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THE SYNTHESIS OF 11β-ALKYL-19-NORSTEROIDS: A NOVEL CLASS OF POTENT STEROID HORMONES—I

THE SYNTHESIS OF 11β-METHYL AND 11β-ETHYLESTRADIOL

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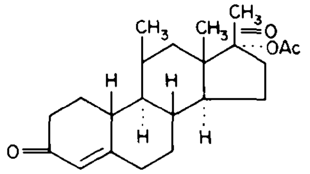
Abstract—The syntheses of 11β-methyl and 11β-ethylestradiol, via Grignard adducts to 11-oxoestra-1,3,5(10)-trienes, attempted modification of the Torgov total synthesis of steroids, and 11β-methylticogenin, are described.

In preliminary communications, the 11β-alkyl derivatives of estrogen and progesterone-like hormones were reported to be a novel and very potent group of hormonal substances.[1-4] For example, 11β - methyl - 17α - acetoxy - 19 - norprogesterone **1** exhibits 300 times the activity of progesterone and is utilized in the synchronization of estrus in breeding cattle.[5,6] The 11β-methyl derivative of 17α - ethynylester - 4 - ene - 3,17 - diol 3,17-diacetate **2a** has 10–25 times the progesterone-like activity of the parent substance **2b**.[2] The latter substance is used in combination with estrogen for human fertility control.[7] The unique hormonal properties which are characteristic of some of the 11β-alkyl-19-nor-steroids[2] make them interesting candidates for the study of the nature of steroid hormone-receptor interactions and improved fertility control in man.



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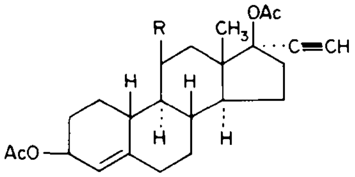

2: **R**
a CH_3
b H

The discovery of the activity of the 11β - alkyl - 19 - norsteroids prompted searches for alternate methods of their synthesis.[8,9] In this paper we report the experimental details of our studies on the synthesis of 11β-methyl and 11β-ethyl-estradiol which were presented in earlier communications.[1-4] The preparation and biological activities of other important 11β-alkyl steroids related to estradiol, testosterone, and progesterone will be described elsewhere.[10] Successful approaches to the synthesis of 11β-alkylestradiols, which play a central role in the synthesis of 11β-alkyl-19-norsteroids, resulted from studies on the addition of Grignard reagents to 11-oxo-9α and 9β-estratrienes, attempted total synthesis, and synthesis from 11β-methyl-5α-25D-spirostan-3-one **16a**.

Reactions of 11-*oxo*-9α *and* 9β-*estradiol derivatives and their conversion to* 11β-*alkylestradiols*

11-Oxo-9β-estradiol **3a** was prepared from estrone in five steps with overall yield of 50%.[11] Its benzyl ether **3b** was shown to be thermodynamically more stable than the 9α-epimer **6a** by 1.47 kcal/mole.[11] The 9α epimer **6a** was obtained from **3b** in a kinetically controlled reaction in which the C-9 anion of **3b** was protonated by acetic acid.[11]

The 9α-epimer **6a** reacted with methyl and allylic Grignard reagent and gave 9α-11-alkyl adducts **7a** and **7b** respectively; the 9β epimer **3b** failed to react with methyl Grignard reagents, but reacted with allyl Grignard reagent to yield **4a**. In the reaction which gave **7a** and **7b** the retention of the 9α-configuration was evident from the NMR (100 MHz) spectrum, which showed that in **7a** the C-9 proton appeared at δ 2.28 (d, $J_{8,9} = 10$ Hz), and in **7b** the C-9 proton appeared at δ 2.29 (d, $J_{8,9} = 10.5$ Hz).† In the reaction of methyl Grignard reagent with the 9β epimer **3b**, enolization of **3b** occurred, so that after protonation of the reaction mixture **3b** and **6a** were obtained. On the other hand, **3b** reacted smoothly with allylic magnesium bromide and the product **4a** possessed the 9β configuration on the basis of NMR analysis.†

The 9α and 9β ketones **6a** and **3b** were reduced with sodium borohydride and lithium aluminum hydride. From the 9α-ketone **6a** both reagents gave the same product **7c**, resulting from α side attack of the hydride. The assignment of the structure **7c** was based on an NMR study in which the C-9 proton appeared at δ 2.27 (q, $J_{8,9} = 10.5$ Hz, $J_{9,11} = 2.5$ Hz) and the C-11 proton appeared at δ 4.74 (q, J = 2.5 Hz). Reduction of 9β-ketone **3b** by lithium aluminum hydride also gave one product and the NMR data showed that it was 11α-hydroxy-9β-estradiol 3-benzyl ether **4b**. The C-9 proton appeared at δ 3.16 (t, $J_{8,9} = 4.5$ Hz, $J_{9,11} = 4.5$ Hz) and the C-11 proton appeared at δ 4.45 (dt, $J_{9,11} = 4.5$ Hz, $J_{11,12\alpha} = 4.5$ Hz, $J_{11,12\beta} = 8.5$ Hz),

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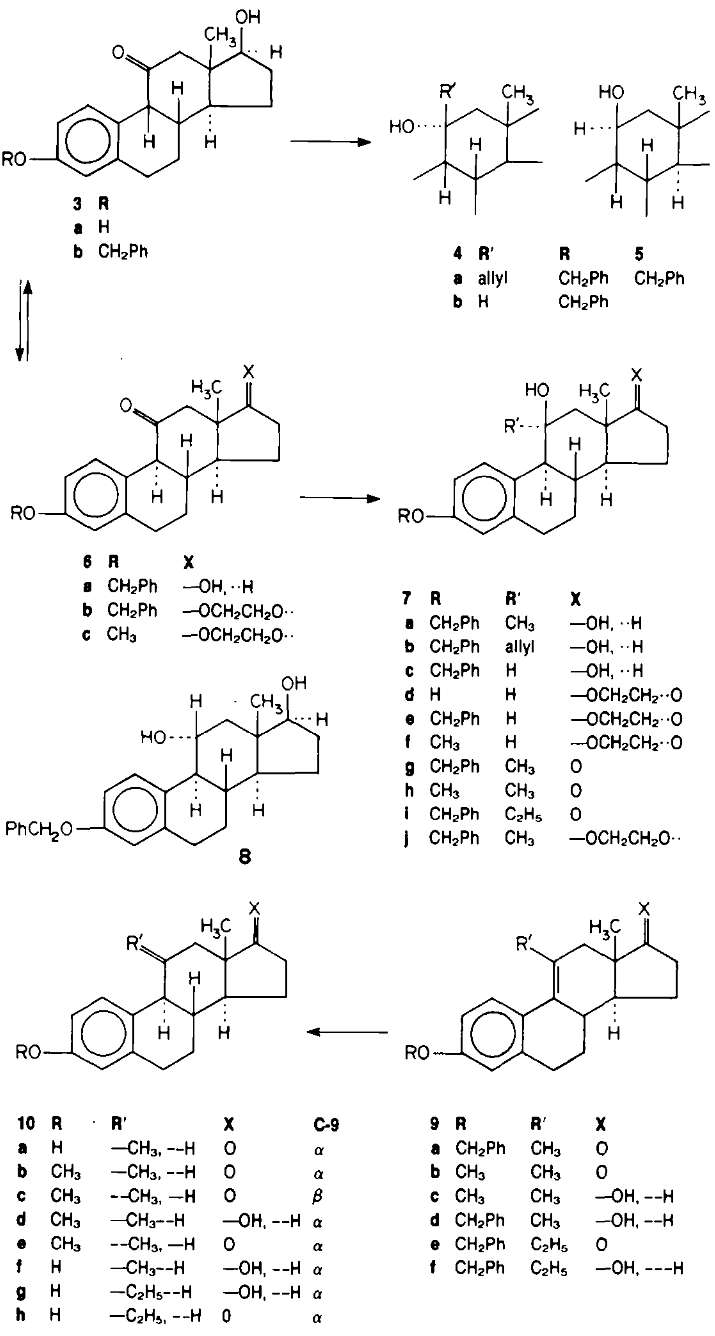
†The 100 MHz NMR analyses of **7a** and **7b** with and without Eu(fod)$_3$ shift reagent indicated that both were 11α-alkyl-11β-hydroxyestradiol 3-benzyl ethers. On the other hand, **4a** was shown to be 11β-allyl-11α-hydroxy-9β-estradiol 3-benzyl ether. The complete NMR analysis will appear in a subsequent paper to be submitted to *J. Magnetic Resonance.*



3	**R**
a	H
b	CH_2Ph

4	**R'**	**R**	**5**
a	allyl	CH_2Ph	CH_2Ph
b	H	CH_2Ph	

6	**R**	**X**
a	CH_2Ph	—OH, ··H
b	CH_2Ph	$—OCH_2CH_2O··$
c	CH_3	$—OCH_2CH_2O··$

8

7	**R**	**R'**	**X**
a	CH_2Ph	CH_3	—OH, ··H
b	CH_2Ph	allyl	—OH, ··H
c	CH_2Ph	H	—OH, ··H
d	H	H	$—OCH_2CH_2··O$
e	CH_2Ph	H	$—OCH_2CH_2··O$
f	CH_3	H	$—OCH_2CH_2··O$
g	CH_2Ph	CH_3	O
h	CH_3	CH_3	O
i	CH_2Ph	C_2H_5	O
j	CH_2Ph	CH_3	$—OCH_2CH_2O··$

10	**R**	**R'**	**X**	**C-9**
a	H	$—CH_3$, --H	O	α
b	CH_3	$—CH_3$, --H	O	α
c	CH_3	$--CH_3$, —H	O	β
d	CH_3	$—CH_3$--H	—OH, --H	α
e	CH_3	$--CH_3$, —H	O	α
f	H	$—CH_3$--H	—OH, --H	α
g	H	$—C_2H_5$--H	—OH, --H	α
h	H	$—C_2H_5$, --H	0	α

9	**R**	**R'**	**X**
a	CH_2Ph	CH_3	O
b	CH_3	CH_3	O
c	CH_3	CH_3	—OH, --H
d	CH_2Ph	CH_3	—OH, --H
e	CH_2Ph	C_2H_5	O
f	CH_2Ph	C_2H_5	—OH, ---H

Scheme 1.

with typical small constants expected for axial and equatorial coupling. The reduction of the 9β-ketone **3b** by sodium borohydride gave two products and one of them was shown to be **4b**. The other product was shown to possess a 9α-configuration and was shown to be identical with **7c**. Apparently the reduction by sodium borohydride was slow enough to allow the epimerization at C-9 to occur, and the 9α-ketone so generated was reduced by sodium borohydride. The reduction of the 9β-ketone **3b** by lithium aluminum hydride and sodium borohydride truly reflected the steric environment of the C-11 carbonyl group in this molecule as well as the thermodynamic vs kinetic control behavior of 9α- and 9β-ketones, **6a** and **3b** respectively.

11α-Hydroxyestradiol 3-benzyl ether **8** was obtained as a minor product when the 9α-ketone **6a** was reduced under Meerwein-Ponndorf conditions.[12] The assignment of structure **8** was based on NMR data. The C-11 proton resonated at δ 4.20 (td, $J_{9,11} = 10.5$ Hz, $J_{11,12ax} = 10.5$ Hz, $J_{11,12eq} = 5.5$ Hz), with typical large constants expected for axial–axial proton coupling. The major product was **7c**. When the 9β-ketone **3b** was reduced under Meerwein-Ponndorf conditions, a total of four 11-hydroxyestradiol 3-benzyl ethers were isolated. Compounds **7c**, **4b**, and **8** were identical with compounds previously isolated, based on TLC and NMR analysis. The fourth component was shown to have structure **5** on the basis of NMR (100 MHz) data. The C-9 proton appeared at δ 3.00 as a broad singlet $W_{1/2} \sim 10$ Hz, and the C-11 proton appeared at δ 4.71 as a quartet J = 3 Hz.

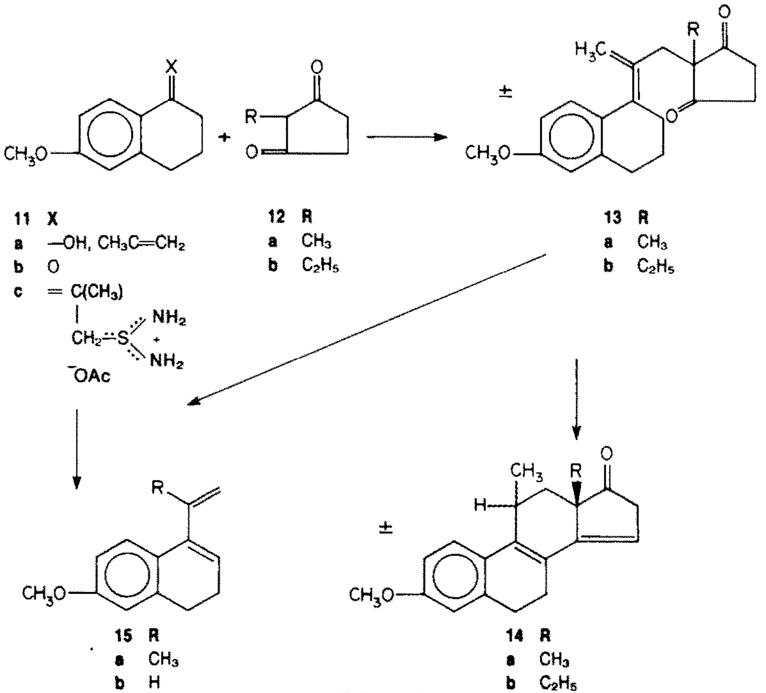
The 11-keto-9α-estratrienes **6b** and **6c** required for the addition of alkylmagnesium bromides were obtained by yet another route. 3,11β - Dihydroxyestra - 1,3,5(10) - trien - 17 - one 17-ethylene ketal **7d** can be obtained readily from androsta - 1,4 - diene - 3,11,17-trione.[13] The 3-ethers **7e** and **7f**,[13] which were obtained from **7d** and then oxidized with chromium trioxide under controlled conditions, yielded the ketones **6b** and **6c**. Addition of methyl magnesium bromide to the ketones, followed by hydrolysis, gave **7g** and **7h** which upon dehydration with strong acid yielded the 11-methylestratetraenes **9a** and **9b**. Catalytic hydrogenation of **9b** in the presence of palladium on charcoal afforded a 75% yield of 11β-methylestrone 3-methyl ether **10b** and a 25% yield of the 11α - methyl - 9β - estratriene derivative **10c**, the products of *cis*-addition of hydrogen. Catalytic reduction of the 17β-ol **9c** provided better steric control in the reduction of the $\Delta^{9,11}$ bond and yielded 85% of the desired isomer **10d**. Reduction of **9b** with lithium and aniline, followed by oxidation of the 17-position, gave 11α-methylestrone 3-methyl ether **10e**, the product of the *trans*-addition of hydrogen. The catalytic reduction of **9a** and **9d** yields 11β-methylestrone **10a** and 11β-methylestradiol **10f**.

The synthesis of 11β-ethylestradiol **10g** and 11β-ethylestrone **10h** was accomplished in an analogous manner to the synthesis of **10d** utilizing the Grignard adduct **7i** derived from **6b** as described in Scheme 1. The low overall yield of 11β-ethylestrone from **6b** was attributed to enolization and reduction of the 11-ketone with ethyl magnesium halide, which is known to occur with this reagent,[14,15] and poor steric control in the sequence of reactions involving the C-11 ethyl group in a crowded environment (*vide infra*).

The configuration of the C-11 methyl group in the reduced products was assigned on the basis of analysis of their NMR spectra and synthesis of 11β-methylestradiol by another route. The C-11α-methyl group in isomers **10c** and **10e** would be expected to be strongly deshielded, being nearly in the plane of the aromatic ring. For this reason, the product of *trans*-addition of hydrogen (δ, 1.15 and 1.23) and *cis*(β)-addition (δ, 1.25 and 1.38) to the $\Delta^{9,11}$-steroid **9b** were assigned structures **10e** and **10c**. The peak for the 13-CH_3 in **10b** (δ 1.03) is at lower field than the 11α-CH_3 counterpart **10c** (δ 0.85), the result of an expected 1,3-diaxial interaction between methyl groups. Resonance peaks for the C-1 hydrogen atom in **10b** are identical to those of estrone 3-methyl ether, whereas in **10c** and **10e** they are shifted to lower fields, indicating the expected interaction with the 11α-CH_3 group.

Studies on total synthesis

An attractive route for the total synthesis of norsteroids has been achieved by Torgov.[16] In order to utilize this synthesis, the adduct **11a** was prepared by the addition of isopropenyl magnesium bromide to the tetralone **11b**. When attempts were made under a variety of conditions to react **11a** or its thiouronium salt[17] **11c** with 2-methyl or 2-ethyl cyclopentane-1,3-dione **12**, only a very low yield of the desired tetracyclic intermediate **14** was obtained. Studies also indicated that a barrier to formation of the tetracyclic derivative **14** was the rapid reversal of the tricyclic intermediate **13** to the stable aromatic conjugated diene **15a** and the diketone **12**. Because the enol of the alkylcyclopentandione is a good leaving group and steric strain is introduced in the tetracyclic system **14** by the addition of a C-11 substituent, the preferred reaction is elimination to **15a** and **12** rather than condensation to **14**. Additional evidence, which exemplifies the steric effect of the added methyl group at the potential C-11 position on product development control in cyclization reactions leading to a steroid-like nucleus, is the fact that, unlike the diene **15b** lacking the methyl group which readily undergoes Diels–Alder dimerization,[17] **15a** is isolated as a monomer and has little tendency



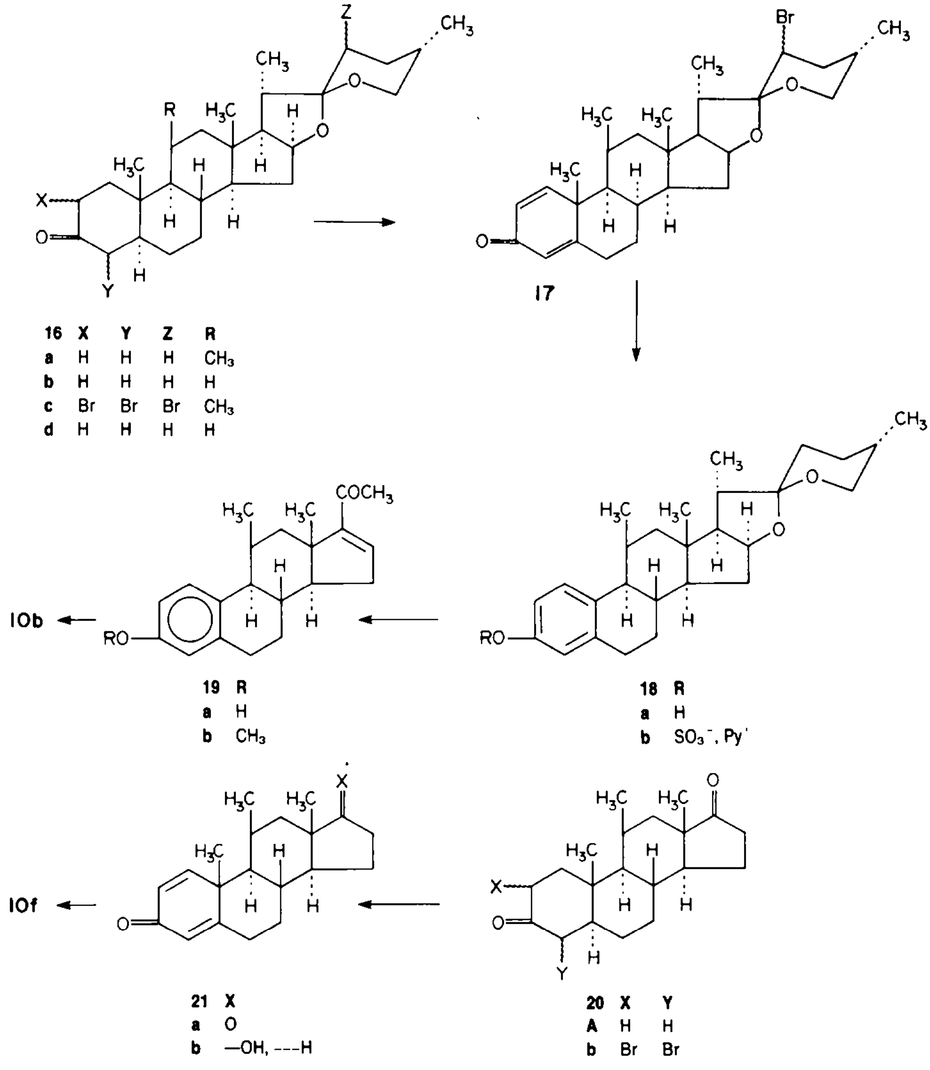
Scheme 2.

to dimerize. The barrier to the formation of 11β-methyl steroids in polyene cyclizations also has been observed by Johnson and DuBois.[8]

Synthesis from 11β-Methyl-5α,25D-spirostan-3-one

The synthesis of 11β-methylestradiol **10d** from **16a** proceeds as follows. 11β-Methyl-5α,25D-spirostan-3-one **16a** can be obtained in excellent yields from hecogenin.[18] Conversion of **16a** to the 23-bromospirosta-1,4-dien-3-one **17** required some special investigation. Selective brominations of 3-oxospirostanes in ring A are complicated by the fact that bromination at C-23 can occur readily.[19] When the 5α-spirostan-3-one **16b**, which was used as a model, was brominated in acetic acid in the presence of HCl, bromination at C-23 occurred more rapidly than at C-2 and C-4. In this case a C-23 dibrominated steroid was obtained. However, when tetrahydrofuran was used, the rates of bromination of **16b** at positions 2 and 23 were changed. In an analogous manner, bromination of **16a** in tetrahydrofuran occurred most rapidly at C-2 and then approximately at the same rate at C-2′ and C-23, followed by rearrangement in good yield to a stable 2,4,23-tribromosteroid **16c**. Tetrahydrofuran most probably changes the acidity of the reaction medium and the rates of enolization of the intermediates that react with bromonium ion. The tribomide **16c** was dehydrobrominated selectively with magnesium oxide and dimethylformamide to the 23-monobromodienone **17**. Reductive aromatization by the method of Dryden[20] with lithium and biphenyl proceeded with removal of bromine to give **18a**, which could be isolated as its sulfate **18b** in aqueous solution. The desired product, 11β-methylestrone, was obtained by the standard degradation scheme for a steroid spirostane to the corresponding 17-keto-steroid (see Scheme 3).[21]

The synthesis of 11β-methylestradiol from 11β-methyl-5α-androstane-3,17-dione, which is readily obtained from **16a**,[21] proceeded as follows. The dibromination of **20a** to **20b**, followed by elimination of hydrogen bromide with magnesium oxide in dimethyl formamide, gave high yields of the dienedione **21a**. Selective reduction of **21a** to **21b** and reductive aromatization of **21b** gave 11β-methylestradiol, which was found to be identical with that obtained by partial synthesis from the 11β-hydroxyestratriene **7f**.



Scheme 3.

EXPERIMENTAL

Microanalyses were performed by Mr. Emmanuel Zielinski and associates and spectra were run by Mr. John Damascus and associates of Searle Laboratories. All UV spectra were run in methanol on a Beckman DK-2A spectrophotometer and are reported as wavelength in nanometers. IR spectra were run in $CHCl_3$ on a Beckman IR-2 spectrophotometer and carbonyl region peaks are reported as wavelength in microns. TLC runs were on 7.6-cm microscope slides covered with a 0.25-mm thickness of Woelm F silica, with a magnesium aluminum silicate binder. Visualization of spots was by phosphomolybdic acid, 5% in EtOH (w/v), followed by heat. Column chromatography used Mallinckrodt SilicAR CC-4 or CC-7 silicic acid. The weight ratio of adsorbent to material was 100:1. Materials were applied as benzene solutions and, unless indicated otherwise, eluted with benzene containing increasing amounts of EtOAc. M.ps were taken on a Fisher-Johns hot-stage apparatus and are uncorrected. NMR spectra were taken on a Varian A-60A or a Varian T-60. All spectra are 60 MHz unless specified otherwise. Location of peaks are in ppm using TMS as an internal standard. Hydrogenations were done by Mr. M. Scaros and Ms. J. Serauskas and chromatography by B. Smith and R. Nicholson and their associates at Searle Laboratories.

3 - *Benzyloxy* - 11α,17β - *dihydroxy* - 11β - *allyl* - 9β - *estra* - 1,3,5(10) - *triene* **4a**. To a soln of 500 mg of **3b** in 20 ml THF was added 5 mmole of allyl magnesium bromide (Ventron). The soln was stirred overnight at 23°. Aqueous NH_4Cl soln was added and the organic layer was extracted with ether. The organic layer was washed until neutral and dried over Na_2SO_4. The solvent was removed and the product was recrystallized from EtOH to yield 480 mg of **4a**, m.p. 100–102°: δ 7.06 (d, J = 9.0 Hz, 1-H) and δ 3.85 (t, 17-H). (Found: C, 77.38; H, 8.66. Calc. for $C_{29}H_{34}O_3 \cdot C_2H_5OH$: C, 77.55; H, 8.68%).

3 - *Benzyloxy* - 11α,17β - *dihydroxy* - 9β - *estra* - 1,3,5(10) - *triene* **4b**. To a soln of 250 mg of **3b** in 10 ml of EtOH was added 50 mg of $NaBH_4$. The mixture was stirred at 20° overnight, water was added and the organic material was extracted with $CHCl_3$. The organic layer was washed with water until neutral and was dried. A TLC of the crude product showed two spots. Separation by column chromatography yielded one component which was shown to be identical with **7c**. The other component was isolated and was recrystallized from hexane to yield **4b**, m.p. 74–76°; δ 7.84 and see text. (Found: C, 79.17; H, 8.05. Calc. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99%). Compound **4b** was also obtained when **3b** was reduced with lithium aluminum hydride. It showed an identical NMR spectrum with compound **4b** obtained from sodium borohydride reduction of **3b**.

Meerwein–Ponndorf Reductions of **3b** *and* **6a**. A mixture of 200 mg of **6a**, 1 g of aluminum isopropoxide and 5 ml ^{i}PrOH was heated at 100° overnight, cooled to 20° and mixed with an aqueous soln of $KHSO_4$ and $CHCl_3$. The organic layer was separated, dried over $MgSO_4$ and distilled to dryness to yield 150 mg of crude product. From the reduction of **6a**, two major components were isolated by column chromatography. One was shown to be identical with **7c**. The other component was assigned as **8** on the following NMR data: δ 7.83 (d, 1H, J = 8.25 Hz, 1-H), 2.80 (t, 2H, 6-H), 4.20 (td, 1H, J = 10.5 Hz, 10.5 Hz, 5.5 Hz, 11β-H).

From the reduction of **3b** a mixture of **7c**, **4b**, **8** and one more component was obtained. The latter substance was separated by column chromatography and this component was assigned structure **5** on the basis of NMR data: δ 7.0–7.5 (m, 1-H) and see text.

3 - *Benzyloxy* - 11β,17β - *dihydroxy* - 11α - *methylestra* - 1,3,5(10) - *triene* **7a**. The addition of 2.5M MeMgBr (0.5 ml) to 180 mg of **6a** in 10 ml of THF was carried out in analogous manner to the preparation of **4a**. The crude product, upon crystallization from hexane and benzene, yielded 120 mg of **7a**, m.p. 151–152°; λ_{max} 6.11, 6.43, 7.10 and 8.10μ; δ 1.00 (s, 3H, 13-Me), 7.75 (d, J = 9.5 Hz, 1-H), 2.28 (d, J = 10 Hz, 9-H) and 3.69 (t, 17-H). (Found: C, 79.90; H, 8.26. Calc. for $C_{28}H_{32}O_3$, C, 79.55; H, 8.22%).

3 - *Benzyloxy* - 11β,17β - *dihydroxy* - 11α - *allylestra* - 1,3,5(10) - *triene* **7b**. In analogy to the preparation of **4a**, allyl MgBr (Ventron) was added to 180 mg of **6a**. **7b** was purified by column chromatography and gave a pale oil, weighing 160 mg; δ 0.99 (s, 13-Me), 7.78 (d, J-9.5 Hz, 1-H), 2.29 (d, J = 10.5 Hz, 9-H), 3.69 and (5, 17-H). (Found: C, 80.70; H, 8.19. Calc. for $C_{28}H_{34}O_3$, C, 80.34; H, 8.19%).

3 - *Benzyloxy* - 11β,17β - *dihydroxy* - *estra* - 1,3,5(10) - *triene* **7c**. To a soln of 250 mg of **6a** in 10 ml THF was added 40 mg of $LiAlH_4$. The mixture was stirred at 20° for 10 min and aq $NaHSO_4$ was added. The organic material was dissolved in $CHCl_3$. The organic layer was separated, washed with sat $KHSO_4$ and water until neutral. After drying over Na_2SO_4 the soln was evaporated and the residue was crystallized from benzene to yield 200 mg of **7c**, m.p. 163–164°; δ 1.06 (s, 3H, 13-Me), 7.22 (d, J ~ 10.5 Hz, 1-H) and see text. (Found: C, 79.25; H, 7.96. Calc. for $C_{25}H_{30}O_3$, C, 79.33; H, 7.99%).

3 - *Benzyloxy* - 11β - *hydroxy* - 11α - *methylestra* - 1,3,5(10) - *trien* - 17 - *one* **7g**. To a soln of 10.0 g of **7d**[13] in 140 ml of EtOH was added 4.22 g of benzyl chloride and 8.5 g of anh K_2CO_3. After the mixture was heated at reflux for 24 h, the K-salts were removed by filtration, the solvent was removed under reduced pressure and the residual oil was crystallized from Et_2O. 11.3 g of **7e** (m.p. 118–120°) was used without further purification. To a stirred soln of 11.3 g of **7e** in 800 ml of acetone, cooled to 0°C, was added 10.5 ml of 8N CrO_3 in H_2SO_4 over a 2 min period. After stirring for 2 additional min, excess CrO_3 was destroyed by the addition of 2 ml of ^{i}PrOH, followed by neutralization with 10 ml of satd $NaHCO_3$ soln. The acetone was removed by distilation, and the residue was dissolved in EtOAc. The organic soln was washed with $NaHCO_3$ soln, water, dried (Na_2SO_4) and distilled to dryness to yield 10.3 g of **6b**; δ 0.87 (s, 3H, C-13 Me), 3.88 (m, 4H, $-OCH_2CH_2O-$), and 5.03 (2H, benzyl CH_2), which resisted crystallization and was used without further purification.

To a soln of 3.0 g of **6b** in 200 ml of dry benzene in a N_2 atmosphere was added 10 ml of a soln of 3M MeMgBr in Et_2O. The soln was stirred for 0.5 h at room temp. and the Grignard adduct was decomposed with the addition of 1.22 ml of MeOH. This procedure was repeated twice with the addition of fresh portions of 20 ml and 40 ml of MeMgBr soln and decomposition of the adducts with the addition of 2.5 and 5.0 ml portions of MeOH, respectively. The benzene soln was then washed with satd NH_4Cl soln, separated, dried over Na_2SO_4 and distilled to dryness to yield 2.84 g of crude **7j**; δ at 1.12 (s, 3H, C-13 Me) and 1.63 (s, 3H, C-11 Me). The preparation of **7j** was scaled upward to yield 70 g of **7j** which was dissolved in 700 ml of MeOH and added to 100 ml of 12M HCl. The reaction mixture was stirred at room temperature for 15 min during which time the 17-ketone precipitated to yield 36.4 g of **7g**, m.p. 201–203°; δ 1.10 (s, 3H, 13-CH_3), 1.63 (s, 3H, 11α-CH_3), 5.03 (s, 2H, benzyl CH_2), 6.69–6.90 (m, 2H, 2,4-H), 7.36 (m, 5H, ArH), 7.69–7.83 (m, 1H, L-H). (Found: C, 79.99; H, 7.69. Calc. for $C_{26}H_{30}O_3$: C, 79.96; H, 7.74%).

3 - *Methoxy* - 11β - *hydroxy* - 11α - *methylestra* - 1,3,5(10) - *trien* - 17 - *one* **7h**. Following the procedure for the preparation of **7g** from **6b**, 29 g of the methyl ether **6c**[13] was converted to 18 g of **7h**. Crystallization of the crude product from ether–hexane gave **7h** m.p. 178–179°; δ 1.12 (s, 3H, 13-CH_3) and 1.66 (s, 3H, 11α-CH_3). (Found: C, 76.15; H, 8.37. Calc. for $C_{20}H_{28}O_3$: C, 76.40; H, 8.34%).

3 - *Methoxy* - 11 - *methylestra* - 1,3,5(10),9(11) - *tetraene* - 17 - *one* **9b**. Dehydration of 10 g of **7h** according to the procedure for the preparation of **9e** or with p-TsOH in refluxing benzene yielded 7.0 g of **9b**. Crystallization of the crude product from ether-hexane yielded **9b** m.p. 88°, λ_{max} 257.5n (ε = 18050), δ 0.92 (s, 3H, 13-Me) and 1.92 (s, 3H, 11-Me). (Found: C, 80.93; H, 8.02. Calc. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16%).

3 - *Hydroxy* - 11β - *methylestra* - 1,3,5(10) - *trien* - 17 - *one* **10a**. 25 g of **7g** was suspended in 1 l of EtOH and heated at reflux with 200 ml of 4.7N HBr in EtOH for 2 h. After 250 ml of EtOH was removed by distillation the reaction mixture was cooled in an ice-bath, and the precipitate was collected by filtration to yield 20.8 g of **9a**, m.p. 166–80°; δ at 0.93 (s, 3H, C-13 Me), and 1.93 (s, 3H, C-11 Me). A soln of 20 g of **9a** in 2.5 l of THF–MeOH (1:4) was reduced in atmosphere of H_2 in the presence of 10% Pd/C as catalyst. Five 3 g portions of catalyst were added periodically during the reduction to complete it. The crude product which was obtained was crystallized from acetone to give 10 g of **10a**, m.p. 302–305°; δ (Py·D_5) 0.87 and 0.98 (d, 3H, 11β-Me) and 0.95 (s, 3H,

13-Me). (Found: C, 80.31; H, 8.35. Calc. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51.)

3 - *Methoxy* - 11β - *methylestra* - 1,3,5(10) - *trien* - 17 - *one* **10b** *and* 3 - *Methoxy* - 11α - *methyl* - 9β - *estra* - 1,3,5(10) - *trien* - 17 - *one* **10c**. A soln of 5.0 g of **9b** in 250 ml of MeOH was stirred in an atmosphere of H_2 in the presence of 0.5 g of 10% Pd/C. After one equivalent of H_2 was taken up in 4.5 h, the catalyst was removed by filtration and the solvent was removed by distillation. Fractional crystallization from hexane ether yielded 3.0 g of pure **10c**, m.p. 149–150°; δ 0.85 and 0.96 (d, 3H, 11β-CH_3), 1.03 (s, 3H, 18-CH_3), 3.75 (s, 3H, OCH_3), 6.60, 6.73, 6.77, 7.00, 7.23 (m, 3H, Ar–H); (Found: C, 80.47; H, 8.64. Calc. for $C_{20}H_{25}O_2$: C, 80.49; H, 8.78%), and 1.0 g of crude **10c** which was purified by column chromatography on silica gel to yield **10c**, m.p. 126–127°; δ 1.25 and 1.38 (d, 3H, 11αCH_3), 1.12 (s, 3H, 18-CH_3), 3.78 (s, 3H, OCH_3), 6.66, 6.75, 7.33, 7.48 (m, 3H, ArH). Found: C, 80.14; H, 8.55. Calc. for $C_{20}H_{28}O_2$: C, 80.49; H, 8.78%. An NMR analysis of the total reduction product indicated that the ratio of **10b** to **10c** was 3 to 1. **10c** was also obtained by Beckmann rearrangement of **19** according to a procedure for side chain degradation described previously.[21]

3 - *Methoxy* - 11β - *methylestra* - 1,3,5(10) - *trien* - 17β - *ol* **10d**. To a soln of 1.0 g of **10b** in 200 ml of THF was added a soln of 4 ml of a 1.5 molar di-i-BuAlH in toluene. The mixture was poured into ice and water containing 5 ml of HOAc. The organic layer was separated, washed with water and then aq $NaHCO_3$ soln, dried over $MgSO_4$ and distilled to dryness. The crude product, when crystallized from ether and hexane yielded **10d**, m.p. 101–103°; δ 0.83 and 0.95 (d, 3H, 11-Me) and 0.90 (3H, 13 Me). (Found: C, 80.12; H, 9.14. Calc. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%).

3 - *Methoxy* - 11α - *methylestra* - 1,3,5(10) - *trien* - 17 - *one* **10e**. To a soln of 3.0 g of **9b** in 25 ml of aniline, 230 ml of THF and 400 ml of distilled ammonia was added 1.5 g of lithium. The mixture was concentrated by distillation and diluted successively with ether, 100 ml of water and 50 ml of 4M HCl. The organic layer was separated, washed with aq Na_2SO_4 soln, with aq $NaHCO_3$ soln, dried over $MgSO_4$ and distilled to dryness. The residue was dissolved in acetone and cooled to 0°. To the soln was added with stirring 1.5 ml of 8N CrO_3–H_2SO_4 soln followed after several min by 10 ml of isopropyl alcohol. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with aq $NaHCO_3$ soln and distilled to dryness. The residue was separated by column chromatography on 150 g of silica gel in benzene. Elution of the column with ethyl acetate–benzene (1:99) yielded 1.0 g of **10e**. Crystallization of the crude product from CH_2Cl_2–MeOH gave pure **10e**. Crystallization of the crude product from CH_2Cl_2–MeOH gave pure **10e**, m.p. 126–127°, NMR δ 0.85 (3H, 18-CH_3) 1.15, 1.23 (3H, C-11αCH_3), 3.78 (s, 3H, OCH_3), 6.66, 6.73–6.77, 7.10, 7.13 (m, 3H, ArH). (Found: C, 80.59; H, 9.08. Calc. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78%).

3,17β - *Dihydroxy* - 11β - *methylestra* - 1,3,5(10) - *triene* **10f**. To a soln of 3.0 g of **9a** in 100 ml of toluene was added 12 ml of 1.5 M soln of di-i-BuAlH in toluene. The reaction was stirred at room temp for 30 min, the excess hydride was destroyed with MeOH and the mixture was poured into ice water and containing an excess of AcOH. The toluene layer was concentrated, washed with water and $NaHCO_3$ soln, dried over Na_2SO_4 and distilled to dryness. The crude 17-ol **9d** was dissolved in 240 ml of MeOH and hydrogenated at 20° and atmospheric pressure using two 300 mg portions of 10% Pd–C as catalyst to yield 860 mg of product, which upon crystallization from acetone–MeOH gave **10f**, m.p. 223–225°; δ (Py) 0.96 and 1.06 (d, 3H, 11β-CH_3) and 1.16 (s, 3H, 13-CH_3). (Found: C, 79.69; H, 9.45. Calc. for $C_{19}H_{28}O_2$: C, 79.68; H, 9.15%).

11β - *Methylestra* - 1,3,5(10) - *trien* - 3,17β - *diol* **10f** *from* **21b**. When 400 mg of **21b** was reduced with 1 g of Li (30% dispersion in wax), 2.5 g of biphenyl and 1.4 g of diphenylmethane according to the procedure used in the preparation of **18a**, 150 mg of crude **21b** was obtained. The product was isolated by extraction of the organic layer with aq KOH and acidification of the aq extract. Crystallization of the crude product from MeOH and acetone yielded **10f**, which was identified by mixture m.p. and NMR spectrum with **10f** obtained by reduction of **9d**.

3,17β - *Dihydroxy* - 11β - *ethylestra* - 1,3,5(10) - *triene* **10g**. When 4.2 g of **9e** was reduced with di-i-BuAlH in toluene according to preparation of **10f** and the product was separated by chromatography on neutral silica gel 2.8 g of the 17β-ol **10g** was obtained. The latter material was then hydrogenated as above and purified by chromatography on neutral silica to give 930 mg of **10g**. Crystallization of the crude product from acetone gave **10g**; m.p. 224–226°; δ (pyridine d5) 0.92 (t, 3H, Me of 11-Et), 1.13 (s, 3H, 13Me) and 3.95 (t, 1H, 17-H). (Found: C, 80.16; H, 9.51. Calc. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%).

3 - *Hydroxy* - 11β - *ethylestra* - 1,3,5(10) - *triene* - 17 - *one* **10h**. Following the procedures for the preparation of **7g** and **9a** from **6b**, using EtMgBr, 16.8 g of **6b** was converted to 17 g of crude **7i** which was purified by column chromatography to yield 7.66 g of **7i**. This material was converted without further purification to 3.8 g of **9e**. A soln of 1.54 g of **9e** in 120 ml of MeOH was reduced at 20° and a H_2 pressure of 3–4 atmospheres using 0.15 g of 10% Pd–C as aa catalyst. The soln was distilled to dryness and the crude product was purified by chromatography on neutral silica gel to give 670 mg of the crude product and crystallization from acetone gave **10h**, m.p. 269–71°; δ (Py-d5) 0.85 (t, 3H, Me of 11-Et) and 0.96 (s, 3H, 13-Me). (Found: C, 80.61; H, 8.80. Calc. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78%).

1 - (2 - *Propenyl*) - 6 - *methoxy* - 1 - *tetralol* **11a**. A mixture of 2.19 g of Mg turnings, 150 ml of THF and 20 g of freshly distilled isopropenyl bromide was stirred in an atmosphere of N_2. Three drops of dibromoethane were added, and the mixture was heated at 40°. After 15 min, a vigorous reaction ensued. The mixture was then cooled with a water bath at 23° and 109 g of the bromide in 300 ml of THF was added dropwise. After the addition of bromide the reaction mixture was heated for 30 min at 50°, allowed to cool, and diluted with 400 ml of toluene. The solution was decanted in an atmosphere of N_2. To this solution at −10° was added with stirring a soln of 70 g of **11b** in 350 ml of toluene. The reaction mixture was stirred overnight at room temperature, cooled to −10° (Gilmen test was positive), and was cautiously diluted with 200 ml ^{i}PrOH. To the mixture at −5° was then added, with stirring a soln of 375 g of ethylene dinitrilotetracetic acid tetrasodium salt (EDTA) in 500 ml of water. The organic layer was decanted and the remaining salts were washed with three 500 ml portions of toluene by decantation. The combined organic layers were washed twice with a soln of 5 g of EDTA in 300 ml of water, with water, dried over sodium sulfate and filtered through supercel. After a trace of triethylamine was added for stability purposes, the toluene was removed by distillation *in vacuo* at <35°. An NMR analysis of the product indicated that it was a mixture of 65 g of the product **11a**, [δ 1.63 (CH_3), 3.79 (OCH_3) and 5.05, 5.20 (m, $=CH_2$)] and 35 g of tetralone **11b** [δ 3.85 (OCH_3)]. The crude tetraolol **11a** was used without further purification.

1 - (2 - *Propenyl*) - 3,4 - *dihydro* - 6 - *methoxynaphthalene* **15a**; *attempted total synthesis of* (±) - 3 - *methoxy* - 11 - *methyl or* 11,13 - *dimethylestra* - 1,3,5(10),8,14 - *pentaen* - 17 - *one* **14a** *or* **14b**. The isothiouronium salt **11c** was prepared by addition of a soln of 66 g of thiourea in 132 g of acetic acid to 20 g of the tetralol in an atmosphere of N_2.[17] After the soln was allowed to stand at 20° for 2 h, it was diluted with 3 l of ether. The precipitated thiouronium salt was collected by filtration and used without purification. A mixture of 40 g of isothiouronium salt **11c** was suspended in 750 ml of water and stirred for 1 h. To this mixture was added dropwise, with stirring over a period of 20 min, a soln of 15 g of **12b**. After the reaction mixture was stirred for 30 min, it was extracted several times with 200 ml portions of ether. The ether extract was dried over $MgSO_4$ and distilled to dryness to yield 5.5 g of crude **13b**. The crude product was dissolved in 550 ml of benzene containing 580 mg of p-TsOH. The product in pentane soln was separated by chromatography on 250 g of cc-7 silica gel in pentane using increasing amounts of pentane in benzene as eluant. Elution with benzene yielded a fraction weighing 180 mg. The material exhibited maxima at 297 mμ (shoulder) ($\epsilon = 15{,}000$), 310 mμ ($\epsilon = 18{,}000$) and 321 mμ (shoulder) ($\epsilon = 15{,}000$) typical of the estra-1,3,5(10),8,14-pentaene system expected for a substance like **14b**.[16,17]

In this experiment and other experiments involving the condensation of the methyl tetralol with **12a** or **12b** in the presence of triethylamine or KOH as described previoudly,[16,17] little or no condensation product could be isolated. Instead, when purification of these reaction mixtures by chromatography on cc-7 silica gel was performed, the first chromatography fractions contained the dehydration product **15a**, a liquid, λ_{max} 272.5 mμ ($\epsilon = 13{,}400$); λ_{max} 6.22 and 6.38 μ; δ 1.93 (s, 3H, C–CH_3), 2.13–2.40 and 2.61–2.86 (m, 4H, –CH_2–), 3.79 (s, 3H, OCH_3), 3.03 (2H, =CH_2), 4.75 (t, 1H, =CH) and 6.65–7.24 (m, 3, aromatic H); (Found by vapor pressure osmometer in $CHCl_3$: MW 203; Calc.: MW 200). **15a** could also be prepared almost quantitatively by heating the tetralol **11a** or its thiouronium salt **11c** in alcohol and HOAc at 60°.

*11β - Methyl - 5α,25*D *- spirostan - 3 - one* **16a**. To a soln of 13.8 g of 11β-methylticogenin[18] in 1.7 l of acetone was added dropwise 13.5 ml of 8N CrO_3–H_2SO_4 with vigorous stirring. About 10 g of $MgSO_4$ was added in portions during the reaction. Then 5 ml ^{i}PrOH was added. Some of the acetone was removed by distillation at reduced pressure and then decanted into water. The product was collected by filtration, washed with water and dried to yield 12.6 g of **16a**. Crystallization of the crude product from acetone yielded **16a**, m.p. 191–194°; δ 1.60 (m, 23-CH_2). (Found: C, 78.40; H, 10.17. Calc. for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35%).

A study on the bromination of spirostan-3-one **16b**. A study was made on the bromination of **16b** in HOAc, HOAc–CH_2Cl_2, or THF in the presence of HCl using one, two or three equivalents of bromine. In each experiment the total crude bromide was prepared, isolated and dehydrobrominated according to the preparation of **17** from **16a**. In each case the bromide and the dehydrobrominated products were analyzed by IR, UV and NMR spectroscopy. Monobromination in HOAc or CH_2Cl_2–HOAc gave predominantly a 23-bromospirostanone, dibromination a 2,23-dibromospirostanone and tribromination a 2,23,23′-tribromospirostanone. Monobromination in THF yielded 2-bromospirostanone, dibromination a mixture of 2,4 and 2,23-dibromospirostanone, and tribromination a 2,4,23-tribromospirostanone. The spectral data used to determine the products of bromination are as follows: Ketone **16b** [λ_{max} 5.82; δ 4.2–4.5 (m, 16-CH), 0.80 (s, 18 CH_3), 1.03 (s, 19-CH_3), 1.62 (23-CH_2), 3.33–3.53 (m, 26-CH_2]; 2-bromo- **16b** [λ_{max} 5.78μ; δ 4.6–4.93 (m, 2-CHBr), 0.96 (s, 19-CH_3), 1.62 (m, 23-CH_2]; 2,23-dibromo-**16b** [λ_{max} 5.78μ; δ 4.05–4.2 (m, 23-CHBr)]; 2,4,23-tribromo-**16b** [λ_{max} 5.69μ; δ 4.6–4.93 (m, 2,4-CHBr)], 0.92 [(s, 18-CH_3), 1.19 (s, 19-CH_3), 4.05–4.25 (m, 2,4-CHBr)]; 23-bromo-**16b** [(λ_{max} 5.83μ; δ 4.2–4.5 (m, 23-CHBr)]; Δ^1-**16b** [(λ_{max} 5.95μ; λ_{max} 231 nm ($\epsilon = 9{,}000$); δ 5.40, 5.46 (m, 1,3-CH); 0.82 (s, 18-CH_3); 1.03 (s, 19-CH_3)]; $\Delta^{1,4}$ **16b** [(λ_{max} 6.01, 6.17 and 6.24μ; λ_{max} 244.8 nm ($\epsilon = 12{,}600$); δ 6.00, 6.16, 6.36, 7.03, 7.20 (m, 1,2,4-CH); 1.62 (m, 23-CH_2)]; $\Delta^{1,4}$-23-bromo-**16b** [λ_{max} 6.01, 6.17 and 6.24μ; λ_{max} 244 nm ($\epsilon = 12{,}000$); δ 1.03 (s, 18-CH_3); 1.26 (s, 19-CH_3)]; Δ'-23-bromo-**16b** [λ_{max} 231 nm ($\epsilon = 9000$)].

*2ξ,4ξ,23ξ - Tribromo - 11β - methyl - 5α,25*D *- spirostan - 3 - one* **16c**. To a soln of 66.1 g of **16a** in 1.6 l of THF containing 48 g of HCl was added, with stirring while the soln was maintained at 18–20°, 74.8 g of Br_2 over a period of 90 min. The reaction mixture was cooled to 10°, stirred for 2.5 h and allowed to warm to 20°. Then 245 g of solid $NaHCO_3$ was added slowly and carefully with stirring. The inorganic salts were removed by filtration, the filtrate was diluted with ^{i}PrOH, and the soln was concentrated by distillation under reduced pressure. The solid bromide was collected by filtration, washed with ^{i}PrOH, and dried. The product **16c** (89.1 g) had m.p. 155–165° (dec); λ_{max} 5.70 (s) and 5.8 (w)μ; δ 0.92 (3H, C-13 Me), 1.19 (3H, C-10 Me), 3.33–3.53 (m, 2H, OCH_2), 4.05–4.25 (m, 1H, 23-CHBr), 4.60–4.93 (m, 2H, 2,4-CHBr). (Found: Br, 35.70. Calc. for $C_{28}H_{41}Br_3$: Br, 36.03%).

*23ξ - Bromo - 11β - methyl - 25*D *- spirosta - 1,4 - dien - 3 - one* **17**. To a mixture of 2.88 g of MgO and 49 ml of DMF heated at vigorous reflux was added, with stirring in portions, 8.9 g of **16c**. The mixture was heated at reflux for 25 min, cooled and then diluted with a mixture of 72 ml of 12M HCl, 90 ml of water and 180 g of ice. The amorphous solid was collected by filtration and washed successively with water, aq $NaHCO_3$ soln and water. The product **16f**, when dried, weighed 5.83 g; λ_{max} 6.02, 6.18, and 6.25μ, λ_{max} 244.8 nm ($\epsilon = 12{,}700$). Found: Br, 16.22. Calc. for $C_{28}H_{39}BrO_3$: Br, 15.87%).

*3 - Hydroxy - 11β - methyl - 25*D *- spirosta - 1,3,5(10) - triene* **18a**. A soln of 38.8 g of **17** was added dropwise with vigorous stirring into a mixture of 28.2 g of biphenyl, 31.2 ml of diphenylmethane, 9.4 g of lithium and 210 ml of THF heated at reflux in an atmosphere of N_2. The rate of addition of steroid was such as to maintain a dark green soln. Then 30 ml of MeOH in 20 THF was added carefully and the mixture was diluted with 60 ml of water and then with 12M HCl until the mixture was slightly acidic. The organic solvent was removed by distillation and the mixture was extracted with benzene. The benzene soln was washed with water, aq $NaHCO_3$ soln, dried over $MgSO_4$ and distilled to dryness under reduced pressure. Trituration of the residue with hexane yielded 13 g of the product **18a**. Crystallization of the crude product from CH_2Cl_2-hexane yielded **18a**, m.p. 234–236°, λ_{max} 281 nm ($\epsilon = 2040$), λ_{max} 2.81, 6.20 and 6.30μ. (Found: C, 78.89; H, 9.54. Calc. for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33%).

In an alternate procedure when 47.5 g of **17** was reduced, the crude product, also containing biphenyl and diphenylmethane, was dissolved in 250 ml of pyridine and added with stirring to 50 g of pyridine-SO_3 complex. The reaction mixture was heated at 95° for 2 h and then added to a slurry of 2.5 l of ice and water. The aq mixture containing **18b** was washed with hexane–ether (1:1), acidified with HCl and heated at 95° to hydrolyse to the ester **18b**. The mixture was cooled at 0° for 20 h. The crude product **18a**, which was collected by filtration and dried, weighed 12 g.

3 - Hydroxy - 11β - methyl - 19 - nor - *pregna* - 1,3,5(10),16 - *tetraen - 20 - one* **19a**. A soln of 17 g of **18a**, 17 ml of pyridine, 34 ml of Ac_2O and 5.7 g of methylamine hydrochloride was heated at reflux in an atmosphere of N_2. The temperature of the reaction mixture was at 154°. After 2.5 h the reaction appeared to be complete as measured by TLC. The cooled soln was added dropwise with vigorous stirring to a slurry of ice and water. The mixture was cooled at 5° for 16 h and the solid was collected by filtration at 0–5° and then dissolved in benzene. The benzene soln was washed with water, dried over $MgSO_4$ and distilled to dryness. The residue was dissolved in 100 ml of AcOH containing 5.2 g of NaOAc. To this soln, maintained at 15–18°, was added a soln of 8.3 g of CrO_3 in 23 ml of water and 11 ml of AcOH. The soln was stirred for 30 min and 5 ml of ^{i}PrOH was added. After another 5 min 17.7 g of NaOAc was added and the mixture was evaporated to dryness under reduced pressure, diluted with water and extracted with $CHCl_4$. The $CHCl_3$ extract was washed with water, dried over $MgSO_4$ and distilled to dryness. The residue was dissolved in 450 ml of MeOH and 50 ml of water. While the soln was heated in an atmosphere of N_2, a soln of 9 g of potassium bicarbonate in 38 ml of water and 12 ml of MeOH was added. The soln was heated at reflux for 20 min and concentrated by distillation to a small volume. The product was collected by filtration, washed with water and dried to yield 13.05 g of crude product. Crystallization of the crude product from acetone–hexane, after treatment with charcoal, gave a purified product **19a** (12.7 g), λ_{max} 223 nm ($\epsilon = 10{,}950$), 230 nm ($\epsilon = 11{,}000$) and 280 nm ($\epsilon = 2400$); λ_{max} 2.77, 2.81, 2.86, 6.02, 6.19 and 6.21μ. The material was used for the conversion to **19b** without further purification.

3 - Methoxy - 11β - methyl - 19 - norpregna - 1,3,5(10),16 - *tetraen - 20 - one* (**19b**). A mixture of 7.25 g of **19a**, 7.2 g of K_2CO_3, 400 ml of EtOH and 15 ml of CH_3I was heated at reflux with stirring for 2.5 h. The mixture was distilled to dryness under reduced pressure and diluted with water. The product was triturated with water and collected by filtration. Crystallization of the crude product weighing 7.3 g from ether yielded **19b**, m.p. 177.5–181°. (Found: C, 81.63; H, 8.63. Calc. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70%).

11β - Methylandrosta - 1,4 - diene - 3,17 - dione **21a**. When 3.96 g of **20a**[21] was brominated with 4.25 g of bromine according to the procedure used in the conversion of **16a** to **16c**, 5.9 g of crude dibromide **20b** was obtained and dehydrobrominated with MgO–DMF according to the procedure used for the preparation of **17**. 3.3 g of **21a** was obtained. Crystallization from acetone and hexane gave **21a**, m.p. 171–174°; λ_{max} 242 nm ($\epsilon = 14{,}000$); δ 1.03 (C-13 Me), 1.37 (C-10 Me), 1.28 and 1.40 (C-11 βMe). (Found: C, 80.32; H, 8.96. Calc. for $C_{20}H_{28}O_2$: C, 80.49; H, 8.78%).

17β - Hydroxy - 11β - methylandrosta - 1,4 - diene - 3,17 - dione **21b**. A soln of 3.3 g of **21a**, 6 g of lithium tri-*t*-butoxyaluminum hydride and 50 ml of THF was stirred for 30 min and then poured into a mixture of 100 g of ice and 100 ml of 20% aq HOAc soln.

The mixture was concentrated by distillation and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, aq $NaHCO_3$ soln, dried over $MgSO_4$ and distilled to dryness under reduced pressure. The residue was crystallized from acetone and hexane to yield 1.6 g of **21b**, m.p. 162–164°; λ_{max} 244 nm (ϵ = 14.700). (Found: C, 79.70; H, 9.40. Calc. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%).

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