small amount of hot water. The solution was placed in the refrigerator and crystallization occurred, yielding 88 mg (63%) of crude product, mp 233–242°, in three crops. The combined solids were dissolved in a small amount of hot water, the solution was decolorized with Norite A, and the product was allowed to crystallize, first at room temperature then in the refrigerator. After a second recrystallization, pure 9-α-D-lyxofuranosyladenine (**4**) was obtained as irregular white crystals (46 mg, 33%), mp 248–250°; $[\alpha]^{23}D$ +93.8° (*c* 0.3, water); $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,600).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.20. Found: C, 44.82; H, 4.95; N, 26.25.

To 10.90 mg of 9-α-D-lyxofuranosyladenine, 1.5 ml of 0.08 *M* sodium periodate was added, and the mixture was allowed to stand at room temperature for 30 min. To the solution 40 mg of sodium borohydride was added and, after 30 min, 0.5 ml of 10% acetic acid was slowly added. When gas evolution ceased (90–120 min), the specific rotation of the solution was obtained, $[\alpha]^{23}D$ −65.0°. Authentic adenosine treated in the same manner showed $[\alpha]^{23}D$ +68.1° (lit.[5b] +66° for 9-β-D-ribofuranosyladenine, −66° for 9-α-D-ribofuranosyladenine). These results indicate that the lyxofuranosyladenine had an α configuration.

1-Substituted Estrone 3-Methyl Ethers

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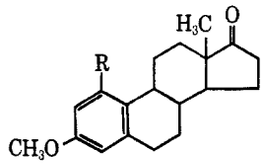
We wish to report the preparation of some 1-substituted derivatives (**5**–**13**) of estrone 3-methyl ether from 1-aminoestrone 3-methyl ether (**1**).[1a]

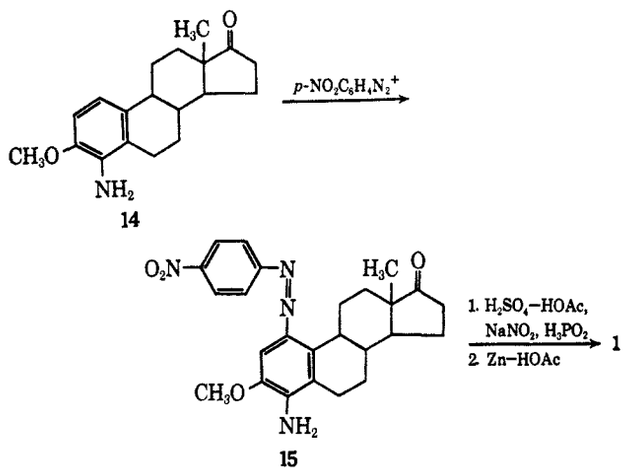


1, R = NH_2	**8**, R = OCH_3
2, R = $N{\equiv}N^+$	**9**, R = $OCOCH_3$
3, R = OH	**10**, R = F
4, R = N_3	**11**, R = Cl
5, R = $NHCH_3$	**12**, R = Br
6, R = $N(CH_3)_2$	**13**, R = I
7, R = $N{=}CHC_6H_5$	

In the aromatic substitution reactions of estrone the attacking species is directed, in a normal way, *ortho* to the C-3 hydroxyl group.[2] It is not surprising, therefore, that while a variety of 2- and 4-substituted derivatives of estrone have been reported,[2] relatively few 1-substituted compounds have been prepared.[3]

With few exceptions,[3d] the only 1-substituted estra-1,3,5(10)-trienes are those derived, either directly or indirectly, from the dienone–phenol[3a,b] or related[3c] rearrangements. Of these compounds only the 1-hydroxy[3a] and 1-methyl[3a] derivatives are oxygenated at the 3 position. Hence this approach was not considered to be readily adaptable[4] to the general preparation of 1-substituted estrone 3-methyl ethers.

Previously we reported on the coupling of 4-aminoestrone 3-methyl ether (**14**) with *p*-nitrobenzene diazonium chloride to give the 1-azo-4-amino derivative (**15**) in good yield.[1a,b] This reaction provided the key to the successful preparation of 1,11-iminoestrones[1a] *via* the intermediate 1-aminoestrone 3-methyl ether (**1**).



14

15

Because of the synthetic utility of arylamines, the 1-amino compound (**1**) proved to be a valuable intermediate for the preparation of a variety of other 1-substituted derivatives of estrone 3-methyl ether, as exemplified by the following syntheses.

When the amine (**1**) was refluxed with methyl iodide and potassium carbonate in methanol for 4 hr, a 1:5 mole ratio of the mono- (**5**) and dimethyl (**6**) derivatives was obtained. After being refluxed for 21 hr the amine (**1**) was completely converted to its dimethyl derivative. No evidence of any quaternary salt was found after this time. The absence of quaternization is probably due to steric hindrance with the 11-methylene group. In this connection, Nagata and coworkers[5] have shown by nuclear magnetic resonance (nmr) studies that appreciable interaction exists between the C-1 and C-11α protons.

The benzylidene derivative (**7**) of 1-aminoestrone 3-methyl ether (**1**) was obtained in 80% yield by refluxing a solution of **1** and benzaldehyde in benzene with azeotropic removal of water during the reaction.

Previously it was noted[1a] that the 1-diazonium salt

(1) (a) E. W. Cantrall, R. B. Conrow, and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 2943 (1964). For the full paper, see E. W. Cantrall, R. B. Conrow, and S. Bernstein, *J. Org. Chem.*, **32**, 3445 (1967). (b) This coupling reaction was also successfully applied to 4-amino-2,3-dimethoxyestra-1,3,5(10)-trien-17-one in the preparation of 1,2,3-trimethoxyestra-1,3,5(10)-trien-17β-ol [R. B. Conrow, E. W. Cantrall, and S. Bernstein, *Steroids*, **9**, 307 (1967)].

(2) For examples of some aromatic substitution reactions of estrone and estrone 3-methyl ether, see: (a) nitration, A. J. Tomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959); (b) halogenation, E. Schwenk, C. G. Castle, and E. Joachim, *ibid.*, **28**, 136 (1963); (c) dialkylaminomethylation, T. L. Patton, *ibid.*, **25**, 2148 (1960); (d) chloromethylation, W. F. Johns, *ibid.*, **30**, 3993 (1965); (e) thiomethoxymethylation, M. G. Burdon and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 4656 (1965).

(3) (a) R. H. Shapiro, "Steroid Reactions," C. Djerassi, Ed., Holden-Day Inc., San Francisco, Calif., 1963, pp 373–402. (b) In an adaptation of Scherrer's procedure (R. A. Scherrer, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 33Q), Morrow and Butler converted 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one to 1-amino-4-methylestra-1,3,5(10)-trien-17-one and then to the 1-bromo and 1-fluoro derivatives *via* the diazo reaction [D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964)]. (c) Androsta-1,4-diene-3,17-dione was converted by Moersch, *et al.*, to 3-chloro- and 3-bromoandrosta-1,3,5-trien-17-one which underwent a dienone–phenol type of rearrangement to give the corresponding 1-chloro- and 1-bromo-4-methylestra-1,3,5(10)-trien-17-one [G. W. Moersch, W. A. Neuklis, T. P. Culbertson, D. F. Morrow, and M. E. Butler, *J. Org. Chem.*, **29**, 2495 (1964)]. (d) H. Dannenberg, D. D. von Dresler, and T. Köhler [*Arzneimittel-Forsch.*, **14**, 780 (1964)] report the nitration of 17-acetoxy-4-methylestra-1,3,5(10)-triene to give the 1-, 2-, and 3-nitro derivatives which were reduced to the corresponding amino compounds.

(4) Possibly 1,3-diacetoxyestra-1,3,5(10)-trien-17-one [A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958)] could be converted to 1-hydroxyestrone 3-methyl ether and then to 1-substituted estrone 3-methyl ethers *via* the procedure of Morrow and Butler.[3b] However, the starting diacetate is only obtainable in poor over-all yield from estrone.

(5) W. Nagata, T. Terasawa, and K. Tori, *ibid.*, **86**, 3746 (1964).

(2) of estrone 3-methyl ether is unstable and decomposes rapidly at 0° in aqueous solutions to give the 1-hydroxy compound (3). This instability is probably another manifestation of steric hindrance between the C-1 and C-11 positions.[6] Methylation of the 1-hydroxy compound (3) with dimethyl sulfate–sodium hydroxide afforded 1-methoxyestrone 3-methyl ether (8) in 91% yield.

When the amine (1) was diazotized at low temperatures (−15 to −30°), the resulting diazonium salt (2) was sufficiently stable to permit most of the usual diazo reactions to be carried out. Thus, as previously reported,[1a] 1-azidoestrone 3-methyl ether (4) was obtained in 85% yield by treatment of the 1-diazonium salt with sodium azide at −20°. 1-Fluoroestrone 3-methyl ether (10) was prepared by the Schiemann reaction[7] in aqueous acetic acid–fluoroboric acid at −15 to −10°. The intermediate diazonium fluoroborate decomposed at approximately −5° to give the 1-fluoro compound directly in a yield of 47%. 1-Chloroestrone 3-methyl ether (11) was obtained in 38% yield by the Sandmeyer reaction[8] in aqueous acetic acid–hydrochloric acid at −20 to +5°. Also isolated was 32% of the 1-hydroxy (3) and 15% of the 1-acetoxy (9) derivatives. In an improved procedure, the yield of the 1-chloro derivative was increased to 70% by using anhydrous conditions in which isobutyric acid–methylene chloride–hydrogen chloride was the solvent and isoamyl nitrite the diazotizing agent. Under these conditions, the main by-product appeared to be the 1-isobutyrate, obtained in 11% yield. Unfortunately this method did not give good results with the 1-bromo derivative (12). In this instance the usual Sandmeyer procedure was more satisfactory and gave a 35% yield of 1-bromoestrone 3-methyl ether (12) together with 30% of the 1-hydroxy (3) and 10% of the 1-acetoxy (9) derivatives.

In view of the previously cited evidence for steric interaction between C-1 substituents and the C-11α proton, an unexpected finding was that the 1-iodo derivative (13) could be prepared in reasonable yield from the 1-diazonium salt (2) by normal procedures. Thus, diazotization of 1-aminoestrone 3-methyl ether (1) in aqueous acetic acid–sulfuric acid at −25°, followed by the addition of potassium iodide solution, afforded 1-iodoestrone 3-methyl ether (13) in a yield of 22%. In addition, the 1-hydroxy (3) and 1-acetoxy (9) derivatives were obtained in yields of 38 and 15%, respectively. The structure of the 1-haloestrone 3-methyl ethers follows from their method of preparation, elemental analysis, spectral evidence (infrared, ultraviolet, and nmr), and a comparison with the known 2- and 4-substituted isomers.[2a,9]

Experimental Section

Solutions were dried over anhydrous sodium sulfate and all evaporations were under reduced pressure: Darco, activated carbon (Atlas Powder Co.); Magnesol, a hydrous magnesium silicate (Food Machinery Chemical Corp.); Celite, a diatomaceous silica (Johns-Manville); and Florisil, a synthetic magnesia-silica gel adsorbent, 60–100 mesh (Floridin Corp.). Silica gel refers to Mallinckrodt SilicAR, CC-7, 100–200 mesh. Petroleum ether refers to fraction boiling at 30–75° (Merck & Co.).

Thin layer chromatography (tlc) was carried out on glass plates coated with a 0.25-mm layer of Mallinckrodt SilicAR, TLC-7GF. Development was effected with the upper phase of benzene–acetone–water (5:1:4) unless otherwise specified. In preparative work a 0.5-mm layer on 20 × 20 cm plates was used. After development the chromatograms were visualized with ultraviolet light and by spraying with a 10% methanolic solution of phosphomolybdic acid. In multiple development the plates were run as usual, then dried, and rerun in the same solvent system.

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 (nmr) were determined on a Varian A-60 spectrometer with tetramethylsilane as internal standard in deuteriochloroform solution unless otherwise noted. The spectral analyses were performed by W. Fulmor, G. O. Morton, and associates and the elemental analyses by L. Brancone and associates.

3-Methoxy-1-methylaminoestra-1,3,5(10)-trien-17-one (5) and 3-Methoxy-1-dimethylaminoestra-1,3,5(10)-trien-17-one (6).—A mixture of 4.0 g (13.4 mmoles) of 1-aminoestrone 3-methyl ether (1), 16.0 g of anhydrous potassium carbonate, 160 ml of methanol, and 16 ml of methyl iodide was stirred and refluxed for 4 hr. The mixture was concentrated, diluted with water, and extracted with methylene chloride. The extract was washed with water, dried, treated with Darco, and evaporated to give 4.1 g of a tan solid.

The crude product was chromatographed on Florisil (400 g), and the material that was eluted with 5% ethyl acetate–petroleum ether was crystallized once from methanol to give 2.7 g (62%) of 3-methoxy-1-dimethylaminoestra-1,3,5(10)-trien-17-one (6) as colorless needles: mp 206–207°; λ_{max} 222 mμ (ϵ 21,200), 260 (4900), and 290 (1960) (sh); $[\alpha]_D$ +153°; ν_{max}^{KBr} 1138, 909, and 844 cm^{-1}.

Anal. Calcd for $C_{21}H_{29}NO_2$ (327.45): C, 77.02; H, 8.93; N, 4.28. Found: C, 76.81; H, 8.91; N, 4.61.

The material that was eluted with 10% and finally 15% ethyl acetate–petroleum ether was crystallized once from methanol to give 556 mg (13%) of 3-methoxy-1-methylaminoestra-1,3,5(10)-trien-17-one (5) as off-white crystals: mp 200–204°; λ_{max} 218 mμ (ϵ 37,800), 252 (8450), and 293 (3440); $[\alpha]_D$ +339°; ν_{max}^{KBr} 3390, 1193, and 814 cm^{-1}.

Anal. Calcd for $C_{20}H_{27}NO_2$ (313.42): C, 76.64; H, 8.68; N, 4.47. Found: C, 76.62; H, 8.65; N, 4.50.

1-Benzylideneamino-3-methoxyestra-1,3,5(10)-trien-17-one (7).—A mixture of 150 mg (0.5 mmole) of 1-aminoestrone 3-methyl ether (1), 106 mg (1.0 mmole) of benzaldehyde, and 150 mg of Magnesol in 10 ml of benzene was stirred and refluxed for 2.5 hr with azeotropic removal of water formed during the reaction.

The mixture was filtered and evaporated to an oil which on trituration with ether gave 156 mg (80%) of a yellow solid, mp 146–148°. The product was crystallized twice from methylene chloride–methanol to give an analytical sample: mp 148–150°; λ_{max} 260 mμ (ϵ 18,400) and 335 (4300); λ_{max} (0.1 *N* HCl) 229 (ϵ 1100), 250 (1330), and 280 (370); ν_{max}^{KBr} 756 and 691 cm^{-1}; $[\alpha]_D$ +21°.

Anal. Calcd for $C_{26}H_{29}NO_2$ (387.5): C, 80.58; H, 7.54; N, 3.61. Found: C, 80.44; H, 7.90; N, 3.63.

1,3-Dimethoxyestra-1,3,5(10)-trien-17-one (8).—To a solution of 600 mg (2.0 mmoles) of 1-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one[1a] (3) in 20 ml of methanol was added 7.5 ml of 30% sodium hydroxide solution and 7.5 ml of dimethyl sulfate intermittently, over 1 hr at 25–30°, such that the mixture was basic throughout the reaction. The mixture was stirred an additional 1 hr, then made strongly basic with 10 ml of 15% sodium hydroxide solution, and extracted with *n*-hexane.

(6) In further support of nonbonded interaction between the 1-diazonium and 11-methylene groups is the observation that the 1-diazonium salt of 2-methoxyestrone 3-methyl ether[1b] appeared to decompose several times faster than the corresponding 4-diazonium salt [L. R. Axelrod, P. N. Rao, and D. H. Baeder, *J. Am. Chem. Soc.*, **88**, 856 (1966)] on warming in dilute sulfuric acid.

(7) A. Roe, *Org. Reactions*, **5**, 193 (1949).

(8) H. H. Hodgson, *Chem. Rev.*, **40**, 251 (1947).

(9) 2- and 4-fluoroestrone 3-methyl ether, unpublished results. For 2- and 4-fluoroestrone and 4-fluoroestradiol, see E. Hecker and G. Farthofer-Boeckh, *Biochem. Z.*, **338**, 628 (1963); M. Nieman and Y. Osawa, *Tetrahedron Letters*, 1987 (1963).

The extract was washed with 10% sodium hydroxide solution, then with water, and evaporated to give 626 mg of colorless crystals, mp 125–135°. The product was dissolved in methylene chloride, treated with Darco, filtered through Celite, and crystallized from *n*-hexane to give 570 mg (91%) of colorless crystals, mp 126–128°. On being dried overnight *in vacuo* at 110° the material melted at 134–136°: λ_{max} 227 mμ (ε 8800) (sh) and 276–284 (1880); ν_{max}^{KBr} 1466, 1147, 1087, and 946 cm^{-1}; $[\alpha]D$ +274°; nmr 6.26 (s, C-2 and C-4 H), 3.77 (s, C-1 and C-3 OCH_3), and 0.92 (s, C-18 CH_3) ppm.

Anal. Calcd for $C_{20}H_{26}O_3$ (314.41): C, 76.40; H, 8.34. Found: C, 76.47; H, 8.52.

1-Fluoro-3-methoxyestra-1,3,5(10)-trien-17-one (10).—To a well-stirred solution of 9.0 g (0.03 mole) of 1-aminoestrone 3-methyl ether (**1**) in 100 ml of acetic acid plus 200 ml of 48% aqueous fluoroboric acid at −10 to −15° was added below the surface a solution of 2.29 g (0.033 mole) of sodium nitrite in 15 ml of water. Stirring was continued and the mixture allowed to warm up to +5° over 30 min, and then diluted with 300 ml of water, and extracted with methylene chloride.

The extract was washed with water, saturated sodium bicarbonate solution, and finally with water, and then dried and filtered through 50 g of Magnesol, using 800 ml of methylene chloride wash. The filtrate was evaporated to 8.3 g of crude solid which was chromatographed on 500 g of Florisil. The product was eluted with 5% ethyl acetate–petroleum ether and crystallized once from cyclohexane–methylene chloride to give 4.25 g (47% yield) colorless crystals: mp 177–180°; λ_{max} 204 mμ (ε 28,200), 221 (10,100) (sh), and 273–282 (1510); $[\alpha]D$ +202°; ν_{max}^{KBr} 869, 862, 832, and 823 cm^{-1}; nmr (in $CDCl_3$ and dimethyl sulfoxide-d_6), 6.46 (d, C-2 H), 6.27 (d, C-4 H), 3.73 (s, OCH_3), and 0.93 (s, C-18 CH_3) ppm.

Anal. Calcd for $C_{19}H_{23}FO_2$ (302.4): C, 75.46; H, 7.67; F, 6.29. Found: C, 75.48; H, 7.66; F, 6.62.

Further elution of the Florisil column with 10% ethyl acetate–petroleum ether followed by 20% ethyl acetate–petroleum ether gave 2.70 g of a mixture of two compounds. Preparative thin layer chromatography of a sample of the mixture indicated an 8% yield of 1-acetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (**9**), mp 152–154° (hexane), and a 17% yield of 1-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**3**), mp 228–233° (ethyl acetate).

1-Acetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (9).—A sample (approximately 700 mg) consisting of approximately 58% 1-hydroxy- (**3**) and 34% 1-acetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (**9**), obtained from chromatography of crude 1-fluoro-3-methoxyestra-1,3,5(10)-trien-17-one (**10**), was crystallized from 150 ml of hexane–acetone to give 382 mg of the 1-hydroxy compound which was almost pure by tlc. The filtrate was evaporated to a glass (335 mg) which was purified by preparative tlc to give an additional 31 mg of the 1-hydroxy derivative plus 244 mg of the 1-acetoxy compound. Two crystallizations of the latter from *n*-hexane–methylene chloride gave 201 mg of colorless crystals: mp 152–154°; λ_{max} 220 mμ (ε 10,250) (sh), 275–285 (1710); $[\alpha]D$ +228°; ν_{max}^{KBr} 1770 (sh), 1745, and 1220 cm^{-1}; nmr 6.55 (d, C-2 H), 6.37 (d, C-4 H), 3.72 (s, OCH_3), 2.25 (s, $OCOCH_3$), and 0.92 (s, C-18 CH_3) ppm.

Anal. Calcd for $C_{21}H_{26}O_4$ (342.42); C, 73.66; H, 7.66. Found: C, 73.84; H, 7.59.

1-Chloro-3-methoxyestra-1,3,5(10)-trien-17-one (11). A. Preparation under Anhydrous Conditions.—To a well-stirred solution of 1.2 g (4.0 mmoles) of 1-aminoestrone 3-methyl ether (**1**) in 8 ml of methylene chloride plus 38 ml of isobutyric acid containing approximately 146 mg (4 mmoles) of anhydrous hydrogen chloride was added a solution of 515 mg (4.4 mmoles) of isoamyl nitrite in 2 ml of methylene chloride at a temperature of −25 to −30°. Stirring was continued at this temperature for 15 min, and then the solution was saturated with dry hydrogen chloride and allowed to warm up to +5° over 30 min.

The solution was made strongly basic by pouring into an ice-cold 10% aqueous sodium hydroxide solution, and then extracted with methylene chloride. The extract was washed with water, dried, and evaporated to an amber oil. The latter was refluxed with 30 ml of methanol plus 5 ml of concentrated hydrochloric acid for 2.5 hr, and then diluted with water and extracted with methylene chloride. The extract was washed with water, dried, and filtered through 20 g of Magnesol using 200 ml of methylene chloride wash.

The filtrate was evaporated to an oil and crystallized from *n*-hexane to give 460 mg of crystalline product, mp 132–134°. The mother liquor was chromatographed on Florisil (50 g) using 5% ethyl acetate–hexane as the eluent. The product was crystallized from *n*-hexane to give 380 mg, mp 131–133°. An additional 60 mg of product was recovered by preparative tlc (cyclohexane–ethyl acetate, 80:20, double development). Hence the total yield of product was 900 mg (70%). The combined fractions were crystallized again from *n*-hexane to give 810 mg of colorless crystals: mp 132–134°; λ_{max} 208 mμ (ε 41,800), 230 (9250) (sh), and 282–290 (1915); $[\alpha]D$ +284°; ν_{max}^{KBr} 854, 830, 812, and 790 cm^{-1}; nmr 6.75 (d, C-2 H), 6.55 (d, C-4 H), 3.73 (s, OCH_3), and 0.95 (s, C-18 CH_3) ppm.

Anal. Calcd for $C_{19}H_{23}ClO_2$ (318.83): C, 71.58; H, 7.27; Cl, 11.12. Found: C, 71.60; H, 7.12; Cl, 11.37.

In a smaller scale (1.0 mmole) reaction, carried out under the same conditions as the larger scale run, there was isolated (tlc, cyclohexane–ethyl acetate, 80:20, double development) 244 mg (76%, mp 129–132°) of 1-chloroestrone 3-methyl ether (**11**) plus 40 mg (11%, mp 105–110°) of material which appeared to be 1-isobutyryloxyestrone 3-methyl ether by infrared spectroscopy (ν_{max}^{KBr} 1754, 1739, 1129, and 864 cm^{-1}).

B. Preparation under Aqueous Conditions.—To a solution of 300 mg (1 mmole) of 1-aminoestrone 3-methyl ether (**1**) in 4 ml of acetic acid plus 3 ml of concentrated hydrochloric acid at −20 to −25° was added a solution of 73 mg (1.05 mmoles) of sodium nitrite in 2 ml of water. The solution was stirred for about 0.5 min, then a cooled (−20°) solution of 500 mg of cuprous chloride in 1.5 ml of concentrated hydrochloric acid was added, and the mixture was stirred and allowed to warm up from −20 to +5° over 0.5 hr.

The mixture was diluted with water and extracted with methylene chloride; the extract was washed with water, dried, and evaporated to a glass which was purified by tlc to give 121 mg (38%) of 1-chloro-3-methoxyestra-1,3,5(10)-trien-17-one (**11**), 51 mg (15%) of 1-acetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (**9**), and 97 mg (32%) of 1-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**3**).

The chloro compound (**11**) was crystallized from *n*-hexane to give 93 mg colorless crystals, mp 132–134°, whose infrared spectrum was identical with material prepared in part A above.

1-Bromo-3-methoxyestra-1,3,5(10)-trien-17-one (12).—A solution of 3.0 g (10 mmoles) of 1-aminoestrone 3-methyl ether (**1**) in 40 ml of acetic acid plus 30 ml of 1 *N* sulfuric acid was diazotized at −25° by the addition, below the surface, of a solution of 760 mg (11 mmoles) of sodium nitrite in 6 ml of water. The solution was stirred for 1–2 min; then to this was added a cooled solution of 4.0 g (28 mmoles) of freshly prepared cuprous bromide[10] in 20 ml of 48% aqueous hydrobromic acid.

The mixture was stirred and allowed to warm up to +10° over 15 min, then diluted with 350 ml of water, and extracted with methylene chloride. The extract was washed with water, saturated sodium bicarbonate solution, and finally with water, then dried, and evaporated to a glass.

The glass was chromatographed on Florisil (250 g) and the product was eluted with 5% ethyl acetate–petroleum ether. The product was crystallized twice from methylene chloride–hexane to give 1.11 g of colorless crystals, mp 162–164°. Further product (176 mg) was recovered from the mother liquors to give a total yield of 1.28 g (35%) of the 1-bromo derivative (**12**): λ_{max} 206 mμ (ε 38,000) and 283–290 (2000); $[\alpha]D$ +266°; ν_{max}^{KBr} 854, 829, 799, and 777 cm^{-1}; nmr 6.98 (d, C-2 H), 6.62 (d, C-4 H), 3.75 (s, OCH_3), and 0.95 (s, C-18 CH_3) ppm.

Anal. Calcd for $C_{19}H_{23}BrO_2$ (363.3): C, 62.81; H, 6.38; Br, 22.00. Found: C, 63.04; H, 6.47; Br, 21.72.

Further elution of the column with 10% ethyl acetate–petroleum ether gave 1.45 g of material which was shown by tlc to consist of 1-acetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (**9**) and 1-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**3**) in yields of 10 and 30%, respectively.

1-Iodo-3-methoxyestra-1,3,5(10)-trien-17-one (13).—To a solution of 2.0 g (6.7 mmoles) of 1-aminoestrone 3-methyl ether (**1**) in 25 ml of acetic acid plus 20 ml of 1 *N* sulfuric acid at −25° was added a solution of 483 mg (7.0 mmoles) of sodium nitrite in 5 ml of water below the surface of the liquid and with efficient stirring. After approximately 1 min there was added a solution

(10) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p 187.

of 2.22 g (13.4 mmoles) of potassium iodide in 5 ml of water and the mixture was stirred and allowed to warm up to +5° over 15 min.

The mixture was diluted with water and extracted with methylene chloride. The extract was washed with water, dilute sodium thiosulfate solution, and finally with water, then dried, and evaporated to a dark oil which was chromatographed on 150 g of silica gel. The product (648 mg, 23%) was obtained after elution of the column with 3% ethyl acetate–petroleum ether followed by 5% ethyl acetate–petroleum ether. Crystallization from hexane gave 610 mg (22%) of off-white product, mp 212–215°. A final crystallization from *n*-hexane gave colorless crystals: mp 213–215°; λ_{max} 211 mμ (ε 34,800), 230 (sh) (11,000), and 284–293 (2050); $[\alpha]_D$ +252°; ν_{max}^{KBr} 857, 830, and 760 cm^{-1}; nmr 7.29 (d, C-2 H), 6.62 (d, C-4 H), 3.73 (s, OCH_3), and 0.95 (s, C-18 CH_3) ppm.

Anal. Calcd for $C_{19}H_{23}IO_2$ (410.29): C, 55.62; H, 5.65; I, 30.94. Found: C, 55.25; H, 5.90; I, 30.63.

Further elution of the column with 5% acetone–petroleum ether followed by 10% acetone–petroleum ether gave 1.39 g of material which was shown by tlc to consist of 1-acetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (**9**) and 1-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**3**) in yields of 15 and 38%, respectively.

Registry No.—**3**, 13871-38-0; **5**, 6654-48-4; **6**, 6654-47-3; **7**, 14795-95-0; **8**, 13639-96-8; **9**, 14795-97-2; **10**, 14795-98-3; **11**, 14795-99-4; **12**, 14796-00-0; **13**, 14796-01-1.

1,11-Iminoestrones.[1] II. Some Derivatives and Reactions

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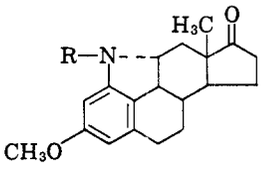
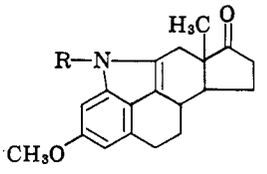
In part I[1] of this work, the synthesis and proof of structure of 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**1a**) and 1,11-imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**2a**) were outlined. The preparation of some N-substituted derivatives and several oxidative reactions of these compounds are now described.



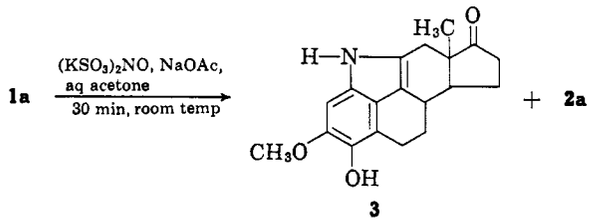


1a, R = H
b, R = H (HCl salt)
c, R = CH_3CO
d, R = *p*-ClC_6H_4CO
e, R = CH_3

2a, R = H
b, R = *p*-ClC_6H_4CO
c, R = CH_3

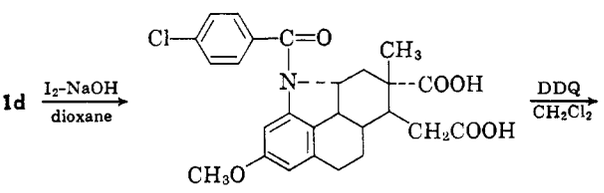
Iminoestrone **1a** was converted to its hydrochloride (**1b**), N-acetyl (**1c**), and N-*p*-chlorobenzoyl (**1d**) derivatives by conventional methods. An attempt to prepare the N-methyl derivative (**1e**) by refluxing **1a** with methyl iodide–potassium carbonate in methanol gave a very polar, water-soluble product which was, presumably, the methiodide of **1e**. The N-methyl derivative was successfully prepared, in 46% yield, by the reaction of **1a** with sodium hydride–methyl iodide in dimethylformamide–benzene solution at 35–40°. Dehydrogenation of the product (**1e**) with 10% palladium on carbon in refluxing xylene gave **2c** in a yield of 91%. While catalytic dehydrogenation of the N-*p*-chlorobenzoyl derivative (**1d**) was unsuccessful, this compound was smoothly dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[2] in methylene chloride at room temperature to give the corresponding 9,11-dehydro derivative (**2b**) in 96% yield.

Teuber and Staiger[3] have shown that the oxidation of indolines with potassium nitrosodisulfonate (Fremy's salt) gives indoles and 5-hydroxyindoles and, with excess reagent, indoloquinones. Similarly, the reaction of **1a** with 2 moles of Fremy's salt gave hydroxyindole **3** in a yield of 54% plus a small yield of indole **2a**.

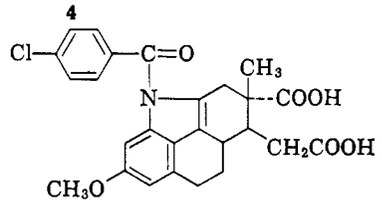


3

Oxidative cleavage of ring D of the *p*-chlorobenzoyl derivative, **1d**, with iodine–sodium hydroxide gave the 16,17-seco diacid **4** in 42% yield. Essentially the method of Heer and Miescher[4] was used except that methanol was replaced by dioxane to avoid ester formation.



4



5

Subsequent dehydrogenation of **4** with DDQ in methylene chloride at room temperature gave, in 77% yield, the desired 1,11-(*p*-chlorobenzoyl)imino-3-methoxy-16,17-secoestra-1,3,5(10),9(11)-tetraene-16,17-dioic acid (**5**), which has certain formal resemblances to the antiinflammatory drug, indomethacin.[5]

In the dehydrogenation of seco diacid **4** there was isolated a by-product (**6a**) in a yield of approximately 5%. This compound was shown to arise by further reaction of the product (**5**) with DDQ. Thus, the treatment of **5** with 2 equiv of DDQ in methylene

(1) For part I, see E. W. Cantrall, R. B. Conrow, and S. Bernstein, *J. Org. Chem.*, **32**, 3445 (1967).

(2) For a recent review on dehydrogenations with DDQ, see D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

(3) H. J. Teuber and G. Staiger, *Ber.*, **87**, 1251 (1954); **89**, 489 (1956).

(4) J. Heer and K. Miescher, *Helv. Chim. Acta*, **28**, 156 (1945).

(5) T. Y. Shen, T. B. Windholz, A. Rosegay, B. E. Witzel, A. N. Wilson, J. D. Willett, W. J. Holtz, R. L. Ellis, A. R. Matzuk, S. Lucas, C. H. Stammer, F. W. Holly, L. H. Sarett, E. A. Risley, G. W. Nuss, and C. A. Winter, *J. Am. Chem. Soc.*, **85**, 488 (1963).