STEROIDS AND RELATED PRODUCTS. LIII.[1] THE SYNTHESIS OF 11-OXA STEROIDS. V.[2] THE SYNTHESIS OF 17-ETHYNYL-11-OXATESTOSTERONE[3]

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In homage to the late PROFESSOR ALBERT SEGALOFF, with gratitude, admiration, and lasting affection

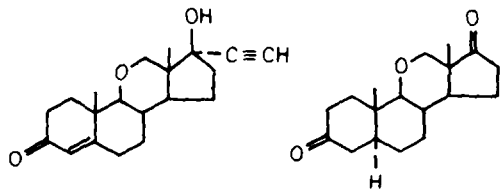
Received June 17, 1986
Revised December 16, 1986

ABSTRACT

The synthesis of 17-ethynyl-11-oxatestosterone, both from 11-oxa-5α-pregnane-3,20-dione and, via a 3,17-dioxygenated 9-oxo 9,12-seco 11-nor 5α-androstan-12-oic ester, from 3β-acetoxy-17-hydroxy-5α-pregnan-12-one - two products available from hecogenin - is reported. The new hormone analogue shows significant progestational activity in the Clauberg test and relatively weak activity in a post-coital antifertility assay.

GENERAL

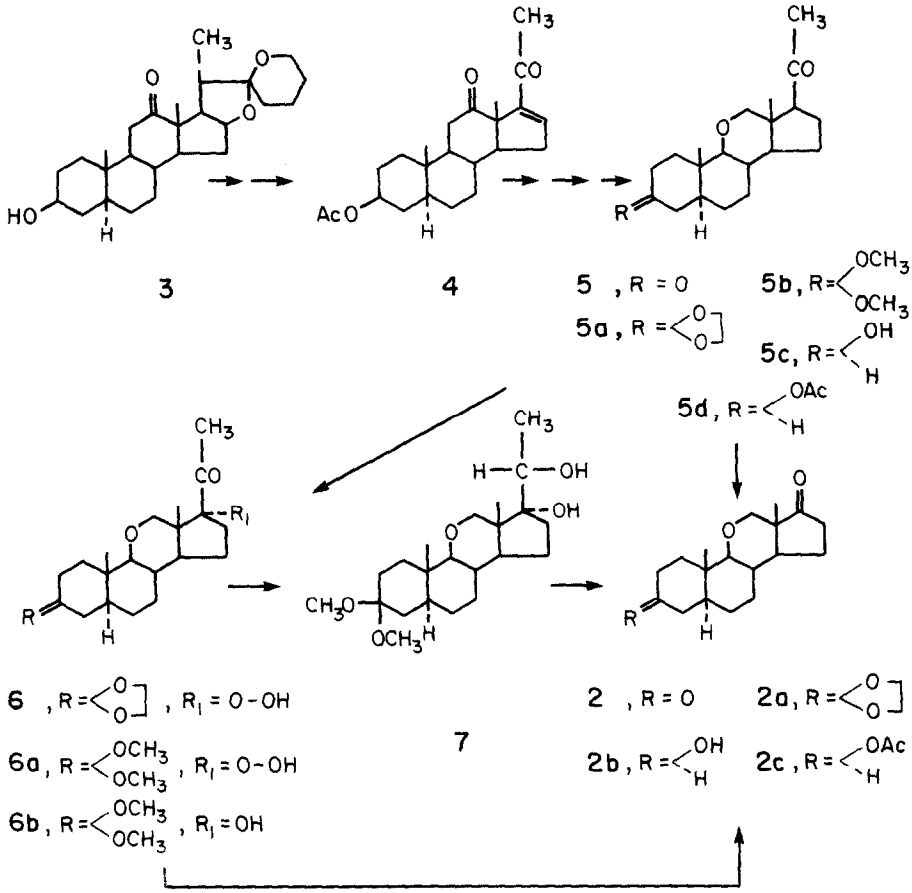
The low progestational activity of 11-oxaprogesterone (4,5) in the McPhail Clauberg assay (6) and its significant ovulation inhibiting activity in rabbits in which ovulation is stimulated with copper acetate (5, 7), made the synthesis and biological evaluation of the 11-oxa analogue **1** of ethisterone (17-ethynyltestosterone), an oral progestogen, attractive. As synthetic precursor we chose 11-oxa-5α-androstane-3,17-dione (**2**).



1 **2**

In a first set of experiments this product (**2**) was prepared from 11-oxa-5α-pregnane-3,20-dione (**5**), which is available from the degradation product **4** of the acetate of hecogenin (**3**) and which we had used as a key intermediate in syntheses of 11-oxaprogesterones (4, 5, 8) and of 11-oxa analogues of glucocorticoids (2). Preliminary experiments (Scheme 1) on a Baeyer-Villiger degradation with m-chloroperbenzoic acid of the acetate

5d of 3β-hydroxy-11-oxa-5α-pregnan-20-one (**5c**) (2) gave unsatisfactory results, the 11-oxa 3,17-diketone **2** obtained from the degradation product **2c** by hydrolysis and Jones oxidation being isolated in yields of only 14 to 25% . The direct degradation of the 3-ethylenedioxy 20-ketone **5a** (9) to the 17-ketone **2a**, according to Sidall's procedure (10), by treatment of the Barton-hydroperoxidation product **6** with potassium t-butoxide, proceeded only in 32% yield. We therefore subjected the 3-dimethylketal **5b** of the oxa diketone **5** to Gardner's modification (11) of Barton's procedure (12), involving the in situ reduction of the 17-hydroperoxide **6a**. The resulting 17-hydroxy 20-ketone **6b** (yield

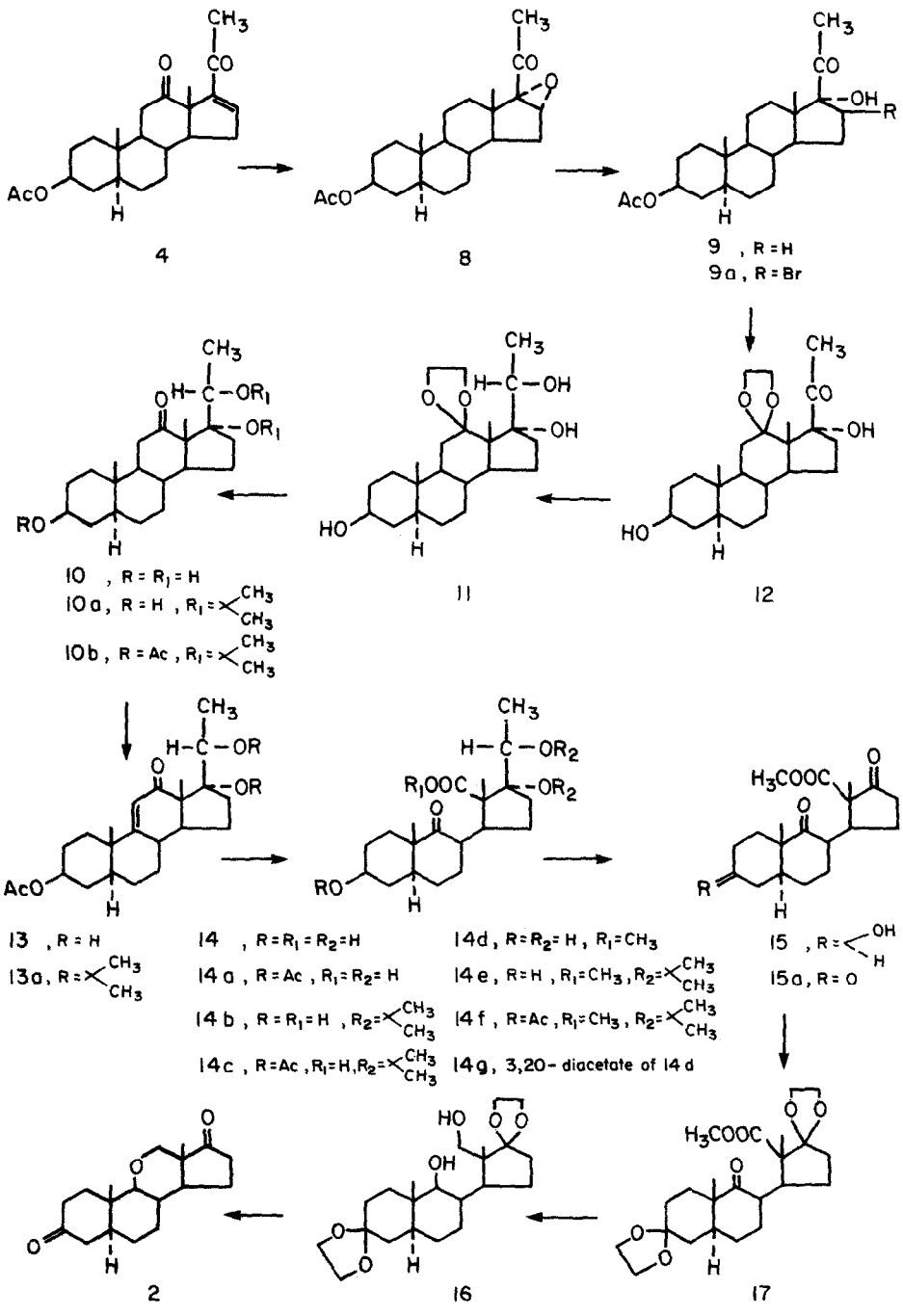


SCHEME 1

after purification: 45%) was reduced with sodium borohydride and the crude reduction product (**7**) was degraded with sodium bismuthate in acetic acid, with concomitant hydrolysis of the 3-ketal, to 11-oxa-5α-androstane-3,17-dione (**2**), obtained in 86% yield (over-all yield from the 3-dimethoxy 20-ketone: 40%).

Because of the efficient degradation of 17,20-diols, which are readily formed from 16-unsaturated precursors, to 17-ketones, we now explored an alternate route to the 11-oxa 3,17-diketone **2** (Scheme 2). The hecogenin degradation product **4** was transformed in approximately 90% yield by Julian's method (13), via the epoxide **8** and the bromohydrin **9a**, into 3β-acetoxy-17-hydroxy-5α-pregnane-12,20-dione (**9**), which was converted with ethylene glycol and boron trifluoride-etherate (cf.14) in approximately 80% yield to the 3β,17-dihydroxy 20-oxo 12-monoketal **12**, the 3-acetate group, already partly hydrolyzed, having been completely saponified with potassium carbonate. Reduction with sodium borohydride gave, in over 90% yield, 12-ethylenedioxy-5α-pregnane-3β,17,20α-triol (**11**) (15), which was transformed with absolute acetone and p-toluenesulfonic acid (cf. 21) into 3β,17,20α-trihydroxy-5α-pregnan-12-one 17,20α-acetonide (**10a**). Its acetate **10b** was dehydrogenated in 62% yield with selenium dioxide (22, cf. also 14) to 3β-acetoxy-17,20α-dihydroxy-5α-pregn-9-en-12-one (**13**).

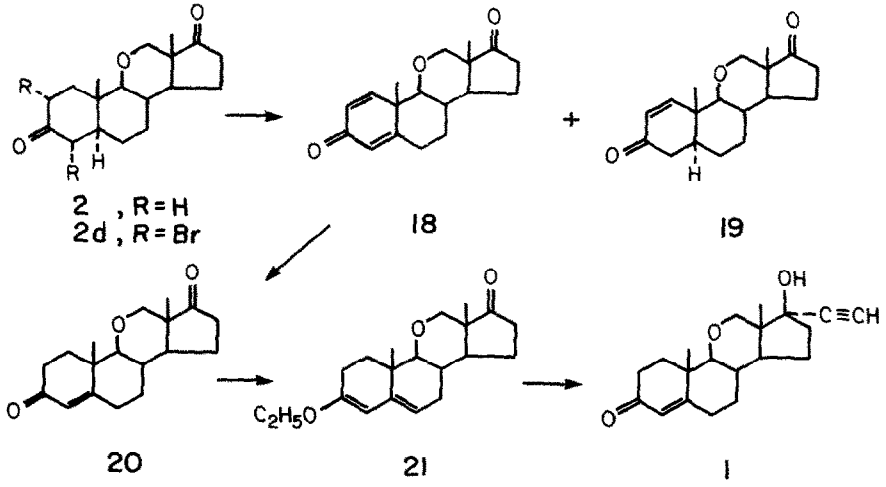
In a first series of experiments the acetonide protection was restored with acetone and perchloric acid and the product (**13a**) subjected to ozonolysis in ethyl acetate, followed by hydrogen peroxide oxidation, under the conditions previously elaborated (14), resulting in acid and neutral materials. The acid fraction consisted, according to its infrared spectrum, chiefly of the 9,12-seco 11-nor 9-oxo 12 acids **14b** and **14c** in which the 3-acetate had been partly hydrolyzed and in which the 17,20-diol moiety was still protected. The neutral fraction, to which we assign tentatively, on the basis of a strong infrared absorption at 1780 cm^{-1} and of other characteristic bands (cf. Experimental), mainly the structure of an anhydride of the 17,20-acetonide of 3β-acetoxy-9-oxo-17,20α-dihydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid (**14c**) and, to a minor extent, of the


4
8
9 , R = H
9a , R = Br
10 , R = R1 = H
10a, R = H , R1 = C(CH3)2
10b , R = Ac , R1 = C(CH3)2
11
12
13 , R = H
13a, R = C(CH3)2
14 , R = R1 = R2 = H
14a , R = Ac , R1 = R2 = H
14b , R = R1 = H , R2 = C(CH3)2
14c , R = Ac , R1 = H, R2 = C(CH3)2
14d, R = R2 = H , R1 = CH3
14e, R = H , R1 = CH3, R2 = C(CH3)2
14f , R = Ac , R1 = CH3, R2 = C(CH3)2
14g, 3,20-diacetate of 14d
15 , R = OH, H
15a, R = O
2
16
17

SCHEME 2

corresponding 3-alcohol **14b**, was hydrolyzed with potassium hydroxide to an acid fraction, corresponding according to its ir spectrum primarily to the carboxy acetonide **14b**. The same product was obtained by treatment of the original acid fraction with potassium hydroxide. Methylation with diazomethane and acetylation of the combined acid fractions led to methyl 3β-acetoxy-9-oxo-17,20α-dihydroxy-9,12-seco-11-nor-5α-pregnan-12-oate 17,20-acetonide (**14f**), obtained in approximately 53% yield, and in 19% yield to methyl 3β,20α-diacetoxy-9-oxo-17-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oate (**14g**), arising from the portion of the ozonolysis product in which the acetonide protection had been hydrolyzed. Treatment of this product with hydrochloric acid gave in 50% yield the trihydroxy keto seco ester **14d** which was also obtained, in 85% yield, by hydrolysis with hydrochloric acid of the acetoxy acetonide **14f**. The over-all yield of that product from 3β-acetoxy-17,20α-dihydroxy-5α-pregn-9-en-12-one 17,20-acetonide (**13a**) amounted to 55%. Oxidation of the trihydroxy keto seco ester **14d** with sodium bismuthate gave in 98% yield crude, amorphous, methyl 3β-hydroxy-9,17-dioxo-9,12-seco-11-nor-5α-androstan-12-oate (**15**), fully characterized in its purified, crystalline form. The crude product was oxidized with Jones' reagent to afford in 72% yield (from the seco pregnanoate **14d**) pure methyl 3,9,17-trioxo-9,12-seco-11-nor-5α-androstan-12-oate (**15a**). Its over-all yield from the acetoxy dihydroxy pregnenone **13** amounted to 37%. A simpler and improved synthesis of the trioxo seco androstanoic ester **15a** started with oxidative ozonolysis of the unprotected 3β-acetoxy 17,20α-dihydroxy 9-unsaturated 12-ketone **13**, leading to a crude product (containing the acetoxy dihydroxy acid **14a** and some neutral material) which was immediately refluxed with methanolic potassium hydroxide. The resulting acidic material (mostly the trihydroxy acid **14**) was methylated with diazomethane and the crude trihydroxy seco ester **14d** thus obtained in approximately 70% yield was treated with sodium bismuthate and subsequently with Jones' reagent. Crystallization afforded in 40% yield (from the pregnenone **13**) the triketo androstanoic ester **15a**. This ester was ketalyzed in 92% yield with ethylene glycol and *p*-toluenesulfonic acid to the diketal **17**, which was

reduced in 88% yield with lithium aluminum hydride to the dihydroxy seco diketal **16**. Ring closure with tosyl chloride in pyridine gave in 75% yield the desired 11-oxa-5α-androstane-3,17-dione (2). In spite of the fact that in the 17,20-dihydroxylated series the introduction of the 9,11-double bond and the ozonolysis of the 9-unsaturated 12-ketone proceed less satisfactorily than in the case of a 17-non-oxygenated product, the over-all yield of the 11-oxa-androstanedione 2 in the pathway depicted in Scheme 2 is by more than 30% superior to the most efficient sequence summarized in Scheme 1.



SCHEME 3

For its conversion to 11-oxa-ethisterone (**1**), the 11-oxa-androstanedione **2** was transformed into the dienedione **18** (Scheme 3). By dehydrogenation with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) this product was obtained in 43% yield and was accompanied by the 1,2-monounsatured 11-oxa derivative **19**, isolated in 13% yield. Better yields (60%) of the diene dione **18** were realized by dibromination in acetic acid of the diketone **2** and by dehydrogenation with lithium bromide and lithium carbonate in dimethylformamide of the crude dibromide **2d**. The unsaturated diketones **18** and **19** were fully characterized by their elemental analyses and by their uv, ir, and nmr spectra (cf. Experimental). Selective hydrogenation with tris-(triphenylphosphine)rhodium chloride (23, 24) gave in

59% yield 11-oxa-4-androstene-3,17-dione (**20**), whose uv, ir, and nmr spectra showed the characteristic absorptions of a Δ^4-3-keto function, and which was transformed in 42% yield, by Djerassi's method (25) into the dienol ether **21** (26). Reaction with acetylene and potassium t-amylate (25), followed by hydrolysis with hydrochloric acid, gave in 54% yield 17α-ethynyl-17β-hydroxy-11-oxa-4-androsten-3-one (**1**), the 11-oxa analogue of ethisterone.

In preliminary assays, the Contraceptive Development Branch of the Center for Population Research of the National Institute of Child Health and Human Development, Bethesda, Md., found 17-ethynyl-11-oxatestosterone (**1**) to have upon subcutaneous administration, significant parenteral progestational activity in the Clauberg assay. Thus, at a dose level of 4.0 mg it had in the McPhail scale (6) an activity of 3.0 ± 0.1. Hence the diminution of progestational activity by replacement of the 11-methylene group by an oxygen atom seems far less pronounced in the case of ethisterone than in the case of progesterone (3b, 5), and drastically less than in the case of 17-acetoxyprogesterone (3b, 8). A full biological evaluation of 11-oxaethisterone (**1**) will be published at a later date.

EXPERIMENTAL

For the methods, materials, and instruments used for melting point determinations, chromatographies, and spectral measurements, see the introductory note to the Experimental of ref. 1 (p.768). The micro-analyses were performed by Ayerst Laboratories, Montreal, Canada, under the direction of Dr. G. Schilling, by Dr. C. Daesslé, Montreal, and by the Dr. F. Pascher Laboratories, Bonn, Germany.

3,3-Dimethoxy-11-oxa-5α-pregnan-20-one (5b). A solution of 4.0 g of 11-oxa-5α-pregnane-3,20-dione (**5**) (4, 5), mp 213-215°, in 300 mL of absolute methanol was stirred at room temperature for 18 h with 50 mg of p-toluenesulfonic acid. After reduction in vacuo to half of its volume, the solution was poured into cold water and the mixture was extracted with ether. The organic solution was washed with a saturated sodium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of the solvent gave 4.4 g of a solid, mp 87-91°, which upon crystallization from ether-hexane gave 3.54 g (83%) of **3,3-dimethoxy-11-oxa-5α-pregnan-20-one** (**5b**), mp 92-93°. A sample was recrystallized twice from ether-hexane for analysis; mp 97.5-98.5°; $[\alpha]_D^{25}$ +11.6 (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1710 (20-ketone), 1110, 1070, and 1050 cm^{-1} (ether absorptions); δ (90 MHz) 0.72 (s, 3 H, 18-CH_3), 0.87 (s, 3 H, 19-CH_3), 1.99 (s, 3 H, 21-CH_3), 3.03 (s, 3 H) and 3.10 (s, 3 H) (3-OCH_3 absorptions), 3.28 (d, J = 11 Hz, 1 H) and 3.94 (d, J = 11 Hz, 1 H) (12-H_2).

Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.65; H, 9.88.

3,3-Dimethoxy-17-hydroxy-11-oxa-5α-pregnan-20-one (6b) . At −5°, dry oxygen was passed through a solution of 750 mg of sodium hydride (50% oil dispersion) in 10 mL of anhydrous t-butanol, 25 mL of dimethylformamide, and 2.0 mL of triethyl phosphite. A solution of 4.0 g of 3,3-dimethoxy-11-oxa-5α-pregnan-20-one **(5b)**, mp 92-93°, in 20 mL of anhydrous tetrahydrofuran was added and oxygen was again passed through the mixture for 1 h, at −5°. Nitrogen was passed through the solution of the thus-formed **3,3-dimethoxy-17-hydroperoxy-11-oxa-5α-pregnan-20-one (6a)** and a solution of 500 mg of sodium hydroxide in 5 mL of water and 10 mL of methanol was added. The mixture was stirred under nitrogen at room temperature for 1 h and was poured into ice water. The product was extracted with ethyl acetate, the organic layer was washed with water and was dried over sodium sulfate. Evaporation of the solvent gave 5 g of an oily residue which was chromatographed on 150 g of aluminum oxide, activity III. Elutions with benzene afforded 1.9 g (45%) of pure **3,3-dimethoxy-17-hydroxy-11-oxa-5α-pregnan-20-one (6b)**, mp 157-159°. A portion was recrystallized twice from methylene chloride-ether for analysis; mp 159-160°; $[\alpha]_D^{25}$ + 8.8 (c, 1.000 in $CHCl_3$); ν_{max} (KBr) 3420 (17-OH), 1700 (20-ketone), 1100, 1080, and 1050 cm^{-1} (acetal absorptions); δ (60 MHz) 0.82 (s, 3H, 18-CH_3), 0.91 (s, 3 H, 19-CH_3), 2.22 (s, 3 H, CH_3-CO), 3.13 (s, 3 H) and 3.17 (s, 3 H) (3-OCH_3 absorptions), 3.62 (s, unresolved, 2 H, 12-H_2).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.37; H, 9.36.

3β-Acetoxy-16,17α-epoxy-5α-pregnane-12,20-dione (8). To a solution of 18.62 g of 3β-acetoxy-5α-pregn-16-ene-12,20-dione **(4)**, mp 176-178°, in 85 mL of chloroform and 215 mL of methanol were added, with stirring, at 5°, 47 mL of a 28% hydrogen peroxide solution and subsequently, over a period of 1 h, 28 mL of aqueous 5 N sodium hydroxide, the temperature of the reaction mixture being kept below 15°. The solution was stored for 18 h at room temperature, water was added and the precipitate was extracted with chloroform. The organic layer was washed with water, was dried over sodium sulfate and the solvents were evaporated in vacuo. The solid residue was dissolved in 16 mL of pyridine and heated for 30 min with 8 mL of acetic anhydride on a steam bath. After cooling, the product was poured on crushed ice and the crystalline precipitate was filtered, washed and dried to give 18.17 g (93% yield) of the epoxide **8**, mp 228-230° [lit. (13) 234-235°]; ν_{max} (KBr) 1740 (acetate), 1715 (12-and 20-ketones), 1245 (acetate), 1035 cm^{-1} (epoxide).

Batches of 100 g of the unsaturated ketone **4** were treated in an analogous fashion with analogous results.

3β-Acetoxy-17-hydroxy-5α-pregnane-12,20-dione (9). To a solution of 5.5 g of epoxide **8**, mp 228-230°, in 55 mL of methylene chloride, was added at 15° 6 mL of a 30% hydrogen bromide solution in acetic acid. The mixture was kept at room temperature for 2 h and was washed with water, till neutral. The solvent was removed in vacuo, the temperature not exceeding 35°. The crystalline residue (6.6 g) represented **16β-bromo-3β-acetoxy-17-hydroxy-5α-pregnane-12,20-dione (9a)**, ν_{max} (KBr) 3500 (17-OH), 1740 (acetate), 1720 (epoxy ketone), 1260 cm^{-1} (acetate). The product (positive bromine test) was dissolved without purification in 135 mL of methanol containing 5 mL of water. Raney nickel (28 g) was added and the mixture was refluxed with vigorous stirring for 4 h and was filtered while still hot. The filtrate was concentrated to turbidity and extracted with ether. The organic layer was washed with water and was dried over sodium sulfate. Removal of the solvent gave 5.4 g of a solid which upon crystallization from ether-petroleum ether gave 4.97 g (90% yield), of **3β-acetoxy-17-hydroxy-5α-pregnane-12,20-dione (9)**, mp 129-130° [lit. (13) 129-130°]; ν_{max} (KBr) 3530 (hydroxyl), 1745 (acetate), 1720 (12,20-ketones), 1255 cm^{-1} (acetate).

Working with large quantities, it was advantageous to reduce the amounts of solvents and of Raney nickel. Thus, 100 g of epoxide **8** was treated in 600 mL of dichloromethane with 150 mL of a 30% hydrogen bromide solution in acetic acid. The solution of the

bromohydrin **9a** was washed with water, a cold sodium bicarbonate solution, and with water, and was worked up as above. The purified bromohydrin was taken up in 1.5 L of methanol containing 5% of water and was refluxed with approximately 60 g of Raney nickel [100 mL by volume of settled Raney nickel W_2, prepared according to Mozingo (29)]. The usual work up gave 88 g (88% yield) of acetoxy hydroxy diketone 9, mp 127-128°.

3β,17-Dihydroxy-12-ethylenedioxy-5α-pregnan-20-one (12). A solution of 10 g of the acetoxy hydroxy diketone 9, mp 129-131°, in 50 mL of absolute methylene chloride was stirred at room temperature for 72 h with 75 mL of ethylene glycol and 50 mL of boron trifluoride etherate, the mixture was poured into cold water, and the precipitate was extracted with methylene chloride. The organic layer was washed with a sodium bicarbonate solution and with water and was dried over sodium sulfate. Removal of the solvent gave 10.9 g of an amorphous material, dissolved in 330 mL of methanol, and was refluxed with a solution of 10.7 g of potassium carbonate in 77 mL of water for 1.5 h. The mixture was cooled, poured into cold water and the precipitate was extracted with methylene chloride. The organic layer was washed and dried over sodium sulfate. Removal of the solvent gave a crystalline material (10.0 g) which, upon recrystallization from methylene chloride-hexane, afforded 8.1 g (78%) of the 12-monoketal **12**, mp 258-259°. A sample was recrystallized twice from methylene chloride-hexane for analysis; colorless plates, mp 261-262°; $[\alpha]_D^{25}$ +45.5 (c, 1.120 in $CHCl_3$); ν_{max} (KBr) 3440 and 3320 (3,17-hydroxyl groups), 1710 (20-ketone) 1060 cm^{-1} (ketal); δ (60 MHz) 0.78 and 0.86 (18- and 19-CH_3), 2.24 (methyl ketone), 4.15 (s, 4 H) (ethylene ketal), 1.62 (s, 1 H) and 5.81 (s, 1 H) (exchanged with D_2O) (OH groups).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 69.99; H, 9.21.

Analogous results were obtained under analogous conditions with 100-g batches of acetoxy hydroxy ketone **9**.

12-Ethylenedioxy-5α-pregnane-3β,17,20α-triol (11). To a solution of 7.4 g of ketone **12**, mp 258-259°, and of 5 g of sodium hydroxide in 900 mL of methanol, a solution of 2 g of sodium borohydride in 200 mL of 50% methanol, was added and the mixture was stirred for 72 h at room temperature. The product was concentrated in vacuo to 500 mL and was cooled; acetic acid was added until the mixture was only slightly alkaline. The product was washed with water and was dried. Evaporation of the solvent gave 7.45 g of a crude product which upon recrystallization from acetone afforded 5.1 g (68.6% yield) of the triol **11**, mp 231-232°. The mother liquors (2.37 g) were chromatographed on 100 g of aluminum oxide, activity V. Elutions with benzene-ether (1:1) gave another 1.74 g (23.1%) of triol **11**, mp 231-232° (total yield: 91.7%). A sample was recrystallized from acetone for analysis; colorless needles, mp 231-232°; $[\alpha]_D^{25}$ +21.2 (c, 1.040 in $CHCl_3$); ν_{max} (KBr) 3500, 3440, 3360 (triol); δ (60 MHz) 0.82 (18-CH_3), 0.96 (19-CH_3), 4.10 (s, 4 H) (ethylene ketal), 2.64 (s, 1 H) and 4.41 (s, 2 H, unresolved) (exchanged with D_2O) (OH-groups).

Anal. Calcd For $C_{21}H_{38}O_5$: C, 70.01; H, 9.71. Found: C, 69.99; H, 9.77.

Under analogous conditions batches of approximately 70 g of ketone **12** were transformed with analogous results into the triol **11**.

3β,17,20α-Trihydroxy-5α-pregnan-12-one 17,20α-Acetonide (10a) (a) A solution of 4.0 g of trihydroxy ketal **11**, mp 231-232°, in 160 mL of absolute acetone was refluxed for 40 min with 460 mg of p-toluenesulfonic acid. The volume was reduced in vacuo to approximately 50 mL and the product was poured into an iced sodium bicarbonate solution. The precipitate was extracted with methylene chloride and the organic solution was washed with water and was dried over sodium sulfate. Removal of the solvent gave 4.0 g of an amorphous material which was adsorbed on 200 g of aluminum oxide, activity V. Elutions with benzene-ether (4:1) afforded 3.54 g (88% yield) of pure keto hydroxy acetonide **10a**, mp 168-169°. A sample was recrystallized twice from ether-hexane for analysis; colorless

needles, mp 168-169°; $[\alpha]_D^{25}$ +9.9 (c, 1.110 in $CHCl_3$); ν_{max} (KBr) 3340 (hydroxyls) 1045, 1020 cm^{-1} (acetonide); δ (60 MHz) 0.88 (18-CH_3), 0.92 (19-CH_3), 1.15 (s, 1 H, exchanged with D_2O) (OH), 1.26 (d, 3 H, J = 6 Hz) (21-CH_3), 1.39 (s, 3 H) and 1.44 (s, 3 H) (acetonide-CH_3), 4.80 (q, 1 H, J = 6 Hz) (20-H).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.82; H, 9.74.

(b) When large quantities were employed, the keto acetonide **10a** was accompanied by some 12-oxo 3,17,20-triol **10**, the 12-ketal group having been removed but the glycol not having been totally transformed into an acetonide. As described below (b) the acetoxy keto acetonide **10b** could be obtained in excellent yield from ketal **12** without purification of the intermediates.

3β-Acetoxy-17,20α-dihydroxy-5α-pregnan-12-one 17,20α-Acetonide (10b). (a) **From the Hydroxy Keto Acetonide 10a.** A quantity of 3.3 g of the hydroxy keto acetonide **10a**, mp 168-169°, was acetylated in the usual fashion, at room temperature, with 5 mL of acetic anhydride in 10 mL of pyridine, affording 3.6 g (98% yield) of pure 3β-acetoxy-17,20α-dihydroxy-5α-pregnan-12-one 17,20α-acetonide **10b**, mp 189-190°. A sample was recrystallized from ether-hexane for analysis; colorless plates, mp 190-191°; $[\alpha]_D^{25}$ +8.7 (c, 0.805 in $CHCl_3$); ν_{max} (KBr) 1735 (acetate); 1705 (ketone), 1240 (acetate), 1040, 1030, 1020 cm^{-1} (acetonide); δ (60 MHz) 0.88 (s) (18-CH_3), 0.92 (s) (19-CH_3), 1.25 (d, 3 H, J = 6 Hz) (21-CH_3), 1.35 (s, 3 H) and 1.44 (s, 3 H) (acetonide-CH_3), 2.0 (s, 3 H) (acetate), 4.86 (q, 1 H, J = 6 Hz) (20-H).

Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.40; H, 9.29.

(b) **From the Trihydroxy Ketal 11, in Large Quantities, without Purification of the Intermediates.** A solution of 145 g of trihydroxy ketal **11**, mp 227-229°, and of 10 g of p-toluenesulfonic acid in 2 L of absolute acetone was refluxed for 4 h. The volume was reduced to 200 mL under reduced pressure, and the solution was poured into an iced sodium bicarbonate solution. The precipitate was extracted with dichloromethane, the organic layer was washed with water and was dried over sodium sulfate. Removal of the solvent gave a solid which was acetylated in 200 mL of pyridine with 100 mL of acetic anhydride at room temperature over 14 h. The solution was poured into water, the precipitate was filtered, washed and dried to give 120 g (84% yield) of the **acetoxy keto acetonide 10b**, mp 189-190°, identified in the usual way by comparison with an authentic sample (see above). The filtrate was extracted with methylene chloride, the organic solution was washed with water, dried over sodium sulfate and the solvent was removed. According to the ir and nmr spectra, the residue (15 g) was mostly composed of a mixture of the acetoxy acetonide **10b** and of only partly acetylated triol **10**. In order to obtain a homogeneous product, the mixture was refluxed for 3 h with 50 mL of a 1 N methanolic potassium hydroxide solution, cooled and diluted with 1 L of water, and extracted with methylene chloride. The organic layer was washed with water and was dried over sodium sulfate. Removal of the solvent gave a gum (13 g), representing crude **trihydroxy ketone 10**, ν_{max} (KBr) 3575, 3410, 3325 (hydroxyls, two associated), 1694 and 1689 (split keto band), 1150, 1070, 1050 cm^{-1} (OH), which was dissolved in 500 mL of absolute acetone and stirred for 2 h with a few drops of perchloric acid, at room temperature. The volume was reduced to 100 mL and 800 mL of water was added. The product was extracted with methylene chloride, the organic solution was washed with a cold sodium bicarbonate solution and with water and was dried over sodium sulfate. Removal of the solvent gave a solid which was dissolved in 30 mL of pyridine and acetylated with 25 mL of acetic anhydride at room temperature to give 13 g of the acetoxy keto acetonide **10b**. Total yield of that product from the trihydroxy ketal **11**: 138 g (90%).

3β-Acetoxy-17,20α-dihydroxy-5α-pregn-9(11)-en-12-one (13). To a solution of 3.5 g of the acetoxy keto acetonide **10b**, mp 190-191°, in 35 mL of a 0.0006 N hydrogen chloride solution in acetic acid, 2.7 g of selenium dioxide was added. The mixture was refluxed for 20 h, cooled, diluted with 600 mL of ether, and filtered over sodium sulfate. The

filtrate was washed with water, iced dilute hydrochloric acid, a cold sodium bicarbonate solution, again with water, and was dried over sodium sulfate. Removal of the solvent gave 3.1 g of a yellow, amorphous product which was adsorbed on 60 g of aluminum oxide, activity III. Elutions with benzene, benzene-ether mixtures, and ether, afforded 1.4 g (45%) of the unsaturated ketone **13**, mp 230-231°. A sample was recrystallized twice from methylene chloride-ether for analysis; colorless prisms, mp 230-231°; $[\alpha]_D^{25}$ +41.0 (c, 1.000 in $CHCl_3$); ν_{max} (KBr) 3540 and 3290 (hydroxyls), 1730 (acetate), 1635 and 1595 ($\Delta^{9(11)}$-12-keto doublet), 1245 cm^{-1} (acetate); δ (60 MHz) 0.92 (s) (18-CH_3), 1.10 (s) (19-CH_3), 1.16 (d, 3 H, J = 6 Hz) (21-CH_3), 2.02 (s, 3 H) (acetate), 3.93 (q, 1 H, J = 6 Hz) (20-H), 2.90 (s, 1 H, exchanged with D_2O) and 5.66 (s, 1 H, exchanged with D_2O) (OH-groups), 5.90 (s, 1 H) (11-H).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.64; H, 8.78.

Better yields were obtained with large batches. Thus, 75 g of the keto acetonide **10b** was transformed under analogous conditions into 41.8 g (62%) of the unsaturated ketone **13**, mp 227-228°.

3β-Acetoxy-17,20α-dihydroxy-5α-pregn-9(11)-en-12-one 17,20α-Acetonide (13a). To a solution of 575 mg of the dihydroxy ketone **13**, mp 230-231°, in 25 mL of absolute acetone, two drops of perchloric acid were added and the mixture was stirred at room temperature for 3 h and was poured into an iced sodium bicarbonate solution. The precipitate was extracted with methylene chloride and the organic layer was washed with water and was dried over sodium sulfate. Removal of the solvent afforded 630 mg (95%) of a white, crystalline product, mp 251-254°. A sample was recrystallized twice from methylene chloride-ether for analysis; colorless plates, mp 255-257°; $[\alpha]_D^{25}$ +44.3 (c, 0.700 in $CHCl_3$); λ_{max}^{EtOH} 238 nm (log ε 4.0); ν_{max} (KBr) 1735 (acetate), 1670 and 1600 ($\Delta^{9(11)}$-12-keto doublet), 1245 (acetate), 1050, 1035, 1020 cm^{-1} (acetonide); δ (60 MHz) 0.82 (s) (18-CH_3), 1.08 (s) (19-CH_3), 1.30 (d, 3 H, J = 6 Hz) (21-CH_3), 1.42 (s, 6 H, unresolved) (acetonide-CH_3), 2.05 (s, 3 H) (acetate), 5.04 (q, 1 H, J = 6 Hz) (20-H), 5.78 (s, 1 H) (11-H).

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.88; H, 8.92.

Methyl 3β-Acetoxy-17,20α-dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate 17,20α-Acetonide (14f) and Methyl 3β,20α-Diacetoxy-17-hydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (14g). At -40 to -50° and for a period of 3 h, a stream of oxygen containing 0.65% of ozone was passed at a flow rate of 360 L/h through a solution of 3 g of the 9-unsaturated ketone **13a**, mp 255-257°, in 100 mL of ethyl acetate. Subsequently 2 mL of a 30% hydrogen peroxide solution and 4 mL of water were added and the mixture was stirred at room temperature for 16 h. The product was diluted with ether and the solution was extracted four times with a 2 N sodium hydroxide solution (in toto 100 mL) and was washed with water. After drying over sodium sulfate, the solvent was evaporated to give 1.1 g of the Neutral Fraction (crude anhydrides of **14b** and **14c**), ν_{max} (KBr) 3480-3410 (weak OH absorption), 1780 (anhydride absorption), 1740 (acetate), 1712 (ketone), 1255 (acetate), 1160 (anhydride) 1100, 1058, 1028 cm^{-1} (acetonide); all methyl groups visible in the nmr. The sodium hydroxide extracts were combined with the first water washings and acified with 6 N sulfuric acid to the Congo-blue reaction. The solution was saturated with sodium chloride and was extracted with ether. The ethereal solution was washed with brine and dried over sodium sulfate. Removal of the solvent afforded 1.7 g of the Acid Fraction I (chiefly **14b** and **14c**), ν_{max} (KBr) 3500-2650 (OH and COOH), 1812 [weak absorption, impurity (anhydride?)], 1725-1705 (COOH, acetate, 9-ketone), 1250 (acetate), 1015 and 1040 cm^{-1} (acetonide).

The Neutral Fraction was refluxed on a steam bath with 30 mL of a 1 N potassium hydroxide solution in 50% aqueous methanol for 30 min. The mixture was concentrated and extracted with ether to remove remaining neutral material. The aqueous alkaline solution was acified with 6 N sulfuric acid to the Congo-blue reaction, the product was saturated

with sodium chloride and the organic product was extracted with ether. The ethereal solution was washed with brine and dried over sodium sulfate. Removal of the solvent gave 800 mg of Acid Fraction II (chiefly **14b**), ν_{max} (KBr) 3400-2600 (broad, COOH and OH), 1700 (COOH and 9-ketone), 1082, 1046, and 1020 cm^{-1} (acetonide).

The combined Acid Fractions I and II were dissolved in 120 mL of absolute ether and 60 mL of absolute methanol and treated with 90 mL of a 3% ethereal diazomethane solution at 0°. The product was allowed to warm up to room temperature and was left 14 h at 22°. The excess reagent was destroyed with acetic acid and the solvent was evaporated *in vacuo*. This crude ester was dissolved in 30 mL of pyridine and treated with 15 mL of acetic anhydride on a steam bath for 1 h. After cooling, 15 mL of methanol was added carefully. The solution was concentrated and poured into ice water. The organic product was extracted with ether and the ethereal solution was washed with a cold sodium bicarbonate solution and with water and was dried over sodium sulfate. Removal of the solvent gave 2.6 g of a crude material which was crystallized from ether–hexane to give 800 mg of **methyl 3β-acetoxy-17,20α-dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate 17,20α-acetonide (14f)**, mp 133-134°. The mother liquors (1.8 g) were adsorbed on 60 g of aluminum oxide, activity III. Crystallizations from ether–hexane of the petroleum ether–benzene (1:1) and pure benzene eluates gave another 900 mg of the acetoxy keto ester **14f**, mp 133-134° (total yield from the unsaturated ketone **13a** : 53%). This product was recrystallized from ether–hexane for analysis; colorless plates; mp 133-134°; $[\alpha]_D^{25}$ -62.5 (c, 1.008 in $CHCl_3$); ν_{max} (KBr) 1720 (acetate and methyl ester), 1705 (9-ketone), 1245 (multiple ester band), 1050, 1030 cm^{-1} (ketal); δ (60 MHz) 0.97 (s) (18-CH_3), 1.13 (s) (19-CH_3), 1.20 (s) and 1.38 (s) (acetonide-CH_3), 1.28 (d, J = 6 Hz) (21-CH_3), 2.01 (s, 3 H) (acetate), 3.75 (s, 3 H) (ester-CH_3), 4.47 (q, 1 H, J = 6 Hz) (20-H).

Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 66.99; H, 8.67.

Crystallization from ether–hexane of the ether eluates of the above-mentioned chromatogram gave 600 mg (19% from the unsaturated ketone **13a**) of **methyl 3β,20α-diacetoxy-17-hydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (14g)**, mp 165-166°. A sample was recrystallized twice from ether–hexane for analysis; colorless needles, mp 165-166°; $[\alpha]_D^{25}$ -38.8 (c, 1.030 in $CHCl_3$); ν_{max} (KBr) 3400 (hydroxyl), 1738 (acetates and methyl ester), 1712 (9-ketone), 1250 cm^{-1} (multiple ester band); δ (60 MHz) 0.68 (s) (18-CH_3), 0.85 (s) (19-CH_3), 1.17 (d, J = 6 Hz) (21-CH_3), 1.95 (s, 3 H) and 2.01 (s, 3H) (acetates), 3.77 (s, 3 H) (ester-CH_3), 4.98 (q, 1 H, J = 6 Hz) (20-H), 5.43 (s, 1 H, exchanged with D_2O) (OH).

Anal. Calcd for $C_{25}H_{38}O_8$: C, 64.36; H, 8.21. Found: C, 64.41; H, 8.09.

Methyl 3β,17,20α-Trihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (14d). (a) **From Methyl 3β-Acetoxy-17,20α-dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate 17,20α-Acetonide (14f).** A solution of 8.1 g of the acetoxy acetonide **14f**, mp 132-134°, in 400 mL of methanol containing 2 mL of concentrated hydrochloric acid, was refluxed for 5 h, concentrated and extracted with methylene chloride. The organic solution was washed with brine, dried over sodium sulfate, and the solvent was removed. The amorphous residue (6.4 g) gave upon crystallization from methylene chloride–ether 5.7 g (85% yield) of the trihydroxy keto ester **14d**, mp 159-160°. A sample was recrystallized from methylene chloride–ether for analysis; colorless prisms, mp 159-160°; $[\alpha]_D^{25}$ -96.5 (c, 0.860 in $CHCl_3$); ν_{max} (KBr) 3390 (broad band of 3,17,20-hydroxyl groups), 1718 cm^{-1} (ester); δ (60 MHz) 0.99 (s) (18-CH_3), 1.17 (d, J = 6 Hz) (21-CH_3), 1.19 (s) (19-CH_3), 2.2 (broad, 2 H, exchanged with D_2O) and 5.85 (s, 1 H, exchanged with D_2O) (3,17,20-hydroxyls), 3.70 (s, 3 H) (ester-CH_3).

Anal. Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 66.11; H, 8.95.

(b) **From Methyl 3β,20α-Diacetoxy-17-hydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (14g).** Hydrolysis of 2.0 g of the diacetoxy hydroxy keto ester **14g** under identical conditions to those described for the hydrolysis of the acetoxy acetonide **14f**, gave 1.4 g of a crude product which, upon crystallization from methylene chloride–ether, furnished 700 mg (50% yield) of pure trihydroxy keto ester **14d**, mp 159-160°, identified by compa-

rison with a sample of the above-described product by the determination of a mixture melting point and by the comparison of the infrared and nmr spectra.

Methyl 3,9,17-Trioxo-9,12-seco-11-nor-5α-androstan-12-oate (15a). (a) **From the Trihydroxy Keto Ester 14d.** A solution of 510 mg of the trihydroxy keto ester **14d**, mp 159-160°, in 400 mL of 50% acetic acid was stirred at room temperature with 9 g of sodium bismuthate for 22 h and was subsequently filtered. The filtrate was extracted with methylene chloride, the organic layer was washed with a sodium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of the solvent afforded 440 mg (98%) of an amorphous material, representing crude **methyl 3β-hydroxy-9,17-dioxo-9,12-seco-11-nor-5α-androstan-12-oate (15).** A sample was crystallized from methylene chloride-ether for analysis; mp 202-203°; $[\alpha]_D^{25}$ +38.6 (c, 0.700 in $CHCl_3$); ν_{max} (KBr) 3520 (OH), 1750 (17-ketone), and 1710 cm^{-1} (broad band of 9-ketone and methyl ester); δ (60 MHz) 0.97 (s) (18-CH_3), 1.15 (s) (19-CH_3), 1.95 (s, 1 H, exchanged with D_2O) (3-OH), 3.73 (s, 3 H) (ester-CH_3).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.81; H, 8.52.

The crude product was dissolved without purification in 200 mL of absolute acetone and was stirred with 2 mL of Jones' reagent (30) at 0° for 15 min. The product was poured into water and the mixture was extracted with methylene chloride. The organic solution was washed with a sodium bicarbonate solution and with brine and was dried over sodium sulfate. Removal of the solvent afforded 440 mg of an amorphous material which, upon crystallization from methylene chloride-ether, gave 300 mg (72% yield from the trihydroxy ester **14d**) of pure **methyl 3,9,17-trioxo-9,12-seco-11-nor-5α-androstan-12-oate (15a)**, mp 187-188°; a sample was recrystallized from methylene chloride-ether for analysis; colorless prisms, mp 187-188°, $[\alpha]_D^{25}$ +20.9 (c, 0.910 in $CHCl_3$); ν_{max} (KBr) 1745 (17-ketone), 1710 cm^{-1} (broad band of 3,9-ketones and of methyl ester); δ (60 MHz) 0.99 (s) (18-CH_3), 1.35 (s) (19-CH_3), 3.73 (s, 3 H) (ester-CH_3).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.18; H, 7.84.

(b) **From 3β-Acetoxy-17,20α-dihydroxy-5α-pregn-9(11)-en-12-one (13) without Purification of the Intermediates.** At -40°, a stream of oxygen containing 0.65% of ozone was passed at a flow rate of 360 L/h through a solution of 5 g of the unsaturated acetoxy dihydroxy 12-ketone **13** in 350 mL of ethyl acetate, over a period of 3 h. Subsequently 10 mL of a 30% hydrogen peroxide solution and 5 mL of water were added and the mixture was stirred at room temperature for 16 h. After dilution with ethyl acetate, the solution was washed with 10% potassium iodide and sodium thiosulfate solutions, and with brine, and was dried over sodium sulfate. Removal of the solvent gave a gum which was dried by repeated evaporation of its benzene solution. The product was dissolved in 300 mL of 2 N methanolic potassium hydroxide and refluxed for 3 h. After cooling, the solution was diluted with 200 mL of water and extracted with ethyl acetate, in order to remove the remaining neutral material. The alkaline portion was carefully acidified with cold 6 N sulfuric acid to the Congo-blue reaction, and the solution was saturated with sodium chloride and extracted with ethyl acetate. The organic layer was washed with brine and was dried over sodium sulfate. Removal of the solvent gave a gum which was dried by repeated evaporation of its benzene solution and dissolved in 200 mL of absolute methanol and 100 mL of absolute ether. To this solution 350 mL of a 3.1% ethereal diazomethane solution was added at 0° and the mixture was allowed to warm to room temperature and was kept at that temperature for 14 h. The excess reagent was destroyed with acetic acid; the product was taken to dryness and dissolved in ether. The ethereal solution was washed with a sodium bicarbonate solution and with brine and was dried over sodium sulfate. Removal of the solvent *in vacuo* gave 3.6 g (70%) of crude **trihydroxy ester 14d** which was taken up without purification in 1.4 L of 50% aqueous acetic acid and treated with 60 g of sodium bismuthate. The mixture was stirred for 24 h at room temperature and was filtered; the filtrate was extracted with methylene chloride; the organic layer was

washed with a sodium bicarbonate solution and with brine and was dried. Removal of the solvent left 2.2 g of a thick gummy product which was dissolved in 50 mL of absolute acetone and oxidized with 8 mL of Jones' reagent at 0°, until a yellowish-brown color persisted in the supernatant. Water was added and the mixture was extracted with methylene chloride. The organic layer was washed with sodium bicarbonate and brine, was dried over sodium sulfate and the solvent was removed. The crude product (1.75 g) gave upon crystallization from methylene chloride–ether 1.25 g (40% yield from the dihydroxy acetoxy enone **13**) of pure triketone **15a**, mp 185–186°, identical with the product prepared as described under (a).

Methyl 3,17-bis-Ethylenedioxy-9-oxo-9,12-seco-11-nor-5α-androstan-12-oate (17). A solution of 300 mg of methyl 3,9,17-trioxo-9,12-seco-11-nor-5α-androstan-12-oate **(15a)**, mp 187–188°, in 100 mL of absolute benzene was refluxed with stirring for 24 h with 5 mL of ethylene glycol and 70 mg of p-toluenesulfonic acid, with repeated removal of the moist benzene formed. Subsequently the solution was cooled and poured into a cold sodium bicarbonate solution and the precipitate was extracted with methylene chloride. The organic solution was washed with water and was dried over sodium sulfate. Removal of the solvent afforded 350 mg (92% yield) of an amorphous product which was crystallized from ether–hexane to give 270 mg (71% yield) of pure diketal **17**, mp 86–88°. A sample was recrystallized from ether–hexane for analysis; colorless needles, mp 86–87°; $[\alpha]_D^{25}$ −27.7 (c, 0.830 in $CHCl_3$); ν_{max} (KBr) 1725 (methyl ester), 1710 (9-ketone), 1070 cm^{-1} (diketal); δ (60 MHz) 0.90 (s) (18-CH_3), 1.13 (s) (19-CH_3), 3.75 (s, 3 H) (ester-CH_3), 3.85 (s, 8 H) (bis-ethylene ketal).

Anal. Calcd for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.09; H, 8.36.

3,17-bis-Ethylenedioxy-9,12-seco-11-nor-5α-androstane-9β,12-diol (16). To a solution of 240 mg of the monoketo seco ester 17, mp 86–87°, in 50 mL of absolute tetrahydrofuran, 500 mg of lithium aluminum hydride was carefully added and the mixture was refluxed with stirring for 4 h. The excess lithium aluminum hydride was carefully decomposed by addition of ice and the white slurry was filtered. The filtrate was taken to dryness and the amorphous product (230 mg) was crystallized from ether–hexane to give 190 mg (88% yield) of pure dihydroxy ketal **16**, mp 147–148°; a sample was recrystallized from ether–hexane for analysis; colorless needles, mp 147–148°, $[\alpha]_D^{25}$ +32.0 (c, 0.720 in $CHCl_3$); ν_{max} (KBr) 3300 (broad diol band), 1030 cm^{-1} (diketal); δ (90 MHz) 0.75 (s) (18-CH_3), 2.97 (d, 1 H, J = 10 Hz) (9α-H), 3.35 (broad, 1 H, exchanged with D_2O) and 3.63 (s, 1 H, exchanged with D_2O) (9,12-OH), 3.22 (d, 1 H, J = 12 Hz) and 3.63 (d, 1 H, J = 12 Hz) (12-H_2).

Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.56; H, 9.27.

11-Oxa-5α-androstane-3,17-dione (2). (a) **From 3β-Hydroxy-11-oxa-5α-pregnan-20-one (5c) by a Baeyer–Villiger Degradation.** A quantity of 260 mg of 3β-hydroxy-11-oxa-5α-pregnan-20-one (**5c**) was acetylated in the usual fashion with 1 mL of acetic anhydride in 2 mL of pyridine. The resulting crude **acetate 5d** [ν_{max} (KBr) 1730 (acetate), 1710 (ketone), 1265 and 1248 cm^{-1} (split acetate band); δ (60 MHz) 0.72 (s, 18-CH_3), 0.92 (s, 19-CH_3), 1.97 (s, methyl ketone), 2.01 (s, acetate), 3.35 (d, J = 10 Hz) and 4.05 (d, J = 10 Hz) (12-H_2), 4.62 (m, 3α-H)] was dissolved in 10 mL of chloroform and treated with 550 mg of m-chloroperbenzoic acid at room temperature for 5 days. Every 24 h another 150 mg of m-chloroperbenzoic acid was added. The product was diluted with chloroform, the organic solution was washed with potassium iodide, potassium thiosulfate, and sodium bicarbonate solutions and with water, and was dried over sodium sulfate. The solvent was removed in vacuo. The crude reaction product (131 mg), representing a complex mixture, was refluxed for 30 min with 20 mL of 1 N methanolic potassium hydroxide. After cooling, the product was poured into water and the mixture was extracted with methylene chloride. The organic solution was washed with water, dried over sodium sulfate and the solvent was

evaporated. There remained an oily product (150 mg) which was dissolved without further purification in 5 mL of absolute acetone and treated with 0.2 mL of Jones' reagent at 0°. The mixture was stirred for 30 min, the excess oxidizing agent was decomposed with methanol, water was added and the organic product was extracted with ether. The ethereal layer was washed with water, with a saturated sodium bicarbonate solution, and again with water, was dried over sodium sulfate and taken to dryness. Thin-layer chromatography on silica gel (benzene–ethyl acetate 8:2) of the crude product showed two main bands, the less polar of which gave upon extraction with ethyl acetate, containing 5% of methanol, crystalline **11-oxa-5α-androstane-3,17-dione (2)**, mp 162.5–164.5°. Recrystallization afforded 30 mg (13.8% yield) of purified product, mp 165.5–168.5°, which showed no depression of melting point with an authentic sample and the infrared spectrum of which was superimposable on that of the product prepared as described under (c). In another experiment, a 25% yield of the degradation was realized.

(b) **From 3-Ethylenedioxy-11-oxa-5α-pregnan-20-one (5a) by the Procedure of Sidall et al (10).** A solution of 400 mg of 3-ethylenedioxy-11-oxa-5α-pregnan-20-one (**5a**) (8), mp 143–144°, in 3 mL of tetrahydrofuran was added to a solution of 500 mg of potassium in 10 mL anhydrous t-butanol, and oxygen was passed through the solution at 0–7° for 70 min. The oxygen flow was replaced by a nitrogen stream and the mixture was heated to 60–70° for 45 min. After cooling, the product was poured into ice water and the precipitate was extracted with methylene chloride. The organic solution was washed with water and was dried over sodium sulfate. Removal of the solvent gave 340 mg of an oil which was chromatographed on 10 g of aluminum oxide, activity III. Elutions with benzene, benzene–ether mixtures, and ether, afforded 119 mg (32% yield) of crystalline **3-ethylenedioxy-11-oxa-5α-androstan-17-one (2a)**, mp 159–160°; ν_{max} (KBr) 1740 (17-ketone) 1102, 1070, and 1050 cm^{-1} (ether linkages); δ (60 MHz) 0.93 (s, 18-CH_3), 1.04 (s, 19-CH_3), 3.35 (d, J = 10.5 Hz) and 3.94 (d, J = 10.5 Hz) (12-H_2), 3.96 (s, 4 H, ethylene ketal).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.42; H, 8.92.

A solution of 98 mg of the above described 3-ethylenedioxy-11-oxa-5α-androstan-17-one (**2a**), mp 159–160°, and of 15 mg of p-toluenesulfonic acid in 20 mL of absolute acetone was refluxed for 3 h. The product was cooled, extracted with methylene chloride and the organic solution was washed with a sodium bicarbonate solution and with water, was dried over sodium sulfate and the solvent was removed. Thus, 84 mg of authentic **11-oxa-5α-androstane-3,17-dione (2)** was obtained. The comparison was made by the usual means with the product described under (c).

(c) **From 3,3-Dimethoxy-17-hydroxy-11-oxa-5α-pregnan-20-one (6b).** To a solution of 15 g of 3,3-dimethoxy-17-hydroxy-11-oxa-5α-pregnan-20-one (**6b**), mp 157–159°, in 300 mL of dry methanol 1.2 g of sodium borohydride was added and the solution was stirred for 6 h at room temperature. The excess reagent was destroyed by careful addition of acetic acid (pH 7–8) and the solution was poured into 3 L of cold water. The organic product was extracted with ether, the ethereal layer was washed with water and was dried over sodium sulfate. Evaporation of the solvent gave 13.62 g (90.3%) of crystalline **3,3-dimethoxy-11-oxa-5α-pregnane-17,20α-diol (7)**, partly deketalized in position 3 [ν_{max} (KBr) 3430 (hydroxyls), 1710 (weak, 3-ketone), 1110, 1075, and 1045 cm^{-1} (ether linkages)]. Without purification, this product was dissolved in 2 L of 50% acetic acid and the solution was stirred at room temperature with 100 g of sodium bismuthate for 22 h. The mixture was filtered through celite and the acetic acid was removed from the filtrate by distillation under reduced pressure. The residue was dissolved in ether, the ethereal solution was washed with water, a saturated sodium bicarbonate solution, again with water, and was dried over sodium sulfate. Evaporation of the solvent gave 10.73 g of a crystalline material which upon one recrystallization from ether–hexane gave 9.26 g (89.7% from the impure pregnanediol **7**, 80.7% from the hydroxy pregnanone **6b**) of **11-oxa-5α-androstane-3,17-dione (2)**, mp 169–170°. A sample was recrystallized twice from ether–hexane for analysis; colorless prisms, mp 173–174°, $[\alpha]_D^{25}$ +65.9 (c, 0.850 in $CHCl_3$), ν_{max} (KBr) 1732 (17-ketone), 1710 (3-ketone), 1080, 1040, and 1000 cm^{-1} (ether linkages); δ (60 MHz)

1.05 (s, 3 H, 18-CH_3), 1.12 (s, 3 H, 19-CH_3), 3.30 (d, 1 H, J = 11 Hz) and 3.88 (d, J = 11 Hz) (12-H_2).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.20; H, 9.19.

(d) **From 3,17-bis-Ethylenedioxy-9,12-seco-11-nor-5α-androstane-9β,12-diol (16).** A solution of 2.3 g of the seco dihydroxy diketal **16**, mp 147-148°, and of 1.6 g of p-toluenesulfonyl chloride in 80 mL of pyridine was heated for 1 h in an oil bath (bath temperature of 115-125°). Another 1.6 g of p-toluenesulfonyl chloride was added and the heating was continued for another 2 h. The reaction mixture was cooled and poured onto crushed ice and the precipitate was extracted with ether. The organic solution was washed with 2 N hydrochloric acid, water, a sodium bicarbonate solution, again with water, and was dried over sodium sulfate. Removal of the solvent gave 2.1 g of an amorphous material which was dissolved in 500 mL of absolute acetone and refluxed for 3 h with 600 mg of p-toluenesulfonic acid. The reaction mixture was cooled and poured into a cold sodium bicarbonate solution. The precipitate was extracted with ether, the organic layer was washed with water and was dried over sodium sulfate. Removal of the solvent gave 1.4 g of an amorphous product which was crystallized from ether to give 1.3 g (75%) of pure 11-oxa-5α-androstane-3,17-dione (**2**), mp 169-170°. After two recrystallizations from ether the material melted at 173-174°. Its identity with the product described under (c) was established by the comparison of the ir and nmr spectra and by the determination of a mixture melting point.

11-Oxa-1,4-androstadiene-3,17-dione (18). (a) **By Dehydrogenation of Diketone 2.** A solution of 1.1 g of 11-oxa-5α-androstane-3,17-dione (**2**), mp 169-170°, in 100 mL of absolute dioxane was refluxed with 2 g of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) for 17 h. Subsequently another 2.0 g of DDQ was added and the mixture was refluxed again for 3 h. After cooling, the product was diluted with 200 mL of methylene chloride and filtered. The solvent of the filtrate was removed in vacuo and the residue was dissolved in methylene chloride and filtered through 30 g of aluminum oxide, activity IV. Elutions with methylene chloride and ether gave 870 mg of an oily product which was dissolved in benzene-petroleum ether (1:1) and adsorbed on 30 g of aluminum oxide, activity IV. Elutions with petroleum ether–benzene (1:1) gave 130 mg (13%) of pure **11-oxa-5α-androst-1-ene-3,17-dione (19)**, mp 162-163°. A sample was recrystallized from ether for analysis; colorless needles, mp 166-167°; $[\alpha]_D^{25}$ +39.0 (c, 0.820 in $CHCl_3$); λ_{max} (EtOH) 227 nm (log ε 3.9); ν_{max} (KBr) 1735 (17-ketone), 1665 and 1610 (Δ^1-3-keto doublet), 1060 and 1040 cm^{-1} (ether linkages); δ (60 MHz) 1.07 (s, 18-CH_3), 1.13 (s, 19-CH_3), 3.37 (d, 1 H = 11 Hz) and 3.97 (d, 1 H, J = 11 Hz) (12-H_2), 5.81 (d, 1 H, J = 10 Hz, 2-H), 7.28 (d, 1 H, J = 10 Hz, 1-H).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: 74.96; H, 8.38.

Further elutions in the above-described chromatogram with petroleum ether–benzene (1:1) and with pure benzene gave 510 mg (43% yield) of pure **11-oxa-1,4-androstadiene-3,17-dione (18)**, mp 136-137°; λ_{max} (EtOH) 242 nm (log ε 4.1); ν_{max} (KBr) 1740 (17-ketone),1670, 1635, and 1610 $\Delta^{1,4}$-3-ketone), 1110, 1080, and 1030 cm^{-1} (ether); δ (60 MHz) 1.12 (s, 18-CH_3), 1.33 (s, 19-CH_3), 3.3 (d, 1 H, J = 11 Hz) and 3.95 (d, 1 H, J = 11 Hz) (12-H_2), 6.07 (br. s, 1 H, superimposed on 2-H-doublet, 4-H), 6.18 (dd, 1 H, $J_{1,2}$ = 10 Hz, $J_{2,4}$ = 2 Hz, with superimposition of 4-H: 2-H), 7.18 (d, 1 H, $J_{1,2}$ = 10 Hz, 1-H).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.53; H, 7.94.

(b) **Via the 2,4-Dibromide 2a.** To a solution of 1.0 g of 11-oxa-5α-androstane-3,17-dione (**2**), mp 169-170°, in 10 mL of glacial acetic acid, there was added, dropwise and with stirring, at room temperature, 7.0 mL of a 2.0 N bromine solution in glacial acetic acid. Within 10 min the solution had decolorized and a crystalline product had precipitated. It was warmed for 5 min in an oil bath to 50° and was then stirred at room temperature for 4 h. The mixture was diluted with water and the crystalline precipitate was filtered, washed with water, and dissolved in methylene chloride. This solution was dried over sodium sulfate and taken to dryness at 30-40° in vacuo, leaving 1.2 g of a

solid, mp 184-185°, $[\alpha]_D^{25}$ +25 (c, 0.830 in $CHCl_3$), ν_{max} (KBr) (31) 1730-1750 cm^{-1} (broad, 2,4-dibromo 3-ketone and 17-ketone); according to an elemental analysis, the product was slightly overbrominated. Without purification, it was dissolved in 60 mL of absolute dimethylformamide, and 1.8 g of lithium bromide and 1.8 g of lithium carbonate were added. The mixture was heated to 100° for 8 h, subsequently cooled and poured into iced 2 N hydrochloric acid. The precipitate was extracted with a mixture of ether and methylene chloride. The organic layer was washed with water, was dried over sodium sulfate and taken to dryness. The residue (1.0 g), a brownish product, was adsorbed on 32 g of aluminum oxide, activity IV. Elutions with benzene furnished 580 mg (60%) of **11-oxa-1,4-androstadiene-3,17-dione (18)**, mp 136-137°. The identity of the product with that described under (a) was established by the comparison of the ir and nmr spectra, and by the determination of a mixture melting point.

11-Oxa-4-androstene-3,17-dione (20). To a solution of 200 mg of the 11-oxa androstadiene dione **18**, mp 137-138°, in 100 mL of absolute benzene, 180 mg of tris-(triphenylphosphine)rhodium chloride was added and the solution was hydrogenated with one molecular equivalent of hydrogen over a period of 8 h at room temperature and at atmospheric pressure. The clear, red solution was concentrated in vacuo and was adsorbed on 20 g of aluminum oxide, activity III. Elutions with petroleum ether–benzene (1:4) afforded 119 mg (58% yield) of pure 11-oxa-4-androstene-3,17-dione **(20)**, mp 150-151°. A sample was recrystallized twice for analysis; colorless prisms, mp 151-152°; λ_{max} (EtOH) 238 nm (log ε 4.14); ν_{max} (KBr) 1740 (17-ketone), 1680 and 1625 (Δ⁴-3-keto doublet), 1085, 1040, 1012 cm^{-1} (ether); δ (60 MHz) 1.1 (s, 18-CH_3) 1.28 (s, 19-CH_3), 2.6 (d, 1 H, J = 10 Hz, 9α-H), 3.72 (d, 1 H, J = 11 Hz) and 3.98 (d, 1 H, J = 11 Hz) (12-H_2), 5.80 (s, 1 H, 4-H).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.12; H, 8.75.

3-Ethoxy-11-oxa-3,5-androstadien-17-one (21). A solution of 67 mg of 11-oxa-4-androstene-3,17-dione **(20)**, mp 150-151°, in 5 mL of absolute benzene was refluxed for 3 h with 25 mg of pyridine hydrochloride, 0.3 mL of absolute ethanol, and 0.3 mL of ethyl orthoformate. The reaction mixture was cooled and poured into a cold sodium carbonate solution. The precipitate was extracted with ether, the organic layer was washed with water and was dried over sodium sulfate. Removal of the solvent afforded 74 mg of an oily material which, upon crystallization from ether–hexane, gave 31 mg (42%) of the pure enol ether **21**, mp 136-138°. A sample was recrystallized from ether–hexane; prisms, mp 136-138°; ν_{max} (KBr) 1755 (17-ketone), 1662 and 1640 (Δ³,⁵-diene), 1100, 1090, 1065, 1055 cm^{-1} (ether); δ (90 MHz) 1.11 (s, 6 H, unresolved, 18- and 19-CH_3), 1.31 (t, 3 H, J = 6 Hz, $\underline{CH_3}$-CH_2-O), 2.84 (d, 1 H, J = 10 Hz, 9α-H), 3.41 (d, 1 H, J = 11 Hz) and 3.87 (d, 1 H, J = 11 Hz) (12-H_2), 3.84 (q, 2 H, J = 6 Hz, CH_3-$\underline{CH_2}$-O), 5.17 (m, 2 H, 4- and 6-H).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.15; H, 8.43.

17α-Ethynyl-17β-hydroxy-11-oxa-4-androsten-3-one (17-Ethynyl-11-oxatestosterone or 11-Oxa-ethisterone) (1). To a solution of potassium t-amylate, prepared from 80 mg of potassium and 6 mL of t-amyl alcohol, there was added, in a nitrogen atmosphere, 74 mg of enol ether **21**, mp 136-138°, dissolved in 4 mL of absolute toluene. Acetylene was passed through the reaction mixture over a period of 22 h, 4 mL of 50% hydrochloric acid was added and the mixture was stirred for 1 h at room temperature. The product was poured into a cold sodium bicarbonate solution and the precipitate was extracted with methylene chloride. The solution was washed with water and was dried over sodium sulfate. Removal of the solvent afforded 57 mg of an oily product which was crystallized from methylene chloride–ether to give 39 mg (54% yield) of pure 17-ethynyl-11-oxatestosterone **(1)**, mp 260-261°. A sample was recrystallized for analysis; slightly yellowish prisms, mp 261-262°; $[\alpha]_D^{25}$ -78.7 (c, 0.560 in $CHCl_3$); λ_{max} (EtOH) 237 nm (log ε 4.1); ν_{max} (KBr)

3400 (17β-OH), 3290 and 2400 (17-ethynyl), 1660 and 1630 (Δ⁴-3-keto doublet), 1060, 1030, and 1020 cm^{-1} (ether); δ (60 MHz) 1.17 (s, 18-CH_3), 1.27 (s, 19-CH_3), 2.60 (s, 1 H, C≡CH), 3.69 (d, 1 H, J = 11 Hz) and 3.88 (d, 1 H, J = 11 Hz) (12-H_2), 5.80 (s, 1 H, 4-H).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.50; H, 8.33.

ACKNOWLEDGMENTS

We pay homage to the memory of the late Mrs. J. Capitaine for her collaboration in some of the experiments and sincerely thank Drs. G. Gumulka and Z. Bończa-Tomaszewski for their cooperation in other experiments, as well as Mrs. D. Thibeault for her expert assistance with spectral measurements. We are indebted to Mrs. G. Pelletier and Mrs. L. Lévesque for technical assistance. The major part of this study was performed pursuant to contracts Nos. NO1-HD-2-2714 and NO1-HD-8-2812 with the National Institutes of Health, U.S. Department of Health, Education, and Welfare, who are also responsible for the biological tests summarized in this paper. We express our gratitude for this support and cooperation, particularly to Dr. M. Karten of the NICHD, Bethesda. We acknowledge with sincere thanks the financial assistance in certain aspects of our investigations of the National Research Council of Canada, the Natural Sciences and Engineering Research Council of Canada, the Ministère de l'Education du Québec, and Ayerst Laboratories, Montreal. To this company and to Drs. R. Deghenghi, G. C. Myers, and G. Schilling and their collaborators we are also very grateful for kindly having degraded for us hecogenin acetate to 3β-acetoxy-5α-pregn-16-ene-12,20-dione (**4**), and for the performance of the majority of the microanalyses and mass spectra.

NOTES AND REFERENCES

1. Paper LII: Gumulka, M., Ibrahim, I. H., Bończa-Tomaszewski, Z., and Engel, Ch. R., CAN. J. CHEM. 63, (1985).
2. Paper IV: Salvi, V. S., Mukherjee, D., Roy Chowdhury, M. N., and Engel, Ch. R., STEROIDS, 27, 717 (1976).
3. For preliminary reports on the subject, cf. (a) Engel, Ch. R., Mukherjee, D., Roy Chowdhury, M. N., Ramani, G., Salvi, V. S., Symposium lecture S-17(2), 4TH INT. CONGRESS ON HORMONAL STEROIDS, Mexico, September 1974; (b) Engel, Ch. R., Mukherjee, D., Roy Chowdhury, M. N., Ramani, G., and Salvi, V.S., J. STEROID BIOCHEM. 6, 585 (1975).
4. Engel, Ch. R. and Roy Chowdhury, M. N., TETRAHEDRON LETTERS, 2107 (1968).
5. Engel, Ch. R., Rastogi, R.C., and Roy Chowdhury, M. N., STEROIDS, 19,1 (1972).
6. McPhail, M. K., J. PHYSIOL. 83, 145 (1935).
7. When the ovulation was stimulated by mating, 11-oxaprogesterone showed, however, at a dose level at which progesterone is 75% active, no ovulation-inhibiting activity (3b).
8. Engel, Ch. R., Salvi, V. S., and Roy Chowdhury, M. N., STEROIDS, 25, 781 (1975).
9. The structures of all products not yet described were substantiated by elemental and spectral analyses (cf. Experimental). In the General Part of this publication only salient points of these proofs are given.
10. Sidall, J. B., Baddely, G. V., and Edwards, J. A., CHEM. AND IND., 25 (1966).
11. Gardner, J. N., Carlon, F. E., and Cnoj, O., J. ORG. CHEM. 33, 3294 (1968).
12. Bailey, E. J., Barton, D. H. R., Elks, J., and Templeton, J. F., J. CHEM. SOC., 1578 (1962).
13. Julian, P. L., Cochrane, C. C., Magnani, A., and Karpel, W. J., J. AM. CHEM. SOC. 78,3156 (1956).
14. Engel, Ch. R. and Rakhit, S., CAN. J. CHEM. 40, 2153 (1962).

15. It is well known that the metal hydride reduction of 17-hydroxy 20-ketones leads predominantly to the 20α-hydroxy derivatives (cf., for instance, refs.16-20).
16. Hirschmann, H. and Hirschmann, F. B., J. BIOL. CHEM. 187, 137 (1950).
17. Turner, R. B., J. AM. CHEM. SOC. 75, 3489 (1953).
18. Fukushima, D. K. and Meyer, E. D., J. ORG. CHEM. 23, 174 (1958).
19. Just, G. and Nagarajan, R., CAN. J. CHEM. 39, 548 (1961).
20. Rakhit, S. and Engel, Ch. R., CAN. J. CHEM. 40, 2163 (1962).
21. Engel, Ch. R., CAN. J. CHEM. 35, 131 (1957).
22. Schwenk, E. and Stahl, E., ARCH. BIOCHEM. 14, 125 (1947).
23. Jardine, F. H., Osborn, J. A., Wilkinson, G., and Young, J. F., CHEM. AND IND., 560 (1965).
24. Bennet, M. A., and Longstaff, P. A., CHEM. AND IND., 846 (1965).
25. Djerassi, C., Miramontes, L., Rosenkranz, G., and Sondheimer, F., J. AM. CHEM. SOC. 76, 4092 (1954).
26. In model experiments on 4-androstene-3,17-dione, not reported in the Experimental, we found the method of Pradhan and Ringold (27) unsatisfactory. Neither did we obtain satisfactory results in an attempt to ketalize that product selectively in position 3 with 2-methyl-2-ethyl-1,3-dioxalane, according to Dauben (28).
27. Pradhan, S. K. and Ringold, H. J., J. ORG. CHEM. 29, 601 (1964).
28. Dauben, H. J., Löken, B., and Ringold, H. J., J. AM. CHEM. SOC. 76, 1359 (1954).
29. Mozingo, R., in: Org. Synth. Coll. Vol. III, John Wiley and Sons, New York-London-Sidney, 1955, E. C. Horning, editor-in-chief. P. 181.
30. (a) Bowden, K., Heilbron, J. M., Jones, E. R. H., and Weedon, B. C. L., J. CHEM. SOC., 39 (1946); (b) Bowers, A., Halsall, T. G., Jones, E. R. H., and Lemin, A. J., J. CHEM. SOC., 2548 (1953).
31. Registered on a Perkin-Elmer 457 instrument.