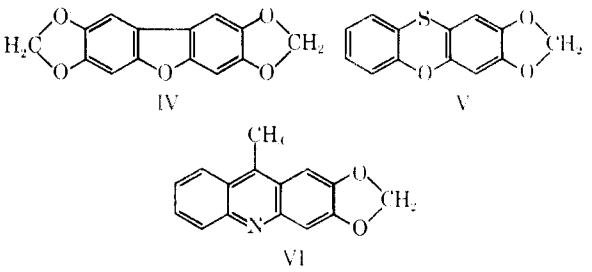
about the same value we found for log P_0 for a variety of bactericides acting on gram-negative bacteria.[3l] This may not be a particularly useful observation; on the other hand, it could be that in both instances drugs are acting on the same type of cellular organelles and about the same lipophilic character is ideal for penetration in each case.

The big improvement in correlation of eq 12 over eq 11 constitutes another illustration of the use of the steric parameter E_s in a nonhomogeneous biochemical reaction. Our own previous work[3e,21,23] indicates that E_s may be a very important parameter for use in nonhomogeneous systems.

The results contained in the above equations do offer useful information for the synthesis of more potent synergists for insecticides. In the first place, one should design quite lipophilic molecules having log P values near 4. Taking advantage of the additive character[12] of π and log P, such molecules can be designed without the effort of first making them and then measuring log P. A hydrogen atom should be built into such compounds and be so situated that the odd electron generated by its homolytic removal can be stabilized by an extensive π-electron system. Keeping in mind that the $-OCH_2O-$ function has a π value of almost zero, and that log P for dibenzofuran is 4.12, 4.05 for phenothiazine, and 3.9 for methylacridine, IV–VI



IV V

VI

and their isomers would be interesting examples. Many other possibilities come readily to mind.

While the homolytic arylation studies reviewed by Williams and the radical work of Yamamoto and Otsu[19] provide excellent sources for leads in such work, this would appear to be an ideal situation to which molecular orbital theory[24] could be applied in the design of π-electron systems best suited to delocalize an odd electron.

The above work is of course most pertinent to the mechanism of action and design of synergists for insecticides. It would also seem to be of use in our general understanding of the metabolism of drugs since there is considerable evidence that the microsomal action of insects is quite similar to that of mammals. It seems likely that the homolytic constants we have formulated from the work of Hey and Williams should be of use in correlating homolytic reactions in biochemical systems.

(23) C. Hansch and E. W. Deutsch, *Biochim. Biophys. Acta*, **126**, 117 (1966).

(24) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1963.

Estra-1,3,5(10),15-tetraenes. I. Birch Reduction

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The addition of organolithium reagents to 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**3**) yielded a series of 17-substituted Δ^{15} derivatives (**6**). Birch reduction of **6a** and **6b** at −78° led to reduction of ring A without reduction of the Δ^{15} double bond. Oppenauer oxidation at room temperature of the intermediate 3-methoxyestra-2,5(10),15-trien-17β-ol (**10**) afforded the ketone **11** which was converted to a series of active progestins. The hypocholesteremic and estrogenic activities of the intermediate aromatic steroids are reported. A simple procedure for ethynylation of base-sensitive ketones is described.

As part of a synthetic program leading to modified steroidal estrogens and their derivatives, some reactions of estra-1,3,5(10),15-tetraenes, in particular 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**3**), were examined.[1] The Δ^{15}-17-one **3** had previously been prepared in five steps from estrone methyl ether (**1**) by Johnson and Johns.[2] We used essentially the same procedure, but reduced the number of steps to four by direct bromination of estrone methyl ether with $CuBr_2$[3] (Scheme I).

In an effort to reduce the number of steps even further, the direct dehydrobromination of bromo ketone **2** was reexamined. In a related series, Pappo, *et al.*,[4] treated 16-bromo-3β-hydroxyandrostan-17-one acetate with γ-collidine and obtained the Δ^{14}-17-one in 5% yield as the only isolable product. In the present work the use of LiBr and Li_2CO_3 in DMF on **2** at 100°[5] gave little reaction after 21 hr. At 130° a mixture of the Δ^{14}-17-one **4** and the 14β-Δ^{15}-17-one **5** was formed with no significant amount of the less stable unsaturated ketone **3** present.[6] On a preparative scale, 39% of **4** and 38% of **5** were obtained. Use of $CaCO_3$ in dimethylacetamide[7] led to similar results; so, no further shortening of our reaction sequence was accomplished.

(1) E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964), have used **3** to prepare a series of 15-substituted derivatives.

(2) W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, **79**, 2005 (1957).

(3) E. R. Glazier, *J. Org. Chem.*, **27**, 4397 (1962).

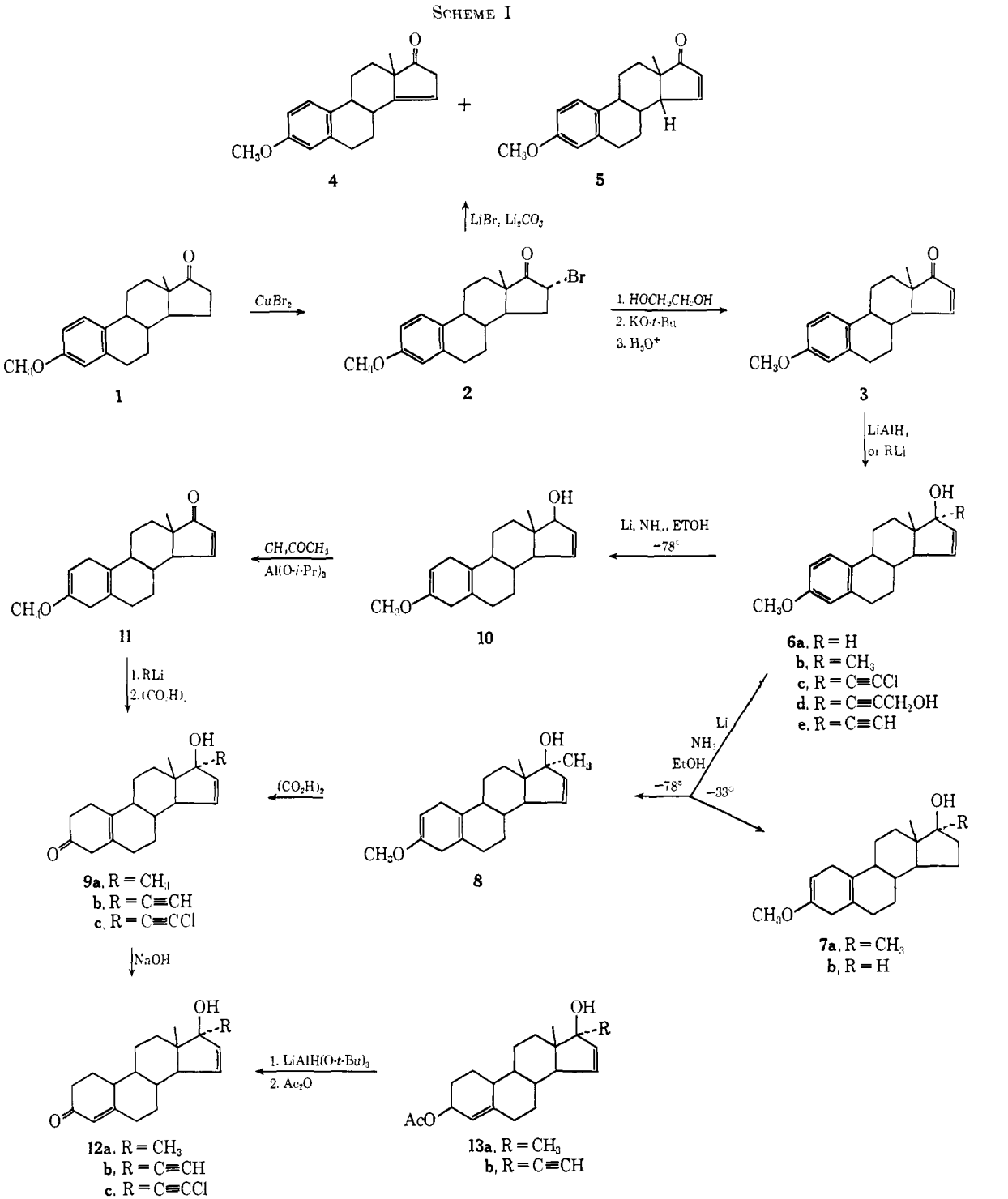
(4) R. Pappo, B. M. Bloom and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 6347 (1956).

(5) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. France*, 366 (1958).

(6) The instability of 14α-Δ^{15}-17-ones to heat [K. Tsuda, N. Ikekawa, Y. Sato, S. Tanaka, and H. Hasegawa, *Chem. Pharm. Bull* (Tokyo), **10**, 332 (1962)] and to acid [ref 2 and E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 214 (1964)] has been noted.

(7) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

SCHEME I



Reduction of the unsaturated ketone **3** with $LiAlH_4$ at 0 to $-5°$ afforded a 78% yield of the Δ^{15}-17β-ol **6a**. At higher temperatures considerable amounts of the saturated alcohol and the saturated ketone **1** were obtained (as demonstrated by tlc).[8] Meerwein–Pondorff reduction using aluminum isopropoxide and *i*-PrOH in refluxing C_6H_6 gave the unsaturated alcohol in 72% yield.

Interaction of the unsaturated ketone **3** with Grignard reagents led to mixtures of compounds. With organolithium reagents, essentially pure products were obtained. Use of MeLi in THF afforded the alcohol **6b**. Reaction with lithium chloroacetylide gave the chloroethynyl derivative **6c**. The reaction with the lithium derivative of 2-(2-propynyloxy)tetrahydropyran[9] yielded an intermediate which, after acid hydrolysis, gave the hydroxypropynyl derivative **6d**. Direct ethynylation of **3** with lithium acetylide–ethylenediamine complex in THF or DMSO or with sodium acetylide in DMSO[10] afforded unpromising mixtures. When lithium acetylide in THF (prepared by addition

(8) J. Fajkos, *Collection Czech. Chem. Commun.*, **23**, 2155 (1958), reported that sodium borohydride reduction of an analogous Δ^{15}-17-one gave the saturated alcohol exclusively.

(9) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, 3646 (1950).

(10) C. H. Robinson, N. F. Bruce, and E. P. Oliveto, *J. Org. Chem.*, **28**, 975 (1963).

of acetylene to a cold solution of BuLi in THF or by addition of BuLi solution to ice-cold THF saturated with acetylene)[11] was used, an 86% yield of the ethynyl alcohol **6e** was obtained. This method worked equally well with ketone **11** and with estrone methyl ether (**1**).

Birch reduction of the aromatic alcohol **6b** with Li and EtOH in liquid NH_3-THF at the boiling point of NH_3 led to a product which showed no Δ^{15} double bond in its nmr spectrum. This compound had the melting point and spectral characteristics of the saturated enol ether **7a**.[12] When the reaction was run at −78°, a 62% yield of the enol ether **8** having the double bond intact was obtained.[13] Hydrolysis of the enol ether **8** with oxalic acid at room temperature afforded the unconjugated ketone **9a**. The conjugated ketone **12a** was obtained by treating **9a** with aqueous NaOH. Reduction of the ketone **12a** with lithium tri-*t*-butoxyaluminum hydride followed by acetylation of the resultant alcohol yielded the unsaturated acetate **13a**.

Birch reduction of the unsaturated alcohol **6a** at −78° afforded the allylic alcohol **10** in about 80% yield. This compound was never obtained pure, but was always contaminated with the saturated alcohol **7b**. Conversion of this alcohol to the unsaturated ketone **11** proved troublesome. Attempted oxidation with chromic acid–pyridine–water,[14] basic MnO_2,[15] acidic MnO_2,[16] 2,3-dichloro-5,6-dicyanobenzoquinone,[17] DMSO–dicyclohexylcarbodiimide–pyridine hydrochloride,[18] or DMSO–Ac_2O[19] gave unpromising mixtures, due mainly to aromatization of ring A. Finally, Oppenauer oxidation with aluminum isopropoxide and acetone in benzene at room temperature[20] afforded the desired ketone **11** in 76% yield with no aromatization of ring A.

This ketone was used to prepare ethynyl and chloroethynyl analogs of **9a**, **12a**, and **13a**. Reaction of ketone **11** with lithium acetylide in THF produced the ethynyl alcohol, which on hydrolysis with oxalic acid gave the unconjugated ketone **9b**. This compound was converted to the Δ^4-3-one **12b** with NaOH. Reduction of **12b** with lithium tri-*t*-butoxyaluminum hydride followed by acetylation of the intermediate alcohol led to the unsaturated acetate **13b**. In a similar manner, the chloroethynyl derivatives **9c** and **12c** were prepared.

Biological Evaluation.—The progestational activity of these compounds was determined by the Clauberg test[21] and the endometrial response was scored according to the index of McPhail.[22] The androgenic activity, based on the increase in weight of the seminal vesicles and ventral prostate of weanling male rats, was estimated by a modification[23] of the method of Hershberger, Shipley, and Meyer.[24]

The uterotrophic activities were estimated in weanling female rats given the test compounds daily for 3 days by intubation. On the fourth day the uteri were excised, blotted dry, and weighed on a microtorsion balance. For purposes of comparison of relative uterotrophic activities the minimal dose of steroid required to increase the uterine weights by 50 mg over that of the control animals is expressed as an MD_{50} value.

The hypocholesteremic activity was estimated following oral administration of the steroids to intact mature male Sprague–Dawley strain rats, 225–275 g, daily for 4 days. On the fifth day blood was withdrawn by cardiac puncture, the serum separated, and the cholesterol concentration was determined by the macro procedure of Turner and Eales[25] with *p*-toluenesulfonic acid as the catalyst in the Liebermann–Burchard procedure. As a measure of their relative hypocholesteremic activities, the dosage of the steroids required to reduce the serum cholesterol 33% (ED_{33}) was estimated graphically on the basis of two or more levels of test of the compound.

Of the compounds found to have progestational activity, the 17-ethynyl-Δ-5(10) derivative **9b** was the most interesting, being four times as active as norethindrone (17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one) in the Clauberg assay with weak estrogenic activity and no significant androgenic activity (Table I). The

TABLE I
ORAL PROGESTATIONAL, ANDROGENIC, AND ESTROGENIC ACTIVITIES

Compd	Progestational (× norethindrone)	Androgenic (× methyltestosterone)	Estrogenic MD_{50},[a] mg/kg/day × 3
8	1	*b*	80
9a	1	1/8	45
9b	4	*c*	>100[d]
9c	1/8	*e*	~100
12a	4	1/3	>100[f]
12b	1	1/32	100
12c	1/8	*g*	~100
13a	4	1/4	>25[h]
13b	1	*b*	>50[h]

[a] Minimum dose required to increase the uterine weight 50 mg over control. [b] Preferential stimulation of the seminal vesicles at 28 mg/kg sc. This response is typical of that produced by estrogens. [c] Preferential stimulation of the seminal vesicles at 160 mg/kg. [d] Significant stimulation at 20 mg/kg. [e] Preferential stimulation of the seminal vesicles at 80 mg/kg. [f] Significant stimulation at 10 mg/kg. [g] Significant stimulation. [h] Inactive at 40 mg/kg.

17-methyl derivatives **12a** and **13a** were equally as progestational but showed considerable androgenic activity. Shift of the double bond of **9b** from 5(10) to 4,5 (**12b**) caused a decrease in progestational activity, in

(11) A modification of Badische Anilin- & Soda-Fabrik Akt.-Ges., British Patent 771,708 (1957).

(12) F. B. Colton, U. S. Patent 2,905,676 (1959).

(13) W. S. Johnson, W. H. Lunn, and K. Fitzi [*J. Am. Chem. Soc.*, **86**, 1972 (1964)] achieved similar results in the reduction of α-(1Δ²-butenyl)-anisole.

(14) R. H. Cornforth, J. W. Cornforth, and G. Popjak, *Tetrahedron*, **18**, 1351 (1962).

(15) J. Attenborrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952). A 2-year-old batch of this reagent in $CHCl_3$ afforded the desired ketone **11** in 72% yield. When freshly prepared reagent was used the reaction product was contaminated with the aromatic ketone **3**.

(16) F. Sondheimer, O. Mancera, M. Urquiza, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 4145 (1955).

(17) A. Bowers, P. G. Holton, E. Necoechea, and F. Kincl, *J. Chem. Soc.*, 4057 (1961).

(18) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963).

(19) J. D. Albright and L. Goldman, *ibid.*, **87**, 4214 (1965).

(20) K. Heusler, J. Kalvoda, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **44**, 179 (1961).

(21) C. Clauberg, *Zentr. Gynaekol.*, **54**, 2757 (1930).

(22) M. K. McPhail, *J. Physiol.* (London), **83**, 145 (1935).

(23) G. O. Potts, A. L. Beyler, and D. F. Burnham, *Proc. Soc. Exptl. Biol. Med.*, **103**, 383 (1960).

(24) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *ibid.*, **83**, 175 (1953).

(25) T. H. Turner and L. Eales, *Scand. J. Clin. Lab. Invest.*, **9**, 210 (1957).

contrast to the norethynodrel (17-hydroxy-19-nor-17a-pregn-5(10)-en-20-yn-3-one) to norethindrone shift.[26]

Compounds **6b**, **6c**, and **6e** were somewhat more active than estrone methyl ether in lowering cholesterol levels in male rats (Table II). The methyl derivative **6b** had a better hypocholesteremic to uterotrophic activity ratio than estrone methyl ether had.

TABLE II

ORAL HYPOCHOLESTEREMIC AND UTEROTROPHIC ACTIVITIES

Compd	Hypocholesteremic ED_{33},[a] mg/kg/day × 4	Estrogenic MD_{50},[b] mg/kg/day × 3	Ratio
Estrone methyl ether	1.6[c]	<0.5[c]	>3
6a	9	1.5	6
6a acetate	5.4	~1.25[d]	~4.3
6b	0.7	~50[e]	~0.018
6c	0.8	2.8	0.03
6d	*f*	>250[g]	...
6e	0.1	0.25	0.4

[a] Minimum dose required to reduce serum cholesterol 33% over control. [b] Minimum dose required to increase uterine weight 50 mg over control. [c] A. Arnold, G. O. Potts, J. McAuliff, R. G. Christiansen, and T. C. Miller, *Proc. Soc. Exptl. Biol. Med.*, **121**, 122 (1966). [d] Significant stimulation at 0.25 mg/kg. [e] Significant stimulation at 0.1 mg/kg. [f] Inactive at 16 mg/kg. [g] Significant stimulation.

However, it showed significant uterotrophic activity at as low a dose as 0.1 mg/kg/day × 3, suggesting that it is an impeded estrogen.[27] Compound **6e** was 16 times as hypocholesteremic as estrone methyl ether was, but was equally as estrogenic. Compound **6d**, with a hydroxypropynyl group at C-17, gave no evidence of hypocholesteremic activity at 16 mg/kg/day × 4 and was not tested further. Minimal estrogenic activity was noted at 250 mg/kg/day × 3.

Experimental Section

Unless otherwise noted, the organic extracts from the reactions were washed (H_2O and saturated aqueous NaCl), dried (Na_2SO_4), and concentrated under reduced pressure. All melting points are corrected. The ir spectra were recorded on a Perkin-Elmer infrared spectrophotometer Model 21, uv spectra on a Cary spectrophotometer Model 15, and nmr spectra on a Varian A-60 spectrometer using precalibrated paper. Solutions (10–20%) were used with $(CH_3)_4Si$ as internal standard. Silica gel G (Brinkmann Instruments) was used for tlc. Spectra were run under the supervision of Dr. R. K. Kullnig, who assisted in the interpretation of the nmr spectra. Microanalyses were carried out under the supervision of Mr. K. D. Fleischer.

16-Bromo-3-methoxyestra-1,3,5(10)-trien-17-one (2).[2]—$CuBr_2$[3] (500 g) was added to a warm solution of 250 g of estrone methyl ether (**1**) in 2 l. of C_6H_6 and 2 l. of MeOH. The mixture was stirred at reflux for 1 hr and filtered while still hot. The filtrate was concentrated under reduced pressure to about 1 l. and then diluted with 3 l. of C_6H_6 and 1 l. of H_2O. The mixture was shaken well, then filtered while still warm. The aqueous layer was extracted with 1:1 Et_2O–C_6H_6. The combined organic extracts were washed (NaCl), dried, concentrated to about 800 ml, and cooled. Filtration afforded 220.9 g (69%) of light yellow crystals, mp 175–178° (vac); second crop, 30.2 g (9%), mp 173–176° (vac).

3-Methoxyestra-1,3,5(10),15-tetraen-17-one (3).—The bromo ketone **2** was converted to the unsaturated ketone in 47–53% yield by the procedure of Johnson and Johns.[2]

Direct Dehydrobromination of Bromo Ketone (2).—A mixture of 47.3 g of the bromo ketone, 70 g of LiBr, and 60 g of Li_2CO_3 in dimethylacetamide was refluxed for 3.5 hr. The red solution was cooled and poured into 1500 ml of 20% aqueous AcOH and the mixture was extracted with 1:1 Et_2O–C_6H_6. Work-up gave a red residue, which was chromatogaphed on silica gel. Elution with 1% Et_2O in C_6H_6 afforded, after recrystallization from EtOH, 14.5 g (39%) of **3-methoxyestra-1,3,5(10),14-tetraen-17-one (4)**: mp 102–103.5° (lit.[2] mp 103–104°); $[\alpha]^{25}D$ +293° (lit.[1] +293°); ir (KBr), 5.74 μ; nmr ($CDCl_3$), 1.13 (CH_3), 3.72 (OCH_3), and 5.57 ppm ($C_{15}H$, unresolved multiplet). Mixture melting point with an authentic sample prepared by the method of Johnson and Johns[2] was not depressed. Their ir spectra were superimposable.

Elution with 2.5% Et_2O in C_6H_6 yielded, after recrystallization from EtOH, 13.9 g (38%) of **3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one**: mp 100–101.5° (lit.[2] mp 101–102°); $[\alpha]^{25}D$ +485° (lit.[1] +477°); ir (KBr), 5.88 μ; nmr ($CDCl_3$), 1.13 (CH_3), 3.70 (OCH_3), 6.13 ($C_{15}H$ quartet, J = 6, 2.5 Hz), and 7.53 ppm ($C_{16}H$ quartet, J = 6, 2.5 Hz). Mixture melting point with an authentic sample prepared by the method of Johnsons and Johns was not depressed. Their ir spectra were superimposable. The 14α-Δ^{15}-17-one **3** (mp 179–183°, lit.[2] 180–181°, $[\alpha]^{25}D$ −54°, lit.[1] −90°) had nmr peaks ($CDCl_3$) at 1.08 (CH_3), 3.75 (OCH_3), 6.08 ($C_{15}H$ quartet, J = 6, 3 Hz), and 7.62 ppm ($C_{16}H$ quartet, J = 6, 1.5–2 Hz).

3-Methoxyestra-1,3,5(10),15-tetraen-17β-ol (6a).—Reduction of 8.47 g of **3** with $LiAlH_4$ in Et_2O–C_6H_6 at 0 to −5° afforded 6.63 g (78%) of once recrystallized colorless crystals, mp 150–153° (vac) (C_6H_6–*i*-PrOH). Additional recrystallization gave colorless rods: mp 152–154° (vac); $[\alpha]^{25}D$ +1.5° ($CHCl_3$); ir (KBr), 2.92 μ; uv (95% EtOH), 221 sh mμ (ε 9700), 279 (2050), and 288 (1900); nmr ($CDCl_3$), 0.85 (CH_3), 3.75 (OCH_3), 4.38 ($C_{17}H$), 5.70 ($C_{15}H$ octet, J = 5.8, 3, 1.4 Hz), and 6.03 ppm ($C_{16}H$ poorly resolved multiplet, J = 5.8, 1.4 Hz). *Anal.* ($C_{19}H_{24}O_2$) C, H.

The **acetate** of **6a** was obtained as colorless prisms: mp 136.5–138° (vac); $[\alpha]^{25}D$ −35.0° ($CHCl_3$); ir (KBr), 5.78 μ. *Anal.* ($C_{21}H_{26}O_3$) C, H.

3-Methoxy-17-methylestra-1,3,5(10),15-tetraen-17β-ol (6b).—A solution of 10.0 g of **3** in 120 ml of THF was added to a stirred ice-cold solution of 75 ml of MeLi in Et_2O (1.68 *M*, Foote Mineral Co.) under N_2 during 7 min. After an additional 15 min of stirring, H_2O was added and the mixture was extracted with Et_2O. Work-up gave 7.04 g (67%) of once recrystallized colorless flakes, mp 92–99° (C_6H_6–MeOH), plus a second crop, 2.67 g (25%), mp 90–95°. Tlc showed these crops to be essentially pure (25% ether in C_6H_6, followed by H_2SO_4, heat). Additional recrystallization afforded colorless flakes: mp (softens at 90–93°) 104–105° (vac); $[\alpha]^{25}D$ −65.3° ($CHCl_3$); ir (KBr), 2.75 and 2.99 μ; nmr ($CDCl_3$), 0.92 (angular CH_3), 1.20 ($C_{17}CH_3$), 5.64 ($C_{15}H$ quartet, J = 6, 3 Hz), and 5.90 ppm ($C_{16}H$ quartet, J = 6, 1 Hz). *Anal.* ($C_{20}H_{26}O_2$) C, H.

21-Chloro-3-methoxy-19-nor-17α-pregna-1,3,5(10),15-tetraen-20-yn-17-ol (6c).—In a manner similar to the preparation of **6b**, 2.00 g of **3** was treated with lithium chloroacetylide [prepared by addition of 5 ml of *cis*-1,2-dichloroethylene in 25 ml of absolute Et_2O to an ice-cold solution of 25 ml of MeLi in Et_2O (1.68 *M*) under N_2]. Work-up afforded 1.62 g (67%) of pale yellow crystals, mp 159–160°. Recrystallization from MeCN gave pale tan crystals: mp 160–162° (vac); $[\alpha]^{25}D$ −254.1° ($CHCl_3$); ir (KBr), 2.92 and 4.52–4.60 μ w; nmr ($CDCl_3$), 0.93 (CH_3), 3.77 (OCH_3), 5.73 ($C_{15}H$ quartet, J = 6, 3–4 Hz), and 6.08 ppm ($C_{16}H$ doublet, J = 6 Hz). *Anal.* ($C_{21}H_{23}ClO_2$) C, H, Cl.

17-(3-Hydroxy-1-propynyl)-3-methoxyestra-1,3,5(10),15-tetraen-17β-ol (6d).—In a manner similar to the preparation of **6b**, 3.00 g of **3** was treated with the lithium salt of 2-(propynyloxy)-tetrahydropyran[9] [prepared by reaction of the substituted acetylene, bp 87–88° (25 mm), with MeLi in Et_2O]. Work-up yielded 5.52 g of yellow oil.

Hydrolysis of this oil with *p*-toluenesulfonic acid monohydrate in EtOH at reflux afforded 2.91 g (79%) of once recrystallized tan crystals, mp 214–217° (EtOAc–MeOH). Additional recrystallization yielded light yellow crystals: mp 217–219° (vac); $[\alpha]^{25}D$ −248.7° (pyridine); ir (KBr), 3.04 μ; nmr (DMSO-d_6), 0.89 (CH_3), 3.70 (OCH_3), 4.15 (CH_2O), 5.70 ($C_{15}H$ quartet, J = 6 Hz), and 6.03 ppm ($C_{16}H$ doublet, J = 6 Hz). *Anal.* ($C_{22}H_{26}O_3$) C, H.

3-Methoxy-19-nor-17α-pregna-1,3,5(10),15-tetraen-20-yn-17-ol (6e).—A solution of 100 ml of BuLi in hexane (1.59 *M*, Foote Mineral Co.) and 100 ml of THF was added during 15 min to a

(26) J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Sarett, and S. L. Steelman, *J. Am. Chem. Soc.*, **83**, 4663 (1961).

(27) C. Huggins and E. V. Jensen, *J. Exptl. Med.*, **102**, 347 (1955).

stirred cooled solution of 400 ml of THF saturated with acetylene. Acetylene was then bubbled through the stirred mixture for 45 min. The stirrred mixture was cooled in ice and a solution of 10.0 g of **3** in 300 ml of THF was added in 20 min. After an additional 20 min of stirring, saturated aqueous Na_2SO_4 was added until the salts coagulated. The organic layer was decanted, diluted with 1:1 Et_2O–C_6H_6, and worked up to yield 9.41 g (86%) of once recrystallized pale tan flakes, mp 146–149° (vac) (C_6H_6–MeOH). Additional recrystallization afforded colorless flakes: mp 150–151° (vac); $[\alpha]^{25}D$ −194.0° ($CHCl_3$); ir (KBr), 2.86, 2.90, 3.05, and 3.09 μ (sharp split peak; shows single peak in $CHCl_3$); nmr ($CDCl_3$), 0.95 (CH_3), 2.62 (C≡CH), 3.73 (OCH_3), 5.73 ($C_{15}H$ quartet, J = 6, 3 Hz), and 6.07 ppm ($C_{16}H$ doublet, J = 6 Hz). *Anal.* ($C_{21}H_{24}O_2$) C, H.

Birch Reduction of Compound 6b. At −78°.—Li wire (3.3 g) was added in small pieces to a stirred solution of 10.0 g of **6b** in 450 ml of THF and 600 ml of liquid NH_3 cooled to −78° in a Dry Ice–Me_2CO bath. Absolute EtOH (50 ml) was added to the blue mixture in 3 min and the mixture was stirred vigorously. After 5 min, 30 g of NH_4Cl was added. When the mixture had become colorless (3 min), the cooling bath was removed and the mixture was warmed to room temperature, diluted with H_2O, and extracted with 1:1 Et_2O-C_6H_6. Work-up gave 6.20 g (62%) of once recrystallized colorless crystals, mp 143–147° (C_6H_6–MeOH). Two additional recrystallizations gave **3-methoxy-17-methylestra-2,5(10),15-trien-17β-ol** (**8**) as colorless flakes: mp 145–148° (vac); $[\alpha]^{25}D$ −9.8° ($CHCl_3$); ir (KBr), 2.90, 3.00 sh, 5.93, and 6.04 μ; uv (95% EtOH), end absorption; nmr ($CDCl_3$), at 0.90 (angular CH_3), 1.36 ($C_{17}H_3$), 3.50 (OCH_3), 4.60 (C_2H), 5.55 ($C_{15}H$ quartet, J = 6, 3 Hz), and 5.84 ppm ($C_{16}H$ doublet, J = 6 Hz). *Anal.* ($C_{20}H_{28}O_4$) C, H.

At −33°.—Reduction of 200 mg of **6b** under similar conditions but at the boiling point of liquid NH_3 (−33°) afforded 108 mg of **3-methoxy-17-methylestra-2,5(10)-dien-17β-ol** (**7a**) as colorless rods, mp 137–141°.[12] Hydrolysis of this product with *p*-toluenesulfonic acid monohydrate in Me_2CO–H_2O afforded **17-hydroxy-17-methylestr-5(10)-en-3-one**[12] as colorless rods: mp 143–145°; ir (KBr), 2.95 and 5.79 μ; uv (95% EtOH), end absorption. The nmr spectra of these two compounds showed no Δ^{15} double bond.

17β-Hydroxy-17-methylestra-5(10),15-dien-3-one (**9a**).—Hydrolysis of 32.9 g of **8** with oxalic acid dihydrate in THF–MeOH–H_2O at room temperature yielded 24.7 g (78%) of once recrystallized colorless crystals, mp 135–137°. Additional recrystallization led to colorless crystals: mp 137–139.5°; $[\alpha]^{25}D$ +55.5° ($CHCl_3$); ir (KBr), 2.80 and 5.83 μ; uv (95% EtOH), 285 mμ (ε 40); nmr ($CDCl_3$), 0.93 (angular CH_3), 1.18 ($C_{17}CH_3$), 5.63 ($C_{15}H$ quartet, J = 6, 3 Hz), and 5.88 ppm (C_{16} quartet, J = 6, 1.5 Hz). *Anal.* ($C_{19}H_{26}O_2$) C, H.

17β-Hydroxy-17-methylestra-4,15-dien-3-one (**12a**).—Treatment of 15.00 g of **9a** with a trace of 35% aqueous NaOH in THF at room temperature gave 12.80 g (85%) of once-recrystallized colorless crystals, mp 166–167.5° (vac) (CH_2Cl_2–Et_2O). Additional recrystallization yielded colorless rods: mp 167.5–169°; $[\alpha]^{25}D$ −40.0° ($CHCl_3$); ir (KBr), 2.99, 6.04, and 6.20 μ; uv (95% EtOH), 240 mμ (ε 17,000); nmr ($CDCl_3$), 0.97 (angular CH_3), 1.15 ($C_{17}CH_3$), 5.62 ($C_{15}H$ quartet, J = 6, 3 Hz), 5.78 ($C_{16}H$ doublet, J = 5 Hz), and 5.82 ppm (C_4H). *Anal.* ($C_{19}H_{26}O_2$) C, H.

17-Methylestra-4,15-diene-3β,17β-diol 3-Acetate (**13a**).—Reduction of 13.8 g of **12a**, with lithium tri-*t*-butoxyaluminum hydride in THF at room temperature gave 20.5 g of partially crystallized oil. This oil was acetylated with Ac_2O-pyridine at room temperature to yield 16.6 g of partially crystalline pale yellow oil. Chromatography on 350 g of silica gel afforded 13 g of solid which after recrystallization from Et_2O-pentane gave 4.36 g (27%) of large colorless crystals: mp 96–98°; $[\alpha]^{25}D$ −104.1° ($CHCl_3$); ir (KBr), 2.96 and 5.75 μ; nmr ($CDCl_3$), 0.92 (angular CH_3), 1.13 ($C_{17}CH_3$), 2.00 ($COCH_3$), 5.32 (C_4H), 5.57 ($C_{15}H$ quartet, J = 6, 3 Hz), and 5.78 ppm ($C_{16}H$ doublet, J = 6 Hz). *Anal.* ($C_{21}H_{30}O_3$) C, H.

3-Methoxyestra-2,5(10),15-trien-17β-ol (**10**).—Li wire (6.8 g) was added to a stirred solution of 14.0 g of **6a** in 1.5 l. of THF and 1.5 l. of liquid NH_3 cooled in a Dry Ice–Me_2CO bath. After the mixture was stirred for 10 min, 90 ml of absolute EtOH was added in 3 min and the mixture was stirred an additional 15 min. NH_4Cl (100 g) was added and the mixture was stirred in the cooling bath until it became colorless (45 min). The reaction was worked up as described before (preparation of **8**) to yield 14 g of colorless solid: ir (KBr), 3.09, 5.91, 6.02, and 6.68 μ; uv (95% EtOH), 240–270 mμ (ε ~100) and 278 (83); nmr ($CDCl_3$), 0.83 (CH_3), 3.54 (OCH_3), 4.33 ($C_{17}H$), 4.65 (C_2H), 5.67 ($C_{15}H$ poorly resolved multiplet), and 6.00 ppm ($C_{16}H$ poorly resolved multiplet). One recrystallization from C_6H_6–MeOH yielded 11.8 g (about 84%) of colorless crystals, mp 133–136° (vac). This material could not be completely purified by chromatography or by recrystallization. The main component was shown by nmr to be 3-methoxyestra-2,5(10),15-trien-17β-ol (**10**).

3-Methoxyestra-2,5(10),15-trien-17-one (**11**).—A solution of 11.4 g of **10**, 3 drops of pyridine, and 20.4 g of aluminum isopropoxide in 200 ml of Me_2CO and 800 ml of C_6H_6 was stirred at room temperature under N_2.[29] After 6 hr glc showed that the reaction was about 50%, complete and an additional 4.1 g of aluminum isopropoxide and 100 ml of Me_2CO were added. After a total of 46 hr reaction time, the yellow solution was diluted with Et_2O, washed first with saturated aqueous sodium potassium tartrate, then with saturated aqueous NaCl, dried, and concentrated under reduced pressure to yield 13.5 g of colorless crystals. Recrystallization from EtOAc afforded 9.27 g of colorless rods: mp 186–194° (vac); ir ($CHCl_3$), 5.84, 6.00, and 6.69 μ (vw); tlc showed two minor more polar impurities which could not be easily removed by chromatography or by recrystallization.

17-Hydroxy-19-nor-17α-pregna-5(10),15-dien-20-yn-3-one (**9b**).—Acetylene was added to an ice-cold solution of 140 ml of BuLi solution (1.6 *M* in hexane) and 425 ml of THF. After 45 min the acetylene inlet was removed and a solution of 15.5 g of **11** in 200 ml of THF was added in 20 min. After 10 min of additional stirring, saturated aqueous Na_2SO_4 was added dropwise until the salts coagulated. The mixture was filtered. The filtrate was diluted with 1:1 Et_2O–C_6H_6 and worked up to yield 17.6 g of pale tan solid.

Hydrolysis of 8.00 g of this solid with oxalic acid dihydrate in THF–MeOH–H_2O at room temperature yielded a colorless solid. Chromatography on silica gel, followed by recrystallization from C_6H_6–*i*-PrOH afforded 5.5 g (about 75%, from ketone **11**) of pale tan crystals, mp 170–173° (vac). Additional recrystallization gave pale tan crystals: mp 171–173° (vac); $[\alpha]^{25}D$ −70.2° ($CHCl_3$); ir (KBr), 2.96, 3.06, 4.77, and 5.80 μ; uv (95% EtOH), 272 mμ (ε 400); nmr ($CDCl_3$), 0.95 (CH_3), 2.62 (C≡CH), 5.78 ($C_{15}H$ quartet, J = 6, 3 Hz), and 6.07 ppm ($C_{16}H$ quartet, J = 6, 1.5 Hz). *Anal.* ($C_{20}H_{22}O_2$) C, H.

17-Hydroxy-19-nor-17α-pregna-4,15-dien-20-yn-3-one (**12b**).—The unconjugated ketone **9b** (14.0 g) was converted to the Δ^{4}-3-one **12b** with NaOH in the manner described for **12a**. The crude product was chromatographed on silica gel to yield 6.58 g (47%) of once-recrystallized colorless crystals, mp 187–189.5° (vac) (Me_2CO–C_6H_6). An additional recrystallization gave fine colorless crystals: mp 188.5–190.5° (vac); $[\alpha]^{25}D$ −172.7° ($CHCl_3$); ir (KBr), 3.04, 3.10 sh, 4.80, and 6.09 μ; uv (95% EtOH), 240 mμ (ε 18,300). *Anal.* ($C_{20}H_{24}O_2$) C, H.

19-Nor-17α-pregna-4,15-dien-20-yne-3β,17-diol 3-Acetate (**13b**).—The ketone **12b** was converted to **13b** in the manner described for the preparation of **13a**. The crude product was recrystallized from Et_2O to yield fine white prisms: mp 153–155°; $[\alpha]^{25}D$ −192.1° ($CHCl_3$); ir (KBr), 5.75 and 5.85 μ; uv (95% EtOH), 275 mμ (ε 170); nmr ($CDCl_3$), 0.83 (CH_3), 2.02 ($COCH_3$), 2.57 ppm (C≡CH). *Anal.* ($C_{23}H_{30}O_3$) C, H.

21-Chloro-17-hydroxy-19-nor-17α-pregna-5(10),15-dien-20-yn-3-one (**9c**) was prepared from **11** in the manner described for the preparation of **9b** using lithium chloroacetylide (see preparation of **6c**). The chromatographed product (silica gel) was recrystallized from Et_2O to yield fine white needles: mp 145.0–145.4°; $[\alpha]^{25}D$ −101.9° ($CHCl_3$); ir (KBr), 2.93 and 5.85 μ. *Anal.* ($C_{20}H_{23}ClO_2$) C, H, Cl.

21-Chloro-17-hydroxy-19-nor-17α-pregna-4,15-dien-20-yn-3-one (**12c**).—The $\Delta^{5(10)}$-3-one **9c** was isomerized to the Δ^{4}-3-one **12c** with NaOH in the manner described in the preparation of **12b**. Recrystallization from C_6H_6–hexane yielded small prisms: mp 157.2–159.6°; $[\alpha]^{25}D$ −203.7° ($CHCl_3$); ir (KBr), 3.02, 6.05, and 6.22 μ; uv (95% EtOH), 240 mμ (ε 17,650). *Anal.* ($C_{20}H_{23}ClO_2$) C, H, Cl.