18-Substituted Steroids. Part 7.[1] Synthesis and Structure of 11β,18-Epoxy-3α,18,21-trihydroxy-5β-pregnan-20-one (3α,5β-Tetrahydroaldosterone)

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3α,5β-Tetrahydroaldosterone (1) has been prepared from 21-deoxy-3α,5β-tetrahydroaldosterone 18-methyl ether 3-(tetrahydropyran-2-yl) ether (6). Kinetically controlled enolisation with lithium di-isopropylamide followed by treatment with chlorotrimethylsilane generated specifically the $\Delta^{20(21)}$-trimethylsilyl enol ether (17), which reacted with 3-chloroperbenzoic acid to give the 18-methyl ether-21-alcohol (18), which was converted into its 21-acetate (27). Acid solvolysis of the protecting groups at C-3 and -18 with anhydrous acetic acid, followed by mild alkaline hydrolysis with sodium hydrogencarbonate afforded 3α,5β-tetrahydroaldosterone (1) in 26% overall yield.

3α,5β-TETRAHYDROALDOSTERONE (11β,18-epoxy-3α,18,-21-trihydroxy-5β-pregnan-20-one) (1), which was first isolated and identified in 1961,[2] is the principal urinary metabolite of aldosterone (18,21-dihydroxy-11β,18-epoxypregn-4-ene-3,20-dione) (2) in man.[2-5] About 30% of artificially administered aldosterone (2) is excreted in this form.[4,6] The metabolism of aldosterone (2) has been studied extensively [4-15] and attention has been focused on the determination of 3α,5β-tetrahydroaldosterone (1) in urine and in blood.[16-20] Several syntheses of aldosterone (2) have been developed [21-28] but an efficient stereospecific chemical synthesis of 3α,5β-tetrahydroaldosterone (1) has not been reported.

Previous chemical syntheses of 3α,5β-tetrahydroaldosterone (1) have involved the reduction of the 4-en-3-one moiety of aldosterone 21-acetate (3) [8] and aldosterone 18,21-diacetate (4).[29] However, these reactions led to the formation of all four possible isomers (at C-3 and -5) of tetrahydroaldosterone, the separation of which required careful chromatography.[29] It has also been reported [30] that aldosterone (2) can be reduced quantitatively to 3α,5β-tetrahydroaldosterone (1) by a microbial transformation, but further investigation in this laboratory in collaboration with the original authors [30] has shown that the isolation of pure 3α,5β-tetrahydroaldosterone (1) from an extract of the incubation medium requires careful chromatography and results at best in rather poor recovery of purified material.

In a previous paper [1] we described the functionalisation of C-18 from a C-20 alcohol and the synthesis of 21-deoxy-3α,5β-tetrahydroaldosterone (3α,18-dihydroxy-11β,18-epoxy-5β-pregnan-20-one) (5). We now report the synthesis of 3α,5β-tetrahydroaldosterone (1) from 21-deoxy-3α,5β-tetrahydroaldosterone 18-methyl ether 3-(tetrahydropyran-2-yl) ether [11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one] (6).

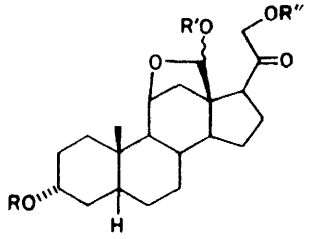
The problem was to introduce functionality at C-21. We attempted to functionalise C-21 at the oxidation level of the 18,11β-hemiacetal-20-ketone (5) or its methyl ether (6) and at the oxidation level of the 18,11β-lactone-20-ketones (7) and (8).

Several methods have been reported for the functionalisation of the C-21 position of pregnan-20-ones.[31-34] None of these, however, afforded the required 21-oxygenated compounds in the present case. 3α-Acetoxy-20-oxo-5β-pregnano-18,11β-lactone (7) was recovered unchanged [35] after subjection to the Henbest acetoxylation conditions of lead tetra-acetate and boron trifluoride–diethyl ether.[31] Similarly, treatment of the 18,11β-lactone-20-ketone (7) under the conditions of the Stork C-21 iodination procedure [32] or with phenyltrimethylammonium perbromide [33] in anhydrous tetrahydrofuran failed to yield the 21-iodo- or 21-bromo-compounds, respectively.[35] Starting material was recovered in both cases. The acid-catalysed enol acetylation of pregnan-20-ones with isopropenyl acetate normally leads to the formation of $\Delta^{20(21)}$-enol acetates.[34] However, the attempted acid-catalysed enol acetylation of the 18,11β-lactone-20-ketone (7) with isopropenyl acetate failed to give either the $\Delta^{20(21)}$-enol acetate (9) or the $\Delta^{17(20)}$-enol acetate (10); the starting material was recovered.[35] The effect of a C-18 oxygenated substituent in preventing the formation of the $\Delta^{20(21)}$-enol acetate under these reaction conditions has been reported previously.[36] The hemiacetal-18-methyl ether (6) would of course be unstable under the acid conditions required.

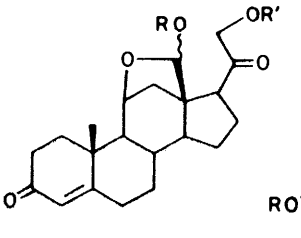
The direct C-21 acetoxylation of 20,18-hemiacetals has also been effected by reaction with lead tetra-acetate in anhydrous acetic acid.[36] However, 21-deoxy-3α,5β-tetrahydroaldosterone [1] (5) failed to react under these conditions [35] and similarly the C-21 hydrogens were not replaced by deuterium when 21-deoxy-3α,5β-tetrahydroaldosterone (5) was treated with deuterioacetic acid in anhydrous chloroform [36] for three days.[35] These results were interpreted as further evidence for the absence in solution of the 20-hydroxy-11β,18;18,20-diepoxy-form of 21-deoxy-3α,5β-tetrahydroaldosterone (5).[1]

The above experiments showed that the 18,11β-lactone moiety exerts a marked effect upon the chemistry of the pregnan-20-one side chain, and inhibits functionalisation of the C-21 position. We therefore considered a different approach, through a kinetically-controlled enolisation by base [37-39] to generate the $\Delta^{20(21)}$-enolate anion.

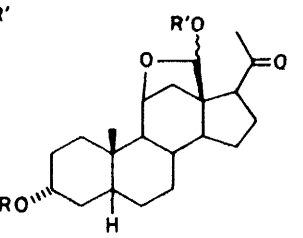
Unsymmetrical ketones have been converted into the thermodynamically preferred enol acetate [40,41] and tri-



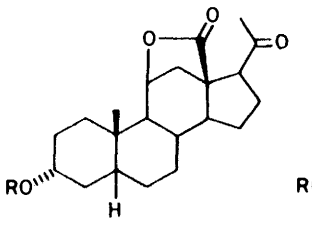
(1) R = R' = R'' = H
(18) R = THP, R' = Me, R''=H
(19) R = R'' = H, R' = Me
(27) R = THP, R' = Me, R''= Ac
(28) R = H, R' = R''= Ac
(29) R = R' = R'' = Ac
(32) R = R' = H, R''= Ac
(37) R = Ac, R' = R''= H



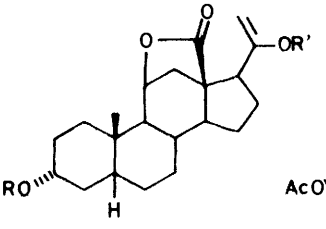
(2) R = R' = H
(3) R = H, R' = Ac
(4) R = R' = Ac



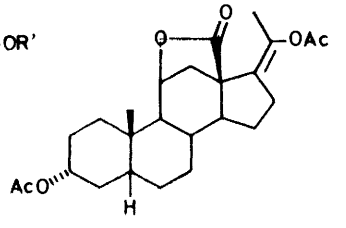
(5) R = R' = H
(6) R = THP, R' = Me



(7) R = Ac
(8) R = THP



(9) R = R' = Ac
(14) R = THP, R' = $SiMe_3$



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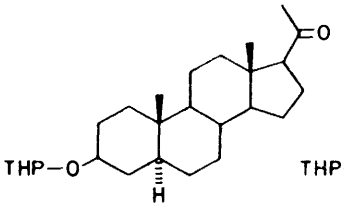

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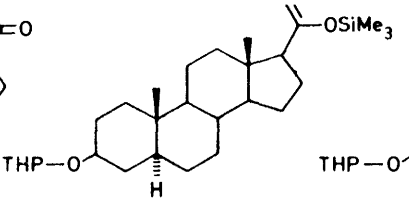

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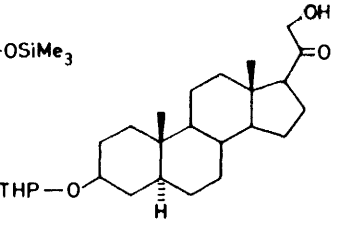

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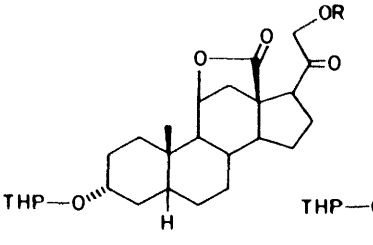
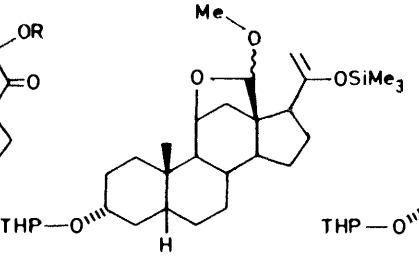


(15) R = H
(16) R = Ac



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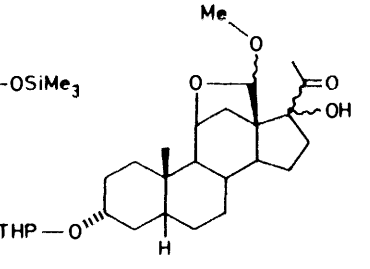

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methylsilyl enol ether[42] derivatives by the use of equilibrating reaction conditions. The kinetically preferred enol acetate and trimethylsilyl enol ether derivatives of unsymmetrical ketones have been prepared by treating the ketone with an excess of a very hindered base such as lithium, sodium, or potassium triphenylmethide,[41,43] potassium tricyclohexylmethoxide,[44] lithium or sodium salts of hexamethyldisilazane,[45-47] or lithium di-isopropylamide.[37,48] The first formed enolate anions are then trapped by addition of excess acetic anhydride or chlorotrimethylsilane. Other lithium dialkylamide bases have been introduced and their applications in synthesis have been studied.[49]

Trimethylsily enol ethers can be transformed into

α-trimethylsilyloxy-ketones by reaction with 3-chloroperbenzoic acid [50-52] or dibenzoyl peroxide [53] and into α-benzoyloxy-ketones by reaction with lead tetrabenzoate.[54] The α-trimethylsilyloxy-ketones are readily hydrolysed with either aqueous acid or aqueous alkali to the corresponding α-hydroxy-ketones.[50,51] Enolate anions derived from ketones or esters have also been transformed directly into α-hydroxy-ketones or α-hydroxy-esters, respectively, by reaction with oxodiperoxoaquohexamethylphosphoramidomolybdenum-(VI).[55]

To test the selectivity of base-promoted enolisation some exploratory reactions were carried out on 3β-(tetrahydropyran-2-yloxy)-5α-pregnan-20-one (11) with lithium di-isopropylamide [37,48] and sodium hexamethyldisilazanyl.[56] The reactions were quenched by addition of an excess of chlorotrimethylsilane.

Both reactions gave the product derived exclusively from the enolate anion formed by kinetically controlled proton abstraction from the less hindered C-21 position. The product, an oil, was identified as the $\Delta^{20(21)}$-trimethylsilyl enol ether (12) from n.m.r. and i.r. spectra, and from subsequent transformation into 21-hydroxy-3β-(tetrahydropyran-2-yloxy)-5α-pregnan-20-one (13) by reaction with 3-chloroperbenzoic acid. The reaction with lithium di-isopropylamide was carried out under much milder conditions, gave a cleaner product, and the reagent itself was more easily prepared. The superiority of lithium di-isopropylamide over lithium and sodium salts of hexamethyldisilazane has been reported previously.[37]

The success of these exploratory reactions prompted us to test the selectivity of lithium di-isopropylamide in reactions with 20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (8) and 11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (6). Both compounds afforded the $\Delta^{20(21)}$-enolate anions derived from kinetically controlled proton abstraction.

Reaction of the 18,11β-lactone-20-ketone (8) with lithium di-isopropylamide followed by chlorotrimethylsilane gave 3α-(tetrahydropyran-2-yloxy)-20-trimethylsilyloxy-5β-pregn-20-eno-18,11β-lactone (14). The trimethylsilyl enol ether (14) was isolated and characterised (i.r. and n.m.r.) but was used without further purification for the subsequent reaction with 3-chloroperbenzoic acid, which gave 21-hydroxy-20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (15), in 23% yield from the 18,11β-lactone-20-ketone (8), after purification of the crude reaction product by preparative t.l.c. (see Experimental section). The 18,11β-lactone-20-ketone (8) was recovered in 15% yield.

The high proportion of 18,11β-lactone-20-ketone (8) recovered was due in part to failure to form the trimethylsilyl enol ether (14) but mainly to hydrolysis of unchanged trimethylsilyl enol ether (14) during aqueous work-up after the reaction with 3-chloroperbenzoic acid. These reaction conditions were later modified.

The 21-acetate (16) was prepared from 21-hydroxy-20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (15) by acetylation with acetic anhydride in pyridine.

However, neither the 21-alcohol (15) nor the 21-acetate (16) were suitable as precursors to 3α,5β-tetrahydroaldosterone (1); we have already reported [1] that the 18,11β-lactone group could not be reduced in the presence of a protecting group at C-20.

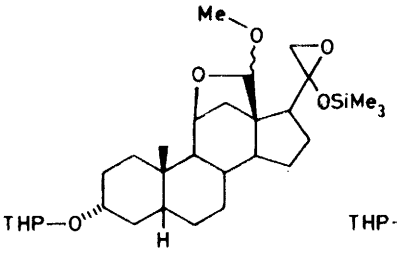
Reaction of 11β-18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (6) with lithium di-isopropylamide followed by chlorotrimethylsilane gave the 20-trimethylsilyl $\Delta^{20(21)}$-enol ether (17) which was isolated and characterised (i.r. and n.m.r.). The n.m.r. spectrum showed the methylene protons at C-21 as an apparent doublet (J 4 Hz) at 3.90 and 3.94 and the i.r. spectrum showed the enolic double bond at 1 650 cm^{-1} and the absence of the ketone. Reaction of the 20-trimethylsilyl $\Delta^{20(21)}$-enol ether (17) with 3-chloroperbenzoic acid at 65 °C for 24 h under nitrogen, followed by aqueous work-up, gave 11β,18-epoxy-21-hydroxy-18-methoxy-3α-(tetra-hydropyran-2-yloxy)-5β-pregnan-20-one (18), in 48% yield from the 20-ketone (6), with recovered 20-ketone (6) (6%) and 3α,21-dihydroxy-11β,18-epoxy-18-methoxy-5β-pregnan-20-one (19) 1.5%) which were separated by column chromatography. The isomeric 11β,18-epoxy-17-hydroxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (20) was not detected. The 3α-alcohol (19) was presumably formed by partial hydrolysis of the tetrahydropyranyl ether during reaction with 3-chloroperbenzoic acid.

The first step in the reaction of the trimethylsilyl enol ether (17) with 3-chloroperbenzoic acid is assumed [50,51] to be the formation of the epoxide (21), which subsequently rearranges regiospecifically to the 21-trimethylsilyloxy-20-ketone (22) and not to the 20-trimethylsilyloxy-21-aldehyde (23). The 21-hydroxy-20-ketone (18) is then isolated after an aqueous work-up. When the reaction was followed by t.l.c. a compound of mobility intermediate between those of the trimethylsilyl enol ether (17) and the hemiacetal-18-methyl ether-20-ketone (6) was observed. This was probably the 21-trimethylsilyloxy-20-ketone (22): α-trimethylsilyloxy-ketones have been isolated from similar reactions after non-aqueous work-up.[50]

A similar series of intermediates can of course be considered in the reaction of the trimethylsilyl enol ether (14) with 3-chloroperbenzoic acid.

The completion of the synthesis of 3α,5β-tetrahydroaldosterone (1) now required the hydrolysis of the two acid-labile protecting groups at C-3 and -18. However, hydrolysis of 11β,18-epoxy-21-hydroxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (18) with aqueous 70% v/v acetic acid at room temperature gave 11β,18;18,21-diepoxy-3α-hydroxy-5β-pregnan-20-one(26) in 67% yield, and not 3α,5β-tetrahydroaldosterone (1). Hydrolysis under these conditions was complete within 24 h whereas only partial hydrolysis of the hemiacetal-18-methyl ether-20-ketone (6) was observed under the same reaction conditions after 48 h.[1] The very ready

hydrolysis of the methoxy-group and the formation of the 11β,18;18,21 doubly bridged acetal (26) to the exclusion of 3α,5β-tetrahydroaldosterone (1) suggested that hydrolysis of the 20-oxo-hemiacetal 18-methyl ether 21-alcohol (18) occurred with intramolecular assistance from the hydroxy-group at C-21 (Scheme). This type of



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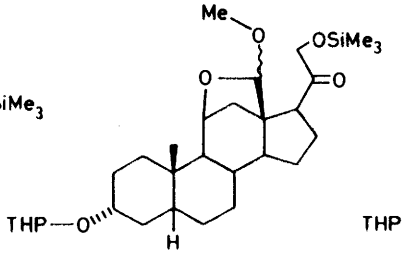

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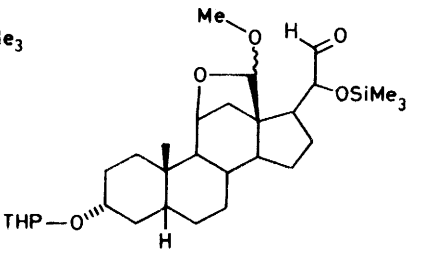

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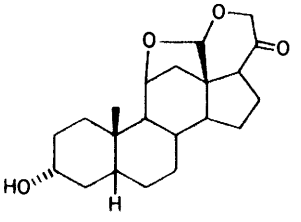

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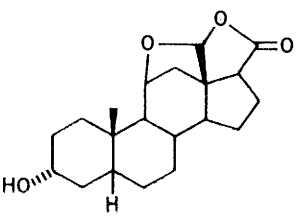

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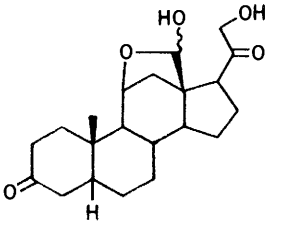

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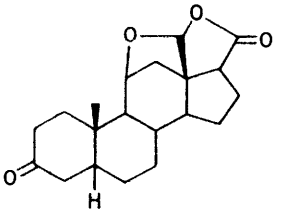

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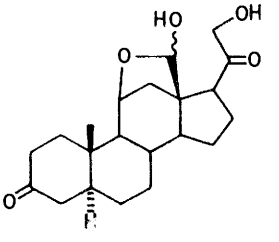

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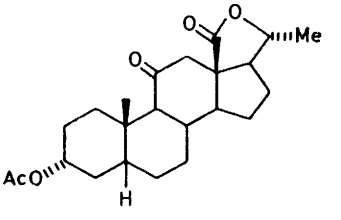

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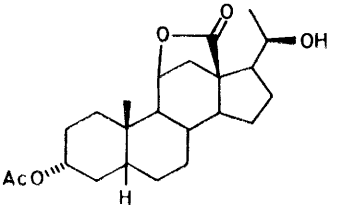

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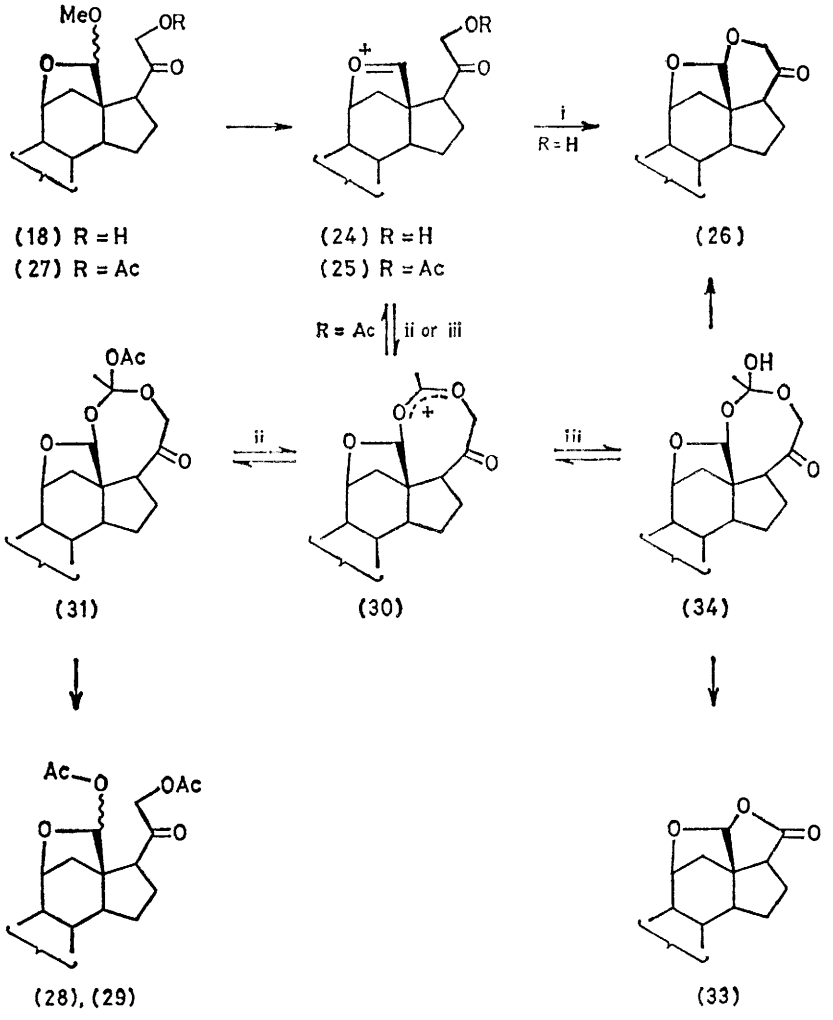
doubly bridged acetal has been reported previously from acid-catalysed dehydration of aldosterone [57] and has been used as a derivative for g.l.c. analysis.[58]

To prevent the formation of the 11β,18;18,21-doubly bridged acetal (26) during acid-catalysed hydrolysis the hemiacetal-18-methyl ether-21-alcohol (18) was acetylated with acetic anhydride in pyridine to give the 21-acetate (27). The hemiacetal-18-methyl ether-21-acetate (27) was then solvolysed with anhydrous acetic acid under nitrogen at 120—125 °C to give a mixture of approximately equal amounts of 3α,5β-tetrahydroaldosterone 18,21-diacetate (28) and 3α,5β-tetrahydroaldosterone 3,18,21-triacetate (29). Solvolysis of the hemiacetal-18-methyl ether-21-acetate (27) with anhydrous acetic acid may involve the intermediate acylium ion (30) which in the presence of anhydrous acetic acid would be in equilibrium with the cyclic orthoester (31) (Scheme). The orthoester (31) could then rearrange to give the mixture of 3α,5β-tetrahydroaldosterone acetates (28) and (29).

The acid-catalysed hydrolysis of aldosterone 18,21-diesters [59,60] in aqueous solvents was reported to give selectively the 21-monoesters. However, our attempts to hydrolyse the hemiacetal-18-methyl ether-21-acetate

(27) directly to 3α,5β-tetrahydroaldosterone 21-acetate (32) with 1M-hydrochloric acid failed to realise the required product but gave instead a mixture of the 11β,18;18,21-doubly-bridged acetal (26) (66%) and 11β,18-epoxy-3α-hydroxy-5β-pregnane-17β,18-carbolactone ('3α,5β-tetrahydroaldosterone γ-lactone') (33) (13%). The 11β,18;18,21-doubly-bridged-acetal may be formed by hydrolysis *via* the acyclium ion (30) and the

The mixture of 3α,5β-tetrahydroaldosterone 18,21-diacetate (28) and 3α,5β-tetrahydroaldosterone 3,18,21-triacetate (29) was hydrolysed with sodium hydrogencarbonate in aqueous methanol at room temperature for 30 h to give a mixture of approximately equal amounts of 3α,5β-tetrahydroaldosterone (1) and its 3-acetate (37), which were separated by preparative t.l.c. Further hydrolysis of the 3-acetate (37) with a 1.5 molar



SCHEME Reagents: i, AcOH–H_2O–THF; ii, AcOH–THF; iii, HCl–H_2O–THF

cyclic orthoester (34) (Scheme). The '3α,5β-tetrahydroaldosterone γ-lactone' (33) isolated from this reaction was identical (t.l.c., g.l.c., i.r., and n.m.r.) with an authentic sample * prepared by the oxidation of 3α,5β-tetrahydroaldosterone (1) with sodium periodate.[2,4,5,8,29] Although its formation under acid conditions has been reported [5] the mechanism has not been elucidated. We have also observed [61] that 5β-dihydroaldosterone (35) [29] is transformed into its 'γ-lactone' (36) under acidic conditions and we are at present attempting to determine the mechanism of this degradation. Dimeric products were not obtained from any of the acid-catalysed hydrolyses.

excess of sodium hydrogencarbonate in aqueous methanol at room temperature for 20 days gave 3α,5β-tetrahydroaldosterone (1). Under these very mild reaction conditions epimerisation at C-17 was not observed.[26,62]

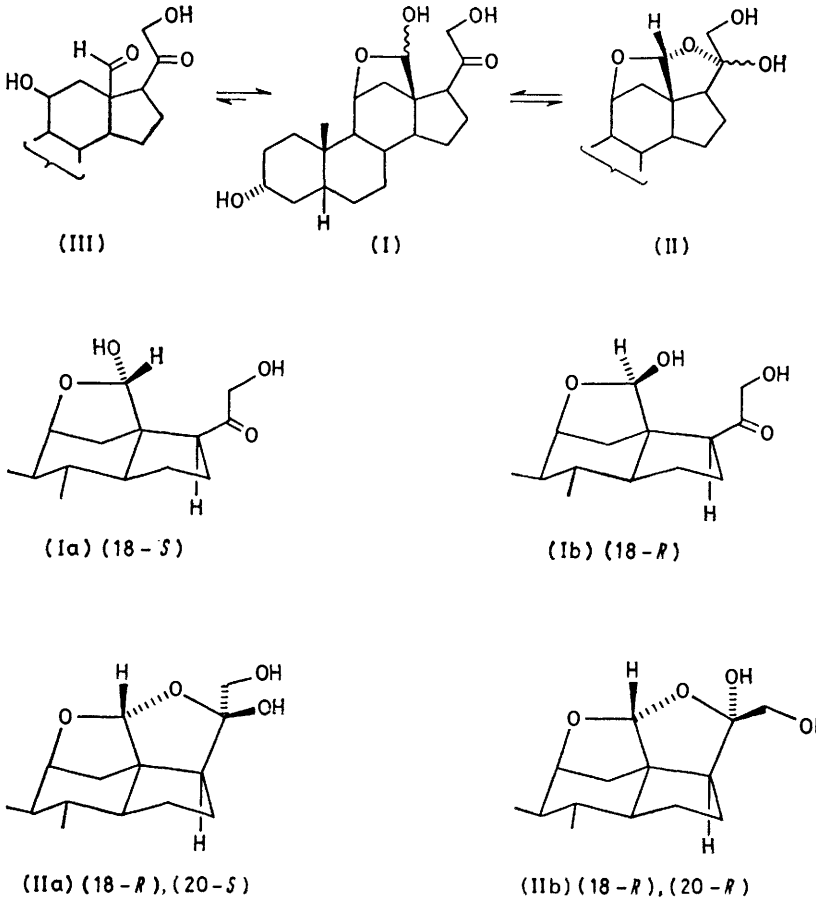
3α,5β-Tetrahydroaldosterone (1) prepared by this method was identical (t.l.c., g.l.c., i.r., and n.m.r.) with a sample prepared by microbial reduction of aldosterone (2),[30] and with a sample of urinary origin kindly supplied by Professor S. Ulick.*

The structure of 3α,5β-tetrahydroaldosterone (1) in solution and in the crystalline state has been assigned

* A gift from Professor S. Ulick, Veterans Administration Hospital, New York.

from its i.r. and n.m.r. spectra (see Experimental section) and by analogy with the structure of aldosterone (2) which has been determined from i.r.[59] and n.m.r.[63,64] spectra and from an *X*-ray crystal determination of aldosterone monohydrate.[65]

The i.r. spectrum of 3α,5β-tetrahydroaldosterone (1) showed a carbonyl band (20-C=O) reduced in intensity by 25% in potassium bromide and by 40% in chloroform solution compared to the corresponding band in the spectrum of the 20-oxo-hemiacetal-18-methyl ether-21-alcohol (18). These results differ from those for 21-deoxy-3α,5β-tetrahydroaldosterone for which the larger reduction in carbonyl intensity occurred in the crystalline state.[1] The n.m.r. spectrum of 3α,5β-tetrahydroaldosterone (1) (Figure) shows signals which we have assigned to two tautomeric forms; the 18,11β-hemiacetal-20-ketone form (I) which can be resolved into *R* and *S* epimers at C-18, and the 20-hydroxy-11β,18;18,20-diepoxy form (II) which can be resolved into (18-*R*), (20-*S*) and (18-*R*), (20-*R*) epimers. We assign the peaks at δ 4.97 and 4.88 to the 18,11β-hemiacetal-20-ketone form (I) and the peaks at δ 5.37 and 5.20 to the 20-hydroxy-11β,18;18,20-diepoxy form (II). For the 18,-11β-hemiacetal-20-ketone form (I) we assign the peak at δ 4.97 to 18-H in the preferred [1,27] (18-*S*) configuration (Ia) and the smaller peak at δ 4.88 to 18-H in the sterically more hindered (18-*R*) epimer (Ib). On the basis of relative peak heights of the C-18 hydrogens the 18-*S* and 18-*R* epimers (Ia) and (Ib) are present in a ratio of *ca.* 6 : 1. A similar result was observed for the 18,11β-hemiacetal-20-ketone form of 21-deoxy-3α,5β-tetrahydroaldosterone (5).[1] For the 20-hydroxy-11β,18;18,-20-diepoxy form (II) the peak at δ 5.37 is assigned to 18-H in the preferred (18-*R*),(20-*S*) configuration (IIa). The much smaller peak at δ 5.20 we assign to 18-H in the



(18-*R*),(20-*R*) epimer (IIb) which is sterically more hindered than the (18-*R*),(20-*S*) epimer (IIa). The (18-*S*),(20-*S*) and (18-*S*),(20-*R*) configurations seem from models to be excessively strained. The assignments of 11α- and 12β-H indicated in the Figure were determined by spin-decoupling experiments.

Spin coupling between the hydroxy-protons at C-18 and -21 and the hydrogens at C-18 and -21 was not observed. The n.m.r. spectra of 5α- and 5β-dihydroaldosterone [29] (38) and (35) gave similar results.[61]

We therefore consider 3α,5β-tetrahydroaldosterone (1) to exist in chloroform solution as an equilibrium mixture of the 18,11β-hemiacetal-20-ketone form (I) and the 20-hydroxy-11β,18;18,20-diepoxy-form (II) in approximately equal concentrations. The hydroxy-aldehyde

form (III) did not make a significant contribution to the equilibrium composition of 3α,5β-tetrahydroaldosterone (1) in solution.

G.l.c. analysis was carried out by converting 3α,5β-tetrahydroaldosterone (1) into its 3α,18,21-tris(trimethylsilyloxy)-20-methoxime derivative and under more forcing conditions * into its 3α,11β,21-tris(trimethylsilyloxy)-18,20-bis(methoxime) derivative. Analysis using a packed column gave a single peak for each derivative, whereas analysis with an open capillary column was able to resolve the *syn*- and *anti*-isomers of the 20-methoxime group. G.l.c.–m.s. analysis of the 3α,11β,21-tris(trimethylsilyloxy)-18,20-bis(methoxime) showed the molecular ion at *m/e* 638. The *syn*- and *anti*-isomers of this derivative gave identical mass spectra.

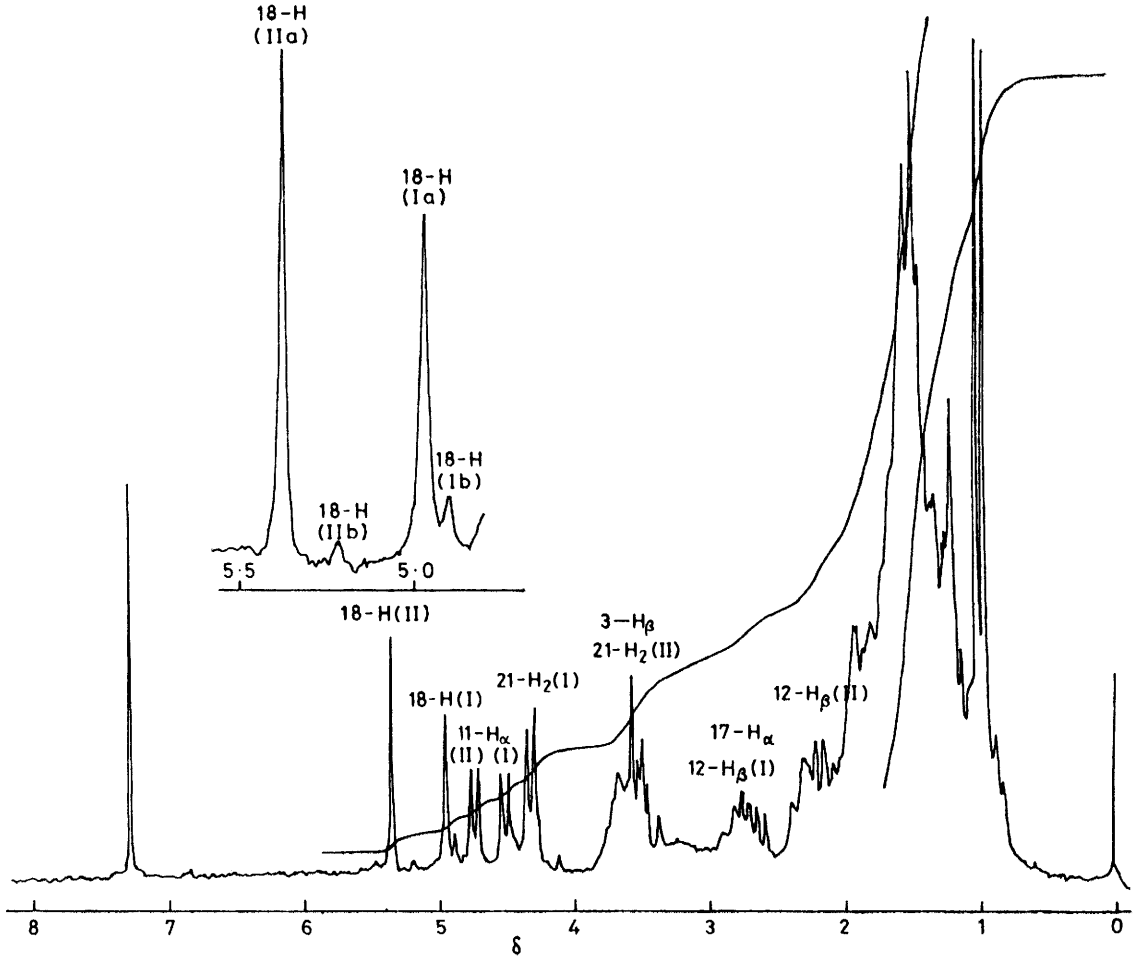


FIGURE 100-MHz ^{1}H n.m.r. spectrum of 3α,5β-tetrahydroaldosterone (1), showing assignments of signals to the 20-oxo-form (I) and the 20-hemiacetal form (II). Inset, expansion of the low-field region to show assignments for the epimers (Ia), (Ib), (IIa), and (IIb)

EXPERIMENTAL

For materials and methods see ref. 1.

3β-(Tetrahydropyran-2-yloxy)-20-trimethylsilyloxy-5α-pregn-20-ene (12). *Enolisation of 3β-(Tetrahydropyran-2-yloxy)-5α-pregnan-20-one* (11) *with Lithium Di-isopropylamide.*—Di-isopropylamine (0.6 ml, 0.43 g, 4.0 mmol) was added to a stirred solution of methyl-lithium (4.0 ml of a 0.94M ethereal solution, 3.8 mmol) in 1,2-dimethoxyethane (10 ml) containing 2,2′-bipyridyl (1 mg) † at −60 °C under nitrogen and the solution was stirred for 10 min. To the resulting solution of lithium di-isopropylamide was added a solution of 3β-(tetrahydropyran-2-yloxy)-5α-pregnan-20-one ‡ (11) (0.402 g, 1.0 mmol) in 1,2-dimethoxyethane (10 ml) and the mixture was stirred at −60 °C under nitrogen for 10 min. The mixture was then treated with chlorotrimethylsilane (1.25 ml), stirred for a further 10 min whilst warming to room temperature and then diluted with diethyl

* G.l.c. and g.l.c.–m.s. analyses were carried out following the method of J. W. Honour and C. H. L. Shackleton, *J. Steroid Biochem.*, 1977, **8**, 299.

† 2,2′-Bipyridyl was added to act as an indicator. In the presence of excess of lithium di-isopropylamide a characteristic red-brown charge-transfer complex is formed (see refs. 37 and 66).

‡ 3β-(Tetrahydropyran-2-yloxy)-5α-pregnan-20-one (11) was prepared from 3β-hydroxy-5α-pregnan-20-one according to the method described for the preparation of tetrahydropyranyl ethers in ref. 1.

ether (100 ml containing 1% triethylamine). The ethereal solution was washed with aqueous sodium hydrogencarbonate (10 ml of a saturated solution), and then with aqueous sodium chloride (2 × 10 ml of a saturated solution) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave 3β-(*tetrahydropyran-2-yloxy*)-20-*trimethylsilyloxy*-5α-*pregn*-20-*ene* (12) (0.51 g) as a viscous oil, which was not purified, $\nu_{max.}$ (neat liquid) 1 635(m), 1 620(m), 1 255(s, $SiCH_3$), 1 060(m, OTHP), 1 030(s, OTHP), and 860(s) cm^{-1}; δ($CDCl_3$) 0.11 [s, $OSi(CH_3)_3$], 0.55 (s, 18-H_3), 0.74 (s, 19-H_3), 3.15—3.95 (3 H, m, 3α-H and 6′-H_2), 3.97br (d, *J* 2 Hz, 21-H_2), and 4.65br (s, 2′-H).

Enolisation of 3β-(*Tetrahydropyran-2-yloxy*)-5α-*pregnan*-20-*one* (11) *with Sodium Hexamethyldisilazanyl.*—A solution of hexamethyldisilazane (1.13 g, 7.0 mmol) in 1,2-dimethoxyethane (20 ml) was added to a stirred suspension of sodamide (0.31 g, 8.0 mmol) in 1,2-dimethoxyethane (20 ml) at room temperature under nitrogen and the mixture was heated under reflux for 4 h and then allowed to cool under nitrogen. To the resulting solution of sodium hexamethyldisilazanyl at room temperature was added a solution of 3β-(tetrahydropyran-2-yloxy)-5α-pregnan-20-one (11) (0.28 g, 0.7 mmol) in 1,2-dimethoxyethane (10 ml) and the mixture was heated under reflux under nitrogen for 2 h. The mixture was then allowed to cool and was then treated with chlorotrimethylsilane (1 ml), stirred for a further 10 min, and then diluted with diethyl ether (75 ml containing 1% triethylamine). The ethereal solution was washed with aqueous sodium hydrogencarbonate (10 ml of a saturated solution), and then with aqueous sodium chloride (2 × 10 ml of a saturated solution) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave 3β-(tetrahydropyran-2-yloxy)-20-trimethylsilyloxy-5α-pregn-20-ene (12) (0.32 g) as a viscous oil, which had spectra identical to those described above.

21-*Hydroxy*-3β-(*tetrahydropyran-2-yloxy*)-5α-*pregnan*-20-*one* (13).—3-Chloroperbenzoic acid * (26 mg, 0.15 mmol) was added to a stirred solution of the trimethylsilyl enol ether (12) (47.4 mg, 0.1 mmol) in 1,2-dimethoxyethane (5 ml) at room temperature and the mixture was stirred at room temperature under nitrogen in the dark for 6 days, then diluted with water (5 ml), stirred for a further 5 min at room temperature, and partitioned between diethyl ether (15 ml containing 1% triethylamine) and aqueous sodium hydrogencarbonate (5 ml of a saturated solution). The aqueous fraction was extracted with more diethyl ether (10 ml), and the ethereal fractions were combined and washed with aqueous sodium chloride (5 ml of a saturated solution) then with water (5 ml) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a glass (49.2 mg) which crystallised from acetone–hexane to give 21-*hydroxy*-3β-(*tetrahydropyran-2-yloxy*)-5α-*pregnan*-20-*one* (13) (30.6 mg, 73%) as needles, m.p. 124—132 °C; $\nu_{max.}$ (KBr) 3 550—3 200(m, br), 1 715(s), 1 080(m, OTHP), 1 060(m, OTHP), and 1 030(s, OTHP) cm^{-1}; δ($CDCl_3$) 0.63 (s, 18-H_3), 0.82 (s, 19-H_3), 3.20—4.05 (3 H, m, 3α-H and 6′-H_2), 4.18 (s, 21-H_2), and 4.71br (s, 2′-H) (Found: C, 74.6; H, 10.25. $C_{26}H_{42}O_4$ requires C, 74.6; H, 10.1%).

11β,18-*Epoxy*-18-*methoxy*-3α-(*tetrahydropyran-2-yloxy*)-20-*trimethylsilyloxy*-5β-*pregn*-20-*ene* (17). *Enolisation of* 11β,18-*Epoxy*-18-*methoxy*-3α-(*tetrahydropyran-2-yloxy*)-5β-*pregnan*-20-*one* (6) *with Lithium Di-isopropylamide.*—Di-isopropylamine (0.8 ml, 0.61 g, 6.0 mmol) was added to a stirred solution of methyl-lithium (6.0 ml of a 0.85M ethereal solution, 5.1 mmol) in 1,2-dimethoxyethane (10 ml) containing 2,2′-bipyridyl (1 mg) at −60 °C under nitrogen, and the solution was stirred for 10 min. To the resulting solution of lithium di-isopropylamide was added a solution of 11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one [1] (6) (0.447 g, 1.0 mmol) in 1,2-dimethoxyethane (15 ml) and the mixture was stirred at −60 °C under nitrogen for 15 min. The mixture was then treated with chlorotrimethylsilane (1.25 ml), stirred for a further 10 min whilst warming to room temperature, and then diluted with diethyl ether (150 ml containing 1% of triethylamine). The ethereal solution was washed with aqueous sodium hydrogencarbonate (15 ml of a saturated solution), and then with aqueous sodium chloride (2 × 10 ml of a saturated solution) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave 11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-20-*trimethylsilyloxy*)-5β-*pregn*-20-*ene* (17) (0.62 g) as a viscous oil, which was used without further purification. $\nu_{max.}$ (neat liquid) 1 650(m), 1 600(m), 1 255(s, $SiCH_3$), 1 080—1 060(s, br), 1 030(s, OTHP), 1 010(s, OTHP), 870(s), and 850(s) cm^{-1}; δ($CDCl_3$) 0.22 [s, $OSi(CH_3)_3$], 1.03 (s, 19-H_3), 2.47 (t, *J* 8 Hz, 17α-H), 2.74 (q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H), 3.25—4.20 (3 H, m, 3β-H and 6′-H_2), 3.30 (s, 18-OCH_3), 3.90 and 3.94 (apparent d, 21-H_2), 4.36 (d, $J_{11\alpha.12\beta}$ 6 Hz, 11α-H), 4.41 (s, 18-H), and 4.73br (s, 2′-H).

11β,18-*Epoxy*-21-*hydroxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (18).—3-Chloroperbenzoic acid (0.26 g, 1.5 mmol) was added to a stirred solution of the trimethylsilyl enol ether (17) (0.62 g, 1.0 mmol) in 1,2-dimethoxyethane (25 ml) at room temperature and the mixture was stirred at 65 °C in the dark under nitrogen for 24 h. The mixture was allowed to cool, diluted with water (10 ml), stirred for a further 5 min at room temperature and then partitioned between diethyl ether (150 ml containing 1% triethylamine) and aqueous sodium hydrogencarbonate (10 ml of a saturated solution). The aqueous fraction was extracted with more diethyl ether (50 ml), and the ethereal fractions were combined, washed with aqueous sodium chloride (4 × 10 ml of a saturated solution) and water (10 ml), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a mixture of crystalline solid and viscous gum (0.51 g). Column chromatography on silica gel (50 g), eluting with ethyl acetate–hexane (3 : 7), gave 11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (6) (27 mg, 6%), powder, m.p. 150—157 °C (crude), which had spectra identical to those of an authentic sample.[1] Further elution of the column with ethyl acetate–hexane (2 : 3) gave 11β,18-*epoxy*-21-*hydroxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (18) (0.22 g, 48%), needles from ethyl acetate–hexane, m.p. 168—177 °C; $\nu_{max.}$ (KBr) 3 600—3 150(m,br), 1 710(m,-sh), 1 695(s), 1 070(s, OTHP), and 1 030(s, OTHP) cm^{-1}; ν($CHCl_3$) 1 705(s, C=O) cm^{-1}; δ($CDCl_3$) 0.97 (s, 19-H_3), 2.58 (q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H), 2.77 (t, *J* 9 Hz, 17α-H), 3.17 (s, 18-OCH_3), 3.30—4.10 (3 H, m, 3β-H and 6′-H_2), 4.08 and 4.38 (dd, J_{gem} 16 Hz, 21-H_2), 4.36 (s, 18-H), 4.42 (d, $J_{11\alpha.12\beta}$ 6 Hz, 11α-H), and 4.72br (s, 2′-H) (Found: C, 70.2; H, 9.2. $C_{27}H_{42}O_6$ requires C, 70.1; H, 9.15%). Further elution of the column with ethyl acetate–hexane

* 3-Chloroperbenzoic acid was purified according to the method of N. N. Schwartz and J. H. Blumberg. *J. Org. Chem.*, 1964, **29**, 1976; L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. 1, p. 135.

(3 : 1) gave 3α,21-*dihydroxy*-11β,18-*epoxy*-18-*methoxy*-5β-*pregnan*-20-*one* (19) (5 mg, 1.5%), powder, m.p. 169—174 °C (crude); $\nu_{max.}$ (KBr) 3 650—3 100(s,br) and 1 710(s) cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 2.57 (q, $J_{12\alpha,12\beta}$ 11, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 2.76 (t, J 9 Hz, 17α-H), 3.18 (s, 18-OCH_3), 3.60 (m, 3β-H), 4.06 and 4.36 (dd, J_{gem} 17 Hz, 21-H_2), 4.35 (s, 18-H), and 4.42 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H).

21-*Acetoxy*-11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (27).—A solution of 11β,18-epoxy-21-hydroxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (18) (0.115 g, 0.25 mmol) and acetic anhydride (0.6 ml) in pyridine (2.5 ml) was stirred at room temperature in the dark for 20 h. The mixture was then poured onto ice–water (25 ml), stirred at room temperature for a further 10 min and then extracted with ethyl acetate (1 × 50 ml and 2 × 25 ml). The ethyl acetate fractions were combined, washed successively with dilute hydrochloric acid (3 × 5 ml), water (10 ml), aqueous sodium hydrogencarbonate (5 ml of a 10% solution), water (10 ml), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a glass (0.126 g). Column chromatography on silica gel (6.5 g), eluting with ethyl acetate–hexane (1 : 4), gave 21-*acetoxy*-11β-18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (27) (0.119 g, 95%), as a glass, m.p. 48—51 °C; $\nu_{max.}$ (KBr) 1 755(s), 1 730(s), 1 235(s), 1 070(s, OTHP), and 1 030(s, OTHP) cm^{-1}; ν($CHCl_3$) 1 745(s, C=O) and 1 725(s, C=O) cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 2.14 (s, 21-OAc), 2.61 (q, $J_{12\alpha,12\beta}$ 11, $J_{11\alpha,12\beta}$ 6 Hz, 12α-H), 2.88 (t, J 9 Hz, 17α-H), 3.21 (s, 18-OCH_3), 3.30—4.10 (3 H, m, 3β-H and 6′-H_2), 4.38 (s, 18-H), 4.47 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.72br (3 H, s, 21-H_2 and 2′-H).

Acetolysis of 21-*Acetoxy*-11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (27).—Anhydrous acetic acid* (4.5 ml, 80 mmol) was added to a stirred solution of 21-acetoxy-11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (27) (78.3 mg, 0.16 mmol) in tetrahydrofuran (1.6 ml) at room temperature under nitrogen and the mixture was stirred and heated at 120—125 °C under nitrogen for 6 h. The mixture was allowed to cool under nitrogen and was then diluted with dichloromethane (50 ml). The dichloromethane solution was washed successively with aqueous sodium hydrogencarbonate (6 × 5 ml of a saturated solution), water (5 ml), and aqueous sodium chloride, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid (71.6 mg). Preparative t.l.c. of a sample of the crude product (10.4 mg) on silica gel, developing twice with ethyl acetate–hexane (1 : 1), gave two bands. The less polar band afforded 11β,18-*epoxy*-3α,18,21-*triacetoxy*-5β-*pregnan*-20-*one* (29) (4.5 mg, 43%), needles from ethyl acetate–hexane, m.p. 108—115 °C; $\nu_{max.}$ (KBr) 1 750(s), 1 740(s,br), 1 240(s), 1 030(s), and 1 005(s) cm^{-1}; δ($CDCl_3$) 0.99 (s, 19-H_3), 1.92 (s, 18-OAc), 2.02 (s, 3-OAc), 2.15 (s, 21-OAc), 2.63 (q, $J_{12\alpha,12\beta}$ 11, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 2.96 (1 H, t, J 9 Hz, 7α-H), 4.42—4.84 (m, 3β-H), 4.55 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.76 (s, 21-H_2), and 5.90 (s, 18-H). The more polar band afforded 18,21-*diacetoxy*-11β,18-*epoxy*-3α-*hydroxy*-5β-*pregnan*-20-*one* (28) (4.2 mg, 40%), needles from ethyl acetate–hexane, m.p. 107—111 °C; $\nu_{max.}$ (KBr) 3 550—3 150(s), 1 750(s), 1 730(s), 1 235(s), 1 040(m), and 1 005(m) cm^{-1}; δ($CDCl_3$) 0.99 (s, 19-H_3), 1.93 (s, 18-OAc), 2.15 (s, 21-OAc), 2.63 (q, $J_{12\alpha,12\beta}$ 11, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 2.96 (t, J 9 Hz, 17α-H), 3.66 (m, 3β-H), 4.56 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), 4.76 (s, 21-H_2), and 5.90 (s, 18-H).

Hydrolysis of 21-*Acetoxy*-11β,18-*epoxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (27) *with Hydrochloric Acid*.—Aqueous hydrochloric acid (0.33 ml of a 1M solution) was added to a stirred solution of 21-acetoxy-11β,18-epoxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (27) (16.5 mg, 0.03 mmol) in tetrahydrofuran (0.33 ml). The mixture was stirred at room temperature for 24 h and then diluted with water (5 ml) and extracted with dichloromethane (2 × 10 ml). The dichloromethane extracts were combined, washed with water (3 × 2.5 ml), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid (12.2 mg). T.l.c. on silica gel, developing three times with ethyl acetate–hexane (1 : 1) gave 11β,18;18,21-*diepoxy*-3α-*hydroxy*-5β-*pregnan*-20-*one* (26) (7.6 mg, 66%), needles from ethyl acetate–hexane, m.p. 184—187 °C, which had identical spectra to those described below and 11β,18-epoxy-3α-hydroxy-5β-pregnane-17β,18-carbolactone (' 3α,5β-tetrahydroaldosterone γ-lactone ') (33) (1.5 mg, 13%), a powder, m.p. 247—255 °C (crude) (lit.,[29] 246—248 °C) which had spectra identical to those of an authentic sample, $\nu_{max.}$ (KBr) 3 650—3 100(s,br), 1 780(s, lactone), 1 735(w), 1 080(s), and 1 045(s) cm^{-1}; δ($CDCl_3$) 1.05 (s, 19-H_3), 2.91 (q, $J_{12\alpha,12\beta}$ 11, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 3.68 (m, 3β-H), 4.82 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), and 5.47 (s, 18-H).

Hydrolysis of 11β,18-*Epoxy*-21-*hydroxy*-18-*methoxy*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnan*-20-*one* (18) *with Aqueous Acetic Acid*.—Aqueous 70% acetic acid (1 ml) was added to a stirred solution of 11β,18-epoxy-21-hydroxy-18-methoxy-3α-(tetrahydropyran-2-yloxy)-5β-pregnan-20-one (18) (10.1 mg, 0.02 mmol) in tetrahydrofuran (0.5 ml) and the mixture was stirred at room temperature for 24 h, then diluted with water (5 ml), and extracted with dichloromethane (2 × 10 ml). The extracts were combined, washed with aqueous sodium hydrogencarbonate and water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid (6.1 mg). T.l.c. on silica gel, eluting with ethyl acetate–hexane (2 : 1), gave 11β,18;18,21-*diepoxy*-3α-*hydroxy*-5β-*pregnan*-20-*one* (26) (4.7 mg, 67%), needles from ethyl acetate–hexane, m.p. 184—187 °C; $\nu_{max.}$ (KBr) 3 600—3 200(br), 3 530(s), 1 715(s), and 1 060(s) cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 2.57 (q, $J_{12\alpha,12\beta}$ 11, $J_{11\alpha,12\beta}$ 6 Hz, 12β-H), 2.86 (t, 6 Hz, 17α-H), 3.68 (m, 3β-H), 4.01 (s, 21-H_2), 4.61 (d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H), and 4.88 (s, 18-H); *m/e* 346 (M^+, 10%) 293 (60), 275 (100), 167 (40), and 149 (70); *m/e* (after derivatization as its 3α-trimethylsilyloxy-20-methoxime) 447 (M^+, 10%), 432 (15), 418 (100), 403 (30), 388 (10), 328 (15), 326 (40), 313 (15), 285 (15), 280 (20), 240 (40), and 202 (35).

11β,18-*Epoxy*-3α,18,21-*trihydroxy*-5β-*pregnan*-20-*one* (3α,5β-*Tetrahydroaldosterone*) (1) *and* 3α-*Acetoxy*-18,21-*dihydroxy*-11β,18-*epoxy*-5β-*pregnan*-20-*one* (3α,5β-*Tetrahydroaldosterone* 3-*Acetate*) (37).—A solution of the mixture (see above) of 11β,18-epoxy-3α,18,21-triacetoxy-5β-pregnan-20-one (29) and 18,21-diacetoxy-11β,18-epoxy-3α-hydroxy-5β-pregnan-20-one (28) (71.6 mg, *ca.* 0.16 mmol) and sodium hydrogencarbonate (101 mg, 1.2 mmol) in methanol (10 ml) and water (5 ml) was stirred at room temperature under nitrogen in the dark for 30 h. The mixture was then diluted with ice–water (10 ml) and extracted with dichloromethane (2 × 25 ml). The dichloromethane extracts were combined and washed with water (5 ml), then with aqueous sodium chloride (2 × 10 ml of a saturated solution) and dried

* Glacial acetic acid was azeotropically distilled with benzene and the fraction boiling in the range 118—120 °C was collected.

($MgSO_4$). Removal of the solvent under reduced pressure gave a solid (54.8 mg). Preparative t.l.c. on silica gel, developing three times with ethyl acetate–hexane (2 : 1) gave two bands. The less polar band afforded 3α,5β-*tetrahydroaldosterone* 3-*acetate* (37) (21.6 mg, 33%), needles from ethyl acetate–hexane, m.p. 110—121 °C; $\nu_{max.}$ (KBr) 3 650—3 060(s,br), 1 730(s), 1 710(m,sh), 1 250(s), 1 080—1 050(s,br), and 1 030(s) cm^{-1}; δ($CDCl_3$) 0.99 (s, 19-H_3), 1.04 (s, 19-H_3), 2.04 (s, 3-OAc), 2.54—2.98 [m, 12β-H(I), 17α-H, and 21-OH], 3.06—3.40 (m, 18-OH), 3.40—3.78 [m, 21-H_2-(II)], 4.33 [t, *J* 5 Hz, 21-H_2(I)], 4.52 [d, $J_{11\alpha.12\beta}$ 6 Hz, 11α-H(I)], 4.74br [d, $J_{11\alpha.12\beta}$ 6 Hz, 11α-H(II) and 3β-H], 4.97 [d, *J* 6 Hz, 18-H(I)], and 5.37 [s, 18-H(II)]. Addition of D_2O led to the loss of the signal at δ 3.06—3.40 and the simplification of the signals at δ 2.54—2.98, 3.40—3.78, 4.33, and 4.97, which become, respectively, δ 2.66 [q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H(I)], 2.78 (t, *J* 9.5 Hz, 17α-H), 3.43 and 3.57 [dd, J_{gem} 11.5 Hz, 21-H_2(II)], 4.25 and 4.41 [dd, J_{gem} 18 Hz, 21-H_2(I)], 4.97 [s, 18-H(I)], and 5.37 [s, 18-H(II)]. The more polar band afforded 3α,5β-tetrahydroaldosterone (1) (20.8 mg, 36%), needles from ethyl acetate–hexane, m.p. 106—119 °C (lit.,[2] 107—114 °C); $\nu_{max.}$ (KBr) 3 660—3 000(s,br), 1 710(m), 1 075(s), 1 055(s), and 1 040(s) cm^{-1}; $\nu_{max.}$ ($CHCl_3$) 3 565(m,OH), 3 500—3 200(m,br,OH), and 1 705(m, C=O) cm^{-1}; δ($CDCl_3$) 0.98 (s, 19-H_3), 1.03 (s, 19-H_3), 2.23br [q, 12β-H(II)], 2.66 [q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H(I)], 2.82 (t, *J* 10 Hz, 17α-H), 3.46 and 3.60 [dd, J_{gem} 11.5 Hz, 21-H_2(II)], 3.66 (m, 3β-H), 4.25 and 4.41 [dd, J_{gem} 18 Hz, 21-H_2(I)], 4.52 [d, $J_{11\alpha.12\beta}$ 6 Hz, 11α-H(I)], 4.72 [d, $J_{11\alpha,12\beta}$ 6 Hz, 11α-H(II)], 4.97 and 4.88 [s,s, 18-H(I), in the ratio 6 : 1], 5.37 and 5.20 [s,s, 18-H(II), in the ratio 20 : 1]; *m/e* [after derivatization as its 3α,11β,21-tris(trimethylsilyloxy)-18,20-bis(methoxime)], 638 (M^+, 54%), 607 (M^+ − 31, 51), 591 (M^+ − 47, 57), 575 (M^+ − 63, 43), 535 (M^+ − 103, 16), 517 (M^+ − 31 − 90, 18), 485 (M^+ − 63 − 90, 23), 445 (M^+ − 103 − 90, 8), 427 (M − 31 − 2 × 90, 18), 395 (M^+ − 63 − 2 × 90, 24), and 103 (100) (Found: C, 69.0; H, 8.95. $C_{21}H_{32}O_5$ requires C, 69.2; H, 8.85%).

3α,5β-*Tetrahydroaldosterone* (1). *Hydrolysis of* 3α,5β-*Tetrahydroaldosterone* 3-*Acetate* (37).—A solution of 3α,5β-tetrahydroaldosterone 3-acetate (37) (17.6 mg, 0.04 mmol) and sodium hydrogencarbonate (5.5 mg, 0.065 mmol) in methanol (4.3 ml) and water (0.35 ml) was stirred at room temperature under nitrogen in the dark for 20 days. The mixture was then diluted with ice–water (7.5 ml) and extracted with dichloromethane (2 × 15 ml). The dichloromethane extracts were combined and washed with water (5 ml), then with aqueous sodium chloride (2 × 5 ml of a saturated solution), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid (11.4 mg). Preparative t.l.c. on silica gel, developing three times with ethyl acetate–hexane (2 : 1), gave 3α,5β-tetrahydroaldosterone (1) (9.1 mg, 63%), needles from ethyl acetate–hexane, m.p. 107—119 °C (lit.,[2] 107—114 °C), which had identical spectra to those described above.

3α-*Acetoxy*-20β-*hydroxy*-5β-*pregnano*-18,11β-*lactone* (40).—Zinc borohydride [1] (6.9 ml of 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 [1] (39) (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, then allowed to cool. Excess of reagent was destroyed by addition of ice-water (10 ml), then the mixture was diluted with ether (25 ml containing 1% triethylamine). The filtrates were combined, washed with aqueous sodium hydrogencarbonate (2 × 5 ml of a 10% solution) and water (2 × 5 ml), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a gum (88.5 mg). Preparative t.l.c. on silica gel, developing twice with ethyl acetate–hexane (2 : 1), gave 3α-acetoxy-20β-hydroxy-5β-pregnano-18,11β-lactone (40) (60.8 mg, 72%), needles from acetone–hexane, m.p. 187—190 °C (lit.,[67] 194.5—195.5 °C); $\nu_{max.}$ (KBr) 3 550—3 150(m, br), 1 770(s), 1 735(s), and 1 260(s) cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 1.17 (d, *J* 6 Hz, 21-H_3), 2.02 (s, 3-OAc), 3.09 (q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H), 4.28 (m, 20-H), 4.68br (2 H, d, $J_{11\alpha.12\beta}$ 6 Hz, 11α- and 3β-H); a minor product (4.8 mg, 5%) which was not identified was assumed to be 3α-acetoxy-11β,18-epoxy-5β-pregnane-18,20β-diol.

3α-*Acetoxy*-20-*oxo*-5β-*pregnano*-18,11β-*lactone* (7).—Jones' chromic acid reagent [1] was added dropwise to a stirred solution of 3α-acetoxy-20β-hydroxy-5β-pregnano-18,11β-lactone (40) (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 benzene fractions were combined and washed with aqueous sodium chloride (3 × 5 ml of a saturated solution) and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave crude 3α-acetoxy-20-oxo-5β-pregnano-18,11β-lactone (7) (57 mg, 95%) which crystallised from ethyl acetate-hexane as needles, m.p. 201—203 °C (lit.,[67] 201.5—203 °C); $\nu_{max.}$ 1 770(s), 1 735(s), 1 710(s), and 1 260(s) cm^{-1}; δ($CDCl_3$) 1.01 (s, 19-H_3), 2.02 (s, 3-OAc), 2.18 (s, 21-H_3), 2.66 (t, *J* 10 Hz, 17α-H), 3.05 (q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H), 4.76br (2 H, d, $J_{11\alpha.12\beta}$ 6 Hz, 11α- and 3β-H).

3α-(*Tetrahydropyran*-2-*yloxy*)-20-*trimethylsilyloxy*-5β-*pregn*-20-*eno*-18,11β-*lactone* (14).—Di-isopropylamine (0.14 ml, 100 mg, 1.0 mmol) was added to a stirred solution of methyl-lithium (1.0 ml of a 0.85M ethereal solution, 0.85 mmol) in 1,2-dimethoxyethane (5 ml) containing 2,2′-bipyridyl (1 mg) at −60 °C under nitrogen and the solution was stirred for 10 min. To the resulting solution of lithium di-isopropylamide was added a solution of 20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone [1] (8) (74.3 mg, 0.17 mmol) in 1,2-dimethoxyethane (5 ml) and the mixture was stirred at −60 °C under nitrogen for 15 min, then treated with chlorotrimethylsilane (0.2 ml), stirred for a further 10 min whilst warming to room temperature, and then diluted with diethyl ether (25 ml containing 1% triethylamine). The ethereal solution was washed with aqueous sodium hydrogencarbonate (10 ml of a saturated solution) and aqueous sodium chloride (2 × 5 ml of a saturated solution), and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave 3α-(*tetrahydropyran*-2-*yloxy*)-20-*trimethylsilyloxy*-5β-*pregn*-20-*eno*-18,11β-*lactone* (14) (104 mg), as an oil containing a little unchanged 20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (8); $\nu_{max.}$ (neat liquid) 1775(s) 1 710(w), 1 650(m,br), 1 255(s, $SiCH_3$), 1 030(s, OTHP), and 850(s) cm^{-1}; δ($CDCl_3$) 0.20 [s, $OSi(CH_3)_2$], 0.99 (s, 19-H_3), 2.67 (t, *J* 9 Hz, 17α-H), 2.97 (q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H), 3.30—4.15 (3 H, m, 3β-H and 6′-H_2), 4.17br (s, 21-H_2), 4.70br (2 H, d, $J_{11\alpha.12\beta}$ 6 Hz, 11α- and 2′-H).

21-*Hydroxy*-20-*oxo*-3α-(*tetrahydropyran*-2-*yloxy*)-5β-*pregnano*-18,11β-*lactone* (15).—3-Chloroperbenzoic acid (39 mg, 0.26 mmol) was added to a stirred solution of the trimethylsilyl enol ether (14) (101 mg, 0.17 mmol) in 1,2-dimethoxyethane (10 ml) at room temperature and the

mixture was stirred at room temperature under nitrogen in the dark for 7 days, then diluted with water (5 ml), stirred for a further 5 min at room temperature, and partitioned between diethyl ether (50 ml containing 1% triethylamine) and aqueous sodium hydrogencarbonate (10 ml of a saturated solution). The aqueous fraction was extracted with more diethyl ether (20 ml), and the ethereal fractions were combined and washed with aqueous sodium chloride (2 × 5 ml of a saturated solution), then with water (5 ml), and then dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a mixture of crystalline solid and viscous gum (78.7 mg). Preparative t.l.c. on silica gel, developing with ethyl acetate–hexane (4 : 3), gave 20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (8) (10.7 mg, 15%), as a powder, m.p. 165—172 °C (crude) which had spectra identical to those of an authentic sample,[1] and *21-hydroxy-20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone* (15) (17.3 mg. 23%), plates from acetone–hexane, m.p. 139—142 °C; $\nu_{max.}$ (KBr) 3 650—3 100(m,br), 1 760(s), 1 710(s), 1 080(s, OTHP), and 1 030(s, OTHP) cm^{-1}; δ($CDCl_3$) 0.99 (s, 19-H_3), 2.82 (t, *J* 10 Hz, 17α-H), 3.05 (q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 Hz, 12β-H), 3.30—4.04 (3 H, m, 3β-H and 6′-H_2), 4.30 and 4.56 (dd, J_{gem} 19 Hz, 21-H_2), and 4.77br (2 H, d, $J_{11\alpha.12\beta}$ 6 Hz, 11α- and 2′-H) (Found: C, 70.05; H, 8.5. $C_{26}H_{38}O_6$ requires C, 69.9; H, 8.6%).

21-Acetoxy-20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (16).—A solution of 21-hydroxy-20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone (15) (5.3 mg, 0.012 mmol) and acetic anhydride (0.25 ml) in pyridine (1 ml) was stirred at room temperature in the dark for 20 h. The mixture was then poured onto ice-water (5 ml), stirred for a further 10 min at room temperature and then extracted with ethyl acetate (10 ml). The ethyl acetate fraction was washed successively with dilute hydrochloric acid (5 × 1 ml of a 2N solution), water (1 ml), aqueous sodium hydrogencarbonate (1 ml of a 10% solution), and water (1 ml) and dried ($MgSO_4$ and Na_2CO_3). Removal of the solvent under reduced pressure gave a solid (5.1 mg) which crystallised from acetone–hexane to give *21-acetoxy-20-oxo-3α-(tetrahydropyran-2-yloxy)-5β-pregnano-18,11β-lactone* (16) (4.4 mg, 74%) as needles, m.p. 163—169 °C; $\nu_{max.}$ (KBr) 1 765(s), 1 750(s), 1 715(s), 1 240(s), 1 070(m, OTHP), and 1 030(s, OTHP) cm^{-1}; ν($CHCl_3$) 1 770(s,C=O), 1 755(s,sh,C=O), and 1 730(s,C=O) cm^{-1}; δ($CDCl_3$) 1.00 (s, 19-H_3), 2.14 (s, 21-OAc), 2.83 (t, *J* 10 Hz, 17α-H), 2.99 (q, $J_{12\alpha.12\beta}$ 11, $J_{11\alpha.12\beta}$ 6 12β-H), 3.26—4.04 (3 H, m, 3β-H and 6′-H_2), and 4.69 (4 H, complex, 11α-H, 21-H_2, and 2′-H) (Found: C, 68.5; H, 8.25. $C_{28}H_{40}O_7$ requires C, 68.8; H, 8.25%).

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