(b) A solution of IVb (250 mg.), glacial acetic acid (10 ml.), water (4 ml.), and concentrated HCl (4.0 ml.) was heated under reflux for 4 hr. To this was added 47% aqueous HI (5.0 ml.), and heating under reflux was continued for 30 min. Only 3,5-diiodothyronine could be isolated from the reaction mixture as deduced from mixture melting point and a comparison of infrared spectra.

N-Acetyl-3-[4-(3-*t*-butyl-4-hydroxyphenoxy)-3,5-dinitrophenyl]-L-alanine Ethyl Ester (III).—The method is similar to that described by Meltzer, *et al.*[8] A solution of N-acetyl-3,5-dinitro-L-tyrosine ethyl ester (8.55 g., 0.025 mole) in dry pyridine (40 ml.) was stirred and heated on a steam bath. Freshly distilled methanesulfonyl chloride (3.15 g., 0.027 mole) was then added; a vigorous reaction occurred. After 2 min., nitrogen was passed into the system for 5 min. before 2-*t*-butyl-1,4-hydroquinone[9] (6.2 g., 0.037 mole) was added in one portion. Heating was continued for a further 15 min. in an atmosphere of nitrogen before the reaction mixture was poured onto crushed ice (100 g.). The mixture was then extracted twice with benzene (100 ml.), the benzene extracts were combined and washed consecutively with 100-ml. portions of water, aqueous 2 *N* HCl, water, aqueous 2 *N* NaOH, and finally water. Evaporation of the benzene gave a dark brown oily residue (2.6 g.) which was dissolved in the minimum quantity of benzene and chromatographed on acid-washed alumina (125 g.). Elution with ethyl acetate gave a fraction (1.4 g., 11%) which solidified on addition of petroleum ether (b.p. 30-60°), m.p. 105–120°. Crystallization from benzene-ethyl acetate gave the diphenyl ether (III) as yellow crystals, m.p. 124–126°, $[\alpha]^{25}D$ +33° (*c* 1, $CHCl_3$), containing 1 molecule of benzene of recrystallization. The n.m.r. spectrum showed the characteristic pattern of the dinitrothyronine structure[17] (*t*-BuMe, δ 1.33), also a singlet at δ 7.37 (6 protons) assigned to the benzene of crystallization. The benzene was retained even following recrystallization from aqueous methanol.

Anal. Calcd. for $C_{23}H_{27}N_3O_9 \cdot C_6H_6$: C, 61.37; H, 5.87. Found: C, 61.16; H, 5.88.

Considerable quantities of black tars were obtained, but these were not investigated.

N-Acetyl-3-[4-(3-*t*-butyl-4-hydroxyphenoxy)-3,5-diiodophenyl]-L-alanine Ethyl Ester (IVa).—A solution of III (2.8 g., 4.1 mmoles) in glacial acetic acid (80 ml.) was hydrogenated, bisdiazotized, and converted to the 3,5-diiodo ether as described by Jorgensen and Kaul[20] to give a dark brown residue (2.78 g.) which was dissolved in the minimum quantity of $CHCl_3$ and chromatographed on acid-washed alumina (100 g.). Elution with $CHCl_3$ gave the crude diiodo ether (IVa) (2.6 g., 86%) as a viscous oil. Crystallization from aqueous methanol gave crystals, m.p. 107–109°, $[\alpha]^{25}D$ +44° (*c* 1, $CHCl_3$). The n.m.r. spectrum confirmed the structure[17] (*t*-BuMe, δ 1.37).

Anal. Calcd. for $C_{23}H_{27}I_2NO_5$: C, 42.42; H, 4.18. Found: C, 42.08; H, 4.37.

3-[4-(3-*t*-Butyl-4-hydroxyphenoxy)-3,5-diiodophenyl]-L-alanine (Va).—A solution of IVa (1.0 g., 1.5 mmoles) in glacial acetic acid (75 ml.), concentrated HCl (36 ml.), and water (36 ml.) was heated under reflux for 6 hr. under nitrogen. After 3 hr. of reflux, a portion (30 ml.) of concentrated HCl was added. After 6 hr., distillation decreased the volume of the reaction mixture by two-thirds, and the pH was adjusted to 4.5 with sodium acetate. Addition of water (40 ml.) precipitated amino acid as a brown solid (0.33 g., 37%), m.p. 226–228° dec. Two isoelectric precipitations from the alkaline side gave a tan-colored precipitate (0.22 g.), m.p. 229–230° dec., $[\alpha]^{25}D$ +14° (*c* 1, 1:1 ethanol–aqueous *N* HCl), R_f 0.90 (solvent system: isoamyl alcohol–2*N* NH_4OH). In the same solvent system, 3,5-diiodothyronine had R_f 0.67.

Anal. Calcd. for $C_{19}H_{21}I_2NO_4 \cdot 0.5H_2O$: C, 38.68; H, 3.76; I, 43.02. Found: C, 38.82; H, 3.78; I, 42.70.

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17-Chloroethynylated Steroids. III. The Synthesis of 17α-Chloroethynyl-5,7,9-estratrien-17β-ol-3-one

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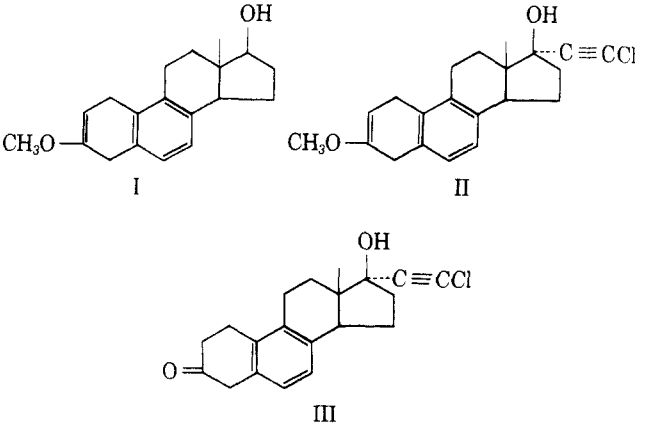
Examination of the structure–activity relationship among the pituitary gonadotrophin-inhibiting and progestational chloroethynylestrenones[1] suggested a rough correlation of activity with increasing planarity of the B-ring. It was, therefore, of interest to prepare the B-ring aromatic derivative III in order to test this correlation.



Birch reduction[2] of 3-methoxy-1,3,5,7,9-estrapentaen-17β-ol[3] afforded 3-methoxy-2,5,7,9-estratetraen-17β-ol (I). Oppenauer oxidation[4] of I led to the corresponding C-17 ketone, which after chloroethynylation[5] to yield II, afforded the required 17α-chloroethynyl-5,7,9-estratrien-17β-ol-3-one (III) after acid hydrolysis.

Compounds II and III were tested in the Merck Institute for Therapeutic Research.[6] Results are summarized in Table I.

Experimental[7]

3-Methoxy-2,5,7,9-estratetraen-17β-ol (I).—A solution consisting of 1.347 g. of 3-methoxy-1,3,5,7,9-estrapentaen-17β-ol[3] (m.p. 150–151°), 20 ml. of tetrahydrofuran,[8] and 20 ml. of *t*-butyl alcohol[8] was added with stirring to 50 ml. of liquid ammonia.[8] A total of 440 mg. of sodium was then added in four approximately equal portions over a period of 5 min. The re-

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(6) We are indebted to Dr. S. L. Steelman for carrying out this determination.

(7) Melting points were taken on a micro hot stage and are corrected. Rotations were determined in benzene at a concentration of 7 mg./ml. at 24–26°. We are indebted to A. Kalowski for the ultraviolet spectra and to R. Boos and his associates for microanalysis herein reported.

(8) The tetrahydrofuran was freshly distilled from $LiAlH_4$. The *t*-butyl alcohol and the ammonia were distilled from sodium.

action was allowed to proceed for an additional 13 min. at which time the solution was colorless. After addition of 7 ml. of methanol the NH_3 was evaporated using a water bath at a temperature of ~40°. The solution was then further concentrated *in vacuo*, and 50 ml. of water was added to the gummy residue to yield a powdery precipitate which was separated by filtration. Crystallization from petroleum ether and ether afforded 1.175 g. of I, m.p. 123–134°. Further recrystallization from the same solvents yielded a sample for analysis: m.p. 134–136°; α_D +46°; ultraviolet $\lambda_{max}^{dioxane}$ 269 mμ (ε 300), 276 mμ (ε 210).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.06; H, 8.55.

TABLE I

Compd.	Oral gonadotrophin inhibition[a] (parabiotic rats)	Progestational activity[b]
17α-Chloroethynyl-4-estren-17β-ol-3-one[c]	1	1[d]
17α-Chloroethynyl-5(10)-estren-17β-ol-3-one[c]	1.2	0.03[d]
17α-Chloroethynyl-4,9(10)-estradien-17β-ol-3-one[c]	2.5	2[d]
III	0.2	0[e]
II	0[f]	0[g]

[a] J. A. Epstein, H. S. Kupperman, and A. Cutler, *Ann. N. Y. Acad. Sci.*, **71**, 560 (1958). [b] M. K. McPhail, *J. Physiol.*, **83**, 145 (1934). [c] Ref. 1. [d] Oral. [e] At 500 γ/kg. s.c. [f] At 400 γ s.c. [g] At 50 γ/kg. s.c.

3-Methoxy-2,5,7,9-estratetraen-17-one.—A solution consisting of 255 mg. of I (m.p. 129–136°), 306 mg. of freshly distilled aluminum isopropoxide, and 13 ml. of dry toluene was heated for 5 min. on the steam bath under an atmosphere of nitrogen. The solution was cooled in ice and 2.6 ml. of distilled cyclohexanone was added. The solution was again heated on the steam bath under nitrogen for 40 min. and cooled in ice. A saturated aqueous solution of Rochelle salts was added with vigorous shaking and the product separated with ether. After evaporation of the ether the remaining solution was steam distilled. The residue was extracted with ether, dried ($MgSO_4$), and concentrated to yield 210 mg. of the product, double m.p. 115–130°, 167–177°. Several crystallizations from methanol and finally from ether afforded a sample for analysis; m.p. 148–153; α_D +72°; ultraviolet λ_{max} 269 mμ (ε 300), 276 mμ (ε 230).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.90; H, 7.61.

17α-Chloroethynyl-3-methoxy-2,5,7,9-estratetraen-17β-ol (II).—A solution of *cis*-1,2-dichloroethylene in 15 ml. of sodium-dried ether was added to a stirred solution consisting of 6.0 ml. of 1.30 *N* methyllithium in 15 ml. of sodium-dried ether maintained under an atmosphere of nitrogen and cooled by an ice bath. Stirring was continued for an additional 20 min. after removal of the ice bath, followed by the dropwise addition of 732 mg. of 3-methoxy-2,5,7,9-estratetraen-17-one in 80 ml. of sodium-dried ether over a 15-min. period. After an additional hour the reaction mixture was poured into ice water and ether. The ether layer was separated, washed with water, dried (K_2CO_3), and concentrated *in vacuo* to yield 620 mg. in two crops, m.p. 114–119° and 111–116°. A sample for analysis was crystallized three times from ether; m.p. 122–125° (sealed evacuated capillary); α_D −92°; ultraviolet λ_{max} 269 mμ (ε 450), 275 mμ (ε 400).

Anal. Calcd. or $C_{21}H_{23}ClO_2$: C, 73.57; H, 6.76; Cl, 10.34. Found: C, 73.27; H, 6.75; Cl, 10.28.

17α-Chloroethynyl-5,7,9-estratrien-17β-ol-3-one (III).—A solution consisting of 352 mg. of II, 35 mg. of *p*-toluenesulfonic acid, and 20 ml. of acetone was stirred at room temperature for 1 hr., diluted with ether, and washed with aqueous $NaHCO_3$ solution. The ether solution was dried (K_2CO_3) and concentrated to yield 251 mg. of III, m.p. 165–178° with slight decomposition. A sample for analysis was recrystallized three times from ether; m.p. 173–179°; α_D −102°; ultraviolet λ_{max} 270 mμ (ε 520), 307 mμ (ε 220).

Anal. Calcd. for $C_{20}H_{21}ClO_2$: C, 73.05; H, 6.44; Cl, 10.78. Found: C, 72.74; H, 6.43; Cl, 10.79.

A-Nor Oxa Steroids[1]

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Although the introduction of an oxygen atom into the steroid nucleus has attracted the attention of chemists for several decades,[2] it was only recently that the synthesis of 17-oxa-5α-androstan-3-one was reported.[3] This represents the first example of a steroid analog in which oxygen has been inserted into a five-membered ring. Since a ring A oxa steroid (17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one)[4] has been demonstrated to be a potent anabolic agent, the synthesis of an A-nor steroid bearing an oxygen atom in ring A appeared an attractive target both from a chemical and biological view.

A-nortestosterone (I)[5] was hydroxylated with osmium tetroxide in pyridine to give A-norandrostan-2-one-3β,5β,17β-triol (II).[6] Periodic acid oxidation of glycol II gave a product whose infrared spectrum exhibited a single carbonyl band at 5.73 μ indicating that the lactol III and not a keto acid had been obtained. This lactol had been previously obtained in low yield by ozonation of 2-hydroxymethylenetestosterone.[7]

Sodium borohydride reduction of III gave 2,5-seco-3,4-bisnorandrostane-5β,17β-diol-2-oic acid (IV) as the major product. The assignment of configuration was based on the fact that sodium borohydride reduction of an unhindered ketone yields the equatorial isomer as the predominant product.[8] It is noteworthy that a similar reduction of a six-membered ring A steroidal lactol leads directly to the lactone *via* cyclization of the hydroxy acid.[9]

Efforts to prepare the γ-lactone by heating IV in refluxing hydrocarbon solvents (benzene, toluene, or *p*-cymene) were unsuccessful leading in each case to recovered starting material. Lactonization was ultimately achieved by treatment of IV with acetic anhydride containing sodium acetate to afford 3-oxa-5α-A-norandrostan-2-on-17β-ol acetate (V). The n.m.r. spectrum of V exhibited a quartet centered at τ 6.16 for the axial proton at C-5.[9b]

The reduction of lactone V with lithium aluminum hydride in ether gave 2,5-seco-3,4-bisnorandrostane-2,5β,-17β-triol (VI). Direct reduction of V to an ether using lithium aluminum hydride and boron trifluoride[10] was unsuccessful. The failure of a γ-lactone to be reduced to its corresponding ether under these conditions has been observed previously.[3]

(1) Presented at the 4th Annual Metropolitan Regional Meeting at Stevens Institute, Hoboken, N. J., Feb. 1, 1965.

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