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SYNTHESIS OF 17α-ETHYNYLOESTRADIOL TRI- AND PENTADEUTERATED IN RING C

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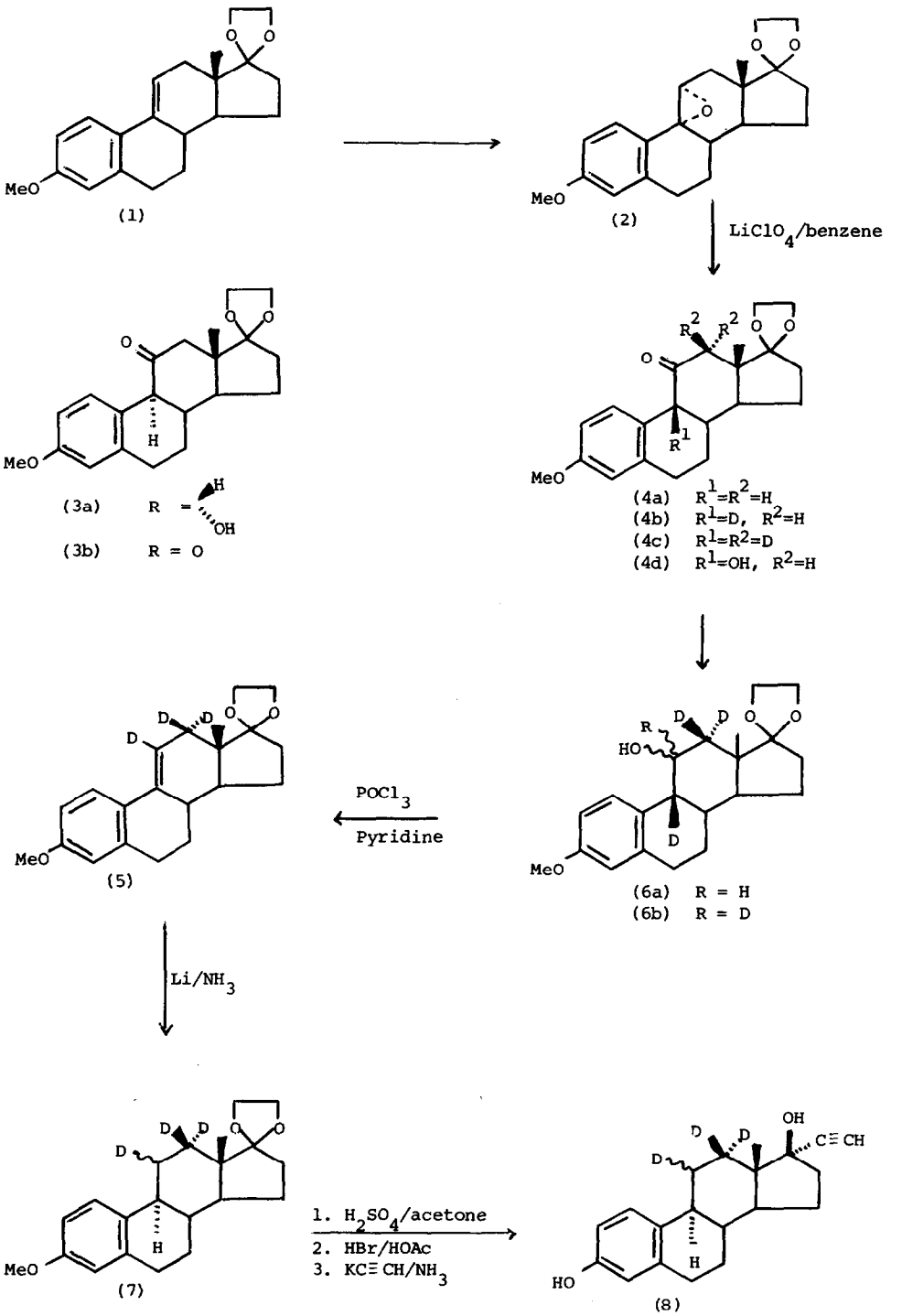
Contraceptive steroids specifically labelled with stable isotopes in metabolically safe positions are required for definitive metabolic studies which will be monitored by gas chromatography-mass spectrometry. For example, accurate data are still lacking on the transfer of 17α-ethynyloestradiol and its metabolites into the milk of lactating women who are using various formulations of oral contraceptives. This paper describes the synthesis of 17α-ethynyloestradiol[11ξ,12,12-$^2H_3$] (8) and 17α-ethynyloestradiol[9α,11,11,12,12-$^2H_5$] (11).

9(11)-Dehydrooestrone 3-methyl ether[1] was converted into the corresponding cyclic ethylene acetal (1), m.p. 154.5-156.5°, $[\alpha]_D$ + 91°, λ_{max} 263(19,500), 298 nm (3,100). The material m.p. 146-147°, $[\alpha]_D$ + 63°, λ_{max} 262-3 (18,800), described in the literature[2] was probably contaminated with the 9(11)-dihydro compound.

Epoxidation of (1) with *m*-chloroperoxybenzoic acid in methylene chloride and aqueous sodium bicarbonate gave 70% of the very labile 9α,11α-epoxide (2), m.p. 160-163.5°, $[\alpha]_D$ + 48.9°. A solution of (2) in benzene containing a trace of anhydrous lithium perchlorate (cf.[3]) was heated under reflux for 3 hours to give an almost quantitative yield of the non-crystalline 9β-ketone (4a), $[\alpha]_D$ + 160.8°, ν_{max} ($CHCl_3$) 1690 cm^{-1}. The unusually low frequency of the 11-carbonyl group is comparable with the reported value [ν_{max} (KBr) 1695 cm^{-1}] for 11-oxo-9β-oestradiol.[4] As in the case of 11-oxooestradiol[4] the 9β-11-ketone (4a) is appreciably more stable than its 9α-isomer (3b) which was obtained from the olefin (1) by hydroboration, and oxidation of the 11α-alcohol with pyridinium chlorochromate. Both (4a) and (3b) were unusually susceptible to hydroxylation on alumina, and the 9α-isomer (3b) was partly epimerised to the 9β-ketone (4a). The pure 9α-11-ketone (3b) was obtained by chromatography on Florisil.

Deuteration of the ketone (4a) (obtained directly from (2) as above) by phase transfer catalysis using tetra-*n*-butylammonium bromide (cf. Starks[5]) in the two-phase system methylene chloride-sodium deuteroxide-deuterium oxide for 3 days under nitrogen gave mainly the 9β-monodeutero ketone (4b) plus an appreciable amount of a deuterium-free hydroxy ketone, tentatively formulated as the 9β-hydroxyketone (4d). Deuteration of (4a) using sodium deuteroxide in MeOD and D_2O under nitrogen gave the trideutero ketone (4c), but this was accompanied by a high proportion of the 12,12-dideutero-9-hydroxy derivative and an unidentified dihydroxyketone. The hydroxylated by-products were revealed and identified by gas chromatography-mass spectrometry


MeO
(1)
(2)
LiClO4/benzene
(3a) R = H, OH
(3b) R = O
(4a) R1=R2=H
(4b) R1=D, R2=H
(4c) R1=R2=D
(4d) R1=OH, R2=H
(5)
POCl3
Pyridine
(6a) R = H
(6b) R = D
Li/NH3
(7)
1. H2SO4/acetone
2. HBr/HOAc
3. KC≡CH/NH3
(8)
HO
OH
C≡CH

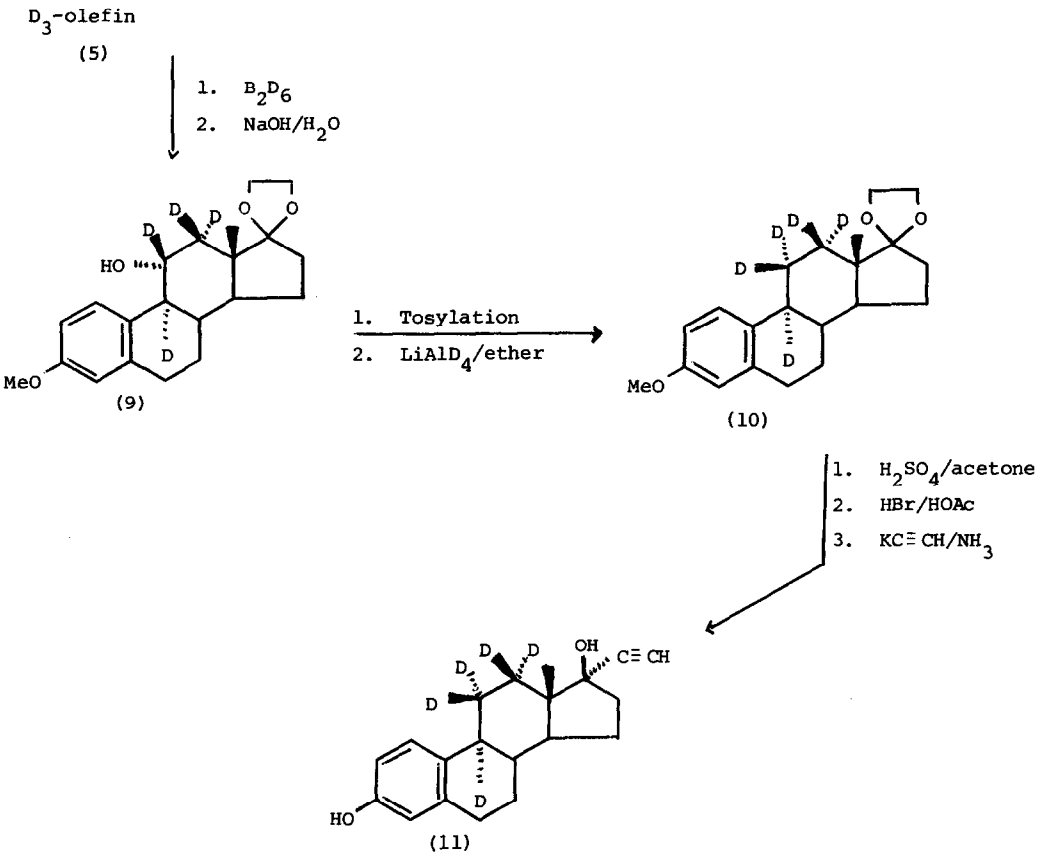
(GC-MS) of the trimethylsilylated product from the mixture of 11-epimeric alcohols obtained by lithium aluminium hydride reduction of the crude deuterated ketone.

To overcome the problem of hydroxylation at C9 the following deuteration procedure was developed. A slight excess of hydroquinone[OD]$_2$ was added to a solution of sodium methoxide in MeOD under nitrogen, the ketone (4a) was added, and the mixture was refluxed gently for 10 days to give the trideuterated ketone (4c) almost free of by-products. Reduction of this with $LiAlH_4$ or $LiAlD_4$ gave the 11-epimeric tri- or tetradeuterated alcohols (6a, 91.6% D_3), or (6b, 89.6% D_4), respectively. Dehydration of (6b) with phosphorus oxychloride in pyridine gave the D_3-olefin (5), 89.9% D_3, m.p. 153-154.5°, undepressed by admixture with (1), and shown to be pure by GC-MS. Reduction of the D_3-olefin (3b) with lithium in anhydrous ammonia and tetrahydrofuran afforded a high yield of the 9α-trideutero compound (7), m.p. 103-104.5° ($^2H_4$, 7.3; $^2H_3$, 85.4; $^2H_2$, 3.0; $^2H_1$, 2.1; $^2H_0$, 2.2%), structurally identical (mixed m.p., GC-MS) with an authentic specimen of the undeuterated compound. The apparent partial redistribution of the label to give 7.3% of tetradeuterated species in this reaction is puzzling, and a study of this phenomenon is in progress.

Treatment of (7) with dilute sulphuric acid in acetone gave trideuterated 11ξ,12,12-trideuteroestrone 3-methyl ether, m.p. 176-177°, which upon demethylation and ethynylation with potassium acetylide in anhydrous ammonia and tetrahydrofuran gave crude D_3-ethynyloestradiol (8). This was treated with Girard's Reagent P to remove a small amount of unreacted D_3-oestrone, then filtered through silicic acid and crystallised from aqueous methanol to give ethynyloestradiol[11ξ,12,12-$^2H_3$] (8, $^2H_4$, 9.2; $^2H_3$, 84.1; $^2H_2$, 3.1; $^2H_1$, 2.2; $^2H_0$, 1.3%) shown to be pure by t.l.c. and GC-MS.

Treatment of (5) with hexadeuterodiborane, and oxidation with alkaline peroxide gave the tetradeuterated alcohol (9), the reductive deoxygenation of which proved troublesome. Reduction of the readily formed methanesulphonate of (9) with lithium aluminium deuteride in ether gave only 28% of (10) together with 51% of (9) and 15% of (5); when the reduction was carried out in tetrahydrofuran the yield of (10) was negligible. Formation of the *p*-toluenesulphonate of (9) was slow. Reduction of the crude product from an 11-day reaction of (9) with *p*-toluenesulphonyl chloride in pyridine with lithium aluminium deuteride in ether afforded the best yield (61%) of (10) together with 11% of the D_3-olefin (5) and 23% of the D_4-alcohol (9). This mixture was resubjected to hexadeuterodiborane and alkaline peroxide, then compound (10) was cleanly separated from (9) by column chromatography. The reported efficacy of lithium triethylborohydride in the reduction of hindered methanesulphonates[6] and *p*-toluenesulphonates[7], with minimal elimination, was not borne out with the hindered sulphonate esters of 11α-alcohol (9). Removal of the protecting groups from (10), and ethynylation, gave ethynyloestradiol[9α,11,11,12,12-$^2H_5$] (11, $^2H_5$, 84.5; $^2H_4$, 8.5; $^2H_3$, 4.4; $^2H_2$, 0.9; $^2H_1$, 0.8; 0.9%), which was purified as for (8).

GC-MS measurements were made with a modified LKB 9000 mass spectrometer, and average isotope contents were determined by comparison with the unlabelled reference compounds using an IBM 1800 computer.



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