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# SYNTHESIS OF ESTRA-1,3,5(10)-TRIEN-3,15α,16α,17β-TETROL A NEW METABOLITE OF ESTRADIOL

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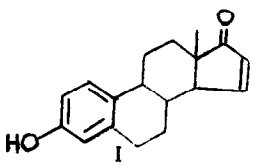
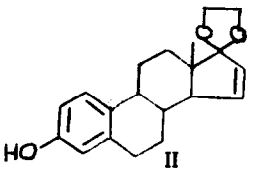
A new metabolite derived from estradiol and considered to be exclusively fetal in origin was obtained from neonatal and pregnancy urine by Hagen et al[1] and Gurpide et al[2]. The compound contained four acylable hydroxy functions and formed an acetonide derivative. One tentative structure suggested was $\Delta^{1,3,5(10)}$-estratrien-3,15α,16α,17β-tetrol[3]. In order to establish the structure of the metabolite and to provide useful quantities of material the synthesis of this interesting compound was undertaken.

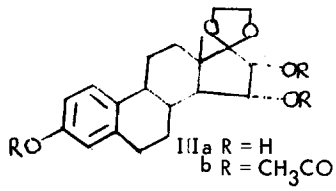
The osmium tetroxide oxidation of the α,β-unsaturated ketal II[4] gave as the major product the triol IIIa, isolated as the triacetate IIIb m.p. 145-147°. The α orientation of the C-15 and C-16 hydroxyl groups was expected from the general preference of reagent attack from the less hindered α side. This was confirmed by n.m.r. evidence discussed later. Removal of the dioxolane group in IIIb was attempted with p-toluene sulfonic acid in acetone at room temperature, conditions which would minimize the hydrolysis of the acetate groups. Although both the α,β-unsaturated II and saturated IVa dioxolanes are efficiently hydrolyzed under these conditions, the ketal IIIb was completely stable. When more drastic sulfuric acid catalysis in dioxane was used, hydrolysis of the acetate groups and subsequent rearrangements took place, giving rise to a multitude of products. The difficult hydrolysis of the C-17 ethylenedioxy group in IIIb is apparently due to the presence of a C-16 substituent and is analogous to the stability of the 16α-bromo-17-ketal IVb under similar conditions.



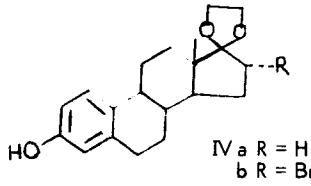

I




II

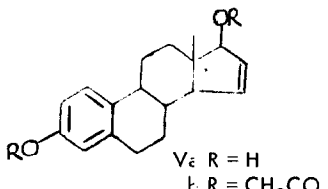



IIIa R = H
b R = $CH_3CO$

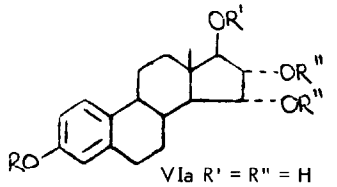



IV a R = H
b R = Br

The cis hydroxylation of ring D with a preformed 17β-hydroxy group was the next objective. With $LiAlH_4$, reduction of the α,β-unsaturated ketone I[4] took the expected course and provided the allylic alcohol Va, isolated in good yield as the diacetate Vb m.p. 90-92° $[\alpha]_D^{26}$ - 19°. The reduction was stereospecific since only estradiol-17β diacetate was obtained after catalytic hydrogenation of the double bond. Oxidation of the diacetate Vb with $OsO_4$ in pyridine gave the tetrol diacetate VIb m.p. 189-192° $[\alpha]_D^{26}$ + 92 and hydrolysis with $K_2CO_3$ in refluxing methanol gave the desired tetrol VIa m.p. 230-235° $[\alpha]_D^{26}$ + 135°. Mild hydrolytic conditions are essential since the use of more drastic conditions reduces the yield substantially.




Va R = H
b R = $CH_3CO$




VIa R' = R" = H
b R' = $CH_3CO$, R" = H
c R' = R" = $CH_3CO$

The orientation of the newly introduced hydroxyl groups was established to be α from n.m.r. evidence. The C-18 methyl group resonances of the pertinent compounds are listed in Table I. It is clear that the C-18 methyl shifts are consistent only with 15α substitution, since a 15β substituent should result in much larger deshielding[5,6]. Although it has been pointed out[7] that the C-18 methyl shifts should be applied with caution to the assignment of ring D substituents this applies primarily to C-16 where the differences between the epimers are small, and to C-20 ketones where the conformation of the side chain can be affected by substitution at C-16. None of these circumstances apply to the tetrol VIa and hence the n.m.r. evidence may be considered valid. In addition, the molecular rotational differences listed in Table II show a strong positive increment. A 15β substitution would lead to levorotatory shifts[4,8].

Comparison of the synthetic tetrol VIa with the natural product[9] exhibited identity in infrared spectra, mass spectra, color reactions and $R_f$ values in various systems and establish the structure of the new metabolite.

TABLE I

| | C-18 Methyl[a] | |
|---|---|---|
| | OBS | CALC[b] |
| Estra-1,3,5(10)-triene-3,17β-diol Diacetate | 49 | -- |
| Estra-1,3,5(10)-triene-3,16α,17β-triol Triacetate | 51 | 52 |
| Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol Tetracetate (VIc) | 56 | 55 |
| Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol 3,17-Diacetate (VIb) | 51 | 52 |
| 17,17-Ethylenedioxyestra-1,3,5(10)-triene-3-ol | 54 | -- |
| 17,17-Ethylenedioxyestra-1,3,5(10)-triene-3,15α,16α-triol Triacetate (IIIb) | 63 | 60[c] |

a) Spectra were obtained on a Varian A60 instrument in deuterochloroform. Chemical shifts are given in cps downfield from tetramethysilane as an internal standard.

b) Using the 49 cps value from estra-1,3,5(10)-triene-3,17β-diol diacetate as the base.

c) Using the 54 cps value from 17,17-ethylenedioxyestra-1,3,5(10)-triene-3-ol as the base.

TABLE II

| | $[\alpha]_D$ | $M_D$ | $\Delta M_D$ |
|---|---|---|---|
| Estra-1,3,5(10)-triene-3,16α,17β-triol | + 61 (diox[a]) | +176 | -- |
| Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol (VIa) | +135 (etoh) | +410 | +234 |
| Estra-1,3,5(10)-triene-3,16α,17β-triol Triacetate | - 17 ($chcl_3$) | - 42 | -- |
| Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol Tetracetate (VIc) | + 92 ($chcl_3$) | +430 | +472 |

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