THE SYNTHESIS OF 3β-HYDROXYESTR-4-EN-17-ONE AND 3β-HYDROXYANDROST-4-EN-17-ONE

P. D. Klimstra and F. B. Colton
Division of Chemical Research
G. D. Searle & Co., Chicago, Illinois 60680

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ABSTRACT

3β-Hydroxyestr-4-en-17-one (Va) and 3β-hydroxyandrost-4-en-17-one (Vb) were synthesized in good yield by a series of reactions from estr-4-ene-3,17-dione (Ia) and androst-4-ene-3,17-dione (Ib), respectively. The estrene derivative Va was required as a key intermediate in the preparation of the potent progestin, 17α-ethynylestr-4-ene-3β, 17β-diol diacetate (XIV).

The importance of 17α-ethynylestr-4-ene-3β,17β-diol diacetate (XIV) (1) necessitated the investigation of methods which might be applicable for the synthesis of this substance. The previously described method (2) involved reduction of 17α-ethynyl-17β-hydroxyestr-4-en-3-one (XV) with lithium-tri-t-butoxyaluminum hydride followed by acetylation of the diol XIII. As an alternate approach, we have found that the diol XIII can be prepared smoothly and in good yield by ethynylating the intermediate, 3β-hydroxyestr-4-en-17-one (Va) (3). The importance of Va as a key intermediate to XIV and possibly to other 17-substituted steroids necessitated the development of a practical synthesis for this compound.

In 1965 Ward and co-workers (4) reported a simplified method for the preparation of 3β-hydroxyandrost-4-en-17-one (Vb). In addition Löken and Gut (5) described a procedure for preparing a mixture of Vb and its 3α-hydroxy isomer. These two approaches, however, are

not suitable for the synthesis of the 19-nor analog Va because of the difficulty of obtaining the corresponding 19-nor starting materials. While the literature describes several additional methods which are useful for the preparation of steroidal substances having a 4-dehydro-3β-hydroxy-17-keto system, most are not conveniently applicable to the 19-nor series (3,6-9). We wish to report here a process which is applicable for the synthesis of both 3β-hydroxyestr-4-en-17-one (Va) and 3β-hydroxyandrost-4-en-17-one (Vb) in good yield.

The selective reduction of the 3-carbonyl with sodium borohydride in 2-propanol as reported by Mateos (10) was completely unsuccessful in our hands for transforming the ketone Ia to alcohol Va indicating random carbonyl reduction. In addition, the use of sodium borohydride in pyridine as suggested by Kupfer (11) produced a significant amount of reduction of the 4,5-double bond when applied to compound Ia (12,13).

The selective reduction of I to V was also investigated using an electrolytic polarographic technique. In 1939, Eisenbrand and Picher (15), and in 1940 Wolfe and co-workers (16) reported the selective polarographic reduction of the 4-dehydro-3-keto system over the 17-ketone in certain steroids. More recently it was established that the products of such reductions are not the desired 3-alcohols but pinacols (17,18). When the diones I were treated under standard polarographic reduction conditions (19), an analogous reaction apparently occurred as evidenced from the reduction potential of one electron taken up per steroid molecule.

Since the transformation of I → V was unsuccessful by direct selective reduction, a series of reactions was investigated involving

the use of selective carbonyl protective groups. In 1953, Ercoli and de Ruggieri (20,21) reported the reaction of the dione Ib with acetone cyanohydrin to form the cyanohydrin IIb. In our hands, the best conditions for this transformation involved warming either compounds Ia or Ib in methanol with acetone cyanohydrin and a trace of triethylamine. The highly insoluble cyanohydrins IIa and IIb which were readily isolated in high yield precipitated as a mixture of C-17 epimers. Attempts to reduce the cyanohydrins with lithium aluminum hydride or lithium-tri-t-butoxyaluminum hydride met with failure. While the 3β-hydroxyl moiety formed in both cases, the basic nature of the reaction media caused concomitant reversion of the cyanohydrin group to the ketone followed by immediate reduction to the diol VI (22).

It was subsequently found that conversion of the cyanohydrins to the pyranyl ethers (III) prevented this reversal and permitted normal reduction of the 3-carbonyl group. Unfortunately, all attempts to selectively hydrolyze the tetrahydropyranyl group under a variety of acid conditions afforded a considerable amount of the 3,5-dienes (XIIa,b) in addition to the desired products.

Obviously, a protective grouping was necessary at C-17 which would be resistant to mild basic reduction, but be cleaved with stronger base conditions. In 1938, Strassberger (23) described the preparation of the acetate ester of a 17-cyanohydrin upon treatment with acetic anhydride at elevated temperatures. Later, in 1946 Ruzicka et al. (24) reported the facile conversion of a cyanohydrin to its acetate by mild treatment with acetic anhydride in pyridine. In this regard, it was found that one could esterify the hydroxyl

group of the cyanohydrins more easily than expected. For example, treatment with acetic anhydride and pyridine at room temperature for about 40 hours gave good yields of the tertiary acetates III(c,d). Subsequent reduction of these esters with lithium-tri-t-butoxyaluminum hydride gave good yields of the alcohols IV(c,d) which were readily hydrolyzed in aqueous potassium hydroxide to the desired ketones, 3β-hydroxyestr-4-en-17-one (Va) and 3β-hydroxyandrost-4-en-17-one (Vb), respectively (25).

Alternatively, a similar series of reactions to those described above was utilized successfully to prepare the intermediate 3-keto-17-cyanohydrin acetate IIIc. The methyl ether of 3-hydroxyestra-2,5(10)-dien-17-one (VII) was treated with acetone cyanohydrin as described above to afford the highly insoluble cyanohydrin VIIIa. Acetylation of VIIIa followed by mild acid hydrolysis of the enol ether with aqueous acetic acid gave the 5(10)-dehydro-3-keto analog IX. Subsequent reduction with lithium-tri-t-butoxyaluminum hydride followed by a brief treatment with aqueous potassium hydroxide afforded 3α-hydroxyestr-5(10)-en-17-one (X) (26). That reduction of the 5(10)-dehydro-3-keto system occurs from the top side has been established by Levine (27). The intermediate 5(10)-dehydro analogs VIIIb and IX could be converted into the 4-dehydro derivative IIIc by treatment with aqueous acetic acid and hydrochloric acid. This intermediate (IIIc) was identical to that prepared by the sequence of reactions described before and was suitable for conversion to the desired final product Va as described above.

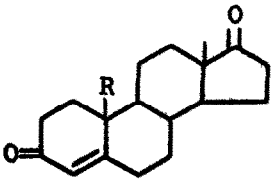
The success of the selective reaction of acetone cyanohydrin with various ketones apparently depends largely upon the rate of

formation and the solubility of the product. In the case of the reaction of the dione I and the 1,4-dihydro derivative VII, the products separated almost immediately and thus prevented any significant further reaction with the excess acetone cyanohydrin. When the dimethyl ketal XI was used, however, the ensuing C-17 cyanohydrin was apparently too soluble and was not readily isolable.

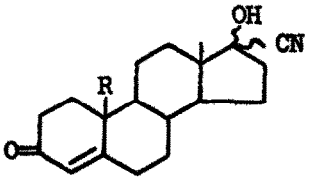
The overall yields of Va and Vb from Ia and Ib were 57 and 52 per cent, respectively. On the other hand, the use of the second sequence of reactions afforded Va in a 43 per cent yield (28). These yields represent a considerable improvement over those previously reported in the literature. For example, the method reported by Ward et al. (4) afforded Vb in only an 11 per cent yield (29).

BIOLOGICAL RESULTS

While compounds Va and Vb are of interest mainly as intermediates to biologically more significant substances, they were evaluated in several endocrine systems. Unfortunately, neither these substances nor intermediates thereto possessed any significant response when evaluated for anabolic, androgenic, estrogenic, or anti-estrogenic activities in the appropriate assays. The 17α-ethynyl analogs XIII-XV have been studied and their progestational activities compared. Using the Clauberg-type test and comparing the results to that produced by progesterone when administered subcutaneously, these substances had the following activity: the diol XIII - 20%, the diacetate XIV - 100-250%, and the 3-ketone XV - 50%. A more detailed and comparative endocrinological profile of these substances will be forthcoming (30).

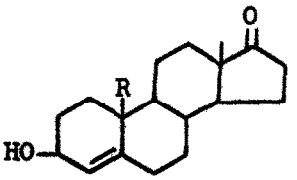


I

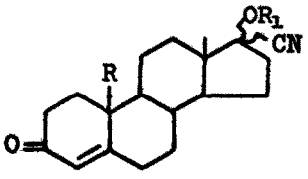


II

a, R=H; b, R=CH_3

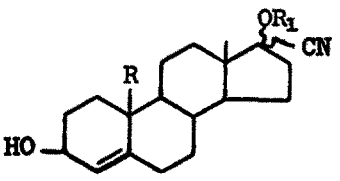


V



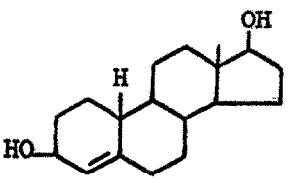
III

a, R=H; R_1=THP
b, R=CH_3; R_1=THP

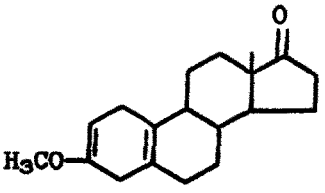


IV

c, R=H; R_1=Ac
d, R=CH_3; R_1=Ac



VI



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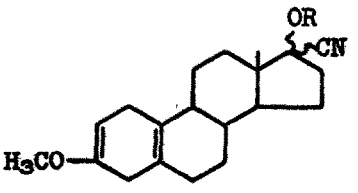
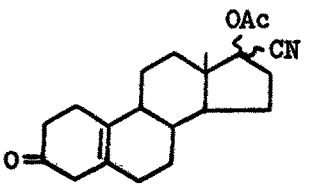


VIII

a, R=H
b, R=Ac



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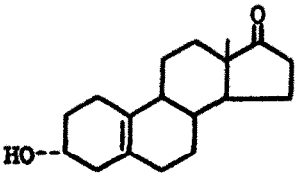
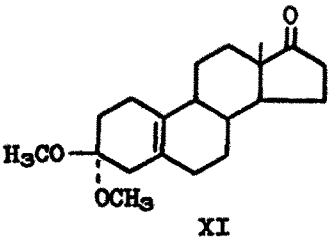


X



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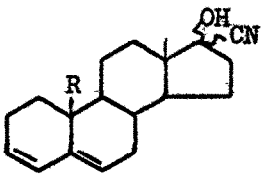
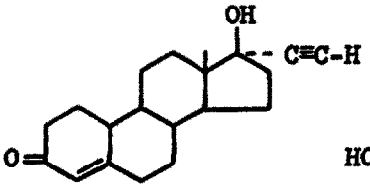
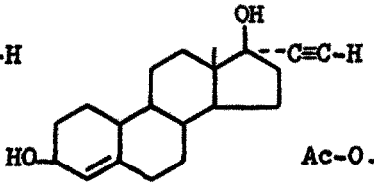


XII

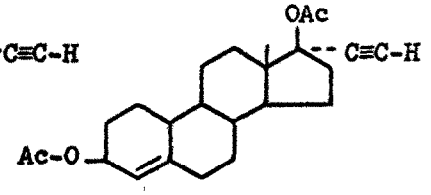
a, R=H; b, R=CH_3



XV



XIII



XIV

EXPERIMENTAL (31)

17ξ-Cyano-17ξ-hydroxyestr-4-en-3-one (IIa).--To a solution of Ia (10.0 g) and triethylamine (2 drops) in methanol (32) (30 ml) was added with efficient stirring acetone cyanohydrin (10 ml). A precipitate began forming in a few minutes. The reaction was allowed to stand for 2 hr at ambient temperature. The product was collected by filtration, washed with a small quantity of cold methanol, and air dried. Recrystallization from ethyl acetate afforded compound IIa (9.0 g, 82%), mp 185-189° dec, $[\alpha]_D$ -5°, λ_{max} 239 mμ (ε 18,038) [lit (20) mp 160-161° dec, $[\alpha]_D$ -21° (dioxane), λ_{max} 240 mμ (ε 15,900].

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.58; H, 8.33.

17ξ-Cyano-17ξ-hydroxyandrost-4-en-3-one (IIb).--To acetone cyanohydrin (15 ml) was added with warming Ib (10 g). A few drops of triethylamine was added and the reaction allowed to stand at room temperature for 18 hr. The homogeneous reaction mixture was cooled in the refrigerator and the product separated. The precipitate was collected, washed with n-hexane, and air dried to give IIb (9.0 g, 82%), mp 187-188° dec, [lit (20) mp 176-178° dec]. Recrystallization from ethyl acetate gave an analytical sample, λ_{max} 240 mμ (ε 16,270).

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.64; H, 8.91.

17ξ-Cyanoestr-4-ene-3β,17ξ-diol 17-Tetrahydropyranyl Ether (IVa).--A mixture of IIa (14.0 g) in benzene (80 ml) containing freshly distilled dihydropyran (3.4 ml) and p-toluenesulfonic acid monohydrate (5 mg) was allowed to stir at room temperature for 24 hr. After 0.5 hr. of the reaction, the mixture became homogeneous. The reaction mixture was washed with water several times and dried over anhydrous sodium sulfate containing decolorizing carbon (Darco). The solvent was removed in vacuo to leave the product IIIa (2.1 g) as a non-crystallizable oil, λ_{max} 239.5 mμ (ε 14,200), λ_{max} 5.97, 6.17, 9.3, 9.62 μ. From the spectral properties, the product without further purification was suitable for the following reaction.

To a solution of IIIa (9.0 g) cooled in an ice-bath in tetrahydrofuran (100 ml) was added with stirring, a mixture of commercial lithium-tri-t-butoxyaluminum hydride (16 g) in tetrahydrofuran (100 ml). The reaction was stirred for 2 hr with the temperature gradually becoming ambient. The solution was poured into an acetic acid-ice and water mixture (5%, 1200 ml). A sticky solid formed and was extracted with ether. The extract was washed with 5% sodium bicarbonate solution followed by water and dried over anhydrous potassium carbonate containing Darco. The solvent was removed in vacuo to leave a non-crystalline product (33) IVa (8.7 g, 96%), $[\alpha]_D$ -18°.

Anal. Calcd for $C_{24}H_{35}NO_3$: C, 74.47; H, 9.34. Found: C, 74.67; H, 9.15.

17ξ-Cyanoandrost-4-ene-3β,17ξ-diol 17-Tetrahydropyranyl Ether (IVb).--A solution of IIb (2.0 g) in benzene (40 ml) and dihydropyran (1.6 ml) containing a few crystals of p-toluenesulfonic acid monohydrate was reacted as described above. Solvent removal left a yellow, non-crystallizable oil (IIIb) which was suitable for reduction as determined from the spectral data.

To the above residual oil (IIIb) in tetrahydrofuran (25 ml) was added a mixture of lithium-tri-t-butoxyaluminum hydride (4.0 g) in tetrahydrofuran (25 ml). The reaction was conducted as described above to give the product IVb as an oil (33), λ_{max} 2.75, 5.98, 9.3, 9.65 μ.

17ξ-Cyano-17ξ-hydroxyestr-4-en-3-one Acetate (IIIc).--A.-To a stirred solution of IIa (5.0 g) in acetic anhydride (25 ml) was added pyridine (50 ml). The reaction was allowed to stand at room temperature for 40 hr. The reaction mixture was poured into cold water and the product extracted with ether. The extract was washed with water, aqueous hydrochloric acid solution (2%), and then water. After drying over anhydrous sodium sulfate containing Darco, the solvent was removed in vacuo to leave an oil which solidified. Recrystallization from acetone-water gave the product IIIc (4.7 g, 82%), mp 159-161°, $[\alpha]_D$ -6°, λ_{max} 238.5 mμ (ε 17,400).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97. Found: C, 73.87; H, 7.82.

B.-A solution of VIIIb (0.3 g) in acetic acid (8 ml) containing hydrochloric acid (0.3 ml, 36%) and water (0.3 ml) was allowed to stand at room temperature for 24 hr. Water was added and the solution cooled. White platelets were collected and recrystallized from aqueous methanol to give IIIc (0.24 g, 83%), mp 157-160°, identical with that prepared above as shown by infrared and ultraviolet spectra, and mixed mp.

C.-A solution of IX in acetic acid was treated as described above to afford after purification IIIc identical with that obtained before as established by the usual criteria.

17ξ-Cyano-17ξ-hydroxyandrost-4-en-3-one acetate (IIId).--To a stirred solution of IIb (3.8 g) in acetic anhydride (19 ml) was added pyridine (38 ml). Reaction as described above and isolation by pouring the solution into cold water afforded a solid product which was collected, washed with water, and air dried. Recrystallization from methanol gave IIId (3.65 g, 85%), mp 157-159°, $[\alpha]_D$ +44°, λ_{max} 239 mμ (ε 17,800).

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22. Found: C, 74.30; H, 8.44.

3β-Hydroxyestr-4-en-17-one (Va).--To a solution of IIIc (4.7 g) in tetrahydrofuran (80 ml) cooled and stirred in an ice-bath and under nitrogen was added a cooled solution of lithium-tri-t-butoxyaluminum hydride (20 g) in tetrahydrofuran (90 ml) all-at-once. The reaction was stirred for 2.75 hr with the temperature gradually becoming ambient.

The solution was poured into ice and water (1.5 l) containing acetic acid (150 ml). The product was extracted with ether, washed with water several times, and dried over anhydrous sodium sulfate. Solvent removal in vacuo left a glass (4.5 g, 96%). An infrared and ultraviolet spectrum indicated the presence of the desired intermediate alcohol IVc, suitable for the following reaction.

A solution of IVc (0.2 g) in methanol (4 ml) was warmed to reflux with sodium carbonate (50 mg) in water (6 ml) for 5 min. The reaction mixture was cooled in the refrigerator and diluted with water. A needle-like precipitate formed and was collected. Recrystallization from methanol-water gave the product (34) Va (0.14 g, 87%), mp 129-132°, $[\alpha]_D$ +120°, nmr 326 (C-4 proton), 240-259 (3α-H), 54 cps (C-18 methyl).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.79; H, 9.55. Found: C, 78.86; H, 9.70.

17ξ-Cyanoandrost-4-ene-3β,17ξ-diol 17-Acetate (IVd).--To a solution of IIId (2.0 g) in tetrahydrofuran (35 ml) under nitrogen and with stirring and cooling in an ice-bath was added lithium-tri-t-butoxyaluminum hydride (10 g) in tetrahydrofuran (40 ml). Isolation as described above gave IVd as a glass (1.8 g, 90%) which could not be crystallized as such, λ_{max} 2.75, 3.39, 5.69, 6.02, 7.99, 9.43, 9.71 μ.

Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74. Found: C, 73.75; H, 8.85.

3β-Hydroxyandrost-4-en-17-one(Vb).--To a solution of IVd (1.5 g) in methanol (25 ml) was added with stirring potassium hydroxide (0.5 g) in water (5 ml). The reaction mixture was allowed to stand at room temperature for 5 min. Water was added to turbidity and a solid formed. The precipitate was collected, washed with water, and air dried (1.3 g). Recrystallization from aqueous methanol afforded Vb (1.02 g, 84%) mp 135-137°, $[\alpha]_D$ +143° {lit mp 133.5-134°, $[\alpha]_D$ +34° (4); mp 135-137.5°, $[\alpha]_D$ +124° (5); mp 128.5-130° (6)}, λ_{max} 2.75, 3.4, 5.75, 6.02, 9.74 μ, nmr 320 (C-4 proton), 240-258 (3α-H), 64.5 (C-19 methyl), and 53.5 cps (C-18 methyl), [lit (4) nmr 319, 246.5, 93, 64.5, 53 cps].

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.99; H, 9.65.

The Acid Hydrolysis of 17ξ-Cyanoestr-4-ene-3β,17ξ-diol 17-Tetrahydropyranyl Ether (IVa).--A.-A solution of IVa (0.2 g) in ethyl alcohol (4 ml) was treated with p-toluenesulfonic acid (0.125 g) at reflux for 1.5 hr. Water was added, the solution cooled, and the precipitate which formed was collected and air dried. An ultraviolet spectrum indicated the presence of a 3,5-diene system, λ_{max} 243 (ε 12,200), 235.5 (ε 19,400), and 228 mμ (ε 18,400). The material isolated was 17ξ-cyanoestra-3,5-dien-17ξ-ol XIIa as indicated by the spectral data.

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89. Found: C, 79.97; H, 8.82.

B.-The above conditions were repeated at room temperature. However, partially unchanged tetrahydropyran derivative remained with a significant amount of 3,5-diene being formed as evidenced by the infrared and ultraviolet spectrum. Changing the solvent in the above procedure to isopropyl alcohol gave no improvement in the results.

17ξ-Cyanoestra-2,5(10)-diene-3β,17ξ-diol 3-Methyl Ether (VIIIa).--A slurry of VII (10.0 g) in acetone cyanohydrin (50 ml) was heated on the steam bath to 80°. Three drops of triethylamine was added and the reaction mixture was allowed to come to room temperature. After 2 hr the total contents of the flask had solidified. The product was collected with the aid of n-hexane to wash the solid onto the filter. After washing with hexane and drying in the air, the crude product (mp 152-158° dec) was recrystallized from ethyl acetate to give VIIIa (7.2 g, 66%), mp 171-174° dec. An additional recrystallization from the same solvent afforded an analytical sample of VIIIa, mp 174-177° dec.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.85; H, 8.96.

17ξ-Cyanoestra-2,5(10)-diene-3,17ξ-diol 3-Methyl Ether-17-acetate (VIIIb).--A slurry of VIIIa (3.5 g) in acetic anhydride (18 ml) and pyridine (35 ml) was stirred at room temperature for 48 hr. The reaction mixture was poured into cold water (300 ml) containing acetic acid (15 ml). A precipitate formed and was collected, washed with water, and air dried (3.4 g, 86%). Recrystallization from ethyl acetate gave VIIIb (2.25 g), mp 160-162.5°, $[\alpha]_D$ +44.0°.

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22. Found: C, 74.31; H, 7.92.

17ξ-Cyano-17ξ-hydroxyestr-5(10)-en-3-one Acetate (IX).--A mixture of VIIIb (1.5 g) in acetic acid (21 ml) and water (2.3 ml) was allowed to stand for 1.5 hr at room temperature. The reaction gradually became homogeneous during this period. Water was added until turbidity and the solution cooled in the refrigerator. A precipitate formed, was collected, washed with water, and air dried. Recrystallization from methanol-water gave IX (1.14 g, 92%), mp 129-132°, $[\alpha]_D$ +105°, λ_{max} no selective absorption.

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97. Found: C, 73.48; H, 8.04.

3α-Hydroxyestr-5(10)-en-17-one (X).--To a stirred solution of IX (0.8 g) in tetrahydrofuran (30 ml) cooled in an ice-bath was added lithium-tri-t-butoxyaluminum hydride (37) (3.5 g) all-at-once. The reaction was allowed to stir for 1.5 hr while coming to ambient temperature. The mixture was poured into ice and 5% acetic acid and the product collected by filtration. The crude product was taken up in methanol (10 ml) and warmed for 5 min with potassium hydroxide (0.5 g) in water (2 ml). The reaction mixture was diluted with water and the product was collected. Recrystallization from acetone-water afforded X (0.5 g, 72%), mp 190-193° [lit (26) mp 192-194°]. The spectral data

compared well with that reported earlier by Johns (26) for compound X.

17α-Ethynylestr-4-ene-3β,17β-diol (XIII).(3,35,36)--A.-To a stirred mixture of lithium-tri-t-butoxyaluminum hydride (37) (75 g) in tetrahydrofuran (250 ml) under nitrogen and cooled in an ice-bath was added all-at-once a solution of XV (36) (30 g) in tetrahydrofuran (400 ml). The reaction was stirred for 2 hr with the temperature gradually becoming ambient. The reaction mixture was poured into a 10% acetic acid-ice and water solution. The crude product (XIII) (39) was collected, washed with water followed by 5% sodium bicarbonate solution, and air dried, (25 g, mp 129-134°). Recrystallization from acetone-water (25) afforded XIII (17.5 g, 58%) melting at 142-144°. An analytical sample of XIII was prepared by an additional recrystallization from acetone-n-hexane, mp 144-145°, $[\alpha]_D$ -30°, $\lambda_{max}^{D(EtOH)}$ no selective absorption [lit (35) mp 147-149°, $[\alpha]_D$ -39°], nmr 325 (C-4 H), 241-259 (3α-H), 154 (C-21 proton), 52.5 cps (C-18 methyl).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.86; H, 9.74.

B.-To a stirred mixture of lithium acetylide-ethylenediamine complex (40) (5.0 g) and tetrahydrofuran (40 ml) under nitrogen was added dropwise over 0.5 hr a solution of Va (2.0 g) in tetrahydrofuran (35 ml). The reaction was stirred for 4 hr at room temperature. Methanol (10 ml) was added cautiously followed by a saturated ammonium chloride solution (50 ml). The subsequent mixture was diluted with water and extracted with ether. The extract was washed with water and sodium bicarbonate solution (5%) and dried over anhydrous sodium sulfate containing Darco. The solvent was removed in vacuo to leave an oil. Crystallization from acetone-water afforded the diol XIII (1.6 g, 73%); mp 138-140°; $[\alpha]_D$ -23°. The nmr and spectral data indicated that this substance was identical to that prepared in method A.

C.-To a rapidly stirred solution of diethylene glycol dimethyl ether (83 ml) and diethylene glycol monomethyl ether (5 ml) heated to 135° under nitrogen was added potassium hydroxide flakes (13 g) over 45 min. The reaction mixture was stirred while heating for an additional 30 min and then cooled very slowly to room temperature. Over this stirred mixture cooled by means of a dry-ice and isopropyl alcohol bath, was passed sulfuric acid washed acetylene gas for 1.5 hr. A solution of Va (3.5 g) in diethylene glycol dimethyl ether (60 ml) was added over 30 min. Cooling, stirring, and acetylene addition were continued for 1 hr longer. The reaction was allowed to slowly reach ambient temperature and water (50 ml) followed by 10% hydrochloric acid solution was added until the mixture was slightly acidic. A solid formed, was collected, washed with 5% sodium bicarbonate solution, and air dried. The crude product was taken up in ethyl acetate and washed with additional 5% sodium bicarbonate and dried over anhydrous sodium sulfate. Solvent removal in vacuo left a glass (2.5 g) which was crystallized from acetone-water to afford pure XIII (1.8 g, 47%), mp 142-145°, $[\alpha]_D$ -29°. The spectral data of this substance were identical with that obtained from the above described samples of XIII.

17α-Ethynylestr-4-ene-3β,17β-diol Diacetate (XIV).--A stirred solution of XIII (2.0 g) in acetic anhydride (10 ml) and pyridine (20 ml) under nitrogen was refluxed for 4.25 hr. The cooled mixture was poured into ice and water (250 ml). A precipitate formed, was collected, washed with water, and dissolved in ether. After washing with 10% hydrochloric acid followed by 5% sodium bicarbonate solution, the ether portion was dried over anhydrous potassium carbonate containing Darco. The solvent was removed in vacuo to leave an oil which was crystallized from methanol-water to give XIV (2.1 g), mp 127-129°, $[\alpha]_D$ -72°. Recrystallization from ether afforded an analytical sample, mp 131-133°.

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39. Found: C, 74.94; H, 8.70.

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cription of this method will be the subject of a subsequent publication.

29. A method involving intermediates similar to those described by Ward was utilized by Dr. J. S. Mihina of our laboratories to prepare compound Vb. The overall yield of this process was, however, also quite low; private communication.

30. R. L. Elton, P. D. Klimstra, F. B Colton, and V. A. Drill, submitted for publication.

31. Optical rotations, spectra, and analytical data were furnished by Dr. R. T. Dillon, Mr. E. Zielinski, and Mr. A. J. Damascus of our analytical department. The optical rotation and infrared spectra were obtained in chloroform and the ultraviolet spectra in methanol at ambient temperatures. The nmr spectra were obtained with a Varian A-60 spectrophotometer and are reported in cps downfield from tetramethylsilane which was used as an internal standard. Deuterochloroform was used as the solvent unless otherwise specified. The melting points were obtained on a Fisher-Johns apparatus and are corrected.

32. This reaction was run using the acetone cyanohydrin as solvent as originally reported by Ercoli et al. By this method, however, the product was difficult to separate from the excess reagent.

33. The product resisted crystallization from a variety of solvents. However, due to the mixture of isomers at C-17 of the cyanohydrin and those formed in the pyranylation reaction, the oily nature of these intermediates is not unexpected.

34. This substance was also obtained as a monohydrate, mp 82-85°; Anal. Calcd for $C_{18}H_{28}O_2 \cdot H_2O$: C, 73.69; H, 9.36. Found: C, 73.89; H, 9.64.

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