tense reflections to 1/25, together with the removal of the ($\bar{1}$22) and (102) because of extinction afforded $R_1 = 0.042$ and $R_2 = 0.045$. The addition of the five hydrogen atoms in calculated positions (the C–H bond length was assumed to be 1.00 Å) and further anisotropic refinement gave final values of $R_1 = 0.032$ and $R_2 = 0.034$. Unobserved reflections were not included. The largest parameter shifts in the final cycle of refinement were less than 0.01 of their estimated standard deviations. The value of the standard deviation of an observation of unit weight was 0.91. A final difference Fourier map showed no peak larger than 0.2 e/Å^3. The final values of the positional and thermal parameters are given in the microfilm supplement.[19]

Registry No.—**12a,** 28735-23-1; **12b,** 59318-39-7; **12c,** 28735-26-4; **12d,** 19542-09-7; **12e,** 28735-29-7; **12f,** 59318-40-0; **12g,** 59318-41-1; **12h,** 59318-42-2.

Supplementary Material Available. A listing of the crystal data, final fractional coordinates, and anisotropic structure factors (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) M. Tisler, *Synthesis*, 123 (1973).
(2) J. H. Boyer and H. W. Hyde, *J. Org. Chem.*, **25**, 458 (1960).
(3) B. Stanovnik and M. Tisler, *Chimia*, **24**, 272 (1971).
(4) T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron*, **27**, 5121 (1971).
(5) C. Wentrup, *Tetrahedron*, **26**, 4969 (1970).
(6) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **30**, 829 (1965).
(7) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **30**, 826 (1965).
(8) J. Kobe, B. Stanovnik, and M. Tisler, *Montash. Chem.*, **101**, 724 (1970).
(9) W. W. Paudler and J. Lee, *J. Org. Chem.*, **36**, 3923 (1971).
(10) M. F. G. Stevens, *J. Chem. So, Perkin Trans. 1*, 1221 (1972).
(11) A. Messmer, G. Hajos, P. Benko, and L. Pallos, *J. Heterocycl. Chem.*, **10**, 575 (1973).
(12) J. L. Atwood and K. D. Smith, *J. Am. Chem. Soc.*, **95**, 1488 (1973).
(13) D. J. Hodgson's version of Dellaca and Robinson's FOURIER Program, as locally implemented for the UNIVAC 1110, University of Alabama.
(14) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFLS, a Fortran Crystallographic Least-Squares Program," Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1964.
(15) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965).
(16) "International Tables for X-Ray Crystallography", Vol. III, Kynoch Press, Birmingham, England, 1962, p 202.
(17) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFFE, a Fortran Crystallographic Function and Error Program", Report ORNL-TM-306, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1964.
(18) C. K. Johnson, "ORTEP, a Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations", Report ORNL-3794, Revised, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(19) See paragraph at end of paper regarding supplementary material.

Synthesis of 2-Azaestratrienes

Robert J. Chorvat* and Raphael Pappo

Searle Laboratories, A Division of G. D. Searle and Company, P.O. Box 5110, Chicago, Illinois 60680

Received March 25, 1976

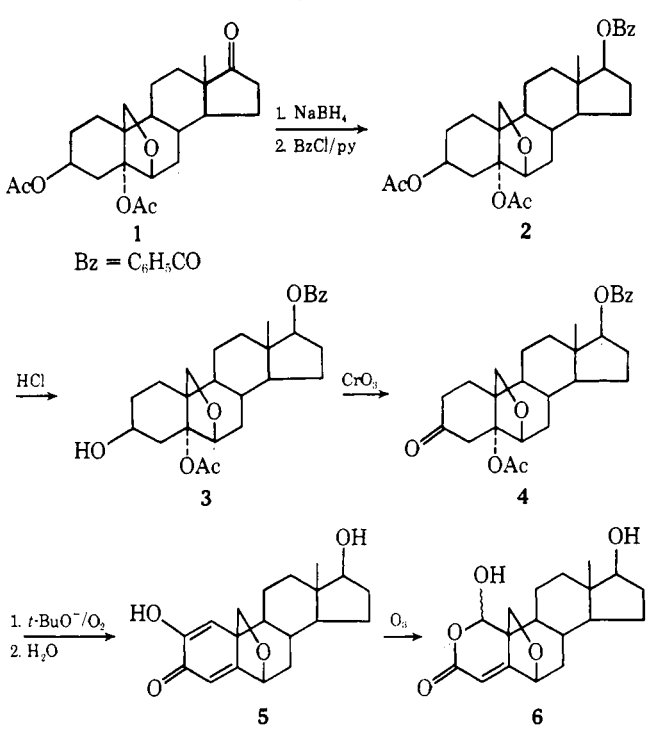
From readily available 3β,5α-dihydroxy-6β,19-oxidoandrostan-17-one 3,5-diacetate (**1**) a facile synthesis of 1,17-dihydroxy-6β,19-oxido-2-oxaandrost-4-en-3-one (**6**) was developed. The key step in this sequence was the regioselective ozonolysis of the bridged, unsaturated α-diketone **5** to the bridged lactol **6** in good yield. This cyclic acid aldehyde **6** was utilized for the preparation of 3-methoxy- and 1,3-dimethoxy-2-azaestratrienes. The 17α-ethynyl-17β-hydroxy derivatives of the 3-methoxy- as well as the 3-cyclopentoxy-2-azaestratrienes were prepared via an alternate pathway from 2-oxaestra-5(10)-ene-3,17-dione (**17**). While these series were devoid of hormonal activity they manifested hypolipemic as well as antiviral properties.

In an earlier communication[1] we had reported the syntheses of several series of 2-aza steroids. This study was an extension of work aimed at determining the effect on biological activity of a heteroatom at the 2 position of the steroid nucleus.[2] In this paper we wish to report in greater detail our investigations into the synthesis of 2-azaestratrienes, the thrust of which has been provided by the interesting biological profile of the 3-methyl ether series (vide infra). Thus, the structural modifications made at the 1 and 3 positions of the aromatic nucleus were attempts to enhance the observed biological properties of this series.

Our initial approach to the 2-aza analogue of estradiol-3-methyl ether utilized the readily available 3β,5α-dihydroxy-6β,19-oxidoandrostan-17-one 3,5-diacetate (**1**)[3] which was converted to the 17-benzoate derivative **2** by treatment with sodium borohydride in methanol[4] and subsequent benzoylation with benzoyl chloride in pyridine, in 85% yield from **1** (Scheme I). Selective hydrolysis of the 3-acetate was accomplished with anhydrous hydrogen chloride in methanol at room temperature providing **3** in 95% yield. Subsequent oxidation of the bridged alcohol **3** with Jones reagent[5] afforded the keto diester **4** in 93% yield.

Following the procedure of Hanna and Ourisson,[6] this material was oxygenated subsequent to the in situ elimination of the 5-acetoxy group by *tert*-butoxide. The conjugated system thus formed enabled oxygenation to occur exclusively at the 2 position generating the bridged α-diketone **5** in yields

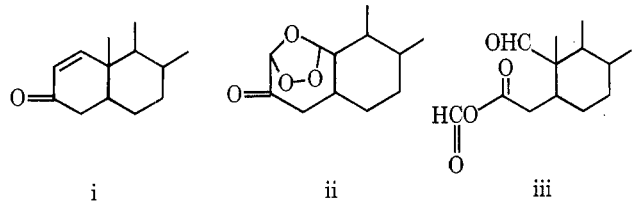
Scheme I



up to 70% after subsequent hydrolysis of the 17-benzoate group.[7] The highly enolic character of this material is demonstrated by the presence of the two vinylic protons of the C-1 and C-4 carbon atoms appearing as singlets in its NMR spectrum at δ 6.23 and 6.27 ppm. It was the enolic character of this compound which enabled its facile conversion to the desired lactol by the method described (vide infra).

On the basis of the work by Hanna and Ourisson,[6] we had originally expected that this α-diketone **5** would provide the bridged lactol **6** upon further oxygenation and this intermediate would readily be converted to the A-ring lactam which we desired. However, further treatment of **5** with base in the presence of oxygen afforded only low yields of the desired product **6**. An investigation of alternate methods for this transformation led to the discovery that ozonolysis of **5** in ethyl acetate at −70 °C followed by warming to room temperature caused rearrangement of the intermediate ozone adduct giving the desired lactol **6** in 60% yield.

This conversion of **5** to **6** via ozone was based on an earlier observation made in these laboratories.[8] It had been found that the ozonide ii of 17β-hydroxy-17α-methyl-5α-androst-1-en-3-one (i) gave the mixed anhydride iii upon warming to



i ii iii

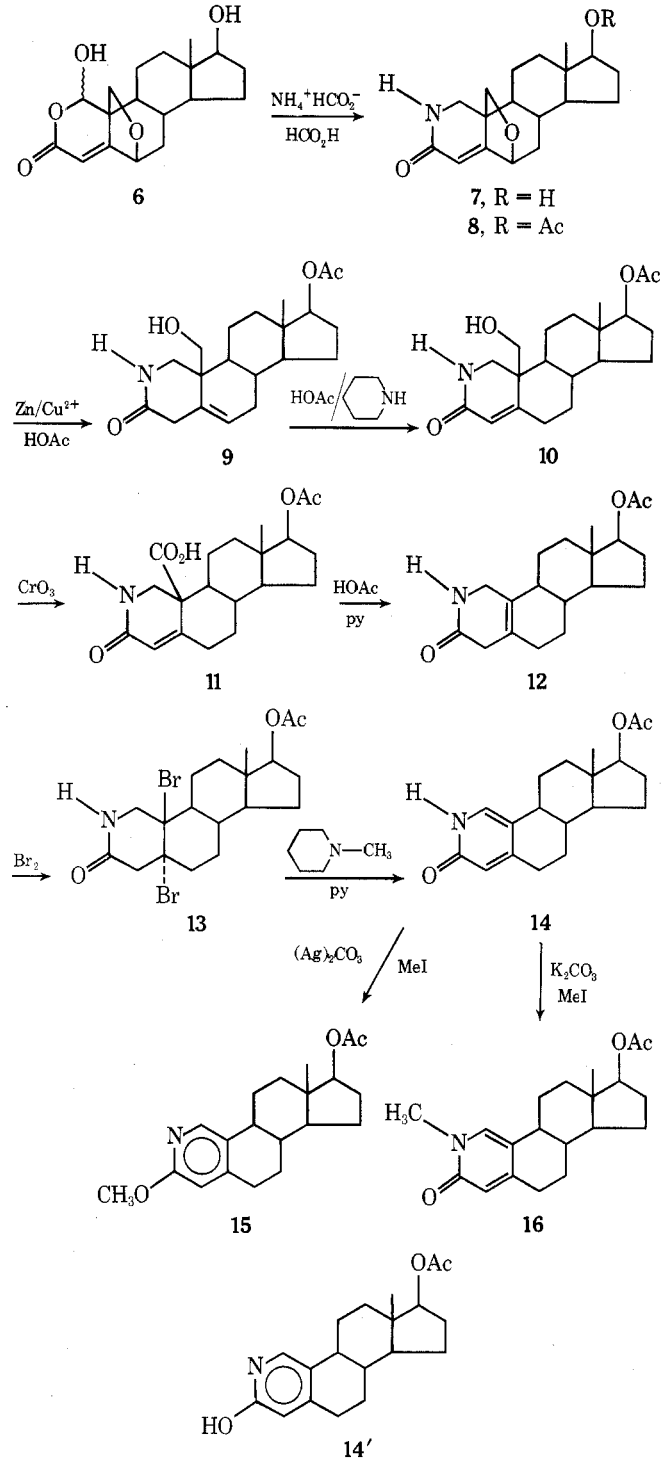
room temperature. This transformation must obviously proceed through a Baeyer–Villiger type rearrangement of the intermediate ozonide ii. On the basis of this mechanism compound **5** must also form an ozonide which rearranges to the mixed anhydride of carbonic acid which in turn spontaneously liberates carbon dioxide to form compound **6**.

We attribute the regioselectivity of ozone for the 1,2 double bond of **5** to the steric shielding of the β face of the 4,5 double bond by the bridged ether, as well as activation of the 1,2 double bond by the 2-hydroxyl group. Experiments in our laboratories and by other investigators[9,10] have demonstrated that ozonolysis of 1,4-diene systems results in a mixture of products due to the indiscriminant attack of the ozone on both double bonds.

Introduction of nitrogen into the steroid ring system was accomplished by treating **6** with ammonium formate and formic acid with no apparent reduction of the conjugated double bond (Scheme II).[11] Thus, Leukart treatment of **6** followed by saponification of the 17-formyloxy substituent gave the A-ring lactam **7** in 50% yield. Acetylation of this bridged lactam **7** in acetic anhydride and pyridine afforded the 17-acetoxy derivative **8** which underwent smooth cleavage of the ethereal bridge with zinc–copper couple in aqueous alcoholic acetic acid solution to provide the 19-hydroxy-Δ^5-lactam **9**. This compound was then isomerized to the conjugated lactam **10** in refluxing acetic acid–piperidine solution in high yield. The conversion of 17,19-dihydroxy-2-azaandrost-4-en-3-one 17-acetate (**10**) to the 19-nor system was accomplished by the methods described in the 2-oxa series.[2d] Oxidation of the alcohol **10** with Jones reagent[5] gave the 10-carboxy derivative **11** which was not purified but rather decarboxylated in pyridine–acetic acid solution to afford the $\Delta^{5(10)}$-lactam **12** in 63% yield from **10**.

The construction of the A-ring pyridone was achieved by bromination of **12** in chloroform which gave the 5,10-dibromo compound **13**.[12] Dehydrobromination with *N*-methylpiperidine produced **14**, exclusive of the cross-conjugated $\Delta^{4,9(10)}$-diene as evinced by spectral data indicative of the A-ring pyridone. The uv spectrum of **14** exhibited λ_{max} at 305 and 231

Scheme II



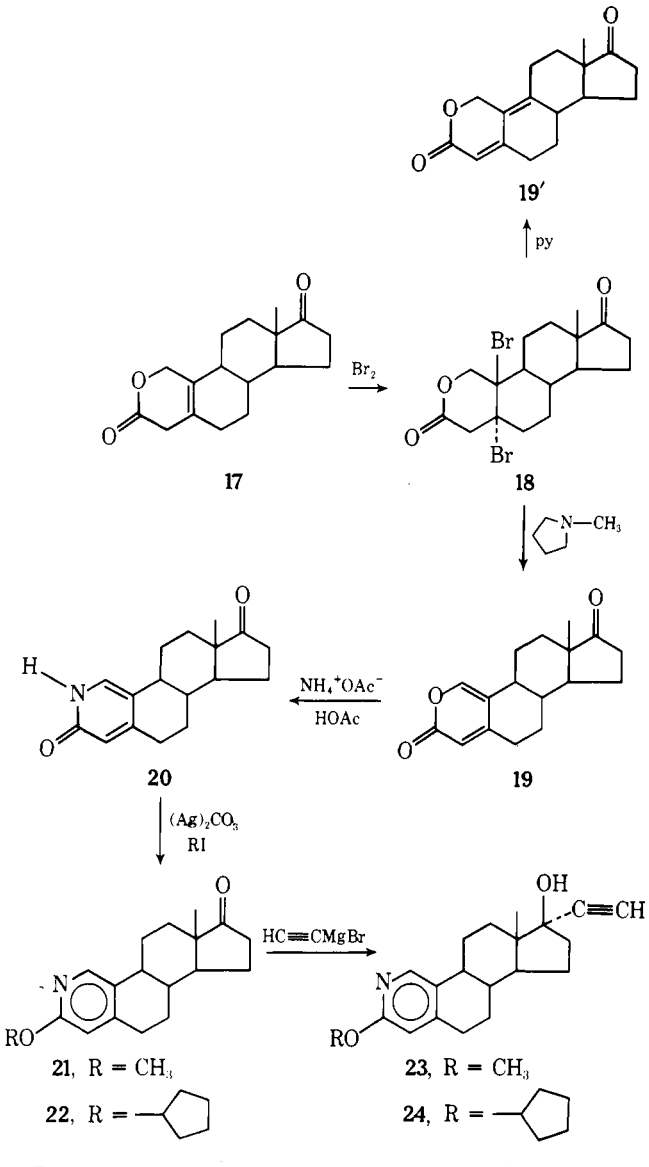
nm (ϵ 5500 and 7900),[13] and the NMR spectrum of **14** exhibited the aromatic protons of the C-1 and C-4 carbon atoms at 8.00 and 7.13 ppm. This compound was of particular interest since its tautomeric form **14′** is the aza analogue of estradiol 17-acetate. However, it has been established that the pyridone form predominates over the pyridinol form by several orders of magnitude[14] and it is perhaps for this reason these A-ring pyridones lack any estrogen-like hormonal activity.

O-Alkylation of the silver salt of **14** with methyl iodide in benzene[15] afforded 2-azaestradiol-3-methyl ether 17-acetate (**15**) in a good yield. The *N*-methyl analogue **16**, which was also formed but to a much lesser degree under these conditions, could be synthesized in high yield by alkylation of **14** with methyl iodide in dimethylformamide in the presence of potassium carbonate.[15] These isomers are readily distinguished

by the position of their A-ring methyl group resonances in their NMR spectrum (O isomer, δ 3.88 ppm; N isomer, δ 3.52 ppm).

Since the 17α-ethynyl-17β-hydroxyl derivatives of 19-nor steroids have been found to possess the greatest amount of oral estrogenic activity,[16] this derivative of the above series as well as that of 2-azaestradiol-3-cyclopentyl ether was synthesized. To obtain the necessary 17-keto-A-ring pyridone precursor **20**, an alternate synthesis was employed utilizing an intermediate available from our previous work on the synthesis of 2-oxa steroids[1d] (Scheme III).

Scheme III



Bromination of 2-oxaestra-5(10)-ene-3,17-dione (**17**) in chloroform at ca. −25 °C afforded the dibromolactone **18**[12] which was not purified but rather treated with *N*-methylpyrrolidine in benzene to yield the α-pyrone **19** in ca. 65% yield from **17**. The generation of the A-ring pyrone from the 5,10-dibromolactone **18** with tertiary amine contrasted with our earlier work in this series. We had previously found that the $\Delta^{9(10)}$ isomer **19′** was the major elimination product when **18** was dehydrohalogenated with pyridine as the base. This type of dienone was also the reported product in the carbocyclic series when the $\Delta^{5(10)}$ ketone was brominated in pyridine.[17] It is conceivable that the preponderant product in each of these reactions is a reflection of different elimination mechanisms (E_1 vs. E_2)[18] and of the different steric requirements of the bases used. However, we have not studied this elimination in any detail to be more definitive about these observations.

Subsequent treatment of **19** with ammonium acetate in acetic acid gave the 17-keto-α-pyridone steroid **20** in moderate yield. Alkylation of the silver salt of **20** with either methyl iodide or cyclopentyl iodide, as previously described, afforded the 3-methoxy or 3-cyclopentoxy steroidal pyridines, **21** and **22**, respectively. Reaction of these compounds with ethynylmagnesium bromide, generated from acetylene and ethyl Grignard, yielded the 17α-ethynyl-17β-hydroxy derivatives **23** and **24**, respectively.[19]

In an effort to determine the effect an additional methoxyl group at the 1 position would have on biological activity, the 1,3-dimethoxy-2-azaestratrienes were also prepared (Scheme IV). Thus, again utilizing the bridge lactol **6** as our key intermediate, oxidation with Jones reagent[5] provided the 17-keto-A-ring anhydride **25**. Ammonium acetate–acetic acid treatment gave the A-ring unsaturated imide **26** which was more resistant to hydrogenolysis of the bridging ether by the zinc–copper couple than in the previous series. However, use of the more powerful zinc–silver couple provided the Δ^5 imide **27** in moderate yield. Oxidation of this material with Jones reagent[5] afforded what appeared to be, by thin layer chromatography, a mixture of oxidized components **28a** and **28b**. This mixture was treated without purification with hot aqueous alcoholic hydroxide solution, followed by acidification affording the A-ring glutaconimide **29** in 53% from **27**. This compound, whose NMR spectrum indicated a mixture of Δ^4 and Δ^5 isomers, did not readily crystallize. Moreover, the silver salt of **29** did not cleanly O-alkylate under the conditions previously utilized. However, treatment with diazomethane yielded, in approximately equal amounts, two dialkylated isomers which were readily separated by column chromatography. The desired bis O-alkylated compound **30** was treated as in the previous cases with ethynylmagnesium bromide to provide 17α-ethynyl-2-azaestra-1,3,5(10)-triene-1,3,17-triol 1,3-dimethyl ether (**31**) in ca. 50% yield.[19]

The other isomer formed in the alkylation reaction (**32**) has been assigned the N-methylated structure with the methoxyl group at the 3 position rather than at the 1 position (**32′**). Sterically, it would appear that the 3-carbonyl is much less hindered than that at the 1 position and should be kinetically favored during the alkylation. Moreover, a nuclear Overhauser effect (NOE)[20] has been observed for the 4 proton of **30** which was comparable to the NOE of the 4 proton of **32**.[21] Since the environment of the 4 proton of our assigned structure is similar to that of the 4 proton of **30** a similar response would be expected upon irradiation of the 3-carbon *O*-methyl groups in the two molecules.[22]

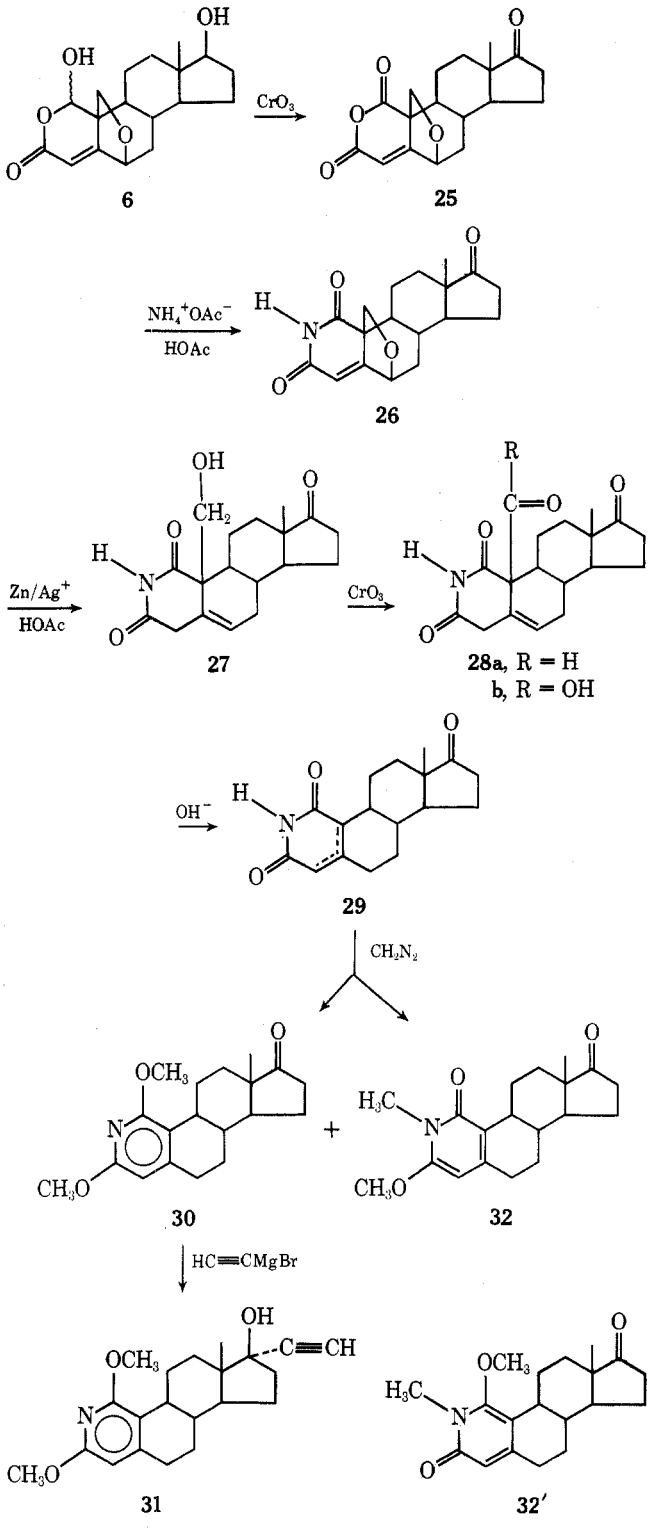
Each of the aforementioned series of 2-azaestratrienes has been tested for biological activity in our laboratories.[23] In addition **15** has been evaluated for anticancer activity when tested under the auspices of the National Cancer Institute.[24] Additional modifications of the 2-azaestratrienes are in progress.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on a Varian A-60A, XL-100-15, or T-60 spectrometer using tetramethylsilane as an internal standard. Uv spectra were obtained in MeOH on a Beckman DK-2A. Infrared spectra were obtained on a Beckman IR-12. TLC runs were on 7.6-cm microscope slides covered with 0.25-mm thickness Woelm F silica with a magnesium silicate binder. Solvents were EtOAc–C_6H_6 combinations (alkoxypyridines) or MeOH–EtOAc combinations (lactams, pyridones). Visualization of spots was by 5% phosphomolybdic acid–EtOH (w/v) followed by heat.

6β,19-Oxidonandrostane-3β,5α,17-triol 17-Benzoate 3,5-Diacetate (2). To 100 g (0.248 mol) of 3β,5α-dihydroxy-6β,19-oxi-

Scheme IV



doandrostan-17-one 3,5-diacetate in 1 l. of methanol cooled to ca. 0 °C was added 6.0 g (0.158 mol) of sodium borohydride in portions over a 10-min period. The reaction mixture was stirred at 0–5 °C for 1.5 h. A sufficient volume of glacial acetic acid was then added to destroy the excess reducing agent before concentrating the solution to about 400 ml in vacuo. Addition of 600 ml of water caused formation of 95.3 g of product (95%). The dried crude material was taken up into 900 ml of pyridine and to this solution was added 60 g (0.43 mol) of benzoyl chloride. After stirring the reaction mixture overnight at room temperature it was diluted with 1.2 l. of water. The resulting oil which solidified upon continued stirring was isolated by filtration to give 113 g (94%) of crude product. Recrystallization from methanol gave **2**: mp 162–165 °C; NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-CH_3), 2.05 (3 H, s, 3-OAc), 2.08 (3 H, s, 5-OAc), 3.87 (2 H, broad s, 19-CH_2), 7.40–8.35 (5 H, aromatic protons).

Anal. Calcd for $C_{30}H_{38}O_7$: C, 70.56; H, 7.50. Found: C, 70.70; H, 7.54.

6β,19-Oxidoandrostane-3β,5α,17-triol 5-Acetate 17-Benzoate (3). To 1 l. of methanol containing 5 g of anhydrous hydrogen chloride was added 55 g (0.108 mol) of the triester (**2**) and the reaction mixture was stirred at room temperature for 4 h. Neutralization of the acid with triethylamine was followed by addition of 1 l. of water which caused formation of 48.0 g (95%) of precipitate which was collected. Recrystallization from methanol resulted in pure **3**: mp 212–214 °C; NMR ($CDCl_3$) δ 0.99 (3 H, s, 18-CH_3), 2.12 (3 H, s, 5-OAc), 3.77 (2 H, broad s, 19-CH_2), 7.25–8.20 (5 H, aromatic protons).

Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.67; H, 7.75.

5α,17-Dihydroxy-6β,19-oxidoandrostan-3-one 5-Acetate 17-Benzoate (4). To 49 g (0.121 mol) of the alcohol **3** in 1 l. of acetone at room temperature was added 31 ml of Jones reagent[5] in portions over a 10-min period. After the reaction mixture was stirred for an additional 15 min, the solution was decanted from the inorganic precipitate now present and an equivalent volume of water was added. The resultant precipitate was collected and provided 46.6 g (95%) of analytically pure **4** after drying: mp 218–219 °C; NMR ($CDCl_3$) δ 1.00 (3 H, s, 19-CH_3), 2.10 (3 H, s, 5-OAc), 3.99 (2 H, broad s, 19-CH_2), 7.15–8.18 (5 H, aromatic protons).

Anal. Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35. Found: C, 72.22; H, 7.36.

2,17-Dihydroxy-6β,19-oxidoandrosta-1,4-dien-3-one (5). To 44.4 g (0.0954 mol) of bridged keto diester **4** in 530 ml of *tert*-butyl alcohol containing 2.7 ml of hexamethylphosphoramide in a 1-l. Parr shaker bottle was added 48.2 g (0.43 mol) of potassium *tert*-butoxide and the reaction mixture was allowed to stand at room temperature for 1 h. Following the in situ elimination of the 5-acetate group, several atmospheres of oxygen were admitted to the reaction vessel which was then shaken under pressure for 1 h after which time 1 equiv of the gas had been absorbed by the reaction mixture. To the reaction vessel was then added 150 ml of water and the aqueous solution was allowed to stand at room temperature overnight. Neutralization of the basic solution with dilute hydrochloric acid solution was followed by addition of a sufficient volume of chloroform to cause formation of two layers after shaking. After separating, the aqueous phase was extracted with two additional portions of chloroform and the combined extracts were washed with water and dried over sodium sulfate. Solvent removal in vacuo gave an oil which was redissolved into benzene. The organic phase was extracted three times with 5% sodium bicarbonate solution prior to extraction of the desired product into 5% sodium hydroxide solution. The combined hydroxide extracts (three) were backwashed twice with chloroform before acidifying the basic solution with dilute hydrochloric acid solution. The resultant acidic solution was extracted with chloroform three times and the combined extracts were washed with water and dried over sodium sulfate. Solvent removal in vacuo gave 20.2 g (67%) of solid product. Recrystallization from methanol resulted in the pure α-diketone **5**: mp 199–201 °C; NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 3.60, 4.43 (2 H, dd, J = 7 Hz, 19-CH_2), 6.23 (1 H, s, vinyl proton), 6.27 (1 H, s, vinyl proton); uv (MeOH) 254 nm (ϵ 9500).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.18; H, 7.84.

1,17-Dihydroxy-6β,19-oxido-2-oxaandrost-4-en-3-one (6). Ozone was passed through a solution of 1.9 l. of ethyl acetate containing 20.0 g (0.063 mol) of the α-diketone **5** cooled to −70 °C until a faint blue color was perceptible. The ozonolysis was then terminated, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature overnight. After solvent removal in vacuo the oily residue was dissolved into 450 ml of 5% sodium bicarbonate solution and this was washed twice with chloroform. The aqueous solution was then acidified with 6 N hydrochloric acid solution which caused formation of 11.8 g of product, isolated by filtration. Addition of sodium chloride to the aqueous filtrate caused formation of an additional 0.8 g of **6** (59% total). This material was generally utilized in the subsequent reactions without further purification. Recrystallization of the crude material from aqueous ethanol provided **6** as the hydrate: mp 142–147 °C; uv (MeOH) 226 nm (ϵ8800); NMR (C_5D_5N) δ 0.98 (3 H, s, 18-CH_3), 4.25 (2 H, dd, J = 8 Hz, 19-CH_2), 5.00 (1 H, broad d, 6-H), 6.14 (1 H, s, 4-H), 6.42 (1 H, broad s, 1-H).

Anal. Calcd for $C_{18}H_{24}O_5 \cdot H_2O$: C, 63.88; H, 7.74. Found: C, 63.79; H, 7.63.

17-Hydroxy-6β,19-oxido-2-azaandrost-4-en-3-one (7). To 400 ml of 98% formic acid was added 350 g (5.55 mol) of ammonium formate and the reaction mixture was heated to homogeneity before addition of 36.5 g (0.11 mol) of bridged lactol **6** and then refluxed for 23 h. Following the addition of 1 l. of water, a precipitate formed which

was collected, affording 14.5 g of product partially formylated at the 17 position. The aqueous filtrate was then extracted three times with chloroform and the combined extracts were washed with water, dried over sodium sulfate, and filtered. Solvent removal in vacuo gave an oil which was combined with the above precipitate in 100 ml of methanol containing 50 ml of 4 N sodium hydroxide solution. The solution was refluxed for 1 h before concentrating to 100 ml. The addition of ca. 300 ml of water caused formation of 10.7 g of product, isolated by filtration. The aqueous filtrate was acidified with dilute hydrochloric acid and extracted three times with chloroform. The extracts were washed with water, dried over sodium sulfate, and filtered. Solvent removal in vacuo gave an oil which upon trituration with ether provided an additional 7.35 g of product of purity comparable to the above (52% total).

The crude product was recrystallized from ethanol: mp 247–250 °C; ir ($CHCl_3$) 2.93, 5.90, 6.03 μ; uv (MeOH) 220 nm (ϵ11 200); NMR ($CDCl_3$) δ 0.84 (3, H, s, 18-CH_3), 3.46 (2 H, broad s, 1-CH_2), 3.58, 4.18 (2 H, dd, J = 7 Hz, 19-CH_2), 4.75 (1 H, broad d, J = 5 Hz, 6-H), 5.67 (1 H, broad s, 4-H).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.08; H, 8.04; N, 4.74.

17-Hydroxy-6β,19-oxido-2-azaandrost-4-en-3-one 17-Acetate (8). To 4.75 g (0.016 mol) of the bridged lactam **7** in 20 ml of pyridine was added 10 ml of acetic anhydride and the reaction mixture was allowed to stand at room temperature overnight. Upon addition of 200 ml of water 4.8 g (89%) of product resulted which was collected by filtration. Recrystallization from ethanol gave the pure compound: mp 299–302 °C dec; NMR ($CDCl_3$) δ 0.87 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.45 (2 H, broad s, 1-CH_2), 3.60, 4.18 (2 H, dd, J = 8 Hz, 19-CH_2), 4.75 (1 H, broad d, J = 5 Hz, 6-H), 5.85 (1 H, broad s, 4-H).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.33; H, 7.97; N, 4.08.

17,19-Dihydroxy-2-azaandrost-5-en-3-one 17-Acetate (9). To 4.8 g (0.014 mol) of the bridged lactam acetate **8** in 250 ml of ethanol containing 75 ml of glacial acetic acid and 75 ml of water was added 52.5 g (0.80 mol) of Zn dust and 10.5 g (0.165 mol) of copper acetate. The mechanically stirred reaction mixture was refluxed overnight, then filtered through diatomaceous earth. The filtrate was reduced to ca. one-third of its original volume in vacuo and to the resultant solution was added 250 ml of water. The precipitate which formed was collected affording 4.25 g of product. Additional water and cooling of the aqueous filtrate afforded another 0.2 g of product (93%). Recrystallization from ethanol provided **9:** mp 271–273 °C; ir ($CHCl_3$) 2.93, 5.79, 6.02, 7.90 μ; NMR ($CDCl_3$ + CF_3CO_2D) δ 0.87 (3 H, s, 18-CH_3), 2.15 (3 H, s, –OAc), 3.89 (2 H, broad s, 19-CH_2), 5.85 (1 H, broad m, 5-H).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 69.11; H, 8.48; N, 4.01.

17,19-Dihydroxy-2-azaandrost-4-en-3-one 17-Acetate (10). To 14.0 g (0.040 mol) of Δ^5-lactam **9** in 120 ml of piperidine was cautiously added 40 ml of glacial acetic acid at room temperature and the reaction mixture was refluxed for 2 h. After cooling 500 ml of water was added to the solution and the precipitate (11.0 g) was collected. The aqueous filtrate was extracted with chloroform and the combined extracts were washed with dilute hydrochloric acid solution, then water and dried over sodium sulfate. Solvent removal gave a residue which upon trituration with ether yielded another 0.5 g of product (82% total). Recrystallization from acetonitrile containing a small amount of acetic acid afforded **10:** mp 265–275 °C; uv (MeOH) 220 nm (ϵ 13 200); NMR ($CDCl_3$ + CF_3CO_2D) δ 0.87 (3 H, s, 18-CH_3), 2.13 (3 H, s, –OAc), 3.40, 3.87 (2 H, dd, J = 14 Hz, 1-CH_2), 4.04 (2 H, broad s, 19-CH_2), 5.95 (1 H, broad s, 4-H).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 69.18; H, 8.35; N, 3.95.

17-Hydroxy-3-oxo-2-azaestr-4-ene-10-carboxylic Acid 17-Acetate (11). To 4.5 g (0.013 mol) of the conjugated lactam **10** in 300 ml of acetone containing 60 ml of acetic acid cooled to ca. 0 °C was added 12 ml of Jones reagent[5] in portions over a 15-min period with the temperature of the solution maintained below 5 °C during the addition. After the reaction mixture was stirred for 1 h at 0–5 °C a few milliliters of 2-propanol were added to destroy the excess oxidizing agent. Prior to concentrating the solution to ca. 75 ml in vacuo, 50 ml of water was added to aid in solubilizing the inorganic salts present. After addition of 200 ml of water to the concentrated solution, it was extracted with chloroform and the combined extracts were washed with saturated salt solution, dried over sodium sulfate, and filtered through diatomaceous earth. Upon solvent removal in vacuo an oil remained which upon trituration with ether gave 3.1 g of product. Concentrating the ethereal filtrate afforded another 0.6 g of product whose purity was poorer than the above. This material was taken up into 5% sodium bicarbonate solution and this solution was extracted with chloroform prior to acidification with dilute hydrochloric acid providing an additional 0.3 g of product whose purity was comparable to that originally isolated (73% total). The combined material was used without purification in the subsequent step: NMR ($CDCl_3$) δ 0.78 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 5.69 (1 H, narrow m, 4-H).

17-Hydroxy-2-azaestr-5(10)-en-3-one 17-Acetate (12). To 6.6 g (0.018 mol) of the crude acid **11** in 35 ml of pyridine was added 7 ml of glacial acetic acid and the reaction mixture was refluxed for 2 h under a nitrogen atmosphere. After cooling 250 ml of water was added and 5.0 g (86%) of **12** was collected. Recrystallization from aqueous acetic acid afforded the pure compound: mp >325 °C; ir ($CHCl_3$) 2.93, 5.79, 6.00, 7.90 μ; NMR ($CDCl_3$ + CF_3CO_2D) δ 0.83 (3 H, s, 18-CH_3), 2.07 (3 H, s, –OAc), 2.90 (2 H, broad m, 4-CH_2), 3.95 (2 H, broad m, 1-CH_2).

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.82; H, 8.65; N, 4.31.

5,10-Dibromo-17-hydroxy-2-azaestran-3-one 17-Acetate (13). To 2.2 g (0.007 mol) of $\Delta^{5(10)}$-lactam **12** in 75 ml of chloroform at room temperature was added dropwise over a 10-min period 15 ml of a carbon tetrachloride solution containing 85 mg of bromine/ml of solution (0.008 mol). The reaction mixture was stirred in the presence of the excess bromine for 30 min before solvent removal in vacuo. The resultant oil was triturated with pentane and the precipitate which formed was isolated by filtration affording 3.15 g of product. This material was used without purification for the dehydrohalogenation reaction: NMR ($CDCl_3$) δ 0.85 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.05, 3.48 (2 H, dd, J = 19 Hz, 4-CH_2), 3.82 (2 H, broad m, 1-CH_2).

17-Hydroxy-2-azaestra-1(10),4-dien-3-one 17-Acetate (14). To 1.4 g (0.003 mol) of the dibromo lactam **13** suspended in 20 ml of pyridine was added dropwise over a 5-min period 5 ml of piperidine at room temperature. After addition the reaction mixture became homogeneous prior to the formation of a precipitate. After stirring at room temperature for 3 h 200 ml of chloroform was added to the reaction mixture and the organic phase was washed with several portions of 1 N hydrochloric acid solution (until the aqueous wash remained acidic), then saturated salt solution and dried over sodium sulfate. The solvent was reduced in volume to afford in two crops (0.77 g) of **14** (83%). Recrystallization from aqueous acetic acid provided the pure compound: mp >330 °C; uv (MeOH) 231 nm (ϵ 7900), 306 (5500); ir ($CHCl_3$) 2.93, 5.78, 6.01, 6.16, 7.90 μ; NMR (CF_3CO_2D) δ 1.02 (3 H, s, 18-CH_3), 2.27 (3 H, s, –OAc), 7.13 (1 H, broad m, 4-H), 8.00 (1 H, broad m, 1-H).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.22; H, 7.94; N, 4.35.

2-Azaestradiol 3-Methyl Ether 17-Acetate (15). To 2.0 g (0.006 mol) of the steroidal α-pyridone **14** suspended in 150 ml of benzene containing 1.2 ml (0.019 mol) of methyl iodide was added 1.0 g (0.0036 mol) of silver carbonate and the heterogeneous reaction mixture was refluxed in the dark for 22 h. After cooling, the reaction mixture was filtered through diatomaceous earth and the solvent was removed from the filtrate in vacuo to afford an oil. The oil was taken up into methanol and upon cooling afforded 1.17 g (56%) of **14** in two crops: mp 102–104 °C; uv (MeOH) 277 nm (ϵ 3700); ir ($CHCl_3$) 5.80, 6.22, 6.70, 7.30, 7.90μ; NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.88 (3 H, s, –OCH_3), 6.44 (1 H, broad s, 4-H), 8.00 (1 H, broad s, 1-H).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.05; H, 8.29; N, 4.09.

17-Hydroxy-2-methyl-2-azaestra-1(10),4-dien-3-one 17-Acetate (16). To 1.95 g (0.006 mol) of **14** in 200 ml of dimethylformamide containing 6 ml (0.096 mol) of methyl iodide was added 0.8 g (0.006 mol) of anhydrous potassium carbonate and the reaction mixture was heated at 70 °C for 18 h. The solvent was then removed in vacuo and 300 ml of water was added to the oily residue which caused formation of a precipitate which was collected. Recrystallization of the crude product from aqueous acetic acid afforded 1.8 g (84%) of **16:** mp 222–226 °C dec; uv (MeOH) 308 nm (ϵ 4850), 231 (5550); NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.52 (3 H, s, N-CH_3), 6.34 (1 H, broad s, 4-H), 7.10 (1 H, s, 1-H).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.79; H, 8.29; N, 4.08.

5,10-Dibromo-2-oxaestrane-3,17-dione (18). To 15 g (0.055 mol) of 2-oxaestra-5(10)-ene-3,17-dione (**17**) in 500 ml of chloroform cooled to −30 °C was added 30.5 ml (0.059 mol) of carbon tetrachloride solution containing 310 mg of bromine per ml of solution over a 7–8-min period. The reaction mixture was stirred at ca. −20 °C for another 20 min before addition of 100 ml of a 5% sodium sulfite solution. After shaking, the two layers were separated and the aqueous phase was

extracted with an additional portion of chloroform. The combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo (heating bath temperature <30 °C) afforded an oil which upon trituration with ether afforded 22 g of product. This material was used without purification in the subsequent reaction: NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 3.35, 3.69 (2 H, dd, J = 16 Hz, 4-CH_2), 4.69, 4.92 (2 H, dd, J = 13 Hz, 1-CH_2).

2-Oxaestra-1(10),4-diene-3,17-dione (19). To 22 g (0.051 mol) of the crude lactone **18** in 150 ml of benzene was added 150 ml of *N*-methylpyrrolidine and the reaction mixture was refluxed for 20 min. After cooling, additional benzene was added and the solution was extracted with dilute hydrochloric acid solution until the aqueous extracts remained acidic. The organic phase was then washed with two portions of saturated salt solution and dried over sodium sulfate, and upon solvent removal in vacuo 11.55 g of solid product remained whose NMR spectrum indicated 80–85% of desired pyrone (~65% from **17**). Recrystallization from ethanol afforded **19:** mp 215.5–217.5 °C dec; uv (MeOH) 300 nm (ε 6000); ir ($CHCl_3$) 5.76, 6.10, 6.50 μ; NMR ($CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 6.10 (1 H, broad s, 4-H), 7.33 (1 H, broad s, 1-H).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.66; H, 7.61.

2-Oxaestra-4,9-diene-3,17-dione (19′). To 0.5 g (0.0012 mol) of **18** in 3 ml of benzene was added 3 ml of pyridine and the reaction mixture was refluxed for 20 min. Workup as in the previous experiment afforded 0.3 g of crystalline solid whose NMR spectrum indicated ca. 75% of $\Delta^{4,9}$-dienone (**19′**). Recrystallization from ethanol provided material which was ca. 90% **19′**. An additional recrystallization from ethanol afforded material which appeared to be >95% of **19′** by NMR spectroscopy: mp 202.5–204 °C; uv (MeOH) 285 nm (ε 17 000); NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-CH_3), 4.92, 5.18 (2 H, 2 broad d, J = 15 Hz, 1-CH_2).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.71; H, 7.24.

2-Azaestra-1(10),4-diene-3,17-dione (20). To 25 ml of glacial acetic acid containing 37.5 g of ammonium acetate heated to homogeneity was added 5.2 g (0.019 mol) of the α-pyrone **19** and the reaction mixture was refluxed for 4 h. After cooling 150 ml of water was added and the precipitate which formed was isolated by filtration affording 3.45 g of crude product. Upon standing overnight at room temperature, the filtrate gave another 0.2 g of precipitate. The initial precipitate was taken up into 40 ml of ether, stirred for 10 min, and filtered giving back 3.25 g of tan solid of comparable purity (TLC) to the second precipitate above (66%). Recrystallization from aqueous acetic acid gave **20** after drying: mp >325 °C; uv (MeOH) 306 nm (ε 5250); NMR ($CDCl_3$ + CF_3CO_2D) δ 1.00 (3 H, s, 18-CH_3), 6.97 (1 H, broad s, 4-H), 7.93 (1 H, broad s, 1-H).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.25; H, 7.61; N, 5.16.

O-Alkylation of 20 with Methyl Iodide and Cyclopentyl Iodide. In a typical experiment, to 2.5 g (0.009 mol) of α-pyridone **20** suspended in 250 ml of benzene was added 1.6 g (0.0058 mol) of silver carbonate and 1.8 ml (0.029 mol) of methyl iodide [8 g (0.041 mol) of cyclopentyl iodide] and the reaction mixture was refluxed overnight in the dark. After cooling, the reaction mixture was filtered through diatomaceous earth and the solvent was removed from the filtrate in vacuo. The reaction from methyl iodide afforded an oil which was taken up into ethanol containing a slight amount of water and upon cooling gave **21** (60%): mp 139.5–140.5 °C; uv (MeOH) 276 nm (ε 3850); ir ($CHCl_3$) 5.73, 6.22, 6.70, 7.18 μ; NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 3.90 (3 H, s, -OCH_3), 6.45 (1 H, broad s, 4-H), 8.07 (1 H, broad s, 1-H).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.77; H, 8.08; N, 4.81.

The reaction with cyclopentyl iodide gave an oily solid which upon washing with pentane gave 87% of crude **22.** Recrystallization from acetone gave the pure compound: mp 182–183 °C; uv (MeOH) 279 nm (ε 3730); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 6.40 (1 H, broad s, 4-H), 8.02 (1 H, broad s, 1-H).

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.78; H, 8.76; N, 4.15.

Ethynylation of 21 and 22 with Ethynylmagnesium Bromide. In a typical experiment, 50 ml of freshly distilled tetrahydrofuran was cooled to −70 °C before 1–2 g of acetylene gas was added to the solution after it had been passed through a scrubber filled with water and two scrubbers filled with concentrated sulfuric acid. To this solution was added 8.5 ml of 3 M ethylmagnesium bromide in ether and the reaction mixture was allowed to come to room temperature before the addition of 1.4 g (0.0049 mol, R = CH_3) of steroid in 10 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 3–4 h before cooling (ice bath) and the addition of ca. 35 ml of 1 N hydrochloric acid solution followed by ether and additional water to form two layers. After separating, 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. Solvent removal in vacuo gave an oil. In the case of the 3-methoxy derivative, the oil was taken up into acetone and Skelly B was added until the solution became turbid. Activated charcoal was added and the solution was filtered through diatomaceous earth. The volume of this filtrate was reduced slightly and Skelly B again added and the above process was repeated to give a crystal clear solution which upon reduction of the volume of the solution and cooling afforded 57% of analytically pure product in three crops: mp 146–147.5 °C; uv (MeOH), 277 nm (ε 3700); NMR ($CDCl_3$) δ 0.88 (3 H, s, 18-CH_3), 2.60 (1 H, s, -C≡CH), 3.89 (3 H, s, -OCH_3), 6.45 (1 H, broad s, 4-H), 8.07 (1 H, broad s, 1-H).

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.06; H, 8.09; N, 4.61.

In the case of the 3-cyclopentoxy derivative, the oil from the reaction mixture was taken up into ether–Skelly B and treated as above to afford an oil (74%). Though this oil would not crystallize its analytical and spectral data indicated desired product: uv (MeOH) 279 nm (ε 3100); NMR ($CDCl_3$) δ 0.90 (3 H, s, 18-CH_3), 2.60 (1 H, s, -C≡CH), 5.34 (1 H, broad m, -OCH), 6.44 (1 H, broad s, 4-H), 8.08 (1 H, broad s, 1-H).

Anal. Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55; N, 3.84. Found: C, 78.93; H, 8.89; N, 3.53.

6β,19-Oxido-2-oxaandrost-4-ene-1,3,17-trione (25). To 4.85 g (0.014 mol) of bridged lactol **6** in 200 ml of acetone cooled to −15 °C was added 10 ml of Jones reagent[5] at a rate so as to maintain a temperature below −5 °C during the addition. The reaction mixture was allowed to stand at 0 °C overnight before the excess oxidizing agent was destroyed with 2-propanol. The cold solution was filtered from the precipitated inorganic salts and the volume of the filtrate was reduced to 50 ml in vacuo. Addition of 100 ml of water afforded 3.25 g of crude anhydride which was isolated by filtration. The aqueous filtrate was extracted three times with chloroform and the combined extracts were washed with 5% sodium bicarbonate solution before drying over sodium sulfate. Solvent removal afforded an additional 0.33 g of **25** (74% total). Recrystallization from acetone gave the pure compound: mp 263–264 °C; uv (MeOH) 223 nm (ε 8550); ir ($CHCl_3$) 5.56, 5.70, 5.73 μ; NMR ($CDCl_3$) δ 0.98 (3 H, s, 18-CH_3), 4.00, 4.36 (2 H, dd, J = 9 Hz, 19-CH_2), 4.93 (1 H, broad d, J = 5 Hz, 6-H), 6.03 (1 H, broad s, 4-H).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.45; H, 6.49.

6β,19-Oxido-2-azaandrosta-4-ene-1,3,17-trione (26). To 150 ml of glacial acetic acid containing 125 g of ammonium acetate heated to homogeneity was added 17.1 g (0.054 mol) of the bridged anhydride **25** and the reaction mixture was refluxed for 90 min. After cooling 500 ml of water was added and 9.55 g of product was collected. Concentration of the aqueous filtrate and cooling afforded another 3.75 g of product as precipitate (78% total). Recrystallization from aqueous acetic acid gave pure **26:** mp 290–292 °C dec; uv (MeOH) end absorption 220 nm; ir ($CHCl_3$) 2.96, 5.80 μ; NMR ($CDCl_3$ + CF_3CO_2D) δ 1.00 (3 H, s, 18-CH_3), 3.93, 4.35 (2 H, dd, J = 8 Hz, 19-CH_2), 4.94 (1 H, broad d, J = 5 Hz, 6-H), 5.85 (1 H, broad s, 4-H).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.84; H, 6.85; N, 4.43.

19-Hydroxy-2-azaandrost-5-ene-1,3,17-trione (27). To 13.3 g (0.042 mol) of the bridged imide **26** in 600 ml of ethanol containing 400 ml of glacial acetic acid and 200 ml of water were added 38 g (0.226 mol) of silver acetate and 260 g (3.98 mol) of zinc dust. The reaction mixture was mechanically stirred while refluxing under an atmosphere of nitrogen for 2 h. The hot reaction mixture was then filtered through diatomaceous earth and the volume of the filtrate was reduced in volume by ca. 300 ml of solvent before addition of 1 l. of water. The turbid solution was extracted with chloroform and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which upon trituration with ether yielded a solid. Recrystallization from aqueous ethanol gave 6.75 g (51%) of product in three crops: mp 231–236 °C dec; ir ($CHCl_3$) 2.97, 5.75, 5.85 μ; NMR (C_5D_5N) δ 0.97 (3 H, s, 18-CH_3), 3.42 (1 H, broad d, J = 19 Hz, 4-H), 3.72 (1 H, broad d, 4-H), 3.97, 5.43 (2 H, dd, J = 10 Hz, 19-CH_2).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.23; H, 7.68; N, 4.37.

2-Azaestrene-1,3,17-trione (29). To 8.15 g (0.026 mol) of **27** in 300 ml of acetone cooled to −10 °C was added 15 ml of Jones reagent[5] in

portions so as to maintain a temperature below −5 °C during the addition. After the reaction mixture was stirred at ca. 0 °C for 1 h, the excess oxidizing agent was destroyed with 2-propanol and the solution was filtered. The solvent was removed from the filtrate and the residue was taken up into a solution containing 50 ml of methanol and 50 ml of 5% aqueous sodium hydroxide solution. After refluxing for 30 min the cooled solution was acidified with acetic acid and extracted with several portions of chloroform. The combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave an oily residue which upon trituration with acetone afforded 3.9 g (53%) of amorphous solid. The NMR spectrum ($CDCl_3$) indicated a mixture of Δ^4 and $\Delta^{5(10)}$ isomers by the appearance of a broad singlet at 6.00 ppm (4-H) and a broad multiplet at 3.32 ppm (4-CH_2) with the latter [$\Delta^{5(10)}$] isomer in predominance. This material was used without purification for the subsequent alkylation: uv (MeOH) 236 nm (ε 2900), 244 (5800).

1,3-Dihydroxy-2-azaestra-1,3,5(10)-trien-17-one 1,3-Dimethyl Ether (30) and 3-Hydroxy-2-methyl-2-azaestra-3,5(10)-diene-1,17-dione 3-Methyl Ether (32). To a slurry of 3.75 g (0.013 mol) of crude **29** in 75 ml of methanol containing 75 ml of ether cooled to −5 °C was added a freshly prepared ethereal solution of diazomethane so as to maintain a temperature below 0 °C during addition. Soon after addition of the diazomethane solution the reaction mixture became homogeneous. When excess diazomethane was present as indicated by its yellow color, the addition was terminated and the reaction mixture was allowed to warm to room temperature. After standing at room temperature for 2 h, the solvents were removed in vacuo to give an oil consisting of a 1:1 mixture of the two isomers. The mixture was chromatographed on 75 g of SilicAR CC-7 using benzene and ethyl acetate as eluents. Compound **30** (1.3 g, 30%) was obtained when eluting with 10% ethyl acetate–90% benzene. Compound **32** (1.1 g, 26%) was obtained when eluting with 50% ethyl acetate–50% benzene. Recrystallization of **30** from Skelly B gave the analytical sample: mp 125.5–127.5 °C; uv (MeOH) 281 nm (ε 7000), 230 (8800); NMR ($CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 3.88 (3 H, s, -OCH_3), 3.93 (3 H, s, -OCH_3), 6.07 (1 H, broad s, 4-H).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; H, 4.44. Found: C, 72.67; H, 8.27; N, 4.04.

The *N*-methyl isomer (**32**) was recrystallized from acetone to afford the analytical sample: mp 219–222 °C; uv (MeOH) 305 nm (ε 10 100), 235 (5200); NMR ($CDCl_3$) δ 0.94 (3 H, s, 18-CH_3), 3.40 (3 H, s, NCH_3), 3.85 (3 H, s, -OCH_3), 5.30 (1 H, broad s, 4-H).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.14; H, 8.14; N, 4.48.

17α-Ethynyl-2-azaestra-1,3,5(10)-triene-1,3,17-triol 1,3-Dimethyl Ether (31). A 1.05-g (0.0033 mol) sample of **30** was treated as was described above for the preparation of **23** and **24**. The crude oil was taken up in ether and Skelly B was added until the solution became turbid, then activated charcoal was added and the solution was filtered through diatomaceous earth. This procedure was repeated two additional times before solvent removal afforded an oil which crystallized upon standing at room temperature. A small amount of pentane was added and the solid was isolated by filtration to give 553 mg of **31**: mp 101–105 °C; uv (MeOH) 281 nm (ε 7350), 230 (9200); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 2.60 (1 H, s, -C≡CH), 3.88 (3 H, s, -OCH_3), 3.92 (3 H, s, -OCH_3), 6.03 (1 H, broad s, 4-H).

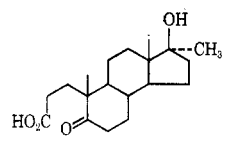
Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.45; H, 7.90; N, 3.97.

Acknowledgment. We would like to acknowledge the assistance of the following members of our development staff for preparing intermediates described in this work: Messrs. R. Erickson, G. Plume, J. Behling, and J. Palmer. The routine spectral data were obtained by the group of Mr. A. J. Damascus and the microanalyses were performed by the group of Mr. E. Zielinski. The assistance of Dr. R. Bible and Ms. L. Swenton in interpretation of the spectral data is also acknowledged. The following members of our Biology Department and their respective groups are responsible for the biological evaluation of these compounds: Dr. J. Miller, Dr. N. P. Rapoza, and Mr. W. Pautsch.

Registry No.—**1**, 807-09-0; **2**, 36334-58-4; **3**, 36405-41-1; **4**, 36334-59-5; **5**, 36334-60-8; **6**, 37147-40-3; **7**, 37147-41-4; **8**, 57178-17-3; **9**, 37147-42-5; **10**, 37147-43-6; **11**, 37147-44-7; **12**, 37147-45-8; **13**, 57178-18-4; **14**, 37147-47-0; **15**, 37147-48-1; **16**, 59433-87-3; **17**, 4623-00-1; **18**, 59433-88-4; **19**, 37695-36-6; **19'**, 21210-47-9; **20**, 57178-20-8; **21**, 57178-21-9; **22**, 57178-25-3; **23**, 57178-22-0; **24**, 57178-26-4; **25**, 53864-77-0; **26**, 53864-78-1; **27**, 53864-82-7; Δ^4-**29**, 53864-85-0; $\Delta^{5(10)}$-**29**, 53864-84-9; **30**, 53864-72-5; **31**, 53864-73-6; **32**, 53913-59-0; benzoyl chloride, 98-88-4; methyl iodide, 74-88-4; cyclopentyl iodide, 1556-18-9; ethynyl bromide, 593-61-3.

References and Notes

(1) R. Pappo and R. J. Chorvat, *Tetrahedron Lett.*, 3237 (1972).
(2) (a) R. Pappo and C. J. Jung, *Tetrahedron Lett.*, 365 (1962); (b) R. Pappo, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., 1964, p 17M; (c) R. Pappo and C. J. Jung, Abstracts, 5th International Symposium on the Chemistry of Natural Products, London, 1968, p F50; (d) R. Pappo, *Intra-Sci. Chem. Rep.* **3**, 105 (1969).
(3) R. Pappo and L. N. Nysted, U.S. Patent 3 176 014 (1965). This material was provided by Searle de Mexico, Mexico 1, D. F.
(4) The β geometry of the 17-hydroxyl group was deduced from inspection of the NMR spectrum of the 17-hydroxy compound which demonstrated a sharp 18-methyl resonance at 0.79 ppm. Since the β-hydroxyl group has been determined to be the preponderant product of the borohydride reduction of 17-ketones (cf. J. Fried and J. A. Edwards, Ed., "Organic Reactions in Steroid Chemistry", Vol. I, Van Nostrand-Reinhold, Princeton, N.J., 1972, Chapter 2) and the 18-methyl resonance of the 17α-hydroxy compound would appear upfield from that of the 17β-hydroxy compound [cf. J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, E. R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards, and P. D. Woodgalt, *J. Chem. Soc. C*, 250 (1970)], this reduction appears to proceed with a high degree of stereoselectivity.
(5) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(6) R. Hanna and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1945 (1961).
(7) These oxygenations were performed by Mr. M. G. Scaros and his group, to whom we are grateful.
(8) L. N. Nysted and R. Pappo, U.S. Patent 3 109 016 (1963). As an additional application of this observation, we have found that ozonolysis of 17α-methyltestosterone in methylene chloride–methanol at −70 °C followed by treatment with 2 equiv of aqueous sodium hydroxide afforded 17α-



methyl-5-oxo-3,4-seco-*A*-norandrostan-3-oic acid in high yield. This method is superior to the generally utilized peroxide treatment of the ozonide product of conjugated ketones (cf. C. Djerassi, Ed., "Steroid Reactions", Holden-Day, San Francisco, Calif., 1963, Chapter 12) and appears to have general applicability.
(9) E. Caspi, B. Taqui Khan, and S. N. Balasubrahmanyam, *Tetrahedron*, **18**, 1013 (1962).
(10) R. Pappo and L. N. Nysted, these laboratories, private communication.
(11) While formic acid is not generally associated with the hydrogenation of double bonds [cf. H. W. Gibson, *Chem. Rev.*, **69**, 673 (1969)], saturation of conjugated double bonds by formate has been reported [cf. M. Sekiya and C, Yanaihara, *Chem. Pharm. Bull.*, **17**, 738 (1969); M. Sekiya and K. Suzuki, *ibid.*, **19**, 531 (1971)].
(12) The assigned trans geometry of the dibromo adduct (5α,10β) is the only reasonable isomer since the alternate dibromide (5β,10α) forces the B ring into an unfavorable boat conformation.
(13) See, for example, A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Macmillan, New York, N.Y., 1964, Chapter 5.
(14) For a discussion of evidence supporting this fact see E. Klingsberg, Ed., "The Chemistry of Heterocyclic Compounds", Part 3, Interscience, New York, N.Y., 1972, Chapters IX–XII, p 619 ff.
(15) G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer, and H. Tiekelmann, *J. Org. Chem.*, **32**, 4040 (1967).
(16) See, for example, D. A. McGinty and C. Djerassi, *Ann. N.Y. Acad. Sci.*, **71**, 500 (1958).
(17) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).
(18) See J. Hine, "Physical Organic Chemistry", 2d ed, McGraw-Hill, New York, N.Y., 1962, Chapter 8.
(19) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, *Chem. Ber.*, **71**, 1024 (1938).
(20) For a comprehensive discussion of NOE, see J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, N.Y., 1971.
(21) These experiments were performed using the pulsed Fourier transform technique described by L. F. Johnson, Abstracts, 14th Experimental NMR Conference, Boulder, Colo., April 15–18, 1973, p 31.
(22) We would like to thank Elisabeth Hajdu for performing the NOE experiments as well as Dr. Roy Bible and Lydia Swenton for assistance in interpretation of these results.
(23) The 3-methyl ether series was devoid of anabolic, androgenic, progestational, estrogenic, and antifertility activity as well as hormonal antagonist properties. However, this series did manifest moderate hypocholesterolemic activity in vivo as well as anti-influenza activity in vitro. Members of the 3-cyclopentoxy series have failed to demonstrate any biological activity. While the 1,3-dimethoxy series was devoid of hormonal and antiviral properties, compound **31** did show lipid mobilization activity.
(24) This compound was active in the L1210 assay (mouse leukemia) at 100 mg/kg when administered at 4-day intervals.