Estra-4,6,8(14)-trienes

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Lithium–aniline–ammonia reduction of *dl*-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (**1**) yields the 8(14)-olefin **2b**. Birch reduction of this compound followed by acid hydrolysis produces 8(14)-dehydro-19-nortestosterone (**8b**) which can be oxidized directly to the corresponding 4,6,8(14)-trienone **7b** by means of chloranil.

The synthesis of estra-4,6,8(14)-triene derivatives was suggested by the physiological potency reported for the 17β-hydroxy-17-methylestra-4,9,11-trien-3-one (**11c**, Δ^{11})[1] and related 4,9,8(14)-trienes (**11**, $\Delta^{8(14)}$).[2] The projected sequence was to start with the readily available 8,14-diene **1**, an intermediate in a recent total synthesis of estrone.[3,4]

Lithium–ammonia reduction of the diene **1** (Scheme I) in the presence of aniline[5] could conceivably effect reduction of either or both of the olefinic double bonds in **1** and thus, by appropriate 1,2 or 1,4 reductions, lead to a nonconjugated monoolefin ($\Delta^{8(14)}$ or Δ^{14}) or the C-D saturated derivative. The reaction afforded in practice a single dihydro derivative (**2b**) in good yield.[6] The presence of a double bond in this molecule was suggested by the downfield shift of the 13-methyl signal (54 cps)[7] in the nmr as compared to that of estradiol methyl ether (47 cps). Since the product lacked both vinyl proton absorption in the nmr spectrum and the styrene chromophore in the ultraviolet spectrum, a logical structural assignment would place the double bond at 8–14, in accord with a 1,4 addition to the conjugated diene system.[8] Proof of the existence of the double bond and also for the lack of skeletal rearrangement was obtained by hydrogenation of this compound (**2b**) to the known *dl*-8-isoestradiol 3-methyl ether (**3**) in high yield.[9] This reduction is in distinct contrast to the inertness of the double bond seen in 8(14)-cholesten-3β-ol[10] and, more recently, in the corresponding etiocholane.[11] Experiments with the cholestene have shown that reduction occurs only after isomerization of the double bond (to 14–15) by acid catalysis. Prereduction isomerization of the double bond here is unlikely since migration to 8–9 would be expected to yield a product with a 14β-hydrogen[12] and migration to 14–15, a product with an 8β-hydrogen.[10]

Further information about the ditertiary double bond in **2b** was furnished by a facile epoxidation which gave two epoxides (**6b** and **c**) in a 4:1 ratio. Initial structural considerations again had to deal with a possible isomerization of the double bond before the principal reaction had occurred; isomerization to 8–9 was precluded by noting the clear distinction in products obtained in the reaction of **2b** as compared to those seen when the Δ^8-olefin was epoxidized;[13] isomerization to a position bearing a secondary carbon was excluded by the absence of an extra nmr signal in the region for a proton on carbon bearing oxygen in either of the oxides or their 17-acetates. Configurational assignment was made in agreement with the expected preponderant rearside attack of the oxidant as specifically exemplified in the formation of 8,14-epoxyetiocholanes,[11] a case in which structure proof of the products by chemical methods was possible. The chemical shifts of the 13-methyl groups in **6b** and **c** also were in qualitative agreement with those of the epoxyetiocholanes. An added upfield shift in the α-oxide **6b** may stem from the proximity of the A ring to the 18-methyl (due to a cupping of the molecule toward the β face).

Osmium tetroxide oxidation of the $\Delta^{8(14)}$-steroid **2e** followed by lithium aluminum hydride reduction yielded mainly the corresponding glycol (**6a**) at a rate appreciably faster than that seen in the cholestenes.[14] The speed of the reaction is presumably a result of decreased steric hinderance although this decrease is not readily apparent from molecular models. The configuration of the glycol **6a** is assigned in analogy to the preferred α addition shown for both hydrogenation and epoxidation reactions.

Substantial decomposition of the 8(14)-dehydroestradiol (**2b**) occurred both in attempts to purify it chromatographically and, in some samples, spontaneously. In the latter case the solid mixture formed was composed of several new compounds possessing enhanced ultraviolet absorption. This instability, combined with an unusually slow rate of oxidation of the 17-hydroxyl group foiled attempts to obtain the 17-keto derivative **2a**, producing instead intractable mixtures.

Reduction of the A ring of **2b** with lithium–ammonia provided the dihydro derivative **5b** which was hydrolyzed (as the 17-acetate) to the unconjugated ketone **9e**, or, on more vigorous treatment, to the conjugated ketone **8b**. This ketone (**8b**), the 8(14)-dehydro

(1) R. Joly, J. Warnant, J. Jolly, and J. Mathieu, *Compt. Rend.*, **258**, 5669 (1964), and references cited therein; T. Feyel-Cabanes, *Ann. Endocrinol.* (Paris), **26**, 5 (1965).

(2) T. B. Windholz, J. H. Fried, H. Schwam, and A. A. Patchett, *J. Am. Chem. Soc.*, **85**, 1707 (1963).

(3) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).

(4) A. V. Zakharichev, S. N. Ananchenko, and I. V. Torgov, *Tetrahedron Letters*, 171 (1964); see also T. B. Windholz, J. H. Fried, and A. A. Patchett, *J. Org. Chem.*, **28**, 1092 (1963).

(5) The use of aniline to moderate Birch reduction was introduced for use in steroids by H. Smith, *et al.*; see ref 3.

(6) After completion of this work a report of a comparable reduction in the D-homo analog of **1** appeared: see V. M. Rzheznikov, A. N. Ananchenko, and I. V. Torgov, *Chem. Nat. Compd.*, **1**, 5 (1965).

(7) See R. F. Zurcher [*Helv. Chim. Acta*, **46**, 2054 (1963)] for a previous example of this effect.

(8) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, Inc., New York, N. Y., 1963, p 223.

(9) Mr. E. A. Brown kindly provided this sample. It was prepared from the known 17-ketone (see ref 3) by hydride reduction.

(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 260. See also M. Fetizon and M. Golfier, *Bull. Soc. Chim. France*, 850, 859 (1966).

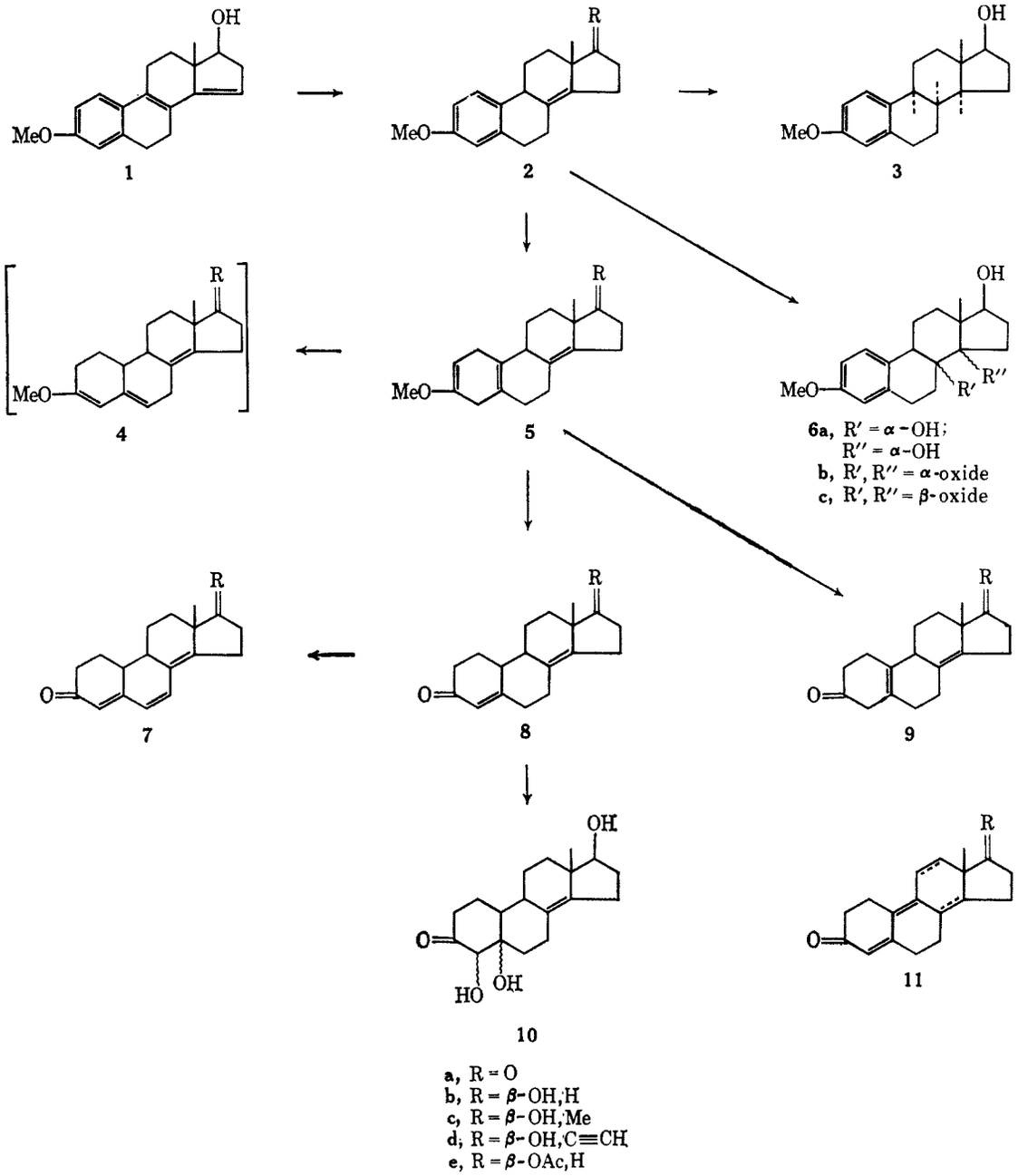
(11) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **46**, 392 (1963).

(12) For examples of the preferred stability of the *cis*-hydrinanone system over the *trans*, see W. L. Meyer, D. D. Cameron, and W. S. Johnson, *J. Org. Chem.*, **27**, 1130 (1962), and references cited therein.

(13) Experiments to be published in a later communication.

(14) J. Castells, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 2917 (1962).

SCHEME I



derivative of 19-nortestosterone, displayed an ultraviolet maximum at 233 mμ, the hypsochromic shift from 19-nortestosterone (240 mμ) being a result of the extra double bond. A display of the relative inertness of the 8(14) double bond in this molecule was provided by the osmium tetroxide oxidation of **8b**, a reaction effecting hydroxylation of the conjugated (4–5) rather than the isolated bond, and yielding the glycol (**10**).

A by-product formed in the acid hydrolysis of the enol ether **5b** was very similar to the major product **8b** in all of its spectral details. However, the melting points of these two compounds and the spectra of their acetates were clearly different, establishing the distinctness of the two materials and suggesting the minor component is a C-10 epimer of **8b**.

With the formation of the dihydroaromatic A ring the molecule was sufficiently stabilized to allow formation of the 17-ketone **5a** in good yield *via* normal Oppenauer oxidation. The dienedione **8a** could be prepared by hydrolysis of **5a**, or alternatively, by oxidation of the 8(14)-dehydrotestosterone derivative **8b** with either chromic acid or aluminum isopropoxide. The latter reaction, however, was unusually slow, allowing partial decomposition of the product to occur.

Both methyl magnesium bromide and sodium acetylide were added to the 17-ketone group of **5a**, providing the adducts **5c** and **d**, respectively. The configurations of these compounds were assigned in analogy to the 8β,14α-dihydro steroids, a geometrically similar system. Either the unconjugated or conjugated ketones could be formed from these compounds by an appropriate acid hydrolysis. The unconjugated ketone **9b** was converted by use of bromine in pyridine[15] to the 4,9,8-(14)-trienone **11c**. Also investigated was the oxidation of the ethynyl adduct **5d** to the aromatic A ring deriva-

(15) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2403 (1960).

tive **2d** with pyridine–chromium trioxide, a reaction which provided an unstable material having the correct spectral characteristics but not affording satisfactory elemental analysis.

Preparation of the trienone system (as in **7**) was attempted by isomerizing the dihydroaromatic system (*e.g.*, **5b**) to the dienol ether (**4b**)[16] followed by manganese dioxide oxidation of the dienol ether to a 3-keto-4,6-diene.[17] The first of these reactions produced a mixture rich in the desired 3,5-diene as evidenced by the ultraviolet absorption (239 mμ). Also in evidence was a small amount of the trienone **7b** (344 mμ), apparently a product of autoxidation. Attempts to oxidize the crude dienol ether **4b** to **7b** by treatment with manganese dioxide or with air met only with limited success.

Direct oxidation of the 4,8(14)-dienes could occur at either a tertiary carbon (to produce the 9-dehydro derivative) or at the more accessible secondary carbon (to give the 6-dehydro compound). The first of these possibilities was realized when N-bromosuccinimide was used. With chloranil (or dichlorodicyanoquinone), however, the major product from each of the dienes (**8b–d**) was the desired trienone (**7b–d**), *e.g.*, treatment of the **8d** with chloranil at 60° for 40 min gave **7d** in 55% yield by direct crystallization. This course of reaction demonstrates the preferred enolization of the unsaturated ketone to give the 3,5(6)-enol; the ensuing removal of the 7-axial proton by quinone[18] is assisted by the allylic 8(14) double bond as reflected in the ease of the reaction. A highly crystalline complex isolated in the early studies of this reaction consisted of 2 mole equiv of the trienone **7c** with one of tetrachlorodihydroquinone. Washing a solution of the complex with base allowed ready isolation of the steroidal component.

Oxidation of the hydroxytriene **7b** occurred at a very slow rate to provide the 17-keto derivative **7a**. This reluctance of the 17-hydroxyl to undergo oxidation, mentioned for several of the 17-hydroxy compounds in this paper, cannot be attributed to steric hinderance for the molecule is planar. One possible explanation is that there is considerable difficulty in introducing a second trigonal carbon atom into an already strained D ring.

Experimental Section[19]

3-Methoxyestra-1,3,5(10),8(14)-tetraen-17β-ol (2b).—Sodium metal (2 g) was added to a solution of 2.2 g of 3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (1)[3,4] in 60 ml of aniline and 600 ml of ammonia.[5] After 30 min, 10 g of ammonium chloride was added, the ammonia was distilled, and the mixture was diluted with water. An ether extract was washed consecutively with excess dilute acid, with water, and with dilute potassium bicarbonate. The product, obtained on distillation of the solvent, crystallized from ether and was recrystallized from ether–petroleum ether (bp 60–80°, Darco), yielding 1.75 g of the olefin **2b**, mp 75–78°, λ_{max} 2.73 μ, λ_{max} 278 mμ (ε 2180), Δν 54 cps (13-CH_3).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.28; H, 8.65.

The instability of **2b** was seen when the entire reaction product was chromatographed,[20] resulting in appreciable decomposition of the product. Also a crystalline sample after 8 weeks at 5° in a capped vial, turned to a cream-colored solid containing about 10% of the original olefin **2b** and several new components. (The nmr showed seven methyl signals.) The material also showed enhanced ultraviolet absorption [λ_{max} 229 mμ (ε 16,900) and 265 mμ (ε 5000) plus several maxima of lower intensity]. Hydroxylation of this mixture with osmium tetroxide yielded as the only crystalline derivative a small amount of the known 8,14-glycol **6a** (see below).

Oxidation of **2b** by use of Jones reagent[21] at reduced temperatures, chromium trioxide–pyridine, or Oppenauer oxidation failed to yield tractable products. With each of these oxidants the intensity of the ultraviolet absorption was increased; however, with the second, this increase was at 309 mμ (ε 11,000) [diene 1 (?)] rather than at the lower wavelengths seen in the products from the other reactions.

Hydrogenation of Olefin 2b.[22]—A solution of 0.80 g of **2b** in 50 ml of 3A ethanol was stirred with 0.8 g of 10% palladium-on-charcoal catalyst in an atmosphere of hydrogen for 15 hr. The mixture was filtered and the filtrate was concentrated to dryness. The resulting residue was crystallized from ethanol yielding 0.40 g of the crystalline 8-iso derivative **3**, mp 84–87°, identical spectrally with an authentic sample.[9] The mother liquors consisted of no less than 80% of this same material as evidenced by the 18-methyl signal in the nmr (52 cps).

3-Methoxyestra-8α,14α-epoxy-1,3,5(10)-trien-17β-ol (6b) and 3-Methoxy-8β,14β-epoxyestra-1,3,5(10)-trien-17β-ol (6c).—The tetraene **2b** (1.9 g) in 100 ml of chloroform was stirred with 2 g of *m*-chloroperbenzoic acid for 30 min. Calcium hydroxide (10 g) was then added[23] and the mixture was stirred for an additional 30 min. The solution was filtered and the filtrate was concentrated to dryness. The residue (1.95 g) consisted of a 4:1 ratio of two isomers as demonstrated by the relative intensities of the 18-methyl signals in the nmr spectrum. The minor isomer crystallized from a methylene chloride–cyclohexane solution of the product, affording 0.41 g of pure **6c**, mp 201–203°, λ_{max} 2.75 μ, Δν 58 cps (13-CH_3). The 17α-H signal was obscured in part by the OCH_3 signal at 227 cps.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.04. Found: C, 75.79; H, 7.94.

From the mother liquors, dissolved in cyclohexane, 0.80 g of the major isomer, **6b**, mp 153–158°, was obtained. Recrystallization from cyclohexane gave the pure compound, mp 171–174°, λ_{max} 2.70 μ, Δν 54 (13-CH_3) and 247 (17-H) cps.

Anal. Found: C, 75.98; H, 7.88.

Epoxidation of the corresponding $\Delta^{8(9)}$-olefin gave no compounds resembling either oxide **6b** or **c** as analyzed by nmr and tlc.[13]

The β-epoxide **6c** was acetylated with acetic anhydride–pyridine at room temperature and the product was recrystallized from aqueous methanol to give 3-methoxyestra-8β,14β-epoxyestra-1,3,5(10)-trien-17β-ol acetate, mp 106–109°, λ_{max} 5.78 μ, Δν 303 cps (17-H).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.53; H, 7.60.

Acetylation of the α-epoxide **6b** as above and recrystallization of the product from aqueous methanol afforded 3-methoxy-8α,14α-epoxyestra-1,3,5(10)-trien-17β-ol acetate, mp 123–127°, λ_{max} 5.78 μ, Δν 295 cps (17-H).

Anal. Found: C, 73.27; H, 7.73.

Estra-1,3,5(10)-triene-3,8α,14α,17β-tetrol 3-Methyl Ether (6a).—A solution of 3.5 g of the alcohol **2b** in 10 ml of pyridine and 5 ml of acetic anhydride was allowed to stand at room temperature for 4 hr. The solution was then diluted with water and extracted with benzene. The extract was washed with aqueous potassium

(16) Personal communication from Dr. F. B. Colton of these laboratories. This reaction normally occurs in very high yield in the presence of anhydrous acid.

(17) F. B. Colton, U. S. Patent 3,194,803 (1965).

(18) S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

(19) Dr. R. H. Bible, Jr., is to be thanked for several informative discussions pertaining to the interpretation of some of the nmr spectra reported here. Also, we wish to thank Dr. R. T. Dillon and staff for the elemental analyses and spectra reported. Unless specified otherwise, the ultraviolet spectra were determined in methanol, infrared in chloroform, and nmr in deuteriochloroform (tetramethylsilane as an internal standard, Δν = 0 cps, on a Varian A-60 spectrometer). All compounds described are *dl*.

(20) We wish to thank Dr. E. G. Daskalakis and staff for all of the chromatographs described. These were uniformly run on a weight of silica gel 60 times the weight of the compound adsorbed.

(21) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(22) The hydrogenations described were performed by Mr. W. M. Selby and staff, for which we thank them.

(23) H. B. Henbest and B. Nicholls, *J. Chem. Soc.* 4608 (1957).

hydroxide solution and concentrated, yielding 3.5 g of the amorphous acetate **2e**.

A solution of 3.5 g of **2e** in 100 ml of pyridine and 3.5 g of osmium tetroxide was allowed to stand at room temperature for 30 hr. Water (50 ml) containing 6 g of sodium bisulfite was added and the solution was stirred for 3 hr. The mixture was extracted three times with chloroform and the extract was concentrated to yield 2.7 g of a black foam. To remove bound osmium from this product it was dissolved in 30 ml of tetrahydrofuran and added to 50 ml of ether containing 1 g of lithium aluminum hydride. The mixture was boiled for 2 hr, was cooled, and was diluted slowly in turn with excess ethyl acetate, 3 ml of water, and 1 ml of 10% aqueous potassium hydroxide. The mixture was then filtered through Super-Cel and the filtrate was concentrated, yielding 2.0 g of a black oil. The product was chromatographed, affording first an oily material containing impure diene **1** [λ_{max} 309 mμ (ϵ 7900); the pure material has E_{310} = 29,400].[3] Continued elution of the column with 10% ethyl acetate–benzene gave fractions which were combined and recrystallized from acetone (Darco) yielding 0.75 g of the glycol **6a**, mp 203–204°, λ_{max}^{KBr} 2.89 and 2.99 μ, $\Delta\nu$ [$(CD_3)_2SO$] 68 cps (13-CH_3).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.41; H, 8.16.

Acetylation of the triol with acetic anhydride–pyridine at room temperature gave **3-methoxyestra-1,3,5(10)-triene-8α,14α,-17β-triol 17-acetate**, mp 183–186°, λ_{max} 2.75 and 5.75 μ, $\Delta\nu$ 72 (13-CH_3) and 292–300 (17-H, multiplet) cps.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.52; H, 7.79.

3-Methoxyestra-2,5(10),8(14)-trien-17β-ol Acetate (5e).—A solution of 54 g of the alcohol **1** in 0.5 l. of tetrahydrofuran was added to 2 l. of ammonia and 0.5 l. of *t*-buty alcohol. Lithium wire (10 g) was added portionwise over 30 min. After 4 hr the blue color had disappeared and the ammonia was distilled. The mixture was diluted with water and the product was extracted with benzene. The product, 55 g of an oil, was taken up in 100 ml of warm benzene and cooled. The resulting crystalline material was collected on a filter and washed with Skellysolve A, yielding 51 g of the 3-methoxyestra-2,5(10),8(14)-trien-17β-ol (**5b**): mp 92–94°; λ_{max} 2.77, 5.90 (m), and 6.00 (m) μ; $\Delta\nu$ 55 (13-CH_3) and 214 cps (OCH_3). The sample did not afford acceptable analytical values due to solvation of the crystals. Although the compound had no ultraviolet maximum, when a sample in methanol was treated with aqueous hydrochloric acid, a maximum appeared at 234 mμ (ϵ 10,500).

A solution of 1.7 g of the alcohol **5b** in 10 ml of pyridine and 5 ml of acetic anhydride was allowed to stand at room temperature for 18 hr. The product was obtained from the reaction mixture by benzene extraction; it crystallized from ether and was recrystallized from ether–petroleum ether (Darco) to give 0.75 g of the pure acetate **5e**, mp 108–110°, λ_{max} 5.76 and 5.99 (m) μ.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.54. Found: C, 76.54; H, 8.59.

Use of pyridine hydrochloride to isomerize this material to the 3,5-dienol ether **4e** was unsuccessful.

17β-Hydroxyestra-4,8(14)-dien-3-one (8b).—A solution of 3.0 g of the dihydro alcohol **5b** in 60 ml of methanol, 10 ml of water, and 4 ml of concentrated hydrochloric acid was mixed at 10° and then stirred at room temperature for 3 hr. The solution was diluted with a small excess of aqueous potassium hydroxide and then extracted with benzene. The product (2.5 g) thus obtained was crystallized and then recrystallized from ether (Darco), yielding 0.83 g of the pure alcohol **8b**, mp 138–141°, λ_{max} 2.73 and 5.98 μ, λ_{max} 233 mμ (ϵ 16,400), $\Delta\nu$ 58 (13-CH_3) and 353 cps (4-H).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.31; H, 8.78.

Chromatography of the mother liquors afforded additional **8b**, eluted at 10% ethyl acetate–benzene. Following this material closely was a second substance which was recrystallized from acetone–petroleum ether to yield crystals, mp 174–177°, λ_{max} 231 mμ (ϵ 14,700). This material had infrared and nmr spectra very similar to those of **8b**, and thus was presumed to be the 10α-epimer of **8b**.

Anal. Found: C, 79.26; H, 8.66.

The acetate of this material was amorphous and clearly different from **8e** in the infrared.

17β-Acetoxyestra-4,8(14)-dien-3-one (8e) was prepared by treatment of the alcohol **8b** in acetic anhydride–pyridine at room temperature overnight. The product was recrystallized from ether–petroleum ether to yield the pure acetate **8e**, mp 110–112°, λ_{max} 5.72 and 5.94 μ.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.34; H, 8.20.

4ξ,5ξ,17β-Trihydroxyestra-8(14)-en-3-one (10).—A solution of 0.54 g of the diene **8b** in 20 ml of pyridine at 5° was treated with 0.56 g of osmium tetroxide. After 18 hr at ambient temperature the solution was diluted with 0.5 g of sodium bisulfite in 10 ml of water and 50 ml of pyridine. The mixture was stirred for 3 hr and extracted with methylene chloride. The extract, on concentration, yielded 0.65 g of product which was crystallized and recrystallized from acetone (Darco) to give 0.32 g of the pure glycol **10**, mp 210–213°, λ_{max}^{KBr} 2.88 and 5.82 μ.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.81; H, 8.58.

3-Methoxyestra-2,5(10),8(14)-trien-17-one (5a).—Solvent (50 ml) was distilled from a solution of 22 g of the alcohol **5b** in 800 ml of toluene and 100 ml of redistilled cyclohexanone under an atmosphere of nitrogen. A solution of 120 ml of toluene containing 12 g of aluminum isopropoxide was then added over a 15-min period to the stirred, boiling solution. After an additional 15 min the solution was cooled and an aqueous solution of Rochelle salts was added. The mixture was steam distilled for 1 hr and cooled. The product was isolated by benzene extraction and recrystallized from ether–methanol (Darco) to yield 14.1 g of the pure ketone **5a**: mp 115–117°; λ_{max} 5.72, 5.85 (m), and 5.98 (m) μ; $\Delta\nu$ 67 cps (13-CH_3).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.16; H, 8.59.

Estra-4,8(14)-diene-3,17-dione (8a).—A solution of 0.40 g of the ketone **5a** in 20 ml of methanol, 3 ml of water, and 1 ml of concentrated hydrochloric acid was allowed to stand at room temperature for 4 hr. The precipitate which resulted from dilution of the reaction mixture was separated and recrystallized from aqueous acetone to yield 0.20 g of the pure diketone **8a**, mp 167–168°, λ_{max} 5.72 μ and 5.96 μ, λ_{max} 233 mμ (ϵ 17,000), $\Delta\nu$ 68 cps (13-Me).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.96; H, 8.26.

The combined aqueous mother liquors were extracted with benzene and furnished an additional 70 mg of pure diketone **8a**.

An alternate but less satisfactory preparation of **8a** entailed oxidation of the alcohol **8b** with Jones reagent.[21] Oppenauer oxidation of the alcohol **8b** (by use of the conditions used to prepare **5a**) gave a mixture of starting material, ketone **8a**, and decomposition products in a ratio of 2:1:1.

17β-Hydroxyestra-4,6,8(14)-trien-3-one (7b). A. Chloranil Oxidation.—Chloranil (0.78 g) was added to a solution of 0.78 g of the alcohol **8b** in 20 ml of *t*-butyl alcohol at 60° under an atmosphere of nitrogen. The mixture became homogeneous in 15 min. After 35 min, the reaction was cooled and diluted with ether. The solution was washed with sodium sulfite and three times with dilute aqueous potassium hydroxide. Concentration of the solution afforded 0.55 g of a foam which crystallized from ether solution to yield 0.30 g of the pure trienone **7b**: mp 157-158°; λ_{max} 2.75 μ and 6.00–6.08 μ; λ_{max} mμ (ϵ 25,800); $\Delta\nu$ 63 (13-CH_3), 354 (4-H), and a quartet (1:2:2:1) 366, 375, 396, 405 cps (6, 7-H).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.62; H, 8.00.

Oxidation with dichlorodicyanoquinone in refluxing benzene containing acid catalyst also yielded the trienone **7b** but the reagent was abandoned in favor of chloranil. Use of N-bromosuccinimide produced material with an ultraviolet maximum typical of the 4,9(10),8(14)-trienone (λ_{max} 358 mμ).

B. Manganese Oxide Oxidation of the Enol Ether 4b.—A stirred mixture of 4.0 g of the dihydro compound **5b** (dried by benzene azeotrope) in 30 ml of ethyl acetate and 20 mg of *p*-toluenesulfonic acid became homogeneous after 10 min. Pyridine (2 ml) was added and the solution was washed with aqueous potassium bicarbonate. The oranic layer yielded 3.5 g of a foam, the impure 3,5-dienol ether **5b**, λ_{max} 239 mμ (ϵ 11,300).

A mixture of 3.0 g of the crude dienol ether **4** and 3 g of manganese dioxide in 50 ml of ethyl acetate was stirred for 18 hr. The solution was filtered and concentrated yielding 2.7 g of an oil, λ_{max} 232 mμ (ϵ 7000) and 340 mμ (ϵ 5000). [In other runs, with small changes in conditions, the crude product exhibited λ_{max} 344 mμ (ϵ 8500).]

Chromatography of this material on silica yielded fractions eluted with 15% ethyl acetate–benzene which were crystallized

to afford small amounts of the desired trienone **7b**, mp 138–144°.

Attempts to use oxygen in anhydrous medium with acid present did not lead to the trienone although spontaneous formation of **7b** had been seen previously from the chromatography of the mother liquors of the unsaturated ketone **8b**

17β-Hydroxy-17-methylestra-4,8(14)-dien-3-one (8c).—The ketone **5a** (7 g) in 50 ml of tetrahydrofuran and 150 ml of ether was added over a 15-min period to a stirred solution of 0.24 mole of methyl magnesium bromine in 400 ml of ether. After 21 hr, the mixture was diluted slowly with water and then with sufficient dilute hydrochloric acid to dissolve the bulk of the salts. The product (7.1 g) was extracted with ether, yielding the amorphous enol ether **5c**. A portion of this material (4.5 g) was dissolved in 100 ml of methanol, 20 ml of water, and 8 ml of concentrated hydrochloric acid. After 3 hr the solution was diluted with water and the product was extracted with benzene. The residue was dissolved in acetone–petroleum ether, affording a crystalline precipitate, 2.35 g, mp 121–125°. Recrystallization of this material from acetone–petroleum ether yielded the pure unsaturated ketone, mp 136–138°, λ_{max} 2.75 and 6.02 μ, λ_{max} 233 mμ (ε 15,700).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.58; H, 9.17.

Chromatography of the mother liquors yielded additional product, eluted at 10% ethyl acetate in benzene.

17β-Hydroxy-17-methylestra-5(10),8(14)-dien-3-one (9c).—A mixture of 2.8 g of the amorphous alcohol **5b** in 50 ml of acetic acid and 10 ml of water was stirred at room temperature. After 10 min the solution was homogeneous and after an additional 15 min, water was added affording 1.8 g of a poorly crystalline material. The product, separated by filtration, was dissolved in methylene chloride and the solution was washed with aqueous potassium bicarbonate. The ketone was then crystallized from methylene chloride–petroleum ether, affording 1.45 g of **9c**, mp 127–130°, λ_{max} 2.70 and 5.78 μ, Δν 62 (13-CH_3) and 67 cps (17-CH_3). No maximum was seen in the ultraviolet.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.64; H, 9.11.

17β-Acetoxyestra-5(10),8(14)-dien-3-one (9e) was prepared by a similar procedure from the acetate **5e**, giving a product which was recrystallized from aqueous acetone to give 0.22 g of the pure **9e**, mp 114–116°, λ_{max} 5.78 μ.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.12; H, 8.39.

17β-Hydroxy-17-methylestra-4,9,8(14)-trien-3-one (11c, $\Delta^{8(14)}$).—A solution of 0.29 g of the dienone **9c** in 4 ml of pyridine at 5° was treated with 0.35 g of pyridinium bromide perbromide resulting in the rapid precipitation of pyridine hydrobromide. After 5 min the solution was diluted with water and the resulting precipitate was collected on a filter and washed with water, and then a small volume of ethyl acetate. The crude dibromide thus obtained (0.27 g) was dissolved in 20 ml of pyridine; after 2 hr the solution was diluted with water and extracted with methylene chloride. The product, 0.19 g of a foam, crystallized and was recrystallized from ether, yielding 0.14 g of the triene (**11c**, $\Delta^{8(14)}$): mp 127–131°; λ_{max} 2.75 and 6.02–6.08 μ; λ_{max} 359 mμ (ε 23,400); Δν 65 (13-CH_3), 68 (17-CH_3), and 342 cps (4-H).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.12; H, 8.40.

17β-Hydroxy-17-methylestra-4,6,8(14)-trien-3-one (7c).—Chloranil (1.5 g) was added to a solution of 1.50 g of the diene **8c** in 30 ml of *t*-butyl alcohol at 55° under an atmosphere of nitrogen. After 45 min the solution was cooled and diluted with aqueous sodium sulfite. The product was extracted with methylene chloride, yielding 2.0 g of an oil. Trituration of this material with acetone yielded 1.17 g of dark crystals which were recrystallized from methanol–ethyl acetate to give 0.80 g of yellow crystals, the complex of 2 mole equiv of **7c** with one of tetrachlorodihydroquinone: mp 218–223°; λ_{max} 2.95, 3.21, and 6.04 μ; λ_{max} 345 mμ (ε 18,700).

Anal. Calcd for $C_{44}H_{50}Cl_4O_6$: C, 64.71; H, 6.17; Cl, 17.37. Found: C, 64.51; H, 6.28; Cl, 17.53.

A methylene chloride solution of this complex was washed with 2% aqueous potassium hydroxide and water. Distillation of the solvent gave a product which was crystallized from ether and recrystallized from aqueous acetone to afford the hemihydrate of the trienone **7c**: mp 164–166°; λ_{max} 2.74 and 6.02–6.09 μ; λ_{max} 344 mμ (ε 26,800); Δν 61 (13-CH_3), 353 (4-H), quartet (1:2:2:1) 363, 373, 393, 403 cps (6, 7-H).

Anal. Calcd for $C_{38}H_{50}O_6$: C, 78.03; H, 8.51. Found: C, 77.71; H, 8.56.

3-Methoxy-17β-hydroxy-17-ethynylestra-2,5(10),8(14)-trien-17-ol (5d).—Sodium metal (5.8 g) was added portionwise to 70 ml of ammonia and 35 ml of 2-propanol containing 50 mg of cupric nitrate. When the blue color had disappeared, 60 ml of dimethylformamide was added and the solution was warmed to 20° allowing the ammonia to distil. The solution was saturated with gaseous acetylene (first washed with water and concentrated sulfuric acid) and then a solution of 5.0 g of the ketone **5a** in 100 ml of dimethylformamide was added over a 20-min period, maintaining a slow stream of acetylene over the surface. After an additional 2 hr at 20°, ice was added to the mixture followed by water.[24] The resulting crystalline precipitate was separated, washed with water, and recrystallized from aqueous acetone to afford 4.2 g of the adduct, mp 129–131°. A further recrystallization from ether–petroleum ether (Darco) afforded pure **5d**: mp 138–142°; λ_{max} 2.75, 3.01, 5.88 (m), and 5.98 (m) μ.

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.24; H, 8.66.

Attempts to prepare the $\Delta^{8(14)}$-analog of 17-ethinylestradiol methyl ether (**2d**) by oxidizing the enol ether **5d** with chromium trioxide–pyridine proceeded to give a low yield of an unstable crystalline compound (**2d?**), mp 143–146°, λ_{max} 2.74 and 3.02 μ, Δν 62 cps (13-CH_3). Although the spectral data were in accord with the desired structure (**2d**), the analytical values for this material were not acceptable.

17β-Hydroxy-17-ethynylestra-4,8(14)-dien-3-one (8d).—A solution of 3.2 g of the adduct **5d** in 80 ml of methanol, 8 ml of water, and 5 ml of concentrated hydrochloric acid was allowed to stand at room temperature for 2.5 hr. The precipitate which resulted from dilution of the reaction mixture was separated, washed with water, and recrystallized from ether (Darco) to yield 1.7 g of the ethynyl compound, **8d**: mp 180–182°; λ_{max} 2.75, 3.02, and 5.98 μ; λ_{max} 231 mμ (ε 17,500).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.96; H, 8.18.

Chromatography of the mother liquors yielded additional product, eluted at 15% ethyl acetate–benzene.

17β-Hydroxy-17-ethynylestra-4,6,8(14)-trien-3-one (7c).—Chloranil (1.50 g, 1.1 mole equiv) was added to a stirred solution of 1.65 g of the dienone **8d** in 60 ml of *t*-butyl alcohol at 60° under an atmosphere of nitrogen. After 40 min at 58–62° the solution was cooled, diluted with ether, and washed consecutively with aqueous sodium sulfite and three times with 2% aqueous potassium hydroxide. Concentration of the dried extract to a volume of 10 ml afforded 0.90 g (55%) of the crystalline trienone, free of appreciable contaminants. Recrystallization of this material from acetone afforded 0.70 g of the pure trienone **7d**: mp 218–220°; λ_{max} 2.72, 2.98, 6.01–6.03, and 6.25 μ; λ_{max} 345 mμ (ε 28,800); Δν 68 (13-CH_3), 355 (4-H), and a quartet (1:2:2:1) 367, 377, 397, 407 cps (6, 7-H).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 81.60; H, 7.53. Found: C, 81.52; H, 7.27.

The mother liquors contained a small amount of starting material besides additional product (tlc analysis).

Estra-4,6,8(14)-triene-3,17-dione (7a).—A solution of 0.36 g of the triene **7b** in 20 ml of acetone and 2 ml of 0.4 *N* chromic–sulfuric acid solution (Jones reagent)[21] was stirred for 90 min. (The product at shorter reaction times showed appreciable amounts of starting material.) The mixture was then diluted with 1 ml of 2-propanol and 20 ml of water. The product, 0.34 g of an oil, was isolated by methylene chloride extraction and was crystallized by ether–acetone trituration. Recrystallization from this pair of solvents gave the pure material solvated with 0.5 mole equiv of acetone: mp 220–225° dec; λ_{max} 5.78 and 6.02–6.08 μ; λ_{max} 238 mμ (ε 25,000).

Anal. Calcd for $C_{39}H_{46}O_5$: C, 78.75; H, 7.80. Found: C, 78.88; H, 7.67.

(24) This procedure was developed by Dr. H. L. Dryden, Jr., and Mr. G. M. Webber, of these laboratories.