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# ESTRA-1,3,5(10),16-TETRAENE-3,16-DIOL DIACETATE AND AN EASY SYNTHETIC ROUTE TO 16β,17α- AND 16α,17α- STEROIDAL GLYCOLS

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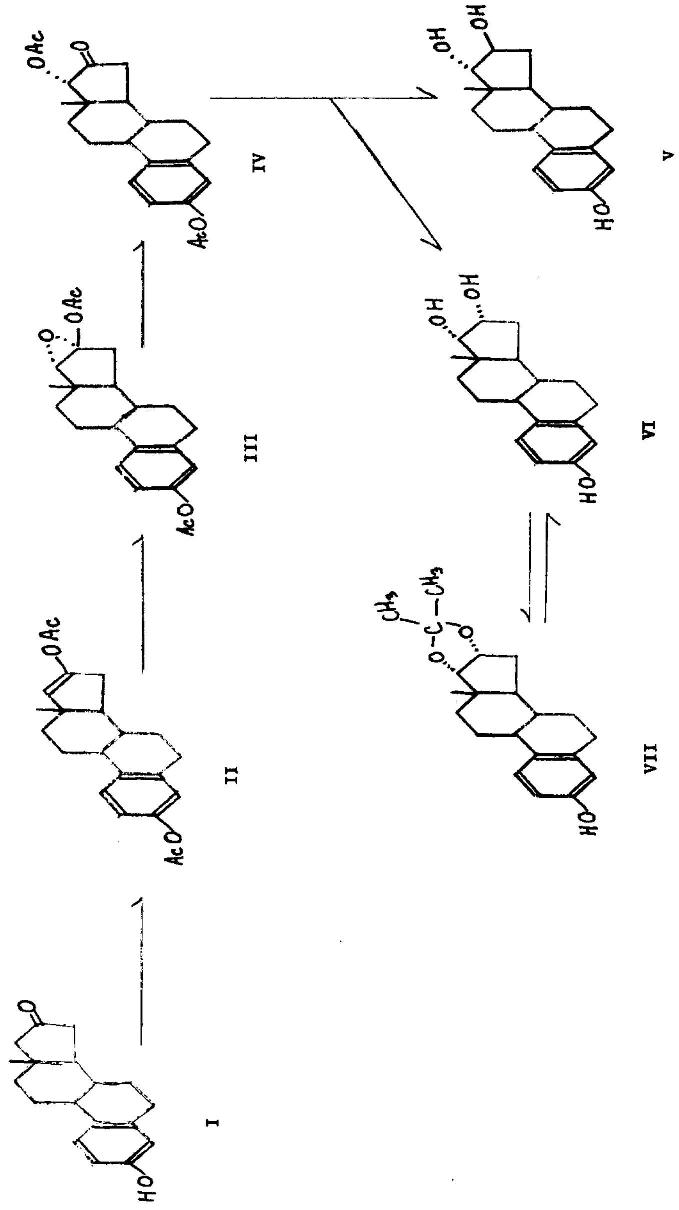
Contrary to a report (1) in the literature that estrone-16 (16-keto-estra-1,3,5(10)-trien-3-ol) (2) fails to form an enol acetate, we have found that, with the aid of <u>anhydrous</u> p-toluenesulfonic acid as a catalyst, estra-1,3,5(10),16-tetraene-3,16-diol diacetate can be successfully obtained in stable form.

This finding opens an easy synthetic route, through 16α,17α-epoxyestra-1,3,5(10)-triene-3,16-diol diacetate, to 16-keto-estradiol-17α (1) and to the difficulty obtainable 16,17-epiestriol (3); it also affords a method of preparation of 17-epiestriol without the need of expensive $OsO_4$(4). The new series of reactions furthermore permits the preparation of large quantities of these steroids without the necessity of chromatographic separation. Estrone-16 can be obtained from estrone in 50-60% yield (2c).

Slow distillation of a solution of 16-keto-estra-1,3,5(10)-trien-3-ol (I) in isopropenyl acetate plus anhydrous p-toluenesulfonic acid furnishes in 65-70% yield estra-1,3,5(10),16-tetraene-3,16-diol diacetate (II), m.p. 136-137° (<u>Anal</u>. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.40. Found: C, 74.93; H, 7.41). Treatment of the enol acetate II with m-chloroperbenzoic acid in carbon tetrachloride for 6-8 hours gives a 75% yield of 16α, 17α-epoxyestra-1,3,5(10)-triene-3,16-diol diacetate (III), m.p. 152-152.5°, $(\alpha)_D^{25}$ +96° (c, 1.054 in $CHCl_3$) (*Anal*. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.47; H, 6.96). When epoxide III is dissolved in glacial acetic acid and treated with 60% perchloric acid, the epoxide ring opens to form a quantitative yield of 16-keto-estra-1,3,5(10)-triene-3,17α-diol diacetate (IV) (1), m.p. 129.5-130°, $(\alpha)_D^{27}$ -172° (c, 0.927 in $CHCl_3$) (*Anal*. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.50; H, 7.16). Upon reduction in ethyl ether with lithium aluminum hydride, diacetate IV yields a 60-40 mixture of *trans*- and *cis*-16,17-glycols. This mixture is easily separable through the acetonide procedure (5) to give 53% of pure estra-1,3,5(10)-triene-3,16β,17α-triol (V) (3,6), m.p. 250-250.5°, $(\alpha)_D^{27}$ +65° (c, 0.771 in ethanol) (*Anal*. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.87; H, 8.12; O, 16.51) as well as 34% of pure estra-1,3,5(10)-triene-3,16α,17α-triol acetonide (VII), m.p. 256-257° (*Anal*. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.66; H, 8.53). Acetonide VII can be readily hydrolyzed to furnish the free triol VI (4).

The reduction of 16-keto-estra-1,3,5(10)-triene-3,17α-diol diacetate (IV) with sodium borohydride at room temperature or at -20° yields a 50-50 mixture of 16β,17α- and 16α,17α-glycols; the same proportion of *trans*- and *cis*-glycols also results from reduction with either lithium borohydride or lithium aluminum hydride in refluxing tetrahydrofuran. One of these reductive procedures is preferable when estra-1,3,5(10)-triene-3,16α,17α-triol (17-epiestriol) (VI) (4) is the desired final product.

It is curious that the presence of an oxygen function at


I
II
III
IV
V
VI
VII
HO
AcO
OAc
OH
CH₃

17α on the steroidal molecule favorably influences the reduction of a $C_{16}$-carbonyl toward the α-epimeric configuration; reduction of a simple $C_{16}$-carbonyl gives an almost quantitative yield of the 16β-ol (7).

All melting points are corrected (Anschutz short-stem thermometer, full immersion).

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(6) A mixed melting point test performed with this product and a sample of pure estra-1,3,5(10)-triene-3,16β,17α-triol kindly supplied by Dr. Heinz Breuer showed no depression. Dr. Ben Stimmel also chromatographed our triol on paper and showed it to be homogenous and identical with known 16,17-epiestriol (personal communication).

(7) Unreported findings in this laboratory.