.6°, analysis for $C_{21}H_{24}O_2$ (308.18); calcd. C 81.78, H 7.84, O 10.38; found: C 81.8, H 7.8, O 10.1; exact mass determination 308.1732 (calcd. 308.1776). IR bands (CH_2Cl_2) at 3300 [ν(≡CH)], 877 + 848 (epoxide). NMR: 0.93 (13-CH_3), 2.41 (≡CH), 3.63 (16β-H), 3.76 (OCH_3) and the ring A aromatic pattern between 6.5 and 7.3.

Reduction of 3-methoxy-16α17-epoxy-17β-ethynyl-1,3,5(10)-oestratriene (**5**)

A suspension of 2 g of $LiAlH_4$ in 40 ml of dry THF was slowly added at ~15°C under nitrogen to a solution of 2 g of **5** in 40 ml of THF and the mixture was stirred at room temperature under nitrogen for 20 h. The reaction mixture was treated cautiously with a mixture of 40 ml THF and 1 ml water under cooling in an ice bath and under nitrogen while stirring vigorously. The grey granular precipitate was separated by filtration after addition of "Hyflo" and washed with ether several times. The ethereal solution was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness after filtration. The crude residue was chromatographed on a silica gel column (200 g) with toluene/ethyl acetate (95 : 5).

The enyne (**4**) was eluted first (1.0 g), followed by *3-methoxy-17α-hydroxy-17β-ethynyl-1,3,5(10)-oestratriene* (**6**). The crude fraction (0.6 g) was crystallised from ethanol, yielding 0.5 g of **6**. M.p. 135–136 °C, $[\alpha]_D^{20}$ +71.8°, analysis for $C_{21}H_{26}O_2$ (310.19); calcd. C 81.25, H 8.44, O 10.31; found C 81.1, H 8.5, O 10.1; exact mass determination 310.1928, calcd. 310.1933. IR bands (CH_2Cl_2) at 3623 [ν(OH)], 3300 [ν(≡CH)], 969 [ν(C–O)], NMR: 0.90 (13-CH_3), 2.50 (≡CH), 3.76 (OCH_3) and the ring A aromatic pattern between 6.5 and 7.3. The third fraction (0.4 g) proved to be a 6 : 1 mixture (TLC) of two products, which could be separated by preparative thick-layer chromatography (Kieselgel 60 PF, Merck, Darmstadt, West-Germany; CH_2Cl_2/acetone 99 : 1).

The major component was *3-methoxy-16α-hydroxy-17α-ethynyl-1,3,5(10)-oestratriene* (**7**), and crystallised from ethanol (0.25 g). M.p. 136–137°C, $[\alpha]_D^{20}$ −84.2°, analysis for $C_{21}H_{26}O_2$ (310.19); calcd. C 81.25, H 8.44, O 10.31; found: C 81.2, H 8.6, O 10.2. Exact mass determination 310.1946, calcd. 310.1933; IR bands (CCl_4) at 3558 [ν(OH)], 3307 [ν(≡CH)] and (CH_2Cl_2) 2101 [ν(C≡C)]. NMR: 0.84 (13-CH_3), 2.43 (≡CH, d, J 2.5 Hz), 2.95 (17β-H, dd, J_1 7.5 Hz, J_2 2.5 Hz), 3.76 (OCH_3), 4.50 (16β-H, broad multiplet) and the ring A aromatic pattern.

The minor compound *3-methoxy-16α-hydroxy-17β-ethynyl-1,3,5(10)-oestratriene* (**8**) was crystallised from ethanol yielding 0.05 g. M.p. 206–210 °C, $[\alpha]_D^{20}$ +67°, exact mass determination 310.1936, calcd. 310.1933. IR bands (CH_2Cl_2) 3604 [ν(OH)], 3300 [ν(≡CH)], 2113 [(C≡C)]. NMR: 0.85 (13-CH_3), 2.22 (≡CH, d, J 1.5 Hz), 2.23 (17α-H, dd, $J_2 \simeq 2.5$ Hz), 3.76 (OCH_3), 4.41 (16β-H, m).

In a similar experiment, a few percent of *the allene* **9** could be isolated by thick-layer chromatography; the product proved to be identical (IR, NMR, TLC) with the compound already described[1]).

3-Methoxy-17α-ethynyl-1,3,5(10)-oestratriene (**11**)

0.5 g of **7** was dissolved in 2 ml of dry pyridine and 0.5 g of *p*-tosyl chloride was added with stirring. After stirring for 16 h the reaction mixture was poured on to ice and the oily precipitate was filtered after stirring 1h. The precipitate was dissolved in methylene chloride and the organic layer was washed with distilled water twice. After the usual working up 0.62 g of an oily residue was obtained. A quantity was purified by thick-layer chromatography and characterized by IR and NMR but could not be obtained in a crystalline state: *3-methoxy-16α-p-tosyloxy-17α-ethynyl-1,3,5(10)-oestratriene* (**10**). $[\alpha]_D^{20}$ +38.3°, IR bands (CCl_4): 3318 [ν(≡CH)], 2121 [ν(C≡C)], 1374, 1193, 1182 (tosylate). NMR: 0.80 (13-CH_3), 2.28 (≡CH, d, J 2.7 Hz), 2.45 (Ar-CH_3), 2.95 (17β-H, dd, J_1 2.7 Hz, J_2 7.5 Hz), 3.78 (OCH_3), 5.21 (16α-H, m), the usual ring A aromatic pattern and an AA′BB′ system at 7.28, 7.43, 7.83 and 7.97 (J_{AB} 9 Hz). Mass spectrum: parent and base peak at 464.3 (calcd. for $C_{28}H_{32}O_4S$: 464.202), 292.1 ($M-C_7H_8O_3S$).

A quantity of 0.5 g of **10** was dissolved in 25 ml of dry THF and this solution was added under nitrogen at room temperature to a solution of 0.5 g of $LiAlH_4$ in 10 ml of dry THF. After heating under reflux for 7 h under nitrogen, the reaction mixture was cooled in an ice bath and water was cautiously added while stirring. After the usual working up the ethereal solution was evaporated to dryness giving 0.36 g of crude material, which was chromatographed on silicagel with hexane/toluene 7 : 3. After crystallisation from ethyl acetate an analytical sample of **11** was obtained. M.p. 84–88 °C, $[\alpha]_D^{20}$ −5.8°. IR bands (CCl_4) at 3317 [ν(≡CH)], 2113 [ν(C≡C)], 626 [δ(CH)]. NMR: 0.80 (13-CH_3), 2.17 (≡CH, d, J 2.5 Hz). Mass spectrum: parent and base peak 294.1 (calcd. for $C_{21}H_{26}O$: 294.1984.

3-Methoxy-17β-ethynyl-1,3,5(10)-oestratriene (**12**)

0.2 g of **8**, obtained from several reductions of the epoxide **5**, was converted into its 16α-*p*-tosylate in the same manner as described for **7**. The crude ester was reduced as described above and afforded, after crystallisation from ethyl acetate, an analytically pure sample, identical with the compound described by *Krubiner* et al.[12]. M.p.: 148–149°C, $[\alpha]_D^{20}$ +118°. IR bands (CCl_4) at 3318 [ν(≡CH)], 2118 [ν(C≡C)], 630 [δ(≡CH)]. NMR: 0.83 (13-CH_3), 2.10

(≡CH, d, J 2.0 Hz), 3.77 (OCH_3) and the usual ring A aromatic pattern. Mass spectrum: parent and base peak 294.2 (calcd. for $C_{21}H_{26}O$: 294.1984).

Isomerisation of 3-methoxy-19-nor-1,3,5(10),17(20),20-pregnapentaene (**9**)

0.7 g of **9** was dissolved in a mixture of 5 ml of dry ether and 5 ml of dry THF; under nitrogen and while stirring 2.1 ml of a solution of butyllithium in hexane (0.144 g/ml) was added. After 2 h stirring at room temperature the reaction mixture was cooled in an ice bath and water was cautiously added till no further reaction was observed. After working up as usual 0.6 g of crude material was obtained which was chromatographed on silicagel with hexane/toluene 7 : 3. After crystallisation from acetone/methanol 0.4 g of analytically pure (TLC, IR, NMR) product was obtained, identical with **12**. The mother liquors were evaporated *in vacuo* and the residue (0.2 g) proved to be a 1 : 1 mixture of **12** : **11** according to NMR, thus leading to a total yield of isomerisation of 85% **12**/15% **11**.

3-Methoxy-19-nor-21α-deuterio-1,3,5(10),17(20),20-pregnapentaene (**9b**)

A solution of 0.25 g of "epimestranol" (**6**) in 10 ml of dry THF was added to a suspension of 0.1 g of $LiAlD_4$ (Merck, Darmstadt, West-Germany, 99% D) and 0.1 g $AlCl_3$ in 10 ml of dry THF. The mixture was refluxed under nitrogen for 2.5 h, cooled and worked up as described for the $LiAlH_4/AlCl_3$[1] reduction of "mestranol". After crystallisation from ethanol 72 mg of pure product was obtained. M.p. 102–103 °C, $[\alpha]_D^{20}$ +40.8°. IR bands (CCl_4) at 2258 [vw, ν(=C–D)], 1953 [ν(C=C=C)]. NMR: 0.90 (13-CH_3), 3.75 (OCH_3), 4.74 (21β-H, t, J 4 Hz) and the ring A aromatic pattern. Parent and base peak in mass spectrum at 295.20436, calc. for $C_{21}H_{25}DO$: 295.20463.

3-Methoxy-19-nor-21β-deuterio-1,3,5(10),17(20),20-pregnapentaene (**9c**)

Completely analogous transformation of "mestranol" with $LiAlD_4/AlCl_3$ afforded 75 mg of **9c**. M.p. 102–103 °C, $[\alpha]_D^{20}$ +41.4°. IR bands (CCl_4) at 2258 [vw, ν(=C–D)]. NMR: 0.89 (13-CH_3), 3.75 (OCH_3), 4.70 (21α-H, t, J 4 Hz) and the ring A aromatic pattern. Parent and base peak in mass spectrum at 295.20485, calcd. for $C_{21}H_{25}DO$: 295.20463.

Reduction of the epoxide **5** *with* $LiAlD_4$

An amount of 0.4 g of **5** was treated with $LiAlD_4$, as described for $LiAlH_4$ and afforded 0.32 g of a crude product; 2 mg of the *allene* **9a** was isolated by thick-layer chromatography of the least polar column fractions. IR bands (CCl_4) at 2258 [ν(=C–D)], 2178 [ν(C–D)] and 1958 [ν(C=C=C)]. NMR: 0.90 (13-CH_3), 3.76 (OCH_3), 4.74 (=C–H, d, J 4 Hz) and the usual ring A aromatic pattern. Parent and base peak in mass spectrum 296.1; 95.7% of d_2 and 2.9% of d_1, confirming (cf. **9b**) *3-methoxy-16β,21α-dideuterio-19-nor-1,3,5(10),17(20),20-pregnapentaene* **9a**. The second chromatographic fraction (about 100 mg) proved to be identical with the deuterium-free enyne **4** (IR, NMR, MS), the third fraction proved to be 40 mg of the starting material **5** (*not* isolated after $LiAlH_4$ reduction of the epoxide!) and the fourth fraction (42.5 mg) was the deuterated "epimestranol":

3-Methoxy-16β-deuterio-17α-hydroxy-17β-ethynyl-1,3,5(10)-oestratriene (**4**, *16β-H = D*)

M.p. 134–136 °C, IR bands (CCl_4): 3617 [ν(OH)], 3313 [ν(≡CH)], 2198 [w, ν(C–D)]. NMR: 0.90 (13-CH_3), 2.50 (≡CH), 3.77 (OCH_3) and the ring A aromatic pattern. Mass spectrum: parent peak 311.1 (calcd. for $C_{21}H_{25}O_2D$: 311.1995), 99% d_1, <0.3 d_2. The fifth fraction (30 mg) proved to be the mono-deuterio analogue of **7**:

3-Methoxy-16α-hydroxy-16β-deuterio-17α-ethynyl-1,3,5(10)-oestratriene (**7**, *16β-H = D*)

IR bands (CCl_4) at: 3560 [ν(OH)], 3313 [ν(≡CH)], 2195 [ν(C–D)], 2114 [ν(C≡C)]. NMR: 0.84 (13-CH_3), 2.43 (≡CH, d, J 2.5), 2.96 (17β-H, d, J 2.5) *no* bands at ≃ 4.5 ppm, 3.77 (OCH_3) and the ring A aromatic pattern. Mass spectrum: parent and base peak 311.1 (calcd. for $C_{21}H_{25}O_2D$: 311.1995).
The last fraction (25 mg) could be characterised as *3-methoxy-16α-hydroxy-17α-deuterio-17β-ethynyl-1,3,5(10)-oestratriene* (**8**, *17α-H = D*). IR bands (CH_2Cl_2) at: 3602 [ν(OH)], 3307 [ν(≡CH)], 2112 [ν(C≡C)]. NMR: 0.85 (13-CH_3), 2.20 (≡CH, *s*), 3.78 (OCH_3), 4.42 (16β-H, dd, J_1 5, J_2 2). Mass spectrum: parent and base peak at 311.1 (calcd. for $C_{21}H_{25}O_2D$: 311.1995), 96% d_1, 0.5% d_2.
At least two other by-products have been isolated; the structures have only roughly been determined, and full evidence has yet to be provided.

3-Methoxy-17α-ethynyl-17β-(p-toluenesulfinyloxy)-1,3,5(10)-oestratriene (**13**)

0.2 g of "mestranol" (**3**) was dissolved in 1 ml of dry THF containing 0.05 ml of dry pyridine, 0.12 g of *p*-toluenesulfinyl chloride[29] in 0.5 ml THF was added dropwise under nitrogen and while stirring at °C. After 1.5 h at 0 °C the slightly turbid solution was filtered and the filtrate was washed with 2*N* aqueous HCl, dilute $NaHCO_3$ and water till neutral. After drying over anhydrous Na_2SO_4 the solution was evaporated *in vacuo*. The crude product (0.24 g) which contained some starting material according to TLC, was chromatographed on neutral alumina (Woelm, see general part) with toluene/ethyl acetate 97 : 3 and 0.175 g of chromatographically pure but oily sulfinate (**13**) was obtained in 60% yield; the compound was identical with that described by *Benn*[22]. IR bands (CH_2Cl_2): 3300 [ν(≡CH)], 1129 [ν(S → O)], 960 [ν(C–O)]. NMR: 0.85 + 0.93 (13-CH_3, 1 : 1, *S*-epimers), 2.42 (Ar-CH_3), 2.93 + 2.97 (≡CH, 1 : 1, *S*-epimers), 3.77 (OCH_3), the ring A aromatic pattern and an AA′BB′ system at 7.23, 7.33, 757 and 7.72 (J_{AB} 9 Hz). As a second product 20 mg of the allene: *3-methoxy-21β-(p-toluenesulfonyl)-19-nor-1,3,5(10),17(20),20-pregnapentaene* (**14**) was isolated, identical with that described by *Benn*[22] and identical with the compound obtained by heating **13** in chlorobenzene for 0.5 h. M.p. 140–142 °C, $[\alpha]_D^{20}$ +169.3°. IR bands (CH_2Cl_2) at 1965 [ν(C=C=C)], 1316 + 1304 [$\nu^a(SO_2)$] and 1143 [$\nu^S(SO_2)$]. NMR: 0.91 (13-CH_3), 2.43 (Ar-CH_3), 6.26 (21α-H, t, J 4 Hz), the ring A aromatic pattern and an AA′BB′ system at 7.25, 7.38, 7.73 and 7.88 (J_{AB} 8 Hz).

Reaction of "epimestranol" with p-toluenesulfinyl chloride

0.2 g of "epimestranol" (**6**) was reacted as described above for "mestranol" under exactly the same conditions. The thin-layer chromatogram was completely different (more products of almost the same intensity of spots) and only two products could be isolated by column chromatography and identified (besides 70 mg of starting material):

3-Methoxy-17α-(p-toluenesulfonyl)-17β-ethynyl-1,3,5(10)-oestratriene (**15**)

46 mg, amorphous, $[\alpha]_D^{20}$ +49.9°. IR bands (CCl_4) at 3313 [ν(≡CH)], 2838 (OCH_3), 1140 [ν(SO_2)]. NMR: 0.98 (13-CH_3), 2.42 (Ar-CH_3), 2.87 (≡CH, *s*), 3.75 (OCH_3), the normal ring A aromatic pattern and an AA′BB′ system at 7.26, 7.40, 7.60 and 7.83 (J_{AB} 8 Hz). Mass spectrum: 448.0 for parent peak (calcd. for $C_{28}H_{32}O_3S$: 448.2072), base peak 293.0 (*M* minus $CH_3C_6H_4SO_2$).

3-Methoxy-17β-(p-toluenesulfonyl)-17α-ethynyl-1,3,5(10)-oestratriene (**16**)

80 mg, amorphous, $[\alpha]_D^{20}$ −64.8°. IR bands (CH_2Cl_2): 3300 [ν(≡CH)], 2839 [ν(OCH_3)], 1134 [ν(SO_2)]. NMR: 0.97 (13-CH_3), 2.41 (Ar-CH_3), 2.93 (≡CH, *s*), 3.74 (OCH_3), the normal ring A aromatic pattern and an AA′BB′ system at 7.26, 7.38, 7.55 and 7.68 (J_{AB} 8 Hz). Mass spectrum: parent peak at 448.1 (calcd. for $C_{28}H_{32}O_3S$: 448.2072), base peak at 293.1 (*M* minus $CH_3C_6H_4SO_2$).

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