Total Synthesis of 2-Azaestratrienes[1]

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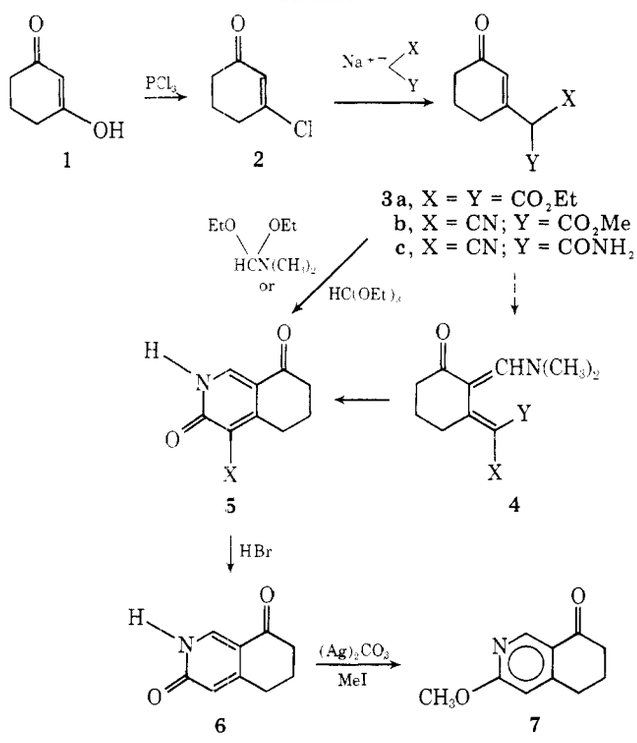
The total synthesis of (±)-2-azaestradiol 3-methyl ether (**15**) as well as its 11β-methyl homologue **28** is described. This work necessitated the development of a synthesis of 6-methoxy-7-aza-1-tetralone (**7**), a heretofore unknown compound. In the course of the preparation of this tetralone, a novel α-pyridone synthesis was developed. The chemical reduction of the 8,9 double bond in each series was accompanied by destruction of the methoxypyridine A ring. Rearomatization of the dihydropyridines **14** and **27** with DDQ regenerated the methoxypyridine nucleus and gave the desired products. A by-product of the DDQ reaction in the 11β-methyl series was identified as (±)-9ξ-hydroxy-2-azaestradiol 3-methyl ether (**29**).

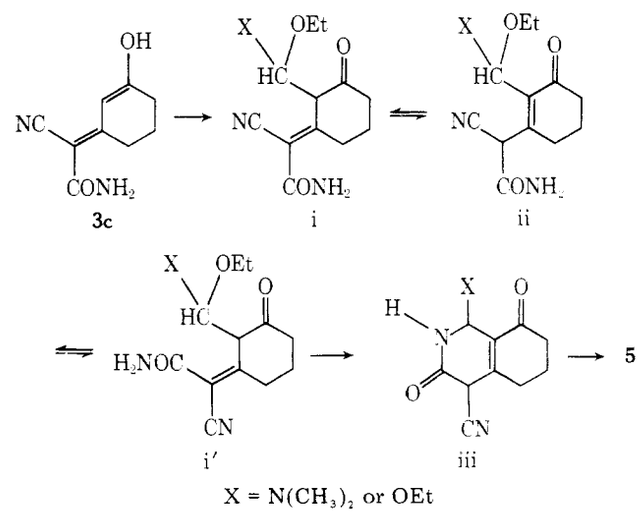
Our study of the effect of a heteroatom at the 2 position of the steroid nucleus had disclosed unique biological properties of the 2-azaestradiol 3-methyl ether series.[2] The lengthy reaction sequence necessary for the preparation of these compounds from naturally occurring steroid starting material prompted an investigation of the total synthesis of this series.[3] Moreover, the development of a total synthetic pathway would provide a means of preparing the 11β-methyl homologues of the parent compounds. These 11-methylated derivatives of the estradiol 3-methyl ether series were shown to possess enhanced biological properties,[4] and it was of interest to determine whether enhancement of the biological properties of the 2-azaestradiol 3-methyl ether series would also result.

The classic approach to the total synthesis of estrone derivatives appeared appropriate for these compounds and a modified Torgov[5] sequence was pursued. This made the 7-aza analogue of 6-methoxy-1-tetralone, an heretofore unknown compound, the key intermediate in the proposed synthesis. Our initial attempts at the preparation of this compound (Scheme I) were to contact 3-chlorocyclohex-2-en-1-one (**2**)[6] with the sodium salts of various malonate derivatives. The resultant products (**3**) were then condensed with the ethyl ketal of dimethylformamide in order to obtain the dimethylaminomethylene derivatives **4**. These in turn were expected to provide the bicyclic α-pyridone **5** after transamination of the dimethylamino functionality of **4** with ammonia and subsequent cyclization. This route proved to be unfruitful with **3a** and **3b** due to the refractory nature of these substances to form dimethylaminomethylene derivatives. In each of these cases the enol ether derivative of the starting material was the observed (by NMR spectroscopy) but uncharacterized product.[7] However, when the 3-cyanoacetamido adduct **3c** was condensed with dimethylformamide diethyl acetal in dimethylformamide at room temperature, the bicyclic α-pyridone **5** (X = CN) was produced rather auspiciously in a single step in high yield.[8]

It was later determined that this transformation could also be realized using the somewhat less reactive but considerably less expensive triethyl orthoformate. Thus, by heating **3c** in dimethylformamide with an excess of this reagent at steam bath temperatures, a yield comparable to that obtained with the ketal reagent (ca. 85%) was obtained. We envision the mechanism of this heterocycle synthesis as proceeding via attack of these reagents, at the carbon atom α to the carbonyl to form i which would be in equilibrium with i′ and ii. This latter form would allow free rotation of the side chain and maximize cyclization to iii, which upon further elimination affords **5**.

Scheme I





To complete our synthesis of the desired tetralone, the nitrile was removed by treatment of **5** with concentrated aqueous hydrobromic acid, which gave 2,3,5,6,7,8-hexahydro-3,8-dioxoisoquinoline (**6**) in 85% yield. This novel approach to α-pyridones has been studied in greater detail and will be reported on more fully in a later manuscript. Alkylation of the silver salt of **6** with methyl iodide in benzene[9] yielded the desired 6-methoxy-7-aza-1-tetralone (**7**) in yields up to 70% and provided **7** in about 30% yield from **1**.

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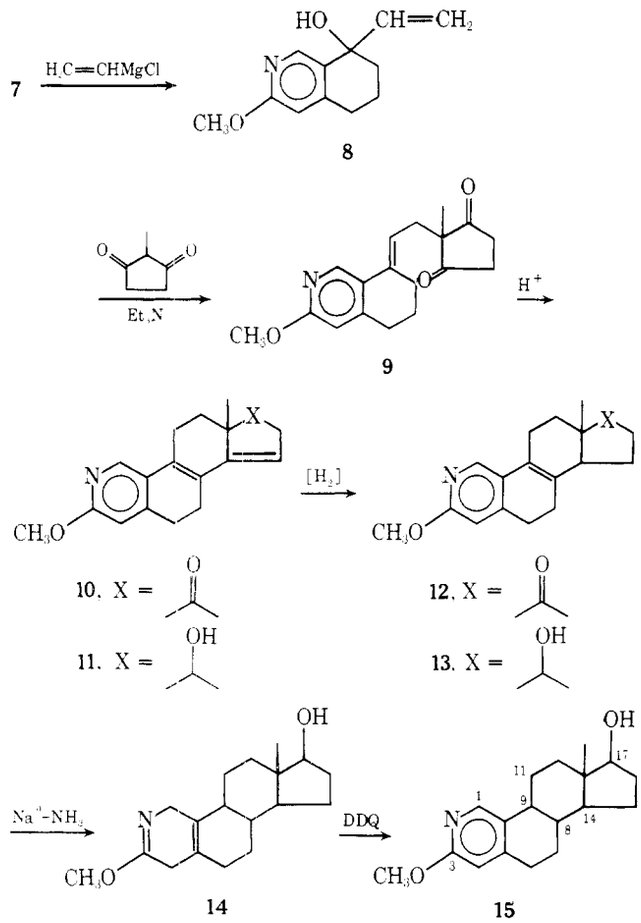
Scheme II



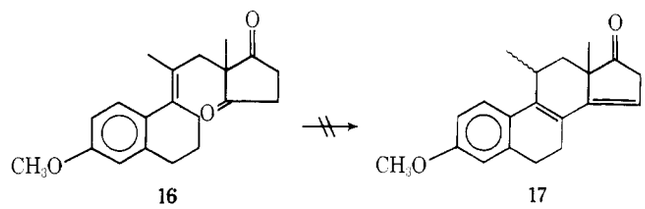
The construction of the steroid ring system is shown in Scheme II. Treatment of **7** with excess vinylmagnesium chloride in xylene gave the vinylcarbinol **8**, which was not characterized but rather condensed with 2-methylcyclopenta-1,3-dione in refluxing xylene to afford **9** in 44% yield from **7**. Cyclization of **9** was sluggish, paralleling the reactivity of the 4-azaestratrienes and the 4,6-diaza steroids reported by Huisman et al.[10] and Bonet et al.,[11] respectively. In each case these molecules become refractory to the acid-catalyzed isomerization of the 9,11 double bond to the 8,9 position, which is necessary for cyclization,[12] due to the presence of a protonated nitrogen in the molecule. However, we found that by refluxing **9** in xylene–dioxane with 2–3 equiv of tosyl acid the tetracyclic product **10** could be obtained in moderate yield.

Reduction of the ketone **10** with sodium borohydride in methanol gave (±)-3-methoxy-2-azaestra-1,3,5(10),8,14-pentaen-17-ol (**11**). This compound underwent catalytic hydrogenation over palladium on calcium carbonate to afford the desired 14α product **13** in 90% yield. The assignment of the stereochemistry at the 14-carbon atom is based on the fact that this compound was the preponderant product of the hydrogenation and the position of the 18-CH_3 resonance of this isomer is upfield (ca. 0.20 ppm) from the 18-CH_3 resonance of the minor isomer.[13,14]

We had also hydrogenated **10** to provide **12** which upon sodium borohydride reduction also gave **13**. However, the 14α/14β isomer ratio which was determined by NMR spectroscopy from the relative intensities of the 18-CH_3 resonances of the two compounds was greater when hydrogenation was carried out on the alcohol **11** rather than the ketone **10** (9:1 vs. 8:2, respectively). This result parallels that previously observed in these laboratories on work done in the carbocyclic series as well as that of Huisman et al. on 6-thia steroids.[15]

The critical step in the total synthesis of the estradiol 3-methyl ether analogue was trans reduction of the 8,9 double bond. Earlier reports by Huisman[14] had indicated that the aromatic nucleus did not survive chemical reduction in the 4-azaestratriene series. Indeed, we also observed this phenomenon when **13** was treated with sodium in liquid ammonia at −70 °C. However, inspection of the NMR spectrum of the product mixture of this reaction indicated that, along with a small amount of the desired 2-azaestratriene, was the preponderant component of the reaction which possessed no aromatic or vinyl protons. The presence of considerable resonance in the allylic proton region (at ~3.7 ppm) suggested that the $\Delta^{2,5(10)}$-diene **14** was the probable product. Treatment of this mixture then with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided the desired 2-azaestradiol 3-methyl ether (**15**) now as the preponderant product. This compound proved to be spectroscopically identical with that prepared from natural steroidal starting material.[2]

Our attention then turned to the preparation of the 11β-methyl analogues of this series. The Torgov approach to these compounds in the carbocyclic series was not particularly successful, because the diketone **16** resisted isomerization of its double bond to the 8,9 position[16] which is necessary for cyclization to **17**.[12] We thus pursued the approach previously

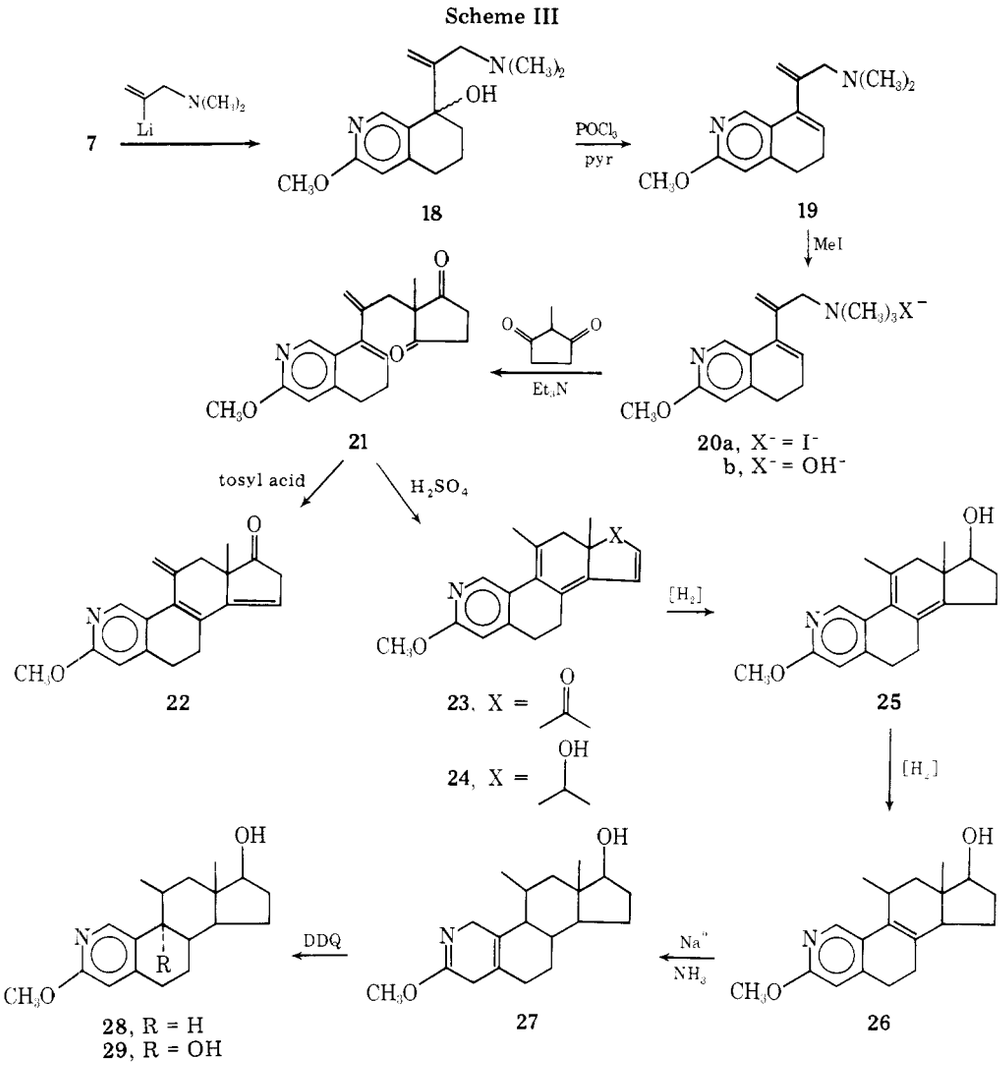


developed in these laboratories for the synthesis of 11-methylated estratrienes, utilizing 2-bromo-3-dimethylamino-1-propene.[17] We found this reagent readily undergoes halogen–metal exchange in the presence of *n*-butyllithium at −25 to −40 °C.[18] This method had several advantages over use of the Grignard reagent of this halide[19] due to the ease of preparation and cleaner resultant product. Thus, treatment of **7** with this lithium reagent (Scheme III) provided the dimethylaminocarbinol **18** in good yield, which was dehydrated to the corresponding diene **19** using phosphorus oxychloride–pyridine. The crude product **19** was then quaternized with methyl iodide to form the ammonium salt **20a.**

As pointed out in the earlier work from these laboratories,[17] C-alkylation of the allylic carbon atom attached to the nitrogen atom with 2-methylcyclopenta-1,3-dione was optimized when the iodide anion was converted to the hydroxide by treatment of the iodide with aqueous silver oxide. We have also found this to be true in our series. Direct alkylation of **20a** with the dione led to low yields of **21** whereas the quaternary ammonium hydroxide **20b** provided the desired adduct **21** in good yield.

Attempts to cyclize the diketone **21** to the tetracyclic product **22** under those conditions utilized in the previous series provided a reaction product comprised of a mixture of components whose characterization was not pursued. The exocyclic triene **22** is apparently unstable to these reaction conditions, and alternate methods for this transformation were investigated. It was found that by using concentrated sulfuric acid at room temperature, **21** is smoothly cyclized with subsequent isomerization of the double bonds into conjugation with the 17-ketone to afford 3-methoxy-11-methyl-2-azaestra-1,3,5(10),9 (11),8 (14),15-hexaen-17-one (**23**) in yields up to 90%.[20] In contrast to the 11-methylene isomer of the carbocyclic series,[17] this tetracyclic hexaene is quite stable at room temperature, apparently due to the conjugation of the double bonds with the carbonyl.

Scheme III



(3)

The 17-ketone was reduced to the corresponding 17-alcohol **24** with diisobutylaluminum hydride. Stepwise catalytic hydrogenation of **24** over palladium on carbon first provided the pentaene **25** and then the tetraene **26.** The initial reduction step procedes via a 1,2 process across the 15,16 double bond, whereas the latter step via a 1,4 addition across the 8(14),9(11) double bonds affording the resultant 3-methoxy-11β-methyl-2-azaestra-1,3,5(10),8-tetraen-17-ol (**26**) with both hydrogen atoms on the same side of the molecule. The 11β-methyl stereochemistry of this product was based on precedent established in previous work in the carbocyclic series where hydrogenation was shown to produce the 11β-methyl isomer.[21]

11β-Methyl-2-azaestradiol 3-methyl ether (**28**) was produced as in the previous series. Reduction of **26** with sodium in liquid ammonia at −70 °C provided a mixture of components, with a structure devoid of aromaticity in preponderance. Subsequent treatment with DDQ gave the desired aromatic product **28** as well as a small amount of polar contaminant (by thin-layer chromatography). Isolation of this latter material by column chromatography afforded a substance whose mass spectrum [M^+ 317 (3.5%), $M^+ - H_2O$ 299 (100%)] and elemental analysis indicated a molecule which differed from **28** by an additional oxygen atom (hydroxyl group). The absence of a downfield proton accompanying this additional hydroxyl group in the NMR spectrum of **29** indicated that it occupied a tertiary position. This would be consistent with its origin, which probably occurred during DDQ treatment. It seems plausible that **28** reacted with the excess DDQ present to generate a benzilic, tertiary carbonium ion which was hydrated during the course of the reaction due to the presence of moisture. This type of product has also been observed in the treatment of 11-oxoestrones with DDQ in a recent study by Turner and co-workers.[22]

The assignment of the configuration of this hydroxyl group has not been unequivocally established. A comparison of the NMR spectra of **28** and **29** reveals only slight variations in the chemical shifts of most resonances with the exception of the 1 proton (7.95 and 8.25 ppm, respectively). The Dreiding model of each isomer fails to reveal an obvious reason for the difference in the chemical shift of this proton on the basis of an interspatial interaction with the hydroxyl group. Furthermore, the 100-MHz proton NMR spectra containing europium shift reagent or the ^{13}C NMR spectrum of this compound failed to provide conclusive evidence for the assignment of its structure.[23] On a mechanistic basis, we favor the structure containing the 9α-hydroxyl group. Hydration of the 9-carbonium ion is sterically hindered on the β face of the molecule by the presence of the two axial methyl groups which would appear to effectively prevent β entry of the water molecule.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on Varian A-60A, T-60, or 100XL-15 spectrometers using Me_4Si as an internal standard. UV spectra were obtained in MeOH on a Beckman DK-2A. Infrared spectra were obtained on a Beckman IR-12 spectrophotometer. The spectra were run by the group of Mr. A. J. Damascus and the microanalyses were performed by the group of Mr. E. Zielinski. Hydrogenations were carried out by Mr. M. Scaros and

associates. Mass spectra were recorded by Dr. J. Hribar and associates using an AEI MS-30. TLC's were run on 7.6-cm microscope slides covered with 0.25-mm thickness of Woelm F silica with a magnesium silicate binder. Visualization of spots was by phosphomolybdic acid (5% by weight in ethanol) followed by heat.

3-Chlorocyclohex-2-en-1-one (2). To 400 g (3.57 mol) of dihydroresorcinol in 2 L of chloroform was added 161.2 g (1.13 mol) of phosphorus trichloride, and the reaction mixture was refluxed under an atmosphere of nitrogen for 3 h. After cooling, the solution was poured into 1 L of an ice–water mixture, and the two layers were separated. The aqueous phase was extracted with two additional portions of ether before washing the combined extracts with 5% sodium hydroxide (1 L) and saturated salt solution. After drying the extracts over sodium sulfate, solvent removal left an oil which was distilled under reduced pressure to afford 276 g (60%) of **2** [bp 50 °C (0.3 mm)]. Anal. Calcd for C_6H_7ClO: Cl, 27.15. Found: Cl, 27.30.

3-(2-Diethylmalonyl)cyclohex-2-en-1-one (3a). To 5.4 g (0.126 mol) of sodium hydride in 100 mL of 1,2-dimethoxyethane in an atmosphere of nitrogen was added 20 g (0.128 mol) of diethyl malonate dropwise, and the reaction mixture was refluxed for 20 min. To the still warm reaction mixture was then added 10.0 g (0.077 mol) of **2** and it was refluxed for 3 h. After cooling the reaction mixture to ca. 0 °C, 350 mL of ice–water was added, and the solution was then acidified with concentrated hydrochloric acid and extracted with three portions of chloroform. The combined extracts were washed with water and dried over sodium sulfate prior to solvent removal in vacuo which afforded an oil. Distillation in vacuo gave **3a:** bp 148 °C (0.6 mm); UV (MeOH) 232 nm (ϵ 13 500); NMR ($CDCl_3$) δ 1.30 (6 H, t, J = 7 Hz, $-CH_3$), 4.25 (1 H, s, malonyl H), 4.27 (4 H, q, J = 7 Hz, CH_2 of ester), 6.04 (1 H, br s, vinyl proton). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.09; H, 7.24.

Methyl α-Cyano-3-oxo-1-cyclohexene-1-acetate (3b). To 2.4 g (0.1 mol) of sodium hydride in 75 mL of 1,2-dimethoxyethane in an atmosphere of nitrogen was added 9.94 g (0.105 mol) of methyl cyanoacetate, and the reaction mixture was refluxed for 1 h and then cooled to room temperature. To the heterogeneous reaction mixture was then added 6.5 g (0.05 mol) of **2** dropwise and stirring was continued for an additional 3 h. The reaction mixture was diluted with 300 mL of ice–water and acidified with concentrated hydrochloric acid, and the insoluble product present was collected by filtration. The filtrate was extracted with three portions of chloroform, and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave a solid residue. This was combined with solid collected by filtration above, and these were washed with Skelly B to provide 8.6 g (9) of **3b.** Recrystallization from ethyl acetate gave the pure compound as the enol: mp 188–189 °C; UV (MeOH) 338 nm (ϵ 27 000); NMR ($CDCl_3$) δ 1.78 (2 H, br quintet, J = 6 Hz, $-CH_2-$), 2.50 (2 H, br t, J = 6 Hz, $-CH_2-$), 2.87 (2 H, br t, J = 6 Hz, $-CH_2-$), 3.67 (3 H, s, $-OCH_3$). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.37; H, 5.95; N, 7.25.

α-Cyano-3-oxo-1-cyclohexene-1-acetamide (3c). To 58 g (2.42 mol) of sodium hydride in 1.8 L of 1,2-dimethoxyethane (DME) under an atmosphere of nitrogen at room temperature was added portionwise over a 30-min period 198 g (2.35 mol) of cyanoacetamide. The reaction mixture was then refluxed for 30 min before cooling to room temperature, whereupon 145.2 g (1.12 mol) of 3-chlorocyclohex-2-en-1-one (**2**) in 100 mL of benzene was added over a 15-min period. The reaction mixture was refluxed for 1 h before cooling in an ice bath, followed by the dropwise addition of a solution of 10 mL of water in 20 mL of methanol. An additional 500 mL of water was then added before removal of most of the organic solvents in vacuo. Acidification of the remaining aqueous solution to pH 1 with dilute hydrochloric acid caused formation of a precipitate which was collected and washed with several portions of water. Recrystallization from ethanol–water–ethyl acetate (4:1:2) gave in two crops 147.7 g of **3c:** mp 181–183 °C; UV (MeOH) 370 nm (ϵ 21 900); NMR (C_5D_5N) δ 1.73 (2 H, m), 2.41 (2 H, m), 2.93 (2 H, m). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.94; H, 5.88; N, 15.55.

Treatment of 3a with Dimethylformamide Diethyl Acetal. To 1.0 g (0.0039 mol) of **3a** in 5 mL of dimethylformamide was added 0.5 g (0.0034 mol) of dimethylformamide diethyl acetal, and the solution was stirred at room temperature for 16 h. After addition of water the solution was extracted with ether, and the extracts were washed with a saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave an oil whose NMR and UV spectra indicated a preponderance (>80%) of starting material. When **3a** was treated with excess acetal reagent at 70–75 °C for 30 h, the usual workup gave a residue whose NMR spectrum gave little indication of the desired adduct but rather the ethyl enol ether of the starting material. Further characterization was not pursued.

Treatment of 3b with Dimethylformamide Diethyl Acetal. To 1.0 g (0.0052 mol) of **3b** in 8 mL of dimethylformamide was added 1.0 g (0.0068 mol) of dimethylformamide diethyl acetal, and the reaction mixture was stirred at room temperature for 19 h. A small amount of water was added to destroy the excess reagent, and the solvent was removed in vacuo to give an oil whose NMR spectrum indicated a mixture of starting material and the ethyl enol ether of the starting material. Further characterization was not pursued.

(a) 2,3,5,6,7,8-Hexahydro-3,8-dioxo-4-isoquinolinecarbonitrile (5, X = CN) via Dimethylformamide Diethyl Acetal. To 40 g (0.225 mol) of **3c** in 125 mL of dimethylformamide under an atmosphere of nitrogen at room temperature was added 40 g (0.27 mol) of dimethylformamide diethyl acetal dropwise over a 10-min period. After stirring the reaction mixture overnight at room temperature, 10 mL of water was added and the solvent was removed in vacuo. The oily residue was taken up into 450 mL of 2.5% sodium hydroxide solution and then washed eight times with chloroform. Neutralization of the basic solution with dilute hydrochloric acid solution afforded 33.6 g (80%) of **5.** Recrystallization from aqueous acetone gave the pure material: mp >290 °C; UV (MeOH) 227 nm (ϵ 17 900), 232 sh (16 000), 279 (13 000), 324 (6800); NMR (C_5D_5N) δ 1.92 (2 H, m), 2.58 (2 H, m), 2.97 (2 H, m), 8.72 (1 H, s, 1-H). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.60; H, 4.45; N, 15.02.

(b) 5 (X = CN) via Triethyl Orthoformate. To 75 g (0.42 mol) of **3c** in 400 mL of dimethylformamide was added 75 g (0.505 mol) of triethyl orthoformate, and the reaction mixture was heated at steam bath temperature for 3 h. The solvent was then removed in vacuo to afford an oil which was taken up into hot ethyl acetate. Upon cooling 60 g (75%) of **5** resulted, identical in all respects with that produced as in (a) above. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.94; H, 4.53; N, 15.02.

2,3,5,6,7,8-Hexahydro-3,8-dioxoisoquinoline (6). A solution of 89.5 g (0.476 mol) of **5** in 4 L of 48% hydrobromic acid solution was refluxed for 16 h. The acid was removed in vacuo and the residue was taken up into 200 mL of water. After cooling the solution in an ice bath, sufficient 50% sodium hydroxide solution was cautiously added until the solution assumed a slightly basic pH. The solid which formed was collected and washed with several portions of water and, after drying, afforded 63.5 g (82%) of **6.** Recrystallization from aqueous acetone provided the pure material: mp 246–248 °C dec; UV (MeOH) 279 nm (ϵ 16 700), 221 (13 500); NMR (C_5D_5N) δ 1.96 (2 H, m), 2.57 (2 H, m), 2.92 (2 H, t), 5.50 (1 H, s, 4-H), 8.70 (1 H, s, 1-H). Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.93; H, 5.63; N, 8.59.

3-Methoxy-8-oxo-5,6,7,8-tetrahydroisoquinoline (7). To 63.5 g (0.5 mol) of **6** in 4 L of benzene was added 56.0 g (0.2 mol) of silver carbonate and 110.0 g (0.775 mol) of methyl iodide, and the heterogeneous reaction mixture was refluxed in the dark in an atmosphere of nitrogen for 5 h. The cooled reaction mixture was then filtered through a cake of diatomaceous earth which was washed with an additional portion of benzene. The filtrate was then extracted three times with 4 N hydrochloric acid solution, and the combined aqueous extracts were washed three times with chloroform. The acidic extracts were cooled before neutralization with 50% sodium hydroxide solution and the neutralized aqueous solution was extracted four times with ether. The combined extracts were washed with saturated salt solution and dried over sodium sulfate, and upon solvent removal an oil remained which crystallized upon standing at room temperature. Recrystallization from Skelly B gave 46.4 g (68%) of product. An additional recrystallization from Skelly B gave the analytical sample: mp 55.5–57 °C; UV (MeOH) 268 nm (ϵ 13 100); IR ($CDCl_3$) 5.92, 6.23, 7.80 μm; NMR ($CDCl_3$) δ 2.14 (2 H, m, 6-H's), 2.64 (2 H, br t, 7-H's), 2.91 (2 H, br t, 5-H's), 3.97 (3 H, s, $-OCH_3$), 6.56 (1 H, br s, 4-H), 8.83 (1 H, br s, 1-H). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 68.17; H, 6.48; N, 7.68.

3-Methoxy-5,6,7,8-tetrahydro-8-[(2-methyl-1,3-dioxocyclopent-2-yl)ethylidene]isoquinoline (9). To 10.0 g of **7** (0.057 mol) in 140 mL of xylene cooled to −20 °C in an atmosphere of nitrogen was added 45 mL of 2.85 M vinylmagnesium chloride in tetrahydrofuran (0.126 mol), diluted with 60 mL of xylene dropwise over a 45-min period. The reaction mixture was stirred at ca. −15 °C for an additional 90 min before addition of 100 mL of saturated ammonium chloride solution. After warming to room temperature the layers were separated, and the aqueous phase was extracted with an additional portion of ether. The combined extracts were washed with saturated ammonium chloride solution and then saturated salt solution and dried over sodium sulfate. To this solution was added 6.9 g (0.058 mol) of 2-methylcyclopenta-1,3-dione and 5.8 g (0.058 mol) of triethylamine, and it was then heated so as to remove the ether and tetrahy-

drofuran present. After removal of these lower boiling solvents, the reaction mixture was refluxed over a Dean-Stark trap for 16 h under an atmosphere of nitrogen. After cooling, 75 mL of 5% sodium hydroxide solution was added and after shaking the layers were separated. The aqueous phase was extracted with an additional portion of benzene and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. The dried solution was treated with activated charcoal and filtered before solvent removal in vacuo. The residual oil was taken up into ether and upon cooling 7.5 g (4) of product resulted: mp 79–80.5 °C; UV (MeOH) 262 nm (ϵ 13 000); IR ($CHCl_3$) 5.78, 6.20, 6.73 μm; NMR ($CDCl_3$) δ 1.17 (3 H, s, $-CH_3$), 2.73 (4 H, s, cyclopentyl CH_2's), 3.92 (3 H, s, $-OCH_3$), 5.72 (1 H, br t, vinyl H), 6.44 (1 H, br s, aromatic H), 8.25 (1 H, br s, aromatic H). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.25; H, 7.11; N, 4.74.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8,14-pentaen-17-one (10). To 15 g (0.079 mol) of tosyl acid monohydrate in 750 mL of dioxane was added 8.75 g (0.029 mol) of **9** in 1.5 L of xylene, and the reaction mixture was refluxed in an atmosphere of nitrogen for 3 h. To the cooled solution was added 200 mL of 5% sodium bicarbonate solution and the two layers were separated. The organic phase was washed three times with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave a deep red oil which upon trituration with acetone afforded 3.95 g (48%) of product. Recrystallization from acetone gave the pure compound: mp 167–169 °C dec; UV (MeOH) 298 nm (ϵ 28 000); NMR ($CDCl_3$) δ 1.14 (3 H, s, 18-CH_3), 3.93 (3 H, s, $-OCH_3$), 5.89 (1 H, t, J = 3 Hz, 15-H), 6.55 (1 H, br s, 4-H), 8.08 (1 H, br s, 1-H). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.14; H, 6.93; N, 5.04.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8,14-pentaen-17-ol (11). To 3.75 g (0.013 mol) of **10** in 125 mL of methanol was added 1.4 g of sodium borohydride in portions at room temperature. The reaction mixture was then stirred for 10 min before acetone was added to destroy the excess reducing agent. The volume of the solution was reduced to ca. 50 mL before addition of a small amount of water, and cooling afforded 3.9 g (97%) of yellow crystalline product (hydrate) in two crops. Recrystallization from aqueous acetone gave **11**: mp 130–136 °C; UV (MeOH) 300 nm (ϵ 28 000); NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-CH_3), 3.93 (3 H, s, $-OCH_3$), 5.56 (1 H, br t, 15-H), 6.57 (1 H, br s, 4-H), 8.10 (1 H, br s, 4-H). Anal. Calcd for $C_{18}H_{21}NO_2 \cdot H_2O$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.56; H, 7.51; N, 4.51.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8-tetraen-17-one (12). A solution of 0.678 g (0.0024 mol) of **10** in 100 mL of benzene was hydrogenated over a 70-mg portion of 5% $Pd/CaCO_3$ at room temperature and atmospheric pressure. After 1 equiv of hydrogen had been consumed, the catalyst was removed by filtration and the solvent removed from the filtrate. Recrystallization of the residue from methanol gave 0.519 g (77%) of product in two crops: mp 146–149.5 °C; UV (MeOH) 267 nm (ϵ 18 000); NMR ($CDCl_3$) δ 0.90 (3 H, s, 18-CH_3), 3.92 (3 H, s, $-OCH_3$), 6.57 (1 H, br s, 4-H), 7.97 (1 H, br s, 4-H). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.62; H, 7.59; N, 4.96.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8-tetraen-17-ol (13). A solution of 3.85 g (0.0135 mol) of **11** in 150 mL of benzene was hydrogenated over 1.5 g of 5% $Pd–CaCO_3$ at atmospheric pressure. After the theoretical amount of hydrogen had been consumed, the catalyst was removed by filtration and the filtrate was reduced in volume. Upon cooling, 2.35 g of analytically pure product resulted: mp 155–157.5 °C; UV (MeOH) 267 nm (ϵ 18 200); NMR ($CDCl_3$) δ 0.79 (3 H, s, 18-CH_3), 3.93 (3 H, s, $-OCH_3$), 6.52 (1 H, br s, 4-H), 7.97 (1 H, br s, 1-H). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.81; H, 8.31; N, 4.87.

The catalyst was then washed with chloroform and from these washes 1.1 g of additional product (90% total yield) was obtained whose purity was suitable for the subsequent reduction and whose NMR spectrum indicated only the presence of the 14α isomer. The mother liquors of the crystallized material indicated a preponderance of the 14β isomer by the presence of an 18-methyl resonance at 1.02 ppm.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8-tetraen-17-ol (13) from 12. To 0.50 g (0.0017 mol) of **12** in 25 mL of methanol and 5 mL of water was added 0.25 g of sodium borohydride in portions. After addition the reaction mixture was stirred at room temperature for 15 min. Acetone was added to destroy the excess reducing agent and the volume of the solution was reduced to ca. 10 mL. Water was then added which caused formation of an oil which solidified upon continued stirring and was collected, providing 0.436 g (87%) of product. Recrystallization from acetone gave material identical with that obtained by hydrogenation of **11**: mp 155.5–158 °C. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.96; H, 8.19; N, 5.00.

(±)-2-Azaestradiol 3-Methyl Ether (15). To 40 mL of distilled ammonia cooled to ca. −70 °C under an atmosphere of nitrogen was added 0.40 g (0.0014 mol) of **13** in 25 mL of tetrahydrofuran, followed by 0.40 g of sodium metal previously cut into small pieces. After 90 min an additional 0.15-g portion of sodium metal was added and stirring continued for 45 min at the above temperature before addition of 4 g of ammonium chloride portionwise. The reaction mixture was allowed to warm to room temperature, ether was added to the heterogeneous mixture, the organic phase was decanted from the inorganic salts present, and the solvent was removed in vacuo. The resultant oily residue (containing a preponderance of **14**) was taken up into 20 mL of benzene and 10 mL of acetone, and the solution was cooled to ca. −10 °C before addition of 0.32 g (0.0014 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in portions. After addition, the temperature was allowed to rise to 10 °C where it was maintained for 40 min. To the reaction mixture was then added 50 mL of 10% sodium bisulfate solution. After shaking, the layers were separated and the aqueous phase was extracted with two additional portions of ether. The combined extracts were washed three times with 5% sodium hydroxide solution and three times with saturated salt solution and dried over sodium sulfate. After decanting the solution from the drying agent a portion of Skelly B was added and the solution was filtered through a cake of diatomaceous earth. Solvent removal in vacuo gave an oil which upon trituration with methanol gave 120 mg of crude product (30%). Recrystallization from methanol gave **15**: mp 153–156 °C; UV (MeOH) 276 nm (ϵ 3700); NMR ($CDCl_3$) δ 0.78 (3 H, s, 18-CH_3), 3.90 (3 H, s, $-OCH_3$), 6.44 (1 H, br s, 4-H), 8.03 (1 H, br s, 1-H). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.07; H, 8.66; N, 4.72.

***N,N*-Dimethyl-*N*-[2-(5,6,7,8-tetrahydro-8-hydroxy-3-methoxyisoquinol-9-yl)prop-2-en-1-yl]amine (18).** To 179.4 g (1.10 mol) of 2-bromo-3-dimethylamino-1-propene in 2 L of toluene cooled to ca. −40 °C under an atmosphere of nitrogen was added dropwise 1.0 mol of *n*-butyllithium in hexane over a 20-min period. After 30 min of stirring, a solution of 62.0 g (0.35 mol) of **7** in 300 mL of toluene was added to the reaction mixture at a rate so as to maintain a temperature below −30 °C during the addition. After stirring the reaction mixture between −20 and −30 °C for 30 min, saturated ammonium chloride solution was added, and the layers were separated. The organic phase was washed with an additional portion of saturated ammonium chloride solution and then water before extracting five times with 5% aqueous formic acid solution. The combined acidic extracts were washed with benzene–ether (1:1) and then cooled in an ice bath before basifying the solution with concentrated ammonium hydroxide solution. The heterogeneous solution was then extracted five times with ether–benzene (1:1), and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave 61.2 g (67%) of a brown oil which was suitable for utilization in the subsequent step. An analytical sample was prepared by dissolving a portion of the oil into ether, adding Skelly B until the solution became turbid, and filtering through a cake of diatomaceous earth. After concentrating the filtrate, additional Skelly B was added until the solution again became turbid and was filtered as above. Concentrating the filtrate and cooling provided the pure material: mp 66–68 °C; UV (MeOH) 276 nm (ϵ 3900); NMR ($CDCl_3$) δ 2.35 (6 H, s, NCH_3's), 3.92 (3 H, s, $-OCH_3$), 4.38 (1 H, d, J = 1 Hz, vinyl H), 5.02 (1 H, br s, vinyl H), 6.43 (1 H, br s, 4-H), 8.25 (1 H, br s, 1-H). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.70; H, 8.51; N, 10.84.

***N,N*-Dimethyl-*N*-[2-(5,6-dihydro-3-methoxyisoquinol-8-yl)prop-2-en-1-yl]amine (19).** To 7.1 g (0.027 mol) of **18** in 35 mL of benzene containing 35 mL of pyridine was added dropwise at room temperature 4.5 g (0.029 mol) of phosphorus oxychloride. After stirring at ambient temperature for 4 h, the reaction mixture was cooled in an ice bath before the cautious addition of 25 mL of water. Sufficient 5% sodium hydroxide solution was then added to raise the pH of the aqueous solution to 10, and after addition of ether the layers were separated. The aqueous phase was extracted with two additional portions of ether, and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. An equivalent volume of Skelly B was added to the solution before treating it with activated charcoal and filtering the solution through a cake of diatomaceous earth. Solvent removal in vacuo gave a yellow oil which crystallized upon standing to provide 4.3 g (65%) of product suitable for quaternization. An analytical sample was prepared by subliming a small portion of the oily solid and recrystallizing the sublimate from aqueous methanol: mp 42–45 °C; UV (MeOH) 262 nm (ϵ 12 900); NMR ($CDCl_3$) δ 2.23 (6 H, s, NCH_3's), 3.10 (2 H, br s, NCH_2), 3.83 (3

H, s, $-OCH_3$), 5.30 (2 H, br m, $=CH_2$), 5.95 (1 H, t, =CH), 6.56 (1 H, br s, 4-H), 7.96 (1 H, br s, 1-H). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.66; H, 8.31; N, 11.64.

***N,N,N*-Trimethyl-*N*-[2-(5,6-dihydro-3-methoxyisoquinol-8-yl)prop-2-en-1-yl]ammonium Iodide (20a).** To 4.3 g (0.018 mol) of crude **19** in 100 mL of benzene was added 10 mL of methyl iodide, and the solution was let stand at room temperature for 3.5 h. The precipitate which formed was collected, washed with additional benzene, and dried, providing 5.9 g (87%) of **20a.** Recrystallization from acetone–ethyl acetate provided the analytical sample: mp 165–169 °C dec; UV (MeOH) 263 nm (12 900); NMR ($CDCl_3$) δ 3.47 (9 H, s, NCH_3's), 3.93 (3 H, s, $-OCH_3$), 4.67 (2 H, br s, NCH_2), 5.88 (1 H, br s, $=CH_2$), 6.22 (1 H, br s, $=CH_2$), 6.35 (1 H, t, =CH), 6.62 (1 H, br s, 4-H), 7.87 (1 H, br s, 1-H). Anal. Calcd for $C_{16}H_{23}N_2OI$: C, 49.75; H, 6.00; N, 7.25. Found: C, 49.81; H, 6.04; N, 6.97.

5,6-Dihydro-3-methoxy-8-[3-(2-methyl-1,3-dioxocyclopent-2-yl)prop-1-en-2-yl]isoquinoline (21) via the Ammonium Hydroxide 20b. To 5.8 g (0.015 mol) of **20a** in 80 mL of methanol and 20 mL of water was added 1.9 g (0.0082 mol) of silver oxide, and the reaction mixture was stirred for 1 h at room temperature in the dark. The solution was filtered through diatomaceous earth before addition of 2.0 g (0.018 mol) of 2-methylcyclopenta-1,3-dione and solvent removal in vacuo with a bath temperature of ca. 50 °C. The resultant oily residue was taken up into 25 mL of dioxane and 150 mL of xylene, and 4 mL of triethylamine was added. The reaction mixture was heated until the solution reached a temperature of ca. 125 °C before addition of a condenser to the reaction flask. After refluxing overnight under an atmosphere of nitrogen, 5% sodium hydroxide solution was added to the cooled reaction mixture, and the layers were separated. The organic phase was washed with saturated salt solution before extracting three times with 2.5% aqueous formic acid solution. The aqueous extracts were washed with three portions of benzene, these were combined with the earlier organic phase, and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo afforded an oil which crystallized upon standing to provide 3.55 g (75%) of **21** which was recrystallized from acetone; mp 102–106 °C; UV (MeOH) 261 nm (ϵ 12 200); NMR ($CDCl_3$) δ 1.08 (3 H, s, 18-CH_3), 2.68 (4 H, s, cyclopentyl CH_2's), 2.75 (2 H, s, 12-CH_2), 3.95 (3 H, s, $-OCH_3$), 5.13 (2 H, m, $=CH_2$), 5.74 (1 H, t, =CH), 6.59 (1 H, br s, 4-H), 7.84 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.06; H, 6.61; N, 4.40.

21 via the Ammonium Iodide 20a. To 0.75 g (0.00625 mol) of 2-methylcyclopenta-1,3-dione in 20 mL of dimethylformamide was added 1.0 g (0.010 mol) of triethylamine, and the reaction mixture was heated to ca. 50 °C in an atmosphere of nitrogen before addition of 1.9 g (0.0005 mol) of **20a.** After heating the homogeneous solution at ca. 135 °C for 5 h, it was allowed to cool and the solvent was removed in vacuo. The residual oil was taken up into water–ether, the pH of the aqueous phase was adjusted to pH 10 with 5% sodium hydroxide solution, and the layers were separated. The aqueous phase was extracted with two additional portions of ether, and the combined extracts were then extracted three times with 2.5% aqueous formic acid solution and once with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which was taken up into a small amount of ether and Skelly B was added until the solution became turbid. After treating with activated charcoal and filtering through a cake of diatomaceous earth, solvent removal gave 0.3 g (<20%) of an oil which crystallized upon standing. Recrystallization from aqueous acetone afforded **21** identical in all respects with the product obtained in the previous reaction.

(±)-3-Methoxy-11-methyl-2-azaestra-1,3,5(10),8(14),9(11),-15-hexaen-17-one (23). To 40 mL of concentrated sulfuric acid cooled to 0–5 °C was added 2.4 g (0.0077 mol) of **21** in portions with the reaction temperature kept below 10 °C during the addition. After addition, the cooling bath was removed and the reaction mixture was allowed to assume room temperature over a 20-min period. The solution was then cautiously added to ca. 100 mL of water cooled in an ice bath and the aqueous solution was basified with concentrated ammonium hydroxide to afford 2.1 g (93%) of solid collected by filtration. Recrystallization from acetone gave **23:** mp 197–198.5 °C; UV (MeOH) 244 nm (ϵ 19 000), 280 (15 500), 372 (8200); NMR ($CDCl_3$) δ 1.12 (3 H, s, 18-CH_3), 2.17 (3 H, br s, 11-CH_3), 3.97 (3 H, s, $-OCH_3$), 6.20 (1 H, d, J = 5.5 Hz, 16-H), 6.62 (1 H, br s, 4-H), 7.97 (1 H, d, J = 5.5 Hz, 15-H), 8.18 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78. Found: C, 77.98; H, 6.66; N, 4.73.

(±)-3-Methoxy-11-methyl-2-azaestra-1,3,5(10),8(14),9(11),-15-hexaen-17-ol (24). To 2.1 g (0.0072 mol) of **23** suspended in 75 mL of benzene and 50 mL of ether cooled to ca. 0 °C under an atmosphere of nitrogen was added 12 g (0.017 mol) of a 20% solution of diisobutylaluminum hydride in toluene over a 10-min period. The reaction mixture was stirred at the above temperature for 15 min before destroying the excess reducing agent with a small amount of 2-propanol. Water was then added, followed by sufficient 1 N hydrochloric acid solution so that the pH of the aqueous solution was adjusted to 6.5–7. The two phases were separated and the aqueous phase was extracted three times with ether–benzene (1:1) and once with chloroform. The combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which upon trituration with alcohol afforded 2.0 g (95%) of solid product. Recrystallization from ethanol gave **24** as the solvate: mp 95–100 °C; UV (MeOH) 257 nm (ϵ 30 700), 263 (29 700); NMR ($CDCl_3$ δ 0.80 (3 H, s, 18-CH_3), 2.15 (3 H, br s, 11-CH_3), 3.97 (3 H, s, $-OCH_3$), 4.40 (1 H, m, 17-H), 6.07 (1 H, m, 16-H), 6.48 (1 H, d, 15-H), 6.60 (1 H, br s, 4-H), 8.18 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{21}NO_2 \cdot C_2H_5OH$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.82; H, 8.08; N, 4.12.

(±)-3-Methoxy-11-methyl-2-azaestra-1,3,5(10),8(14),9(11)-pentaen-17-ol (25). A solution of 1.0 g (0.0034 mol) of **24** in 200 mL of benzene was hydrogenated over a 0.5-g portion of 5% $Pd/CaCO_3$ at room temperature and atmospheric pressure. After two-thirds of an equivalent of hydrogen had been consumed uptake ceased. An NMR spectrum of an aliquot taken from the reaction mixture after this time indicated an absence of vinyl protons. The catalyst was removed by filtration and the solvent removed from the filtrate. Recrystallization of the residue from ethanol gave 0.62 g (62%) of **25** in two crops as the solvate: mp 93–100 °C; UV (MeOH) 242 nm (ϵ 21 900), 247 (20 900), 291 (6700); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 2.03 (3 H, br s, 11-CH_3), 2.25 (2 H, br s, 12-CH_2), 3.93 (3 H, s, $-OCH_3$), 6.54 (1 H, br s, 4-H), 8.13 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{23}NO_2 \cdot C_2H_5OH$: C, 73,43; H, 8.51; N, 4.08. Found: C, 73.54; H, 8.64; N, 4.10.

(±)-3-Methoxy-11β-methyl-2-azaestra-1,3,5(10),8-tetraen-17-ol (26). A solution of 3.7 g (0.017 mol) of **25** in 100 mL of ethanol was hydrogenated over a 1.8-g portion of 5% Pd/Al_2O_3 at room temperature and atmospheric pressure. After an equivalent of hydrogen had been consumed, the catalyst was removed by filtration and the solvent removed from the filtrate. The residual oil was taken up into methanol and gave 2.65 g (72%) of product in two crops: mp (after drying) 164–167.5 °C; UV (MeOH) 267 nm (ϵ 16 400); NMR ($CDCl_3$) δ 0.93 (3 H, s, 18-CH_3), 1.25 (3 H, d, J = 7.5 Hz, 11-CH_3), 3.93 (3 H, s, $-OCH_3$), 6.55 (1 H, br s, 4-H), 7.95 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{25}NO_2 \cdot CH_3OH$: C, 72.47; H, 8.82; N, 4.47. Found: C, 72.64; H, 8.75; N, 4.17.

(±)-3-Methoxy-11-methyl-2-azaestra-2,5(10)-dien-17-ol (27). To ca. 225 mL of freshly distilled liquid ammonia cooled to −70 °C under an atmosphere of nitrogen was added in portions 1.5 g (0.065 mol) of sodium metal previously cut into small pieces. After stirring the blue solution for 20 min, 2.3 g (0.0077 mol) of **26** in 100 mL of tetrahydrofuran was added dropwise over a 15-min period. The reaction mixture was stirred at the above temperature for 30 min after addition before 10 g of ammonium chloride was added portionwise, and the reaction mixture was allowed to reach ca. −33 °C, at which temperature the ammonia evaporated out of the solution. Ether was then added to the residual solution, followed by saturated sodium chloride solution, and the layers were separated. The organic phase was washed with additional saturated salt solution and dried over sodium sulfate. Solvent removal gave ca. 2.3 g of yellow oil whose NMR spectrum indicated a large amount of resonance centered around 3.8 ppm, attributed to the presence of the C-1 and C-4 methylene groups of **27.** In addition, the oil exhibited no aromatic protons and possessed no UV absorption at 267 (**26**) or 278 nm (**28**). This material was used for the subsequent reaction without purification.

(±)-3-Methoxy-11β-methyl-2-azaestra-1,3,5(10)-trien-17-ol (28) and (±)-9-Hydroxy-3-methoxy-11-methyl-2-azaestra-1,3,5(10)-trien-17-ol (29). To the crude oil **27** in 25 mL of acetone and 25 mL of benzene at room temperature was added dropwise over a 5-min period 2.3 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.01 mol) in 10 mL of acetone and 10 mL of benzene. The reaction mixture was stirred at the above temperature for 15 min before 25 mL of saturated sodium bisulfite solution was added, followed by sufficient ether so as to form two layers. After separating, the aqueous phase was extracted with an additional portion of ether, and the combined extracts were washed once with saturated sodium bisulfite solution, three times with 5% sodium hydroxide solution, and three times with saturated sodium chloride solution. The solution was then dried over sodium sulfate and filtered through a cake of diatomaceous earth. Solvent removal in vacuo gave ca. 1.5 g of an oil which upon trituration with ether–methanol gave 0.5 g of **28.** Recrystallization from methanol–water gave the pure material: mp 168–169 °C; UV

(MeOH) 278 nm (ε 3760); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 0.93 (3 H, d, J = 7 Hz, 11-CH_3), 3.90 (3 H, s, -OCH_3), 6.42 (14, br s, 4-H), 7.95 (1 H, s, 1-H). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.95; H, 9.09; N, 4.51.

The mother liquors from the trituration above were chromatographed over silica gel using benzene–ethyl acetate solution as the eluent. Additional **28** was obtained, eluting with 2% ethyl acetate–benzene solution, and provided another 0.14 g after recrystallization from aqueous alcohol. Upon eluting with ethyl acetate (neat) 0.15 g of **29** was obtained. Recrystallization from ethyl acetate provided the pure compound: mp 181–185 °C; UV (MeOH) 275 nm (ε 3650); NMR ($CDCl_3$) δ 0.89 (3 H, s, 18-CH_3), 0.94 (3 H, d, J = 7 Hz, 11-CH_3), 3.90 (3 H, s, -OCH_3), 6.48 (1 H, br s, 4-H), 8.25 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.75; H, 8.52; N, 4.39.

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Registry No.—**1**, 30182-67-3; **2**, 5682-75-7; **3a**, 64761-52-0; **3b**, 64761-53-1; **3c**, 64761-55-3; **5** (X = CN), 56053-56-6; **6**, 56053-57-7; **7**, 65053-58-8; **9**, 56053-60-2; **10**, 56053-61-3; **11**, 64761-51-9; **12**, 56053-64-6; **13** (14α isomer), 64811-74-1; **13** (14β isomer), 64811-75-2; **14**, 64761-54-2; **15**, 64811-76-3; **18**, 58653-16-0; **19**, 58653-17-1; **20a**, 58653-18-2; **20b**, 64761-56-4; **21**, 58653-19-3; **23**, 58653-20-6; **24**, 64761-57-5; **25**, 64761-58-6; **26**, 64811-77-4; **27**, 64811-78-5; **28**, 64811-79-6; **29**, 64761-59-7; diethyl malonate, 105-53-3; methyl cyanoacetate, 105-34-0; cyanoacetimide, 107-91-5; dimethylformamide diethyl acetal, 1188-33-6; triethyl orthoformate, 122-51-0; methyl iodide, 74-88-4; benzyl chloride, 75-01-4; 2-methyl-cyclopenta-1,3-dione, 765-69-5; 2-bromo-3-dimethylamino-1-propene, 14326-14-8.

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cis-4,4′-Stilbenediols. Synthesis from Dienestrol, Structure, and Photocyclization to Dihydrophenanthrenes

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Diels–Alder cycloaddition reactions between dienestrol or its diacetate and dienophiles maleic anhydride, 4-phenyl-1,2,4-triazoline-3,5-dione, dimethyl maleate, 1,4-naphthoquinone, and tetracyanoethylene yielded adducts representing 4,4′-stilbenediols with obligate cis configuration. These compounds are ideally suited for studying the photochemical conversion of stilbene-like molecules to dihydrophenanthrenes without intereference from the *trans*-stilbene isomers. The structures and stereochemistry of the Diels–Alder adducts were established by detailed interpretation of their NMR and mass spectra. UV irradiation of the synthesized *cis*-stilbenes caused photocyclization to the respective 4a,4b-dihydrophenanthrenes without interfering side reactions and with quantum yields in excess of 0.85.

The photooxidative ring closure of stilbenes to phenanthrenes proceeds through nonoxidized 4a,4b-dihydrophenanthrene (DHP) intermediates.[1] Most previous studies of the mechanism of the photocyclization step have been complicated by simultaneous cis–trans isomerization of starting stilbene, by rapid subsequent oxidation of DHP to phenanthrene, or by reverse ring opening of DHP to *cis*-stilbene. Naef and Fischer[2a] circumvented the cis–trans complication by use of precursor stilbenes[2b,c] constrained to cis conformation by their cyclic structures. These authors also eliminated subsequent oxidation to phenanthrenes by rigorous degassing or by substitution of methyl for hydrogen at the appropriate sites. However, thermal and photochemical ring opening of the DHP's remained a complication; the intermediates could not be isolated, but were observed only in situ in photoequilibrium with precursor stilbenes.

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