The infrared spectrum was identical with that of an authentic sample.[5]

Deoxyrutaevin (8).—To a solution of 200 mg of rutaevin in 40 ml of 1:1 acetic acid–dioxane was added an excess aqueous chromous chloride solution under inert atmosphere. The mixture was allowed to stand overnight at room temperature. A large volume of water was added and the mixture extracted with chloroform. The chloroform extracts were dried and concentrated to give 100 mg of deoxyrutaevin. A second impure crop of 25 mg was obtained after further concentration and was recrystallized from chloroform–ethanol, mp 286–293 dec. Deoxyrutaevin showed major mass spectrum peaks at *m/e* 95 (20), 133 (13), 148 (20), 316 (100), 317 (15), 358 (8), 374 (40), 375 (8), 455 (4), 469 (2); ν 3417 (hydroxyl), 1761, 1717, 1693 (carbonyl), 1503, 882 cm^{-1} (β-substituted furan) (Nujol); ORD in dioxane (*c* 0.9) at 25°, $[\alpha]_{600}$ −89°, $[\alpha]_{310}$ −635°, $[\alpha]_{277}$ +667°, $[\alpha]_{250}$ −1820°, $[\alpha]_{245}$ −1560° (last reading).

Anal. Calcd for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43. Found: C, 66.3; H, 6.36.

Registry No.—**2**, 13942-86-4; **3**, 13942-87-5; **4**, 13942-88-6; **5**, 13942-89-7; **6**, 989-95-7; **7**, 991-07-1; **8**, 14120-03-7.

Acknowledgment.—The author is indebted to L. M. White for the analytical data, to Dr. D. J. Bertelli for the 100-Mc nmr spectrum, and to Drs. R. M. Horowitz and W. E. Thiessen for helpful discussions.

1,11-Iminoestrones.[1] I. Synthesis and Proof of Structure

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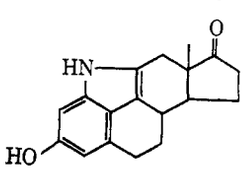
1-Aminoestrone 3-methyl ether (**10b**) has been synthesized (five steps, 40% yield) from 4-nitroestrone using diazo coupling in the key step. 1-Azidoestrone 3-methyl ether (**13**), prepared from **10b**, on pyrolysis underwent a nitrene insertion reaction to give 1,11α-iminoestrone 3-methyl ether (**14**) in 73% yield. The structure of the latter was supported by nmr and mass spectral analyses. Dehydrogenation of **14** with palladium on charcoal gave, in 90% yield, 1,11-imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**15**) which, on fusion with pyridine hydrochloride, gave 3-hydroxy-1,11-iminoestra-1,3,5(10),9(11)-tetraen-17-one (**1**).

In our program on the synthesis of modified estrogens,[2] the preparation of some 1-substituted derivatives was considered worthwhile since few of these compounds have been reported.[3] In particular, an appealing aspect of this problem was the possibility of forming a nitrogen bridge[4] between the C-1 and C-11 positions *via* a nitrene[5] insertion reaction. The resulting indoline (**14**) should then be easily converted to **1** an interesting heterocyclic steroid which would incorporate the structural features of estrone with those of a highly substituted indole.



1

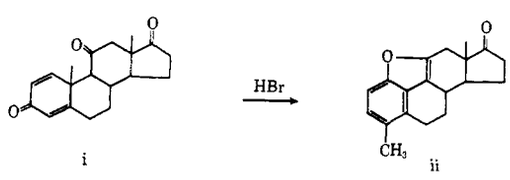
The projected synthesis of **1** required the development of a method for gaining access to the C-1 position of estrone and specifically for the preparation of 1-aminoestrone 3-methyl ether (**10b**). To accomplish this by an electrophilic substitution reaction required that the estrone molecule should first be substituted with a group that would overcome the *ortho* orienting effect of the C-3 hydroxyl or methoxyl group and direct substitution to C-1. Another factor which we thought would impede reaction at C-1 was steric hindrance by the 11-methylene group.[6,7] However,

(1) For a preliminary announcement of this work, see E. W. Cantrall, R. B. Conrow, and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 2943 (1964).

(2) E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64, 214 (1964); S. Gordon, E. W. Cantrall, W. P. Cekleniak, H. J. Albers, S. Mauer, S. M. Stolar, and S. Bernstein, *Steroids*, **4**, 267 (1964); and R. B. Conrow E. W. Cantrall, and S. Bernstein, *ibid.*, **9**, 307 (1967).

(3) For the preparation of various 1-substituted estrone 3-methyl ethers and references to previously reported 1-substituted 1,3,5(10)-estratrienes, see E. W. Cantrall, R. B. Conrow, and S. Bernstein *J. Org. Chem.*, in press.

(4) Related bridged compounds having an oxygen atom between these positions have been described in the C-19 and C-21 series: C. Tamm and G. Volpp, U. S. Patent 3,057,860 (Oct 9, 1962); J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailovic, K. Schaffner, and A. Wettstein, *Helv. Chim. Acta*, **44**, 186 (1961); K. Heuser, J. Kalvoda, G. Anner, and A. Wettstein, *ibid.*, **46**, 352 (1963); Ch. Meystre, J. Kalvoda, G. Anner, and A. Wettstein, *ibid.*, **46**, 2844 (1963); L. Canonica, G. Jommi, F. Pelizzoni, and C. Scolastico, *Gazz. Chim. Ital.*, **95**, 138 (1965); and G. Jommi, P. Manitto, and C. Scolastico, *ibid.*, **95**, 151 (1965). The corresponding oxygen derivative (ii) of estrone has been reported in the patent literature [F. B. Colton, U. S. Patent 2,923,709 (Feb 2, 1960)] as arising from the aromatization of androsta-1,4-diene-3,11,17-trione (i).

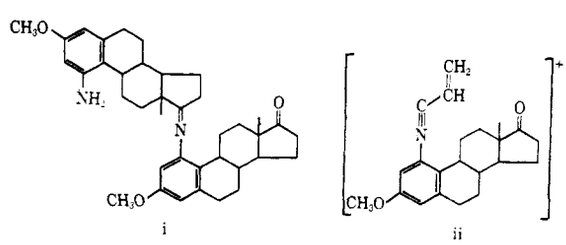


i ii

(5) For recent reviews on the chemistry of nitrenes, see L. Horner and A. Christmann, *Angew. Chem.*, **75**, 707 (1963); *Angew. Chem. Intern. Ed. Engl.*, **2**, 599 (1963); and R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

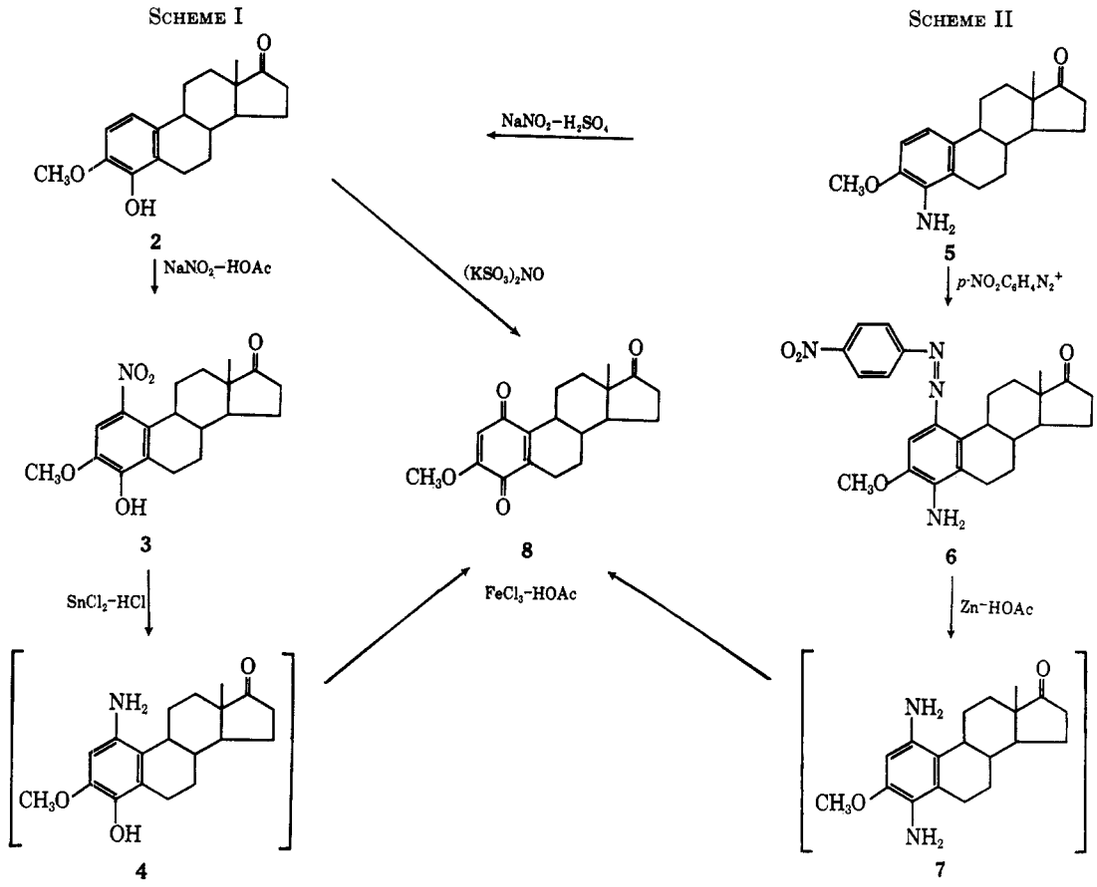
(6) In a nmr study, appreciable van der Waals interaction between the C-4 and C-5 protons of ring-A-aromatic octahydrophenanthrenes has been demonstrated by W. Nagata, T. Terasawa, and K. Troi, *J. Am. Chem. Soc.*, **86**, 3746 (1964). However, experimental evidence indicates that this steric hindrance is not as great as one would predict from an inspection of molecular models.

(7) In one reductive cleavage performed at 55–85° for 25 min, there was isolated in 20% yield a compound (mp 250–260°) with structure i. Evidence



i ii

for i was the presence of an imino band at 1670 cm^{-1} in the infrared spectrum. Also, hydrolysis of the product with 10% hydrochloric acid–methanol gave the 1-amino compound **10b**. Conclusive evidence for the structure of i was obtained by high-resolution mass spectrometry. Thus, the molecular ion M^+ was found to be 580.3649 (calcd for $C_{38}H_{46}NO_3$: 580.3662). The base peak (II) occurred at *m/e* 336 which is consistent with the predicted fragmentation of the imino structure i.



substitution at C-1 was finally accomplished by two different routes and the structure of the products confirmed as shown in Schemes I and II.

The results of some initial nitration experiments suggested that a weaker, that is, a more selective electrophilic reagent, should be tried. One such attacking species is the nitrosonium ion.[8] Accordingly, treatment of 4-hydroxyestrone 3-methyl ether (**2**)[9,10] with sodium nitrite in acetic acid (Scheme I) did, in fact, give a 1-substituted derivative, 4-hydroxy-1-nitroestrone 3-methyl ether (**3**), in a yield of 22%. Presumably, an intermediate 1-nitroso compound was formed which was rapidly oxidized to the nitro derivative (**3**).[8] The ring-A quinone (**8**)[11] was also obtained as an oxidative by-product. However, the nitrosation approach was not altogether satisfactory owing to low yields and the potential difficulty of removing the 4-hydroxyl group. Therefore, a different route was sought.

Diazo coupling is an electrophilic substitution reaction which is remarkably sensitive to small differences in electron density of the aromatic substrate.[12] At first it was thought that steric factors[6] might prevent reaction at the 1 position, but, on the contrary, the reaction of *p*-nitrobenzenediazonium chloride with 4-aminoestrone 3-methyl ether (**5**)[10,13] (Scheme II) gave the 1-coupled product (**6**) directly,[14] and in excellent yield. Preliminary evidence for the structure of the resulting 4-amino-3-methoxy-1-(*p*-nitrophenylazo)estra-1-3,5(10)-trien-17-one (**6**),[15] and also for that of **3**, was obtained by the following reactions. Reduction of **6** with zinc–acid[16] gave 1,4-diaminoestrone 3-methyl ether (**7**) and reduction of **3** with stannous chloride–hydrochloric acid gave 1-amino-4-hydroxyestrone 3-methyl ether (**4**). Neither **4** nor **7** was isolated in a pure state since both were very susceptible to oxidation and on treatment with ferric chloride–acetic acid gave the same *p*-quinone, **8**.[11] This quinone was also synthesized independently by the oxidation of **2** with Fremy's salt.[17] Thus, the 1-substituted structure of **3** and **6** was indicated. Subsequent transformations and spectral data reported herein confirmed this assignment. The aminoazo compound (**6**) was successfully converted to the desired indoloestrone (**1**) as shown in Scheme III.

Diazotization of **6** followed by treatment with hypophosphorous acid provided 3-methoxy-1-(*p*-nitrophen-

(8) P. B. D. De La Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation," Academic Press Inc., New York, N. Y., 1959, p 94.

(9) This compound was originally prepared[10b] by photodecomposition of the 4-diazonium salt. However, refluxing the diazonium salt in strong sulfuric acid is a more convenient procedure and gives excellent yields (see Experimental Section).

(10) (a) A. J. Tomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959); (b) S. Krazchy, *J. Am. Chem. Soc.*, **81**, 1702 (1959).

(11) The corresponding 17β-acetoxy compound (λ_{max} 274 mμ, ε 15,500) has been described by E. Hecker and R. Lattrell, *Ann.*, **662**, 48 (1963).

(12) (a) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961, p 199; (b) H. Zollinger and H. H. Bosshard, *Helv. Chim. Acta*, **44**, 1985 (1961).

(13) The preparation of **10b** was facilitated by the reduction of 4-nitroestrone 3-methyl ether[10a] to 4-aminoestrone 3-methyl with zinc–acetic acid. Under these conditions the next two steps can be carried out without isolation of the intermediate aminoazo compound **6** to give compound **9** in an over-all yield of 62%. With this modification, 1-aminoestrone 3-methyl ether (**10b**) can be prepared in five steps from 4-nitroestrone[10a] in an over-all yield of 40%.

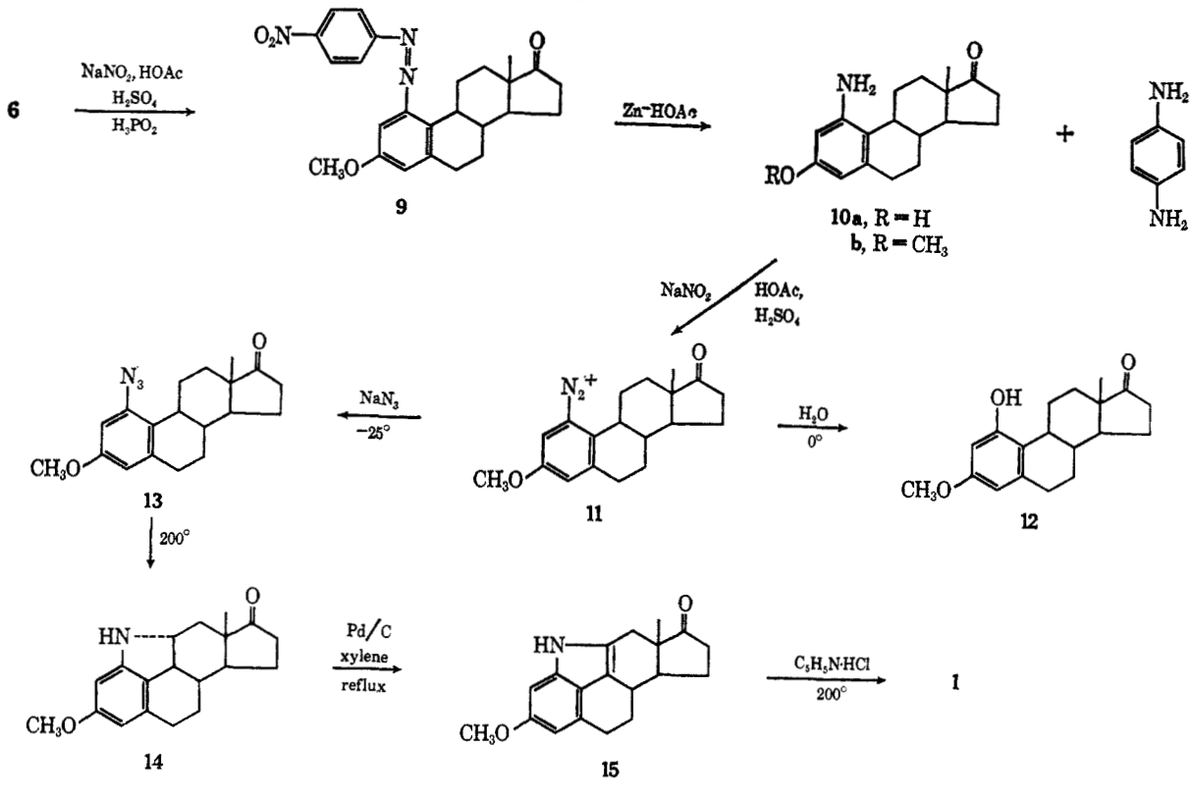
(14) The deep red, C-coupled product formed immediately and no evidence for an intermediate N-coupled product was observed. According to Zollinger (see ref 12a, p 178) direct C coupling is possible when the aromatic ring is appropriately substituted with activating groups.

(15) Previous workers [L. F. King and W. R. Franks, *J. Am. Chem. Soc.*, **63**, 2042 (1941), and J. B. Niederl and H. J. Vogel, *ibid.*, **71**, 2566 (1949)] obtained diazo-coupled products of estrone and estrone methyl ether but were unable to convert these to aminoestrones.

(16) M. Khalifa, *J. Chem. Soc.*, 1854 (1960).

(17) H. J. Teuber and G. Staiger, *Ber.*, **88**, 802 (1955); A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958).

SCHEME III



ylazo)estra-1,3,5(10)-trien-17-one (**9**) in 89% yield. Reductive cleavage of the azo function with zinc–acetic acid[16] at 40–45° [7] afforded the key intermediate, 1-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**10b**), in 70% yield.[13] Subsequent demethylation of the product (**10b**) by pyridine hydrochloride fusion gave 1-aminoestrone (**10a**) in a yield of 66%.

The infrared and nmr spectra of **10b** differed significantly from those of the corresponding isomeric 2-amino[10] and 4-aminoestrone 3-methyl ether[10] (see Figure 1). The nmr spectrum of **10b** showed two aromatic proton signals barely separated from each other at 366 and 367 cps. In contrast, the C-1 and C-4 protons in the 2-amino compound were seen as singlets at 388 and 397 cps, while in the 4-amino compound the C-1 and C-2 protons showed a single sharp line at 399 cps which integrated for two protons.

The next stage of the synthesis required the preparation of 1-azidoestrone 3-methyl ether (**13**) from the 1-amino compound (**10b**). The first attempt to carry out this conversion gave a 41% yield of 1-hydroxyestrone 3-methyl ether (**12**), resulting from hydrolysis of the diazonium derivative (**11**). The latter is very unstable[18] when compared to the isomeric diazonium derivatives of the 2-amino and 4-aminoestrone 3-methyl ether[10] and decomposes in a few seconds at 0°. The instability is probably ascribable to nonbonded interaction with the C-11 methylene group.[6] Subsequently it developed that if the temperature was lowered to −25° and the sodium azide added rapidly after complete diazotization had taken place, the azide could be prepared in 85% yield.

Smolinsky has shown that aryl azides on thermal or photolytic decomposition yield nitrenes[5] which, either

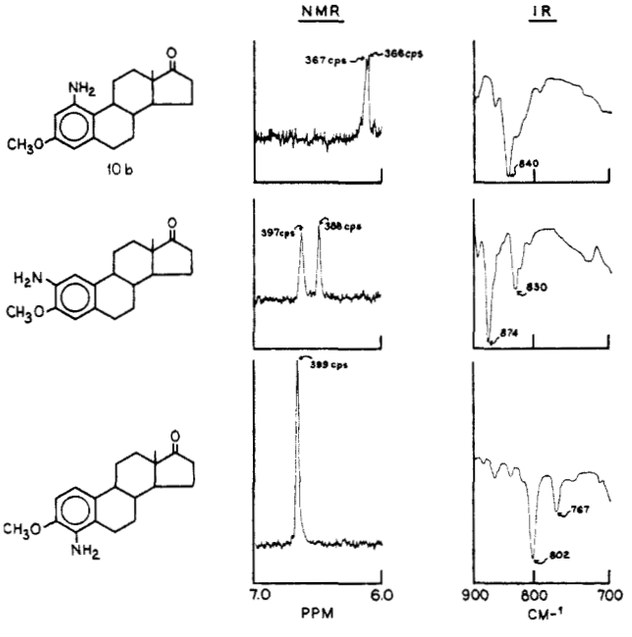


Figure 1.—Spectra of aminoestrone methyl ethers.

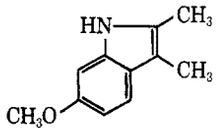
by a direct insertion (singlet process) or by abstraction of hydrogen and subsequent closure of the resulting diradical (triplet process), yield cyclic products. In particular he has shown that the thermal decomposition of *o*-azidoalkylbenzenes give indolines, possibly by a singlet process.[19] Thereby, it was anticipated that 1-azido 3-methoxyestra-1,3,5(10)-trien-17-one (**13**) on thermal decomposition would afford the corresponding 1,11-imino (indoline) derivative (**14**) because of the favorable, fixed positions of the azido and C-11 methylene groups. This expectation was realized on pyrol-

(18) Instability was also noted in the 1-diazonium derivative of 4-methylestra-1,3,5(10)-trien-17-one by D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964).

(19) G. Smolinsky, *J. Am. Chem. Soc.*, **83**, 2489 (1961); G. Smolinsky and B. I. Feuer, *ibid.*, **86**, 3085 (1964).

ysis[20] of **13** in *n*-hexadecane at 200° for 5 min to produce, in 73% yield, a product which has been assigned the structure 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**).[21] The amine (**10b**) and indole (**15**) were isolated as by-products of the reaction in yields of approximately 8 and 2%, respectively.

Dehydrogenation of **14** with palladium on charcoal gave a 90% yield of the indole, 1,11-imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**15**). The ultraviolet absorption spectrum of the latter was consistent with the indole chromophore. In fact, a comparison (see Figure 2) of its spectrum with that of 2,3-dimethyl-6-methoxyindole (**16**)[22] showed a high correspondence of absorption.



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Demethylation of the indole **15** with pyridine hydrochloride at 200° gave 3-hydroxy-1,11-iminoestra-1,3,5(10),9(11)-tetraen-17-one (**1**) in 81% yield.

Additional evidence for the N-bridged compounds was obtained by nmr and mass spectroscopic analyses. An examination of the Dreiding model of 1-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**10b**) indicated that the nitrene insertion reaction could occur at C-11 either from the α or β direction. The former appeared to be somewhat sterically favored when ring B assumes a normal half-chair conformation. In addition, if a two-step biradical mechanism pertained then the 11α face would be favored for ring closure since formation of the β isomer would require the nitrogen radical to form a bond by an approach which would be 1,3-diaxial to the C-18 methyl group.

The 60-Mc nmr spectrum of **14** did not indicate whether the C-9 and C-11 hydrogens were *cis* or *trans* relative to each other. However, it is known[23] that an 11β-hydroxyl group shifts the "normal" C-18 methyl signal about 15 cps downfield, while an 11α-hydroxyl group produces a similar shift of only 2 cps. The position of the C-18 methyl group signal of **14** (59 cps) is shifted only 2 cps downfield from that of the unbridged compound **10b** (57 cps), which observation supports assignment of the α configuration of the C-11–N bond. Conclusive evidence for the α-configurational assignment was obtained from nmr by spin–spin decoupling.[24] In the 100-Mc spectrum (Figure 3) of a fully N-deuterated sample of **14** (see Experimental Section and Figure 4), the C-11 proton signals show up as a well-defined octet centered at 3.45 ppm resulting from vicinal coupling with the C-9 axial proton and the two C-12 protons.

(20) Irradiation of the azide **13** (200-w, high-pressure Hanovia ultraviolet lamp, unfiltered light) in cyclohexane solution at room temperature gave five or six products, none of which appeared to be the desired 1,11-imino derivative (**14**) by tlc. While **14** was unstable under the same conditions, it gave a different multiplicity of products than did **13**.

(21) None of the 11β isomer could be detected, either by column, thin layer, or vapor phase chromatography of an acetylated sample of the total crude reaction mixture (see Experimental Section).

(22) N. Neuss, H. E. Boaz, and J. W. Forbes, *J. Am. Chem. Soc.*, **76**, 2463 (1954).

(23) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962); and E. Caspi, T. A. Wittstruck, and P. K. Grover, *Chem. Ind.* (London), 1716 (1962).

(24) We are indebted to Mr. J. L. Holcomb of Varian Associates, Palo Alto, Calif., for these data.

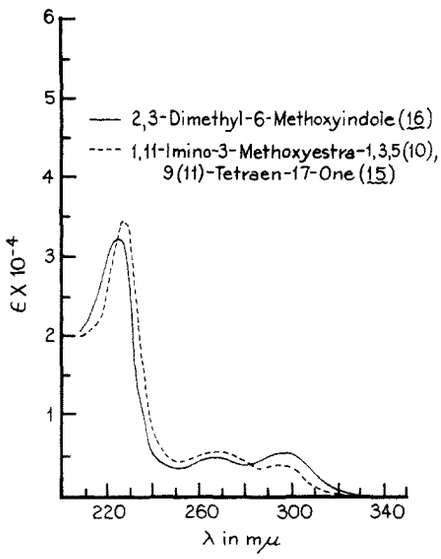


Figure 2.—Comparison of the ultraviolet spectra of 2,3-dimethyl-6-methoxyindole and 1,11-imino-3-methoxyestra-1,3,5-(10),9(11)-tetraen-17-one.

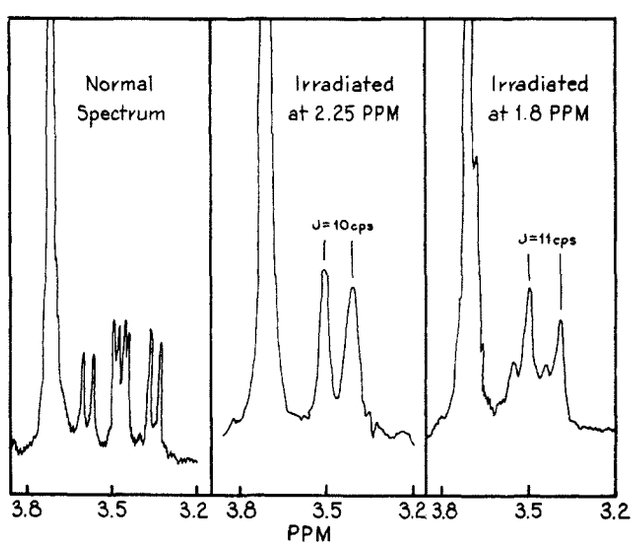


Figure 3.—100-Mc nmr spectra ($CDCl_3$) of the C-11β proton of N-deuterio-1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**).

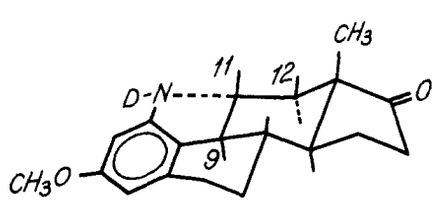


Figure 4.—N-Deuterio compound **14**.

Irradiation at this frequency then revealed the C-12 axial proton signal at 1.8 ppm and the C-9 axial plus C-12 equatorial protons signal at 2.25 ppm. When the lowest field group (2.25 ppm) was irradiated, the C-11 octet was reduced to a doublet having a typical axial–axial coupling constant of 10 cps, a result of the coupling of the C-11 proton with the C-12 axial proton. Irradiation of the high field group at 1.8 ppm produced a quartet at 3.45 ppm composed of a large coupling constant (J = 11 cps, axial–axial C-9 and C-11 protons) and a small coupling constant of J = 5 cps (axial–equatorial, C-11 and C-12β protons).

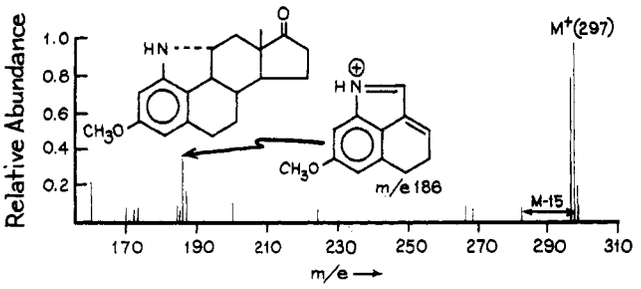


Figure 5.—Mass spectrum of **14**.

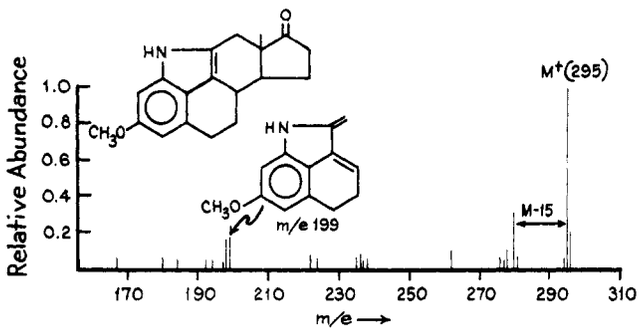
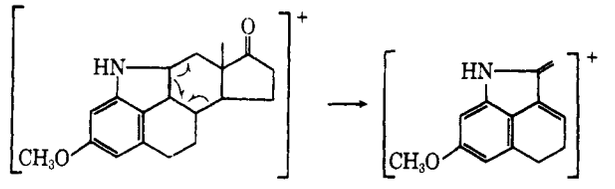


Figure 6.—Mass spectrum of **15**.

Mass spectrometry supplied additional evidence for the structures **14** and **15** (Figures 5 and 6, respectively). The strongest peak in the spectrum of **15** was the molecular ion M^+ (*m/e* 295), while in that of **14** there were two of comparable intensity at *m/e* 296 and 297. The intensity of the lower peak increased with time, indicating that **14** was undergoing dehydrogenation in the spectrometer. The second most abundant peak in the spectrum of **15** was the $M-CH_3$ peak at *m/e* 280. The third (*m/e* 199) has been assigned the structure **17**.



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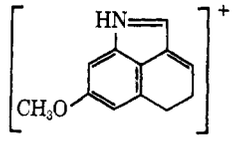
In the spectrum of the indoline **14** (Figure 5), there occurs a peak at *m/e* 186 to which has been assigned the structure **18**. Both of these assignments are consistent



18

with what is known about the fragmentation of 2,3-dialkylated indoles.[25]

Experimental Section

Thin layer chromatography was carried out on glass plates coated with a 0.25-mm layer of silica gel G (Merck, Darmstadt) containing approximately 0.3% Radelin Phosphor GS-115 (U. S. Radium Corp.). Development was effected with benzene–acetone–water 2:1:2 (upper phase) unless otherwise noted. In preparative work a 0.5-mm layer on 20 × 20 cm plates was used. After development, the chromatograms were visualized by ultraviolet light and by spraying with a 10% phosphomolybdic acid–methanol solution. Solutions were dried over anhydrous magnesium sulfate and all evaporations were under reduced pressure unless otherwise noted.

The following materials were used in the experiments: Magnesol, a hydrous magnesium silicate (Food Machinery Chemical Corp.); Celite, a diatomaceous silica (Johns-Manville); Florisil, a synthetic magnesium silicate adsorbent, 60–100 mesh (Floridin Corp.); silica gel, which refers to Mallinckrodt SilicAr, CC-7, 100–200 mesh; and Darco, activated carbon (Atlas Powder Co.).

Melting points were determined on a Mel-Temp apparatus in open capillaries and are uncorrected. Infrared spectra were determined in pressed potassium bromide disks on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were determined in methanol solution on a Cary Model 11 recording spectrophotometer. Optical rotations were measured at 25° in chloroform solution unless otherwise noted. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer with tetramethylsilane as internal standard in deuteriochloroform solution unless otherwise noted. The chemical shifts are expressed in parts per million (ppm). Mass spectra of **14** and **15** were determined on a CEC-103A spectrometer (Consolidated Electrodynamics Corp.) by T. Mead and associates, Stamford Research Laboratories, American Cyanamid Co. The high resolution mass spectrum[7] was determined on an AEI MS-9 spectrometer (Associated Electrical Industries Ltd.) by Dr. J. Karliner of these laboratories. The infrared and nuclear magnetic resonance spectra and optical rotations were performed by W. Fulmor, G. O. Morton, and associates, the elemental analyses by L. Brancone and associates, and the vapor phase chromatography by C. Pidacks and associates.

4-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**2**).—A solution of 6.9 g (20 mmoles) of 4-amino-3-methoxyestra-1,3,5-(10)-trien-17-one[10,13] in 115 ml of 22% (w/w) sulfuric acid at 5° was diazotized by the addition of a solution of 1.38 g (20 mmoles) of sodium nitrite in 10 ml of water. The solution was stirred for 5 min and then heated on the steam bath overnight (16 hr). The mixture was filtered to give 5.85 g of tan solid, mp 223–230°. Recrystallization from acetic acid afforded 4.98 g (83%) of tan crystals: mp 225–232°; λ_{max} 276–285 mμ (ε 2100); λ_{min} 252 (ε 375); $[\alpha]D$ +149° ($CHCl_3$); ν_{max}^{KBr} 3378, 1733, 1495, 797, 764 cm^{-1} (lit.[10b] mp 220–224° (methanol); $[\alpha]D$ +154° (ethanol); λ_{max} 277–283 mμ (ε 2110); λ_{min} 252 mμ (ε 370)).

4-Hydroxy-3-methoxy-1-nitroestra-1,3,5(10)-trien-17-one (**3**).—A suspension of 5.5 g (18.3 mmoles) of 4-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**2**) in aqueous acetic acid was prepared by the addition of 73 ml of ice water to a warm solution of the steroid in 146 ml of acetic acid.

To the resulting mixture, cooled to −5°, was added 1.26 g (18.3 mmoles) of solid sodium nitrite and the mixture stirred for 0.5 hr at −5 to −4°. Urea (0.22 g, 3.6 mmoles) was added and stirring was continued at −5° for an additional 15 min. The cold mixture was filtered through a bed of Celite to remove unreacted starting material (2.88 g, 52%) and the filtrate was diluted with 440 ml of water and refiltered to give 1.8 g of crude product.

Extraction of the aqueous filtrate with chloroform followed by chromatography of the extracted material (833 mg) on a silica gel column (80 g) using 15% acetone–petroleum ether (bp 30–75°) for final elution of the product gave 180 mg of a yellow solid which was identical in every respect with an authentic sample of 3-methoxyestra-2,5(10)-diene-1,4,17-trione (**8**).

The crude product (1.8 g), obtained previously by filtration of the diluted reaction mixture, was chromatographed, first on Florisil using 10% acetone–petroleum ether as eluant, and then on silica gel using 15% acetone–petroleum ether as eluant. However, neither of these procedures was effective in removing traces of the slightly less polar by-product, 3-methoxyestra-2,5-diene-1,4,17-trione (**8**). Purification was finally accomplished by crystallization from 75% aqueous methanol and again from 70% aqueous acetic acid, giving 447 mg of yellow crystals, mp 219–221°, which was completely pure by thin layer chromatography. When combined with second crop material (136 mg, mp 214–218°) the yield was 583 mg (22% yield): λ_{max} (neutral) 252, 362 mμ (ε 8450, 4100), (0.1 *N* NaOH) 270, 460 mμ (ε 6900, 15,800); ν_{max}^{KBr} 3500, 1510, 1486, 1330, 760 cm^{-1}; nmr (in d_6-DMSO), 7.37 (s, C-2 H), 3.86 (s, OCH_3), 0.83 ppm (s, C-18 CH_3).

(25) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier Publishing Co., Amsterdam, The Netherlands, 1960, pp 397–403.

Anal. Calcd for $C_{19}H_{23}NO_5$ (345.4): C, 66.07; H, 6.71; N, 4.06. Found: C, 66.25; H, 6.81; N, 3.82.

4-Amino-3-methoxy-1-(*p*-nitrophenylazo)estra-1,3,5(10)-trien-17-one (6).—To a stirred solution of 7.0 g (50.5 mmoles) of *p*-nitroaniline in 50 ml of glacial acetic acid and 75 ml of 2.0 *N* hydrochloric acid (150 mmoles) at −5° was added a solution of 3.48 g (50.1 mmoles) of sodium nitrite in 15 ml of water below the surface of the liquid and stirring was continued for 15 min.

The resulting solution of *p*-nitrobenzene diazonium chloride was poured into a well-stirred solution of 14.97 g (50.0 mmoles) of 4-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**5**)[13] (mp 189–193°) in 250 ml of glacial acetic acid and 25 ml of 5.0 *N* sodium hydroxide (125 mmoles) at room temperature. The deep red mixture was diluted with 1 l. of water, allowed to stand overnight, then filtered, and the product washed thoroughly on the filter with water. The yield of crude material after being dried was 21.0 g (94%), mp 185–190°.

The crude product, which contained some combined hydrogen chloride, was dissolved in methylene chloride (250 ml), and then methanol (500 ml) plus triethylamine (5.0 ml) were added portionwise to the boiling solution until all of the methylene chloride had been removed. The resulting mixture afforded 19.61 g (87% yield) of very deep red crystals, mp 242–243° dec, which contained only minor impurities by thin layer chromatography and was sufficiently pure for the next step.

A pure sample was obtained by chromatography on Florisil using 15% ether–benzene as eluent. Crystallization of the product from methylene chloride–methanol, as above, gave material of mp 243–244° dec; λ_{max} 280, 406 mμ (ε 10,000, 24,750); $[\alpha]_{6907A}$ −468°; ν_{max}^{KBr} 3370, 1511, 1479, 1332, and 856 cm^{-1}; nmr (in d_6-DMSO), 8.33 (m, [*o*-NO_2] H), 7.80 (m, [*o*-N=N] H), 7.37 (s, C-2 H), 3.85 (s, OCH_3), 0.87 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{25}H_{28}N_4O_4$ (448.53): C, 66.94; H, 6.29; N, 12.49. Found: C, 66.97; H, 6.34; N, 12.35.

3-Methoxyestra-2,5(10)-diene-1,4,17-trione (8). A. From 4-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (2).—To a solution of 3.22 g (12.0 mmoles) of potassium nitrosodisulfonate (Fremy's salt) and 1.32 g (16.0 mmoles) of sodium acetate in 250 ml of water was added a solution of 1.8 g (6.0 mmoles) of 4-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**2**) in 180 ml of acetone and the mixture was stirred at room temperature for 3 hr.

The mixture was diluted with approximately 200 ml of water and extracted with chloroform. The extract was dried, filtered through Celite, and evaporated to a yellow oil which, on being mixed with ether, gave 1.826 g (97% yield) of yellow crystals, mp 170–179°. A single crystallization from methylene chloride–ether gave 1.66 g: mp 179–180.5°; λ_{max} 274 mμ (ε 16,700); $[\alpha]_D$ +282°; ν_{max}^{KBr} 1675, 1645, 1600, 1227, and 842 cm^{-1}; nmr (in d_6-DMSO), 5.98 (s, C-2 H), 3.75 (s, OCH_3), 0.83 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{19}H_{22}O_4$ (314.37): C, 72.59; H, 7.05. Found: C, 72.50; H, 7.26.

B. From 4-Hydroxy-3-methoxy-1-nitroestra-1,3,5(10)-trien-17-one (3).—To a solution of 60.0 mg (0.174 mmole) of 4-hydroxy-3-methoxy-1-nitroestra-1,3,5(10)-trien-17-one (**3**) in 10 ml of acetic acid was added a solution of 126 mg (0.61 mmole) of stannous chloride dihydrate in 1.0 ml of concentrated hydrochloric acid. The mixture was stirred and heated at 60–70° for 1 hr, then an additional 90 mg (0.435 mmole) of stannous chloride dihydrate in 1.0 ml of concentrated hydrochloric acid was added and heating continued at 60–70° for 4 hr. The mixture was made basic with 10 g (0.25 mole) of sodium hydroxide in 80 ml of water, and then reacidified with 5 ml of acetic acid and extracted with chloroform. Work-up of the extract gave 52 mg (95%) of a tan solid which was very susceptible to air oxidation.

To the above aminophenol (**4**, 50 mg 0.159 mmole) in 10 ml of acetic acid was added a solution of 50 mg (0.184 mmole) of ferric chloride hexahydrate in 1.0 ml of concentrated hydrochloric acid. The solution was stirred for 15 min at room temperature, and then made basic with dilute sodium hydroxide solution and extracted with chloroform. Work-up of the extract afforded a crude tan product which was purified by preparative thin layer chromatography, giving 32 mg (63% yield) of a yellow crystalline solid which was identical in every respect with the product obtained from part A above.

C. From 4-Amino-3-methoxy-1-(*p*-nitrophenylazo)estra-1,3,5(10)-trien-17-one (6).—To a suspension of 224 mg (0.5 mmole) of 4-amino-3-methoxy-1-(*p*-nitrophenylazo)estra-1,3,5(10)-trien-17-one (**6**) in 10 ml of acetic acid was added 0.5 g of zinc dust and the mixture stirred, without cooling, until it was completely decolorized (10 min). The mixture was filtered, 1.35 g (5.0 mmoles) of ferric chloride hexahydrate was added to the filtrate followed by 1.0 ml of water, and the solution was heated on the steam bath for 2 hr. Water (50 ml) was added and the dark mixture was extracted with chloroform. The extract was washed with water, dried, treated with Darco, and filtered through Celite. Evaporation of the filtrate gave 140 mg of a dark semisolid which was subjected to preparative thin layer chromatography. The two leading yellow bands of the chromatogram were isolated and the least polar band ($R_f \approx 0.6$) consisted of 25 mg of a greenish yellow crystalline solid which was identical with an authentic sample of *p*-benzoquinone. The second band ($R_f \approx 0.48$) consisted of 61 mg (39% yield) of material which was identical with the 3-methoxyestra-2,5(10)-diene-1,4,17-trione (**8**) obtained in sections A and B above.

3-Methoxy-1-(*p*-nitrophenylazo)estra-1,3,5(10)-trien-17-one (9). A. From 4-Amino-3-methoxy-1-(*p*-nitrophenylazo)estra-1,3,5(10)-trien-17-one (6).—To a stirred solution of 17.94 g (0.04 mole) of 4-amino-3-methoxy-1-(*p*-nitrophenylazo)estra-1,3,5(10)-trien-17-one (**6**), mp 242–243° dec, in 400 ml of glacial acetic acid and 100 ml of 30% with aqueous sulfuric acid at 0° was added a solution of 3.04 g (0.044 mole) of sodium nitrite in 30 ml of water below the surface of the liquid. Stirring was continued at 0° for 15 min, then 450 ml of 50% aqueous hypophosphorous acid was added, and the mixture was stirred overnight (16 hr) at room temperature.

The precipitate was filtered, washed thoroughly with water, and dried to give 16.4 g (95% yield) of a crude red-brown product, mp 203–205°. Crystallization from methylene chloride–methanol gave 15.31 g (89% yield) of red crystals, mp 216–219°, which contained only trace impurities by thin layer chromatography and was sufficiently pure for use in the next step.

Chromatography of a sample on Florisil using 5% ether–benzene as eluent, followed by crystallization of the product from methylene chloride–methanol, gave an analytical sample: mp 223–224°; λ_{max} 279, 350 mμ (ε 9500, 16,200); $[\alpha]_{6907A}$ −348°; ν_{max}^{KBr} 1520, 1340, and 860 cm^{-1}; nmr, 8.36 (m, [*o*-NO_2] H), 7.91 (m, [*o*-N=N] H), 7.06 (m, C-2 H), 6.85 (m, C-4 H), 3.83 (s, OCH_3), 0.97 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{25}H_{27}N_3O_4$ (433.51): C, 69.26; H, 6.28; N, 9.69. Found: C, 69.28; H, 6.28; N, 9.56.

B. From 3-Methoxy-4-nitroestra-1,3,5(10)-trien-17-one[10a] without Isolation of Intermediates.—To a stirred suspension of 16.46 g (0.05 mole) of 3-methoxy-4-nitroestra-1,3,5(10)-trien-17-one in 250 ml of acetic acid at room temperature was added 19.6 g (0.3 g-atom) of zinc dust in one portion; the mixture stirred for 1 hr. During this time the temperature rose rapidly to 76° and then gradually fell to 40°. The mixture was filtered and the residue of zinc was washed on the filter with acetic acid (50 ml). The total filtrate was used for the next step.

A solution of *p*-nitrobenzene diazonium chloride was prepared by the addition of a solution of 3.48 g (0.05 mole) of sodium nitrite in 12 ml of water to a well-stirred solution of 7.0 g (0.05 mole) of *p*-nitroaniline in 50 ml of acetic acid plus 100 ml of 2 *N* hydrochloric acid (0.2 mole) at 0 to −5°. The addition was carried out below the surface of the liquid to avoid loss of nitrous fumes. The resulting diazonium solution was added to the filtrate from step 1 at room temperature. An immediate deep red solution was obtained which was stirred for approximately 5 min before proceeding with step 3.

The deep red solution from step 2 was cooled to 0° and then a solution of 3.48 g (0.05 mole) of sodium nitrite in 12 ml of water was added below the surface of the liquid. The resulting red-brown solution was stirred for 5 min, then diluted with 600 ml of 25% aqueous hypophosphorous acid and stirring continued 2 hr at room temperature. The product was filtered off, washed thoroughly with water, and vacuum dried to give 16.8 g of crude product which was dissolved in methylene chloride (150 ml) and filtered through Magnesol (17 g) using 250 ml of methylene chloride wash. The filtrate was concentrated to a small volume and crystallized from methanol to give 13.35 g (62% yield) of product, mp 208–211°, which contained minor impurities by tlc.

1-Amino-3-methoxyestra-1,3,5(10)-trien-17-one (10b).—A solution of 13.0 g (0.03 mole) of 3-methoxy-1-(*p*-nitrophenylazo)-estra-1,3,5(10)-trien-17-one (**9**) (mp 215–217°) in 100 ml of methylene chloride was added to a stirred mixture of 30 g of zinc dust in 300 ml of glacial acetic acid over approximately 10 min. The initial temperature of 23° soon rose to 40–45° and was maintained[7] in this range during the reaction by occasional

cooling with a water bath. An additional 30 g of zinc dust was added after half of the steroid had been fed in. The mixture was stirred for an additional 10 min, then filtered, and the residue of zinc was washed on the filter with acetic acid. The filtrate was concentrated to approximately 125 ml, diluted with 500 ml of water, and extracted with chloroform. The extract was washed with two portions of water, dried, concentrated to a volume of 100 ml, and filtered through a bed of Magnesol (60 g) using 300 ml of chloroform wash. The filtrate was concentrated to a small volume and crystallized from methanol to give 5.58 g of a grey solid, mp 198–208°, which contained a trace of *p*-phenylenediamine impurity. An additional 1.0 g of product, mp 209–213°, was obtained by chromatography of the filtrate on Florisil using 20% ethyl acetate–*n*-hexane as eluent, followed by crystallization of the product from methylene chloride–ether. The total yield of product was therefore 6.58 g (73%). Analytical material was obtained by chromatography of a sample on Florisil, as above, followed by crystallization from methanol to give a white crystalline product: mp 213–214°; λ_{max} 245 (sh), 291 mμ (ε 6720, 3000); $[\alpha]D$ +301; ν_{max}^{KBr} 3425, 3344, 1149, and 840 cm^{-1}; nmr, 6.10 6.11 (d, C-2 + C-4 H), 3.70 (s, OCH_3), 0.95 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{19}H_{25}NO_2$ (299.40): C, 76.22; H, 8.42; N, 4.68. Found: C, 76.37; H, 8.45; N, 4.63.

1-Amino-3-hydroxyestra-1,3,5(10)-trien-17-one (10a).—To 25.0 g of molten pyridine hydrochloride at 200° was added 2.5 g (8.35 mmoles) of 1-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**10b**). The mixture was stirred briefly and heating was continued at 200–210° for 15 min in an atmosphere of argon.

The melt was cooled, dissolved in 40 ml of water, made basic with 120 ml of 2 *N* sodium hydroxide, and reacidified with 5 ml of acetic acid. The precipitate was extracted with three 150-ml portions of chloroform; the extract was washed with water, dried over sodium sulfate, treated with Darco, filtered through Celite, and evaporated in the presence of toluene (to completely remove pyridine). The resulting crude product (2.27 g, 96%) contained an appreciable amount of "dimer"[7] and was refluxed in 100 ml of 10% (v/v) concentrated hydrochloric acid in methanol for 2.5 hr. The dark solution was concentrated, made basic with 50 ml of 2 *N* sodium hydroxide, and reacidified with 2 ml of acetic acid. The precipitate (1.95 g) was filtered and the filtrate extracted with chloroform. Work-up of the extract afforded an additional 0.24 g of product.

The total product (2.19 g) was crystallized from methanol to give 1.42 g of dark tan solid, mp 275–280° dec, which was crystallized again from methanol giving 1.14 g of a tan solid. The filtrates from both crystallizations were evaporated, dissolved in chloroform, and filtered through Magnesol. Elution of the Magnesol with ethyl acetate gave an additional 430 mg of recovered product. Thus the total yield of product was 1.57 g (66%).

The analytical sample was prepared by chromatograpy of the product on a silica gel column using 1:1 ethyl acetate–*n*-hexane for final elution of the product. The resulting tan solid melted at 280–285° with decomposition: λ_{max} 212, 240 (sh), 292 mμ (ε 40,000, 7850, 3080); $[\alpha]D$ +264° (pyridine); ν_{max}^{KBr} 3413 (sh), 3350, 1710, 823 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_2$ (285.37): 7, 75.75; H, 8.12; N, 4.91. Found: C, 75.97; H, 8.10; N, 5.09.

1-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (12).—A solution of 600 mg (2 mmoles) of 1-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**10b**) in 20 ml of 10% (w/w) sulfuric acid at −10° was diazotized by the addition of a solution of 138 mg (2 mmoles) of sodium nitrite in 2 ml of water below the surface of the liquid. An immediate evolution of nitrogen and separation of a pink solid occurred. The mixture was allowed to warm to 0° and was diluted with water and the product filtered off. The crude solid (610 mg) was refluxed with benzene and the resulting solution treated with Darco, filtered through Celite, and placed on a silica gel column (50 g). The product was eluted from the column with 2% acetone–benzene (1.6 l.) and crystallized from methylene chloride–*n*-hexane to give 430 mg (71% yield) of off-white crystals, mp 222–231°. Analytical material was obtained by two additional crystallizations from methylene chloride–*n*-hexane followed by a final crystallization from ethyl acetate. The resulting colorless crystalline product was pure by thin layer chromatography and melted at 231–234°: λ_{max} 227 (sh), 280, 286 mμ (ε 8100, 1950, 1950); $[\alpha]D$ +262° (chloroform); ν_{max}^{KBr} 3247, 1724, 1144, 1064, and 826 cm^{-1}; nmr (in d_6-DMSO), 6.25 (m, C-2 H), 6.10 (m, C-4 H), 3.63 (s, OCH_3), 0.85 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{19}H_{24}O_3$ (300.4): C, 75.97; H, 8.05. Found: C, 75.75; H, 8.35.

1-Azido-3-methoxyestra-1,3,5(10)-trien-17-one (13).—To a stirred solution of 20.0 g (0.067 mole) of 1-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**10b**) (mp 198–208°) in 300 ml of acetic acid plus 201 ml of 1.0 *N* sulfuric acid (0.201 equiv) at −25° (Dry Ice–acetone bath) was added a solution of 5.0 g (0.072 mole) of sodium nitrite in 15 ml of water below the surface of the liquid. The solution was stirred for 2 min; then a solution of 17.4 g (0.268 mole) of sodium azide in 60 ml of water was added as quickly as the resulting vigorous evolution of nitrogen would allow.

The orange mixture was stirred for 1–2 min, then diluted with 500 ml of water, and extracted with chloroform. The extract was washed with water, saturated sodium bicarbonate solution, and finally with water and dried over anhydrous sodium sulfate. The resulting chloroform solution (approximately 550 ml) was filtered through a bed of Magnesol (100 g) and the Magnesol was washed with an additional 350 ml of chloroform. The filtrate was evaporated to a yellow oil which on trituration with ether afforded 18.4 g (85% yield) of a pale tan solid, mp 141–145°, which was pure by thin layer chromatography. A single crystallization from methylene chloride–methanol gave the analytical sample: mp 147–149°; λ_{max} 218, 255, 293, 303 mμ (sh) (ε 23,000, 6500, 3620, 3000); $[\alpha]D$ +235°; ν_{max}^{KBr} 2100, 1062, and 831 cm^{-1}; nmr, 6.47 (m, C-2 + C-4 H), 3.75 (s, OCH_3), 0.96 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{19}H_{23}N_3O_2$ (325.4): C, 70.13; H, 7.12; N, 12.91. Found: C, 69.81; H, 7.33; N, 12.84.

1,11α-Imino-3-methoxyestra-1,3,5(10)-trien-17-one (14).—To 150 ml of purified hexadecane at 200° was added 7.96 g (24.5 mmoles) of 1-azido-3-methoxyestra-1,3,5(10)-trien-17-one (**13**) and the mixture stirred at 190–210° for 7 min in a nitrogen atmosphere. The mixture was cooled, filtered, and the product washed with hexane, Additional product was recovered from the filtrate by filtration through 20 g of Magnesol which was then washed with hexane to remove traces of hexadecane. The solid product which was previously separated by filtration was dissolved in methylene chloride and filtered through the same Magnesol as used above. Thorough elution of the Magnesol with methylene chloride followed by evaporation of the filtrate gave a total of 7.18 g of crude, tan product which was divided in half and purified by methods A and B, below.

Method A.—Half of the crude product (3.58 g) was acetylated by briefly warming with 100 ml of acetic acid plus 5 ml of acetic anhydride and allowing to stand for 30 min. Water (50 ml) was then added, the solution warmed for 30 min, diluted with 200 ml of water, and extracted with methylene chloride. The extract was washed with water and saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated to 4.06 g of tan solid.

Vapor phase chromatography (F & M model 400 gas chromatograph, column packing Chromosorb G, Johns Manville) of the acetylated mixture indicated that it consisted of a mixture of 1,11-imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**15**), and the N-acetyl derivatives of 1-amino-3-methoxyestra-1,3,5-(10)-trien-17-one (**10b**) and 1,11α-imino-3-methoxyestra-1,3,5-(10)-trien-17-one (**14**) in a mole ratio of approximately 2:6:73, respectively. This result was in good agreement with that obtained by column chromatography of the acetylated mixture on 240 g of silica gel. Thus, elution of the column with 3% acetone–benzene gave impure **15** which was purified further by tlc (10% acetone–benzene) to give 73 mg (2%) of a brown glass; infrared and ultraviolet spectra were identical with those of an authentic sample of **15**. Further elution of the column with 5% acetone–benzene gave N-acetylated **14** which on crystallization from methylene chloride–methanol afforded 3.05 g (73%) as colorless crystals, mp 250–254°. Finally, elution of the column with 7% followed by 10% acetone–benzene gave N-acetylated **10b** which was purified further by tlc (20% acetone–benzene) to give 352 mg (8%) of a tan solid, mp 170–190°, whose infrared spectrum was identical with those of an authentic sample of N-acetylated **10b**.

The N-acetyl derivatives obtained above were hydrolyzed by refluxing in 30% hydrochloric acid–methanol for 3 hr. The solution was made basic with 5 *N* sodium hydroxide and extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate, and evaporated. The resulting residue

was crystallized from methylene chloride–methanol. In this way N-acetylated **10b** gave material with mp 212–214°, identical in every respect with a known sample of 1-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**10b**). The main product afforded colorless crystals (2.40 g) of 1,11α-imino-3-methoxy-estra-1,3,5(10)-trien-17-one (**14**), mp 199–201°. Material of comparable purity, obtained from another run, had the following properties: λ_{max} 212, 235 (sh), 293 mμ (ε 28,000, 5800, 3550); $[\alpha]D$ +164°; ν_{max}^{KBr} 3300, 1130, 824, 794, and 667 cm^{-1}; nmr, 6.20 (s, C-2 + C-4 H), 3.72 (s, OCH_3), 0.98 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{19}H_{23}NO_2$ (297.38): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.81; H, 7.70; N, 4.66.

Method B.—The second half of the crude product was warmed and stirred with 125 ml of 1 *N* hydrochloric acid. The aqueous solution was decanted from some dark insoluble material, extracted with ether, and made basic with 30 ml of 5 *N* sodium hydroxide solution. The mixture was extracted with methylene chloride, the extract washed with water, dried over sodium sulfate, and evaporated to 2.85 g of tan solid. This material was acetylated as in method A and the product crystallized from methylene chloride–methanol to furnish 2.82 g (68%) pale tan crystals, mp 249–253°, which was pure N-acetylated **14** by infrared and tlc analysis. Hydrolysis of the product, as in method A, followed by a single crystallization from methylene chloride–methanol, gave 2.26 g of 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**), mp 199–200°.

1,11α-Deuterioimino-3-methoxyestra-1,3,5(10)-trien-17-one.—1-Butanol (5 ml) was shaken with three 5-ml portions of heavy water (Matheson Coleman and Bell, 99.5 mole %) taking 2–3 min for each equilibration. The resulting deuterated 1-butanol was dried over anhydrous sodium sulfate, filtered, and warmed for a few minutes on the steam bath with 200 mg of 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**) (mp 199–201°). The solution was allowed to stand overnight at room temperature, then evaporated to give 194 mg of colorless crystals, mp 198–202°, which were completely N-deuterated as shown by nmr analysis.

1,11-Imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (15).—A mixture of 892 mg (3.0 mmoles) of 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**) and 300 mg of 10% palladium on carbon (Baker) in 45 ml of xylene was stirred and refluxed for 1 hr. After cooling to room temperature, the mixture was filtered through 18 g of Magnesol which was washed with *n*-hexane to remove the xylene and the product desorbed with 250 ml of methylene chloride. Evaporation of the methylene chloride filtrate gave 847 mg (95% yield) of white crystalline product, mp 197–201°. Crystallization from methanol in the presence of 1 drop of pyridine gave 739 mg, mp 202–204°, plus a second crop of 56 mg, mp 199–203°. Hence, the total yield of crystallized product was 794 mg (90%).

A single recrystallization from methanol gave an analytical sample: mp 203–205°; λ_{max} 229, 272, 298 mμ (ε 34,000, 5470, 3690); $[\alpha]D$ +225°; ν_{max}^{KBr} 3344, 1730, 1289, 1185, 1135, 819, and 802 cm^{-1}; nmr, 6.53 (s, C-2 + C-4 H), 3.75 (s, OCH_3), 1.15 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{19}H_{21}NO_2$ (295.37): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.33; H, 7.28; N, 4.85.

3-Hydroxy-1,11-iminoestra-1,3,5(10),9(11)-tetraen-17-one (1).—To 25.0 g of pyridine hydrochloride at 200° was added 1.1 g (3.72 mmoles) of 1,11-imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**15**) and the mixture was heated at 200–210° for 10 min in an atmosphere of argon. The mixture was cooled and dissolved in 75 ml of water. The tan precipitate (0.73 g) was filtered off and the filtrate was extracted with chloroform. Work-up of the extract gave an additional 0.23 g of crude product. The total product (0.96 g) was crystallized from methanol to give 851 mg (81% yield) of off-white crystals decomposing over the range 290–300°.

A single recrystallization from methanol gave material of analytical purity and unchanged decomposition point: λ_{max} 229, 270, 301 mμ (ε 32,000, 5080, 3530); $[\alpha]D$ +331° (pyridine); ν_{max}^{KBr} 3380, 1725, 1133, 1062, and 828 cm^{-1}; nmr (in d_6-DMSO), 6.47 (m, C-2 H), 6.27 (m, C-4 H), 4.58 (m, OH), 1.12 ppm (s, C-18 CH_3).

Anal. Calcd for $C_{18}H_{19}NO_2$ (281.34): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.67; H, 7.06; N, 5.31.

Registry No.—**1**, 13211-86-4; **2**, 5976-62-5; **3**, 13871-33-5; **6**, 6654-12-2; **8**, 13871-34-6; **9**, 6654-39-3; **10a**, 6770-02-1; **10b**, 6654-42-8; **12**, 13871-38-0; **13**, 6654-40-6; **14**, 13871-40-4; **15**, 13211-82-0.

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Syntheses with Partially Benzylated Sugars. X.[1] A New Method for the Synthesis of Ketoses

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A sequence of reactions which involves the reduction of C-1 in a partially benzylated aldose and subsequent oxidation at C-4 or C-5 has been studied as a means of converting aldoses into ketoses. In the hexopyranose series the following transformations were carried out (Scheme I): 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) → 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**2**) → 2,3,4,6-tetra-*O*-benzyl-1-*O*-triphenylmethyl-D-glucitol (**3**) → 1,3,4,5-tetra-*O*-benzyl-6-*O*-triphenylmethyl-*keto*-L-sorbose (**5**) → 1,3,4,5-tetra-*O*-benzyl-L-sorbopyranose (**6**) → L-sorbose (**7**); the over-all yield from **1** to **7** was 33%. In the pentofuranose series an analogous procedure was applied to the synthesis of D-*threo*-pentulose (D-xylulose, Scheme II, **17**). 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**8**) was reduced to 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**) from which both 2,3,5-tri-*O*-benzyl-1-*O*-triphenylmethyl-D-arabinitol (**11**) and 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinitol (**13**) were prepared. Oxidation of **11** and **13** with dimethyl sulfoxide–acetic anhydride gave 1,3,4-tri-*O*-benzyl-5-*O*-triphenylmethyl-*keto*-D-*threo*-pentulose (**14**) and 5-*O*-benzoyl-1,3,4-tri-*O*-benzyl-*keto*-D-*threo*-pentulose (**15**), respectively; removal of the masking groups from **14** or from **15** gave D-*threo*-pentulose (**17**). The potential utility of this general synthetic approach for the synthesis of substituted or otherwise difficultly accessible ketoses is pointed out. In pyridine solution at room temperature tosyl chloride converts 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**) into 1,4-anhydro-2,3,5-tri-*O*-benzyl-D-arabinitol (Scheme III, **18**). Two crystalline derivatives of **8**, namely, 2,3,5-tri-*O*-benzyl-D-arabinono-1,4-lactone (**21**) and *N*-benzyl-2,3,5-tri-*O*-benzyl-D-arabinonamide (**22**), are described.

Compared with the aldoses, the ketoses are less frequently encountered in nature and the methods available for their synthesis are both fewer and often either laborious or of limited applicability. For these reasons, our knowledge of the chemistry of the ketoses is rather narrower than that of the aldoses. The

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