Alkylated Steroids. Part 3.[1] The 21-Alkylation of 20-Oxopregnanes and Synthesis of a Novel Anti-inflammatory 16α,17α,21-Trimethyl Steroid (Org 6216)

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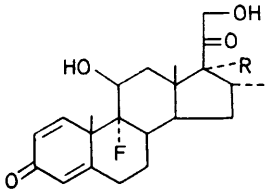
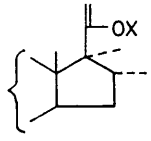
The development of a 21-alkylation reaction which proceeds *via* the lithium 20(21)-*enolate* is described and its scope demonstrated by the preparation of a variety of 21-alkylpregnane derivatives. Application of this process to 11β-acetoxy-16α,17α-dimethyl-5α-pregnane-3,20-dione (28a) and its 5β-analogue (28b) led to the corresponding 16α,17α,21-trimethyl derivatives. Several routes from these saturated trimethylpregnane-3,20-diones to 11β-hydroxy-16α,17α,21-trimethylpregna-1,4-diene-3,20-dione (Org 6216) were explored. The best method gave Org 6216 in 75% yield.

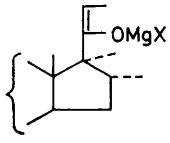
We have previously described [2] the preparation of a 16α,17α-dimethyl corticosteroid, dimesone (1), and demonstrated [3] an increase in the ratio of local to systemic anti-inflammatory effect when compared to dexamethasone (2) or 17-deoxydexamethasone (3). In addition, Llaurado has shown [4] that a 21-methyl group is effective in eliminating the undesirable salt-retaining activity of 9α-fluoroprednisolone. As an extension of these observations it was of interest to prepare a 16α,17α,21-trimethyl steroid related to known anti-inflammatory agents, for biological evaluation.



(1) R = Me
(2) R = OH
(3) R = H



(4) a; X = MgBr
b; X = Li



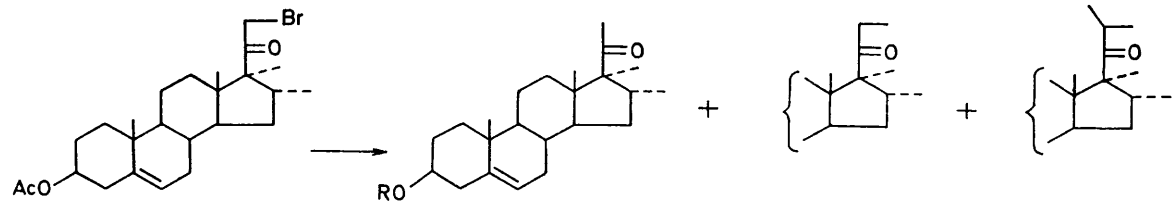
(10)

In our previous work [1,5] on the preparation of 16α,17α-dimethyl steroids from pregn-16-en-20-ones by treatment with methylmagnesium halide followed by reaction of the resulting 17(20)-enolate with methyl iodide, the isolation and characterisation of 16α,17α,21-trimethylpregnanes consistently present as impurities was described. In order to confirm their proposed structures, these trimethyl derivatives were independently synthesised; however the procedure involved a rather laborious Mannich reaction on the corresponding 16α,17α-dimethylpregnanes. The present work describes the development of an efficient alkylation reaction for the preparation of 16α,17α,21-trimethyl steroids in high yield, and subsequent investigations for the elaboration of ring-A-saturated 16α,17α,21-trimethylpregnanes to the corresponding 1,4-dien-3-ones.

In the 16α,17α-dimethylation reaction,[5] alkylation of a small amount of the 20(21)-enolate (4a) [formed by the action of an excess of methyl Grignard reagent on the main product, 3β-hydroxy-16α,17α-dimethylpregn-5-en-20-one (6)] by an excess of methyl iodide was considered to be the most likely source of the 16α,17α,21-trimethyl impurity. To investigate this possibility further the 21-bromo-compound (5), prepared from copper(II) bromide and 16α,17α-dimethylpregnenolone acetate (7), was treated with methylmagnesium bromide to give the enolate (4a). However, although reaction with methyl iodide gave the 16α,17α,21-trimethyl derivative (8), equal amounts (g.l.c.) of the 16α,17α-dimethyl and 16α,17α,21,21-tetramethyl derivatives (6) and (9) were also formed. Formation of the tetramethyl compound (9) probably arises by an exchange between unchanged enolate (4a) and the mono-alkylation product (8), giving the dimethyl compound (6) and the enolate (10) which undergoes further alkylation. Barton and his co-workers [6] have described a similar enolate exchange reaction between a 3-sodium-1,3,5-trienolate and an 11-ketone.

An alternative approach to the desired 20(21)-enolate involved base-induced enolisation of a 16α,17α-dimethyl-20-oxo-derivative. For this reaction it was necessary to protect an oxygen function at C-3 appropriately as an ether or acetal derivative. Treatment of the tetrahydropyranyl ether (12) with an excess of sodium amide (16 mol equiv.) in liquid ammonia, and then methyl iodide, gave as the main product the 16α,17α,21,21-tetramethyl derivative (13) (90% conversion) rather than the required trimethyl derivative (14). With 8 mol equiv. of sodium amide a mixture of the 16α,17α-dimethyl (11), 16α,17α,21-trimethyl (14), and 16α,17α,21,21-tetramethyl (13) derivatives was formed.

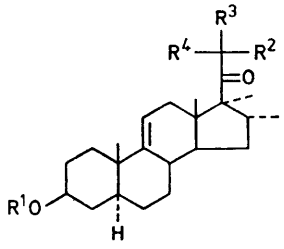
More precise control of the base required for the reaction was achieved utilising the self-indicating property of trityl-lithium.[7] In this way the acetal (15a) afforded the trimethyl derivative (16a) on titration with 1 mol equivalent of trityl-lithium followed by reaction with methyl iodide. The disadvantage of this method is the



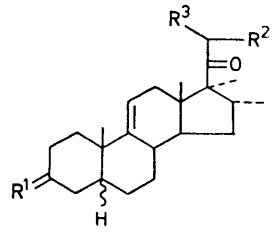
(5) (6) R = H (7) R = Ac (8) (9)

formation of triphenylmethane (*ca.* 50%) which makes it difficult to isolate the product without chromatography.

With the acetal (15a) a purer alkylated product (16a)

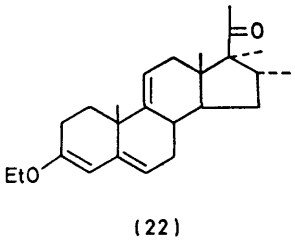


(11) $R^1 = R^2 = R^3 = R^4 = H$
(12) $R^1 = THP, R^2 = R^3 = R^4 = H$
(13) $R^1 = R^2 = H, R^3 = R^4 = Me$
(14) $R^1 = R^2 = R^3 = H, R^4 = Me$
(20) $R^1 = THP, R^2 = H, R^3 = R^4 = Me$
(21) $R^1 = H, R^2 = R^3 = R^4 = Me$



(15) $R^1 = (OMe)_2, R^2 = R^3 = H$
(16) $R^1 = O, R^2 = H, R^3 = Me$
(17) $R^1 = O, R^2 = R^3 = H$
(18) $R^1 = O, R^2 = R^3 = Me$
(19) $R^1 = O, R^2 = H, R^3 = Et$
a = 5α-series, b = 5β-series

[97% (g.l.c.)] was obtained by using lithium di-isopropylamide as base. Lithium diethylamide on the other hand gave a product containing a substantial amount of starting material. Additional reactions to establish the general applicability and advantages of lithium di-isopropylamide for the 21-alkylation procedure are shown in the Table.



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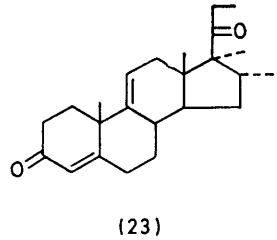

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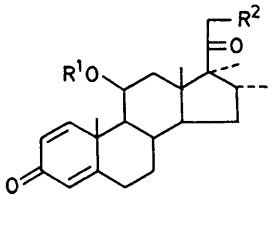
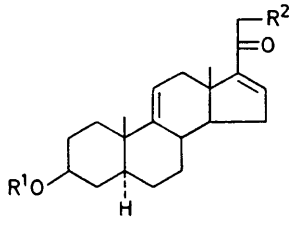


(24) $R^1 = Ac, R^2 = H$
(25) $R^1 = H, R^2 = Pr$



(26) $R^1 = THP, R^2 = H$
(27) $R^1 = H, R^2 = Me$

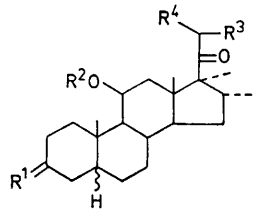
In the 9(11)-ene series it was found necessary to use an excess of lithium di-isopropylamide for complete 21-alkylation and this led consistently to some 21,21-dialkylation. With the 11β-acetoxy-3-acetal (29a) the

Summary of 21-alkylation reactions (with lithium di-isopropylamide as base)

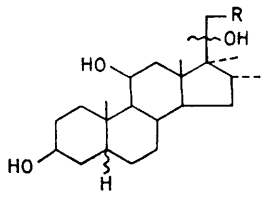
Starting material	Alkyl halide	Product	Yield (%)
(15a)	EtI	(19a)	82
(20)	MeI	(21)	95 [a]
(22)	MeI	(23)	56.5
(24)	Pr^nI	(25)	30 [b]
(26)	MeI	(27)	82

[a] A second treatment with base and methyl iodide can be applied if the reaction is not complete. [b] After hydrolysis of the 11-ester.

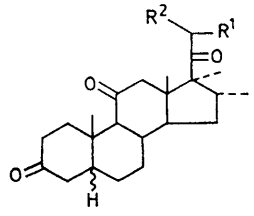
general procedure gave a complex mixture (g.l.c.) after deacetalisation. The reaction was complicated by concomitant alkylation of the 11-ester grouping. This was shown to occur by the absence of a signal due to



(28) $R^1 = O, R^2 = Ac, R^3 = R^4 = H$
(29) $R^1 = (OMe)_2, R^2 = Ac, R^3 = R^4 = H$
(30) $R^1 = O, R^2 = Ac, R^3 = H, R^4 = Me$
(31) $R^1 = O, R^2 = COEt, R^3 = R^4 = H$
(32) $R^1 = O, R^2 = COEt, R^3 = H, R^4 = Me$
(33) $R^1 = O, R^2 = COPr^i, R^3 = R^4 = H$
(34) $R^1 = O, R^2 = COPr^i, R^3 = H, R^4 = Me$
(40) $R^1 = O, R^2 = COEt, R^3 = R^4 = Me$



(35) R = H
(36) R = Me

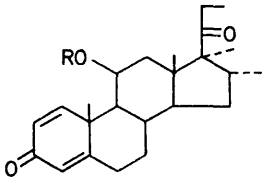


(37) $R^1 = R^2 = H$
(38) $R^1 = H, R^2 = Me$
(39) $R^1 = R^2 = Me$
a = 5α-series, b = 5β-series

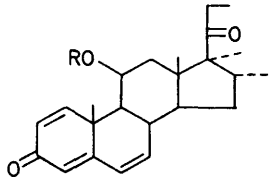
acetate protons in the n.m.r. spectrum of the product, and the presence of peaks in the mass spectrum at *m/e* 430 and 444 [corresponding to the propionate (32a) and isobutyrate (34a) esters)], and 356 (loss of propionic or

butyric acid), and a fragmentation pattern typical of the side-chain and ring-D cleavage of 16α,17α,21-trimethyl steroids.[1] Also, reduction of the crude reaction product to the triols (35a) and (36a), followed by Jones oxidation, gave a mixture of the triones (37a) and (38a). There was no evidence (g.l.c.) for the presence of the 21,21-dimethyl product (39a) in this case. These observations were fortuitous for the main application we had in mind carried out on mixtures of the propionates and isobutyrates in both the 5α- and 5β-series [(32a) and (34a), and (32b) and (34b)].

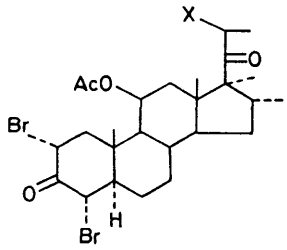
Dehydrogenation of (30a) with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone; 2.4 mol equiv.) gave the 1,4-diene (41) (40%) contaminated with the 1,4,6-triene (42) (15%). The latter could only be removed as the water-soluble sulphite [8,9] to give the pure diene (41).



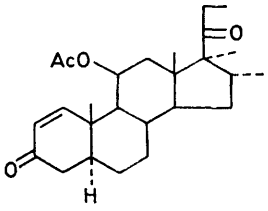
(41) R = Ac
(48) R = H
(61) R = COEt
(65) R = COPr^{i}



(42) R = Ac
(62) R = COEt



(43) X = H
(44) X = Br



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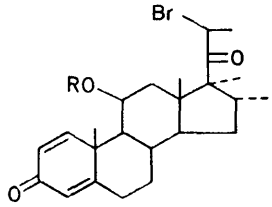
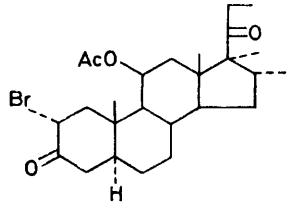


(46) R = COMe
(53) R = H



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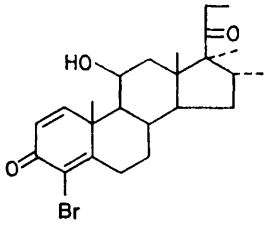

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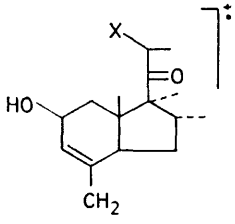
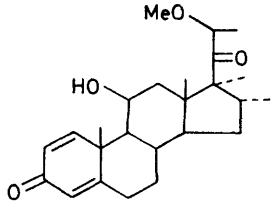


(49) X = H
(50) X = Br
(51) X = OMe



(54)

for these reactions since impurities formed by over-alkylation at C-21 could not be removed from the final product by crystallisation.

Thus conditions were established for optimal 21-methylation of (29a) with minimal formation of the 21,21-dimethyl derivative (40a) [<1% (g.l.c.)]. Similarly, application of the same alkylation procedure to the dione (28b) [as the 3,3-dimethyl acetal (29b)] gave a mixture of esters (32b) and (34b) in much the same proportions (84 and 16% respectively).

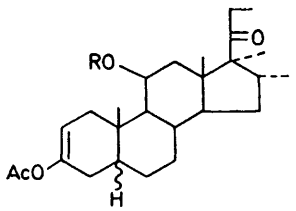
Introduction of the 1,4-dien-3-one grouping was first studied with the 11-acetate (30a). Further studies were

In another approach, bromination of the 3-oxo-compound (30a) gave the 2α,4α-dibromo-derivative (43) [δ 4.81 (2β-H) and 4.65 (4β-H)] contaminated with the product (44) from additional bromination at C-21 [δ 1.66 ($CHBrCH_3$)]. Dehydrobromination of the crude bromination product gave a mixture (g.l.c.) of the 1,4-diene (41) (60%), the 1-ene (45) (20%), and the 21-bromide (46) (20%). Further reaction of the crude dehydrobromination product with DDQ converted the 1-en-3-one (45) in the mixture into the 1,4-dien-3-one (41), without affecting the 21-bromo component (46). The 21-bromine atom proved difficult to remove by debromination.

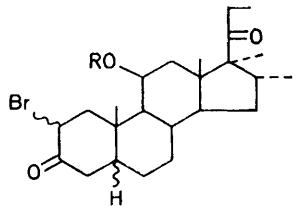
Sodium iodide in boiling acetone or zinc in boiling ethanol were ineffective. Zinc in acetic acid led to a bromine-free product with u.v. absorption at 323, 335, and 351 nm. The absence of absorption at 240 nm established that the 1,4-dien-3-one was on longer present and the compound was not investigated further. Kirk *et al.*[10] obtained a similar unidentified product from the reaction of cholesta-1,4-dien-3-one with zinc in acetic acid.*

DDQ converted the mixture into the pure 1,4-diene (41) in 50% yield from (30a).

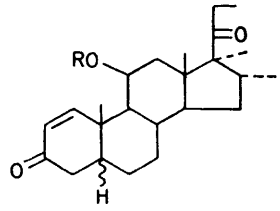
Insertion of the 1,4-diene system by the above route could not be applied in the 5β-series. Monobromination of a mixture of (32b) (84%) and (34b) (16%) led to a mixture of brominated and unbrominated products. Dibromination of the same mixture, dehydrobromination of the product, and hydrolysis of the ester groups gave



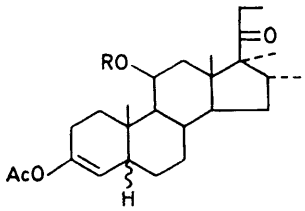
(55) R = COEt



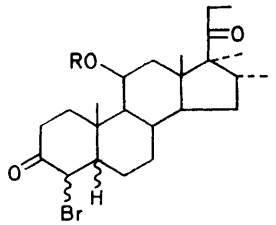
(57) a; R = COEt, 2α-Br
b; R = COEt, 2β-Br



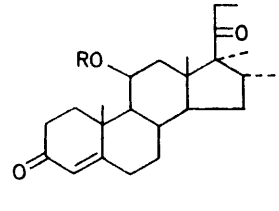
(59) R = COEt
(66) R = H



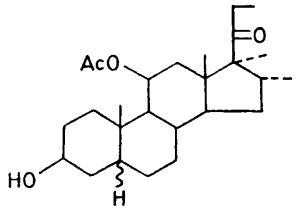
(56) R = COEt



(58) a; R = COEt, 4α-Br
b; R = COEt, 4β-Br



(60) R = COEt
(63) R = Ac
(67) R = H

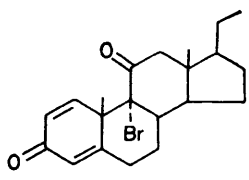


(64)

a = 5α-series, b = 5β-series

Monobromination of (30a) gave the 2α-bromo-derivative (47) which on dehydrobromination gave the 1-en-3-one (45) containing a small amount of the 1,4-diene (41).

* In a separate investigation the 1,4-dien-3-one (i) gave a small amount of a dimer $\lambda_{max.}$ 320 (ε 36 600), 333 (57 000) and 350 nm



(i)

(61 000); $\nu_{max.}$ 1 707 cm^{-1} (11-ketone) (Found, M^+, 592.4262. $C_{42}H_{56}O_2$ requires M, 592.4280) with zinc in acetic acid.

the 1,4-diene (48) contaminated with three impurities (t.l.c.). These were isolated by chromatography and shown by mass spectrometry [peaks at *m/e* 249, 329/327, and 279 due respectively to the ions (49), (50), and (51)] to be the 4-bromo-derivative (52) (9%) ($\lambda_{max.}$ 256 nm),[11] the 21-bromo-derivative (53) (15%) [δ 1.69 ($CHBrCH_3$)], and the 21-methoxy-derivative (54) (1.5%) [an artefact from the action of methanolic alkali on the 21-bromide (53)].

As an alternative approach to the required 1,4-diene, a 1 : 1 mixture of the enol acetates (55b) and (56b) was treated with hypobromous acid (1.3 mol equiv.) and the two products were separated by chromatography and identified as the 2β-bromo (57b) [δ 4.68 (2α-H)] and 4β-bromo (58b) [δ 4.93 (4α-H)] derivatives. Dehydrobromination of the crude bromo-ketones (57b) and (58b)

gave a mixture of the 1-en-3-one (59b) and 4-en-3-one (60) which on treatment with DDQ (1.2 mol equiv.) gave the 1,4-diene (61). Two impurities, the 1-en-3-one (59b) (2%) and the 1,4,6-trien-3-one (62) (4%) were readily removed as water-soluble products by treatment with boiling aqueous ethanolic sodium hydrogensulphite [8,9] to give the pure 1,4-diene (61) [75% from (32b)]. Alkaline hydrolysis gave the required product (48) (Org 6216). Application of the same procedure to the mixed 5α-3-oxo-esters (32a) (84%) and (34a) (16%) was completely satisfactory and led to the desired product (48) (Org 6216) in 75% overall yield.

Hydrolysis of the 11-ester group in the mixture of (61) and (65) proved surprisingly easy. The hydrolysis was complete in 2 h with boiling aqueous methanolic potassium hydroxide. Investigation of a series of related 11-acetoxy-derivatives variously unsaturated in ring A established that the rate of hydrolysis of the 11-ester is as follows: 1,4-dien-3-one (41) > 1-en-3-one (45) > 4-en-3-one (63) > saturated 3-one (30a) ≫ 3-hydroxy (64). Dreiding models revealed that with increasing unsaturation in ring A the strain due to the increasing planarity of the ring is transmitted to rings B and C and results in an increase in the dihedral angle; 9α-H, 11β-O, and hence in the equatorial character of the 11β-bond, which directly correlates with the ease of hydrolysis. An additional effect due to the absence of steric hindrance from a 1α-hydrogen atom is another factor operating in the 1,4-diene and 1-ene compounds. In the 1,4-diene series the rate of hydrolysis of an 11-ester decreased with increasing size of the ester as follows: acetate (41) > propionate (61) > isobutyrate (65).

EXPERIMENTAL

Physical measurements were determined as described in Part 1.[5]

3β-Acetoxy-21-bromo-16α,17α-dimethylpregn-5-en-20-one (5).—3β-Acetoxy-16α,17α-dimethylpregn-5-en-20-one (7) (4 g) in tetrahydrofuran (140 ml) was treated with copper(II) bromide (5.6 g, 2.3 mol equiv.) and the stirred mixture heated under reflux for 1 h. The cooled reaction mixture was filtered, water (500 ml) was added to the filtrate, and the product was extracted into ether. The ether extracts were washed with water, then dried and evaporated to give the *21-bromo-derivative* (5) (4 g), m.p. 166—167 °C (from ether–methanol), $[\alpha]_D$ −37.1° (*c*, 0.4); $\nu_{max.}$ (KCl) 1 734 (acetate) and 1 720 cm^{-1} (20-ketone); δ 0.73 (3 H, s, 13-Me), 0.89 (3 H, d, *J* 7 Hz, 16α-Me), 1.02 (3 H, s, 17α-Me), 1.12 (3 H, s, 10-Me), 2.02 (3 H, s, OAc), 2.95 (1 H, m, 16 β-H), 4.13, 4.00 (2 H, AB quartet, *J* 14 Hz, 2 × 21-H), 4.65 (1 H, m, 3α-H), and 5.38 (1 H, m, 5-H) (Found: C, 64.1; H, 7.9; Br, 17.8. $C_{25}H_{37}O_3Br$ requires C, 64.5; H, 8.0; Br, 17.2%).

Treatment of the Bromo-derivative (5) *with Methylmagnesium Chloride–Methyl Iodide*.—To a stirred solution of the 21-bromo-compound (5) (1 g) in dry tetrahydrofuran (25 ml) under nitrogen was added dropwise methylmagnesium chloride (0.1M in tetrahydrofuran) (35 ml). After 5 min, dry methyl iodide (5 ml) was added and the solution was heated under reflux overnight. A sample, hydrolysed by potassium hydroxide in methanol, consisted of 3β-hydroxy-16α,17α-dimethylpregn-5-en-20-one (6) (*ca.* 27%; t_R 1.04), 3β-hydroxy-16α,17α,21-trimethylpregn-5-en-20-one (8) (*ca.* 35%; t_R 1.28) and 3β-hydroxy-16α,17α,21,21-tetramethylpregn-5-en-20-one (9) (*ca.* 38%; t_R 1.43).

3β-Hydroxy-16α,17α,21,21-tetramethyl-5α-pregn-9(11)-en-20-one (13).—3β-Hydroxy-16α,17α-dimethyl-5α-pregn-9(11)-en-20-one (11) (25.0 g) suspended in stirred dry benzene (750 ml) was treated with dihydropyran (50 ml) followed by toluene-*p*-sulphonic acid (1.25 g). Complete solution was achieved in 5 min. After 1 h, solid sodium hydrogencarbonate was added and stirring was continued for a further 5 min. The solution was washed with sodium carbonate solution, then with water to neutrality, dried, and evaporated to give the tetrahydropyranyl ether (12) (32.0 g).

To stirred liquid ammonia (500 ml), refluxing under a condenser containing solid CO_2, was added sodium metal (27 g) in small pieces over 15 min, iron(III) chloride (100 mg) being added after the addition of the first few pieces of sodium to catalyse the conversion of sodium into sodamide. Stirring was continued until the blue colour of the sodium solution had been completely discharged (*ca.* 1½ h) and only the black colour of the catalyst remained. A solution of the crude tetrahydropyranyl ether (12) (27.0 g) in dry tetrahydrofuran (500 ml) was slowly added over 30 min. After a further 1 h, a solution of dry methyl iodide (135 ml) in dry tetrahydrofuran (500 ml) was added dropwise over 1½ h. The CO_2 condenser was replaced by a water condenser and the stirred solution was allowed to warm to room temperature overnight. A solution of ammonium chloride (16 g) in water (500 ml) was added, and the stirring was continued for a further 10 min. The excess of methyl iodide was removed by distillation under reduced pressure and the resulting mixture was extracted three times with ether. The combined ether extracts were washed with sodium hydrogensulphite solution, water, potassium hydroxide solution, then water until neutral, dried and evaporated to give 16α,17α,21,21-tetramethyl-3β-tetrahydropyranyloxy-5α-pregn-9(11)-en-20-one (20) (30.5 g).

To a solution of a sample (0.5 g) of this material in acetic acid (5 ml) was added water (2 ml). The solution was heated on a steam-bath for 30 min, then cooled, and the product precipitated by addition of water. The product was extracted into ether, and the ether solution was washed with water, sodium carbonate solution, then water to neutrality, dried over sodium sulphate, and evaporated. Two recrystallisations from ether–light petroleum (b.p. 40—60 °C) gave the *tetramethyl derivative* (13) (0.15 g), m.p. 147—151 °C, $[\alpha]_D$ +6.9° (*c*, 1.1), t_R 1.27; $\nu_{max.}$ (CH_2Cl_2) 3 615 (OH) and 1 698 cm^{-1} (20-ketone); δ 0.66 (3 H, s, 13-Me), 0.87 (3 H, d, *J* 7 Hz, 16α-Me), 0.95 (3 H, s, 17-Me), 1.05 (6 H, d, *J* 6 Hz, 2 × 21-Me), 1.10 (3 H, s, 10-Me), 2.88 (2 H, septet, couplings 6 Hz, 21-H, m, 16β-H), 3.25—3.85 (1 H, m, 3α-H), and 5.3 (1 H, d, *J* 5 Hz, 11-H) (Found: C, 80.4; H, 10.9. $C_{25}H_{40}O_2$ requires C, 80.6; H, 10.8%).

16α,17α,21-Trimethyl-5β-pregn-9(11)-ene-3,20-dione (16b).—To a stirred suspension of 16α,17α-dimethyl-5β-pregn-9(11)-ene-3,20-dione (17b) (23.5 g) in methanol (450 ml) was added toluene-*p*-sulphonic acid (140 mg). The steroid soon dissolved and after 1 h the solution was basified with potassium carbonate and water (4 l) was added. The product was filtered off, washed to neutrality, and dried to give 16α,17α-dimethyl-5β-pregn-9(11)-ene-3,20-dione 3,3-dimethyl acetal (15b) (26.0 g). To a stirred solution of this acetal (15b) (26.0 g) in dry tetrahydrofuran (650 ml) under oxygen-free nitrogen, cooled in an ice–salt bath, was slowly

added trityl-lithium solution [7] (265 ml) until the red colour of the reagent just persisted. Dry methyl iodide (130 ml) was then added very rapidly through a wide-necked funnel while the reaction solution was stirred vigorously. The cooling-bath was removed, and, after 1 h, the reaction solution was evaporated to dryness under reduced pressure. The residue was dissolved in acetic acid (260 ml) and water (52 ml), and the solution heated at 90 °C for 30 min. The solution was cooled, and water (2 l) was added to precipitate the product. The gummy solid was dissolved in ether and the solution washed successively with potassium hydrogencarbonate solution, sodium hydrogensulphite solution, and finally water until neutral. The dried solution was evaporated under reduced pressure to give a solid consisting of equal parts of the product (16b) and triphenylmethane. Removal of triphenylmethane was achieved by the addition of hexane (370 ml) and 20 glass balls (5 mm diameter) followed by rotation of the flask for 3 h to grind the product. This procedure gave a white solid which was filtered off, washed with hexane, and dried *in vacuo* to give the *trimethyl derivative* (16b) (20.5 g), m.p. 168—185 °C [97% pure (g.l.c.)]. A sample, recrystallised from acetone–hexane had m.p. 185—189 °C, $[\alpha]_D$ −1.7° (*c*, 1.0), t_R 1.03; $\nu_{max.}$ (CH_2Cl_2) 1 717 (3-ketone) and 1 700 cm^{-1} (20-ketone); δ 0.64 (3 H, s, 13-Me), 0.90 (3 H, d, *J* 7 Hz, 16α-Me), 1.03 (3 H, t, *J* 6 Hz, 21-Me), 1.05 (3 H, s, 17-Me), 1.14 (3 H, s, 10-Me), 3.0br (1 H, m, 16β-H), and 5.59 (1 H, d, *J* 5 Hz, 11-H) (Found: C, 80.95; H, 10.4. $C_{24}H_{36}O_2$ requires C, 80.85; H, 10.2%).

21-*Ethyl*-16α,17α-*dimethyl*-5α-*pregn*-9(11)-*ene*-3,20-*dione* (19a).—A solution of di-isopropylamine (1.23 ml) in dry tetrahydrofuran (8 ml), stirred under nitrogen at 0 °C, was treated dropwise with a solution of ethyl-lithium in ether (1.15M; 6.7 ml). After 15 min, a solution of 16α,17α-dimethyl-5α-pregn-9(11)-ene-3,20-dione 3,3-dimethyl acetal (15a) (2.0 g) in dry tetrahydrofuran (50 ml) was slowly added. The ice-bath was removed for 30 min, then replaced, and dry ethyl iodide (12 ml) was added rapidly with vigorous stirring. The ice-bath was again removed, and after a further 30 min, the reaction mixture was evaporated to dryness under reduced pressure. The residue was purged with tetrahydrofuran, then dissolved in acetic acid (20 ml) and water (4 ml) and the solution allowed to stand at room temperature for 30 min. A little aqueous sodium hydrogensulphite was added, then the product was precipitated by the slow addition of water. The solid was filtered off, washed with water until neutral, dried *in vacuo*, and dissolved in methylene chloride. The solution was run through a short column of alumina grade H, which was eluted with methylene chloride, and the eluant evaporated to dryness under reduced pressure. The residue was crystallised from acetone–hexane to give the *diketone* (19a) (1.56 g) (82%), m.p. 154—160 °C (from acetone–hexane), $[\alpha]_D$ +10.1° (*c*, 1.0), t_R 1.47; $\nu_{max.}$ (CH_2Cl_2) 1 698 (20-ketone) and 1 713 cm^{-1} (3-ketone); δ 0.62 (3 H, s, 13-Me), 0.87 (3 H, d, *J* 7 Hz, 16α-Me), 0.89 (3 H, distorted t, ethyl-Me), 1.00 (3 H, s, 17-Me), 1.13 (3 H, s, 10-Me), 2.97 (1 H, m, 16β-H), and 5.38br (1 H, d, *J* 6 Hz, 11-H) (Found: C, 81.3; H, 10.4. $C_{25}H_{38}O_2$ requires C, 81.0; H, 10.3%).

3β-*Hydroxy*-16α,17α,21,21,21-*pentamethyl*-5α-*pregn*-9(11)-*en*-20-*one* (21).—To a stirred solution of di-isopropylamine (28 ml) in dry tetrahydrofuran (110 ml) under nitrogen at 0 °C was added dropwise a solution of methyl-lithium in ether (1.3M; 136 ml). After 15 min, a solution of 16α,17α,21,21-tetramethyl-3β-tetrahydropyranyloxy-5α-pregn-9(11)-en-20-one (20) (30 g) in dry tetrahydrofuran (280 ml) was slowly added. The ice-bath was removed for 3 h, then the reaction was again cooled to 0 °C and dry methyl iodide (150 ml) was added. After a further 10 min, the ice-bath was again removed, and 1 h later the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in acetone and the solution was poured into ice–water. The mixture was allowed to stand overnight and the solid product was filtered off, washed with water, and dried *in vacuo* to give 16α,17α,21,21,21-pentamethyl-3β-tetrahydropyranyloxy-5α-pregn-9(11)-en-20-one (30 g). The crude product (30 g) was dissolved in acetic acid (500 ml) and water (50 ml) and the solution was heated on a steam-bath for 30 min, left overnight at room temperature, then poured into ice–water. The solid product was filtered off, washed with water, and dried *in vacuo* at 60 °C to give the *pentamethyl derivative* (21) (23.3 g), m.p. 172—174 °C (from methylene chloride–methanol), $[\alpha]_D$ 0° (*c*, 1.0), t_R 1.59; $\nu_{max.}$ (CH_2Cl_2) 3 615 (3-OH) and 1 674 cm^{-1} (20-ketone); δ 0.62 (3 H, s, 13-Me), 0.84 (3 H, d, *J* 7 Hz, 16α-Me), 0.92 (3 H, s, 17-Me), 1.15 (3 H, s, 10-Me), 1.19 (9 H, s, 3 × 21-Me), 2.8—3.85 (2 H, m, 3α-H and 16β-H), and 5.29br (1 H, d, *J* 6 Hz, 11-H) (Found: C, 80.35; H, 11.15. $C_{26}H_{42}O_2$ requires C, 80.8; H, 10.95%).

16α,17α,21-*Trimethylpregna*-4,9(11)-*diene*-3,20-*dione* (23).—A mixture of 16α,17α-dimethylpregna-4,9(11)-diene-3,20-dione (10 g), dry dioxan (100 ml), triethyl orthoformate (10 ml), and toluene-*p*-sulphonic acid (0.5 g) was stirred at room temperature for 1.75 h. Pyridine (2 ml) and potassium carbonate (0.5 g) were added, and the product was precipitated by the slow addition of water. The yellow solid was filtered off, washed with water, and dried *in vacuo* to give 3-ethoxy-16α,17α-dimethylpregna-3,5,9(11)-trien-20-one (22) (10.4 g). To a stirred mixture of di-isopropylamine (8.8 ml) and dry tetrahydrofuran (54 ml), under nitrogen at 0 °C, was slowly added a solution of methyl-lithium in ether (1.36M; 49.7 ml). After 15 min, a solution of the 3-ethyl ether (22) (9.1 g) in dry tetrahydrofuran (180 ml) was slowly added. The reaction was allowed to warm for 30 min, then recooled to 0 °C and dry methyl iodide (55 ml) added rapidly with vigorous stirring. The ice-bath was again removed, and, after a further 30 min, the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in acetic acid (50 ml) and water (5 ml), and the solution was stirred for 30 min, then the product was precipitated by the slow addition of water. The brown solid was filtered off, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated under reduced pressure to a dark gum (8.3 g). This was dissolved in methylene chloride and the solution was passed through a short column of silica and washed through with ether. The eluant was evaporated to dryness and the residue crystallised from methylene chloride–methanol to give the *trimethyl diketone* (23) (4.5 g), the mother-liquors being chromatographed on silica to yield more product (0.93 g), m.p. 149—151 °C (from methylene chloride–methanol), $[\alpha]_D$ +68.5° (*c*, 1.3), t_R 1.35; $\lambda_{max.}$ 239 nm (ε 16 900); $\nu_{max.}$ (CH_2Cl_2) 1 695 (20-ketone), 1 666 (3-ketone), and 1 614 cm^{-1} (4-C=C); δ 0.64 (3 H, s, 13-Me), 0.88 (3 H, d, *J* 7 Hz, 16α-Me), 1.02 (3 H, t, *J* 7 Hz, 21-Me), 1.02 (3 H, s, 17-Me), 1.3 (3 H, s, 10-Me), 2.99br (1 H, m, 16β-H), 5.5 (1 H, d, *J* 6 Hz, 11-H), and 5.72 (1 H, s, 4-H) (Found: C, 81.3; H, 9.6. $C_{24}H_{34}O_2$ requires C, 81.3; H, 9.7%).

11β-*Hydroxy*-16α,17α-*dimethyl*-21-*propylpregna*-1,4-*diene*-3,20-*dione* (25).—A stirred mixture of di-isopropylamine (0.98 ml) and dry tetrahydrofuran (7 ml), under nitrogen at

−10 °C, was slowly treated with a solution of methyl-lithium in ether (1.61M; 3.89 ml), the temperature of the reaction mixture being maintained at −10 to 0 °C. The suspension of lithium di-isopropylamide thus formed was stirred at −10 to 0 °C for 10 min, then cooled to −50 °C. A solution of 11β-acetoxy-16α,17α-dimethylpregna-1,4-diene-3,20-dione (24) (1 g) in dry tetrahydrofuran (25 ml) was then slowly added, the temperature of the reaction mixture being maintained at −50 to −45 °C. The stirred suspension was allowed to warm to 0 °C over *ca.* 15 min, n-propyl iodide (5 ml) was added rapidly, and the reaction mixture was allowed to warm to room temperature. Solution became complete during the following hour, and, 2.25 h after the addition of the n-propyl iodide, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in the minimum of methanol, and the solution was acidified with acetic acid, treated with sodium hydrogensulphite solution to remove a trace of iodine, and water (100 ml) was added. The aqueous liquor was decanted, and the gummy product was dissolved in hot methanol (50 ml). This solution was heated to reflux with stirring under nitrogen, and potassium hydroxide solution (10N; 4 ml) was added. Reflux was continued for 4 h then the reaction mixture was cooled, acidified with acetic acid, and water (300 ml) was added. The solid product was filtered off, washed with water until neutral, and dried *in vacuo* to give a mixture (0.81 g) of the desired product (25) and material not alkylated at C-21. This solid was chromatographed on a column of fine silica (25 g), using gradient elution and a toluene–ethyl acetate system. The appropriate fractions (0.3 g) were crystallised twice from acetone–ether to give the 21-*propyl derivative* (25) (0.16 g), m.p. 222—232 °C, $[\alpha]_D$ +54.1° (*c*, 1.04), t_R 4.73; $\lambda_{max.}$ 244 nm (ε 15 000); $\nu_{max.}$ (CH_2Cl_2) 3 650 (OH), 1 692 (20-ketone), 1 663 (3-ketone), 1 623 (4-C=C), and 1 604 cm^{-1} (1-C=C); δ 0.88 (3 H, d, *J* 7 Hz, 16α-Me), 0.93 (3 H, distorted t, propyl-Me), 0.93 (3 H, s, 13-Me), 0.99 (3 H, s, 17-Me), 1.53 (3 H, s, 10-Me), 2.96br (1 H, m, 16β-H), 4.45 (1 H, m, 11α-H), 5.98 (1 H, s, 4-H), 6.22 (1 H, dd, $J_{2,4}$ 2, $J_{2,1}$ 10 Hz, 2-H), and 7.28 (1 H, d, $J_{1,2}$ 10 Hz, 1-H) (Found: C, 78.4; H, 9.6. $C_{26}H_{38}O_3$ requires C, 78.35; H, 9.6%).

3β-*Hydroxy*-21-*methyl*-5α-*pregna*-9(11),16-*dien*-20-*one* (27).—To a stirred mixture of di-isopropylamine (11.8 ml) and dry tetrahydrofuran (80 ml), under nitrogen at 0 °C, was slowly added a solution of methyl-lithium in ether (1.1M; 68.4 ml). After 15 min, a solution of 3β-tetrahydropyranyl-oxy-5α-pregna-9(11),16-dien-20-one (26) (20 g) in dry tetrahydrofuran (500 ml) was slowly added, and the ice-bath was removed. After a further 30 min, dry methyl iodide (100 ml) was slowly added, stirring was continued for a further 30 min, and the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in acetic acid (200 ml) and water (80 ml), and the solution was allowed to stand overnight at room temperature, partial crystallisation of the product occurring during this time. A little sodium hydrogensulphite solution was added then the product was fully precipitated by the slow addition of water (1 l). The solid was filtered off, washed with 5% sodium carbonate solution, then with water until neutral, and dried *in vacuo*. This yellow product (17.2 g) was dissolved in methylene chloride (*ca.* 250 ml) and the solution was run through a column of silica (100 g) on top of alumina grade H (40 g) and washed through with methylene chloride (500 ml) followed by ether (500 ml). The eluant was evaporated to give a white solid (14.8 g), which was a mixture of 3β-hydroxy-21-methyl-5α-pregna-9(11),16-dien-20-one (27) [(92%) g.l.c.] and 3β-hydroxy-5α-pregna-9(11),16-dien-20-one [8% (g.l.c.)]. To convert the impurity into its 21-benzylidene derivative (which is more easily removed by crystallisation), the crude product (12.7 g) was dissolved in t-butyl alcohol (254 ml) at 40 °C and treated with benzaldehyde (0.63 ml) and potassium t-butoxide (0.25 g). The stirred solution was allowed to cool to room temperature over 1 h then poured into stirred water (1 l) containing acetic acid (1 ml). The solid product was filtered off, washed with water, 5% sodium carbonate solution, and then water until neutral, and dried *in vacuo*. The product (13.5 g) was crystallised twice from aqueous acetone to give the 21-*methyl derivative* (27) (10 g), m.p. 76 and 137—147 °C (from aqueous acetone), $[\alpha]_D$ +120.2° (*c*, 0.96), t_R 0.73; $\lambda_{max.}$ 239 nm (ε 7 500); $\nu_{max.}$ (CH_2Cl_2) 3 615 (OH), 1 667 (20-ketone), and 1 591 cm^{-1} (16-C=C); δ 0.78 (3 H, s, 13-Me), 0.93 (3 H, s, 10-Me), 1.05 (3 H, t, *J* 7 Hz, 21-Me), 3.5 (1 H, m, 3α-H), 5.28 (1 H, d, *J* 5 Hz, 11-H), and 6.63 (1 H, m, 16-H) (Found: C, 80.7; H, 10.05. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%).

Alkylation of 11β-*Acetoxy*-16α,17α-*dimethyl*-5α-*pregnane*-3,20-*dione* 3,3-*Dimethyl Acetal* (29a).—A solution of methyl-lithium in ether (180.5 ml; 1.36M; 2.2 mol equiv.) which had been cooled to 0 °C, was added to a stirred solution of di-isopropylamine (35.2 ml, 2.25 mol equiv.) in dry tetrahydrofuran (100 ml) at −10 °C under nitrogen. The rate of addition was controlled so that the temperature did not exceed 0 °C. The resulting solution of lithium di-isopropylamide was stirred at −5 °C for 10 min, then cooled to −50 °C. A solution of the dimethyl acetal (29a) (50 g) in dry tetrahydrofuran (900 ml) was added while maintaining the temperature in the range −50 to −45 °C. The cooling-bath was removed and the reaction mixture allowed to warm until a clear solution had formed. (This occurred at −15 °C, 20 min after the cooling-bath had been removed.) As soon as solution was complete, methyl iodide (125 ml) was added rapidly, which caused the temperature to rise quickly to between 8 and 12 °C. Stirring was continued at ambient temperature for 30 min, then the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of acetic acid (400 ml) and water (100 ml), and the solution was kept at 25 °C for 30 min. Sodium hydrogensulphite (0.6 g) in water (2 ml) was then added, and the reaction mixture was poured into ice–water (2.5 l) to give an emulsion which was coagulated to a gummy solid by addition of 2.5M-sulphuric acid (250 ml). The product was filtered off, washed with water, and dissolved in ether (500 ml). The ether solution was washed with sodium carbonate solution, then to neutrality with water, dried, and evaporated to dryness. This gave a mixture (48 g) of 11β-propionyloxy-16α,17α,21-trimethyl-5α-pregnane-3,20-dione (32a) (85%) [t_R 2.59 (M^+, 430.3092. $C_{27}H_{42}O_4$ requires *M*, 430.3083)] and the corresponding iso-butyrate (34a) (15%) [t_R 2.87 (M^+ 444.3250. $C_{28}H_{44}O_4$ requires *M*, 444.3239)].

A sample of the product (100 mg) in tetrahydrofuran (1 ml) was added to a suspension of lithium aluminium hydride (50 mg) in dry ether (5 ml). The resulting mixture was refluxed for 1 h, then cooled and the excess of hydride destroyed by dropwise addition of ethyl acetate. Saturated ammonium chloride solution (5 ml) was added, the mixture was shaken, and then the organic phase was separated off and evaporated to dryness. The residue (36a) was dissolved in acetone (1 ml) and treated with a few drops of Jones'

Reagent. Dilution with water gave a precipitate of 16α,17α,21-trimethyl-5α-pregnane-3,11,20-trione (38a) (t_R 1.5), identical with an authentic sample. [The trione (38a) contained a small amount (<2%) of the 16α,17α-dimethyl derivative (37a) (t_R 1.2).]

Alkylation of 11β-*Acetoxy*-16α,17α-*dimethyl*-5β-*pregnane*-3,20-*dione* 3,3-*Dimethyl Acetal* (29b).—By a route identical to that described above for the 5α-compound (29a), the acetal (29b) (500 g) gave a mixture (470 g) of the propionate (32b) (84%) and the isobutyrate (34b) (16%).

11β-*Acetoxy*-16α,17α,21-*trimethyl*-5α-*pregnane*-3,20-*dione* (30a).—11β-Acetoxy-16α,17α-dimethyl-5α-pregnane-3,20-dione (28a) (10 g) was suspended in dry methanol (50 ml) and toluene-*p*-sulphonic acid (0.2 g) was added. Within 20 s a clear solution had formed, and after 1 min the acetal had crystallised out. After 15 min, solid potassium carbonate (0.8 g) was added, and the mixture was stirred for a further 15 min before being poured into water (500 ml). The product was filtered off, washed with water, and dried *in vacuo* at 80 °C to give the crude acetal (29a) (11 g) containing a trace of starting material (28a).

A solution of the acetal (29a) (11 g) in dry tetrahydrofuran (220 ml) was stirred under oxygen-free nitrogen and cooled in an ice-bath. Trityl-lithium was added over 5 min, until a permanent pink colouration was obtained. Dry methyl iodide (50 ml) was then added rapidly. After 10 min, the reaction mixture was evaporated to dryness, and the residue was dissolved in acetic acid (50 ml) and water (5 ml). The solution was allowed to stand at room temperature for 30 min then the product was precipitated by the addition of water (500 ml). The resulting gummy solid was filtered off and dissolved in ether. This organic solution was washed with sodium hydrogensulphite solution, sodium hydrogencarbonate solution, and then with water until neutral. The solution was then dried and evaporated to dryness. The gummy residue was dissolved in hexane and the required product (30a) (7.2 g) crystallised out. A further crop (1.7 g) was obtained by chromatography of the mother liquors on silica. The combined crops were recrystallised from acetone–ether–hexane to give the *acetate* (30a) (6.9 g), m.p. 158—163 °C, $[\alpha]_D$ +50.1° (*c*, 1.0), t_R 2.5; $\nu_{max.}$ (CH_2Cl_2) 1 728(OAc), 1 712 (3-ketone), and 1 698 cm^{-1} (20-ketone); δ 0.83 (3 H, s, 13-Me), 0.89 (3 H, d, *J* 6 Hz, 16α-Me), 1.00 (3 H, s, 17-Me), 1.00 (3 H, t, *J* 7 Hz, 21-Me), 1.10 (3 H, s, 10-Me), 2.02 (3 H, s, COMe), 3.00br (1 H, m, 16β-H), and 5.43 (1 H, d, *J* 5 Hz, 11β-H) (Found: C, 75.2; H. 9.8. $C_{26}H_{40}O_4$ requires C, 75.0; H, 9.7%).

11β-*Acetoxy*-16α,17α,21-*trimethylpregna*-1,4-*diene*-3,20-*dione* (41).—A solution of 11β-acetoxy-16α,17α,21-trimethyl-5α-pregnane-3,20-dione (30a) (6.5 g) in toluene (85 ml) containing acetic acid (8.5 ml) was treated with 2,5-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (8.5 g, 2.4 mol equiv.). The stirred reaction mixture was heated under reflux for 18 h, then cooled and filtered to remove the hydroquinone (DDHQ). Sodium carbonate solution (20%, 40 ml) was carefully added to the stirred filtrate. The organic layer was separated and washed with water (2 × 35 ml) the washes being back-extracted with ether (2 × 20 ml). The combined organic phases were dried, then passed through a short column of acid-washed alumina (25 g), and eluted with more ether. The combined eluates were evaporated to dryness to give the crude diene (41) as a gum. Crystallisation from acetone–ether–hexane gave the product (41) (3.5 g), m.p. 200—205 °C, $\lambda_{max.}$ 242 nm (ε 14 870). However, the presence of a plateau between 280 and 310 nm in the u.v. spectrum was attributed to the 1,4,6-triene (42) and this could not be removed by further crystallisation.

The crude dehydrogenation product (41) (3.5 g) was dissolved in ethanol (10 ml) and the stirred solution was heated to boiling and a solution of sodium metabisulphite (3.5 g) in water (5 ml) was added. The resulting solution was refluxed for 2 h and then distilled, maintaining the volume by the addition of water, until the temperature of the vapour reached 99 °C. The mixture was then cooled to 20 °C with vigorous stirring and the resulting solid filtered off and washed with water. The damp solid was dissolved in ether, and the solution was dried and passed through a short column of acid-washed alumina (15 g), and eluted with more ether. The eluate was evaporated to dryness to give the *diene* (41) (3.0 g), m.p. 203—205 °C (from ether–n-hexane), $[\alpha]_D$ +99.6° (*c*, 1.0), t_R 3.08; $\lambda_{max.}$ 242 nm (ε 14 530); $\nu_{max.}$ (CH_2Cl_2) 1 732(11-OAc), 1 698 (20-ketone), 1 666 (3-ketone), 1 628 (4-C=C), and 1 608 cm^{-1} (1-C=C); δ 0.86 (3 H, s, 13-Me), 0.89 (3 H, d, *J* 6 Hz, 16α-Me), 0.95 (3 H, s, 17-Me), 1.00 (3 H, t, *J* 7 Hz, 21-Me), 1.27 (3 H, s, 10-Me), 2.06 (3 H, s, COMe), 3.04br (1 H, m, 16β-H), 5.49 (1 H, d, *J* 5 Hz, 11α-H), 6.00 (1 H, s, 4-H), 6.22 (1 H, dd, $J_{2,1}$ 10, $J_{2,4}$ 2 Hz, 2-H), and 6.92 (1 H, d, $J_{1,2}$ 10 Hz, 1-H) (Found: C, 75.5; H, 8.9. $C_{26}H_{36}O_4$ requires C, 75.7; H, 8.8%).

Dibromination–Dehydrobromination of 11β-*Acetoxy*-16α,17α,21-*trimethyl*-5α-*pregnane*-3,20-*dione* (30a).—The saturated ketone (30a) (1 g) in acetic acid (20 ml) was treated at room temperature over 20 min with a solution of bromine (0.25 ml; 2 mol equiv.) in acetic acid (5 ml). The reaction was warmed to 55 °C over 15 min, then cooled and poured into an excess of 5% sodium acetate solution (100 ml). The bromo-compound (43), filtered off and dried *in vacuo* at 40 °C, showed δ 1.66 (d, *J* 6 Hz, $CHBrCH_3$), 4.65 (d, $J_{4\beta,5\alpha}$ 12 Hz, 4β-H), and 4.81 (dd, $J_{1\alpha,2\beta}$ 13, $J_{1\beta,2\beta}$ 6 Hz, 2β-H). The crude product (43) (1.4 g) was added rapidly to a boiling mixture of calcium carbonate (1.4 g), lithium bromide (0.7 g), and dimethylformamide (14 ml) under nitrogen. After 10 min at reflux temperature the mixture was cooled and poured into water (200 ml) containing 1% acetic acid. The product was filtered off and washed well with water. The solid was dissolved in ether and the solution was washed with sodium hydrogencarbonate solution then water, dried, and evaporated to dryness (0.87 g). G.l.c. showed peaks at t_R 2.50 (1-en-3-one) (45) (20%), 3.00 (1,4-dien-3-one) (41) (60%), and 3.33 (21-bromo) (46) (20%). The mixture gave a positive result in the Beilstein test. Reaction of this crude mixture (0.87 g) with toluene (9.5 ml), acetic acid (0.5 ml), and DDQ (0.1 g) as described above for (30a) substantially converted the 1-en-3-one (45) into the 1,4-dien-3-one (41), but there was no change in the amount of 21-bromo-derivative (46) (g.l.c.). A sample (100 mg) of this mixture was dissolved in glacial acetic acid (2 ml) and stirred at 25 °C for 16 h in the presence of zinc dust (100 mg). The product, isolated by removal of the zinc followed by addition of water and filtration, showed $\lambda_{max.}$ 323, 335, and 351 nm.

Monobromination–Dehydrobromination–Dehydrogenation of 11β-*Acetoxy*-16α,17α,21-*trimethyl*-5α-*pregnane*-3,20-*dione* (30a).—The saturated 3-ketone (30a) (34.5 g) was dissolved in acetic acid (350 ml) at room temperature, and a 10% solution of bromine in acetic acid (42 ml) added over 5 min to the stirred solution. After a further 5 min the reaction mixture was poured into 5% sodium acetate solution (1.5 l) and the resulting solid was filtered off, washed well with water, and dried *in vacuo* at 60 °C. The total crude product (47) (41 g) was dehydrobrominated with calcium

carbonate (40 g) and lithium bromide (20 g) in boiling dimethylformamide (400 ml) as described above. The resulting crude 1-en-3-one (45) (34 g) was dehydrogenated as described above with a mixture of boiling toluene (300 ml), acetic acid (34 ml), and DDQ (22.3 g). One recrystallisation of the crude product from ether–n-hexane gave the 1,4-dien-3-one (41) (16.9 g).

Dibromination–Dehydrobromination of 11β-*Propionyloxy*-16α,17α,21-*trimethyl*-5β-*pregnane*-3.20-*dione* (32b).—The saturated ketone (32b) (5 g) [containing *ca.* 16% of the isobutyrate (34b)] was dissolved in chloroform (125 ml), and a solution of hydrogen bromide in acetic acid (6.25 ml; 4M) added. The stirred reaction was cooled to 0 °C and a solution of 5% bromine in chloroform (2.2 mol equiv.) was added dropwise over 30 min. After a further 20 min the product was isolated by pouring the reaction mixture into an excess of 5% sodium acetate, separating the organic layer, and evaporating the washed and dried extract to dryness (7.8 g).

A solution of the crude product (7.8 g) in dimethylacetamide (20 ml) was added to a stirred, boiling mixture of dimethylacetamide (150 ml), calcium carbonate (5 g), and lithium bromide (2.5 g) under nitrogen. After 10 min at reflux temperature the product was isolated as described above to give (61) (4.87 g), containing *ca.* 16% of (65) (g.l.c.). Crystallisation from ether–n-hexane gave a crop (1.2 g) which was hydrolysed at room temperature with 50% potassium hydroxide (5 ml) in methanol (24 ml) for 38 h. The resulting precipitate was filtered off and washed with cold methanol to give crude (48) (0.66 g). Neutralisation of the mother-liquors with acetic acid and the addition of water gave a further crop (0.34 g). Chromatography of the first crop (0.66 g) on silica with methylene chloride containing increasing proportions of ethyl acetate gave three compounds in addition to the required 1,4-diene-3,20-dione (48) (R_F 0.42). In increasing order of polarity, these were (a) the 4-bromo-compound (52) (60 mg), R_F 0.75, $\lambda_{max.}$ 256 nm [Found: M^+, 450.1580, 448.1592. $C_{24}H_{33}O_3Br$ requires M 450.1594, 448.1613. Ion at *m/e* 249 corresponds with (49)]; (b) the 21-bromo-compound (53) (90 mg), R_F 0.5, δ 1.69 (d, *J* 6 Hz, $CHBrCH_3$) [Found: M^+ 450.1606, 448.1607. $C_{24}H_{33}O_3Br$ requires M, 450.1594, 448.1613. Ions at *m/e* 329 and 327 correspond with (50)]; and (c) the methoxy-derivative (54) R_F 0.12. [Found: M^+, 400.2611. $C_{25}H_{36}O_4$ requires M, 400.2613. Ion at *m/e* 279 corresponds with (51)].

Enol Acetylation of 11β-*Propionyloxy*-16α,17α,21-*trimethyl*-5β-*pregnane*-3,20-*dione* (32b).—A solution of the propionate (32b) (1 kg) [containing *ca.* 16% of the corresponding 11-isobutyrate (34b)] in freshly distilled isopropenyl acetate (5 l) containing toluene-*p*-sulphonic acid (20 g) was heated to boiling and slowly distilled so that the temperature of the vapour remained above 92 °C. The reaction required between 7 and 10 h to go to completion (t.l.c.; 2 : 1 v/v toluene–ethyl acetate on silica). The cooled reaction mixture was concentrated under reduced pressure and the oily residue was dissolved in ethyl acetate (4 l). This solution was washed with water (2 × 1 l), then saturated sodium chloride solution (1 l), and each wash was back extracted sequentially with ethyl acetate (2 × 500 ml). The combined extracts were dried, and evaporated under reduced pressure. The residue was purged twice with ethyl acetate to remove the last traces of isopropenyl acetate, giving an equal mixture of the 2- and 3-enol acetates (55b) and (56b) (1.15 kg), δ 2.11 (s, $COCH_3$), 5.18 (d, *J* 12 Hz, 4-H), and 5.32br (dd, *J* 6 Hz, 2-H). The product, which contained *ca.* 16% of the corresponding 11-isobutyrate, decomposes on standing and was carried to the next stage as quickly as possible.

Reaction of the Enol Acetates (55b) *and* (56b) *with Hypobromous Acid.*—Sulphuric acid (10 l; 0.5M) was added rapidly to a stirred solution of *N*-bromosuccinimide (0.6 kg) in tetrahydrofuran (10 l) and this mixture was added as quickly as possible to a stirred solution of the mixed enol acetates (55b) and (56b) (1.15 kg) in tetrahydrofuran (10 l). The stirring was stopped and the reaction was kept for 2 h in the absence of light at 25 °C. A saturated solution of sodium sulphite (*ca.* 300 ml) was added with stirring until the solution had decolourised. The mixture was then poured into water (100 l) and the mixture stirred for 2 h giving the product as an oil on the surface of the water. The water was syphoned off and the gum was dissolved in ether (10 l). The solution was washed with water (3 × 1 l) and dried, and the solvent was removed under reduced pressure to give a mixture of the 2- and 4-bromo-compounds (57b) and (58b). Attempted chromatographic purification on silica of the product from a small scale reaction gave impure samples of the 2β-bromo-compound (57b), δ 4.69 (dd, *J* 14 and 6 Hz, axial 2α-H), and the 4β-bromo-compound (58b) δ 4.93 (d, *J* 12 Hz, axial 4α-H).

Dehydrobromination of Mixed Bromo-compounds (57b) *and* (58b).—The crude mixture of 2- and 4-bromo-compounds (57b) and (58b) was dissolved in dimethylformamide (2 l) and the resulting solution was immediately added rapidly (*ca.* 3 min) to a boiling suspension of lithium bromide (250 g) and calcium carbonate (500 g) in dimethylformamide (8 l) under nitrogen. Reflux was continued for 15 min and the cooled (30 °C) reaction mixture was poured into water (100 l) mixed with acetic acid (1 l). The resulting suspension was stirred overnight and the solid was filtered off, washed neutral with water, and dried *in vacuo* at 50 °C to give a mixture (850 g) of the 1-en-3-one (59b) and the 4-en-3-one (60).

A similar product from a small-scale reaction (26 g) was dissolved in ethanol (620 ml) and treated with sodium metabisulphite (31 g) in water (300 ml) under reflux for 4 h. The mixture was cooled, poured into water (3 l), and the precipitated product was extracted into ether (5 × 250 ml), each extract being washed with water (2 × 50 ml). The combined aqueous solution was acidified with 2.5M-sulphuric acid and boiled for 2 h. After cooling of the reaction mixture, the product was filtered off, dried *in vacuo*, and recrystallised from ether–n-hexane to give 11β-propionyloxy-16α,17α,21-trimethyl-5β-pregn-1-ene-3,20-dione (59b) (7.38 g), m.p. 104—107 °C, t_R 2.81. However, this compound was contaminated with the corresponding 11-isobutyrate and could not be purified further by crystallisation. A sample (1.2 g) was hydrolysed in boiling methanol (20 ml) containing 10M-potassium hydroxide solution (5 ml) for 2 h. The reaction was cooled, neutralised with acetic acid, and the product was precipitated by addition of water (100 ml), filtered, and dried. The crude product was chromatographed on silica and recrystallised from methylene chloride–methanol to give 11β-*hydroxy*-16α,17α,21-*trimethyl*-5β-*pregn*-1-*ene*-3,20-*dione* (66b) (530 mg), m.p. 252—265 °C, $[\alpha]_D$ +126° (*c*, 1.0), t_R 2.09; $\lambda_{max.}$ 229 nm (ε 8 700); $\nu_{max.}$ ($CHCl_3$) 3 610 (OH), 1 695 (20-ketone), 1 683 (3-ketone), and 1 610 cm^{-1} (1-C=C); δ 0.87 (3 H, d, *J* 6 Hz, 16α-Me), 0.92 and 0.94 (6 H, 2 s, 13-Me and 17-Me), 0.99 (3 H, t, *J* 7 Hz, 21-Me), 1.42 (3 H, s, 10-Me), 4.19

(1 H, t, *J* 3 Hz, 11α-H), 5.88 (1 H, d, *J* 10 Hz, 2-H), and 7.02 (1 H, d, *J* 10 Hz, 1-H) (Found: C, 77.2; H, 10.0. $C_{24}H_{36}O_3$ requires C, 77.4; H, 9.7%).

The ether extract from the hydrogensulphite reaction above was evaporated to lower bulk and passed through a short column of alumina to decolourise it. The combined ether eluates were evaporated to dryness and the residue recrystallised from ether–n-hexane to give 11β-*propionyloxy*-16α,17α,21-*trimethylpregn*-4-*ene*-3,20-*dione* (60) (4.8 g), m.p. 121—124 °C, $[\alpha]_D$ +134° (*c*, 1.0), t_R 3.53; $\lambda_{max.}$ 239 nm (ε 16 120); $\nu_{max.}$ (CH_2Cl_2) 1 730 (11-ester), 1 699 (20-ketone), 1 670 (3-ketone), and 1 622 cm^{-1} (4-C=C); δ 0.86 (3 H, s, 13-Me), 0.92 (3 H, d, *J* 6 Hz, 16α-Me), 1.01 (3 H, s, 17-Me), 1.15 (3 H, t, *J* 7 Hz, 21-Me), 1.28 (3 H, s, 10-Me), 2.80—3.35 (1 H, m, 16β-H), 5.5 (1 H, d, *J* 3 Hz, 11α-H), and 5.68 (1 H, s, 4-H) (Found: C, 75.3; H, 9.3. $C_{27}H_{40}O_4$ requires C, 75.7; H, 9.4%).

A sample hydrolysed for 4 h in refluxing methanolic potassium hydroxide as described above for (59b) gave 11β-*hydroxy*-16α,17α,21-*trimethylpregn*-4-*ene*-3,20-*dione* (67) m.p. 200—202 °C (from ether), $[\alpha]_D$ +111° (*c*, 1.0), t_R 2.75; $\lambda_{max.}$ 243 nm (ε 15 300); $\nu_{max.}$ 3 420 (OH), 1 699 (20-ketone), 1 660 (3-ketone), and 1 619 cm^{-1} (4-C=C); δ 0.89 (3 H, d, *J* 6 Hz, 16α-Me), 0.95 (6 H, s, 13-Me and 17-Me), 1.00 (3 H, t, *J* 7 Hz, 21-Me), 1.41 (3 H, s, 10-Me), 2.65—3.30 (1 H, m, 16β-H), 3.39 (1 H, t, *J* 3 Hz, 11α-H), and 5.62 (1 H, s, 4-H) (Found: C, 77.15; H, 10.0. $C_{24}H_{36}O_3$ requires C, 77.4; H, 9.7%).

11β-*Propionyloxy*-16α,17α,21-*trimethylpregna*-1,4-*diene*-3,20-*dione* (61).—The mixture (1 kg) of the 1-en-3-one (59b) and the 4-en-3-one (60) was suspended in toluene (9 l) and acetic acid (1 l) containing DDQ (607 g) and the mixture was refluxed with stirring for 2.5 h. The cooled reaction mixture was filtered and the stirred filtrate was treated with 20% sodium carbonate solution (6 l). The organic layer was separated and washed with water (2 × 5 l), the washes were back-extracted with toluene (2 × 3 l), and the combined organic solutions were evaporated under reduced pressure to a final volume of 8 l. Ether (8 l) was added and the solution was run through a column of alumina (2 kg), and elution continued with ether–methylene chloride (1 : 1 v/v). The combined eluates were evaporated under reduced pressure to give the crude 1,4-diene (61) (0.91 kg). This product was shown (u.v.) also to contain the corresponding 1,4,6-triene, which was removed by treatment with sodium metabisulphite (0.18 kg) in ethanol (4.5 l) for 2 h under reflux. The solvent was distilled until 1.2 l of distillate had been collected and the cooled reaction mixture was poured into 1% sodium chloride solution (22.5 l). The product (0.79 kg) was isolated by extraction into ether containing 10% methylene chloride. A sample recrystallised from ether–n-hexane gave 11β-*propionyloxy*-16α,17α,21-*trimethylpregna*-1,4-*diene*-3,20-*dione* (61), m.p. 152—154 °C, $[\alpha]_D$ +86° (*c* 1.1), t_R 3.80; $\lambda_{max.}$ 242 nm (ε 14 150); $\nu_{max.}$ (CH_2Cl_2) 1 732 (11-ester), 1 700 (20-ketone), 1 666 (3-ketone), 1 630 (4-C=C), and 1 608 cm^{-1} (1-C=C); δ 0.87 (3 H, s, 13-Me), 0.89 (3 H, d, *J* 6 Hz, 16α-Me), 0.96 (3 H, s, 17-Me), 1.01 (3 H, t, *J* 7 Hz, 21-Me), 1.18 (3 H, t, *J* 8 Hz, ester Me), 1.27 (3 H, s, 10-Me), 2.70—3.40 (1 H, m, 16β-H), 5.56 (1 H, d, *J* 3 Hz, 11α-H), 6.03 (1 H, s, 4-H), 6.26 (1 H, dd, $J_{2,1}$ 10, $J_{2,4}$ 2 Hz, 2-H), and 6.94 (1 H, d, $J_{1,2}$ 10 Hz, 1-H) (Found: C, 76.25; H, 8.8. $C_{27}H_{38}O_4$ requires C, 76.0; H, 9.0%).

11β-*Hydroxy*-16α,17α,21-*trimethylpregna*-1,4-*diene*-3,20-*dione* (48).—The crude 11β-propionyloxy-16α,17α,21-trimethylpregna-1,4-diene-3,20-dione (61) (0.79 kg) was dissolved in methanol (20 l) under nitrogen and hydrolysed by refluxing with a 50% potassium hydroxide solution in water (2.5 l) for 2 h. The product isolated as described above was recrystallised from methylene chloride–methanol to give the 1,4-*diene* (48) (0.518 kg), m.p. 230—273 °C (decomp.), $[\alpha]_D$ +100° (*c*, 0.92 in pyridine), t_R 3.10; $\lambda_{max.}$ 244 nm (ε 14 600); $\nu_{max.}$ 3 380 (11-OH), 1 697 (20-ketone), 1 650 (3-ketone), 1 610 (4-C=C), and 1 594 cm^{-1} (1-C=C); δ [$CDCl_3$–CD_3OD (4 : 1 v/v)] 0.89 (3 H, d, *J* 6 Hz, 16α-Me), 0.94 (3 H, s, 13-Me), 0.99 (3 H, s, 17-Me), 1.00 (3 H, t, *J* 7 Hz, 21-Me), 1.46 (3 H, s, 10-Me), 2.72—3.45 (1 H, m, 16β-H), 3.39 (1 H, d, *J* 3 Hz, 11α-H), 6.01 (1 H, s, 4-H), 6.24 (1 H, dd, $J_{2,1}$ 10, $J_{2,4}$ 2 Hz, 2-H), and 7.37 (1 H, d, $J_{1,2}$ 10 Hz, 1-H) (Found: C, 77.9; H, 9.35. $C_{24}H_{34}O_3$ requires C, 77.8; H, 9.25%).

Conversion of 11β-*Propionyloxy*-16α,17α,21-*trimethyl*-5α-*pregnane*-3,20-*dione* (32a) *to* 11β-*Hydroxy*-16α,17α,21-*trimethylpregna*-1,4-*diene*-3,20-*dione* (48).—The saturated 3-ketone (32a) containing *ca.* 16% of the isobutyrate (34a) (1 kg) was treated as described above with isopropenyl acetate (5 l) and toluene-*p*-sulphonic acid (20 g) to give a 4 : 1 mixture of the enol acetates (55a) and (56a) (also containing the corresponding 11-isobutyrate). The mixed enol acetates (55a) and (56a) (1.15 kg) reacted with hypobromous acid as described above to give a 4 : 1 mixture (1.2 kg) of the 2-bromo-compound (57a) and 4-bromo-compound (58a). Dehydrobromination of this mixture (1.2 kg) in dimethylformamide (2.4 l) with lithium bromide (300 g), calcium carbonate (600 g), and dimethylformamide (9.6 l) gave a 4 : 1 mixture (1 kg) of the 1-en-3-one (59a) and 4-en-3-one (60). The mixture (1 kg) of the 1-en-3-one (59a) and the 4-en-3-one (60) was dehydrogenated in toluene (9 l) and acetic acid (1 l) containing DDQ (0.63 kg, 1.2 mol equiv.) as described above to give the 1,4-diene (61) (0.9 kg) contaminated with the isobutyrate (65). Treatment of this crude diene (61) (0.9 kg) with aqueous sodium hydrogensulphite removed any remaining 1-en-3-one (59a) and any 1,4,6-trien-3-one (62) to give the 1,4-diene (61) (0.75 kg) which was hydrolysed in methanol (15 l) containing a 50% solution of potassium hydroxide in water (3 l). The product after one crystallisation from methylene chloride–methanol was 11β-hydroxy-16α,17α,21-trimethylpregna-1,4-diene-3,20-dione (48) (0.5 kg).

11β-*Hydroxy*-16α,17α,21-*trimethyl*-5α-*pregn*-1-*ene*-3,20-*dione* (66a).—A sample of the mixture (12 g) of 1-en-3-one (59a) and 4-en-3-one (60) was hydrolysed with methanol (240 ml) containing 50% aqueous potassium hydroxide (48 ml) as described above. The crude product was chromatographed on silica and eluted with toluene–ethyl acetate to give after recrystallisation from aqueous methanol 11β-*hydroxy*-16α,17α,21-*trimethyl*-5α-*pregn*-1-*ene*-3,20-*dione* (66a) (3 g), m.p. 195—200 °C, $[\alpha]_D$ +28° (*c*, 1.0); $\lambda_{max.}$ 230 nm (ε 10 800); $\nu_{max.}$ (CH_2Cl_2) 3 600 (OH), 1 695 (20-ketone), 1 678 (3-ketone), and 1 602 cm^{-1} (1-C=C); δ 0.91 (3 H, d, *J* 6 Hz, 16α-Me), 0.96 (6 H, s, 13-Me and 17-Me), 1.02 (3 H, t, *J* 7 Hz, 21-Me), 1.25 (3 H, s, 10-Me), 2.6—3.4 (1 H, m, 16β-H), 4.58 (1 H, m, 11α-H), 5.87 (1 H, d, *J* 10 Hz, 2-H), and 7.25 (1 H, d, *J* 10 Hz, 1-H) (Found: C, 77.2; H, 9.7. $C_{24}H_{36}O_3$ requires C, 77.4; H, 9.7%).

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