18-Substituted Steroids. Part 5.[1] Further Studies on the Synthesis of 11β,18,21-Trihydroxypregn-4-ene-3,20-dione ('18-Hydroxycorticosterone')

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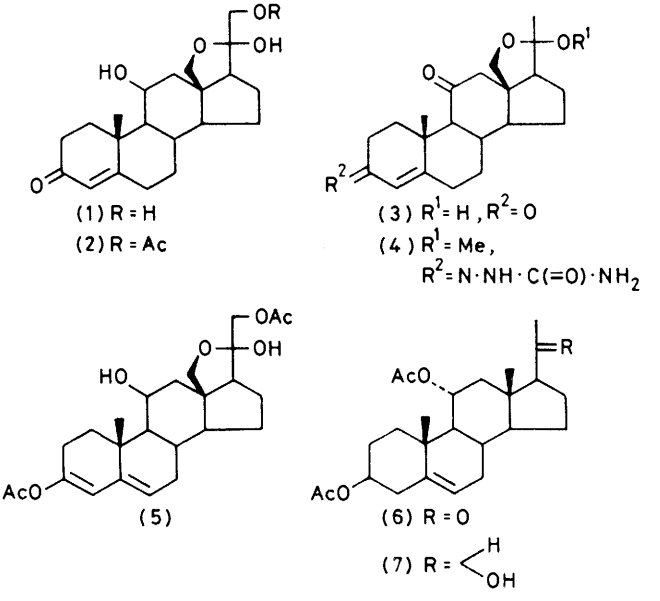
18-Hydroxycorticosterone' (1) has been prepared from 3β,11α-diacetoxypregn-5-en-20-ol (7) by application of the 'hypoiodite' reaction sequence [$Pb(OAc)_4$–I_2–$h\nu$; oxidation; solvolysis] to obtain the 18-hydroxy-20-one (in the hemiacetal form; 8). Hydrolysis followed by oxidation at C-3 and C-11 gave 18-hydroxypregn-4-ene-3,11,20-trione 18,20-hemiacetal (3), which was then doubly protected as its 20-methoxy 3-semicarbazone derivative (4) to allow reduction of the 11-oxo group to the 11β-alcohol. Brief reaction of the product with lead tetra-acetate–acetic acid then gave '18-hydroxycorticosterone' 21-acetate in a single step. The readily available 3β,11α-diacetoxypregn-5-eno-18,20-lactone (10) was also investigated as a possible precursor of 18-hydroxycorticosterone, but with disappointing results.

THE biosynthetic pathway to aldosterone is still a subject for speculation.[2] Despite much study,[2,3] the role of the closely related 18-hydroxycorticosterone (11β,18,21-trihydroxypregn-4-ene-3,20-dione) is still far from certain. 18-Hydroxycorticosterone (1) was first characterised in 1964.[4] It has only very weak mineralocorticoid activity compared with that of aldosterone, but has been suspected as possibly being implicated in hypertension.[3]

Although racemic 18-hydroxycorticosterone was synthesized by the CIBA group as early as 1961,[5] supplies of the natural enantiomer, required for thorough biological and chemical study, were for several years available only from fungal [6] or adrenal [7] incubations of suitable steroids. Two chemical syntheses have been described recently. Barton and his co-workers [8] photolysed the 11β-nitrite of 1,2-didehydrocorticosterone 21-acetate under oxygen to obtain the 18-nitrate, which could be converted in two further steps into 18-hydroxycorticosterone 21-acetate with *ca.* 10% overall yield. We have reported a synthesis from 3β-acetoxypregn-5-ene-11,20-dione,[9] *via* the 'hypoiodite' reaction [10] to functionalise C-18. The latter route, however, suffered from an exceptionally low yield in the hypoiodite reaction, apparently as a consequence of the presence of the 11-oxo group. Major difficulties were also encountered in the Oppenauer oxidation of the 3β-hydroxy-Δ^5-system; extensive purification by chromatography produced 18-hydroxycorticosterone, but in an overall yield of only *ca.* 5%.

We now describe experiments with the same objective, but aimed at increasing the yield in the hypoiodite reaction by starting from 3β,11α-diacetoxypregn-5-en-20-ol (7), instead of the 11-oxo analogue. A previous report [10] indicated that the 11α-acetoxy substituent does not interfere with the hypoiodite reaction. We have also avoided the need for an Oppenauer oxidation step in producing the key intermediate 18,20-epoxy-20-hydroxypregn-4-ene-3,11-dione (18-hydroxy-11-oxoprogesterone 18,20-hemiacetal) (3).

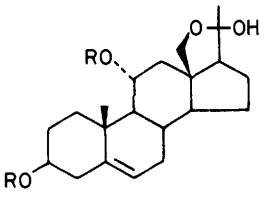
3β,11α-Diacetoxypregn-5-en-20-one (6), obtained from 6β,11α-dihydroxy-3α,5-cyclo-5α-pregnan-20-one (see Experimental section), was reduced by sodium borohydride in methanol at 0 °C to give 3β,11α-diacetoxypregn-5-en-20-ol (7) (mainly 20β-isomer) which was normally pure enough to be used directly. Treatment of the 20-ol (7) with lead tetra-acetate and iodine in cyclohexane at reflux temperature, with irradiation by 500 W photoflood lamps (hypoiodite reaction), gave the required 18-iodo derivative together with material



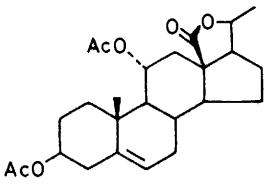
bifunctionalised at C-18. The total product was submitted to Jones' oxidation, followed by silver ion-assisted hydrolysis, to give 3β,11α-diacetoxy-18,20-epoxypregn-5-en-20-ol (8) and 3β,11α-diacetoxypregn-5-eno-18,20-lactone (10), as the major products, which were separated by column chromatography.

The amount of iodine was found to be critical in optimizing the yield of the required product. In the absence of any C-11 substituent we had found 0.5 mol of iodine per mol of steroid to be most satisfactory, giving *ca.* 30% overall yield of 18,20-hemiacetal.[11]

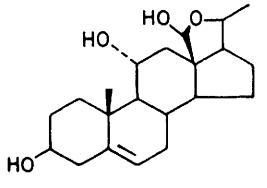
The 11-oxo derivative required 0.9 mol of iodine.[9] In the present work with the 11α-acetoxy compound, 0.7—0.8 mol of iodine were required to consume all the 20-ol (7),



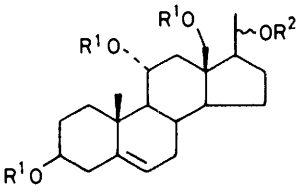
(8) R = Ac
(9) R = H



(10)



(11)

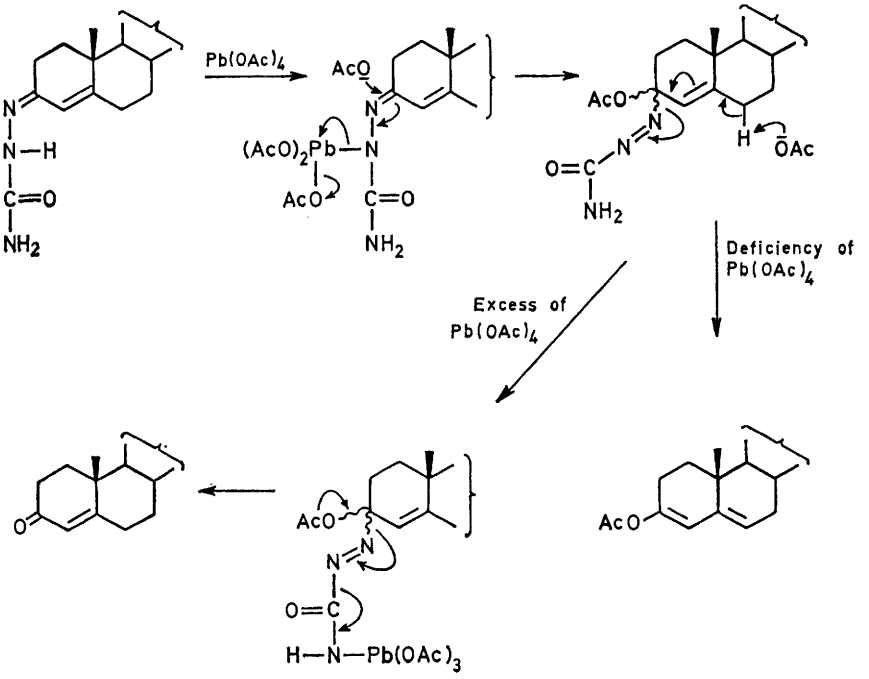


(12) $R^1=R^2=H$
(13) $R^1=R^2=Ac$
(14) $R^1=H$, $R^2=Ac$

giving the hemiacetal (8) in 20—25% yield, accompanied by *ca.* 35% of the lactone (10). By increasing the iodine to 1.0 molar proportion it was possible to obtain the lactone in 60% yield at the expense of the hemiacetal (see below).

The acetoxy groups in the hemiacetal (8) were hydrolysed by alcoholic potassium hydroxide to give 18,20-epoxypregn-5-ene-3β,11α,20-triol (9). It was then necessary to effect oxidations at C-3 and C-11. Experience has shown that the 18,20-hemiacetal structure is stable to mild oxidants. The use of chromium trioxide and pyridine in dichloromethane at 0 °C [12] gave a product believed to be 18,20-epoxy-20-hydroxypregn-4-ene-3,6,-11-trione, from its n.m.r. spectrum. Since over-oxidation of 3β-hydroxy-Δ^5-steroids, introducing a 6-oxo-group, is a familiar problem with this reagent, the base was changed to 3,5-dimethylpyrazole.[13] Cholesterol was smoothly oxidized to cholest-4-en-3-one by chromium trioxide–3,5-dimethylpyrazole, although difficulties were encountered in separating the oxidized product from 3,5-dimethylpyrazole. When this oxidizing reagent was used on the triol (9) however, the results were not reproducible, and extensive chromatography was required to isolate 18-hydroxy-11-oxoprogesterone (3). The required oxidation was ultimately achieved in 60% yield by use of the calculated amount of Jones' reagent in acetone at *ca.* −5 °C. The 18,20-hemiacetal function remained intact under these conditions.

Before reduction of the 11-oxo group in 18-hydroxy-11-oxoprogesterone (3) it was necessary to protect the 3-oxo group and the 18,20-hemiacetal. This was conveniently achieved by first converting the hemiacetal into the corresponding 20-methoxy derivative, then forming the semicarbazone at C-3 (4). Semicarbazones are known to be stable to borohydride.[14] Reduction of the 11-oxo group by sodium borohydride gave a crude product which was treated directly with an excess of lead tetra-acetate [15] in acetic acid to regenerate the 3-oxo and hemiacetal groups, and simultaneously effect 21-acetoxylation.[16] The product comprised 18-hydroxycorticosterone 21-acetate (2) together with the corresponding 3-enol acetate (5),[15] which was probably formed by a mechanism of the type outlined in the



Scheme. Hydrolysis of the mixture of products with methanolic potassium hydroxide gave 18-hydroxycorticosterone (1), in an overall yield of *ca.* 4.3% from the 3β,11α,20-triol 3,11-diacetate (7).

In a further attempt to increase the yield of 18-hydroxycorticosterone an investigation was undertaken into the possible use of the lactone (10) as an intermediate. This lactone is always a major contaminant from the hypoiodite reaction when the hemiacetal (8) is the required product, and can be obtained in 60% yield by increasing the amount of iodine used in the hypoiodite reaction (see above).

An attempt to reduce the lactone with di-isobutylaluminium hydride to obtain the lactol (11) was only partially successful, giving also pregn-5-ene-3β,11α,18,20-tetraol (12) as the product of over-reduction. Preliminary experiments in our laboratory (by Dr. N. Whittaker) had indicated the possibility of isomerising lactols of types corresponding to (11) to the required hemiacetals by aluminium t-butoxide-catalysed intramolecular hydride transfer. Further work, however, failed to establish the feasibility of this transformation in the present case.

Lithium aluminium hydride reduced the lactone (10) efficiently to pregn-5-ene-3β,11α,18,20-tetraol (12), so several attempts were made to effect selective oxidation of the three secondary alcoholic groups to give 18-hydroxy-11-oxoprogesterone (3). Three oxidative procedures [17-19] which have been claimed to oxidise only secondary alcohols in the presence of primary alcohols were used unsuccessful in the present case. Oxidation could not be carried to completion with either hexabutyldistannoxane and bromine [17] or hexamethylphosphoric triamide and bromine,[18] whereas hydride transfer under Oppenauer conditions, or catalysed by alumina,[19] resulted in preferential oxidation of the C-18 alcohol, and regeneration of the lactone ring. The 11α-hydroxy group may be responsible for the enhanced reactivity of the 18-alcohol, for the corresponding 3β,18,20β-triol has been oxidised under Oppenauer conditions at C-3 and C-20, to give 18-hydroxyprogesterone 18,20-hemiacetal.[20]

Attempts at selective esterification of the tetraol (12) using either acetic anhydride–pyridine or trimethylacetyl (pivaloyl) chloride gave mixtures of products and were of little synthetic value (see Experimental section). Selective hydrolysis of the acetate groups of the derived tetra-acetate (13) gave predominantly the tetraol 20-monoacetate (14). Had we obtained either the 18-monoacetate, allowing oxidation at C-3, -11, and -20, or the 11-monoacetate, we could have proceeded to 18-hydroxy-11-oxoprogesterone (3) (11α-OAc does not interfere with selective Oppenauer oxidation of the 18.20-diol system to produce the 18,20-hemiacetal, as we have found by parallel work in the 3,3-ethylenedioxy-Δ^5 series [21]). The tetrakispivaloate was resistant to normal alkaline hydrolysis, but was converted by potassium t-butoxide with 1 mol of water in ether ('anhydrous hydroxide' [22]) into a complex mixture of products of partial hydrolysis, or into the tetraol by the reagent in excess. Despite its ready availability, the lactone (10) cannot yet be regarded as a useful intermediate for the preparation of 18-hydroxycorticosterone.

EXPERIMENTAL

For methods and materials, see ref. 16.

3β,11α-*Diacetoxypregn-5-en-20-one* (6).—6β,11α-Dihydroxy-3α,5-cyclo-5α-pregnan-20-one (900 mg) in glacial acetic acid (20 ml) was treated with perchloric acid (0.3 ml; 72%) at room temperature for 4 h. The solution was then poured into stirred ice–water (200 ml) and the precipitated steroid was collected. The dried product, in pyridine (10 ml) and acetic anhydride (10 ml), was left overnight, then again precipitated into water (100 ml), dried, and crystallised from acetone to give 3β,11α-diacetoxypregn-5-en-20-one (1.00 g, 98%), m.p. 172—175 °C (lit.,[23] 172—174 °C); $\nu_{max.}$ 1 730, 1 705, 1 250, 1 240, and 1 030 cm^{-1}; δ 0.70, (s, 13β-Me), 1.11 (s, 10β-Me), 2.0 (s, AcO), 2.1 (s, 21-H$_3$), *ca.* 4.5 (m, 3α-H), *ca.* 5.3 (m, 11β-H), and *ca.* 5.4 (m, 6-H) (Found: C, 72.4; H, 8.8. Calc. for $C_{25}H_{36}O_5$, C, 72.1; H, 8.7%).

3β,11α-*Diacetoxypregn-5-en-20-ol* (7).—3β,11α-Diacetoxypregn-5-en-20-one (6) (1.6 g) in methanol (100 ml) was cooled to 0—5 °C, then sodium borohydride (0.3 g; 8-fold excess) was added, and the mixture stirred for 30 min, when t.l.c. showed complete reaction. The solution was then poured into water (200 ml), the steroid was extracted into ether (3 × 100 ml), and the extracts were washed with saturated sodium chloride solution, dried (K_2CO_3), and taken to dryness under reduced pressure to give 3β,11α-*diacetoxypregn-5-en-20-ol* (7). This product (1.57 g), mainly the 20β-alcohol, was pure enough to use in the next reaction. An analytical sample (from acetone) had m.p. 163—165 °C, $\nu_{max.}$ 3 430, 1 730, 1 250, and 1 030 cm^{-1}; δ 0.82 (s, 13β-Me), 1.13 (d, *J* 6 Hz, 21-H$_3$), 1.1 (s, 10β-Me), 2.0 (s, AcO), 2.05 (s, AcO), *ca.* 3.7 (m, 20-H), *ca.* 4.6 (m, 3α-H), *ca.* 5.3 (m, 11β-H), and *ca.* 5.4 (m, 6-H) (Found: C, 71.75; H, 9.2. $C_{25}H_{38}O_5$ requires C, 71.7; H, 9.15%).

3β,11α-*Diacetoxy*-18,20-*epoxypregn-5-en-20-ol* (8).—3β,-11α-Diacetoxypregn-5-en-20-ol (7) (2.0 g) in cyclohexane (500 ml) was stirred with lead tetra-acetate (6.0 g) and iodine (0.9 g) and heated to reflux temperature, while being irradiated with two 500 W photoflood lamps until the colour due to iodine had disappeared (*ca.* 40 min). The solution was then cooled and the precipitated lead diacetate was filtered off, with Celite as a filter aid. The filtrate was washed with sodium thiosulphate solution (2 × 200 ml; 5%), followed by saturated sodium chloride solution (100 ml), and dried (K_2CO_3). The solvent was removed under reduced pressure with the bath temperature not exceeding 35 °C. The resulting gum was redissolved in acetone (50 ml) and the solution cooled to ice-bath temperature. Jones' chromic acid reagent was added slowly to the stirred solution until a persistent orange colour was attained, then sodium acetate (20 g) in water (50 ml) was added, and the steroid was extracted into benzene (2 × 100 ml). The combined benzene solutions were washed with saturated sodium chloride solution (100 ml) and dried (K_2CO_3), and the solvent was removed under reduced pressure, while again ensuring that the bath temperature remained below 35 °C. The resulting gum was dissolved in 70% aqueous dioxan (200 ml), silver acetate (2.0 g) added, and the mixture quickly brought to reflux temper-

ature and maintained there, with stirring, for 2 h. The cooled mixture was filtered, and the filtrate concentrated to *ca.* 100 ml. Sodium chloride solution (100 ml) was then added, and the steroid was extracted into ether (3 × 100 ml). The combined ethereal extracts were dried (K_2CO_3) and taken to dryness to yield a semi-solid product (2.5 g). T.l.c. showed three main components, which were separated by column chromatography (100 g of silica gel) Elution with benzene–hexane (1 : 1) gave a mixture (0.2 g) of 17α- and 17β-iodoandrostane derivatives, recognised from the n.m.r. spectrum (d, δ 4.3, 17β-H in 17α-iodo-derivative; t, δ 3.7, 17α-H in 17β-iodo-derivative). Crystallisation from methanol gave 17β-*iodoandrost*-5-*ene*-3β,11α-*diol* 3,11-*diacetate*, m.p. 240—242 °C, $\nu_{max.}$ 1 730, 1 720, 1 245, and 1 028 cm^{-1}; δ 0.90 (s, 13β-Me), 1.12 (s, 10β-Me), 2.0 (s, AcO), 3.75 (t, *J* 9 Hz, 17α-H); *ca.* 4.6 (m, 3α-H), *ca.* 5.3 (m, 11β-H), and *ca.* 5.4 (m, 6-H); c.d. (dioxan) Δε +0.41 (250 nm); +2.09 (210 nm) [*cf.* 3β-acetoxy-17β-iodoandrost-5-ene, +0.60 (251 nm) [24]] (Found: C, 55.2; H, 6.8; I, 25.2. $C_{23}H_{33}IO_2$ requires C, 55.2; H, 6.65; I, 25.4%).

Gradual increase in the proportion of benzene (to 80%) eluted unidentified gums (total 257 mg) off the column. Between 80% and 100% benzene, 3β,11α-*diacetoxypregn*-5-*eno*-18,20-*lactone* (10) (0.72 g, 35%) was eluted, m.p. 176—178 °C (acetone), $\nu_{max.}$ 1 740, 1 725, 1 260, 1 250, 1 240, and 1 028 cm^{-1}; δ 1.22 (s, 10β-Me), 1.37 (d, *J* 6 Hz, 21-H_3), 2.0 (s, AcO), 2.02 (s, AcO), 4.38 (q, *J* 6 Hz, 20-H), *ca.* 4.55 (m, 3α-H), *ca.* 5.45 (m, 6-H), and 5.64 (t of d, $J_{9\alpha,11\beta} = J_{12\beta,12\alpha} = 11$ Hz, $J_{11\beta,12\beta} = 5$ Hz 11β-H) (Found: C, 69.6; H, 8.05. $C_{25}H_{34}O_6$ requires C, 69.7; H, 8.0%).

Benzene containing small amounts of ether eluted more gums (280 mg). Elution with up to 15% ether in benzene finally eluted 3β,11α-*diacetoxy*-18,20-*epoxypregn*-5-*en*-20-*ol* (8) (0.44 g, 22%), m.p. 139—141 °C (acetone), $\nu_{max.}$ 3 440, 1 720, 1 250, and 1 028 cm^{-1}, δ 1.0 (s, 10β-Me), 1.46 (s, 21-H_3), 2.0 (s, AcO), 3.8 (dd, *J* 8 Hz, 18-H_2), *ca.* 4.56 (m, 3α-H), *ca.* 4.9 (m, 11β-H), and *ca.* 5.4 (m, 6-H) (Found: C, 69.0; H, 8.4. $C_{25}H_{36}O_6$ requires C, 69.4; H, 8.4%).

18-*Hydroxy*-11-*oxoprogesterone* (3).— 3β,11α-Diacetoxy-18,20-epoxypregn-5-en-20-ol (8) (100 mg) in methanol (10 ml) and methanolic potassium hydroxide (0.5 ml, 6.0%) were heated under reflux for 2 h, when t.l.c. showed complete hydrolysis. The methanol was removed under reduced pressure, water added, and the steroid extracted into ethyl acetate (2 × 50 ml). This solution was dried (K_2CO_3) and evaporated to yield 18,20-epoxypregn-5-ene-3β,11α,20-triol (81 mg) (i.r.: no absorption at *ca.* 1 730 cm^{-1}). This product was not purified but was oxidised directly in acetone (5 ml), cooled to −5 °C, by adding Jones' reagent (50 μl) slowly until the orange colour persisted. The mixture was quickly worked up by adding sodium acetate (2 g in 10 ml of water) and extracting the steroid into benzene (2 × 50 ml). The combined benzene solutions were washed with saturated sodium chloride solution, then dried (K_2CO_3). The solvent was removed under reduced pressure to give a semi-solid product (80 mg) which was purified by preparative t.l.c. Two bands were observed, one by its u.v. absorption, the other by spraying one edge of the plate with sulphuric acid–ethanol (1 : 1). The u.v.-absorbing steroid was 18-*hydroxy*-11-*oxoprogesterone* (3) (51 mg, 63%), m.p. 156 °C, $\nu_{max.}$ (CH_2Cl_2) 3 570, 1 705, 1 670, 1 620, 1 100, and 1 030 cm^{-1}; δ 1.38 (s, 10β-Me), 1.5 (s, 21-H_3), 3.66 (s, 18-H_2), and 5.74 (s, 4-H) (Found: C, 73.0; H, 8.2. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%). The u.v.-transparent band was believed to be 18-hydroxy-11-oxopregnenolone (18,20-epoxy-3β,20-dihydroxypregn-5-en-11-one) (13.5 mg, 17%), $\nu_{max.}$ (CH_2Cl_2) 3 570, 1 705, 1 175, and 1 030 cm^{-1}.

18,20-*Epoxy*-20-*methoxypregn*-4-*ene*-3,11-*dione* 3-*Semicarbazone* (4).—18-Hydroxy-11-oxoprogesterone (3) (100 mg) in dry methanol (3 ml), with a drop of aged chloroform to provide acidic catalysis, quickly formed the methoxy derivative (t.l.c.), and the product was isolated by removing the solvent under reduced pressure. The i.r. spectrum showed a characteristic signal at 860 cm^{-1} for the methoxy derivative.

This product was redissolved in methanol (4 ml) and water (1 ml) was added. Pyridine (0.1 ml) and semicarbazide hydrochloride (100 mg) were added, and the mixture was warmed until all the reagent had dissolved and the set aside to cool. T.l.c. of the cold mixture showed only a very polar product. Water was added and the precipitated steroid collected and dried *in vacuo* over phosphorus pentaoxide. The resulting semicarbazone (4) (86 mg), m.p. >300 °C, was characterised spectroscopically: $\nu_{max.}$ 3 450, 3 350, 1 680, 1 570, 1 090, and 860 cm^{-1}; δ(C_5D_5N) 1.22 (s, 10β-Me), 1.32 (s, 21-H_3), 3.14 (s, 20-OMe), 3.3 and 3.6 (dd, *J* 8 Hz, 18-H_2), and 5.82 (s, 4-H).

18,20-*Epoxy*-11β-*hydroxy*-20-*methoxypregn*-4-*en*-3-*one* 3-*Semicarbazone*.—The foregoing semicarbazone (4) (80 mg) in freshly distilled tetrahydrofuran (5 ml) was diluted with 95% ethanol (5 ml) and potassium hydroxide solution (0.15 ml; 6%) added. Sodium borohydride (50 mg) was then added and the solution heated at reflux temperature for 8 h. The solvent was partially removed under reduced pressure and water (20 ml) was added. The precipitated steroid was filtered off and dried *in vacuo* to give crude 18,20-epoxy-11β-hydroxy-20-methoxypregn-4-en-3-one 3-semicarbazone (75 mg), m.p. >300 °C; δ(C_5D_5N) 1.14 (s, 10β-Me), 1.54 (s, 21-H_3), 3.12 (s, 20-OMe), 4.03 and 4.49 (dd, *J* 10 Hz, 18-H), *ca.* 4.5 (m, 11α-H), and 5.98 (s, 4-H).

21-*Acetoxy*-18,20-*epoxy*-11β,20-*dihydroxypregn*-4-*en*-3-*one* (18-*Hydroxycorticosterone* 21-*acetate*) (2).—The foregoing semicarbazone (70 mg) was dissolved in anhydrous acetic acid (5 ml) and stirred with lead tetra-acetate (140 mg) for 10 min before being poured into water (20 ml). The steroid was extracted into ether (2 × 50 ml) and the combined ethereal solutions were washed with sodium hydrogen carbonate solution until neutral. The ethereal solution (with a drop of triethylamine as stabilizer) was then dried (K_2CO_3) and taken to dryness to give a yellow gum (57 mg). T.l.c. showed the presence of one strongly u.v.-absorbing spot and two less-polar constituents which appeared after spraying with sulphuric acid–ethanol. Preparative t.l.c. separated the three components. The major product (30 mg, *ca.* 40%), was 3,21-diacetoxy-18,20-epoxypregn-3,5-diene-11β,20-diol (5), gum, $\nu_{max.}$ ($CHCl_3$) 3 550, 1 730, and 1 270 cm^{-1}; δ 1.24 (s, 10β-Me), 2.03 (s, 3-OAc), 2.12 (s, 21-OAc), *ca.* 4.0 (dd, *J* 10 Hz), 18-H_2), *ca.* 4.2 (m, 21-H_2), *ca.* 4.4 (m, 11α-H), *ca.* 5.2 (m, 4-H), and *ca.* 5.4 (m, 6-H).

The u.v.-absorbing product (22%, 15 mg) was 18-hydroxycorticosterone 21-acetate (2), $\nu_{max.}$ ($CHCl_3$) 3 530, 1 720, 1 660, and 1 350 cm^{-1}; δ 1.48 (s, 10β-Me), 2.06 (s, 21-OAc), 3.88 and 4.49 (dd, *J* 11 Hz, 18-H_2), 4.28 (s, 21-H_2), *ca.* 4.44 (m, 11α-H), and 5.71 (s, 4-H).

The third component (3 mg) was not investigated.

18-*Hydroxycorticosterone* (1).—The foregoing two major fractions (the 4-en-3-one and its enol acetate; 40 mg) were

combined in methanol (2 ml) and aqueous potassium hydroxide (0.1 ml; 6%) was added. The solution was heated at reflux temperature for 30 min, water (20 ml) was added, and the steroid extracted into ethyl acetate (3 × 20 ml). The combined organic layers were dried (K_2CO_3) and taken to dryness on a rotary evaporator. The resulting oil (35 mg) was purified by preparative t.l.c. and crystallised from acetone, containing a trace of triethylamine, to give 18-hydroxycorticosterone (1) (20 mg), m.p. 147—150 °C [lit., 148—150 °C [9] and 163—164 °C (racemate) [5]], $\nu_{max.}$ 3 400, 1 670, 1 620, and 1 028 cm^{-1}; δ 1.44 (s, 10β-Me), 3.7 (d, *J* 6 Hz, 21-H_2), 3.8 and 4.35 (dd, *J* 11 Hz, 18-H_2), *ca.* 4.4 (m, 11α-H), and 5.65 (s, 4-H). The product was identical with material prepared previously.[9]

3β,11α-*Diacetoxypregn*-5-*eno*-18,20-*lactone* (10).—When the lactone (10) was required as the major product, the hypoiodite reaction was adjusted accordingly. 3β,11α-Diacetoxypregn-5-en-20-ol (7) (2.0 g) was added to cyclohexane (250 ml). To this mixture was added lead tetra-acetate (6.0 g) and iodine (1.32 g). The reaction was performed as described above for the synthesis of the hemi-acetal (8). The resulting gum, in acetone (25 ml), was cooled in ice and oxidised with Jones' reagent. The product was worked up as above, but without the silver acetate-assisted hydrolysis Crystallisation from acetone gave the lactone (10) (700 mg, 35%). A further 500 mg was obtained by column chromatography of the residues, which also afforded some 17-iodoandrostane derivative (340 mg, 17%). The total yield of lactone was 60%.

Pregn-5-*ene*-3β,11α,18,20-*tetraol* (12).—The lactone (10) (1.0 g) was dissolved in tetrahydrofuran (20 ml) and lithium aluminium hydride (300 mg) was added. The mixture was heated under reflux for 8 h, when t.l.c. showed a single very polar product. Ethyl acetate was carefully added to destroy excess of reagent, followed by a saturated solution of magnesium sulphate (10 ml) and additional solid magnesium sulphate, with stirring. The fine grey–white precipitate was filtered off, and thoroughly washed with ethyl acetate. The resulting solution was taken to dryness to yield the *tetraol* (12) as a white solid (0.79 g) which crystallised from methanol, m.p. 240—242 °C, $\nu_{max.}$ 3 350 and 1 028 cm^{-1}; δ($CDCl_3$–C_5D_5N, 1 : 1) 1.20 (s, 10β-Me), 1.23 (d, *J* 7 Hz, 21-H_3), *ca.* 3.1 (m, 20-H), *ca.* 3.75 (m, 18-H_2), *ca.* 4.35 (m, 3α-H), *ca.* 4.6 (m, 11β-H), and *ca.* 4.45 (m, 6-H) (Found: C, 71.5; H, 9.9. $C_{21}H_{34}O_4$ requires C, 71.9; H, 9.8%).

Pregn-5-*ene*-3β,11α,18,20-*tetraol Tetra-acetate* (13).—The foregoing tetraol (12) (500 mg) in pyridine (10 ml) and acetic anhydride (10 ml) was left overnight, then poured into water (10 ml), and the steroid was extracted into ether (3 × 100 ml). The combined extract was washed with sodium hydrogen carbonate solution and saturated sodium chloride solution, dried (K_2CO_3), and taken to dryness under reduced pressure. The resulting semi-solid product crystallised from acetone–hexane to yield the *tetra-acetate* (13) (0.70 g, in two crops), m.p. 136—140 °C, $\nu_{max.}$ 1 770, 1 380, 1 260, and 1 040 cm^{-1}; δ 1.08 (s, 10β-Me), 1.17 (d, *J* 6 Hz; 21-H_3), 2.00 and 2.02 (s, H_6, and s, H_3, 3-, 11-, and 20-OAc), 2.08 (s, 18-OAc), 4.28 and 3.65 (dd, *J* 12 Hz, 18-H_2), *ca.* 4.6 (m, 3α-H), *ca.* 4.7 (m, 20-H), *ca.* 5.0 (m, 11β-H), and *ca.* 5.45 (m, 6-H).

11α,18,20-*Triacetoxypregn*-5-*en*-3β-*ol*.—The foregoing tetra-acetate (13) (30 mg) in methanol (2 ml) with sodium hydrogen carbonate (10 mg) in water (0.5 ml) was left at room temperature for 48 h. Conventional work-up afforded 11α,18,20-triacetoxypregn-5-en-3β-ol (25 mg), $\nu_{max.}$ (CH_2Cl_2) 3 500, 1 770, 1 370, 1 050, and 900 cm^{-1}; δ 1.07 (s, 10β-Me), (d, *J* 6 Hz, 21-H_3), 2.0 (s, 11- and 20-OAc), 2.08 (s, 18-OAc), *ca.* 3.5 (m, 3α-H), 4.28 and 3.65 (dd, *J* 12 Hz, 18-H_2), *ca.* 4.7 (m, 20-H), *ca.* 5.0 (m, 11β-H), and *ca.* 5.4 (m, 6-H).

Further Hydrolysis.—The foregoing triacetate in methanol (2 ml) with methanolic potassium hydroxide (0.5 ml; 6%) was heated under reflux for 20 min and then worked up. T.l.c. showed the presence of at least three derivatives, all more polar than the triacetate. The major product (10 mg) isolated by preparative t.l.c. was 20-acetoxypregn-5-ene-3β,11α,18-triol (14), δ 1.06 (s, 10β-Me), 1.17 (d, *J* 6 Hz, 21-H_3), 2.02 (s, 20-OAc), *ca.* 3.4 (m, 3β-H), *ca.* 3.6 (m, 18-H_2), *ca.* 3.9 (m, 11β-H), *ca.* 4.8 (m, 20-H), and *ca.* 5.4 (m, 6-H).

Of the two other minor derivatives the most polar (5 mg) had the same t.l.c. mobility as pregn-5-ene-3β,11α,18,20-tetraol, while the other (3 mg) had a mobility intermediate between the triacetate and the 20-acetate, so could well be a diacetate, probably 18,20-diacetoxypregn-5-ene-3β,11α-diol.

Pregn-5-*ene*-3β,11α,18,20-*tetraol Tetrapivaloate*.—The tetraol (12) (50 mg) in pivaloyl chloride (5 ml) was left at room temperature for 18 h, then poured into water, and worked up in the usual way to give the tetrapivaolate (72 mg), m.p. 170—174 °C (acetone), $\nu_{max.}$ 1 770, 1 270, and 1 170 cm^{-1}; δ 1.14, 1.18, 1.20, and 1.25 (each s, Me_3C), 4.0 (s, 18-H_2), *ca.* 4.6 (m, 3α-H), *ca.* 4.9 (m, 20-H), *ca.* 5.2 (m, 11β-H), and *ca.* 5.4 (m, 6-H).

Hydrolysis of the Tetrapivaloate.—The tetrapivaloate was stable to methanolic or ethanolic potassium hydroxide at reflux temperature. Hydrolysis was achieved by dissolving the ester (50 mg) in anhydrous ether (5 ml), and adding water (4 μl) followed by potassium t-butoxide (200 mg). The resulting yellow solution was stirred for 6 h, when t.l.c. showed a single spot with the same mobility as the tetraol. The tetraol (12) (20 mg) was isolated after conventional work-up.

Oppenauer Oxidation of Pregn-5-*ene*-3β,11α,18,20-*tetraol* (12).—The tetraol (12) (100 mg) was dissolved in toluene (5 ml) to which was added *N*-methyl-4-piperidone (0.5 ml), then 0.5 ml of toluene was distilled off. Aluminium isopropoxide (250 mg) was added and the mixture was heated under reflux for 5 h. After cooling and conventional work-up, t.l.c. showed three distinct products, which were isolated by preparative thin-layer chromatography and characterised by n.m.r. spectroscopy. The most mobile was 11α-hydroxy-3-oxopregn-4-eno-18,20-lactone (55 mg), δ 1.37 (d, *J* 6 Hz, 21-H_2), 1.4 (s, 10β-Me), 4.4 (q, *J* 6 Hz, 20-H), *ca.* 4.5 (m, 11β-H), and 5.74 (s, 4-H). The middle fraction was 18,20-epoxy-11α,20-dihydroxypregn-4-en-3-one (20 mg), δ 1.28 (s, 10β-Me), 1.50 (s, 21-H_3), *ca.* (3.784) 11β-H), *ca.* 3.75 (dd, *J* 8 Hz, 18-H_2), and 5.74 (s, 4-H). The most polar compound was 11α,18,20-trihydroxypregn-4-en-3-one (15 mg), δ 1.19 (d, *J* 6 Hz, 21-H_3), 1.28 (s, 10β-Me), 3.6 (s, 18-H_2), *ca.* 3.8 (m, 20-H), *ca.* 4.1 (m, 11β-H), and 5.7 (s, 4-H).

Cholest-4-*en*-3-*one*.—Cholesterol (200 mg) in dry dichloromethane (5 ml) was added to chromium trioxide (100 mg) and 3,5-dimethylpyrazole (100 mg) and the mixture then stirred for 18 h. The solution was poured into ether (20 ml) and filtered through Celite. The filtrate was stirred with finely powdered sodium hydrogen sulphate (2.0 g), filtered, and taken to dryness under reduced pressure to yield a yellow gum. Preparative t.l.c. gave cholest-4-en-3-one (150 mg) identical with an authentic sample.

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