37-9; phthalazine, 253-52-1; benzothiazole, 95-16-9; 1-methyl-4,5-diphenyl-1*H*-imidazole, 50609-88-6; 1,2-dimethyl-1*H*-imidazole, 1739-84-0; 1-methyl-2-isopropylthio-1*H*-imidazole, 63348-50-5; 1-propylimidazole, 35203-44-2; 1-pehnylimidazole, 7164-98-9; 2-bromopropane, 75-26-3; 1-(3-hydroxyphenacyl)-1*H*-imidazole hydrobromide, 121704-81-2; 1-(3-hydroxyphenacyl)-1*H*-imidazole, 108957-92-2; methyl *p*-toluenesulfonate, 80-48-8; 1-(3-methoxyphenacyl-3-oxoprop-1-yl)-1*H*-imidazole, 121704-82-3.

11β-Nitrate Estrane Analogues: Potent Estrogens

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Various estrane derivatives 1 reacted with cerium ammonium nitrate (CAN) selectively and efficiently to provide 9α,11β-difunctionalized derivatives **2**, which were subsequently deoxygenated at C-9 with triethylsilane/boron trifluoride etherate to the desired target 11β-nitratoestranes **3a**, **3b**, and **5**. When examined for estrogenic and postcoital antifertility activity, 11β-nitrates **2c**, **2d**, and **3b** most notably displayed more potent oral activity than did ethynylestradiol.

It has long been recognized that estrogenic hormones are important pharmacological materials and consequently are found to have a wide range of beneficial applications in human and veterinary therapy: for example, they are supplements for the maintenance of estrogen levels in hypogonadic states and are routinely incorporated into oral contraceptives. In our ongoing efforts to provide estrogens with reduced side effects, we describe herein 11-nitratoestrogen analogues that are extremely potent as orally active estrogens in the absence of the classical 17β-hydroxyl-17α-ethynyl group for oral activity.

Inhoffen et al.[1] first reported in the late 1930s that ethynylestradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol, EE) was an orally active estrogen. Since then, EE has been widely employed with progestins (such as norethindrone and norethindrone acetate) in oral contraceptive formulations. However, these products have been blamed for various possible drawbacks, which are extremely serious for the large number of women who take oral contraceptives or estrogen supplements routinely on a long-term basis. These suspected problems can include enhancing the risk of endometrial carcinoma; induction of malignant carcinoma, especially of the cervix, breast, vagina, and liver; and promotion of gallbladder disease, thromboembolic and thrombotic diseases, myocardial infarction, hepatic adenoma, elevated blood pressure and hypercalcemia, and hypersensitized glucose tolerance.

These maladies apparently manifest themselves at the dosage levels needed to achieve the desired primary estrogenic and contraceptive effects. In the event that these side effects are dose-related and more potent orally active extrogens are available, they might in principle be used in lower amounts with a consequential lowering of the body's metabolic burden. Hypothetically, the side effects could, at least in part, then be avoided.

Within this context, we felt that estrogens that were selectively substituted at C-11 presented potentially useful orally active contraceptive agents.

Chemistry

We found that C-11 functionalized estrone derivatives are conveniently available from the process outlined in Scheme I, which reflects our efforts targeted for the production of 11β-nitrato compounds **3**. In the first step of Scheme I, ceric ammonium nitrate (CAN) effected oxidation of estrone 3-acetate (**1a**) and $\Delta^{9,11}$-estrone 3-acetate (**1b**) to selectively provide 9α,11β-difunctionalized estrones **2**, which were subsequently deoxygenated at the C-9-benzylic position with retention of configuration to the 11β-nitratoestrones **3**. The overall transformation **1** → **2** → **3** circumvents problems that we encountered with the generalization of an existing approach, which involved the aromatization by lithium biphenyl of the 17-ketal of 11β-hydroxyandrosta-1,4-diene-3,17-dione,[2] followed by deprotection to the 17-ketone, possible introduction of other functionality at C-17, and formation of the nitrate ester. We examined alternative methods within the context of Scheme I, and some of these efforts are discussed below. In summary, we found that the process shown in Scheme I was very efficient and stereoselective and allowed for a wide range of structural complexity in the substrate estrones **1**.

The selection of CAN as an oxidant stemmed from a report by Sykes et al.[3] on the isolation of a C-9 isomeric mixture of 9α-hydroxy-11β-nitratoestrone 3-acetates from the oxidation of estrone 3-acetate. In general, CAN has been reported[4] to introduce heteroatoms at a variety of other sites under similar conditions and in a manner highly dependent on the substrate estrone functionality. Despite the reported lack of selectivity, in our hands the use of 2 molar equiv of CAN in 90% acetic acid proved satisfactory. For example, 7α-methylestrone 3-acetate (**1b**) and $\Delta^{9,11}$-7α-methylestrone 3-acetate (**1c**), were each converted into isomerically pure 9α-hydroxy-7α-methyl-11β-nitratoestrone 3-acetate (**2b**, R_1 = =O, R_2 = CH_3) in high yield. Routine NMR examination of the derivatives **2b** confirmed the equatorial position of the 11α-hydrogen, and the 9α-hydroxyl orientation was tenatively assigned by analogy to prior chemical correlations made by Sykes.[3]

Sykes[3] also proposed a possible mechanism for the reaction with CAN, which is pictorially depicted in Scheme II. For estrone 3-acetate (**1a**, R_1 = =O, R_2 = H), initial dehydrogenation to 9,11-dehydroestrone 3-acetate was assumed on the basis of the identical results obtained with either compound as substrates with CAN. The styrene **1g** ($\Delta^{9,11}$, R_1 = =O, R_2 = H) presumably becomes a ligand for cerium(IV) via attachment from the α-underside to form

(1) (a) Inhoffen, H. H.; Hohlweg, W. *Nature* **1938**, *26*, 96. (b) Inhoffen, H. H.; Hohlweg, W. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1024.

(2) Baron, J. S. *J. Med. Chem.* **1967**, *10*, 1188.

(3) (a) Sykes, P. J.; Rutherford, F. J. *Tetrahedron Lett.* **1971**, *37*, 3393. (b) Sykes, P. J.; Phillipps, G. H.; Laing, S. B.; Turnbull, J. P. Ger. Offen. 2,057,171, May 27, 1971.

(4) (a) Laing, S. B.; Sykes, P. J. *J. Chem. Soc. C* **1968**, 2915. (b) Syper, L. *Tetrahedron Lett.* **1966**, 4493. (c) Pratak, D. M.; Eichmeier, L. S. *Chem. Commun.* **1971**, 772.

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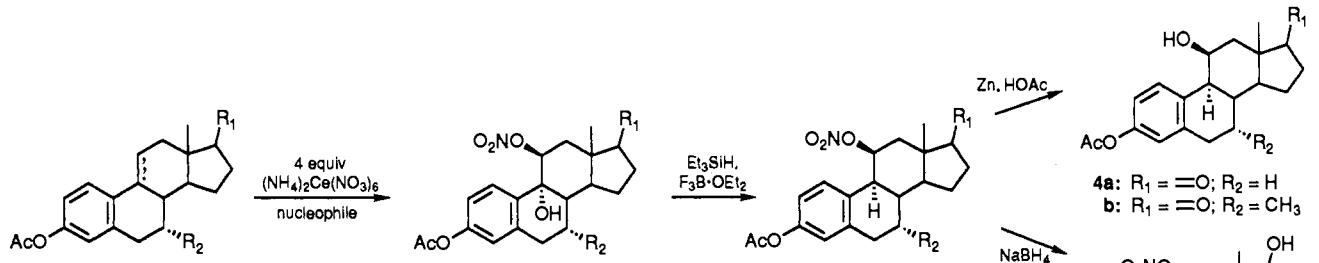
Scheme I



1a: $R_1 = {=}O$; $R_2 = H$
b: $R_1 = {=}O$; $R_2 = CH_3$
c: $\Delta^{9,11}$; $R_1 = {=}O$; $R_2 = CH_3$
d: $R_1 = \beta$-OH, α-C≡CH; $R_2 = H$
e: $R_1 = \beta$-CH_2CH_3, α-H; $R_2 = H$
f: $R_1 = \beta$-CH_2CH_3, α-H; $R_2 = CH_3$
g: $\Delta^{9,11}$; $R_1 = {=}O$; $R_2 = H$

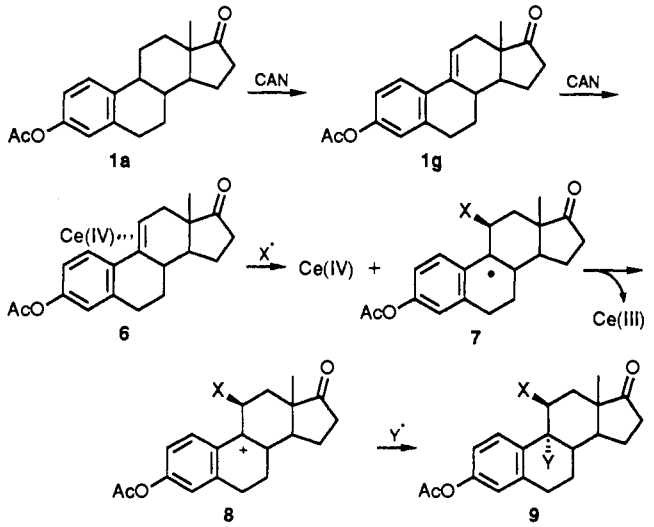
2a: $R_1 = {=}O$; $R_2 = H$
b: $R_1 = {=}O$; $R_2 = CH_3$
c: $R_1 = \beta$-OAc, α-C≡CH; $R_2 = H$
d: $R_1 = \beta$-CH_2CH_3, α-H; $R_2 = H$
e: $R_1 = \beta$-CH_2CH_3, α-H; $R_2 = CH_3$

3a: $R_1 = {=}O$; $R_2 = H$
b: $R_1 = {=}O$; $R_2 = CH_3$

4a: $R_1 = {=}O$; $R_2 = H$
b: $R_1 = {=}O$; $R_2 = CH_3$

5

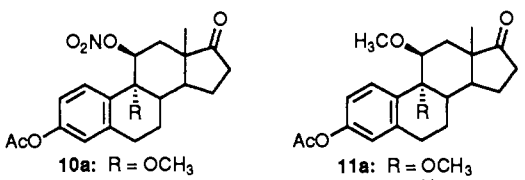
Scheme II



1a **1g** **6** **7** **8** **9**

π-complex **6**, which undergoes subsequent nucleophilic addition from the open β-face and dissociation of the cerium(IV) to give 11β-substituted, benzylic C-9 radical species **7**. An oxidative turnover of cerium(IV) to cerium(III) is coupled to the production of corresponding benzylic C-9 carbonium intermediate **8**, which is trapped from the α-underside by a second nucleophile (usually solvent) to afford 9α,11β-difunctionalized estrones **9**.

Aside from the preparation of the title 9-hydroxy-11-nitrato derivative **9** (X = ONO_2, Y = OH), the reactive cerium π-complex **6** (Scheme II) could undergo substitution by other preselected nucleophiles and this suggested that other 9,11-diheterosubstituted estrones were accessible: when the CAN reaction was carried out in methanol, a mixture was obtained. The solvent presumably competed with nitrate anions for the π-complex **6** of Scheme II to provide a mixture of **7**, X = OMe and ONO_2. The corresponding benzylic carbonium intermediate **8**, X = OMe and ONO_2, were then trapped by solvent to afford the mixture of **10a** and **11a**, respectively.

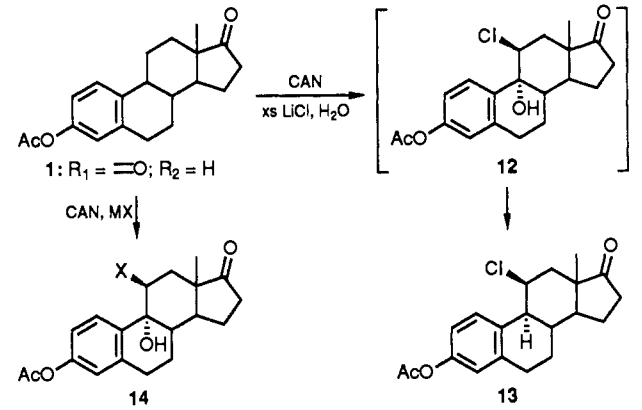


10a: R = OCH_3

11a: R = OCH_3
b: R = H

Better selectivity was observed when CAN was employed in a medium of excess aqueous lithium chloride. Under these conditions, 9,11-dehydroestrone-3-acetate was converted to the corresponding regio- and stereochemically pure chlorohydrin **12**. This attractive functionalization is currently being explored for the ability to employ other halosalts (depicted as MX) or mixed cerium(IV) salts (either as a prior additives or from in situ generation) in a general method for the preparation of isomerically pure halohydrins **14** (Scheme III).

Scheme III



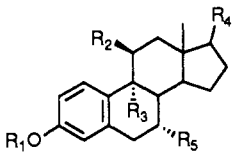
1: $R_1 = {=}O$; $R_2 = H$ **12** **14** **13**

For the removal of the benzylic C-9 hydroxyl, we envisioned the exposure of alcohols **2** to Lewis acid conditions to form the highly stabilized carbonium intermediate **8** (Scheme II), which would react with triethylsilane[5] as an in situ hydride source. Once again we expected that carbonium **8** would be substituted from the more accessible α-underside to provide, in this instance, the 9α-hydrogen selectively, as in **3**. The target 11β-nitratoestrones **3** were indeed obtained when the alcohols **2** were placed in a medium of boron trifluoride etherate and triethylsilane. NMR analysis of the deoxygenation products via decoupling experiments, in which the C-11 hydrogen signal at 5.93 ppm was irradiated, revealed that the C-9 hydrogen absorption was at 2.74 ppm. In addition, this experiment allowed the determination of the $J_{9,11}$ = 12 Hz, which tentatively indicated a trans-diaxial relationship between the adjacent C-9,11 hydrogens.[6] However, ultimate verification of the stereochemistry at C-9,11 of 11β-nitrato compound **3** and 11β-methoxy derivative **11b** were made

(5) (a) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758. (b) Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Chem. Soc.* **1972**, *94*, 3659. (c) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675.

(6) (a) Segaloff, A.; Gabbard, R. B.; Flores, A.; Borne, R. F.; Baker, J. K.; Duax, W. L.; Strong, P. D.; Rohrer, D. C. *Steroids* **1980**, *3*, 335. (b) Hasegawa, H.; Nozoe, S.; Tsuda, K. *Chem. Pharm. Bull.* **1963**, *11*, 1037.

Table I. Estrogenic (Oral and Subcutaneous) and Postcoital Antifertility (Oral) Activities of 9α,11β-Nitrate-Substituted Estrane Derivatives in Rats



compd	R_1	R_2	R_3	R_4	R_5	estrogenic potency[a] (oral)	postcoital antifertility potency[a]	estrogenic potency[b] (subcutaneous)
EE	H	H	H	β-OH α-C≡H	H	100	100	
estradiol								100
2a	Ac	O_2NO	OH	=O	H			4
2b	Ac	O_2NO	OH	=O	CH_3		c	34
2c	Ac	O_2NO	OH	β-OAc α-C≡CH	H	531	5000	
2d	Ac	O_2NO	OH	β-Et α-H	H	228	4000	
2e	Ac	O_2NO	OH	β-Et α-H	CH_3	780	-	-
3a	Ac	O_2NO	H	=O	H	400	-	-
3b	Ac	O_2NO	H	=O	CH_3	696	>4000	7472
5	H	O_2NO	H	OH	CH_3	1400	-	-

[a] Minimum protective doses for prevention of pregnancy (cf. 200 μg for EE): Numbers given are relative to EE or a maximum dose given in mg/kg per day. [b] Numbers given are relative to estradiol. [c] Inactive at 2 mg/kg per day.

through correlations with authentic samples of the corresponding C-9α,11β stereoisomers, which were also prepared independently by us. As shown in Scheme I, the parent nitrate ester **3a** (R_1 = =O, R_2 = H) was prepared and hydrolyzed to an 11-alcohol that matched in all respects 11β-alcohol **4a** with the 9α-hydrogen.[7] The 9α,11β-dimethoxyestrone (**11a**) was converted to **11b**, which was identical with an authentic sample prepared from 11β-methoxyestrone.[8]

Biology

As can be seen from the data presented in Table I, several of the 11β-nitrate ester compounds have extremely potent oral estrogenic activities in rats. Most notably, **3b** and **5** provide as much as 7 and 14 times, respectively, the potency of EE, which is one of the most potent orally active estrogens. There are only a few examples of estradiol derivatives that exceed the oral estrogenic activity of EE. Steroid estrogens that lack a 17α-ethynyl group generally exhibit poor oral activity, and since the 17α-ethynyl side chain has been implicated in the possible hepatotoxicity shown by EE,[9] these 11β-nitrate esters form an exceptionally novel and potentially useful class of orally active estrogens.

At what first appears to be a contradiction, the 11β-nitrato-substituted estrane derivatives exhibit oral postcoital activity 40 (**2d** and **3b**) and 50 (**2c**) times as high as EE (see Table I), but they were found by us to only moderately bind (6% or less relative to EE) to the rat uterine cytosol receptor. It appears that the 11β-nitrato group may have an effect similar in consequences to an 11β-methoxy group[10] on decreasing the binding to the serum and cytoplasmic receptor and yet preserving potent antifertility activity. We observed this upon the syntheses of 11β-methoxyestrone acetate and 11β-methoxy-EE (moxestrol). Subsequent assays for oral estrogenic activity and for uterine cytosol receptor binding affinity were carried out and permitted a comparison of these biological parameters. Although high-affinity binding with the estrogen receptor is a conventional goal and criterion for potent estrogenic activity, it has been shown that pharmacokinetic parameters may supercede these considerations.[11] For example, Raynaud found that 11β-methoxy-17β-ethynylestradiol (moxestrol) bound only 10% relative to EE for rat uterine cytosol receptors in vitro,[12] but it was 20 times more potent than EE in stimulating uterine growth in vivo. Then it was found that moxestrol binds poorly to estradiol-binding protein (EBP) and sex-steroid-binding protein (SBP), which are the high-affinity, specific steroid receptors in rat serum. These observations suggested that the observed difference between in vitro and in vivo activities may be due to a high effective concentration of moxestrol at target tissues.

The 11β-nitrato compounds are some of the first potent orally active estrogens in which the 17β-hydroxy-17α-ethynyl functionality is absent. Although our results are still preliminary in scope, if 11β-nitrato estradiol proves as potent as oral estrogen and poscoital contraceptive agent in women as it is in rats, theoretically only 3 μg would be required in the pill for contraceptive efficacy compared to the 50 μg of EE that is currently required. The novel 11β-nitratoestradiol class thus promises better estrogenic agents and might ultimately lead to improved antifertility agents for women.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data (IR, Perkin-Elmer 137; NMR, Varian T-60 and XL-100 or Jeol FX-90Q) were recorded for all compounds in $CDCl_3$ unless otherwise stated. Mass spectral data were obtained with a CEC 21-110B high-resolution, double-focusing spectrometer. Microanalytical data were determined by Galbraith Labs, Knoxville, TN, for C and H and agreed to within ±0.4% of the calculated values. Tetrahydrofuran (THF) was dried by distillation from methylmagnesium bromide and stored over 4Å molecular sieves. R_f values were determined with 250-μm thickness silica gel GF on glass plates.

3,9α,11β-Trihydroxy-7α-methylestra-1,3,5(10)-trien-17-one 3-Acetate 11-Nitrate Ester (2b). To a stirred solution of 20.0

(7) Magerlein, B. J.; Hogg, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 2220.
(8) Azadian-Boulanger, G.; Bertin, D. *Chim. Ther.* **1937**, *4*, 451.
(9) Baldratti, G.; Barbiere, W.; Consonni, A.; Sciaky, R.; Scrascia, E.; Suchowsky, G. K. *Experientia* **1969**, *25*, 1018.
(10) Raynaud, J. B. *Steroids* **1973**, *21*, 249.
(11) Bolt, H. M. *Pharmacol. Ther.* **1979**, *4*, 37.
(12) Raynaud, J. P.; Ojasoo, T.; Bouton, M. M.; Philibert, D. In *Drug Design*; Ariens, E. J., Ed.; Academic Press: New York, 1979; Vol. 8, p 170.

g (64.3 mmol) of 7α-methylestrone acetate in 400 mL of 90% HOAc under a nitrogen atmosphere was added 140 g (266 mmol) of ceric ammonium nitrate. The reaction mixture was stirred for 6 h at room temperature and then added to H_2O. The precipitate dissolved upon addition of Et_2O, and the separated aqueous phase was extracted with additional Et_2O. The Et_2O extracts were combined and washed with H_2O, 5% $NaHCO_3$ solution, and H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to afford 24.8 g of residue. Crystallization from Et_2O gave 10.5 g of **2b**. An analytical sample was prepared by recrystallization from Et_2O: mp 184–186 °C; NMR δ 6.88–7.50 (m, 3 H, aromatic), 5.68 (t, J = 3 Hz, 1 H, $CHONO_2$), 2.22 (s, 3H, $COCH_3$), 1.13 (d, J = 8 Hz, 3 H, 7-CH_3); 1.00 (s, 3 H, 18-CH_3); HRMS calcd for $C_{21}H_{25}NO_7$ – NO_2 (M^+ – NO_2) 357.1702, found 357.1712; R_f = 0.50, benzene–25% Et_2O.

Treatment of $\Delta^{9,11}$-7α-methylestrone acetate (**1c**) with 2 equiv of ceric ammonium nitrate gave **2b** identical with the material obtained above in similar yield.

3,11β-Dihydroxy-7α-methylestra-1,3,5(10)-trien-17-one 3-Acetate 11-Nitrate Ester (3b). To a stirred solution of 10.5 g (25.5 mmol) of carbinol **2b** in 400 mL of dry CH_2Cl_2, under a nitrogen atmosphere at salt–ice-bath temperature, were added in succession 10.0 g (76.5 mmol) of triethylsilane and 26.8 mL of boron trifluoride etherate. The reaction mixture was stirred for 1 h and then warmed to room temperature. The CH_2Cl_2 solution was washed with 10% K_2CO_3 solution and H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to give a solid, which upon recrystallization from Et_2O gave 5.75 g of deoxygenation product **3b**. An analytical sample was prepared by recrystallization from Et_2O: mp 195–196 °C; NMR δ 6.78–7.30 (m, 3 H, aromatic), 5.93 (m, 1 H, $CHONO_2$), 2.22 (s, 3 H, $COCH_3$), 1.02 (s, 3 H, 18-CH_3), 0.89 (d, J = 8 Hz, 3 H, 7-CH_3). Anal. ($C_{21}H_{25}NO_6$) C, H, N.

3,11β-Dihydroxy-7α-methylestra-1,3,5(10)-trien-17-one 3-Acetate (4b). A mixture of 0.272 g of **3b** in 10 mL of HOAc containing 0.5 g of zinc was stirred at room temperature for 0.5 h. The zinc was collected by filtration and the HOAc was removed at reduced pressure. The resulting residue was dissolved in H_2O–Et_2O. The Et_2O solution was washed with H_2O, 1 N NaOH, and H_2O. The Et_2O solution was dried over Na_2SO_4 and evaporated at reduced pressure to afford 0.200 of **4b**. An analytical sample was obtained by recrystallization from CH_2Cl_2–Et_2O: mp 130–132 °C; NMR δ 6.82–7.37 (m, 3 H, aromatic), 4.80 (m, 1 H, CHOH), 2.22 (s, 3 H, $COCH_3$), 1.10 (s, 3 H, 18-CH_3), 0.90 (d, J = 8 Hz, 3 H, 7-CH_3). Anal. ($C_{21}H_{26}O_4$) C, H.

3,9α,11β-Trihydroxyestra-1,3,5(10)-trien-17-one 3-Acetate 11-Nitrate Ester (2a). Treatment of 5.0 g of estrone acetate with ceric ammonium nitrate by the procedure described for the synthesis of **2b** gave a solid, which upon recrystallization from Et_2O afforded 2.1 g of 9-hydroxy-11-nitrate ester **2a**. An analytical sample prepared by recrystallization from Et_2O, mp 183–184 °C, had spectral properties identical with those reported in the literature:[3] NMR δ 6.89–7.38 (m, 3 H, aromatic), 5.79 (t, J = 3 Hz, 1 H, $CHONO_2$), 2.24 (s, 3 H, $COCH_3$), 1.00 (s, 3 H, 18-CH_3).

17α-Ethynyl-3,9α,11β,17β-tetrahydroxyestra-1,3,5(10)-triene 3,17-Diacetate 11-Nitrate Ester (2c). By the procedure described for compound **1**, 1.00 g of ethynylestradiol diacetate gave 0.300 g of 9-hydroxy-11-nitrate ester **2c** on crystallization from Et_2O. An analytical sample was prepared by recrystallization from Et_2O: mp 173–175 °C; NMR δ 6.89–7.38 (m, 3 H, aromatic), 5.83 (t, J = 3 Hz, 1 H, $CHONO_2$), 2.68 (s, 1 H, C≡CH), 2.25 (s, 3 H, 3-$COCH_3$), 2.02 (s, 3 H, 17-$COCH_3$), 1.01 (s, 3 H, 18-CH_3); HRMS calcd for $C_{24}H_{27}NO_8$ – NO_2 (M^+ – NO_2) 457.1736, found 457.1772; R_f = 0.31, benzene–10% Et_2O.

3,9α,11β-Trihydroxy-19-norpregna-1,3,5(10)-triene 3-Acetate 11-Nitrate Ester (2d). By the procedure described for compound **2b**, 1.00 g of 3-hydroxy-19-norpregna-1,3,5(10)-triene 3-acetate gave, on crystallization from Et_2O–petroleum ether, 0.350 g of **2d**. An analytical sample was prepared by recrystallization from Et_2O: mp 177–179 °C; NMR δ 6.89–7.38 (m, 3 H, aromatic), 5.78 (t, J = 3 Hz, 1 H, $CHONO_2$), 2.26 (s, 3 H, $COCH_3$), 0.80 (s, 3 H, 18-CH_3); HRMS calcd for $C_{22}H_{29}NO_6$ – NO_2 (M^+ – NO_2) 357.2066, found 357.2100; R_f = 0.52, benzene–5% Et_2O.

3,9α,11β-Trihydroxy-7α-methyl-19-norpregna-1,3,5(10)-triene 3-Acetate 11-Nitrate Ester (2e). By the procedure described for compound **2b**, reaction of 0.15 g of 3-hydroxy-7α-methyl-19-norpregna-1,3,5(10)-triene 3-acetate gave, upon separation by preparative TLC, 0.059 g of 9-hydroxy-11-nitrate ester **2e**. An analytical sample was prepared by recrystallization from Et_2O: mp 140–143 °C; NMR δ 6.78–7.35 (m, 3 H, aromatic), 5.61 (t, J = 3 Hz, 1 H, $CHONO_2$), 2.22 (s, 3 H, $COCH_3$), 1.00 (d, J = 8 Hz, 3 H, 7-CH_3), 0.94 (s, 3 H, 18-CH_3); HRMS calcd for $C_{23}H_{31}NO_6$ – NO_2 (M^+ – NO_2) 371.2220, found 371.2231; R_f = 0.64, benzene–5% Et_2O.

3,11β-Dihydroxyestra-1,3,5(10)-trien-17-one 3-Acetate 11-Nitrate Ester (3a). By the procedure used for compound **3b**, 0.310 g of compound **2a** gave, on crystallization from Et_2O, 0.150 g of pure deoxygenated product **3a**: mp 190–192 °C; NMR δ 6.80–7.30 (m, 3 H, aromatic), 6.00 (m, 1 H, $CHONO_2$), 2.24 (s, 3 H, $COCH_3$), 1.05 (s, 3 H, 18-CH_3). Anal. ($C_{20}H_{23}NO_6$) C, H, N.

3,11β-Dihydroxyestra-1,3,5(10)-trien-17-one 3-Acetate (4a). To a solution of 2.8 g of **3a** in 409 mL of HOAc was added 2.8 g of zinc dust. The mixture was stirred at room temperature for 2.0 h, filtered through Celite, and evaporated to dryness at reduced pressure. The residue was dissolved in Et_2O and washed with H_2O. The aqueous phase was acidified with 4% HCl to dissolve some solid, which was then extracted with Et_2O. The combined Et_2O extracts were washed with H_2O and saturated $NaHCO_3$. The Et_2O was dried over $MgSO_4$ and evaporated to dryness at reduced pressure to afford 2.11 g of a yellow solid, which was triturated with Et_2O to afford 1.86 g of crude **4a**. Purification by column chromatography using 55 g of silica gel and elution with Et_2O–hexane (1:1) afforded 1.54 g of pure **4a**, mp 183–184 °C (lit.[8] mp 186–187 °C).

3,11β,17β-Trihydroxy-7α-methylestra-1,3,5(10)-triene 11-Nitrate Ester (5). To a stirred solution of 0.100 g of **3b** in 12 mL of MeOH was added 0.048 g of $NaBH_4$. The reaction mixture was stirred for 15 min and then added to 75 mL of H_2O. The product was extracted into 75 mL of Et_2O. The ethereal layer was separated, washed with H_2O, dried ($NaSO_4$), and concentrated at reduced pressure to give 0.100 g of crude **5**. An analytical sample of **5** was prepared by crystallization from CH_2Cl_2: mp 179–182 °C; NMR ($CDCl_3$–CD_3OD, 1:1) δ 6.52–7.30 (m, 3 H, aromatic), 6.01 (m, 1 H, $CHONO_2$), 3.81 (m, 1 H, C*H*OH), 0.90 (s, 3 H, 18-CH_3), 0.82 (d, J = 8 Hz, 3 H, 7-CH_3). Anal. ($C_{19}H_{25}NO_5$) C, H, N.

3,9α,11β-Trihydroxyestra-1,3,5(10)-trien-17-one 3-Acetate 9-Methyl Ether 11-Nitrate Ester (10a) and 3,9α,11β-Trihydroxyestra-1,3,5(10)-trien-17-one 3-Acetate 9,11-Dimethyl Ether (11a). To a stirred solution of 0.310 g of **1a** in 10 mL of MeOH was added 1.096 g of ceric ammonium nitrate. The reaction was stirred at room temperature for 1.0 h and then poured into H_2O. The mixture was extracted with Et_2O. The ethereal solution was washed with H_2O, dried (Na_2SO_4), and evaporated at reduced pressure to afford 0.370 g of crude **10a** and **11a**. The samples were purified by thick-plate chromatography using benzene–10% Et_2O to afford 0.160 g of **10a** as a glass: NMR δ 6.83–7.30 (m, 3 H, aromatic), 6.94 (t, J = 3 Hz, 1 H, $CHONO_2$), 2.85 (s, 3 H, OCH_3), 2.22 (s, 3 H, $COCH_3$), 1.00 (s, 3 H, 18-CH_3), and 0.190 g of **11a** as a glass; NMR δ 6.83–7.30 (m, 3 H, aromatic), 4.13 (t, J = 3 Hz, 1 H, C*H*OCH_3), 3.29 (s, 3 H, 9-OCH_3), 2.85 (s, 3 H, 11-OCH_3), 2.22 (s, 3 H, $COCH_3$), 1.02 (s, 3 H, 18-CH_3). Anal. for **10a** ($C_{21}H_{24}NO_7$) C, H, N and for **11a** ($C_{22}H_{28}O_5$) C, H.

Treatment of 10a and 11a with Triethylsilane. To a solution of a 0.370-g mixture of **10a** and **11a** in 20 mL of CH_2Cl_2 (dried by passing through Wohlm alumina Activity I) at −5 to 0 °C was successively added 0.5 mL of triethylsilane and 1.0 mL of boron trifluoride etherate. The reaction was then stirred at room temperature for 1.5 h and 0.5 g of solid K_2CO_3 was added. After 15 min, the reaction mixture was diluted with additional CH_2Cl_2 and H_2O. The separated CH_2Cl_2 was washed with 10% Na_2CO_3 and H_2O and dried over Na_2SO_4; then the solvent was removed at reduced pressure to afford 0.320 g of crude products. Purification by thick-plate chromatography using benzene–10% Et_2O afforded 0.048 g of a product identical with **3a** and 0.075 g of **11b**, respectively. Recrystallization of both **3a** and **11b** (mp 180–182 °C) from ether afforded respective analytical samples of each: NMR for **11b** δ 6.70–7.18 (m, 3 H, aromatic), 4.14 (m, 1 H, 11-C*H*OCH_3), 3.24 (s, 3 H, OCH_3), 2.21 (s, 3 H, $COCH_3$), 1.03 (s, 3 H, 18-CH_3).

11β-Methoxyestrone 3-Acetate (11b). To a solution of 0.048

g of 11β-methoxyestrone,[8] in 2 mL of dry pyridine with 0.010 g of 4-(*N*,*N*-dimethylamino)pyridine under argon, was added dropwise 22 μL of Ac_2O. After three days at ambient temperature, the mixture was stirred with 10 mL of 10% aqueous HCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to give 0.055 g of yellow amorphous solid, which was recrystallized from EtOAc–hexane. In this manner 0.043 g of **11b**, mp 180–181 °C, was obtained in successive crops: NMR δ 6.67–7.15 (m, 3 H, aromatic), 4.12 (m, 1H, 11-C*H*OCH_3), 3.23 (s, 3 H, OCH_3), 2.70–3.00 (m, 2 H, ArCH), 2.21 (s, 3 H, O_2CCH_3), 1.09 (s, 3 H, 18-CH_3). Anal. ($C_{21}H_{26}O_4$) C, H.

3-Hydroxy-11β-chloroestra-1,3,5(10)-trien-17-one 3-Acetate (13). To a stirred solution of 2.0 g of estrone acetate **1a** and 2.5 g of lithium chloride in 60 mL of HOAc (90%) was added 7.5 g of ceric ammonium nitrate. The reaction was stirred at room temperature for 1 h and then poured into H_2O. The resultant precipitate was extracted with Et_2O and then washed with H_2O, 5% $NaHCO_3$, and H_2O and dried over Na_2SO_4. Then the solvent was removed at reduced pressure to afford 2.0 g of crude **12**. Upon trituration from Et_2O, 0.760 g of **12** was obtained: NMR δ 6.80–7.50 (m, 3 H, aromatic), 4.80 (m, 1 H, CHCl), 2.23 (s, 3 H, $COCH_3$), 1.20 (s, 3 H, 18-CH_3). To a stirred solution of 0.362 g of **12** and 0.5 mL of triethylsilane in 15 mL of dry CH_2Cl_2 at −5 to 0 °C was added 1.0 mL of boron trifluoride etherate. Stirring was continued at −5 to 0 °C for 1 h. The reaction was slowly poured with stirring into a 10% K_2CO_3 solution and then extracted with Et_2O. The etheral solution was washed with H_2O, dried over Na_2SO_4, and evaporated at reduced pressure to afford 0.333 g of crude product. Recrystallization from Et_2O afforded 0.12 g of pure **13**: mp 187–190 °C; NMR δ 6.80–7.34 (m, 3 H, aromatic), 5.05 (m, 1 H, CHCl), 2.32 (s, 3 H, $COCH_3$), 1.28 (s, 3 H, 18-CH_3). Anal. ($C_{20}H_{23}O_3Cl$) C, H.

Biology. The orgal estrogenic and antifertility assays were conducted as previously reported.[13]

Subcutaneous Estrogenic Activity. Immature (approximately 45–55 g), female rats of Sprague–Dawley strain, purchased from accredited animal suppliers, were housed under standard laboratory conditions. Commercial laboratory feed and tap water were provided ad libitum. Total dose, per animal, of the test substance and the standard material were dissolved or suspended in fixed volumes of the required vehicle before subcutaneous administration. Generally three or more dose levels of the standard and test substance were utilized. Animals were treated once daily on days 21, 22, and 23 of age. On day 24 of age, approximately 24 h after the final treatment, the animals were sacrificed and both uterine horns were excised, cervix and oviducts excluded. The uteri were cleaned free of fat and other tissues, bisected in the middle and gently squeezed between absorbent paper to remove all fluid from the lumen. The weight of the uterus for each animal was recorded to the nearest 0.2 mg using a torsion balance. The potency of the unknown compound relative to the standard was determined using analysis of regression.[14] If the lines were not parallel or did not overlap, then an estimate of potency ratio or potency range was made.

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Registry No. **1a**, 901-93-9; **1b**, 36014-09-2; **1c**, 122069-89-0; **1e**, 108887-20-3; **1f**, 122069-90-3; **2a**, 33767-88-3; **2b**, 108887-16-7; **2c**, 108887-18-9; **2d**, 108887-19-0; **2e**, 108887-21-4; **3a**, 108887-24-7; **3b**, 108887-23-6; **4a**, 95342-26-0; **4b**, 108887-31-6; **5**, 108887-25-8; **10a**, 108887-26-9; **11a**, 108887-27-0; **11b**, 52301-53-8; **12**, 108887-29-2; **13**, 108887-28-1; ethynylestradiol diacetate, 13258-68-9; 11β-methoxyestrone, 21375-11-1.

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