18-Substituted Steroids. Part 6.[1] Synthesis of 3α,18-Dihydroxy-11β,18-epoxy-5β-pregnan-20-one (21-Deoxy-3α,5β-tetrahydroaldosterone)

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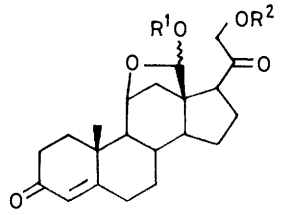
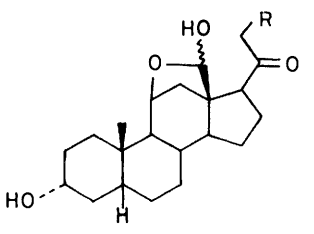
21-Deoxy-3α,5β-tetahydroaldosterone (5) has been prepared from 3α-acetoxy-20β-hydroxy-5β-pregnan-11-one (7) *via* the hypoiodite reaction sequence (lead tetra-acetate–iodine–*hν*; oxidation) followed by reduction and rearrangement of 18,20β-lactone-11-ketone (13) to the 18,11β-lactone-20β-alcohol (14). Reduction of the 18,11β-lactone-20β-alcohol (14) with di-isobutylaluminium hydride afforded the 18,11β-hemiacetal-20β-alcohol (17), which gave the 18,20-diacetate (18). Treatment of the diacetate with acidic methanol gave the 18-methoxy-20β-acetate (19) by selective solvolysis at C-18. Removal of the 20-acetate with lithium aluminium hydride, followed by oxidation with Collins' reagent, and acid hydrolysis of the protecting groups then afforded 21-deoxy-3α,5β-tetrahydroaldosterone (5) in 20% overall yield.

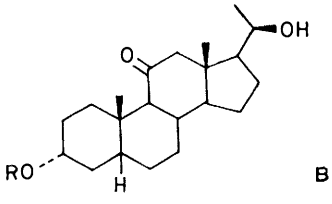
THE metabolism of aldosterone (18,21-dihydroxy-11β,18-epoxypregn-4-ene-3,20-dione) (1) has been the subject of extensive research.[2-15] Ten urinary metabolites have been isolated from artificially administered aldosterone,[6] but efficient chemical syntheses of many of these metabolites have not been reported. We have explored



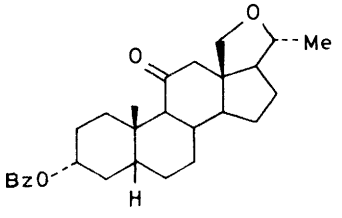
(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = Ac$
(3) $R^1 = R^2 = Ac$



(4) R = OH
(5) R = H



(6) R = Bz
(7) R = Ac



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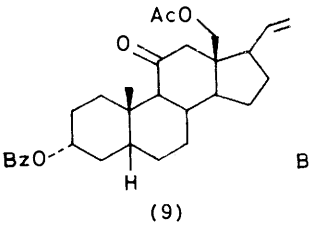

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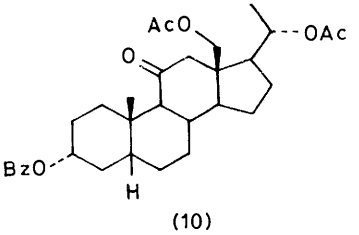

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methods for the synthesis of two of the metabolites, 3α,5β-tetrahydroaldosterone (11β,18-epoxy-3α,18,21-trihydroxy-5β-pregnan-20-one) (4) and 21-deoxy-3α,5β-tetrahydroaldosterone (3α,18-dihydroxy-11β,18-epoxy-5β-pregnan-20-one) (5). Approximately 30% of artificially administered aldosterone is excreted as 3α,5β-tetrahydroaldosterone[4,6] and approximately 1% as 21-deoxy-3α,5β-tetrahydroaldosterone.[7]

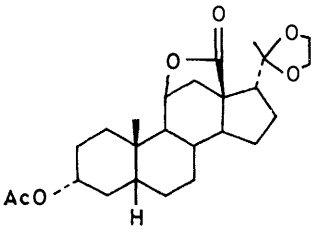
Previous chemical syntheses of 3α,5β-tetrahydroaldosterone have involved the reduction of the 4-en-3-one unit of aldosterone 21-acetate (2)[8] and aldosterone 18,21-diacetate (3).[16] However, these reactions led to the formation of the four possible isomers (at C-3 and C-5) of tetrahydroaldosterone, the separation of which required careful chromatography.[16] To avoid these problems the starting material for our synthesis was chosen to possess the required configurations at C-3 and C-5. The main objectives of the synthesis were, therefore, the introduction of functionality at C-18 and C-21. This paper reports the synthesis of 21-deoxy-3α,5β-tetrahydroaldosterone (5) from 3α-acetoxy-20β-hydroxy-5β-pregnan-11-one (7). The synthesis of 3α,5β-tetrahydroaldosterone (4) will be reported in a later paper.

The Barton reaction of an 11β-nitrite was unsuitable for our purpose, since attack on C-18 is favoured only in the presence of a 1,4-dien-3-one system.[17] We therefore explored two reaction schemes for the introduction of functionality at C-18 from a C-20 alcohol. In the first, irradiation of 3α-benzoyloxy-20β-hydroxy-5β-pregnan-11-one (6) with a high pressure mercury lamp in the presence of lead tetra-acetate[18] gave 3α-benzoyloxy-18,20β-epoxy-5β-pregnan-11-one (8).[19] Cleavage of the 18,20β-ether with acetic anhydride and toluene-*p*-sulphonic acid is reported to give 18-acetoxy-3α-benzoyloxy-5β-pregn-20-en-11-one (9).[20] However, an attempt to repeat this reaction gave only a low yield of 18,20α-diacetoxy-3α-benzoyloxy-5β-pregnan-11-one (10) and the unchanged 18,20β-ether (8).[19] Treatment of the 18,20β-ether (8) with acetic anhydride in the presence of boron trifluoride–diethyl ether, hydrogen bromide, iron(III) chloride, or methylamine hydrochloride also gave mixtures of the diacetate (10) and unchanged 18,20β-ether (8).[19] Only unchanged starting material was obtained from an attempt to cleave the 18,20β-ether (8) with formic acid.[19]

Since even the 18,20-diacetate (10) seemed an inconvenient intermediate for further manipulation of

functionality, this approach was abandoned in favour of a sequence of reactions based upon the hypoiodite reaction [21] of 3α-acetoxy-20β-hydroxy-5β-pregnan-11-one (7) with lead tetra-acetate and iodine which gave 3α-acetoxy-11-oxo-5β-pregnano-18,20β-lactone (11) in 55% yield.

Hydrolysis of the 3α-acetoxy-18,20β-lactone (11) with potassium carbonate in aqueous methanol followed by reaction of the 3α-alcohol (12) with 2,3-dihydropyran gave 11-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,20β-lactone (13) in 95% yield. Reduction of the 11-oxo group in the 18,20β-lactone (13) then gave the 18,11β-lactone (14) *via* the 11β-hydroxy-18,20β-lactone (33), which rearranged under the reaction conditions to



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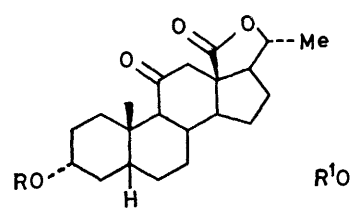
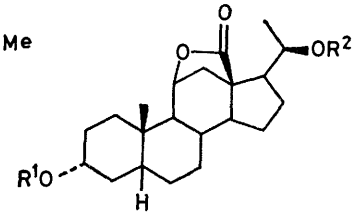
the more stable 18,11β-lactone (14). When reduction of the 11-oxo-18,20β-lactone (13) was carried out with sodium borohydride and sodium hydroxide in tetrahydrofuran and ethanol [22] for 30 h the required 20β-hydroxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (14) was obtained only in 40% yield, with 17% of unchanged 11-oxo-18,20β-lactone (13). Reduction of the 11-oxo-18,20β-lactone (13) with zinc borohydride, however, was completed in 1.5 h and gave the 18,11β-lactone (14) in 75% yield, with a little (7%) of the corresponding hemiacetal (17). The hemiacetal (17) was not formed from further reduction of the 18,11β-lactone (14), since this lactone was stable to an excess of zinc borohydride for up to 36 h. The hemiacetal (17) was therefore probably formed by reduction at the 18,20β-lactone stage, followed by rearrangement to the 18,11β-hemiacetal (17) (Scheme 1).

The rearrangement of the 11-oxo-18,20β-lactone (13) to the 18,11β-lactone (14) was characterised in the n.m.r. spectrum by the disappearance of the singlet at δ 2.59 for 12-H_2 and the appearance of a double doublet at δ 3.13 ($J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz) for the strongly deshielded 12β-hydrogen, as well as a doublet at δ 4.69 ($J_{11\alpha,12\beta}$ 6 Hz) for 11α-H. The 12α-proton was located at δ 1.80 by decoupling experiments. This pattern of signals is characteristic of compounds which possess either the 18,11β-lactone or 18,11β-hemiacetal units (Experimental section), the chemical shifts of the signals being sensitive to the oxidation level at C-18. Analogous results have been reported for the C-1 and C-2 hydrogens in compounds possessing 19,2β-lactone and 19,2β-ether units.[23]

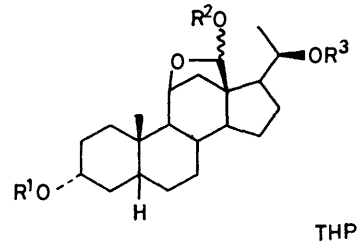
Reduction of the 18,11β-lactone (14) with di-isobutylaluminium hydride gave quantitatively the 18,11β-hemiacetal (17). Typically the reduction of a lactone with di-isobutylaluminium hydride is carried out with two molar equivalents [24–26] of the reducing agent, but the 18,11β-lactone (14) required five molar equivalents for complete reduction. With two molar equivalents of di-isobutylaluminium hydride the reduction proceeded only to about 50% completion even in refluxing toluene. This suggests that a proportion of the reducing agent



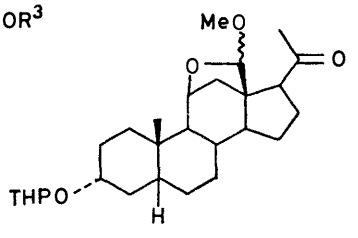
(11) R = Ac
(12) R = H
(13) R = THP



(14) R^1 = THP R^2 = H
(15) R^1 = THP, R^2 = CH_2Ph
(16) R^1 = Ac, R^2 = H



(17) R^1 = THP, R^2 = R^3 = H
(18) R^1 = THP, R^2 = R^3 = Ac
(19) R^1 = THP, R^2 = Me, R^3 = Ac
(20) R^1 = H, R^2 = Me, R^3 = Ac
(21) R^1 = THP, R^2 = Me, R^3 = H
(22) R^1 = R^2 = H, R^3 = Ac
(23) R^1 = THP, R^2 = H, R^3 = CH_2Ph



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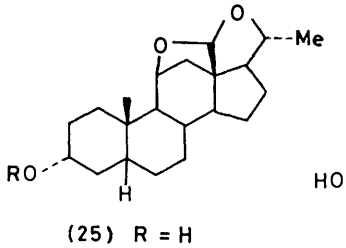
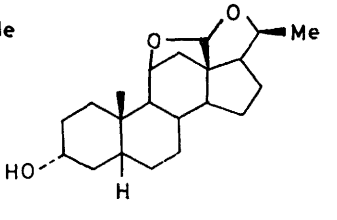


(25) R = H
(26) R = THP



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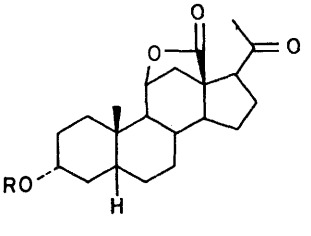
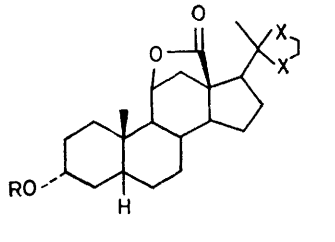


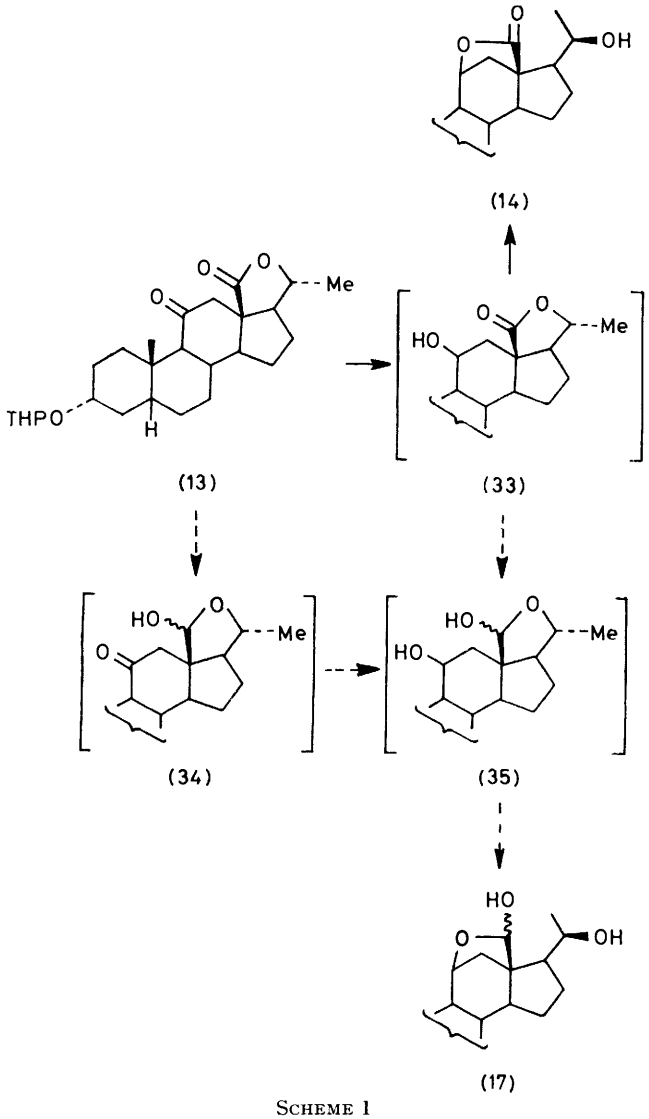
(28) R = THP
(29) R = Ac



(30) R = Ac, X = O
(31) R = H, X = S

THP = tetrahydropyran-2-yl

becomes complexed to the molecule in such a way that the hydride cannot be delivered to C-18.

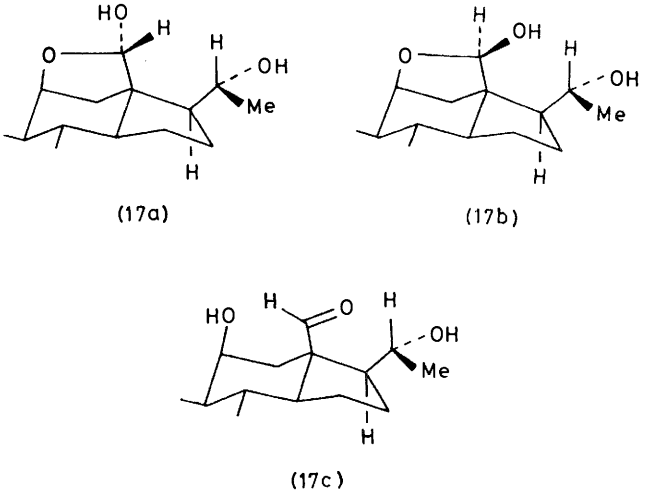


SCHEME 1

Reduction of the 18,11β-lactone (14) to the 18,11β-hemiacetal (17) introduced a new asymmetric centre at C-18 but the n.m.r. spectrum of the 18,11β-hemiacetal (17) showed only a single peak at δ 5.03 for the 18-hydrogen, and t.l.c. showed only one spot. From examination of models the preferred configuration at C-18 appears to be that with the hydroxy-group *exo* [27] (18*S*) (17a), in which the hydroxy-group is directed away from the axial 8β-hydrogen. The (18*S*)-isomer (17a) can also be stabilised by hydrogen bonding between the hydroxy-groups at C-18 and C-20. However, the preferred direction of attack of the hydride at C-18 on the 18,11β-lactone (14) would appear to be from the less hindered *exo* side; [27] an initially formed 18*R* isomer (17b) would be expected to isomerise readily *via* the aldehyde form (17c).

The 18,11β-hemiacetal (17) had the required oxidation levels at C-3, C-11, and C-18; the final series of transformations was concerned with achieving a selective oxidation at C-20.

The 18,11β-hemiacetal (17) can be protected as the base-stable tetrahydropyranyl ether [28] or the methyl ether.[5,29,30] In this laboratory it has been observed that hemiacetal methyl ethers can be prepared readily by treating a methanolic solution of the hemiacetal with a little aged ethanol-free chloroform.* However,



when the 18,11β-hemiacetal (17) was treated with slightly acidic methanol in this manner the products were 11β,-18;18,20β-diepoxy-5β-pregnan-3α-ol (25), and its 3-tetrahydropyranyl ether (26) in a ratio of about 1 : 1, formed from intramolecular dehydration of the 18,11β-hemiacetal (17) (Scheme 2). The 11β,18;18,20β-bridged ether (25) has not been found as a naturally occurring metabolite of aldosterone (1), although its 20α-isomer (27) has been isolated from urine to the extent of 8% of artificially administered aldosterone.[6,32]

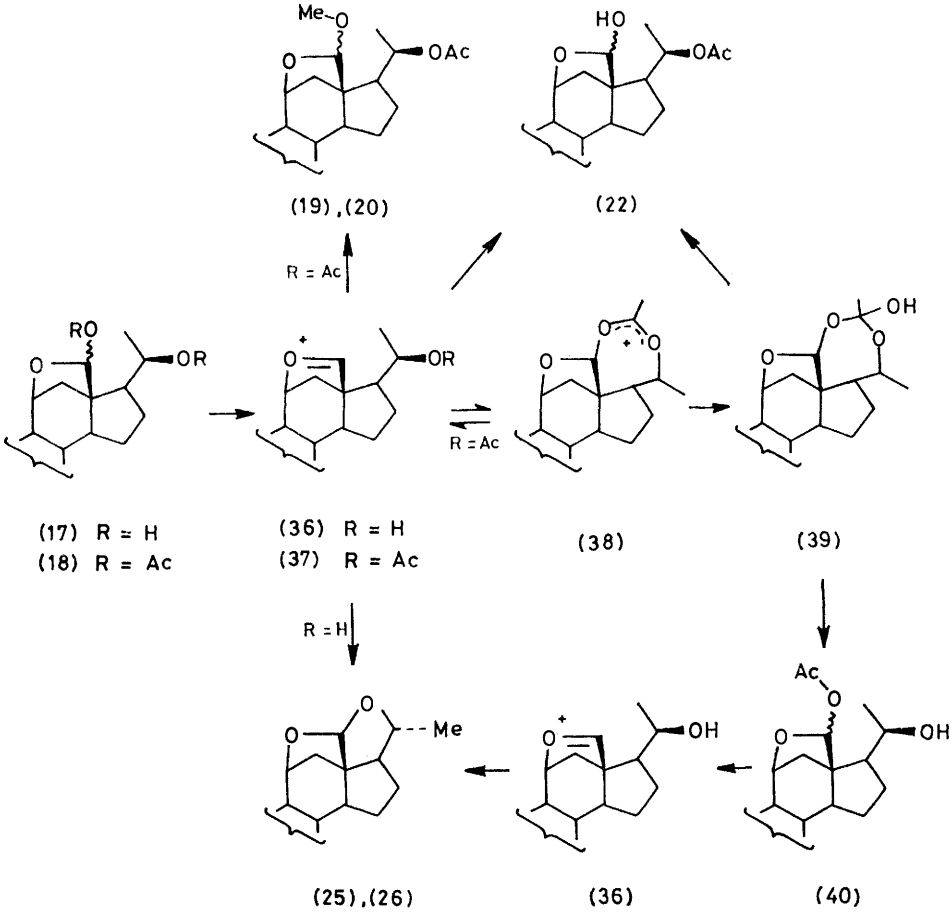
In order to protect the 18,11β-hemiacetal (17) as its methyl ether (21) it was necessary first to protect the hydroxy-group at C-20, to prevent the intramolecular quenching of the oxonium ion (36). Acetylation of the 18,11β-hemiacetal (17) with acetic anhydride in pyridine gave the 18,20β-diacetate (18) which when treated with acidic methanol was selectively solvolysed at C-18 *via* the oxonium ion (37), which was then trapped by methanol. The product, a mixture of 20β-acetoxy-11β,18-epoxy-18-methoxy-3β-(tetrahydropyran-2-yloxy)-5β-pregnane (19) and the corresponding free 3α-hydroxy compound (20), was treated with 2,3-dihydropyran and toluene-*p*-sulphonic acid in anhydrous tetrahydrofuran to give 20β-acetoxy-11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnane (19) in 81% overall yield from the 18,11β-hemiacetal (17).

Similarly, hydrolysis of the diacetate (18) with 50% (v/v) aqueous acetic acid at room temperature gave 20β-acetoxy-11β,18-epoxy-5β-pregnane-3α,18-diol (22) as the

* Reagent grade chloroform was purified [31] to remove ethanol, redistilled, and set aside in a clear bottle for several days.

major product, with a little 11β,18;18,20β-diepoxy-5β-pregnan-3α-ol (25), probably formed *via* an intramolecularly assisted hydrolysis of the diacetate (18) through the cyclic orthoester (39) (Scheme 2).

Reduction of the 18-methoxy-20-acetate (19) with lithium aluminium hydride gave the required 20-alcohol (21) in 72% yield, together with some 11β,18;18,-20β-diepoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnane (26) (9%).



SCHEME 2

The formation of the 18-methoxy-20-acetate (19) by the action of methanol on the oxonium ion (37) gives rise to the possibility of there being products epimeric at C-18. The n.m.r. spectrum of the product showed only one set of signals and t.l.c. with ethyl acetate–hexane mixtures gave evidence for only one compound. Similarly the n.m.r. spectrum of the derived 18-methoxy-20-alcohol (21) appeared to be that of a single compound, but t.l.c. with chloroform–methanol (19 : 1) clearly showed the presence of two components. A series of n.m.r. experiments using the lanthanoid shift reagent tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium, $Eu(fod)_3$, also clearly showed that the 18-methoxy-20-alcohol (21) was a mixture of two components, presumably epimeric at C-18, in the ratio of *ca.* 1 : 1. The experiments showed the expected lanthanoid-induced downfield shifts for all of the signals, and also splitting of the signals assigned to the 18-methoxy group and the 18-hydrogen. For example, after addition of 1 mol. equiv. of $Eu(fod)_3$ the chemical shifts for the 18-methoxy group were δ 4.16 and 4.21 and those for the 18-hydrogen were δ 5.87 and 5.96. No splitting was observed for the 20-proton. It is not known whether the composition of the mixture was kinetically or thermodynamically determined. A similar series of experiments on the 18-methoxy-20-ketone (24) showed the expected lanthanoid-induced downfield shifts, and some line-broadening, but unlike the experiments with the 18-methoxy-20-alcohol (21) failed to give evidence of the presence of two distinct epimers. In this case, however, t.l.c. with chloroform–methanol (19 : 1) showed that the 18-methoxy-20-ketone (24) was a mixture of two closely similar compounds.

Oxidation of the 20-hydroxy-function in the presence of acid-sensitive 3-tetrahydropyranyloxy and 18-methoxy groups required a non-acidic reagent.

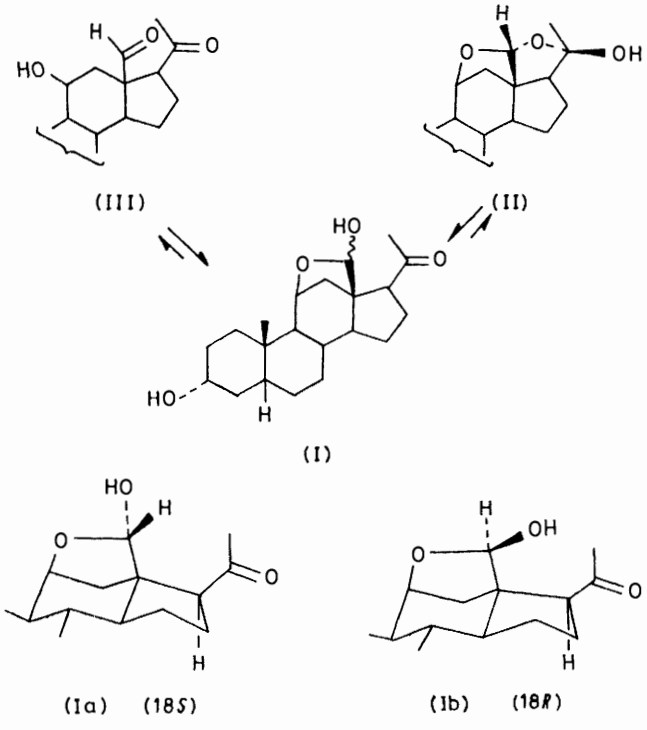
Exploratory reactions were first carried out on 20β-hydroxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (14). Oxidation with pyridinium chlorochromate [33] buffered by anhydrous potassium acetate gave 20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-

18,11β-lactone (28) in 81% yield, but oxidation with the chromium trioxide–3,5-dimethoxylpyrazole complex [34] was less satisfactory as partial hydrolysis of the tetrahydropyranyl ether occurred during work-up. When 11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20β-ol (21) was oxidised with buffered pyridinium chlorochromate, however, the product was a mixture of the required 20-oxo derivative (24) with the 11β,18;18,20β-diepoxide (26) and unchanged 18-methoxy-20-alcohol (21) in a ratio of 3 : 1 : 1.

The required oxidation of the 20-alcohol (21) to the 20-ketone (24) was finally achieved in 83% yield using a 12 molar excess of Collins' reagent (CrO_3·2pyridine) [35] prepared *in situ* in dichloromethane.[36,37]

21-Deoxy-3α,5β-tetrahydroaldosterone (5) was obtained from 11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (24) in 80% yield by hydrolysis with 1M hydrochloric acid in tetrahydrofuran at room temperature. When hydrolysis was attempted with 50% (v/v) aqueous acetic acid at room temperature the methoxy-group was only partially removed even after 48 h. This observation contrasted with complete hydrolysis of the 18,20β-diacetate (18) in 30 h under the same conditions.

The i.r. spectrum of 21-deoxy-3α,5β-tetrahydroaldosterone (5) (Experimental section) showed a carbonyl peak which was reduced in intensity by 35% in potassium bromide and 20% in chloroform solution compared with the carbonyl peak of the 18-methoxy-20-ketone



(24). The n.m.r. spectrum of 21-deoxy-3α,5β-tetrahydroaldosterone (5), however, showed only those signals assigned to the 18,11β-hemiacetal-20-ketone form (I). The methyl protons at C-19 and C-21 appeared only as singlets and there was an absence of the multiplicity of signals between δ 2.0 and 6.0 which is characteristic of the n.m.r. spectra of aldosterone (I) [38,39] and 3α,5β-tetrahydroaldosterone (4).[40] These results suggest that in solution 21-deoxy-3α,5β-tetrahydroaldosterone (5) exists mainly in the 18,11β-hemiacetal-20-ketone form (I); the proportion of the 20-hydroxy-11β,18;18,-20β-diepoxy form (II) in the equilibrium mixture must be small. On the evidence of the i.r. spectrum in potassium bromide the 20-hydroxy-11β,18;18,20-diepoxy form (II) is relatively more important in the crystalline state, but is still a minor component. The hydroxy-aldehyde form (III) did not make any observable contribution to the equilibrium state of 21-deoxy-3α,5β-tetrahydroaldosterone (5).

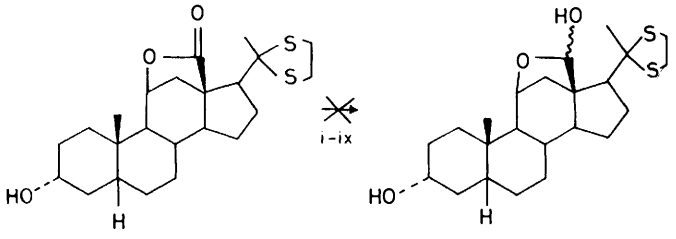
The n.m.r. spectrum of 21-deoxy-3α,5β-tetrahydroaldosterone (5) showed two sets of signals for both the 18-proton and the 11α-proton, indicating the presence of two epimeric forms at C-18 of the 18,11β-hemiacetal-20-ketone (I). The 18-proton appeared as two singlets at δ 4.95 and 4.88 in a ratio of peak heights of *ca.* 5 : 1, and the 11α-proton appeared as two overlapping doublets (*J* 6 Hz) centred at δ 4.51 and 4.48, also with a peak height ratio of *ca.* 5 : 1. The preferred configuration at C-18 is probably (18*S*) (Ia), the minor (18*R*)-isomer (Ib) being sterically more hindered.

Finally we report briefly on alternative routes which were explored, but found to be unsuitable, for introducing the correct oxidation levels at C-18 and C-20.

At the stage of the 20β-hydroxy 18,11β-lactone (14) the 20β-alcohol was protected as the benzyl ether (15), and the lactone was then reduced to give the 18,11β-hemiacetal-20β-benzyl ether (23). However, this procedure was less efficient (Experimental section) than the preparation of the 18,11β-hemiacetal (17) and its subsequent transformation into the 18-methoxy-20β-alcohol (21) according to the procedure described above.

Attempts were also made to protect the functional group at C-20 at the oxidation level of the ketone, to permit subsequent reduction of the 18,11β-lactone. Oxidation of the 18,11β-lactone-20-alcohol (16) with Jones' reagent gave the 18,11β-lactone-20-ketone (29). However, the ethylene acetal proved to be an unsuitable protecting group for the ketone as epimerisation occurred at C-17 under the conditions necessary for reaction with ethane-1,2-diol, giving a mixture of ethylene acetals (30) and (32), in which the 17α-isomer (32) predominated. Other examples of epimerisation at C-17 have been reported.[41,42] To overcome this problem the use of the ethylene thioacetal as a protecting group was investigated. Reaction of 20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (28) with ethane-1,2-dithiol and boron trifluoride–diethyl ether [43] gave 20,20-ethylenedithio-3α-hydroxy-5β-pregnano-18,-11β-lactone (31) in 80% yield, with no epimerisation at C-17. The accompanying loss of the tetrahydropyranyl ether from C-3 was not important as this protecting group could readily be reintroduced. However, all

attempts to reduce the lactone group in the ethylene thioacetal (31) to the 18,11β-hemiacetal-20-ethylene thioacetal (41) failed. The complex metal hydrides i—viii (Scheme 3) all gave unchanged ethylene thioacetal (31) as the only product, presumably owing to excessive steric hindrance by the thioacetal unit to hydride attack. Sodium–liquid ammonia gave a complex mixture of products in which both the ethylene thioacetal unit and the pregnane side chain appeared to have been cleaved.



(31) (41)

SCHEME 3 *Reagents:* i, $AlHBu^{i}_2$, C_6H_{14}, −60 °C; ii, $LiAl(OEt)_3H$, DME (1,2-dimethoxyethane), 0 °C; iii, $LiAl(OEt)_3H$, DME, heat; iv, $LiAlH_4$, THF (tetrahydrofuran), 0 °C; v, $LiAlH_4$, THF, heat; vi, $LiAlH_4$, $(MeOCH_2CH_2)_2O$, heat; vii, $LiAlH_4$, PhMe, heat; viii, $NaBH_4$, $LiBH_4$, $Pr^{i}OH$, heat; ix, Na–liquid NH_3

EXPERIMENTAL

M.p.s were determined on a Reichert melting point microscope. I.r. spectra were determined for potassium bromide discs and for solutions in chloroform. N.m.r. spectra were determined at 100 MHz for solutions in deuteriochloroform with tetramethylsilane as internal standard. All solvents were purified before use.[31] ' Hexane ' refers to the petroleum fraction of boiling range 60—80 °C. Column chromatography was carried out on silica gel (Joseph Crosfield M.60 grade). Thin layer chromatography (t.l.c.) was carried out on Kieselgel 60 $PF_{254+366}$.

3α-*Acetoxy*-20β-*hydroxy*-5β-*pregnan*-11-*one* (7).—A solution of sodium borohydride (3.15 g, 0.08 mol) in methanol (120 ml) and water (120 ml) was added to a rapidly stirred solution of 3α-acetoxy-5β-pregnane-11,20-dione [44] (25.8 g, 0.07 mol) in methanol (800 ml) at 0 °C dropwise over 30 min. The mixture was stirred at 0 °C for 1.5 h and then diluted with water (250 ml) and filtered. The residue was washed with water (4 × 50 ml) and dried to give crude 3α-acetoxy-20β-hydroxy-5β-pregnan-11-one (7) (12.37 g) as a white powder which crystallised from ethyl acetate–hexane as needles (9.56 g, 37%), m.p. 206—207 °C (lit.,[45] 205—208 °C); $\nu_{max.}$ (KBr) 3 460s, 1 735s, 1 695s, and 1 253s cm^{-1}; δ($CDCl_3$) 0.67 (s, 18-H_3), 1.13 (d, *J* 6 Hz, 21-H_3), 1.15 (s, 19-H_3), 2.48 (dd, *J* 12 Hz, δ_A 2.29, δ_B 2.67, 12-H_2), 3.66 (m, 20-H), and 4.70 (m, 3β-H). The filtrates were concentrated under reduced pressure to a volume of 350 ml and then diluted with water (200 ml), and filtered. The residue was washed with water (4 × 50 ml) and dried as described above to give more crude product (12.37 g) which was combined with the mother liquors and chromatographed on silica gel (350 g). Elution with hexane–ethyl acetate (7 : 3) gave more pregnanone (7) (6.13 g, 24%) which crystallised from ethyl acetate–hexane as needles, m.p. 200—203 °C.

3α-*Acetoxy*-11-*oxo*-5β-*pregnano*-18,20β-*lactone* (11).—3α-Acetoxy-20β-hydroxy-5β-pregnan-11-one (7) (3.01 g, 0.008 mol) was dissolved with warming and stirring in cyclohexane (450 ml). To the vigorously stirred solution was added iodine (2.35 g, 0.009 6 mol) and lead tetra-acetate (17.74 g, 0.04 mol) and the mixture was heated under reflux while being irradiated with two 500 W tungsten lamps. After 1.5 h the iodine colour was lost, leaving a white precipitate and a clear supernatant solution. The mixture was allowed to cool and was filtered. The precipitate was washed with cyclohexane (2 × 100 ml) and diethyl ether (4 × 50 ml), and the filtrates were combined and washed successively with aqueous sodium thiosulphate (2 × 20 ml and 1 × 10 ml of a 10% w/v solution) and water (2 × 20 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure below 40 °C yielded a colourless viscous oil which was immediately dissolved in acetone (100 ml). The solution was cooled to 0 °C and was stirred while Jones' chromic acid reagent [46] was added dropwise until an orange colour remained (3 ml). The mixture was stirred at 0 °C for 1 h and was then treated with aqueous sodium acetate (120 ml of a 20% w/v solution) and extracted with benzene (4 × 100 ml); the extracts were washed with saturated aqueous sodium chloride (2 × 20 ml and 1 × 10 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded crude 3α-acetoxy-11-oxo-5β-pregnano-18,20β-lactone (11) (5.75 g), as a yellow oil which crystallised when set aside.

This procedure was repeated four more times. The products were combined and crystallised (hexane–ethyl acetate) to give the lactone (11) (11.61 g, 55%), as colourless needles, m.p. 234—239 °C (lit.,[47] 242—243 °C); $\nu_{max.}$ (KBr) 1 760s, 1 735s, 1 715s, and 1 245s cm^{-1}; δ($CDCl_3$) 1.22 (s, 19-H_3), 1.34 (d, *J* 6 Hz, 21-H_3), 2.00 (s, OAc), 2.60 (s, 12-H_2), 4.40 (q, *J* 6 Hz, 20-H), and 4.70 (m, 3β-H) (Found: C, 71.1; H, 8.4. Calc. for $C_{23}H_{32}O_5$, C, 71.1; H, 8.3%).

3α-*Hydroxy*-11-*oxo*-5β-*pregnano*-18,20β-*lactone* (12).—A solution of 3α-acetoxy-11-oxo-5β-pregnano-18,20β-lactone (11) (8.22 g, 0.021 mol) and potassium carbonate (3.48 g, 0.025 mol) in methanol (250 ml) and water (17.5 ml) was heated under reflux for 1 h then concentrated under reduced pressure to about 50 ml. The residue was diluted with ice–water (50 ml) and extracted with ethyl acetate (2 × 100 ml). The aqueous layer was then acidified (pH 3) with dilute hydrochloric acid and extracted with more ethyl acetate (3 × 100 ml). The ethyl acetate solutions were combined, washed with water (2 × 50 ml), and dried ($MgSO_4$). Removal of the solvent gave crude 3α-*hydroxy*-11-*oxo*-5β-*pregnano*-18,20β-*lactone* (12) (7.38 g) which crystallised from hexane–acetone as colourless plates, m.p. 180—183 °C; $\nu_{max.}$ (KBr) 3 590s, 3 500—3 150s,br, 1 750s, 1 730s, 1 705s, 1 250m, 1 050m, and 945m cm^{-1}; $\nu_{max.}$ ($CHCl_3$) 3 550m, 1 760s, 1 705s, and 1 200m cm^{-1}; δ($CDCl_3$) 1.20 (s, 19-H_3), 1.34 (d, *J* 6 Hz, 21-H_3), 2.60 (s, 12-H_2), 3.63 (m, 3β-H), 4.40 (q, *J* 6 Hz, 20-H) (Found: C, 72.8; H, 8.8. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%).

11-*Oxo*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnano*-18,20β-*lactone* (13).—2,3-Dihydropyran (9.6 ml, 0.105 mol) and toluene-*p*-sulphonic acid monohydrate (0.16 g, 0.84 mmol) were added to a solution of 3α-hydroxy-11-oxo-5β-pregnano-18,20β-lactone (12) (7.38 g, 0.021 mol) in tetrahydrofuran (210 ml) and the mixture was stirred at room temperature for 1.5 h. The solution was then diluted with ether (240 ml containing 1% v/v of triethylamine) and the ethereal solution was washed with aqueous sodium hydrogen carbonate (2 × 15 ml of a saturated solution). The aqueous washings

were combined and extracted with ethyl acetate (50 ml) and the combined ether and ethyl acetate extracts were washed with water (2 × 15 ml) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave the crude *tetrahydropyranyl ether* (13) (8.57 g, 95%) which crystallised from hexane–ethyl acetate as needles, m.p. 185—194 °C; $\nu_{max.}$ (KBr) 1 760s, 1 710s, 1 245m, 1 150m, 1 080s (OTHP), and 1 030s (OTHP) cm^{-1}; δ($CDCl_3$) 1.21 (s, 19-H_3), 1.33 (d, *J* 6 Hz, 21-H_3), 2.59 (s, 12-H_2), 3.30—4.06 (3 H, m, 3β-H and 6′-H_2), 4.40 (q, *J* 6 Hz, 20-H), and 4.70br (s, 2′-H) (Found: C, 72.2; H, 8.8. $C_{26}H_{38}O_5$ requires C, 72.5; H, 8.9%).

20β-*Hydroxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnano*-18,11β-*lactone* (14): *Reduction of the* 11-*Oxo*-18,20β-*lactone* (13) *with Zinc Borohydride*.[48]—Zinc borohydride (585 ml of a 0.1M solution in 1,2-dimethoxyethane, 0.058 5 mol) was added to a stirred solution of the 11-oxo-18,20β-lactone (13) (8.41 g, 0.019 mol) in 1,2-dimethoxyethane (65 ml) at room temperature under nitrogen and the mixture was stirred and heated under reflux under nitrogen for 1.5 h. The mixture was allowed to cool and excess of reagent was destroyed by addition of aqueous sodium hydrogen carbonate (26 ml of a saturated solution added in 2 ml portions) and then water (5 ml). The mixture was filtered and the grey solid residue was washed on the filter with diethyl ether (3 × 100 ml containing 1% of triethylamine) and ethyl acetate (3 × 50 ml). The filtrates were combined, washed with water until the aqueous washings were clear (5 × 20 ml), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure left a gum (10.13 g) which was chromatographed on silica gel (350 g). Elution with ethyl acetate–hexane (1 : 1) gave 20β-*hydroxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnano*-18,11β-*lactone* (14) (6.30 g, 75%), plates from acetone–hexane, m.p. 177—182 °C; $\nu_{max.}$ (KBr) 3 520m, 1 765s, 1 065m (OTHP) and 1 030s (OTHP) cm^{-1}; δ($CDCl_3$) 0.99 (s, 19-H_3), 1.17 (d, *J* 6 Hz, 21-H_3), 3.13 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.30—4.10 (3 H, m, 3β-H and 6′-H_2), 4.27 (m, 20-H), and 4.69br (2 H, d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H and 2′-H) (Found: C, 72.1; H, 9.4. $C_{26}H_{40}O_5$ requires C, 72.2; H, 9.3%). Further elution with ethyl acetate–hexane (3 : 2) gave 11β,18-*epoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnane*-18,20β-*diol* (17) (0.62 g, 7%), needles from acetone–hexane, m.p. 174—179 °C; $\nu_{max.}$ (KBr) 3 600—3 050 s,br, 1 115m, 1 060s (OTHP), 1 025s (OTHP), and 1 015s (OTHP) cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 1.17 (d, *J* 6 Hz, 21-H_3), 2.76 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.30—4.25 (4 H, m, 3β-H, 20-H, and 6′-H_2), 4.40 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.71br (s, 2′-H), and 5.03 (s, 18-H); (Found: C, 71.6; H, 9.2. $C_{26}H_{42}O_5$ requires C, 71.85; H, 9.7%).

Reduction of the 11-*Oxo*-18,20β-*lactone* (13) *with Sodium Borohydride*.[22]—A solution of sodium borohydride (19.3 mg, 0.5 mmol) in absolute ethanol (2.5 ml) and 1M aqueous sodium hydroxide (0.2 ml, 0.2 mmol) was added to a stirred solution of the 11-oxo-18,20β-lactone (13) (44.1 mg, 0.1 mmol) in tetrahydrofuran (2.5 ml) and the mixture was stirred at 40—45 °C for 2 days. The mixture was then poured on to ice–water (10 ml) and 2M aqueous hydrochloric acid was added to neutrality. The aqueous solution was then extracted with chloroform (2 × 10 ml) and the combined chloroform solutions were washed with water (2 × 5 ml) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a white solid (43.3 mg) which by preparative t.l.c. with ethyl acetate–hexane (1 : 1) as eluant (×3) gave the required 20β-hydroxy-18,11β-lactone (14) (17.4 mg, 40%) and unchanged 11-oxo-18,20β-lactone (13) (7.3 mg, 17%).

11β,18-*Epoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnane*-18,20β-*diol* (17): *Reduction of the* 20β-*Hydroxy*-18,11β-*lactone* (14) *with Di-isobutylaluminium Hydride*.—Di-isobutylaluminium hydride (25 ml of a 20% w/v solution in hexane, 4.97 g, 35 mmol) was added in five portions of 5 ml at 1 min intervals to a stirred solution of the 20β-hydroxy-18,11β-lactone (14) (3.01 g, 7.0 mmol) in toluene at 0 °C under nitrogen, and the mixture was stirred under these conditions for 2 h. Excess of di-isobutylaluminium hydride was destroyed by addition of aqueous sodium hydrogen carbonate (1.5 ml of a saturated solution), then the mixture was stirred with Celite until a granular precipitate was obtained, and filtered. The Celite was washed successively with toluene (50 ml), diethyl ether (50 ml), and dichloromethane (50 ml). The organic fractions were combined with the original toluene filtrate, washed with water (20 ml) and aqueous sodium chloride (2 × 15 ml of a saturated solution), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvents under reduced pressure gave the crude product (15) (3.02 g), m.p. 148—154 °C. Crystallisation of a small sample from ethyl acetate–hexane gave 11β,18-epoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnane-18,20β-diol (15) as needles, m.p. 179.5—185 °C (174—179 °C from acetone–hexane), which had spectra identical with those already described.

18,20β-*Diacetoxy*-11β,18-*epoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnane* (18).—Acetic anhydride (16 ml) was added to a stirred solution of the crude 18,20β-diol (17) (2.97 g, 6.8 mmol) in pyridine (50 ml) and the mixture was stirred at room temperature in the dark for 24 h. It was then poured into water (150 ml), stirred for 1 h with cooling, and the residual gum was washed with water (5 × 5 ml) to remove traces of pyridine before being dissolved in ether (50 ml containing 1% of triethylamine). The ethereal solution was washed with water (2 × 5 ml) and dried ($MgSO_4$ and Na_2CO_3). The aqueous washings were combined with the original aqueous filtrate, and concentrated to a volume of about 10 ml. The residue was dissolved in ether (50 ml containing 1% of triethylamine) and the ethereal solution was washed with water (2 × 10 ml) and dried ($MgSO_4$ and Na_2CO_3). The ethereal extracts were combined and the solvent was removed under reduced pressure to give the crude 18,20β-diacetate (18) (3.27 g, 93%), as a colourless glass. Chromatography on silica gel (100 g), and elution with ethyl acetate–hexane (3 : 7) gave 18,20β-*diacetoxy*-11β,18-*epoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnane* (18) (2.56 g, 73%), needles from hexane, m.p. 98—104 °C; $\nu_{max.}$ (KBr) 1 735s, 1 250s, 1 025s (OTHP), and 1 015s (OTHP) cm^{-1}; δ($CDCl_3$) 0.97 (s, 19-H_3), 1.16 (d, *J* 6 Hz, 21-H_3), 2.02 (6 H, s, 18-OAc and 20-OAc), 2.61 (q, $J_{12\sigma,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.25—4.20 (3 H, m, 3β-H and 6′-H_2), 4.43 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.71br (s, 2′-H), 4.89 (m, 20-H), and 5.97 (s, 18-H) (Found: C, 70.45; H, 8.7. $C_{30}H_{46}O_7$ requires C, 70.6; H, 8.9%).

20β-*Acetoxy*-11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnane* (19).—Aged ethanol-free chloroform [31] (1 ml) (see Discussion section) was added to a solution of the foregoing 18,20β-diacetate (18) (2.42 g, 4.6 mmol) in methanol (25 ml) and the mixture was stirred at room temperature for 30 min, then diluted with ether (125 ml containing 1% v/v of triethylamine). The ethereal solution was washed with aqueous sodium hydrogen carbonate (5 ml of a saturated solution) and water (2 × 15

ml), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave the crude product (1.77 g), a white solid, identified as a mixture of 20β-acetoxy-11β,18-epoxy-18-methoxy-5β-pregnan-3α-ol (20) and its 3-tetrahydropyranyl ether (19) from its spectral characteristics: $\nu_{max.}$ (KBr) 3 650—3 150s, 1 735s, 1 715m,sh, 1 250s, 1 080s (OTHP), 1 065s (OTHP), and 1 025s (OTHP) cm^{-1}; δ($CDCl_3$) essentially as for the product (19) below except 3.20—3.80 (*ca.* 2 H, m, 3β-H and 6′-H_2), and 4.75br (*ca.* 0.5 H, s, 2′-H), indicating partial loss of the tetrahydropyranyl ether protecting group. The crude product was dissolved in tetrahydrofuran (46 ml), with 2,3-dihydropyran (2.1 ml, 23 mmol) and toluene-*p*-sulphonic acid (35 mg, 0.18 mmol) and the solution stirred at room temperature for 6 h. The mixture was diluted with ether (150 ml containing 1% of triethylamine), and worked up as above to give the crude tetrahydropyranyl ether (2.71 g) as an oil. Chromatography on silica gel (110 g), and elution with ethyl acetate–hexane (1 : 4) gave 20β-*acetoxy*-11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnane* (19) (1.95 g, 87%), as a viscous oil, single spot on t.l.c.; $\nu_{max.}$ (film) 1 735s, 1 255s, 1 080s (OTHP), 1 065m (OTHP), and 1 025s (OTHP) cm^{-1}; δ($CDCl_3$) 0.96 (s, 19-H_3), 1.13 (d, *J* 6 Hz, 21-H_3), 1.95 (s, 20-OAc), 2.59 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.25 (s, 18-OMe), 3.30—4.20 (3 H, m, 3β-H and 6′-H_2), 4.33 (d, 11α-H, $J_{11\alpha,12\beta}$ 6 Hz), 4.42 (s, 18-H), 4.71br (s, 2′-H), and 5.18 (m, 20-H).

20β-*Acetoxy*-11β,18-*epoxy*-5β-*pregnane*-3α,18-*diol* (22).—50% Aqueous acetic acid (6.6 ml) was added to a stirred solution of the tetrahydropyranyl ether (18) (0.169 g, 0.33 mmol) in tetrahydrofuran (3.3 ml) and the mixture stirred at room temperature for 30 h. It was then diluted with water (10 ml) and extracted with dichloromethane (2 × 25 ml). The dichloromethane extracts were combined, washed with aqueous 10% sodium hydrogen carbonate until the washings were neutral, then with water (5 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a white solid (0.139 g) which by preparative t.l.c. with ethyl acetate–hexane (1 : 1) as eluant (×2) gave 11β,18;18,20β-*diepoxy*-5β-*pregnan*-3α-*ol* (25) (19.9 mg, 18%), needles from acetone–hexane, m.p. 170—172 °C; $\nu_{max.}$ (KBr) 3 600—3 050s,br, 1 075s, and 1 040s cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 1.30 (d, *J* 6 Hz, 21-H_3), 2.28 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.40—3.85 (2 H, m, 3β-H and 20-H), 4.72 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), and 5.00 (s, 18-H) (Found: C, 75.5; H, 9.4. $C_{21}H_{32}O_3$ requires C, 75.4; H, 9.2%) and 20β-*acetoxy*-11β,18-*epoxy*-5β-*pregnane*-3α,18-*diol* (22) (88.5 mg, 68%), needles from ethyl acetate–hexane, m.p. 211—217 °C; $\nu_{max.}$ (KBr) 3 560m, 3 320s, 1 725s, 1 260s, and 1 250s cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 1.17 (d, *J* 6 Hz, 21-H_3), 2.01 (s, 20-OAc), 2.49 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.08br (d, *J* 6 Hz, 18-OH), 3.64 (m, 3β-H), 4.39 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.96br (d, *J* 6 Hz, 18-H), and 5.41 (m, 20-H) (Found: C, 70.1; H, 9.2. $C_{23}H_{36}O_5$ requires C, 70.4; H, 9.2%).

11β,18-*Epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20β-*ol* (21).—Lithium aluminium hydride (0.745 g, 19.5 mmol) was added in small portions during 5 min to a stirred solution of the crude tetrahydropyranyl ether (19) (1.90 g, 3.9 mmol) in tetrahydrofuran (18 0 ml) and the mixture was stirred at room temperature under nitrogen for 4 h. The mixture was then diluted with ether (100 ml), excess of lithium aluminium hydride was destroyed by addition of saturated aqueous sodium hydrogen carbonate (5.5 ml added dropwise), and the resulting mixture filtered. The residue was washed successively with ether (4 × 50 ml containing 1% of triethylamine) and ethyl acetate (50 ml). The organic fractions were combined with the original filtrate, washed with water (2 × 15 ml) and saturated aqueous sodium chloride (2 × 15 ml and 1 × 5 ml) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a white solid (1.71 g) which crystallised from ethyl acetate–hexane to give 11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20β-*ol* (21) (1.26 g, 72%), as needles, m.p. 187—192 °C; $\nu_{max.}$ (KBr) 3 530s, 3 500—3 250m, br, 1 060s (OTHP), 1 030s, (OTHP), and 1 015s (OTHP) cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 1.13 (d, *J* 6 Hz, 21-H_3), 2.62 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.39 (s, 18-OMe), 3.30—4.15 (5 H, m, 3β-H, 6′-H_2, 20-OH, and 20-H), 4.35 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.52 (s, 18-H), and 4.72br (s, 2′-H) (Found: C, 72.6; H, 9.8. $C_{27}H_{44}O_5$ requires C, 72.3; H, 9.9%). T.l.c. of the residues (0.390 g) on silica gel, with ethyl acetate–hexane (2 : 3), gave 11β,18;18,20β-*diepoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnane* (26) (0.145 g, 9%), needles from acetone–hexane, m.p. 139—146 °C; $\nu_{max.}$ (KBr) 1 135s, 1 120s, 1 060s (OTHP), and 1 035s (OTHP) cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 1.30 (d, *J* 6 Hz, 21-H_3), 2.29 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.20—4.20 (4 H, m, 3β-H, 20-H, and 6′-H_2), 4.71br (2 H, d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H and 2′-H), and 5.00 (s, 18-H) (Found: C, 75.0; H, 9.4. $C_{26}H_{40}O_4$ requires C, 75.0; H, 9.7%). Additional pregnanol (21) (48 mg, 3%) was also isolated from the plate.

11β,18-*Epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (24).—A solution of pyridine (4.5 ml, 55 mmol) in dichloromethane (37.5 ml) was cooled to 0 °C under nitrogen. To the rapidly stirred solution was added chromium trioxide (2.76 g, 27.6 mmol) in small portions during 5 min. Stirring was continued for a further 5 min at 0 °C and then at room temperature for 10 min. To the resulting deep red solution was added a solution of the epoxide (21) (1.01 g, 2.3 mmol) in dichloromethane (12.5 ml) and the mixture was stirred at room temperature under nitrogen for 24 h. The mixture was then diluted with ether (250 ml), stirred for a further 15 min, filtered, and the brown granular residue was washed with ether (5 × 100 ml). The combined ethereal solutions were washed with saturated aqueous sodium hydrogen carbonate (50 ml) and saturated aqueous sodium chloride until the washings were colourless, then with water (2 × 25 ml) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave crude 11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (24) (1.01 g), which crystallised from ethyl acetate–hexane as needles (0.831 g, 83%), m.p. 154—159 °C; $\nu_{max.}$ (KBr) 1 707s, 1 070s (OTHP), 1 035s (OTHP), and 1 010s (OTHP) cm^{-1}; $\nu_{C=O}$ ($CHCl_3$) 1 695—1 705s cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 2.13 (s, 21-H_3), 2.68 (12β-H, q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz), overlapping 2.70 (17α-H, t, *J* 9 Hz), 3.20 (s, 18-OMe), 3.35—4.10 (3 H, m, 3β-H and 6′-H_2), 4.37 (s, 18-H), 4.46 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), and 4.73br (s, 2′-H) (Found: C, 72.3; H, 9.45. $C_{27}H_{42}O_5$ requires C, 72.4; H, 9.5%).

Oxidation of the 18-*Methoxy*-20β-*ol* (21) *with Pyridinium Chlorochromate*.[33]—A solution of the 18-methoxy-20β-ol (21) (22.3 mg, 0.05 mmol) in dichloromethane (0.5 ml) was added to a stirred suspension of pyridinium chlorochromate (16.7 mg, 0.075 mmol) and anhydrous sodium acetate (1.4 mg, 0.015 mmol) in dichloromethane (1 ml) and the mixture was stirred at room temperature in the dark for 20 h. The mixture was then diluted with ether (10 ml),

stirred for a further 5 min, and filtered, and the brown granular residue was washed with ether (2 × 5 ml). The combined ethereal solutions were washed, dried, and evaporated as described above to give a gum (22.2 mg) shown by t.l.c. and n.m.r. spectroscopy to be a mixture of the 20-ketone (24), unchanged 20-alcohol (21), and the 11β,18;18,-20β-diepoxy derivative (26) in a ratio of 3 : 1 : 1.

11β,18-Epoxy-3α,18-dihydroxy-5β-pregnan-20-one (*21-Deoxy-3α,5β-tetrahydroaldosterone*) (5).—Aqueous hydrochloric acid (1 ml of a 1.0M solution) was added to a stirred solution of the epoxide (24) (44.8 mg, 0.1 mmol) in tetrahydrofuran (1 ml) and the solution was stirred at room temperature for 24 h. The mixture was diluted with water (5 ml) and extracted with dichloromethane (2 × 10 ml); the extracts were washed with aqueous sodium hydrogen carbonate (2.5 ml of a 10% solution) and water, and dried ($MgSO_4$), and the solvent removed under reduced pressure to give the crude product (27.8 mg, 80%). Crystallisation from hexane–ethyl acetate gave *11β,18-epoxy-3α,18-dihydroxy-5β-pregnan-20-one* (5), m.p. 117—121 °C; $\nu_{max.}$ (KBr) 3 650—3 100s,br, 1 705s, 1 100—1 080br, 1 065s, 1 040m, 1 005m, and 915w cm^{-1}; ν_{O-H} ($CHCl_3$) 3 575m,sh and 3 500—3 200m,br cm^{-1}; $\nu_{C=O}$ ($CHCl_3$) 1 700s cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 2.20 (s) and 2.18 (s) (ratio of peak heights 5 : 1, 21-H_3), 2.66—2.93 (2 H, m, 12β-H, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz and 17α-H, t, *J* 9 Hz), 3.39br (18-OH), 3.67 (m, 3β-H), 4.51 and 4.48 (each d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), and 4.84—5.04br (18-H). Addition of D_2O led to the loss of the OH signal at δ 3.39 and the collapse of the broad signal at δ 4.84—5.04 into two singlets at δ 4.95 and 4.88 (in ratio of peak heights of 5 : 1); *m/e* after derivatization as its 3α,11β-bis(trimethylsilyloxy)-18,20-bis-(*O*-methyl oxime)[49] 550 ($C_{29}H_{54}O_4Si_2$, M^+; 98%), 519 ($M^+ - 31$; 98%), 503 ($M^+ - 47$; 80%), 487 ($M^+ - 63$; 48%), 429 ($M^+ - 121$; 77%), 339 ($M^+ - 211$; 100%), 254 (65%), and 178 (88%) (Found: C, 72.5; H, 9.2. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%).

20-Oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (28).—A solution of the 20β-hydroxy-18,11β-lactone (14) (213 mg, 0.5 mmol) in dichloromethane (20 ml) was added to a stirred suspension of pyridinium chlorochromate [33] (158 mg, 0.74 mmol) and anhydrous potassium acetate (15.4 mg, 0.15 mmol) in dichloromethane (20 ml) and the mixture was stirred at room temperature in the dark for 20 h. The mixture was diluted with ether (150 ml), stirred for a further 5 min, and filtered, and the brown residue was washed with ether (6 × 15 ml). The ethereal fractions were combined with the original filtrate, washed with saturated aqueous sodium chloride (3 × 10 ml) and water (3 × 10 ml and 2 × 5 ml), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent gave the crude product (203 mg) which crystallised from acetone–hexane to give *20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone* (28) (174.6 mg, 81%), needles, m.p. 171—177 °C; $\nu_{max.}$ (KBr) 1 770s, 1 710s, 1 090s, 1 075s, 1 040s (OTHP), and 1 030s (OTHP) cm^{-1}; δ($CDCl_3$) 1.00 (s, 19-H_3), 2.19 (s, 21-H_3), 2.66 (t, *J* 10 Hz, 17α-H), 3.00 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.28—4.08 (3 H, m, 3β-H and 6′-H_2), and 4.76br (2 H, d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H and 2′-H) (Found: C, 72.4; H, 8.9. $C_{26}H_{38}O_5$ requires C, 72.5; H, 8.9%).

Oxidation of the 20β-Hydroxy-18,11β-lactone (14) *with Chromium Trioxide–3,5-Dimethylpyrazole Complex.*[34]—3,5-Dimethylpyrazole (18.4 mg, 0.2 mmol) was added to a rapidly stirred suspension of chromium trioxide (20 mg, 0.2 mmol) in dichloromethane (5 ml) and the mixture was stirred at room temperature for 15 min. To the resulting orange solution was added a solution of the 20β-hydroxy-18,11β-lactone (14) (43.2 mg, 0.1 mmol) and the mixture was stirred at room temperature for 20 h. The mixture was then diluted with ether (70 ml), stirred over finely powdered sodium hydrogen sulphate until colourless, filtered, washed with water (1 × 10 ml and 1 × 5 ml) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent gave a glass (24.4 mg); $\nu_{max.}$ (KBr) 3 600—3 200m,br, 1 770s, and 1 710s cm^{-1}. T.l.c. (ethyl acetate–hexane; 1 : 1) showed the presence of the 20-oxo-18,11β-lactone (28) and a more polar product which was identified on the basis of its i.r. spectrum as 3α-hydroxy-20-oxo-5β-pregnano-18,11β-lactone.

20β-Benzyloxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (15).—A solution of the 20β-hydroxy-18,11β-lactone (14) (43.2 mg, 0.1 mmol) in toluene (2 ml) was added to a rapidly stirred suspension of sodamide powder (39.6 mg, 1.0 mmol) in toluene (2 ml) at room temperature under nitrogen. The suspension was stirred for a further 10 min at room temperature then benzyl chloride (30 μl, 0.26 mmol) was added and the mixture was stirred and heated under reflux under nitrogen for 20 h. The cooled mixture was partitioned between ether (15 ml) and ice–water (5 ml). The aqueous fraction was extracted with more ether (10 ml), and the combined ethereal extracts were washed with saturated aqueous sodium chloride (5 ml) and water then dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a gum (45.5 mg). Preparative t.l.c. (ethyl acetate–hexane; 1 : 2) gave *20β-benzyloxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone* (15) (19.7 mg, 38%) as a colourless glass; $\nu_{max.}$ (KBr) 1 760s, 1 600m, 1 075s (OTHP), and 1 020s (OTHP) cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 1.18 (d, *J* 6 Hz, 21-H_3), 2.96 (q, $J_{11\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.20—4.30 (4 H, m, 3β-H, 20-H, and 6′-H_2), 4.40 (dd, *J* 11 Hz, δ_A 4.30 and δ_B 4.50, OCH_2Ph), 4.71br (2 H, d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H and 2′-H), and 7.28br (s, OCH_2Ph).

Reduction of the 20β-Benzyloxy-18,11β-lactone (15) *with Di-isobutylaluminium Hydride.*—Di-isobutylaluminium hydride (80 μl of a 20% solution in hexane, 0.11 mmol) was added to a stirred solution of the 20β-benzyloxy-18,11β-lactone (15) (25.5 mg, 0.05 mmol) in toluene (2.5 ml) at 0 °C and the mixture was stirred at 0 °C under nitrogen for 2 h. Excess of reagent was destroyed by addition of saturated aqueous sodium hydrogen carbonate (1 ml) and the mixture was treated with ice–water (5 ml) and extracted with ether (2 × 15 ml); the extracts were washed with saturated aqueous sodium chloride (2 × 2.5 ml) and water (5 ml), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent gave a viscous oil (22.5 mg). Preparative t.l.c. (ethyl acetate–hexane; 1 : 4) gave unchanged 20β-benzoyloxy-18,11β-lactone (15) (7.5 mg, 30%) and 20β-benzyloxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-18-ol (23) (8.2 mg, 31%), as a colourless glass; $\nu_{max.}$ (KBr) 3 600—3 150m,br, 3 010w, 1 600m, 1 075s, 1 060s (OTHP), and 1 025s (OTHP) cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 1.24 (d, *J* 6 Hz, 21-H_3), 2.62 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.20—4.35 (4 H, m, 3β-H, 20-H, and 6′-H_2), 4.34 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.46 (d,d, *J* 11 Hz, δ_A 4.29 and δ_B 4.63, OCH_2Ph), 4.72br (s, 2-H), 4.87 and 4.96 (s, s, 18-H, two epimers), and 7.29br (s, OCH_2Ph).

3α-Acetoxy-20β-hydroxy-5β-pregnano-18,11β-lactone (16).—Zinc borohydride [48] (6.9 ml of a 0.1M solution in

1,2-dimethoxyethane, 0.69 mmol) was added to a stirred solution of 3α-acetoxy-11-oxo-5β-pregnano-18,20β-lactone (11) (84.2 mg, 0.23 mmol) in 1,2-dimethoxyethane (3 ml) at room temperature under nitrogen and the mixture was stirred and heated under reflux under nitrogen for 2 h. The mixture was allowed to cool and excess of reagent destroyed by addition of ice–water (10 ml). The mixture was diluted with ether (25 ml containing 1% of triethylamine) and filtered and the grey solid residue was washed on the filter with more ether (2 × 25 ml containing 1% of triethylamine). The filtrates were combined, washed with aqueous sodium hydrogen carbonate (2 × 5 ml of a 10% solution) and water (2 × 5 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure left a gum (88.5 mg) which by preparative t.l.c. with ethyl acetate–hexane (2 : 1) as eluant (× 2) gave 3α-acetoxy-20β-hydroxy-5β-pregnano-18,11β-lactone (16) (60.8 mg, 72%), needles from acetone–hexane, m.p. 187—190 °C (lit.,[50] 194.5—195.5 °C); $\nu_{max.}$ (KBr) 3 550—3 150m,br, 1 770s, and 1 735s cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 1.17 (d, J 6 Hz, 21-H_3), 2.02 (s, OAc), 3.09 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 4.28 (m, 20-H), 4.68br (2 H, d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H and 3β-H). A second minor product (4.8 mg, 5%) which was also isolated from the plate was not identified but was probably 3α-acetoxy-11β,18-epoxy-5β-pregnane-18,20β-diol.

3α-Acetoxy-20-oxo-5β-pregnano-18,11β-lactone (29).—Jones' chromic acid reagent [46] was added dropwise to a stirred solution of 3α-acetoxy-20β-hydroxy-5β-pregnano-18,11β-lactone (16) (60 mg, 0.15 mmol) in acetone (3 ml) at 0 °C until an orange colour remained (0.15 ml). The mixture was stirred at 0 °C for 1 h and was then treated with aqueous sodium acetate (5 ml of a 20% solution) and extracted with benzene (2 × 20 ml). The combined benzene solutions were washed with saturated aqueous sodium chloride (3 × 5 ml) and dried ($MgSO_4$), and removal of the solvent under reduced pressure gave crude 3α-acetoxy-20-oxo-5β-pregnano-18,11β-lactone (29) (57 mg, 95%), which crystallised from ethyl acetate–hexane as needles, m.p. 201—203 °C (lit.,[50] 201.5—203 °C); $\nu_{max.}$ 1 770s, 1 735s, 1 710s, and 1 260s cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 2.02 (s, OAc), 2.18 (s, 21-H_3), 2.66 (t, J 10 Hz, 17α-H), 3.05 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$, 6 Hz 12β-H), and 4.76br (2 H, d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H and 3β-H).

20,20-Ethylenedithio-3α-hydroxy-5β-pregnano-18,11β-lactone (31).—Boron trifluoride–diethyl ether (66 μl, 0.5 mmol) was added to a solution of the 20-oxo-18,11β-lactone (28) (113 mg, 0.26 mmol) in ethane-1,2-dithiol (90 μl, 1.1 mmol) at room temperature and the mixture was set aside for 10 min. The resulting gum was then diluted with dichloromethane (1.5 ml) and the solution stirred for 30 min. More dichloromethane (20 ml) was then added and the solution was washed successively with aqueous 10% sodium hydrogen carbonate (2 × 5 ml), water (5 ml), and saturated aqueous sodium chloride (2 × 5 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a gum (154 mg). Preparative t.l.c. (ethyl acetate–hexane 1 : 1) followed by crystallisation from acetone–hexane gave *20,20-ethylenedithio-3α-hydroxy-5β-pregnano-18,11β-lactone* (31) (89.3 mg, 80%), needles, m.p. 195—198 °C; $\nu_{max.}$ (KBr) 3 600—3 150m,br, 1 770s, and 1 750s,sh cm^{-1}; ν_{O-H} ($CHCl_3$) 3 600m and 3 550—3 300w,br cm^{-1}; $\nu_{C=O}$ ($CHCl_3$) 1 765s cm^{-1}; δ($CDCl_3$) 0.99 (s, 19-H_3), 1.78 (s, 21-H_3), 2.67 (t, J 10 Hz, 17α-H), 3.08 (q, $J_{12\alpha,12\beta}$ 11 Hz, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.30 (complex m, $-S-CH_2CH_2-S-$), 3.60 (m, 3β-H), and 4.68 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H) (Found: C, 65.5; H, 8.1; S, 15.7. $C_{23}H_{34}O_3S_2$ requires C, 65.35; H, 8.1; S, 15.2%).

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