Tetrahedron Vol. 38, No. 23, pp. 3447 to 3455, 1982
Printed in Great Britain.

0040-4020/82/233447-09$03.00/0

A SYNTHESIS OF 11-HOMO-ALDOSTERONE

MASATERU MIYANO,* JEFFREY N. SMITH and C. R. DORN
Department of Medicinal Chemistry, G. D. Searle & Co., Box 5110, Chicago, IL 60680, U.S.A.

(*Received in U.S.A.* 1 *March* 1982)

Abstract—A synthesis of 11-homo-aldosterone acetate (**1a**) is described. 3β-Acetoxy-11-methylene-5α,25D-spirostan (**3**) was converted in 4 steps into 3β-acetoxy-11β-acetoxymethyl-5α-pregnan-20-one (**9**, Chart I), which was photocyclized to **20a**, saponified regioselectively, and oxidized to 3-oxo-11β-acetoxymethyl-18,20-cyclopregnan-20α-ol-3-one (**22**, Chart II). Introduction of the 1,4-diene in **22** followed by a selective reduction of the 1-ene afforded 11β-acetoxymethyl-18,20-cyclopregn-4-en-20α-ol-3-one (**26**). Finally, the 18,20-cyclo ring of **26** was manipulated through **30**, **31**, **32**, **33** to produce **1a**. The bulky 11β-acetoxymethyl group distorted the steroid molecule to such an extent that the routine photochemical functionalization of the angular Me-18 via a nitrite or a hypoiodite became inoperative, and routine procedures for introduction of a 4-ene into 5α-3-one via a 1,4-dien-3-one were unsuccessful. Two new methods for the introduction of a 4-ene into steroidal 5α-3-ones were investigated using 5α-cholestanone and 5α-dihydrotestosterone as models. The first route, which was applicable to the synthesis of **1a**, was the stepwise introduction of a 1-ene and a 4-ene utilizing Sharpless's acidic phenylselenyl chloride procedure, followed by a selective reduction of the 1-ene. The second route, which appeared equally promising, was protection of the C-2 site with N-methylanilinomethylene followed by introduction of the 4-ene and subsequent deprotection of the C-2.

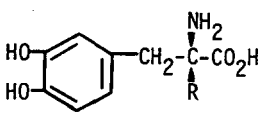
The addition of one C to a biologically active compound can result in a very useful homologue† eliciting a subtle biological difference from the parent substance. The direction of the change in the biological activities of a homologue is unpredictable. It could result in a more potent agonist, a more selective agonist, or an antagonist. This paper deals with a synthesis of 11-homo-aldosterone acetate (**1a**) and its hydrolysis to 11-homo-aldosterone (**1b**), a hitherto unknown homologue of aldosterone (**2b**).

†Methyldopa (i, R = Me), a homologue of L-dopa (i, R = H), is marketed in the U.S. for the treatment of hypertension. Norgestrel (ii, R = Me), a homologue of Norethindron (ii, R = H), is an ingredient of contraceptive pills. The 11β-methyl homologue (iii, R = Me) of Ethinodiol Diacetate (iii, R = H) is 10–25 times more progestational (Ref. 1). ω-Homo-PGE$_1$ (iv, R = Me) is 4 times more active than PGE$_1$ (iv, R = H) in inhibiting the aggregation of human platelets (Ref. 2).

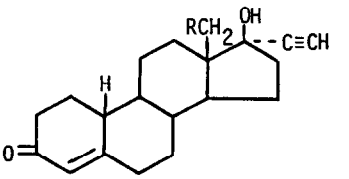
RESULTS AND DISCUSSION

Starting material. 3β-Acetoxy-11-methylene-5α,25D-spirostan (**3**), prepared from hecogenin by the known procedure,[3] was hydroborated to give a monoacetate (**5**) and a diol (**4**). The mixture of **4** and **5** was acetylated to the diacetate (**6**). The oxidative degradation[1,4] of the spirostan rings of **6** produced **7** in a 66% overall yield from **3**. Hydrogenation of **7** gave either **8** (predominantly β-ol[5]; PtO_2, HOAc) or a saturated ketone **9** (Pd-C, THF) in good yields. Since both **8** and **9** contained the proper C skeleton required for the synthesis of **1a**, the remaining work was centered on the modification of the oxidation level of C-3, 18, and 21, and on the introduction of a double bond into C-4,5.

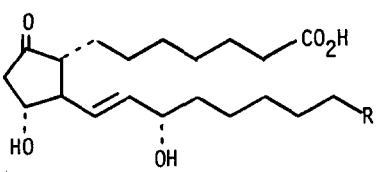
Functionalization of C-18. The most efficient way of introducing a functional group onto the Me-18 of steroids appeared to be a photolysis[6] of either the nitrite ester or the hypoiodite of the 20-ol. Unfortunately, irradiation of



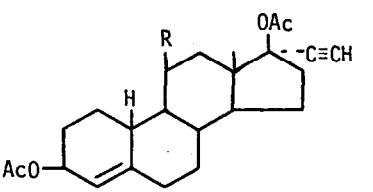
i



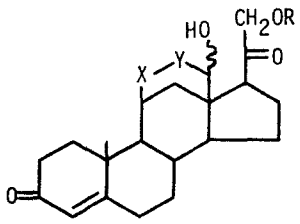
ii



iv



iii



1a X-Y=CH_2O, R=Ac

1b X-Y=CH_2O, R=H

2a X-Y=O, R=Ac

2b X-Y=O, R=H

10 in benzene did not produce the desired C-18 nitroso compound (or the isomeric C-18 oxime). The ^{1}HMR and IR spectra of the major product were consistent with the hydroxamic acid (**12**), which was further characterized as the crystalline triacetate (**13**). Apparently a free radical intermediate **14** was in equilibrium with **15**, and the latter recombined with a nitrosyl radical to give **16** which was hydrolyzed to **12** during work-up. The IR absorption of **12** at 1675 cm^{-1} was in good agreement with 1664 cm^{-1} for N-octanoylhydroxylamine in chloroform,[7] or ~6 μ for N-acetylhydroxylamine.[8] The IR absorption of **13** at 1793 cm^{-1} was in good agreement with 1785 cm^{-1} for O-acetyl of N-benzoyl-O-acetylhydroxylamine in chloroform.[7]

Irradiation of the hypoiodite (**11**) under the standard conditions[6] did not produce the desired material (this time **18**) either. Only one compound (**17**) was isolated from the complex reaction mixture.†

A successful functionalization of C-18 could only be achieved by stifling the recombination of the C-11a radical. A logical approach was the photocyclization of **9**. This afforded 25% of **20a** and 15% of **20b**. A selective saponification of **20a** with potassium carbonate produced **21** as the major product which was then oxidized to **22** with pyridinium chlorochromate. Alternatively, **9** could be selectively saponified to **19**, which was then photocyclized to **21**. The latter route gave a better overall yield than the first one.

Introduction of the $\Delta^{4,5}$ double bond. The synthesis of **1a** from **22** involved two problems: (1) transformation of the 20α-hydroxy-18,20-cyclopregnane to 18-oxo-20-oxo-21-acetoxypregnane, and (2) introduction of a double bond into the ring A. The latter problem was worked out first. The 11β-substituent of **22** significantly changed the chemical properties of A/B ring system of **22** and the unsaturated relatives (**23–27**). The extent of deviation was far more than expected simply from the steric bulk of the 11β-acetoxymethyl group. DDQ oxidation of **22**, a routine operation for the transformation of a 3-oxo-5α steroid to the 3-oxo-1,4-diene,[9] invariably gave rise to a significant amount of **25** along with **23** and **24**.‡ The introduction of the first double bond was unusually slow,§ and the second and third double bonds rather fast. The bromination-dehydrobromination sequence[11] instead of DDQ turned out to be equally unsuccessful.

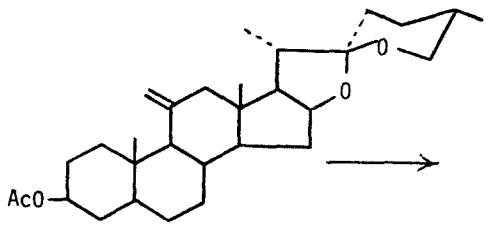
Sharpless[12] prepared cholest-1-en-3-one from 5α-cholestan-3-one by treatment with phenylselenyl chloride in ethyl acetate followed by oxidative elimination. We repeated the Sharpless' procedure and did obtain cholest-

†The ^{1}HMR spectra suggested that most products from this reaction, though not identified, still contained the Me-18. The free radical group on the C-18 of the initial intermediate was probably transferred onto other carbons prior to recombination with the iodine (or acetate) radical.

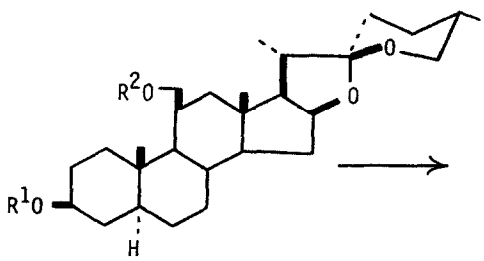
‡Worse still, **24** (desired) could not be separated from **25** by the ordinary method (recrystallization, TLC, column). In the absence of the 11β-substituent the chromatographic separation was not difficult at all. The selective hydrogenation of **24/25** mixture over Wilkinson's catalyst produced an inseparable mixture of **26** and **27** along with **22**, though a successful example of such hydrogenation is recorded in the literature (Ref. 10).

§This can be explained by the steric hindrance of 11β-substituent on C-2.

Chart I



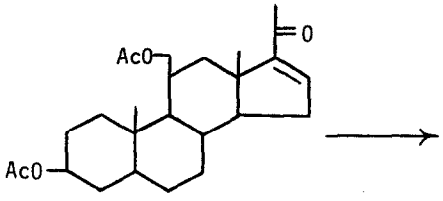
3



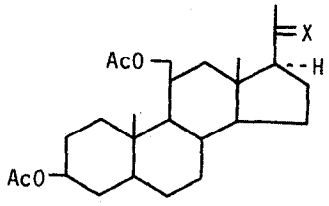
4 R^1=R^2=H

5 R^1=Ac, R^2=H

6 R^1=R^2=Ac



7 (66.2% from **3**)



8 X=H,OH (predominantly β)

9 X=O (92% from **7**)

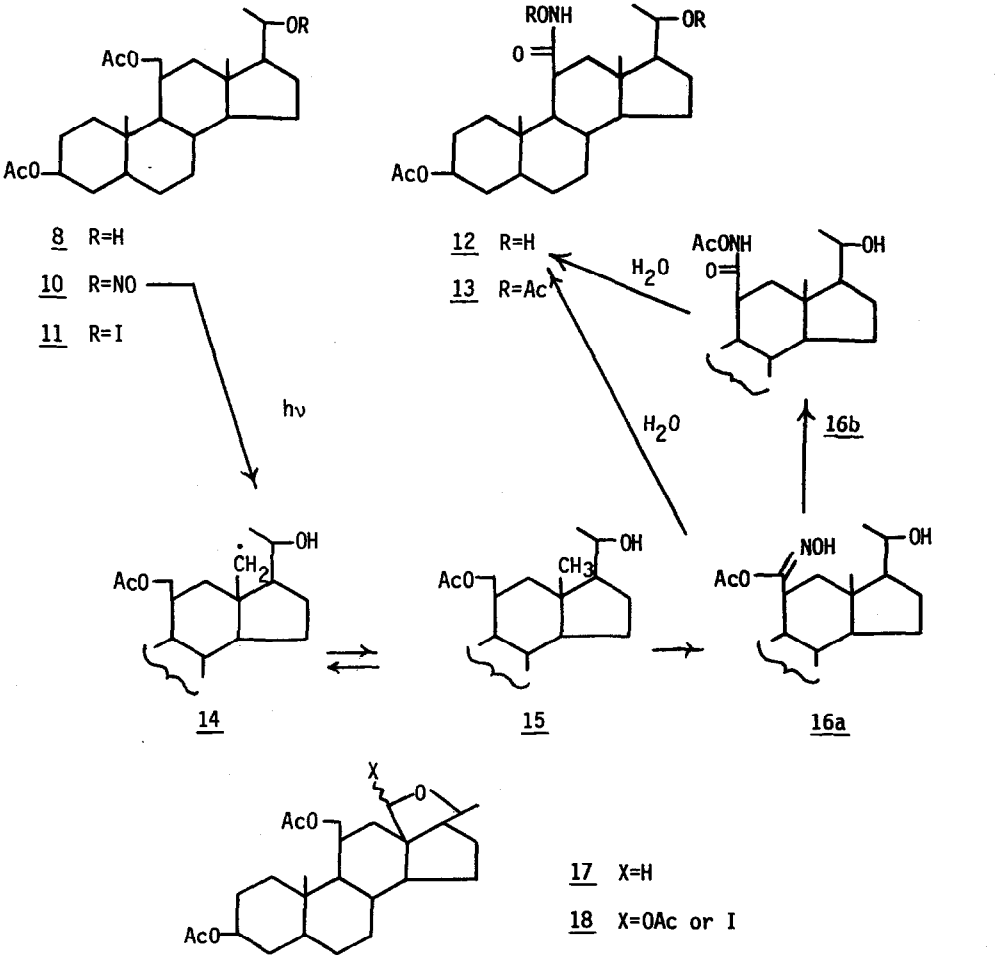
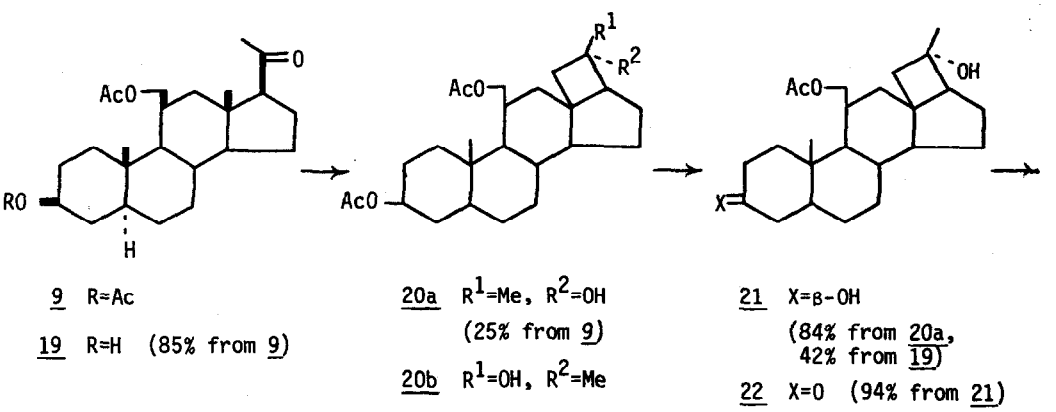
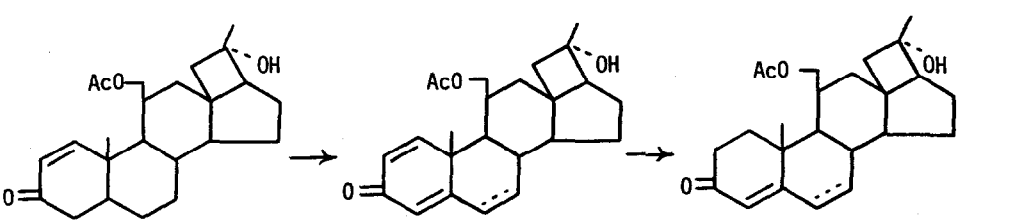
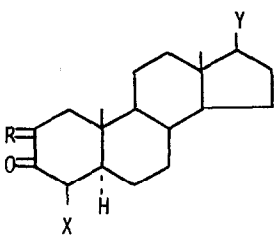

AcO
OR
RONH
O
8 R=H
10 R=NO
11 R=I
12 R=H
13 R=Ac
AcONH
OH
H_2O
hν
16b
CH_2
CH_3
NOH
14
15
16a
X
17 X=H
18 X=OAc or I

Chart II


AcO
RO
H
O
R^1
R^2
OH
X
9 R=Ac
19 R=H (85% from 9)
20a R^1=Me, R^2=OH (25% from 9)
20b R^1=OH, R^2=Me
21 X=β-OH (84% from 20a, 42% from 19)
22 X=O (94% from 21)


AcO
OH
O
23 (89.9%)
24 1,4-diene (65.4%)
25 1,4,6-triene
26 4-ene (54% from 22)
27 4,6-diene

Diagram†

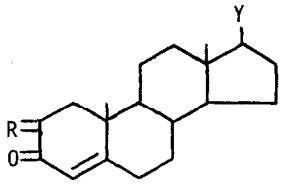


28a,A R=H_2, X=H

28b,B R=CHOH, X=H

28c,C R=C_6H_5NMeCH, X=H

28d,D R=C_6H_5NMeCH, X=SeC_6H_5



29a,A R=C_6H_5NMeCH

29b,B R=H_2

1-en-3-one as the major product though the yield was lower (57.6%) in our hands. Two other products which were not mentioned by Sharpless were isolated and identified to be cholest-4-en-3-one (12.8%) and cholesta-1,4-dien-3-one (11.6%). No 4,6-dien-3-one was found in the reaction mixture. Further, we found that the second double bond could be introduced into 5α-cholest-1-en-3-one by repeating the same procedure to give cholesta-1,4-dien-3-one (89% based on the recovered 1-en-3-one). This was somewhat surprising, because a treatment of enones with phenylselenyl chloride in pyridine produced the α-phenylselenoenones in good yields[13] which reacted further with excess phenylselenyl chloride to give the α-chloroenones also in excellent yields.[14] In addition, we found that the reaction proceeded, though at a slower rate, in the presence of epihalohydrin, a HCl scavenger. Therefore this reaction is applicable to acid sensitive compounds, for instance, 20-hydroxy-18,20-cyclosteroids. This two-step procedure was then applied successfully to the conversion of **22** into **24**. The latter prepared in this manner was free of **25** and gave pure **26** upon a selective hydrogenation over the homogeneous catalyst. The overall yield of **26** from **22** was 54%, based upon the recovered intermediates. The 1-ene could also be reduced selectively (**24**→**26**) with iron pentacarbonyl in the presence of alkali.[15]

An alternative route from 5α-3-one to the 4-en-3-one gave a comparable overall yield. 5α-Cholestan-3-one (**28a**), a model compound, was protected with an N-methylanilinomethylene group (**28c**), and then treated with one equivalent each of lithium diisopropylamide and phenylselenyl chloride to give **28d**. The latter was immediately treated with hydrogen peroxide to generate the 4-en-3-one (**29a**) and deprotected to give cholest-4-en-3-one (**29b**). This procedure was applicable to a compound having a free hydroxyl group as demonstrated by the conversion of dihydro-5α-testosterone (**28A**) into testosterone through **28B**, **C**, **D** and **29A**.

Creation of the aldosterone type side chain. A model experiment for the transformation of the 20α-hydroxy-18,20-cyclo structure into the aldosterone side chains was published elsewhere.[16] Dehydration of **26** to **30** in the usual manner (phosphorus oxychloride, pyridine, 100°) gave variable results due to the susceptibility of the 4-en-3-one system. More consistent results were obtained with thionyl chloride and 1,4-diazabicyclooctane in methylene chloride-pentane at 0°. The *exo*/*endo* ratio‡ in **30** was 5:1 by phosphorus oxychloride and 4:1 by thionyl chloride. The kinetic addition of phenylselenyl bromide to **30** followed by the oxidative elimination as described in the model work[16] produced **31** in a moderate yield. Saponification of **31** afforded a diol (**32**) which was isolated as a crystalline toluene solvate. A regioselective acetylation of the allylic hydroxy group of **32** with acetic anhydride in pyridine afforded the desired monoacetate (**33**) as the major product, along with recovered **32** and some diacetate. The ^{1}HMR signal of **32** at 4.08 ppm (H-21) shifted to 4.48 ppm in **33** demonstrating that the allylic alcohol was selectively acetylated. The target compound, 11-homo-aldosterone acetate (**1a**), was obtained by an oxidative cleavage of the 18,20-double bond of **33**. The ^{1}HMR spectrum of **1a** in deuteriochloroform was remarkably similar to that of aldosterone acetate (**2a**) except for three multiplets at δ 3.63 (two H-11a of minor lactol), 3.87 (a H-11a of major lactol), and 4.02 (the other H-11a of major lactol) ppm. The rest of the ^{1}HMR assignment is given in the experimental. This spectrum demonstrated that in the solution **1a** existed as a 4:1 mixture of the anomeric lactol forms (**1a**).

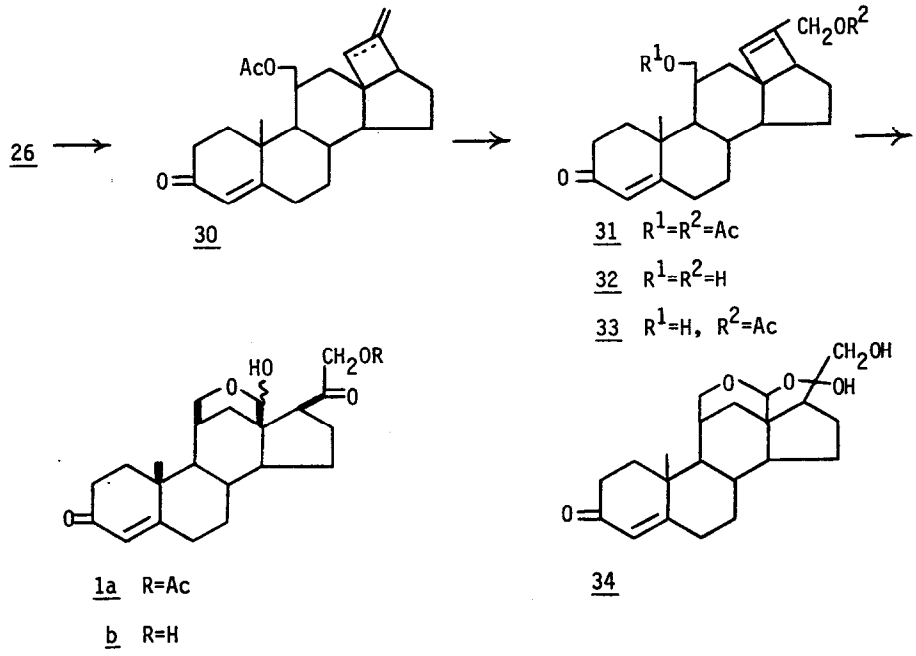
The homologous acetate (**1a**) exhibited 23% of the affinity of the natural aldosterone to the rat aldosterone receptor.§ The affinity of **1a** was as high as that of Spironolactone, an antialdosterone steroid available on the market.

The acetyl group of **1a** was removed by treatment with anhydrous methanol in the presence of potassium carbonate at 25°. The major product showed a single spot on TLC and crystallized from ethyl acetate. The crystalline **1b** showed no 20-ketone group in the IR spectrum (KBr disc), demonstrating that it existed as a double acetal form (**34**). In a chloroform solution **1b** did exhibit a moderately intense absorption of 20-ketone at 1705 cm^{-1}. The ^{1}HMR spectrum of **1b** suggested that it consisted of three lactol forms in the deuteriochloroform solution,

†Y was C_8H_{17} for *a*, *b*, *c*, and *d*; and was OH for **A**, **B**, **C** and **D**.

‡The ratio is important because only the *exo* olefin undergoes the next reaction.

§Assayed by Mrs. E. Muir and associates, Endocrinology Screening Laboratories, G. D. Searle & Co.



probably two **1bs** and a **34**. Three H-18 signals as well as three Me-19 signals were observed as described in the experimental.

EXPERIMENTAL

Mps are uncorrected. IR spectra were taken in $CHCl_3$ solutions. ^{1}HMR spectra were run on a Varian XL-100, A FT-80A, or on a 60AT spectrometer in $CDCl_3$ solns with TMS as internal standards, unless otherwise specified. The coupling constants *J* are given in Hz. Unless otherwise stated, the organic extracts from the mixtures were dried over $NaSO_4$ and then concentrated under reduced pressure. The solvent system for a chromatographic separation is described, for example, EtOAc in toluene. This implies the elution was started with 100% toluene and continued with toluene containing increasing amounts of EtOAc until all the material was eluted. When a solvent system is stated like 10–50% EtOAc in cyclohexane, the elution was initiated with cyclohexane containing 10% (volume) of EtOAc and finished with cyclohexane containing 50% of EtOAc.

11β-Hydroxymethyl-tigogenine (**4**) *and its* 3-O-*acetate* (**5**)

To a soln of 4.7 g of **3**[1,3] in 100 ml THF was added, under N_2 at 7°, 10 ml of 1 M borane in THF. The mixture was allowed to stand at 25° for 1 hr then cooled to 5°, and stirred with 5 g AcOK in 5 ml water and 6 ml 30% H_2O_2. After stirring at 35° for 0.5 hr the THF layer was separated and washed with a sat. NaClaq. The aqueous wash was extracted with CH_2CL_2. The THF and CH_2Cl_2 solns were combined, dried over $MgSO_4$, stripped of the solvent, and chromatographed on a silica gel column using 10–50% EtOAc in benzene. The less polar major product was recrystallized from CH_2Cl_2–EtOAc to give pure **5**: m.p. 248°; δ (60 MHz) 4.65 (m, 1H, H-3α), 4.35 (m, 1H, H-16α), 3.76 (broad d, 1H, *J* 7), 3.55 (broad d, 1H, *J* 7), 3.35 (m, 2H, H-27), 2.02 (s, 3H), 0.93 (s, ~3H), 0.85 (s, ~3H); ν_{max} 3630, 1728 cm^{-1}. (Found: C, 73.77; H, 9.95. $C_{30}H_{48}O_5$ requires: C, 73.73; H, 9.90).

The more polar minor product was recrystallized from EtOAc to give **4**: m.p. 245°; ν_{max} 3610, 1455, 1050, 1013, 980, 895 cm^{-1}. (Found: C, 77.89; H, 10.49. $C_{28}H_{44}O_3 \cdot \frac{1}{4}H_2O$ requires: C, 78.00; H, 10.40).

The combined yields for **4**, **5**, and the mixture of both were over 85%.

11β-Hydroxymethyltigogenine diacetate (**6**)

Either **4** or **5** or a mixture of both was quantitatively acetylated with excess (3x) Ac_2O in pyridine (25°, 3 days). Recrystallization from MeOH gave pure **6**: m.p. 132–133°; δ (60 MHz) 4.7 (m, 1H, H-3α), 4.5 (m, 1H, H-16α), 4.2 (m, 2H, H-11a), 3.40 (m, 2H, H-27), 2.03 (s, 3H), 2.00 (s, 3H), 0.89 (s, ~3H), 0.80 (s, ~3H). (Found: C, 72.35; H, 9.48. $C_{32}H_{50}O_6$ requires: C, 72.41; H, 9.50).

3β - Acetoxy - 11β - acetoxymethyl - 20 - oxo - 5α - pregn - 16 - ene (**7**)

From **6**. To a soln of 3 g pyridine hydrochloride in 45 ml Ac_2O, 9.8 g of **6** was added. The resulting mixture was refluxed for 3 hr. After cooling the mixture was diluted with 5 ml AcOH and 7.9 ml water. When the heat evolution had subsided, a soln of 5.4 g CrO_3 in 50 ml 90% AcOH was added. This mixture was kept at 20–25° for 2 hr, then treated with 3 ml 36% formalin and 8 g NaOAc, and finally heated with steam for 1 hr. The mixture was diluted with water and extracted with CH_2Cl_2. Chromatography on 800 g of silica gel using 15% EtOAc in benzene afforded 3.77 g of **7** (recrystallized from CH_2Cl_2—Skelly B): m.p. 158.5°; δ (60 MHz) 6.69 (m, 1H), 4.73 (m, 1H, H-3α), 4.16 (m, 2H, H-11a), 2.25 (s, 3H, Me-21), 2.10 (s, 3H, AcO-11a), 2.02 (s, 3H, AcO-3β), 0.98 (s, 3H), 0.93 (s, 3H); ν_{max} 1735, 1670, 1589, 1370, 1260, 1034 cm^{-1}; λ_{max} 237.5 nm (ε 9,750). (Found: C, 73.37; H, 9.03. $C_{26}H_{38}O_5$ requires: C, 73.27; H, 8.65).

From **3**. Starting from 241 g of **3**, using the crude intermediates (without chromatography), 328 g of greenish gum was obtained from which 106 g of **7** was isolated by recrystallization from i-PrOH. An additional 40 g of **7** was obtained by chromatography of the final mother liquor. The total yield was 146 g (66.2%).

3β - Acetoxy - 11β - acetoxymethyl - 20 - hydroxy - 5α - pregnane (**8**)

A soln of 7.46 g of **7** in 200 ml glacial AcOH in a Parr shaker was hydrogenated (2 hr 25°) in the presence of 0.70 g PtO_2 under an initial pressure of 64.5 p.s.i. The product was freed of the catalyst and the solvent, and recrystallized from Skellysolve C to give 7.25 g of **8**: m.p. 148–149°; δ (60 MHz) 4.58 (m, 1H, H-3α), 4.22 (m, 2H, H-11a), 3.70 (m, 1H, H-20), 2.04 (s, 3H), 2.02 (s, 3H), 1.12 (d, 3H, *J* 6, Me-21), 0.90 (s, 3H, Me-19), 0.78 (s, 3H, Me-18); ν_{max} 3615, 1730, 1370, 1030 cm^{-1}. (Found: C, 72.09; H, 9.84. $C_{26}H_{42}O_5$ requires: C, 71.85; H, 9.74).

Photolysis of nitrite ester (**10**)

Formation of **12**. To an ice cold soln of 1.4 g of **8** in 20 ml pyridine nitrosyl chloride gas was introduced. After 20 min, **8** had completely reacted. A less polar 20β-nitrite (R_f 0.74 on Woelm silica gel plate with 15% EtOAc in benzene) and a very minor product (perhaps 20α-nitrite, R_f 0.705) were formed. The pyridine soln was diluted with 500 ml benzene and treated with ice water. The organic layer was washed with cold 1% NaClaq., dried over Na_2SO_4, and irradiated with a 200 W Hanovia high pressure mercury lamp through a Pyrex filter under N_2 at 17° for 2.5 hr. The crude product containing no less than 6 compounds was chromatographed on neutral silica gel using EtOAc in CH_2Cl_2. The major product (**12**, 0.25 g) was found in the 100% EtOAc fractions: thick glass; δ (60 MHz) 4.63 (m, 1H, H-3α), 3.67 (m, 1H, H-20), 2.02 (s, 3H); ν_{max} 3610, 3425, 3300, 1725 (ester), 1675 (amide), 1260, 1030, 966 cm^{-1}. (Found: C, 68.28; H, 9.38; N, 3.13. $C_{24}H_{39}NO_5$ requires: C, 68.37; H, 9.33; N, 3.32).

The glassy **12** (0.2 g) was acetylated with 0.075 ml Ac_2O in 5 ml pyridine at 25°. Chromatography on a silica gel column using EtOAc in benzene gave a crystalline triacetate which was recrystallized from ether to give pure **13**: m.p. 184°; δ (100 MHz), 9.20 (s, 1H, O=C–N(H)–O), 4.7 (m, 2H, H-3 and H-20), 2.73 (m, 1H, H-11α), 2.22 (broad d, 1H, H-12β), 2.21 (s, 3H, AcO–N), 2.05 (s, 3H, AcO-20), 2.02 (s, 3H, AcO-3), 1.14 (d, 3H, Me-21), 0.88 (s, 3H), 0.78 (s, 3H); ν_{max} 3360 (broad), 1793, 1730 (broad), 1450, 1376, 1260, 1033, 896 cm^{-1}.† (Found: C, 66.14; H, 8.70; N, 2.51. $C_{28}H_{43}O_7N$ requires: C, 66.51, H, 8.75; N, 2.77).

Photolysis of hypoiodite (**11**)

An attempt to prepare **18**. A suspension of 2.0 g $CaCO_3$ and 6.0 g lead tetraacetate in 170 ml cyclohexane was refluxed for 5 min and then treated with 1.6 g I_2 under reflux for 1 hr. To the refluxing reagent 1.0 g of **8** was added and the mixture was irradiated with a 1 kW sun lamp with vigorous stirring until the color of I_2 had disappeared (25 min). The mixture was washed with $Na_2S_2O_3$aq., washed with water, dried over $MgSO_4$, and concentrated. The residue was treated with 3 g NaOAc in 30 ml DMF for 2 hr on steam. The mixture was diluted with water and extracted with ether. The ethereal extract containing no less than 6 products was chromatographed on a low pressure column (100 g silica gel) using EtOAc in CH_2Cl_2. Only one product (28%) was cleanly separated (13% EtOAc in CH_2Cl_2). It was recrystallized from cyclohexane to give **17**: m.p. 132.5°; δ (60 MHz) 4.6 (m, 1H, H-3α), 4.52 (q, 1H, *J* 6 and 11, H-20), 3.98 (t, 1H, *J* 6.5, H-11a), 3.66 (broad s, 2H, H-18), 3.57 (t, 1H, *J* 11, H-11a), 2.06 (s, 3H), 2.01 (s, 3H), 1.17 (d, 3H, *J* 6, Me-21), 0.875 (s, 3H). (Found: C, 72.02; H, 9.43. $C_{26}H_{40}O_5$ requires: C, 72.19; H, 9.32).

3β - *Acetoxy* - 11β - *acetoxymethyl* - 20 - *oxo* - 5α - *pregnane* (**9**)

From **8**. A Jones' oxidation of **8** produced **9** as a sole product which was recrystallized from EtOAc: m.p.160–162°; δ (60 MHz) 4.68 (m, 1H, H-3α), 4.41 (q, 1H, *J* 6.5 and 11, H-11a), 3.97 (q, 1H, *J* 9.5 and 11, H-11a), 2.12 (s, 3H, Me-21), 2.03 (s, 3H), 2.00 (s, 3H), 0.91 (s, 3H), 0.67 (s, 3H); ν_{max} 1736, 1710, 1373, 1260, 1030 cm^{-1}. (Found: C, 71.95; H, 9.54. $C_{26}H_{40}O_5$ requires: C, 72.19; H, 9.32).

From **7**. A soln of 9.8 g of **7** in 100 ml THF was shaken under an initial pressure of 58 p.s.i. of H_2 in the presence of 0.98 g 5% PdC. During 45 min, 98% of the calculated amount of H_2 was taken up. The product was freed from the catalyst and the solvent, and recrystallized from Skellysolve C to give 9.0 g (91.8%) of pure **9**: m.p. 160.5°; no UV absorption as a 5 mg% MeOH soln. The ^{1}HMR and IR spectra were indistinguishable from the specimen prepared from **8**.

†N-benzoyl-O-acetylhydroxylamine exhibited IR absorption in $CHCl_3$ at 3311, 3195 (both N–H), 1785 (acetyl), 1701 (benzoyl), 1451, 1366, 898 (ref. 7).

‡The mother liquor, diol, the other monoacetate and the recovered **9** were combined, reacetylated, and recycled. On this basis the yield of **19** was 85%.

3β - *Acetoxy* - 11β - *acetoxymethyl* - 20α - *hydroxy* - 18,20 - *cyclo* - 5α - *pregnane* (**20a**) *and its* 20β - *hydroxy isomer* (**20b**)

A stirred suspension of 20 g of **9** in 900 ml EtOH was irradiated with a 200 W medium pressure Hanovia lamp at 20° under a N_2 stream. The starting material had disappeared after 7 hr. The photolysis product was chromatographed on a silica gel (2 kg) column using EtOAc in benzene. The fractions eluted with 20% EtOAc in benzene gave 2.52 g of **20b**, followed by 2 g of a mixture of **b** and **a**, and finally 3.78 g of **20a**. The mixture fractions were rechromatographed. The yields of **20a** and **20b** amounted to 25 and 15% respectively. For analysis, **20a** was recrystallized from CH_2Cl_2–cyclohexane; m.p. 182°; δ (100 MHz) 4.68 (m, 1H), 4.40 (q, 1H, *J* 6.5 and 11, H-11a), 3.73 (t, 1H, *J* 11.5, H-11a), 2.15 (q, 1H, *J* 1.7 and 13, H-12β), 2.11 (s, 3H), 2.03 (s, 3H), 1.09 (s, 3H, Me-21), 0.86 (s, 3H); ν_{max} 3600, 1730, 1372, 1255, 1030 cm^{-1}. (Found: C, 72.01; H, 9.54. $C_{26}H_{40}O_5$ requires: C, 72.19; H, 9.32%). The analytical specimen of **20b** was provided by recrystallization from ether; m.p. 157.5°; δ (60 MHz) 4.6 (m, 1H, H-3α), 4.37 (q, 1H, *J* 11 and 6.5, H-11a), 3.67 (t, 1H, *J* 11.5, H-11a), 2.43 (broad d, 1H, H-12β), 2.09 (s, 3H), 2.03 (s, 3H), 1.40 (s, 3H, Me-21), 0.85 (s, 3H, Me-19); ν_{max} 3600, 1730, 1370, 1250, 1027 cm^{-1}. (Found: C, 72.05; H, 9.35. $C_{26}H_{40}O_5$ requires: C, 72.19; H, 9.32%).

3β - *Hydroxy* - 11β - *acetoxymethyl* - 20 - *oxo* - 5α - *pregnane* (**19**)

A soln of 34 g of **9** in 800 ml THF was stirred as a soln of 11 g K_2CO_3 in 800 ml 80% MeOH was added. The slightly cloudy mixture was stirred for 6 hr and then allowed to stand overnight. The bulk of the solvent was removed under reduced pressure, and the residue was diluted with water. The solid product was collected by filtration, air-dried, taken up in CH_2Cl_2, and filtered to recover the insoluble diol (4 g). The filtrate was concentrated and chromatographed on a silica gel column using EtOAc. Following the recovered **9** (12 g), a small amount of the other monoacetate and **19** (16 g) was eluted. The pure **19** (13 g, 42%)‡ was obtained by recrystallization from CH_2Cl_2-Skellysolve B; m.p. 132–133°. (Found: C, 73.57; H, 9.69. $C_{24}H_{38}O_4$ requires: C, 73.80; H, 9.80).

3β - *Hydroxy* - 11β - *acetoxymethyl* - 20α - *hydroxy* - 18,20 - *cyclo* - 5α - *pregnane* (**21**)

From **19**. A soln of 13 g of **19** in 900 ml EtOH was irradiated with a medium pressure Hanovia lamp under N_2 for 11 hr. Chromatography on silica gel using EtOAc in toluene gave 5.5 g (42.3%) of **21**. The analytical specimen was provided by recrystallization from CH_2Cl_2–cyclohexane; m.p. 105°; δ (80 MHz) 4.37 (q, 1H, *J* 7 and 12, H-11a), 3.68 (t, 1H, *J* 12, H-11a), 3.6 (m, 1H, H-3α), 2.08 (s, 3H), 1.44 (s, cyclohexane), 1.08 (s, 3H), 0.86 (s, 3H); ν_{max} 3590, 1730 cm^{-1}. (Found: C, 74.56; H, 10.80. $C_{24}H_{38}O_4 \cdot \frac{1}{2}C_6H_{12}$ requires: C, 74.95; H, 10.25).

From **20a**. A soln of 700 ml of 0.1 M K_2CO_3 in 80% MeOH was added into a cold soln of 25 g of **20a** in 400 ml MeOH in an ice water bath. The mixture was stirred at 25° for 2 hr then neutralized with AcOH. The work-up procedure was the same as for **9**→**19**. The triol (6.54 g) was recovered by filtration of the CH_2Cl_2 extract. The filtrate was separated on a Waters' column (Polasil, ethyl acetate in toluene) to give 2.1 g of **20a**, 11.3 g (50.1%, or 83.9% based upon the recovered intermediates which could be recycled) of **21**, and 1.83 g of a mixture of the other monoacetate and the triol.

3 - *Oxo* - 11β - *acetoxymethyl* - 20α - *hydroxy* - 18,20 - *cyclo* - 5α - *pregnane* (**22**)

A mixture of 10.5 g of **21**, 10.5 g NaOAc, and 11 g pyridinium chlorochromate in 500 ml CH_2Cl_2 was stirred at 25° for 3 hr. The mixture was treated with water and extracted with CH_2Cl_2. The organic layer was washed with cold 1% HCl, washed with 2% $NaHCO_3$aq., dried, and passed through a short column of Florisil. The crystalline **22** (9.81 g, 94%) was obtained upon evaporation of the solvent. The analytical sample was obtained by recrystallization from CH_2Cl_2–ether; m.p. 183°; δ (60 MHz) 4.45 (q, 1H, *J* 12 and 6.5, H-11a), 3.77 (t, 1H, *J* 12, H-11a), 2.06 (s,

3H), 1.06 (s, 3H), 1.04 (s, 3H); ν_{max} 3580, 1729, 1705 cm^{-1}. (Found: C, 74.35; H, 9.41. $C_{24}H_{36}O_4$ requires: C, 74.19; H, 9.34).

11β - Acetoxymethyl - 20α - hydroxy - 18,20 - cyclo - 5α - pregn - 1 - en - 3 - one (**23**)

The procedure was essentially the same as for 5α-cholest-1-en-3-one. The mixture obtained from 4.81 g of **22** was chromatographed on silica gel (a low pressure column) using EtOAc in toluene to produce 2.88 g (60.1%) of **23**, 0.64 g (13.4%) of **26**, 0.20 g (4.2%) of a mixture of **26/24**, and 0.58 g (12.2%) of **24** eluted from the column in this sequence. The total yield of useful substances (**23**, **26**, **24**) amounted to 89.9%. The analytical specimen of **23** was crystallized from ether–cyclohexane; 139°; δ (80 MHz) 7.20 (d, 1H, *J* 10.5, H-1), 5.88 (d, 1H, *J* 10.5, H-2), 4.41 (q, 1H, *J* 11 and 7, H-11a), 3.88 (t, 1H, *J* 11, H-11a), 2.09 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H); λ_{max} 227 nm (ε 12,000). (Found: C, 74.38; H, 8.95. $C_{24}H_{34}O_4$ requires: C, 74.08; H, 8.87%).

11β - Acetoxymethyl - 20α - hydroxy - 18,20 - cyclopregna - 1,4 - dien - 3 - one (**24**)

By PhSeCl. A soln of 4.67 g of **23** and 2.72 g phenylselenyl chloride in 120 ml EtOAc was stirred at 25° for 3 hr. After the usual work-up (see cholesta-1,4-dien-3-one), the residue was chromatographed on silica gel (a low pressure column) using EtOAc in toluene to give 2.22 g of recovered **23**, 0.21 g of a mixture of **23/24**, and 1.46 g (65.4% based upon the consumed **23**) of **24**. The analytical sample of **24** was crystallized from EtOAc; m.p. 198°; δ (80 MHz) 7.22 (d, 1H, *J* 10, H-1), 6.25 (q, 1H, *J* 10 and 2, H-2), 4.55 (q, 1H, *J* 10 and 6, H-11a), 3.95 (t, 1H, *J* 10, H-11a), 2.12 (s, 3H), 1.26 (s, 3H), 1.09 (s, 3H); ν_{max} 3585, 1733, 1659, 1622, 1600 cm^{-1}; λ_{max} 244 nm (ε 17,300). (Found: C, 74.80; H, 8.42. $C_{24}H_{32}O_4$ requires: C, 74.97; H, 8.39%).

By DDQ. A soln of 2.0 g of **22** and 2.5 g DDQ in 40 ml dioxane was refluxed for 20 hr. After cooling, the mixture was filtered to remove the hydroquinone, diluted with CH_2Cl_2, washed with 2% NaOHaq., washed with 1% NaClaq., dried, and concentrated. The residue, upon chromatography on silica gel, produced 0.96 g of recovered **22** containing a little **23**, 0.70 g of **24** contaminated by **25**. The last fraction was recrystallized from CH_2Cl_2–ether to give impure **24**; m.p. 193°; λ_{max} 243 nm (ε 13,000), 300 nm (ε 3,100). To show that **24**, obtained by DDQ oxidation, was contaminated by **25** was verified by subsequent hydrogenation over Wilkinson's catalyst. The reduced product, recrystallized from CH_2Cl_2–ether, was a 2:1 mixture of **26** and **27**; m.p. 150.5°; δ (80 MHz) in addition to all the signals of **26**, 6.13 (broad s, H-6 and H-7 of **27**), 5.60 (broad s, H-4 of **27**), 1.18 (s, **27**), 1.13 (s, **27**); λ_{max} 241.5 nm (ε 14,500 due to **26**), 282 nm (ε 7,500, due to **27**).

11β - Acetoxymethyl - 20α - hydroxy - 18,20 - cyclopregn - 4 - en - 3 - one (**26**)

By Wilkinson's catalyst. A soln of 0.58 g of **24** and 1.16 g tris(triphenylphosphine)-rhodium chloride in 25 ml deoxygenated THF was shaken under H_2 until 45.5 ml (101% of the calculated) of H_2 was taken up. The reduced soln was diluted with CH_2Cl_2, washed with 2% NaOH, washed with 2% NaClaq., dried, and stripped of the solvent. Chromatography on Woelm silica gel (a low pressure column) using ethyl acetate–toluene system gave 0.10 g of recovered **24** and 0.45 g (93.2% based on recovered **24**) of **26**. The analytical sample of **26** was recrystallized from EtOAc–cyclohexane; m.p. 153°; δ (80 MHz) 5.62 (broad s, 1H, H-4), 4.43 (q, 1H, *J* 12 and 6, H-11a), 3.79 (t, 1H, *J* 12, H-11a), 2.10 (s, 3H), 1.25 (s, 3H), 1.09 (s, 3H); λ_{max} 240.5 nm (ε 17,500). (Found: C, 74.51; H, 8.98. $C_{24}H_{34}O_4$ requires: C, 74.58; H, 8.87%).

By $Fe(CO)_5$. A soln containing 0.55 g of **24** and 10 ml iron pentacarbonyl in 150 ml ether was stirred vigorously with 3.6 ml 20% NaOHaq. for 24 hr. The mixture was treated with an ethereal soln of I_2 until the evolution of CO ceased. The mixture in ether was washed with Na_2SO_3aq., washed with NaClaq., and dried. Chromatography on silica gel produced 0.15 g of **26** and 0.30 g of deacetylated-**26**. The latter was reacetylated to **26** with Ac_2O in pyridine. A total of 0.44 g (88%) of **26** was obtained.

11β - Acetoxymethyl - 18,20 - cyclopregna - 4,20 - dien - 3 - one (**30**)

With $POCl_3$. A soln of 0.65 g of **26** and 2.5 ml $POCl_3$ in 15 ml pyridine was heated on steam for 60 min. After cooling, the mixture was poured onto ice, acidified with HCl, and extracted with CH_2Cl_2. The organic layer was washed with 1% NaClaq., dried, and chromatographed on Florisil using EtOAc in CH_2Cl_2 to give 0.42 g (68%)† of crude **30**. The *exo*/*endo* ratio of the impure **30** was better than 5:1 based upon the intensity of the OAc peaks in the ^{1}HMR.

With $SOCl_2$. To a soln of 1.35 g of **26** and 1.5 g 1,4-diazabicyclooctane in 100 ml CH_2Cl_2-n-pentane (1:1) was added 4.5 ml of 10% (in volume) $SOCl_2$ in n-pentane at −20° under vigorous stirring. The mixture was stirred at −20 to 0° for 3 hr, then diluted with CH_2Cl_2, washed with 1% $NaHCO_3$aq., dried, and chromatographed on Woelm silica gel using EtOAc in cyclohexane to give 0.52 g (40.4%) of pure **30** and 0.45 g (34.9%) of somewhat impure **30**. Based on the intensity of the OAc peaks in the ^{1}HMR spectrum, the *exo*/*endo* ratio in **30** was better than 4:1. ^{1}HMR δ (80 MHz) 5.63 (broad s, 1H, H-4), 4.70 (m, 2H, H-21 of *exo*), 4.50 (q, 1H, *J* 11 and 6, H-11a), 3.73 (t, 1H, *J* 11, H-11a), 2.09 (s, >2.4H, OAc of *exo*), 2.06 (s, <0.6H, OAc of *endo*), 1.27 (s, 3H), ν_{max} 1740, 1672, 1620, 1373, 1034, 882 cm^{-1}.

11β - Acetoxymethyl - 21 - acetoxy - 18,20 - cyclopregna - 4,18 - dien - 3 - one (**31**)

Using the same conditions as described in the model work,[16] 0.55 g of **30** was treated with 0.45 g phenylselenyl bromide followed by oxidative elimination. Chromatographic separation on a silica gel column afforded 0.18 g (28.3%) of **31**, along with a mixture (0.30 g) of recovered **30** and the vinylic bromide. ^{1}HMR of **31**: δ (80 MHz) 5.77 (q, 1H, *J* ~ 1, H-18), 5.63 (broad s, 1H, H-4), 4.48 (broad s, 2H, H-21), 4.1 (m, 2H, H-11a), 2.07 (s, 6H, two acetoxys), 1.27 (s, 3H); ν_{max} 1742, 1666, 1623, 1374, 1255, 1033 cm^{-1}.

11β - Hydroxymethyl - 21 - hydroxy - 18,20 - cyclopregna - 4,18 - dien - 3 - one (**32**)

Crude **31** (0.27 g) was dissolved in 4 ml EtOH and treated with 1 ml of 20% NaOHaq. at 25° for 2 hr. The saponified product was extracted with CH_2Cl_2 and chromatographed on 3 g of Florisil. Fractions eluted with 20% EtOAc in CH_2Cl_2 afforded 98 mg (40% from crude **31**) of crystalline **32** which was recrystallized from toluene to form an insoluble toluene solvate.‡ The m.p. 189° (the crystalline form changed at 85–90° due to the loss of the solvent); δ (80 MHz) 7.18 (broad s, 5H, toluene), 5.82 (q, 1H, *J* ~ 1, H-18), 5.66 (broad s, 1H, H-4), 4.08 (broad s, 2H, H-21), 3.93 (m, 1H, H-11a), 3.62 (t, 1H, *J* 10, H-11a), 2.34 (s, 3H, toluene), 1.30 (s, 3H); ν_{max} 3610, 3440, 1663, 1617 cm^{-1}. Found: C, 79.03; H, 8.78. $C_{22}H_{30}O_3 \cdot \frac{1}{2}C_7H_8$ requires‡: C, 78.83; H, 8.82%).

11β - Hydroxymethyl - 21 - acetoxy - 18 - 20 - cyclopregna - 4,18 - dien - 3 - one (**33**)

A soln of 99.3 mg of **32** in 7 ml pyridine was treated with 88.7 mg Ac_2O at 25° for 2.5 hr. The mixture was decomposed with MeOH (25°, 0.5 hr) and blown down under a N_2 stream. Chromatography on 6 g of Florisil using EtOAc in CH_2Cl_2 gave 20.0 mg of **31** (found in 10% EtOAc fractions), 47.7 mg (95.4% based upon recovered **31** and **32**) of **33** (20% EtOAc fractions), and 30.7 mg of **32** (50% EtOAc fractions). ^{1}HMR δ (80 MHz) 5.79 (q, 1H, *J* ~ 1, H-18), 5.63 (s, 1H, H-4), 4.48 (s, ≤2H, H-21), 4.06 (broad s, ≪1H, H-21 of the other monoacetate), ~3.7 (m, ~2H, H-11a), 2.08 (s, 3H).

11β - Hydroxymethyl - 3,18,20 - trioxo - 21 - acetoxy - 4 - pregnene: *11 - Homo - aldosterone acetate* (**1a**)

A soln of 47.7 mg of **33**, 24 mg of N-methylmorpholine N-oxide,

†The yield fluctuated. In two other runs the yields were 48 and 51%.

‡The freshly crystallized substance contained one mole of toluene (based upon ^{1}HMR). The air-dried crystals contained only about 0.5 mole of toluene. When recrystallized from CH_2Cl_2–EtOAc, **32** contained 0.5 mole EtOAc.

and 3 mg osmium tetroxide in 12 ml t-BuOH–THF–water (10:3:1) was stirred for 2 days. The mixture was taken up with CH_2Cl_2, washed with 1% HCl, and washed with water. The crude product contained **1a** (R_f 0.38)† and the intermediate glycol (R_f 0.075)† but only minor amount of **33**. This mixture was dissolved in 7 ml of t-BuOH and treated with a soln of **43** mg sodium periodate in 0.4 ml water. The crude product showed virtually one spot of R_f 0.38 which was chromatographed on 2 g of Florisil. The combined fractions eluted with 20% EtOAc in CH_2Cl_2 produced 23.6 mg (45.8%) of crystalline **1a**. Later fractions (50–100% EtOAc) contained **1a** and a more polar product (R_f 0.136). The latter was indistinguishable from **1b** on TLC. The crude **1a** (m.p. 167–178°) was recrystallized from ether to give pure **1a** as an ether solvate: m.p. 187–188.5°; δ (80 MHz) 1.16 (s, 3H), 1.21 (t, 3H, *J* 7, ether), 2.10 (s, acetoxy of isomer A), 2.12 (s, acetoxy of isomer B), 3.46 (q, 2H, ether), 3.63 (m, two H-11a of isomer B), 3.87 (m, H-11a of isomer A), 4.02 (H-11a of isomer A), 4.10 (d, 1H, *J* 11, H-21), 4.35 (d, 1H, *J* 11, H-21), 4.80 (s, 0.8H, H-18 or isomer A), 5.05 (s, 0.2H, H-18 of isomer B), 5.68 (broad s, 1H, H-4); ν_{max} 3690, 3580, 1745 (20-*oxo*, 21-acetoxy), 1670 (3-*oxo*), 1640 cm^{-1}; $[\alpha]_{589}^{25}$ + 20.3, $[\alpha]_{365}^{25}$ + 18.4 (0.103% in $CHCl_3$). (Found†: C, 68.15; H, 7.85. $C_{24}H_{32}O_6 \cdot 1/3H_2O$ requires: C, 68.22; H, 7.79%).

11β - *Hydroxymethyl* - 21 - *hydroxy* - 3,18,20 - *trioxo* - 4 - *pregnene* (**1b**)

A soln of 27 mg of **1a** in 5 ml MeOH was stirred with 46 mg of anhyd. K_2CO_3 at 25° until **1a** (R_f 0.38)[1] disappeared completely (45 min). The mixture was shaken with CH_2Cl_2 and water. The major product (26 mg, R_f 0.136) and the minor product (1.2 mg, R_f 0.197) could be separated by a thick layer chromatography on a 8 × 2 in. silica gel plate using 75% EtOAc–toluene. Neither OMe nor acetyl peak (^{1}HMR) was found in the methanolysis products. The major product crystallized from EtOAc: m.p. 173.5°; δ (80 MHz) 5.68 (broad s, 1H, H-4), 5.00 (s, 0.3H, H-18), 4.97 (s, 0.2H, H-18), 4.78 (s, 0.5H, H-18), ~3.8 (m, 4H, H-11a, H-21), 1.31 (s, Me-19), 1.26 (s, major Me-19), 1.17 (s, Me-19); ν_{max} 3680, 3590, 3470 (20-OH), 1705 (20-*oxo*), 1665 (3-*oxo*), 1618 (4-*ene*) cm^{-1}; ν_{max} (KBr) 3465, 2930, 1651 (3-oxo), 1610 (4-ene) cm^{-1}. (Found: C, 70.37; H, 8.09. $C_{22}H_{30}O_5$ requires: C, 70.56; H, 8.08%).

Conversion of cholestanone into cholest-1-en-3-one, cholest-4-en-3-one (**29b**), *and cholesta-1,4-dien-3-one*

The crude product, obtained from 5 g of cholestanone as described,[12] was chromatographed on Woelm silica gel using EtOAc in toluene to give 0.82 g of recovered cholestanone, 2.88 g of cholest-1-en-3-one (m.p. 100°),‡ 0.64 g (12.8%, m.p. 84°, lit.[17] 82°; λ_{max} 242 nm, ϵ 15,300) of cholest-4-en-3-one, and 0.58 g (11.6%; m.p. 114°, lit.[17] 112°; λ_{max} 245 nm, ϵ 14,500) of cholesta-1,4-dien-3-one.

Cholesta-1,4-dien-3-one from cholest-1-en-3-one

To a soln of 0.55 g cholest-1-en-3-one and 0.7 ml epibromohydrin in 12.5 ml EtOAc was added 0.63 g phenylselenyl chloride. The mixture was stirred for 20 hr and then washed with 2.5 ml water. The organic layer was diluted with 5.5 ml THF and treated with 0.65 ml 30% H_2O_2. A chromatographic separation of the crude product on a silica gel column gave 0.32 g of recovered cholest-1-en-3-one, and 0.23 g (m.p. 114°)§ of cholesta-1,4-dien-3-one: δ (80 MHz) 6.03 (broad s, H-4), 6.18 (q, *J* 10 and 2, H-2), 7.01 (d, *J* 10, H-1).

2 - (*N* - *methylanilinomethylene*) - 5α - *cholestan* - 3 - *one* (**28c**)

A soln of 7.6 g of **28b** and 6.0 ml N-methylaniline in 140 ml EtOH was refluxed for 4 hr. The mixture was freed from the solvent and chromatographed on a silica gel column to give 7.6 g (84%) of a yellow glass. ^{1}HMR: δ (60 MHz) 7.64 (m, 1H), 6.9–7.5 (m, 5H), 3.40 (s, 3H); λ_{max} 341 nm (ϵ 19,500). (Found: C, 83.20; H, 10.49; N, 2.79. $C_{35}H_{53}NO$ requires: C, 83.44; H, 10.60; N, 2.78%).

2 - (*N* - *methylanilinomethylene*) - 4 - *phenylselenyl* - 5α - *cholestan* - 3 - *one* (**28d**)

To a soln of 15.7 mmoles lithium diisopropyl amide prepared from 1.59 g diisopropylamine and 7.3 ml n-BuLi (2.17 M in hexane) in 50 ml of THF, was added at −70° a soln of 6.8 g (13.5 mmoles) of **28c** in 30 ml THF. The mixture was stirred at −70° for 15 min, then treated with 3.0 g (15.7 mmole) phenylselenyl chloride in 30 ml THF at −70° for 0.5 hr. After warming to 25°, the mixture was poured into cold 5% $NaHCO_3$aq. and extracted with EtOAc. The organic phase was washed with 5% $NaHCO_3$aq., and satd NaClaq. Chromatography on a silica gel gave 5.13 g (58%) of **28d**: m.p. 81–82°; δ (60 MHz) 7.70 (m, 3H), 6.9–7.5 (m, 8H), 3.48 (s, 3H), 3.28 (d, 1H, *J* 10); λ_{max} 360 nm (ϵ 20,400). (Found: C, 75.11; H, 8.62; N, 2.01. $C_{41}H_{57}NOSe$ requires: C, 74.74; H, 8.72; N, 2.13%).

2 - (*N* - *methylanilinomethylene*) - *cholest* - 4 - *en* - 3 - *one* (**29a**) *and cholest* - 4 - *en* - 3 - *one* (**29b**)

A soln of 3.0 g of **28d** in 30 ml THF was treated with 1.3 ml 30% H_2O_2 and 0.05 ml pyridine at 0° for 1 hr. The mixture was poured into cold 5% $NaHCO_3$aq. and extracted with EtOAc. The organic phase was washed with NaClaq., dried, and concentrated to give 2.03 g (89%) of oily **29a** which was used for the next step. The analytical specimen was prepared by chromatography of crude **29a** on a silica gel column to give oily **29a**: δ (60 MHz) 7.42 (m, 1H), 6.9–7.4 (m, 5H), 5.78 (s, 1H), 3.40 (s, 3H); λ_{max} 375 nm (ϵ 15,600). (Found: C, 83.55; H, 10.40; N, 2.58. $C_{35}H_{51}NO$ requires: C, 83.77; H, 10.24; N, 2.79%).

A soln of 0.68 g of crude **29a** in 4 ml AcOH was treated with 1 ml 10% HCl at 25° for 1.5 hr. The crystalline product was isolated and washed with AcOH to give 0.43 g (77%) 2-hydroxymethylene-cholest-4-en-3-one. A second crop (0.10 g) was obtained from the mother liquor making the total 0.53 g (95%). A portion (0.20 g) of the hydromethylene derivative was dissolved in 1.5 ml toluene and treated with 1.5 ml 10% NaOHaq. under reflux for 2 hr. The material in the toluene layer was washed with a NaClaq., dried, concentrated, and recrystallized from MeOH to give 0.13 g (70%) of **29b**: m.p. 82°, lit.[17] 82°; λ_{max} 241 nm (ϵ 15,400); δ (60 MHz) 5.74 (s, 1H, H-4); ν_{max} 1686 (3-one), 1623 (4-ene) cm^{-1}.

2 - (*N* - *methylanilinomethylene*) - 5α - *androstan* - 17β - *ol* - 3 - *one* (**28C**)

The procedure essentially the same as for **28c**, afforded 7.7 g (86%) of **28C** (glass) from 7.0 g of **28B**. ^{1}HMR δ (60 MHz) 7.67 (m, 1H), 6.9–7.6 (m, 5H), 3.62 (t, 1H, *J* 8), 3.42 (s, 3H), 0.75 (s, 3H), 0.70 (s, 3H); ν_{max} (KBr) 3415 (OH), 1655 (3-one), 1542 (C=C) cm^{-1}; λ_{max} 344 nm (ϵ 19,600). (Found: C, 79.55; H, 8.98; N, 3.24. $C_{27}H_{37}NO_2$ requires: C, 79.56; H, 9.15; N, 3.43%).

2 - (*N* - *methylanilinomethylene*) - 4 - *phenylselenyl* - 5α - *androsta* - 17β - *ol* - 3 - *one* (**28D**) *and* 2 - (*N* - *methylanilinomethylene*) - *testosterone* (**29A**)

The phenylselenylation of 1.0 g (2.45 mmole) of **28C** with 2 equivs lithium diisopropylamide and 1 equiv. phenylselenyl chloride gave 1.1 g (95%) of oily **28D**; δ (60 MHz) 7.5–7.8 (m, 3H), 6.8–7.4 (m, 8H), 3.62 (t, 1H, *J* 8), 3.39 (s, 3H), 3.28 (d, 1H, *J* 10), 0.67 (s, 3H), 0.65 (s, 3H); ν_{max} 3621, 1648, 1535, 1499 cm^{-1}. (Found: C, 70.69; H, 7.30; N, 2.38. $C_{33}H_{41}NO_2Se$ requires: C, 70.44; H, 7.34; N, 2.49%).

The oxidative elimination of the phenylselenyl group from 2.75 g of **28D** gave 1.47 g (74%) of **29A**‖: M.P. 190–191°; δ (60 MHz) 7.56 (m, 1H), 6.85–7.4 (m, 5H), 5.78 (t, 1H, *J* 1.5), 3.62 (t, 1H, *J* 8), 3.42 (s, 3H), 0.98 (s, 3H), 0.75 (s, 3H); ν_{max} (KBr) 3410 (OH), 1647 (3-oxo), 1600 (C=C), 1545 (C=C) cm^{-1}; λ_{max}

†Woelm silica gel plate, 75% EtOAc in toluene, short wave UV detector.

‡For elemental analysis, **1a** was dried at 60°/0.01 mm for 10 hr in order to remove the ether.

§The m.ps were taken after recrystallization from MeOH. The yields are for the crude material.

‖ Although **29a** was disclosed by H. J. Ringold in U.S. Pat. 3,338,890 (08.29.1967), it was not characterized at all. We assume that our compound is the same as Ringold's.

374 nm (ε 14,500). (Found: C, 80.01; H, 9.09; N, 3.33. $C_{27}H_{35}NO_2$ requires: C, 79.96; H, 8.70; N, 3.45%).

Testosterone (**29B**)

The removal of the protecting group from 0.50 g of **29A**, first with HCl then with alkali, produced 0.28 g of **29B**; m.p. 154°; ^{1}HMR and IR spectra indistinguishable from the authentic testosterone.

Acknowledgements—The authors would like to give thanks to Dr. F. B. Colton, Dr. J. S. Baran, Dr. L. Chinn, and Dr. George Lenz for their helpful discussions. The hydrogenation was carried out by Messrs. M. G. Scaros, O. J. Goodmonson, and James Pilney. Most of the chromatographic separations were performed by Miss Janet Mueller and associates. The starting material (**3**) was prepared by Messrs. R. Shubart, J. A. Schulz and Craig E. Scott.

REFERENCES

[1]J. S. Baran, D. D. Langford, I. Laos and C. D. Liang, *Tetrahedron* **33**, 609 (1977).
[2]R. K. Beerthuis, D. H. Nugteren, H. J. J. Pabon and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas* **87**, 461 (1968).
[3]J. Elks, *J. Chem. Soc* 3333 (1960).
[4]R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.* **61**, 3592 (1939); *Ibid.* **62**, 518 (1940).
[5]D. N. Kirk, M. P. Hartshorn, *Steroid Reaction Mechanism*, p. 145. Elsevier, Amsterdam (1968).
[6]For review see K. Heusler and J. Kalvoda, *Organic Reactions in Steroid Chemistry*, (Edited by J. Fried and J. H. Edwards), Vol. II, p. 237. Van Nostrand Reinhold, New York (1972).
[7]W. P. Jencks, *J. Am. Chem. Soc.* **80**, 4581 (1958).
[8]H. Lenormant, *Bull. Soc. Chim. Fr.* 41 (1948).
[9]D. Walker and J. D. Hiebert, *Chem. Rev.* **67**, 153 (1967).
[10]J. P. Collman and L. S. Hegedus, *Principles and Applications of Organotransition Metal Chemistry*, p. 330. University Science Books, Mill Valley, California (1980).
[11]R. Owyang, *Steroid Reactions* (Edited by C. Djerassi), Holden-Day, San Francisco (1963).
[12]K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.* **95**, 6137 (1973).
[13]G. Zima, D. Liotta, *Synthetic Comm.* **9**, 697 (1979).
[14]S. V. Ley, A. J. Whittle, *Tetrahedron Lett.* **22**, 3301 (1981).
[15]R. Noyori, I. Umeda, T. Ishigami, *J. Org. Chem.* **37**, 1542 (1972).
[16]M. Miyano, *Ibid.* **46**, 1846 (1981).
[17]L. F. Fieser and M. Fieser, *Steroids*, pp. 28, 287. Reinhold, New York (1959).