STRUCTURE-ACTIVITY RELATIONSHIPS OF FOUR 11-HYDROXYESTRONES ISOMERIC AT THE C-9 AND C-11 POSITIONS

R. Bruce Gabbard, Leslie F. Hamer
and Albert Segaloff

Alton Ochsner Medical Foundation
1520 Jefferson Highway
New Orleans, Louisiana 70121

Received 4-14-80

ABSTRACT

The synthesis of 11α-hydroxyestrone, 11α-hydroxy-9β-estrone, and 11β-hydroxy-9β-estrone are presented.

The reduction of 11-keto-9β-estrone 17-ethyleneketal by sodium in ethanol or sodium borohydride resulted in 11-hydroxy-9β-estrones. The 11-hydroxyl group configurations were opposite to expectations: sodium in boiling ethanol afforded the axial 11β-hydroxy-9β-estrone, while sodium borohydride in boiling tetrahydrofuran gave the equatorial 11α-hydroxy-9β-estrone.

In immature rat uterotropic bioassays using subcutaneous injections, 11α-hydroxyestrone was 2 times as active as 11α-hydroxy-9β-estrone, and 11β-hydroxyestrone was 10 times as active as 11β-hydroxy-9β-estrone.

In view of the remarkable estrogenicity exhibited by 11-keto 9β-estrone (1), the two configurational isomers (11β and 11α) of 11-hydroxy-9β-estrone (IV and V, respectively) were required for structure-activity studies in which they were to be compared with their corresponding 9α isomers, 11β-hydroxyestrone (X) and 11α-hydroxyestrone (IX).

Herzog et al (2) reported that sodium in boiling propanol reduced 11-ketosteroids to equatorial 11α-hydroxysteroids; Henbest and Wilson (3) reported that sodium borohydride reduced 11-ketosteroids to axial 11β-hydroxysteroids. However, Baran et al (4) observed that sodium borohydride reduced 11-keto-9β-estradiol 3-benzyl ether to the equatorial 11α-hydroxy-9β-estradiol 3-benzyl ether. Whether this apparent "exception to the rule" is usual

for any 11-ketosteroid having the 9β configuration remained to be demonstrated.

In numerous reports on the reduction of ketosteroids by sodium in boiling aliphatic alcohols, the products have been predominantly or exclusively the corresponding equatorial hydroxysteroids (5). Inasmuch as Baran et al have demonstrated that an "exception to the rule" can happen with sodium borohydride (4), there was the possibility that "exceptions to the rule" could occur as well in experiments involving sodium in boiling aliphatic alcohols. Accordingly, we investigated the reductions of 11-keto-9β-estrone 17-ethyleneketal (III) by sodium in boiling ethanol or sodium borohydride in boiling tetrahydrofuran to ascertain whether these would effect the syntheses of the desired two configurational isomers of 11-hydroxy-9β-estrone (IV and V).

The only report on the synthesis of 11α-hydroxyestrone (IX) that we were aware of was that by Magerlein and Hogg which involved 11α-hydroxyprogesterone in a circuitous multistep process (6). A simpler approach to the synthesis of IX was therefore desired. The synthesis of 11α-hydroxyestradiol by Bowers et al using the Brown hydroboration of 9,11-dehydroestradiol diacetate (7) suggested to us that 9,11-dehydroestrone 17-ethyleneketal 3-tetrahydropyranyl ether (VIII) could be used for the preparation of IX. This possibility was investigated, since 9,11-dehydroestrone (VI) is easily obtained from estrone by the action of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in methanol (8).

For the preparation of 11β-hydroxyestrone (X), the method of Baran (9) was used.

EXPERIMENTAL

Infrared spectra (ir) were from KBr pellets and obtained from a Perkin Elmer infrared spectrophotometer model 710B. Melting points were determined on a Kofler micro-hotstage, and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were obtained from a Jeolco C-60 Hl spectrometer, and are reported in ppm relative to tetramethylsilane (TMS) as internal standard (δ=0).

11β-Hydroxyestrone 17-ethyleneketal 3-acetate (I). - - 11β-Hydroxyestrone 17-ethyleneketal (9), 4 g, was acetylated by 28 mL acetic anhydride in 28 mL pyridine at room temperature for 30 min. The excess acetic anhydride was decomposed by 175 mL crushed ice, and the gummy product was collected by filtering through a cotton plug. The product was extracted from the cotton plug with methylene chloride, dried with anhyd Na_2SO_4, and evaporated to dryness under N_2 on a steam bath. The residue (I) was an oil (4 g) that resisted crystallization.

ir ν_{max}: 3520 m (11β-OH); 2935 s, 2880 m (CH); 1760 s (C=O of phenyl acetate); 1613 w, 1585 w, 1495 s (benzene ring); 1370 s (CH); 1210 s (C-O-C of phenyl acetate); 1105 m (C-O-C of ketal); 1020 s (C-O of 11β-OH) cm^{-1}.

11-Ketoestrone 17-ethyleneketal 3-acetate (II). - - The oily compound I, 4 g, was dissolved in 100 mL acetone and placed on an ice bath. Jones' reagent (8N CrO_3 in 25% aqueous H_2SO_4) was carefully added dropwise until a brown color persisted. Ethanol was added to decompose excess CrO_3, 250 mL water was added, and the mixture was extracted with 100 mL methylene chloride. The methylene chloride extract was washed with 5% aqueous $NaHCO_3$ until neutral, separated, dried over anhyd Na_2SO_4, and evaporated to dryness under N_2 on a steam bath. Recrystallization of the residue from methanol afforded 3 g of II, mp 145-147° C.

ir ν_{max}: No OH; 2940 m, 2880 S (CH); 1755 s (C=O of phenyl acetate); 1710 S (C-11 ketone); 1605 w, 1585 w, 1495 s (benzene ring); 1200 s (C-O-C of phenyl acetate); 1105 m (C-O-C of ketal) cm^{-1}.

11-Keto-9β-estrone 17-ethyleneketal (III). - - Compound II, 3 g, was mixed with 15 mL ethanol, 15 drops of a saturated solution of KOH was added, and warmed on a steam bath for 15 min. The solution was allowed to cool to room temperature, 50 mL water was added to it and it was neutralized with 10% aqueous HCl. The gummy precipitate was collected by filtering through a cotton plug, extracted with methylene chloride, dried with anhyd Na_2SO_4, and evaporated to dryness under N_2 on a steam bath. The residue was induced to crystallize from petroleum ether containing small amounts of methylene chloride and yielded 1.7 g III, mp 178-180° C.

ir ν_{max}: 3345 s, (phenolic OH); 2900 s, 2925 s, 2875 m (OH); 1672 s (C-11 ketone; the shift to lower wave number is typical of a 9β-11-keto structure (10)); 1608 s, 1500 m (benzene ring); 1440 s (OH); 1223 s (C-O of phenol); 1095 s (C-O-C of ketal) cm^{-1}.

11β-Hydroxy-9β-estrone (IV). - - Compound III, 300 mg, was dissolved in 15 mL ethanol, warmed to 50° C, and while under vigorous stirring under a N_2 blanket, 1.5 g sodium metal chips were added portionwise during 30 min; the mixture was allowed to reflux from the heat of the reaction. Afterwards, more heat was applied to maintain the refluxing for 1 hr. After the solution was allowed to cool to room temperature, it was diluted with 100 mL water, extracted with petroleum ether to remove the mineral oil that had coated the sodium chips used in the reaction, and the basic aqueous solution remaining after extraction was acidified with conc HCl. The precipitate was collected by filtration under reduced pressure, and was dissolved in 25 mL methanol containing 1 mL water and 0.5 mL conc HCl. The solution was warmed on a steam bath for 5 min to effect the solvolysis of any ketal group that remained. After dilution with 75 mL water, the precipitate was collected by filtration under reduced pressure, dried in air, and recrystallized from ethyl acetate to afford 114 mg of IV, small prisms, mp 265-270° C (dec).

ir ν_{max}: 3350 s (phenolic OH; 11-OH obscured); 2940 m, 2910 s, 2850 m (OH); 1705 s (17-ketone; the shift to lower wavenumber than usual is anomalous); 1608 s, 1500 m (benzene ring); 1450 s (CH); 1290 s, 1185 s (C-O of phenol); 1080 s (C-O of 11β-OH) cm^{-1}.

^{1}H-NMR (pyridine-d_5 solvent); δ 1.45 (s, 13β-CH_3).

11α-Hydroxy 9β-estrone (V). - - Compound III, 200 mg, was dissolved in 10 mL freshly redistilled tetrahydrofuran, and to this was added 400 mg sodium borohydride that was previously dissolved in 1 mL 0.2% aqueous NaOH. The solution was brought to a slow boil on a steam bath, and moderate refluxing was maintained for 1 hr. Afterwards, while the solution was still warm, 10% aqueous HCl was added until pH 1, and after 5 min, 50 mL water was added. The mixture was extracted with methylene chloride, dried with anhyd Na_2SO_4, and evaporated to dryness under N_2 on a steam bath. The oily residue was taken up in methylene chloride and chromatographed through a 10 g silica gel column; the desired compound (V) was eluted by 10 to 30% ethyl acetate in methylene chloride. Evaporation of the combined eluates to dryness under N_2 on a steam bath and recrystallization of the residue from petroleum ether yielded 125 mg V, small prisms, mp 99-103° C.

ir ν_{max}: 3400 s (phenolic OH; 11-OH obscured); 2925 s, 2850 m (CH); 1720 s (C-17 ketone); 1610 m, 1585 w, 1495 m (benzene ring); 1450 m (CH); 1240 s (C-O of phenol); 1070 w, 1020 m (C-O of 11α-OH) cm^{-1}.

^{1}H-NMR (pyridine-d_5 solvent): δ 1.01 (s, 13β-CH_3)

9,11-Dehydroestrone (VI). - - Estrone, 8 g, was dissolved in 1.2 L methanol on a steam bath, and the solution was allowed to cool to 45° C before adding 7 g 2,3-dichloro-5,6-dicyanobenzoquinone all at once under vigorous stirring. After 45 min, the straw-colored solution was diluted with 4.8 L water, and the precipitate was collected on filter paper under reduced pressure. The filter cake was alternately washed with aqueous 5% $NaHCO_3$ and water until colorless, and dried in air. Recrystallization from ethyl acetate afforded 4 g VI, pale yellow plates, mp 255-258° C. (Lit. (6) mp 257-259° C.)

ir ν_{max}: 3250 s (phenol OH); 3020 m ($\Delta^{9,11}$ CH); 2925 s, 2890 m (CH); 1715 s (C-17 ketone); 1603 s, 1497 m (benzene ring); 1450 s (CH); 1222 s (C-O phenol) cm^{-1}.

9,11-Dehydroestrone 17-ethyleneketal (VII). - - Compound VI, 4 g, was vigorously stirred in a mixture of 40 mL ethylene glycol, 160 mL benzene, and 50 mg p-toluenesulfonic acid. The mixture was brought to a boil, and the refluxing vapors were collected in a Stark-Dean trap. When no more water accumulated in the trap (about 2 hr), the mixture was allowed to cool to room temperature; 200 mL water containing 1 g $NaHCO_3$ was added; and the benzene extract was worked up as usual to afford, after recrystallization from methanol, 3.4 g colorless heavy needles of VII, mp 185-189° C.

ir ν_{max}: 3400 s, 3220 m (phenol OH, assoc.); 3025 m ($\Delta^{9,11}$ CH); 2970 s, 2930 s, 2890 s (CH); no carbonyl; 1610 m, 1675 m, 1495 s (benzene ring); 1290 s, 1210 s (C-O phenol); 1170 s, 1020 s, 958 m, 930 m, 880 m (C-O and C-O-C of ketal) cm^{-1}.

9,11-Dehydroestrone 17-ethyleneketal 3-tetrahydropyranyl ether (VIII). - - Compound VII, 3.4 g, 3.4 mL dihydropyran, 25 mg p-toluenesulfonic acid, and 15 mL methylene chloride were all mixed together and warmed on a steam bath until solution was effected (about 4 min). The solution was immediately taken off the steam bath, and allowed to stand at room temperature for 30 min. Four drops of pyridine was added, the solution shaken with 100 mL water containing 1 g $NaHCO_3$, and the methylene chloride extract was worked up as usual to afford, after recrystallization from methanol, 2.4 g colorless plates of VIII, mp 103-105° C.

ir ν_{max}: No OH; 3040 w ($\Delta^{9,11}$ CH); 2950 s, 2875 s (CH); no carbonyl; 1610 s, 1570 w, 1495 s (benzene ring); 1230 m (C-O-C of phenyl ether); 1120 s (C-O-C ketal); 1020 m, 1050 m, 975 s (C-O ketal and tetrahydropyranyl ether) cm^{-1}.

11α-Hydroxyestrone (IX). - - Compound VIII (2 g) in 50 mL freshly distilled tetrahydrofuran was placed in a 500 mL Erlenmeyer flask fitted with a graduated pressure-equalizing dropping funnel and inlet and outlet adapters for the maintenance of a N_2 blanket, and set up for magnetic stirring on an ice bath. The dropping funnel had a rubber septum instead of the usual glass stopper

to allow the insertion of a Flex-needle (Aldrich Chemical Co.) so that a borane-tetrahydrofuran solution could be "pumped" into the funnel from a "Sure/Seal" bottle (Aldrich Chemical Co.) by N_2 pressure. Borane-tetrahydrofuran complex, 1 M in tetrahydrofuran (Aldrich Chemical Co.), 30 mL, was admitted into the funnel, added dropwise to the stirred mixture within 20 min, and stirred for an additional 2 hr while maintaining the N_2 blanket throughout. Tetrahydrofuran containing 20% water (25 mL) was cautiously added dropwise to decompose excess borane; 30 mL aqueous 10% KOH was added; and 30 mL 30% hydrogen peroxide was added dropwise within 15 min to the stirred mixture on the ice bath. After 1 hr additional stirring, the mixture was diluted with 100 mL water and extracted with 100 mL methylene chloride. The methylene chloride extract was shaken with 100 mL aqueous 10% sodium bisulfite, dried with anhyd Na_2SO_4, and evaporated to dryness under N_2 on a steam bath. The residue was taken up in 10 mL petroleum ether-methylene chloride 1:1 and chromatographed through a 10 g silica gel column. The first two 50 mL petroleum ether-methylene chloride 1:1 eluates were rejected; these contained unreacted VIII (560 mg). The eluates from 100% methylene chloride to 25% ethyl acetate in methylene chloride (500 mL total) were combined and evaporated to dryness under N_2 on a steam bath. The residue was dissolved in 25 mL methanol containing 1 mL water and 0.5 mL conc HCl, warmed on a steam bath for 15 min, and diluted with 75 mL water. The precipitate was collected by filtration under reduced pressure, dried in air, and recrystallized from ethyl acetate to afford colorless small prisms of IX, 300 mg, mp 265-269° C (dec).

ir ν_{max}: 3425 s (11α-OH); 3250 s (phenol OH); 2920 s, 2867 m, 2825 m (CH); 1719 s (C-17 ketone); 1615 w, 1580 s, 1490 s (benzene ring); 1410 s (CH); 1245 s (C-O phenol); 1050 s, 1000 s (C-O of 11α-OH) cm^{-1}.

(A small sample of IX was reduced with sodium borohydride in the usual way to give 11α-hydroxyestradiol, mp 249-251° C (lit. (6) mp 250-251° C), which ir spectrum was identical to that of an authentic sample of IX, and the mixed mp showed no depression.)

11β-Hydroxyestrone (X). - - The method of Baran (9) was used; the overall yield of X from 1,4-androstadiene-3,11,17-trione was consistently around 32%. The mp of X recrystallized from ethyl acetate was 266-269° C. (Lit. (6) mp 254-257° C).

ir ν_{max}: 3490 s (11-OH); 3410 s, 3225 s (phenol OH, assoc.); 2960 m, 2960 m, 2920 s (CH); 1722 s (C-17 ketone); 1618 m, 1583 m, 1497 m (benzene ring); 1350 m (CH); 1290 s, 1245 s (C-O of phenol); 1080 m, 1050 m, 1018 s (C-O of 11β-OH) cm^{-1}.

Pharmacology. - - The methodology of the quantal uterotropic bioassays for determination of estrogenic activity has been previously described (1).

RESULTS AND DISCUSSION

The reduction of 11-keto-9β-estrone 17-ethyleneketal (III) by sodium in boiling ethanol gave, after acidic solvolysis of the ketal goup, an 11-hydroxyestrone (IV) which was determined to be neither 11α-hydroxyestrone (IX) nor 11β-hydroxyestrone (X) after comparing their ir spectra. The reduction of III by sodium borohydride in boiling tetrahydrofuran gave, after acidic solvolysis of the ketal group, an 11-hydroxyestrone (V) which ir spectrum was not identical to those of IV, IX, or X. It was concluded that IV and V were the two 11-hydroxy-9β-estrones that were needed for our structure-activity studies. ^{1}H-NMR analyses were depended upon to indicate the configurations of the hydroxyl group of IV and V. Because of the 1,3-diaxial interaction between the strongly deshielding hydroxyl group and a methyl group, it was expected that the 13β-CH_3 signal in 11β-hydroxy-9β-estrone would be located downfield from that for 11α-hydroxy-9β-estrone. The 13β-CH_3 signal for IV appeared at δ 1.45, while that for V appeared at δ 1.01. Thus the product IV from the sodium-ethanol experiment was identified as 11β-hydroxy-9β-estrone, and the product V from the sodium borohydride experiment was identified as 11α-hydroxy-9β-estrone. The observation made by Baran *et al* (4) on the reduction of an 11-keto-9β-estra-1,3,5(10)-triene to its 11α-hydroxy derivative by sodium borohydride was confirmed.

Ring C chair-boat conformational interconversions would explain the apparently anomalous results that were observed of the reductions of III by sodium-ethanol or sodium borohydride. An 11β-hydroxyl group would be *equatorial* if ring C was in the

boat conformation, explaining the result from the sodium-ethanol reduction. The least hindered side of the C-11 carbonyl group would be at the equatorial (β) side of C-11 when ring C is in the boat conformation, explaining the 11α-hydroxyl group that resulted from the sodium borohydride reduction. The ring C boat conformation is expected to convert back to the stable chair conformation after the reduction of the C-11 carbonyl group, thus reversing the axial-equatorial conformational assignments for the C-11 hydroxyl group and thereby causing the appearance of the observed anomaly.

The Brown hydroboration method was successfully applied to the synthesis of 11α-hydroxyestrone (IX), although the yield was rather low (15% from 9,11-dehydroestrone 17-ethyleneketal 3-tetrahydropyranyl ether (VIII)). However, Bowers et al reported a 17% yield of 11α-hydroxyestradiol from 9,11-dehydroestradiol diacetate (7); therefore, low yields from the Brown hydroboration of 9,11-dehydro-1,3,5(10)-estratrienes are to be expected. Nevertheless, hydroboration would be the most convenient method for the synthesis of 11α-hydroxy-1,3,5(10)-estratrienes at the present moment.

Table 1 lists the total subcutaneous doses of test compounds required to double the uterine weight of immature female Fischer rats in 5 days.

Table 1. QUANTAL UTEROTROPIC BIOASSAY DATA

Compound	Total dose (μg) required to double uterine weight (5 days)
11α-Hydroxyestrone (IX)	24
11α-Hydroxy-9β-estrone (V)	42
11β-Hydroxyestrone (X)	6.5
11β-Hydroxy-9β-estrone (IV)	63
Estrone (a)	0.53 (b)
11-Ketoestrone (c)	8.13 (b)
11-Keto-9β-estrone (c)	0.67 (b)

(a) Reference compound
(b) Data from reference 1
(c) Synthesis reported in reference 1

In contrast to the 11-ketoestrones, the 9β configuration decreases the uterotropic activities of 11-hydroxyestrones. 11α-Hydroxyestrone (IX) is approximately 2 times as active as 11α-hydroxy-9β-estrone (V), and 11β-hydroxyestrone (X) is approximately 10 times as active as 11β-hydroxy-9β-estrone (IV). For the 11-hydroxyestrones with the 9α configuration, the 11β-hydroxyl group is more compatible with uterotropic activity than is the 11α-hydroxyl group; X is approximately 4 times more active than IX. On the other hand, there apparently is not much difference between the 11α- and 11β-hydroxyl groups in their effects on estrogenicity when the hydroxyestrones are of the 9β configuration. Of the four 11-hydroxyestrones reported in this paper, X was the most active, being 8% as active as estrone. This compares with the value of 5% reported for X by Magerlein and Hogg (6).

It is interesting that the 11-hydroxyestrones (especially those with the 9β configuration) and 11-ketoestrone are weak estrogens, while 11-keto-9β-estrone is as active as estrone. In this connection, it is pertinent to remark that it must always

be remembered that bioassays are *in vivo*, which means that several factors (apart from the structural features of the drug) determine the physiological activity of any drug: the species of animal and its genetic characteristics, health of the animal, type of administration and the vehicle that is employed, susceptibility to metabolic enzymes, rate of absorption and excretion, ability to enter the target cells, affinities for "binding" or "transport" proteins (albumin, prealbumins, globulins) and intracellular "receptors" (cytosolic or nuclear), presence or absence of cofactors, and other factors yet to be discovered or determined. Therefore, *in vitro* results (such as comparative binding assays involving "cytoplasmic receptors") cannot be expected to extrapolate nicely to *in vivo* expectations, nor can *in vivo* results be expected to correlate beautifully with *in vitro* observations. It would have been expedient if an *in vitro* result had correlated with an *in vivo* observation, but whenever this occurs, it can be merely coincidence. While many publications purport to relate receptor binding affinities to physiological activity, there have been reports that mentioned large discrepancies between physiological activity and receptor binding affinities.

Someday we hope to answer conclusively the perplexing question of why certain compounds (such as 11-keto-9β-estrone) are powerfully estrogenic despite having structures that are radically different from those of estrone and estradiol-17β.

ACKNOWLEDGEMENTS

This work was supported in part by the annual gift program of the Alton Ochsner Medical Foundation through donors who have designated their gifts to this project. We thank Dr. R.F. Borne of the University of Mississippi for ^{1}H-NMR spectra, Dr. J.C. Babcock of the Upjohn Co. for C and H analyses, and Syntex, Inc., for a gift of 11α-hydroxyestradiol.

REFERENCES

1. A. Segaloff, R.B. Gabbard, A. Flores, R.F. Borne, J.K. Baker, W.L. Duax, P.D. Strong, and D.C. Rohrer, Steroids
2. H.L. Herzog, E.P. Oliveto, M.A. Jevnik, and E.B. Hershberg, J. Am Chem. Soc., 74, 4470 (1952).
3. H.B. Henbest and R.A.L. Wilson, J. Chem. Soc., 3289 (1956).
4. J.S. Baran, D.D. Langford, I. Laos, and C.D. Liang, Tetrahedron, 33, 609 (1977).
5. Reviewed in: L.F. Fieser and M. Fieser, Steroids, Reinhold, New York (1959), pp 254-258.
6. B.J. Magerlein and J.A. Hogg, J. Am. Chem. Soc., 80, 2220 (1958).
7. A. Bowers, J.S. Mills, C. Casas-Campillo, and C. Djerassi, J. Org. Chem., 27, 361 (1962).
8. W. Brown, J.W.A. Findlay, and A.B. Turner, Chem. Commun., 10 (1968).
9. J.S. Baran, J. Med. Chem., 10, 1188 (1967).
10. C.D. Liang, J.S. Baran, N.L. Allinger, and Y. Yuh, Tetrahedron, 32, 2067 (1976).

APPENDIX

Trivial name-IUPAC systematic name list. The trivial name is given first, and its IUPAC name follows.

I. 11β-Hydroxyestrone 17-ethyleneketal 3-acetate
3-Acetoxy-17-ethylenedioxy-1,3,5(10)-estratrien-11β-ol

II. 11-Ketoestrone 17-ethyleneketal 3-acetate
3-Acetoxy-17-ethylenedioxy-1,3,5(10)-estratrien-11-one

III. 11-Keto-9β-estrone 17-ethyleneketal
3-Hydroxy-17-ethylenedioxy-9β-estra-1,3,5(10) trien-11-one

IV. 11β-Hydroxy-9β-estrone
3,11β-Dihydroxy-9β-estra-1,3,5(10)-trien-17-one

V. 11α-Hydroxy-9β-estrone
3,11α-Dihydroxy-9β-estra-1,3,5(10)-trien-17-one

VI. 9,11-Dehydroestrone
3-Hydroxy-1,3,5(10),9-estratetraen-17-one

VII. 9,11-Dehydroestrone 17-ethyleneketal
17-ethylenedioxy-1,3,5(10),9-estratetraen-3-ol

VIII. 9,11-Dehydroestrone 17-ethyleneketal 3-tetrahydropyranyl ether
3-(Tetrahydropyran-2'-yl)oxy-17-ethylenedioxy-1,3,5(10),9-estratetraene.

IX. 11α-Hydroxyestrone
3,11α-Dihydroxy-1,3,5(10)-estratrien-17-one

X. 11β-Hydroxyestrone
3,11β-Dihydroxy-1,3,5(10)-estratrien-17-one

11-Keto-9β-estradiol 3-benzyl ether: 3-benzyloxy-17β-hydroxy 9β-estra-1,3,5(10)-trien-11-one

11α-Hydroxy-9β-estradiol 3-benzyl ether: 3-benzyloxy-9β-estra-1,3,5(10)-triene-11α, 17β-diol

11α-Hydroxyestradiol: 1,3,5(10)-estratriene-3,11α,17β-triol

9,11-Dehydroestradiol diacetate: 3,17β-diacetoxy-1,3,5(10),9-estratetraene

11-Ketoestrone: 3-hydroxy-1,3,5(10)-estratriene-11,17-dione

11-Keto-9β-estrone: 3-hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione

ADDENDUM

The identification of compound IV as 11β-hydroxy-9β-estrone is further supported by x-ray crystallographic data which will be the subject of a future publication with Dr. W.L. Duax and his coworkers of the Medical Foundation of Buffalo, Inc., Buffalo, New York.

The definitive identification of compound IV, of course, also further supports by logical deduction our determination of the other isomer, compound V, as 11α-hydroxy-9β-estrone.

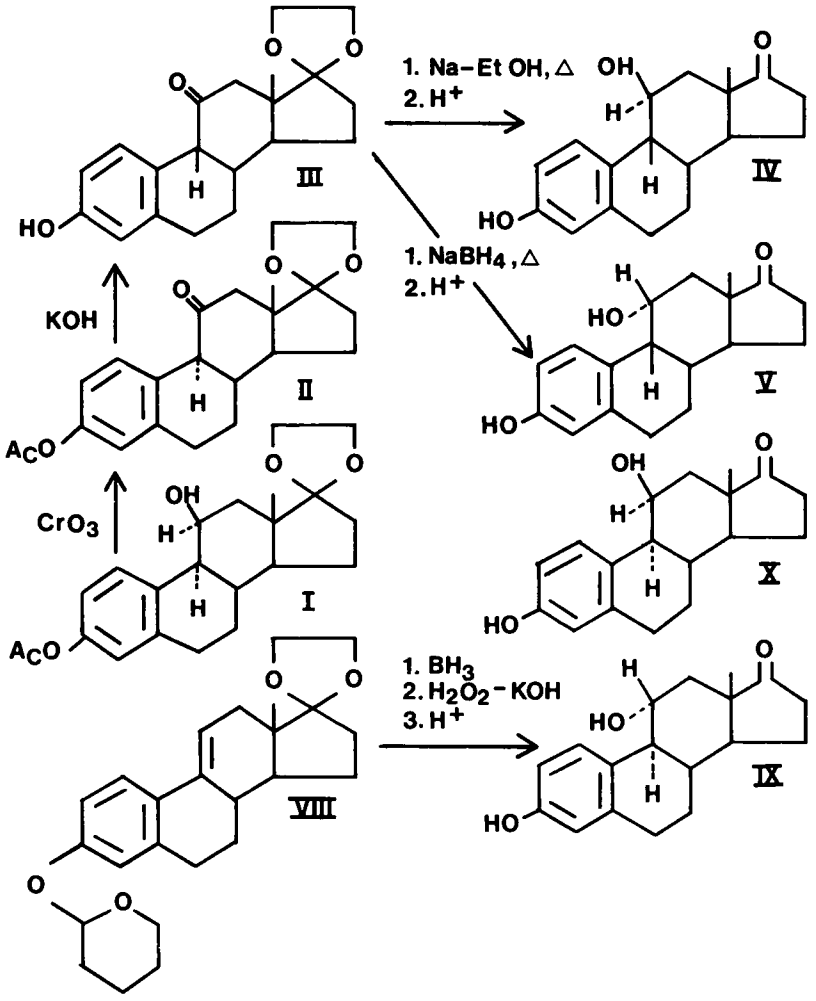

Figure 1. Schemes illustrating the steps in the syntheses of the two 11-hydroxy-9β-estrones IV and V, and of 11α-hydroxyestrone IX. The structure of 11β-hydroxyestrone X is also depicted.