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Synthesis and Biological Inactivity of Some 4α,6-Cyclo Steroids

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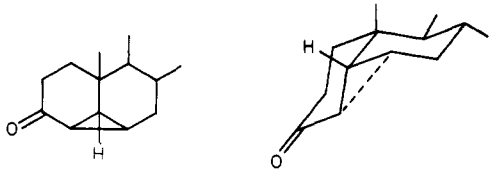
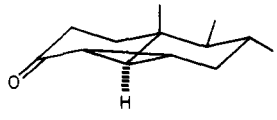
Two different synthetic routes have been used to synthesize a series of cyclopropyl conjugated ketones in which 4α,6-unsaturation replaces the usual 4,5-unsaturation. The synthetic routes involve intramolecular ketocarbene addition to a 5–6 double bond and intramolecular 1,3-elimination of 6β-substituted 5β-3-keto steroids. Both routes give 5β products. The analogs of progesterone, testosterone acetate, and norethisterone have been prepared and shown to be remarkably biologically inactive when compared with the corresponding standard. Possible reasons for such inactivity are discussed.

With the exception of the estrogens, practically all biologically active steroids possess characteristic Δ^4-en-3-one unsaturation in ring A or are capable of in vivo transformations to such functionality. This is particularly true among progestational agents[1] where a large number of modified steroids have been shown to be active, all of which contain either Δ^4 or $\Delta^{5(10)}$ unsaturation. Indeed, the saturated dihydro derivatives are often inactive metabolites.[2] It was the object of this work to change the nature of that unsaturation from olefinic to cyclopropyl via synthesis of 4,6-cyclopropyl steroids I. In this paper we report the synthesis of a number of 4α,6 (A–B cis) de-



I

Ia

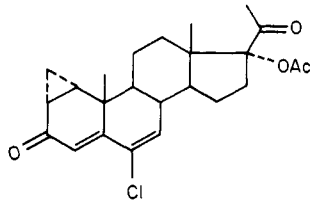


Ib

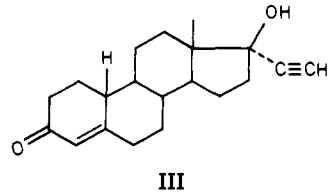
rivatives, Ia. Synthetic routes to the 4β,6 isomers Ib have proven more difficult and will be reported later.

The rationale that such a change might lead to enhanced activity lies in the well-known "unsaturated" character of the cyclopropane ring[3] which makes the electronic features of I similar to those of the natural steroids. At the same time, metabolism by allylic oxidation at C-6[4] should be vastly retarded and metabolism[5] via reduction of the double bond would be expected to be more difficult. Examination of models shows some change in the overall shape of the A–B ring system in Ia and less in Ib, but it was hoped that receptor fit would not be drastically altered by such a small, if dramatic, structural isomerism.

There is widespread evidence that cyclopropyl conjugation can replace olefinic conjugation in active steroids.[6] In particular, the profound activity of cyproterone acetate II[5a] and related compounds which show dramatic increases



II



III

in activity over their 1–2-unsaturated analogs justified synthesis of compounds such as I which contain the unsaturation within[7] rather than exo to the ring system. Activity, or lack thereof, in compounds such as I should help define those features necessary for action and might help in predicting the nature of the chemical interaction responsible for initiation of such activity.[8] Further rationale for possible activity of compounds such as Ia in the progesterone series comes from the known enhancement of activity in such compounds caused by 6α-methylation.[9] Finally, in the 19-nor series the analog of norethisterone III could not undergo endogenous conversion to an estrogen, a known[10] problem with III.

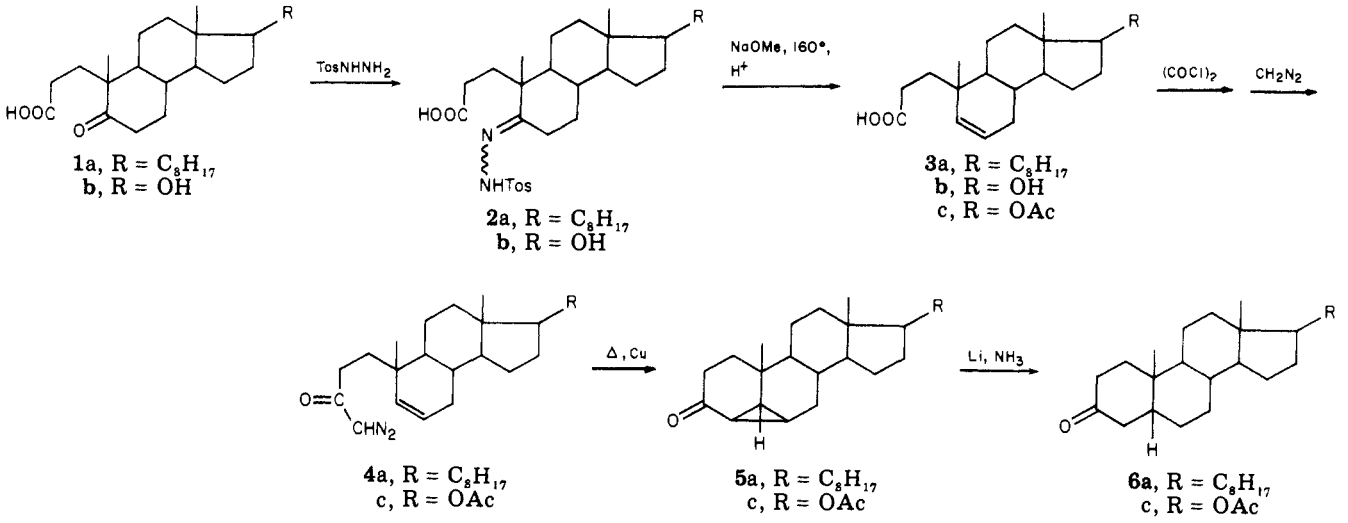
In this paper we report the synthesis of a variety of compounds of type Ia and in particular the analogs **10**, 18, and **5c** of progesterone, norethisterone, and testosterone acetate, respectively.

Synthetic Routes. Two different routes were developed for the synthesis of the 4α,6-cyclopropyl steroids. The first involved intramolecular addition of a diazo ketone[11] to a 5,6 double bond. The initial experiments were developed in the cholesterol series. The well-known seco acid **1a**[12] was prepared and converted into its *p*-toluenesulfonylhydrazone derivative **2a**. Although attempts to prepare **3a** from **2a** had been unsuccessful[13] we found that carbenoid decomposition[14] of the sodium salt of **2a** afforded noncrystalline but apparently pure **3a** in high yield. The acid was converted into diazo ketone **4a** in the usual manner and this was decomposed using copper powder in cyclohexane. The cyclopropyl ketone **5a** was obtained along with two minor side products, one unidentified and the other the methyl ester of **3a**. The structure of **5a** was suggested by its infrared spectrum which showed the carbonyl group at 1688 cm^{-1}, the ultraviolet spectrum with λ_{max} (95% EtOH) at 215 nm (ε 6700),[15] and the NMR spectrum which showed no vinyl hydrogens. These spectral properties confirm the expected conjugation in compounds such as I. The structure was confirmed and the stereochemistry was shown to be 4α–6 by lithium–ammonia reduction[16] of **5a** to give 5β-cholestan-3-one (**6a**), identical with authentic material. When the crude product from **4a** was reduced under similar conditions, no 5α-cholestan-3-one could be detected under TLC conditions, which clearly separated authentic material, so that the keto carbene addition appears to go exclusively from the α side of the molecule.

A similar reaction sequence was carried out on the testosterone seco acid **1b** to give crystalline **3b** which as its acetate **3c** was converted via **4c** and then into the testosterone analog **5c**.

The overall yield in this sequence was discouraging, however, and an alternate route, also more amenable to preparation of the analog of norethisterone, proved overall more acceptable. This route involved the 1,3-elimination[17] of a 6-substituted 5β-3-keto steroid, known[18] to enolize toward C-4.

The required intermediate in the progesterone series was prepared by hydroboration of the Δ^5 progesterone diketal



1a, R = C_8H_{17}
b, R = OH

2a, R = C_8H_{17}
b, R = OH

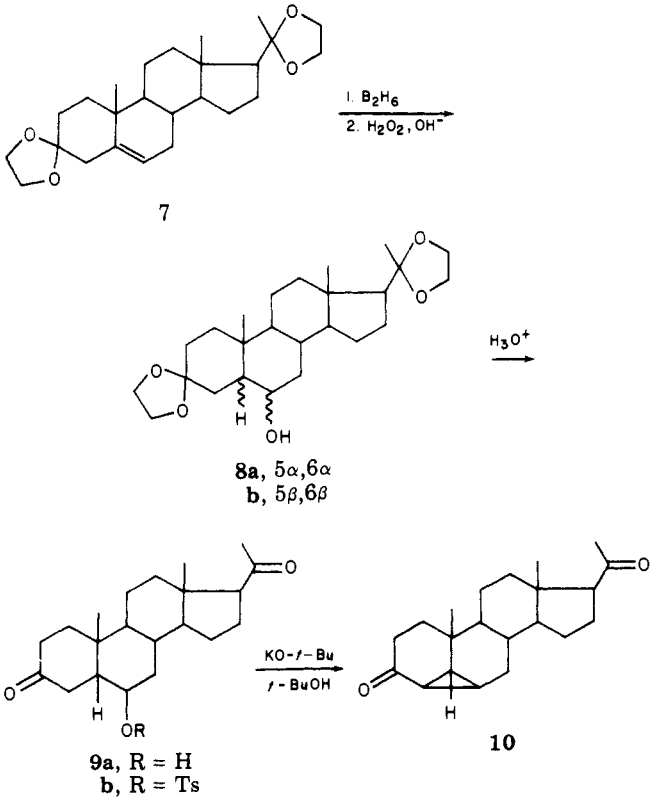
3a, R = C_8H_{17}
b, R = OH
c, R = OAc

4a, R = C_8H_{17}
c, R = OAc

5a, R = C_8H_{17}
c, R = OAc

6a, R = C_8H_{17}
c, R = OAc

7 which gave, as expected,[19] an approximately 1:1 mixture of the 5α,6α isomer **8a** and the desired 5β,6β isomer **8b**. Hydrolysis of **8b** gave the alcohol **9a**, NMR of which confirmed the stereochemical assignment. This was converted into tosylate **9b** which, on treatment with potassium *tert*-butoxide in *tert*-butyl alcohol gave **10** in high yield. Spectral properties (see Experimental Section) were fully in agreement with the assigned structure.



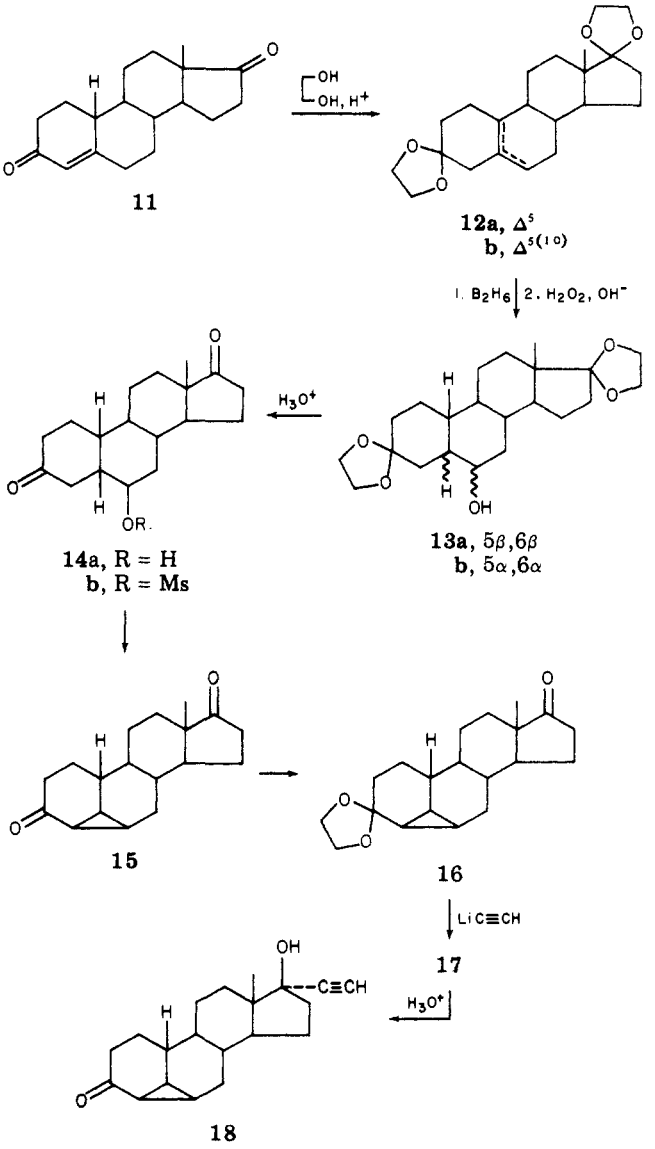
7

8a, 5α,6α
b, 5β,6β

9a, R = H
b, R = Ts

10

A similar sequence was used in the 19-nor series. Diketone **11** was converted into a mixture of the desired Δ^5 ketal **12a** and isomer **12b** which could be separated and the latter recycled. As with **7**, hydroboration of **12a** gave a mixture of the desired **13a** and lesser amounts of the 5α,6α isomer **13b**. Hydrolysis of **13a** afforded **14a** which was converted into its mesylate (the tosylate underwent elimination more slowly) **14b** which underwent elimination to give the 19-nor diketone **15**. This could be selectively ketalized at C-3 to give **16** which was converted by standard methods to the norethisterone analog **18**.



11

12a, Δ^5
b, $\Delta^{5(10)}$

13a, 5β,6β
b, 5α,6α

14a, R = H
b, R = Ms

15

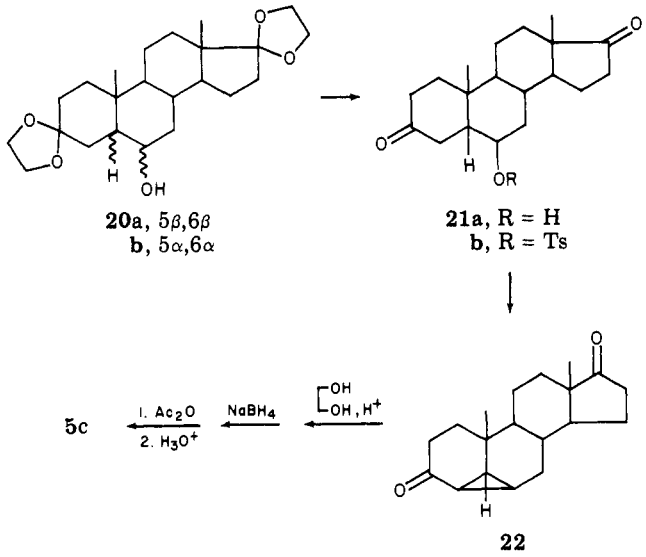
16

17

18

The elimination route was also used in the testosterone series; hydroboration of the Δ^5 diketal of 4-androstene-3,17-dione **19** afforded the desired **20a** which, after separation from the isomer **20b**, was converted as above into **21a**, **21b**, and then **22**. The ring-A carbonyl of **22** could be selectively ketalized, the 17-ketone reduced and the hydroxyl acetylated, and the ketal hydrolyzed to give **5c**,

identical with material prepared via the diazo ketone route. This confirms the stereochemical assignment expected from the 1,3-elimination.



20a, 5β,6β
b, 5α,6α

21a, R = H
b, R = Ts

22

Biological Activity. Biological assays were performed by Mason Research Institute under the direction of the Contraceptive Development Branch of National Institutes of Health. The progesterone analog **10** showed no progestational activity in the rabbit (Clauberg[1a]) at dose levels of 0.1, 1.0, and 10.0 mg. No antiprogestational activity (anti-Clauberg) was detected for **10** at a dose level of 20.0 mg vs. progesterone (0.4 mg). The norethisterone analog **18** was also inactive in the Clauberg at dose levels to 6.4 mg and in the anti-Clauberg at 20.0 mg vs. progesterone (0.4 mg). Compound **18** also exhibited low activity in a postcoital interruption of pregnancy in female rats, with nine of ten rats pregnant at a dose level of 5.0 mg/day on days 0–4. Compound **18** was also tested in a 2-day rat antiovulatory test. Nine of ten animals ovulated at a 20.0 mg/kg dose level.

The testosterone analog **5c** was tested for androgenicity in male rats[25] at dose levels of 0.1, 1.0, and 10.0 mg and had less than 20% the activity of testosterone. The same was true for **15** at a dose level of 10.0 mg. Both **5c** and **15** were tested for antiandrogenic activity, the former at 10 mg vs. 2.4 mg of testosterone and the latter at 10.0 mg vs. 1.2 mg of testosterone. The inhibition of increase in weight of the seminal vesicle, ventral prostate, and levator ani was less than 20% with both compounds.

The inactivity of these compounds confirms the long-known sensitivity of such activity to minor structural changes, in this case simple isomerization from 4–5 to 4–6 unsaturation. Either the loss of near-planarity in the A–B ring system or the change in the nature of the unsaturation would seem the likely cause(s) of this dramatic decrease in activity. Studies in the trans series Ib should help solve these questions. The lack of appreciable androgenic activity in **5c** and **15** is perhaps more surprising.

Experimental Section

All melting points were determined in glass capillaries and are uncorrected. NMR spectra were determined in $CDCl_3$ on a Varian T-60 or HR 220 instrument. Chemical shifts are in δ units from internal Me_4Si. Only significant absorption bands are reported. All reactions were run under nitrogen. Worked up in the usual manner means that solutions of crude product were washed, as appropriate, with either 5% bicarbonate or 5% HCl, then water, and saturated salt, dried over sodium sulfate, and concentrated in vacuo. Thin-layer chromatography experiments were performed on 0.25 mm E. Merck precoated silica gel plates (no. 5763). The solvent system employed was 20% ether in benzene except for **3a** in which it was 40% ether in benzene, 25% ethyl acetate in ether, and 50% benzene, 40% ether, and 10% acetic acid. Analyses are indicated by the symbols of the elements measured. All such results were within ±0.3% of the theoretical values.

3,5-Seco-*A*-norcholest-5-en-3-oic Acid (3a). To freshly prepared sodium methoxide (from 0.253 g of sodium) in 300 ml of methanol was added 2.86 g (5.0 mmol) of **2a** (mp 171–172°[13]) and the resulting solution was stirred at room temperature for 1 hr and the solvent evaporated and dried in vacuo overnight. Diglyme (ca. 150 ml) was distilled into the flask from lithium aluminum hydride. The stirred suspension was heated at reflux for 45 min, cooled, poured onto ice, and acidified. The resulting amorphous precipitate (1.83 g, 94%) of **3a** appeared to be pure (TLC in three systems) but resisted attempts at crystallization and was used without further purification. The NMR spectrum shows vinyl absorption (2 H) from δ 5.2 to 5.8, the C-18 methyl at δ 0.67, and the C-19 methyl at δ 0.93.

4α,6-Cyclo-5β-cholestan-3-one (5a). The crude acid **3a** (0.730 g, 1.8 mmol) was thoroughly dried, covered with an excess of freshly distilled oxalyl chloride, and allowed to stand overnight at room temperature. Excess oxalyl chloride was removed at 0.1 mm, 50 ml of benzene was added, and the solution evaporated to dryness. The residue was dissolved in 10 ml of ether and added dropwise to a freshly prepared ethereal solution of excess diazomethane. After stirring at room temperature for 2 hr the solvent was removed in vacuo to give crude **4a** (infrared carbonyl at 2105 cm^{-1}) which was used immediately.

A stirred suspension of 1.0 g of copper powder in 30 ml of dry cyclohexane was brought to reflux. Crude **4a**, dissolved in 30 ml of dry cyclohexane, was added dropwise through the condenser to the refluxing solution over a period of 10 min. The suspension was heated an additional 2 hr, by which time TLC indicated the disappearance of **4a**. The suspension was filtered and evaporated to give 0.690 g of crude product which was chromatographed on 50 g of activity III neutral alumina. After elution of two minor impurities, 0.270 g of **5a** (37% from **3a**), mp 90–90.5°, was obtained with benzene.

The infrared spectrum shows carbonyl absorption at 1694 cm^{-1}. The NMR spectrum shows no vinyl hydrogens, the C-18 methyl at δ 0.68, and the C-19 methyl at δ 1.18. Anal. ($C_{27}H_{44}O$) C, H.

5β-Cholestan-3-one (6a). To a solution of 0.080 g of lithium wire in ca. 100 ml of freshly distilled ammonia was added 0.100 g (0.26 mmol) of **5a** in 15 ml of dry ether. The reaction was stirred for 2 hr, solid ammonium chloride was added, and the ammonia evaporated. The residue was taken up in ether, washed thoroughly, dried, and evaporated to give 0.097 g of an oil. TLC examination of this material in two different solvent systems which cleanly separated authentic samples of 5α- and 5β-cholestan-3-one showed the presence of only the latter and a small amount of starting material. Recrystallization from chloroform–hexane afforded 0.078 g of colorless crystals, mp 60–62° (lit.[20] mp 61–62°), mixed with authentic material undepressed, ir and NMR spectra identical with those of authentic material.

3,5-Seco-17β-hydroxy-*A*-norandrost-5-en-3-oic Acid (3b). The *p*-toluenesulfonylhydrazone (4.76 g, 10 mmol, mp 209–211°) of **1b** was prepared in the usual manner, converted into its sodium salt as described for **2a**, and dried. The salt was heated under reflux in ca. 400 ml of dry diglyme for 30 min, cooled, acidified, and worked up to give a colorless solid recrystallized from acetone–hexane to give **3b** as colorless crystals (2.55 g, 87%), mp 168–170°. Anal. ($C_{18}H_{28}O_3$) C, H.

The acetate **3c** was prepared in the usual manner as colorless crystals, mp 124–125°, from ether–hexane. The NMR shows vinyl absorption from δ 5.05 to 5.62 (2 H), the C-17 H as a multiplet at δ 4.53 (1 H), and three-proton singlets at δ 0.78, 0.92, and 2.00. Anal. ($C_{20}H_{30}O_4$) C, H.

17β-Hydroxy-4α,6-cyclo-5β-androstan-3-one Acetate (5c). The acid **3c** (1.86 g, 5.57 mmol) was dissolved in 15 ml of freshly distilled oxalyl chloride and stirred at room temperature for 24 hr. Excess oxalyl chloride was removed in vacuo and 50 ml of benzene added and evaporated. This operation was repeated twice. The oily residue was dissolved in 30 ml of dry benzene and added to a fresh solution (excess) of ethereal diazomethane. The addition took 30 min after which the solution was stirred

30 min and evaporated. The residue was dissolved in 80 ml of cyclohexane.

Under nitrogen, a stirred suspension of 2 g of copper powder in 50 ml of dry cyclohexane was brought to reflux. The diazo ketone solution was added dropwise over a 30-min period and the solution heated under reflux an additional 3 hr. After cooling the solution was filtered and evaporated to a residue of 1.91 g. TLC showed two spots. The mixture was chromatographed on 120 g of activity III Woelm alumina, elution with benzene affording several fractions of crystalline material which were combined to give 1.29 g (70%) of colorless solid, mp 127–131°. Two recrystallizations from ether–hexane afforded **5c**, 0.84 g (46%), as fine colorless needles, mp 136–137°.

The ir spectrum shows carbonyl bands at 1730 and 1693 cm^{-1}. The NMR spectrum has sharp three-proton singlets at δ 0.76, 1.15, and 2.00. Anal. ($C_{21}H_{30}O_3$) C, H.

17β-Hydroxy-5β-androstan-3-one Acetate (6c). Lithium–ammonia reduction of **5c** as described for **5a** above afforded crude material which cochromatographed on TLC with authentic **6c** and which showed no TLC evidence for the presence of the 5α isomer. Chromatography on silica gel afforded pure **6c**, mp 146.5–147°, identical (ir, NMR, TLC) with authentic **6c**.

6β-Hydroxy-5β-pregnane-3,20-dione (9a). The diketal **7** of progesterone was prepared in the usual manner, mp 178–180° (lit.[21] mp 180–183°). This material was subjected to hydroboration using procedure b of Nussim et al.[19] From 3.00 g (7.5 mmol) of **7** there was obtained 2.81 g of crude material, TLC of which indicated two major spots. Recrystallization from methanol containing a trace of pyridine gave 2.1 g of material enriched in the less polar of these two materials. Chromatography of this material on 100 g of silica gel gave on elution with pentane–ether (1:1) 1.89 g of TLC pure material **8b**, mp 147–150°. Later fractions appeared to contain **8a**. Material **8b** was dissolved in 10 ml of chloroform, 40 ml of methanol, 5 ml of water, and 2 ml of concentrated HCl, and the solution was stirred at room temperature overnight. The reaction was worked up to give 1.61 g of **9a** as a colorless foam which could be used directly in the preparation of **9b** or chromatographed on silica gel to afford pure **9a**, eluted with hexane–ethyl acetate (1:1), mp 186–189°.

The NMR spectrum has sharp three-proton singlets at δ 0.68, 1.18, and 2.12 and a broad one-proton peak at δ 3.68 (C-6 H). The calculated[22] values for **9a** are C-18 (δ 0.66) and C-19 (δ 1.16). Anal. ($C_{21}H_{32}O_3$) C, H.

4α,6-Cyclo-5β-pregnane-3,20-dione (10). A solution of 1.50 g (4.5 mmol) of **9a** in 50 ml of dry pyridine was treated with 1.86 g (9.8 mmol) of *p*-toluenesulfonyl chloride at 4° for 4 days and then allowed to warm to room temperature for 3 additional days whereupon TLC revealed complete disappearance of starting material. At this time the solution was poured onto ice and worked up to give 1.67 g of **9b** as a colorless foam which could not be induced to crystallize. A solution of 1.30 g (2.67 mmol) of this product in 100 ml of dry *tert*-butyl alcohol was prepared and treated, with stirring, with 25 ml of a 0.12 *M* solution of potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction was stirred at room temperature for 20 min and worked up in the usual manner to give 0.95 g of a yellow solid. Recrystallization from 95% ethanol afforded 0.66 g (79%) of **10**, mp 172–173°.

The ir spectrum shows carbonyl absorption at 1708 and 1694 cm^{-1}. The NMR spectrum has no vinyl hydrogen absorption and sharp three-proton singlets at δ 0.67, 1.21, and 2.10. Anal. ($C_{21}H_{30}O_2$) C, H.

5-Estrene-3,17-dione Cyclic Bis(ethylene acetal) (12a). Ketalization[23] of 28.4 g (104 mmol) of **11** under standard conditions afforded a quantitative yield of crude **12** which was dissolved in 75 ml of hot methanol (containing 1 ml of pyridine) and allowed to stand at room temperature for 3 days. The resulting crystals, 9.3 g, were collected and washed with cold methanol. Two recrystallizations from methanol containing a trace of pyridine afforded 7.11 g (19%) of **12a**, mp 130–132° (lit.[24] mp 132°). The mother liquors from the reaction and crystallizations still showed substantial amounts of **12a** and a second major spot, presumed to be **12b**. Chromatographic separation proved difficult and the mixture was best hydrolyzed and recycled.

The NMR spectrum of **12a** shows a three-proton singlet at δ 0.84 (C-18), an eight-proton ketal pattern at δ 3.84 and 3.95, and a one-proton multiplet at δ 5.42 for the C-6 vinyl hydrogen. NMR analysis of the crude reaction product suggests an approximate 1:1 mixture of **12a** and **12b**. Anal. ($C_{22}H_{32}O_4$) C, H.

6β-Hydroxy-5β-estrane-3,17-dione Cyclic Bis(ethylene acetal) (13a). To a solution of 11.0 g of **12a** (30.5 mmol) in 1.2 l. of dry THF was added 152 ml of a 1 *M* solution of diborane in THF over a 20-min period. The reaction was stirred at room temperature for 4 hr, cooled to 5°, and treated dropwise with 45 ml of water. Sodium hydroxide (216 ml of a 10% solution) was added over a 10-min period followed by dropwise addition of 162 ml of 30% hydrogen peroxide. The solution was stirred for 2 hr at 5° and then worked up in the usual manner to give 11.94 g of crude product shown by TLC to contain two major and two minor products. Chromatography on 800 g of silica gel using pentane–ether elution was followed by TLC. Early fractions contained mixtures of the minor products and what appeared to be the one major product followed by several fractions eluted with pentane–ethyl ether (1:1), which appeared to be the pure major component. These were combined and evaporated to give 4.53 g (39%) of **13a**, mp 177–182°. Further elution with ether gave 2.5 g of what appeared to be **13b** as an oil.

Compound **13a** was quite moisture sensitive and was used immediately. Its NMR spectrum shows a three-proton singlet at δ 1.17, a broad singlet (1 H) at δ 3.64, and an eight-proton ketal pattern centered at δ 3.82.

6β-Hydroxy-5β-estrane-3,17-dione (14a). A solution of 4.50 g (11.9 mmol) of **13a** in 60 ml of chloroform, 100 ml of methanol, 40 ml of water, and 3 ml of concentrated hydrochloric acid was heated at reflux for 30 min. The reaction was cooled and worked up in the usual manner to give 3.05 g (93%) of **14a**, mp 126–129°. Recrystallization of a small sample from methanol afforded the analytical sample, mp 130–133°.

The NMR spectrum shows a three-proton singlet at δ 0.90 and a broad one-proton peak at δ 3.11. Anal. ($C_{18}H_{26}O_2$) C, H.

4α,6-Cyclo-5β-estra-3,17-dione (15). The mesylate **14b** was prepared in pyridine in the usual manner and isolated as an uncharacterized white solid. This material (2.81 g, 8.07 mmol) was suspended in 250 ml of *tert*-butyl alcohol and treated with 7.2 ml of a 1.23 *M* solution of potassium *tert*-butoxide in *tert*-butyl alcohol. The mixture was stirred with warming to effect solution and then stirred at room temperature for 1 hr. Work-up in the usual manner gave 2.35 g of a yellow solid, chromatographed on 150 g of silica gel to give, after recrystallization from ethanol, 1.92 g (87%) of **15**, mp 163–165°.

The ir spectrum shows carbonyl absorption at 1730 and 1689 cm^{-1}. The NMR spectrum has a single sharp three-proton peak at δ 0.98 and no absorption below δ 2.3. Anal. ($C_{18}H_{24}O_2$) C, H.

4α,6-Cyclo-5β-estra-3,17-dione 3-Cyclic (Ethylene Acetal) (16). To a solution of 3.00 g (11 mmol) of **15** in 350 ml of dry benzene was added 1.0 g of oxalic acid and 10 ml of ethylene glycol. The solution was heated under reflux for 4 hr using a Dean-Stark trap to remove water and following the disappearance of **15** by TLC. The cooled solution was poured onto bicarbonate and worked up in the usual manner to give 3.85 g of a colorless solid which was chromatographed on 120 g of silica gel to give 2.09 g (55%) of **16** and then recrystallized from methanol to afford 1.89 g of colorless crystals, mp 189–193°.

The ir spectrum shows carbonyl absorption only at 1730 cm^{-1}. Anal. ($C_{21}H_{30}O_3$) C, H.

17α-Ethynyl-17β-hydroxy-4α,6-cyclo-5β-estr-3-one (18). To 100 ml of dry THF, saturated with acetylene, was added 7.9 g of lithium acetylide–EDTA complex (Foote Chemical Co.) followed by addition of 1.69 g (5.11 mmol) of **16** in 70 ml of THF over a 20-min period. After stirring overnight under an atmosphere of acetylene the reaction was worked up in the usual manner to give 1.79 g of crude **17**, mp 249–259°, which was immediately suspended in 150 ml of 90% acetic acid and stirred for 1.5 hr. Pouring onto water afforded **18** as a colorless solid (1.07 g, 70%) which was recrystallized twice from acetonitrile–chloroform to afford 0.710 g (47%) of **18** as colorless crystals, mp 242–245°.

The ir spectrum shows significant bands at 3605, 3315, 2250, and 1689 cm^{-1}. The NMR spectrum has a three-proton singlet at δ 0.88 and a one-proton singlet at δ 2.53. Anal. ($C_{20}H_{26}O_2$) C, H.

6β-Hydroxyandrostane-3,17-dione (21a). Hydroboration of the diketal of androstane-3,17-dione,[19] as described for **8**, followed by oxidation afforded a mixture of **20a** and **20b** which was

separated by chromatography on silica gel using hexane–ethyl acetate. Hydrolysis of **20a** afforded **21a** as a colorless solid which was recrystallized from acetone–hexane to give needles, mp 206–208°.

The ir spectrum shows absorption at 3600, 1734, and 1713 cm^{-1}. The NMR spectrum shows three-proton singlets at δ 0.90 and 1.25 and a broad one-proton signal at δ 3.70. Anal. ($C_{19}H_{28}O_3$) C, H.

4α,6-Cyclo-5β-androstane-3,17-dione (22). The tosylate **21b** was prepared in the usual manner as a white foam. To a solution of **21b** (1.40 g, 3.16 mmol) in 100 ml of *tert*-butyl alcohol was added 3.2 ml of a 1.0 *M* solution of potassium *tert*-butoxide. The solution was stirred for 30 min and worked up in the usual manner to give 0.90 g of a pale yellow solid. Two recrystallizations from ethanol afforded 0.65 g (72%) of colorless crystals, mp 195–197°.

The ir spectrum shows carbonyl absorption at 1730 and 1679 cm^{-1}. The NMR spectrum has three-proton singlets at δ 0.85 and 1.21. Anal. ($C_{19}H_{26}O_2$) C, H.

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Synthesis and Pharmacology of 2,9α-Dimethyl-2'-hydroxy-6,7-benzomorphan

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2,9α-Dimethyl-2'-hydroxy-6,7-benzomorphan (14) has been synthesized in six to seven steps from *trans*-3,4-dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2*H*)-naphthalenone (1). The key reaction of the sequence was mercuric acetate cyclization of *trans*-1,2-dihydro-1-(2-methylaminoethyl)-7-methoxy-2-methylnaphthalene (8) which gave a mixture of 9α-methyl-8α-hydroxy-6,7-benzomorphan (9, 49%), the corresponding acetate (10, 13%), and the 9β-methyl-8α-hydroxy-6,7-benzomorphan (11, 5%). In the presence of Et_3N, the yields were 16, 37, and 0%, respectively. Structural assignments are based on ir, NMR, and mass spectral data and on chemical conversions.

Recently,[2] we reported that cyclization of 2,3-*trans*-3,4-*cis*-2-bromo-3,4-dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2*H*)-naphthalenone gave 2,9β-dimethyl-2'-methoxy-8-oxo-6,7-benzomorphan methobromide from which 2,9β-dimethyl-2'-hydroxy-6,7-benzomorphan was obtained. The corresponding 2,3-cis-3,4-trans isomer gave, instead of the expected 9α-methylbenzomorphan methobromide, 4-(2-dimethyl-