Alkylated Steroids. Part 2.[1] 16α,17α-Dimethylpregnanes functionalised in Ring c

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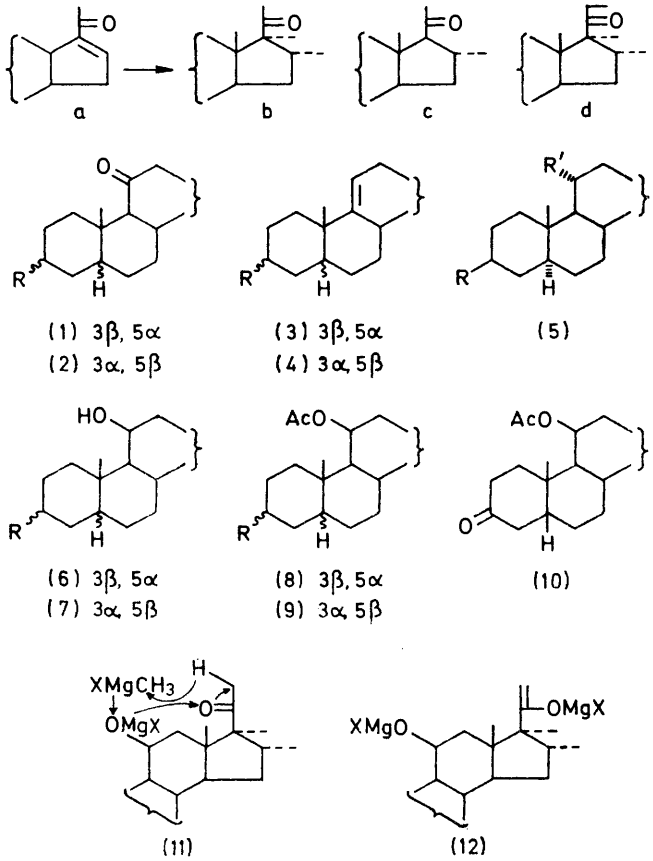
An improved process for the preparation of 16α,17α-dimethylpregnanes (1b)—(9b) from pregn-16-en-20-ones has been developed and applied to ring c functionalised steroids (1a)—(9a) as a route to corticosteroid analogues. Good to excellent yields of the 16α,17α-dimethyl derivatives were achieved in all cases except with 11β-hydroxy-compounds and this was overcome by using the acetate. Two by-products, formed in variable amounts, were the 16α-methyl and 16α,17α,21-trimethyl derivatives (c) and (d) respectively.

In Part 1[1] we recorded our interest in the biological activity of steroids with alkyl substituents at the adjacent positions C-16 and C-17 and described in detail the scope and limitations of a composite reaction for the preparation of 16α,17α-dimethylpregnanes from 16-en-20-oxo-steroids. The by-products of the reaction were identified and characterised. In principle the reaction is conducted in two stages, the first of which involves treatment with methylmagnesium halide to give a 16α-methyl-17(20)-enolate salt which is then converted, with excess methyl iodide, into the 16α,17α-dimethyl derivative. Since the earlier work had shown that one of the main by-products is formed by further alkylation of the 16α,17α-dimethyl-20-oxo-product in the presence of an excess of methyl Grignard reagent and methyl iodide, a reverse addition technique has been developed to limit the impurities formed in this way. Though largely successful, varying amounts (3—30%) of the corresponding 16α,17α,21-trimethyl derivatives are still formed, and these can be detected either by t.l.c. as less-polar spots running very close to the major product, or by their longer retention times on g.l.c. (See Tables 1 and 3.)

Our reason for developing this reaction was the preparation of 16α,17α-dimethyl analogues of corticosteroids and the purpose of the present work was to find suitable routes for the preparation of 11-oxo-16α,17α-

[1] Part 1, J. Cairns, C. L. Hewett, R. T. Logan, G. McGarry, D. F. M. Stevenson, and G. F. Woods, *J.C.S. Perkin I*, 1976, 1558.

dimethyl derivatives of progesterone and 1,2-dehydroprogesterone, with the possibility of additional substituents at positions 9 and 21. We already had evidence that, because of a dissociation of systemic from local anti-inflammatory effects, in favour of the latter, such compounds were of interest for topical use on skin. We decided to limit our investigations to commercially available starting materials, by first investigating 3β-acetoxy-5α-pregn-16-ene-11,20-dione (1a; R = OAc),[2] an intermediate in the hecogenin route to corticosteroids, and 3α-acetoxy-5β-pregn-16-ene-11,20-dione (2a; R = OAc),[3] an intermediate in the bile acid route to



corticosteroids. Using the reverse addition modification of the general reaction, the 16-ene-11,20-diones (1a; R = OAc) and (2a; R = OAc) were converted into the corresponding 16α,17α-dimethyl derivatives (1b; R = OAc) and (2b; R = OAc) in high yield (70—80%). There was no evidence of attack on the 11-carbonyl group but the expected 16α-monomethyl derivatives (1c; R = OAc) and (2c; R = OAc), and 16α,17α,21-trimethyl derivatives (1d; R = OAc) and (2d; R = OAc) were formed. After removal of the 16α-monomethyl product as the Girard P derivative, the required product was isolated in only *ca.* 50% yield in each case because of the difficulty in removing the respective 16α,17α,21-trimethyl impurity.

Having prepared the 16α,17α-dimethyl-11,20-diones (1b; R = OAc) and (2b; R = OAc), no simple means of converting them into the 11β-hydroxy derivatives (6b; R = OH or OAc) and (7b; R = OH or OAc) could be found because both the 11- and 20-carbonyl groups in (1b; R = OH or OAc) and (2b; R = OH or OAc) were equally reactive and no selectivity could be demonstrated either for reduction or protection. Thus further elaboration of these products for our purpose was impossible.

Since the 5α- and 5β-9(11),16-dien-20-ones (3a; R = OAc) and (4a; R = OAc) were also readily available, and the conversion of (3a; R = OAc) into the 16α,17α-dimethyl derivative (3b; R = OH) in 20% yield had been described,[4c,d] we next investigated these compounds. The general procedure gave a conversion of 80—85% into the corresponding 16α,17α-dimethyl product (3b; R = OAc) and (4b; R = OAc). In the 5α series the product was readily purified to give 74% of the dimethyl compound (3b; R = OAc), but in the 5β-series 2—3% of the 16α,17α,21-trimethyl derivative (4d; R = OAc) persisted and could not be removed by crystallisation from a variety of solvents. A pure sample of the 16α,17α-dimethyl derivative (4b; R = OAc) was obtained *via* the *p*-nitrobenzoate (4b; R = O·CO·$C_6H_4NO_2$). Conversion of (3b; R = OH) to 9α-fluoro-11β,21-dihydroxy-16α,17α-dimethylpregna-1,4-diene-3,20-dione has already been described.[4a]

Although the 9(11)-ene-dimethyl compounds provided access to 11β-hydroxy-derivatives substituted and unsubstituted at 9α a more direct route to the 9-unsubstituted 11β-hydroxy-compounds was desirable to avoid the wasteful exercise of introducing an 11-hydroxy-group twice, once for the formation of the 9(11)-double bond and again for the final product. We first investigated the 3β,11α-diacetoxy-16-ene (5a; R = R′ = OAc), prepared from the 3β,11α-dihydroxy-5α-spirostane,[5] in the general reaction and found that it was converted in high yield (*ca.* 87%) into the 16α,17α-dimethyl compound (5b; R = R′ = OAc). This was largely due to the fortuitous choice of the diacetate and the protective effect of the 11-ester group. Application of the general reaction to the 5α- and 5β-11β-hydroxy-16-en-20-oxo derivatives (6a; R = OAc) and (7a; R = OAc),[6] prepared from the corresponding 16-ene-11,20-diones (1a; R = OAc) and (2a; R = OAc) as detailed below, gave very poor conversions (*ca.* 30%) to the corresponding 11β-hydroxy dimethyl derivatives (6b;

[2] E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, I. M. Aliminosa, R. L. Erickson, G. E. Sita, and M. Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396.

[3] S. A. Szpilfogel and V. Gerris, *Rec. trav. Chim.*, 1955, **74**, 1462.

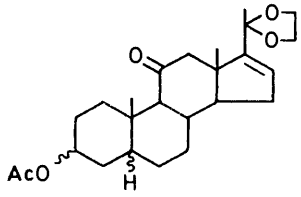
[4] (*a*) C. L. Hewett, G. F. Woods, and R. T. Logan, B.P. 1,105,013/1968 and U.S.P. 3,520,908/1970; (*b*) G. F. Woods, C. L. Hewett, and W. R. Buckett, 'Abstracts Third International Congress Hormone Steroids, 1970.' International Congress Serial No. 210, Abstract No. 152; (*c*) R. E. Schaub and M. J. Weiss, *J. Medicin. Chem.*, 1967, **10**, 789; (d) R. E. Schaub and M. J. Weiss, U.S.P. 3,483,236/1969.

[5] C. Djerassi, E. Batres, J. Romo, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 3634.

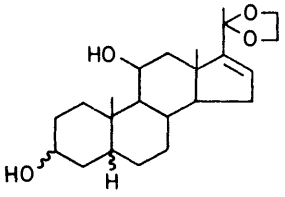
[6] F. A. Cutler and J. M. Chemerda, U.S.P. 3,013,031/1961.

R = OAc) and (7b; R = OAc) respectively. Surprisingly, these poor yields were due to unusually high conversions into the respective 16α,17α,21-trimethyl derivatives (6d; R = OAc) and (7d; R = OAc). We now believe that this can be explained by the intramolecular reaction of the magnesium salt of the 11β-hydroxy-group (11) with the 20-oxo-group which is then alkylated by the excess of methyl iodide. Circumstantial evidence for this explanation comes from the observation, discussed below, that, as with the 11α-hydroxy-compound, when the 11β-hydroxy-group is protected as the acetate, yields of both the main 16α,17α-dimethyl product and the 16α,17α,21-trimethyl by-product are comparable to those [11-oxo- and 9(11)-ene] when the 11-hydroxy-group is absent.

Because of the marked quantitative differences between the products formed from the dimethylation reaction applied to the 11α-acetoxy-derivative (5a; R = OAc) and the 11β-hydroxy-compounds (6a; R = OAc) and (7a; R = OAc) it was decided to investigate the 11β-acetates (8a; R = OAc) and (9a; R = OAc). These were prepared from the 5α- and 5β-16-ene-11,20-diones by selective protection of the 20-oxo-group prior to borohydride reduction at C-11. Of the several possibilities for protecting the 20-oxo-group, such as the semicarbazone,[7] methoxime,[8] or ethylene acetal,[9] the last was chosen for its ease of formation and removal. The usual acetalisation conditions [10] were modified by using diglyme to produce a homogeneous solution and triethylorthoformate to remove the last traces of water.* Reduction of the crude product (13), deacetalisation of the diol (14), and mild acetylation gave the 3-monoacetates (6a; R = OAc) and (7a; R = OAc). Further



(13) a; 3β, 5α
b; 3α, 5β



(14) a; 3β, 5α
b; 3α, 5β

acetylation with acetic anhydride, pyridine, and methylamine hydrochloride then gave excellent yields of the corresponding diacetates (8a; R = OAc) [11b] and (9a; R = OAc). Dehydration [12] of the monoacetates (6a; R = OAc) and (7a; R = OAc) also provided a convenient source of 9(11),16-dien-20-oxo-compounds (3a; R = OAc) and (4a; R = OAc).[11]

When the diacetates (8a; R = OAc) and (9a; R = OAc) were subjected to the dimethylation reaction, the crude products contained 85—90% of the corresponding 16α,17α-dimethyl compounds (8b; R = OAc) and (9b; R = OAc). In the 5α-series the diacetate (8b; R = OAc) was readily purified by crystallisation in 63% yield without prior removal of the 16-monomethyl derivative (8c; R = OAc). Difficulty was encountered in the 5β-series because neither the diacetate (9b; R = OAc) nor the monoacetate (9b; R = OH) could be obtained crystalline. However, oxidation of the monoacetate (9b; R = OH) with Jones reagent gave the crystalline 3,20-dione (10b) in 55% overall yield. The 11-acetate, in addition to influencing the quantitative course of the reaction would also provide protection of the sensitive 11β-hydroxy-group on further elaboration of the molecule. In both the 5α- and 5β-series it was found almost impossible to hydrolyse the 11β-acetate, whereas the presence of a 4-double bond greatly facilitates the hydrolysis, and the effect of the 1,4-diene system is even more marked.[12] From a study of models this is attributed to the increased equatorial character of the 11β-bond caused by conformational changes resulting from the strain transmitted through ring B from the doubly unsaturated planar ring A with an additional contribution from reduced steric hindrance by loss of the 1α-hydrogen atom. Thus we were reassured that at some point we would be able to remove the 11β-acetoxy-group successfully.

As well as investigating the 16-en-20-ones (1a—9a; R = OAc) under the standard conditions of dimethylation reaction for the formation of the 16α,17α-dimethyl product the total product was investigated in each case for the nature and extent of the by-products. Qualitatively these corresponded closely with those previously reported [1] and consisted of the 16α-monomethyl (c) and 16α,17α,21-trimethyl (d) derivatives. The former were readily separated as soluble Girard P derivatives and identified by comparison with authentic samples. The 16α-monomethyl derivatives do not separate from the corresponding 16α,17α-dimethyl compounds on t.l.c., but they can be detected by their relatively short retention times on g.l.c. In the n.m.r. the 16α-monomethyl compounds (1c)—(9c) are characterised by a doublet for the 16α-methyl group, at δ 0.93—0.99 (Table 3) which appears upfield at δ 0.86—0.92 in the 16α,17α-dimethyl series (1b)—(9b) with the 17α-methyl group appearing at δ 0.90—1.13 (Table 1).

The 16α,17α,21-trimethyl derivatives were more difficult to separate because of their similarity to, and

* We thank Dr. D. R. Rae of these Laboratories for his part in the development of this process.

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[8] S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 1958, 4614; S. Eardley and A. G. Long, *ibid.*, 1965, 130.

[9] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, 1953, **18**, 70; P. F. Beal and J. E. Pike, *ibid.*, 1961, **26**, 3887; J. W. ApSimon and J. A. Eenkhoorn, *Canad. J. Chem.*, 1974, **52**, 4113; R. Royer, *Khim. Geterotsikl. Soedin.*, 1977, No. 5, 579.

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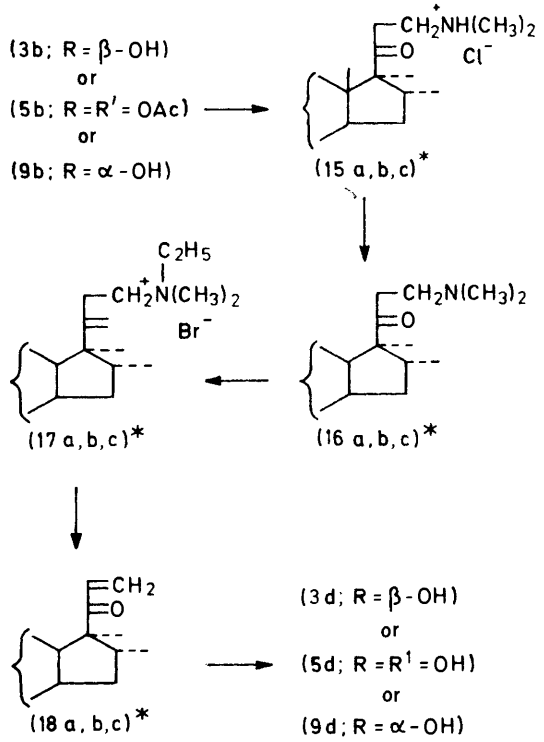
[12] Unpublished work.

[13] S. K. Figdor and G. D. Laubach, U.S.P. 3,064,017/1962, S. K. Figdor, H-J. E. Hess, and G. D. Laubach, U.S.P. 3,069,416/1962.

close association with, the 16α,17α-dimethyl product. In three cases the trimethyl compounds (2d; R = OAc), (6d; R = OAc), and (7d; R = OAc) were isolated by chromatography and their structures established by physical methods. The remainder were identified by t.l.c. and g.l.c. comparison with authentic samples prepared from the dimethyl derivatives. Using the Mannich reaction,[1,13] the dimethyl compounds (3b; R = OH), (5b; R = R¹ = OH), and (9b; R = OAc) were converted into the corresponding 21-methyl derivatives (3d; R = OH), (5d; R = R¹ = OH), and (9d; R = OAc) *via* the intermediates (15)—(18). The remaining 16α,17α,21-trimethyl compounds were pre-



* a = 9(11)ene series, b = 11α-OAc series, c = 11β-OAc series.

pared from those described above. Oxidation of the 11β-hydroxy-compound (6d; R = OAc) with Jones reagent gave the 11-oxo-compound (1d; R = OAc), and acetylation with boiling acetic anhydride in pyridine furnished the diacetate (8d; R = OAc). Treatment of the 11β-hydroxy-compound (7d; R = OAc) with acid and reacetylation gave the 9(11)-ene compound (4d; R = OAc).

The 16α,17α,21-trimethyl derivatives (1d)—(9d) were readily distinguished from the corresponding 16α,17α-dimethyl compounds (1b)—(9b) by the presence in the n.m.r. spectrum of a triplet (δ 0.93—1.02) for the 21-methyl group and the absence of a signal for the acetyl group (δ 2.03—2.10) present in the dimethyl series. In addition, trimethyl derivatives (1d)—(9d) display characteristic fragmentation patterns in their mass spectra, the most important features of which are the loss of fragments C_3H_5O and $C_7H_{12}O$ due to cleavage of the C(17)–C(20) and C(13)–C(17) and C(15)–C(16) bonds respectively. In each case the base peak occurs at *m/e* 113, and is formulated as $C_7H_{13}O$, arising *via* the ring D fragmentation noted above and accompanied by hydrogen transfer.

With the exception of the 11β-hydroxy-16-en-20-ones, moderate to good yields of the 16α,17α-dimethyl derivatives were achieved in all cases. The 11-carbonyl group remained unattacked and so did the acetates of both the 11α- and 11β-hydroxy derivatives. Thus, our primary objective of finding commercially viable routes to 16α,17α-dimethyl analogues of corticosteroids was achieved and a route to novel 11β-hydroxy steroids unsubstituted at C-9 has been developed.

The further elaboration of the 16α,17α-dimethyl intermediates in both the 5α- and 5β-series will be reported in a later publication.

EXPERIMENTAL

M.p.s were taken with a Kofler micro hot-stage apparatus. I.r. spectra were determined with a Perkin-Elmer 457 spectrometer. U.v. spectra were determined for solutions in ethanol with a Perkin-Elmer 402 spectrometer. Optical rotations were measured for solutions in chloroform at room temperature unless otherwise stated. G.l.c. was performed with a Pye–Argon chromatograph and quoted retention times are relative to cholestane (t_R 1.0 on SE 30 at 225 °C). N.m.r. spectra for solutions in $CDCl_3$ were determined at 60 MHz with a Perkin-Elmer R12B spectrometer (tetramethylsilane as internal standard). Mass spectra were determined with an A.E.I. MS902 high resolution spectrometer. Elemental analyses were carried out with a Perkin-Elmer 240 CHN analyser. T.l.c. was carried out by using silica gel (Merck GF_{254}) (layers 0.25 mm thick). Column chromatography was carried out with silica gel (Merck type 7734) or alumina (Spence grade H).

Methyl iodide was dried by two distillations from P_2O_5; diethyl ether and tetrahydrofuran were dried over sodium wire; solutions of products were dried over anhydrous sodium sulphate.

Modified Procedure for 16α,17α-*Dimethylation* (*Table* 1).—The steroid was dissolved in dry tetrahydrofuran (3 vol) and treated with anhydrous powdered cupric acetate (0.1 mol equiv.) and a 0.1% solution of phenylazodiphenylamine in benzene (1 drop) as indicator. The stirred mixture was titrated under nitrogen with a solution of methylmagnesium halide (*ca.* 1 molar) from a pressure equalisation funnel, the temperature being kept below 25 °C with external cooling, until the indicator turned red. A 5% excess of the reagent was then added and after 5 min this was followed by methyl iodide (2 vol) and the mixture, still under nitrogen, was heated for 16 h. The product, isolated as previously described,[1] was then either hydrolysed with potassium hydroxide in methanol, or acetylated with acetic anhydride in pyridine under standard conditions.

A solution of the crude hydrolysed or acetylated-product, in ethanol (4.5 vol) and acetic acid (0.5 vol), was treated with Girard's Reagent P [2 mol equiv., based on the 16α-monomethyl (c) content estimated by g.l.c.] and boiled under reflux for 15 h. The cooled (20 °C) reaction mixture was poured into water (20 vol) containing sufficient potassium hydroxide (0.5 part) to bring the final solution to pH 7—8. The product was isolated by filtration (if solid) or

extraction with ether or methylene chloride and crystallised to give the 16α,17α-dimethyl derivative (b).

11β-*Acetoxy*-16α,17α-*dimethyl*-5β-*pregnane*-3,20-*dione* (10b).—A solution of 3α,11β-dihydroxy-16α,17α-dimethyl-5β-pregnan-20-one 11-acetate (9b; R = OH) (10 g) in acetone (48 ml) was treated with Jones reagent [14] (8M; 7.7 ml) and kept at 5 °C. After the mixture had been stirred for 30 min at 5 °C excess of chromic acid was destroyed by addition of isopropyl alcohol until the reaction to starch iodide paper was negative. Water (450 ml) was added and the product was filtered off and dried. Four recrystallisations from acetone–n-hexane gave the *dimethyl dione* (10b) (5.9 g) (Table 1).

Preparation of the 16α-*Methyl Derivatives* (*c*) (*Table* 2).—Using the modified procedure as above, a portion of the reaction mixture was removed after titration with Grignard reagent but before addition of methyl iodide. This was worked up in the usual way to give the 16α-methyl derivative (c) (for further details see Table 2).

11β-*Acetoxy*-16α-*methyl*-5β-*pregnane*-3,20-*dione* (10c).—3α,11β-Dihydroxy-16α-methyl-5β-pregnan-20-one 11-acetate (9c; R = OH) (2.78 g) in acetone (13 ml) was treated with Jones reagent [14] (8M; 2.5 ml) and kept at 5 °C. After 5 min excess of reagent was destroyed by addition of isopropyl alcohol (0.5 ml) (starch iodide paper) and the product was isolated by addition of water (100 ml) and extraction into ether. Crystallisation from ether gave the 3,20-*dione* (10c) (1.2 g) (Table 2).

16α,17α,21-*Trimethyl Derivatives* (*d*) (*Table* 3).—The 16α,17α,21-trimethyl compounds (2d; R = OAc), (6d; R = OAc), and (7d; R = OH) were isolated from the corresponding dimethylation reaction by column chromatography on silica gel.

Mannich Procedure A: 3β-*Hydroxy*-16α,17α,21-*trimethyl*-5α-*pregn*-9(11)-*en*-20-*one* (3d; R = OH).—A solution of the 16α,17α-dimethyl compound (3b; R = OH) (10 g) in isopentyl alcohol (150 ml) containing dimethylamine hydrochloride (20 g), paraformaldehyde (6 g), and 2M-hydrochloric acid (0.6 ml) was boiled under reflux for 2 h. The cooled reaction mixture was washed with water (2 × 50 ml) and the washes re-extracted with isopentyl alcohol (25 ml). The combined isopentyl alcohol solutions were concentrated (25 ml) and the amine hydrochloride (15a) precipitated by addition of ether (10 vol). The product (6 g), isolated by filtration showed a series of peaks, between 2 700 and 2 300 cm^{-1} in the i.r. region, characteristic of the amine salt (15).

The hydrochloride (15a) (5 g) was shaken for 5 min with a mixture of 2M-potassium hydroxide solution (100 ml) and ether (100 ml). The ether layer was separated, washed neutral with water, dried, and evaporated to give the amine (16a) (4.5 g) as a gum. Attempts to purify this material resulted in decomposition.

A solution of the crude amine (16a) (4 g) in methylene

TABLE 1

Physical constants of 16α,17α-dimethylpregnanes

Compound	Yield (%)	M.p. (θ_c/°C)	$[\alpha]_D$ $CHCl_3$ (*c*, %)	t_R	60 MHz ^1H N.m.r. assignments (δ) (*J*/Hz) 10-CH_3	13-CH_3	16α-CH_3	17α-CH_3	Acetyl	Acetate	3-H	11-H	16β-H	Found (%) C	H	Formula	Reqd. (%) C	H
(1b; R = OAc)	45.5	202—205	+22.3° (1.12)	2.06	1.10 (s)	0.63 (s)	0.91 (d, 8 Hz)	1.01 (s)	2.04 (s)	1.99 (s)	4.55 (m, broad)		3.0 (m, broad)	74.35	9.4	$C_{25}H_{38}O_4$	74.6	9.5
(2b; R = OAc)	51.5	167—169	+51.5 (1.0)	1.47	1.13 (s)	0.62 (s)	0.92 (d, 8 Hz)	1.13 (s)	2.05 (s)	2.00 (s)	4.7 (m, broad)		3.0 (m, broad)	74.4	9.7	$C_{25}H_{38}O_4$	74.6	9.5
(3b; R = OH)	73.9	199—201 ‡	−13.9 (1.0)	0.94	0.93 (s)	0.63 (s)	0.88 (d, 8 Hz)	1.02 (s)	2.06 (s)		3.58 (m, broad)	5.34 (m)	2.9 (m, broad)	80.1	10.6	$C_{23}H_{38}O_2$	80.2	10.5
(4b; R = OAc)	70	185—187	+28.6 (1.0)	1.07	1.03 (s)	0.63 (s)	0.88 (d, 8 Hz)	1.03 (s)	2.06 (s)	2.05	4.74 (m, broad)	5.38 (m)	3.0 (m, broad)	77.8	9.9	$C_{25}H_{38}O_3$	77.6	9.9
(5b; R = R′ = OH)	87	246—247	−15 (1.0)	1.16	1.05 (s)	0.69 (s)	0.86 (d, 8 Hz)	0.92 (s)	2.08 (s)		3.8 (m, broad)	3.35 (m)	2.9 (m, broad)	75.85	10.6	$C_{23}H_{38}O_3$	76.2	10.6
(6b; R = OAc)	*	228—230	−72 (1.0)	2.48	1.04 (s)	0.94 (s)	0.88 (d, 8 Hz)	0.99 (s)	2.09 (s)	2.01 (s)	4.7 (m, broad)	4.43 (m)	3.0 (m, broad)	74.2	10.0	$C_{25}H_{40}O_4$	74.2	10.0
(7b; R = OH)	†	231—234	+27.8 (0.85)	1.31	1.16 (s)	0.94 (s)	0.87 (d, 8 Hz)	1.02 (s)	2.10 (s)		3.67 (m, broad)	4.27 (m)	2.95 (m, broad)	76.2	10.4	$C_{23}H_{38}O_3$	76.2	10.6
(8b; R = OAc)	63.4	153—154	+32.3 (0.88)	2.89	1.02 (s)	0.83 (s)	0.87 (d, 8 Hz)	0.90 (s)	2.05 (s)	2.0 (s)	4.6 (m, broad)	5.40 (m)	3.0 (m, broad)	72.7	9.45	$C_{27}H_{42}O_5$	72.6	9.5
(10b)	55	179—182	0 (1.04)	1.82	1.08 (s)	0.83 (s)	0.87 (d, 8 Hz)	1.02 (s)	2.03 (s)	(s, 6 H) 1.98 (s)		5.35 (m)	3.0 (m, broad)	75.7	9.85	$C_{25}H_{38}O_4$	74.6	9.5

* The pure sample was obtained by prolonged hydrolysis of the 11-acetate (8b) and reacetylation at C-3. † A product which was 90% pure could be isolated in 43% yield. ‡ Ref. 2c give m.p. 195—197 °C, $[\alpha]_D$ −11°.

TABLE 2

Physical constants of 16α-methylpregnanes

Compound	M.p. (θ_c/°C)	$[\alpha]_D$ $CHCl_3$ (*c*, %)	t_R	60 MHz ^1H N.m.r. assignments (δ) (*J*/Hz) 10-CH_3	13-CH_3	16α-CH_3	Acetyl	Acetate	3-H	11-H	16β-H	Found (%) C	H	Formula	Reqd. (%) C	H
(1c; R = OAc)	148—150	+78° (1.0)	1.27	1.02 (s)	0.58 (s)	0.99 (d, 6 Hz)	2.08 (s)	2.00 (s)	4.6 (m, broad)		2.5 (m, broad)	73.9	9.4	$C_{24}H_{38}O_4$	74.2	9.3
(2c; R = OAc)	149—151	+11.5 (1.0)	1.03	1.15 (s)	0.58 (s)	0.99 (d, 6 Hz)	2.08 (s)	2.00 (s)	4.65 (m, broad)		2.5 (m, broad)	74.2	9.4	$C_{24}H_{38}O_4$	74.2	9.3
(3c; R = OH)	189—191	+65.1 (0.98)	0.60	0.93 (s)	0.58 (s)	0.93 (d, 6 Hz)	2.12 (s)		3.58 (m, broad)	5.35 (m)	2.6 (m, broad)	80.1	10.5	$C_{22}H_{34}O_2$	79.95	10.4
(4c; R = OAc)	148—151	+105.5 (0.98)	0.73	1.05 (s)	0.56 (s)	0.94 (d, 6 Hz)	2.10 (s)	1.99 (s)	4.7 (m, broad)	5.35 (m)	2.6 (m, broad)	76.9	9.6	$C_{24}H_{36}O_3$	77.4	9.7
(5c; R = R′ = OH)	198—200	+49.1 (1.13)	1.06	0.93 (s)	0.63 (s)	0.94 (d, 6 Hz)	2.11 (s)		3.7 (m, broad) (2H)		2.6 (m, broad)	76.05	10.2	$C_{21}H_{36}O_3$	75.8	10.4
(6c; R = OAc)	146—154	+69.7 (0.64)	1.51	1.04 (s)	0.87 (s)	0.93 (d, 6 Hz)	2.09 (s)	2.00 (s)	4.68 (m, broad)	4.37 (m)	2.6 (m, broad)	73.9	9.8	$C_{24}H_{38}O_4$	73.8	9.8
(7c; R = OH)	179—181	+99 (1.09)	0.83	1.17 (s)	0.86 (s)	0.95 (d, 6 Hz)	2.10 (s)		3.65 (m, broad)	4.25 (m)	2.6 (m, broad)	76.0	10.5	$C_{22}H_{36}O_3$	75.8	10.4
(8c; R = OAc)	150—152	+84.6 (1.08)	2.68	0.89 (s)	0.76 (s)	0.95 (d, 6 Hz)	2.07 (s)	1.99 (s, 6 H)	4.6 (m, broad)	5.37 (m)	2.6 (m, broad)	72.3	9.3	$C_{26}H_{40}O_5$	72.2	9.3
(10c)	159—160	+110 (0.92)	1.17	1.10 (s)	0.80 (s)	0.96 (d, 6 Hz)	2.07 (s)	2.00 (s, 6 H)		5.3 (m)	2.6 (m, broad)	74.4	9.5	$C_{24}H_{36}O_4$	74.2	9.3

[14] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

chloride (40 ml) was treated with ethyl bromide (8 ml). After 16 h at room temperature the solid which separated was filtered off to give the *ethobromide* (17a) (4 g) (Found: Br, 15.6. $C_{28}H_{48}BrNO_2$ requires Br, 15.65%).

A solution of the ethobromide (17a) (4 g) in a mixture of isopropyl alcohol–water (1 : 3) (400 ml) was treated with saturated potassium hydrogencarbonate solution (50 ml) at room temperature. A fine white precipitate formed immediately and after 30 min the product was extracted into ether. The extract was washed with water, dried, and evaporated under reduced pressure to give the 21,21-methylene compound (18a) (2.7 g), m.p. 170—178 °C, t_R 1.09, $\nu_{max.}$(KCl) 3 260 (3-OH), 1 688 (20-ketone), and 1 608 cm^{-1} (C:CH_2). Attempts to purify this compound led to the production of impurities.

The 21,21-methylene compound (18a) (2 g) in isopropyl alcohol (100 ml) was hydrogenated over 10% palladium on charcoal (0.2 g). After removal of the catalyst, water (500 ml) was added to the mixture and the product extracted into methylene chloride (2 × 100 ml). The washed and dried extract was evaporated to give a gum which crystallised from aqueous methanol to give 3β-*hydroxy*-16α,17α,21-*trimethyl*-5α-*pregn*-9(11)-*en*-20-*one* (3d; R = OH) (1.5 g) (Table 3), $\nu_{max.}$(CH_2Cl_2) 3 610 (3-OH) and 1 697 cm^{-1} (20-ketone).

Mannich Procedure B: 3β,11α-*Dihydroxy*-16α,17α,21-*trimethyl*-5α-*pregnan*-20-*one* (5d; R = R′ = OH).—3β,11α-Diacetoxy-16α,17α-dimethyl-5α-pregnan-20-one (5b; R = R′ = OAc) (18 g) in pentyl alcohol (250 ml) containing dimethylamine hydrochloride (32 g) was treated with paraformaldehyde (5 g). The stirred mixture was boiled for 6 h with further additions of paraformaldehyde (3 g) after 2 and 4 h. Most of the pentyl alcohol was then evaporated under reduced pressure and water (200 ml) was added. The remaining pentyl alcohol was removed by azeotropic distillation under reduced pressure and the resultant mixture partitioned between water and ether. The ether layer was separated and washed with water. The combined aqueous fractions, which contained the amine hydrochloride (15b), were made alkaline with 4M-sodium hydroxide (50 ml) to give the amine (16b) (9.5 g), isolated by extraction into ethyl acetate.

In a two-phase reaction, the amine (16b) (9.5 g), methylene chloride (50 ml), ethyl bromide (10 ml), and 5% sodium carbonate (50 ml) were stirred overnight at room temperature to give the 21,21-methylene compound (18b) without isolation of the intermediate ethobromide (17b). The product (18b) (6.5 g) was isolated by separation of the methylene chloride layer and evaporation.

Hydrogenation of the crude 21,21-methylene compound (18b) as described in Method A gave the 16α,17α,21-trimethyl derivative (5d; R = R′ = OAc) (6.14 g). Hydrolysis with potassium hydroxide (1.9 g) in methanol (30 ml) gave the *diol* (5d; R = R^1 = OH) (4.38 g) which was crystallised from methanol (Table 3).

11β-*Acetoxy*-16α,17α,21-*trimethyl*-5β-*pregnane*-3,20-*dione* (10d).—3α,11β-Diacetoxy-16α,17α-dimethyl-5β-pregnan-20-one (9b; R = OAc) (26 g) in pentyl alcohol (370 ml) containing dimethylamine hydrochloride (47 g) was treated with paraformaldehyde (16 g) as described above under Mannich procedure B, to give the amine (16c) which was converted *via* the ethobromide (17c) and 21,21-methylene compound (18c) into the trimethyl derivative (9d; R = OAc) (13.2 g). The non-crystalline 3,11-diacetate (9d; R = OAc) (9.9 g) was treated with methanol (30 ml) and potassium hydroxide (1.8 g) to give the 11β-acetoxy-3β-ol (9d; R = OH) (9.1 g) as a gum.

Oxidation of the 3-hydroxy-compound (9d; R = OH) (9.1 g) with Jones reagent [14] in acetone at 5 °C, gave the 3-*ketone* (10d) (8.6 g) (Table 3) which could not be crystallised, even after chromatographic purification from minor impurities.

3β-*Acetoxy*-16α,17α,21-*trimethyl*-5α-*pregnane*-11,20-*dione* (1d; R = β-OAc).—The 3β-acetoxy-11β-ol (6d; R = OAc) (0.2 g) in acetone (2 ml) was maintained at 5 °C and treated with an excess of Jones reagent.[14] Addition of isopropyl alcohol (0.5 ml) followed by water (20 ml) gave the *dione* (1d; R = OAc) (0.15 g) isolated by filtration (Table 3).

3β,11β-*Diacetoxy*-16α,17α,21-*trimethyl*-5α-*pregnan*-20-*one* (8d; R = OAc).—The 3β-acetoxy-11β-ol (6d; R = OAc) (275 mg) in pyridine (1 ml) was treated with acetic anhydride (1 ml) and 4-dimethylaminopyridine (50 mg) at room temperature for 16 h. The product, isolated by addition of water (20 ml) and filtration, was dissolved in methylene chloride, and the dried solution run through a short column of silica. Evaporation of the eluate and crystallisation from cyclohexane gave the *diacetate* (8d; R = OAc) (0.11 g) (Table 3).

3α-*Acetoxy*-11β-*hydroxy*-16α,17α,21-*trimethyl*-5β-*pregnan*-20-*one* (7d; R = OAc).—The diol (7d; R = OH) (0.15 g) was acetylated in pyridine (2.5 ml) and acetic anhydride (2.5 ml) overnight at room temperature. The reaction

TABLE 3

Physical constants of 16α,17α,21-trimethylpregnanes

Compound	Source	M.p. (θ_c/°C)	$[\alpha]_D$ $CHCl_3$ (c, %)	t_R	60 MHz ^{1}H N.m.r. assignments (δ) (J/Hz) 10-CH_3	13-CH_3	16α-CH_3	17α-CH_3	21-CH_3	Acetate	3-H	11-H	16β-H	Found(%) C	H	Formula	Reqd. (%) C	H
(1d; R = OAc)	(6d)	194—196	+22° (1.02)	2.15	1.11 (s)	0.60 (s)	0.92 (d, 7 Hz)	1.02 (s)	1.00 (t, 7 Hz)	2.00 (s)	4.65 (m, broad)		3.0 (m, broad)	74.75	9.7	$C_{26}H_{40}O_4$	75.0	9.7
(2d; R = OAc)	*a*	195—198	+56.8 (1.0)	2.01	1.13 (s)	0.59 (s)	0.93 (d, 7 Hz)	1.13 (s)	1.01 (t, 7 Hz)	2.00 (s)	4.72 (m, broad)		3.0 (m, broad)	74.85	9.7	$C_{26}H_{40}O_4$	75.0	9.7
(3d; R = OH)	*b*	156—157	−11 (1.60)	1.09	1.00 (s)	0.58 (s)	0.87 (d, 7 Hz)	0.91 (s)	1.00 (t, 7 Hz)		3.5 (m, broad)	5.29 (m)	2.95 (m, broad)	80.25	10.7	$C_{24}H_{38}O_2$	80.4	10.7
(4d; R = OAc)	(7d)	171—176	+37.1 (1.0)	1.28	1.05 (s)	0.58 (s)	0.87 (d, 7 Hz)	1.05 (s)	1.02 (t, 7 Hz)	2.00 (s)	4.75 (m, broad)	5.4 (m)	3.0 (m, broad)	77.9	10.1	$C_{26}H_{40}O_3$	77.95	10.1
(5d; R = R′ = OH)	*b*	178—188	−9.6 (1.04)	2.17	1.04 (s)	0.65 (s)	0.86 (d, 7 Hz)	0.92 (s)	1.01 (t, 7 Hz)		3.7 (m broad)		3.0 (m, broad)	76.55	10.6	$C_{24}H_{40}O_3$	76.5	10.7
(6d; R = OAc)	*a*	184—185	+9.5 (1.03)	2.79	1.04 (s)	0.91 (s)	0.87 (d, 7 Hz)	0.99 (s)	1.00 (t, 7 Hz)	1.99 (s)	4.65 (m, broad)	4.38 (m)	3.0 (m, broad)	74.75	10.0	$C_{26}H_{42}O_4$	74.6	10.1
(7d; R = OH)	*a*	256—259	+32 (1.1)	1.79	1.08 (s)	0.82 (s)	0.79 (d, 7 Hz)	0.95 (s)	0.93 (t, 7 Hz)		3.55 (m, broad)	4.05 (m)	2.9 (broad)	76.45	10.7	$C_{24}H_{40}O_3$	76.5	10.7
(8d; R = OAc)	(6d)	117—118	+33 (1.2)	3.46	0.99 (s)	0.78 (s)	0.86 (d, 7 Hz)	0.88 (s)	0.99 (t, 7 Hz)	1.99 (s, 6 H)	4.6 (m, broad)	3.38 (m)	3.0 (m, broad)	72.9	9.5	$C_{28}H_{44}O_5$	73.0	9.6
(10d)	*b*	amorphous	+46.9 (1.04)	1.84	1.10 (s)	0.83 (s)	0.89 (d, 7 Hz)	1.02 (s)	0.99) (t, 7 Hz)	2.00 (s)		3.35 (m)	3.0 (m, broad)	74.9	9.9	$C_{26}H_{40}O_4$	75.0	9.7

a Isolated from the reaction mixture by chromatography. *b* Prepared by the Mannich reaction procedure (see ref. 1).

mixture was poured into ice–water and the product filtered off. Crystallisation from methylene chloride–methanol gave the *monoacetate* (7d; R = OAc) (0.13 g), m.p. 226—233 °C, $[\alpha]_D$ +80.9 (*c* 1.0), t_R 2.38, $\nu_{max.}$(KCl) 3 470 (OH), 1 705 (acetate), and 1 694 cm^{-1} (20-ketone); δ 0.87 (3 H, d, *J* 7 Hz, 16α-Me), 0.90 (3 H, s, 13-Me), 1.0 (3 H, s, 17α-Me), 1.14 (3 H, t, *J* 7 Hz, 21-Me), 1.17 (3 H, s, 10-Me), 2.01 (3 H, s, OAc), 3.0br (1 H, m, 16β-H), 4.28 (1 H, m, 11α-H), and 4.75 (1 H, m, 3α-H) (Found: C, 74.5; H, 10.0. $C_{26}H_{42}O_4$ requires C, 74.6; H, 10.1%).

3α-Hydroxy-16α,17α,21-trimethyl-5β-pregn-9(11)-en-20-one (4d; R = OH).—3α-Acetoxy-11β-hydroxy-16α,17α,21-trimethyl-5β-pregnan-20-one (7d; R = OAc) (5 g) was boiled in ethanol (100 ml) containing concentrated hydrochloric acid (2.5 ml) for 10 h. The reaction mixture was cooled and the product isolated by addition of water and filtration. The dried product (4.6 g) was crystallised from methylene chloride–methanol to give the *9(11)-ene* (4d; R = OH). A pure sample from cyclohexane had m.p. 156—161 °C, $[\alpha]_D$ +12.7° (*c* 1.1), t_R 0.98, $\nu_{max.}$(KCl) 3 280 (hydroxy), 3 040 (11-H), and 1 695 cm^{-1} (20-ketone); δ 0.60 (3 H, s, 13-Me), 0.89 (3 H, d, *J* 7 Hz, 16α-Me), 1.03 (3 H, t, *J* 7 Hz, 21-Me), 1.05 (6 H, s, 10- and 17-Me), 2.95br (1 H, m, 16β-H), 3.65br (1 H, m, 3β-H), and 5.39 (1 H, m, 11-H) (Found: C, 80.4; H, 10.5. $C_{24}H_{38}O_2$ requires C, 80.4; H, 10.7%).

3β-Acetoxy-5α-pregn-16-ene-11,20-dione 20-Ethylene Acetal (13a).—*Method A.* A vigorously stirred solution of 3β-acetoxy-5α-pregn-16-ene-11,20-dione (1a; R = OAc) (50 g) and toluene-*p*-sulphonic acid (0.5 g) in benzene (750 ml) and ethylene glycol (120 ml) was heated under reflux for 21 h. The water formed was collected in a Dean and Stark separator. Potassium carbonate (2.5 g) was added to the cooled reaction mixture which was then poured into water (500 ml). The lower aqueous layer was separated and the benzene solution washed twice with water (2 × 100 ml). The water washes were each re-extracted with a single portion of benzene (100 ml) and the combined organic extracts dried and evaporated to give a gum (59 g).

The crude product (59 g) was treated at room temperature for 16 h with pyridine (100 ml) and acetic anhydride (50 ml) and the reaction mixture poured onto ice (1 kg). The resultant white solid was filtered off, washed with water, and dried. Attempted recrystallisation from ether–n-hexane gave the ketone (1a; R = OAc). The crude *acetal* (13a) was used in the next step.

A pure sample was obtained from n-hexane containing a few drops of pyridine, m.p. 116—119 °C, $[\alpha]_D$ +34.1° (*c* 1.01 in pyridine), t_R 2.19, $\nu_{max.}$(KCl) 1 730 (OAc) and 1 697 cm^{-1} (11-ketone); δ(C_5D_5N) 0.85 (3 H, s, 13-Me), 1.05 (3 H, s, 10-Me), 1.46 (3 H, s, 20-Me), 1.97 (3 H, s, acetate-Me), 2.59 (2 H, d, 12-H_2), 3.78 (4 H, m, O–CH_2CH_2–O), 4.76br (1 H, m, 3α-H), and 5.86 (1 H, m, 16-H) (Found: C, 71.8; H, 8.65. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.7%).

Method B. A solution of 3β-acetoxy-5α-pregn-16-ene-11,20-dione (1a; R = OAc) (5 g) in a mixture of dry benzene (30 ml), ethylene glycol (4 ml), and diglyme (7.5 ml), containing toluene-*p*-sulphonic acid (25 mg) was heated under reflux for 1½ h using a Dean and Stark separator to remove water. Triethyl orthoformate (1.5 ml) was then added to the mixture and heating continued for a further 3 h. The cooled mixture was treated with aqueous sodium hydrogen carbonate (2%; 100 ml) and the product extracted into ether. The extract was washed four times with water, dried and evaporated to give a gummy residue which was shown (g.l.c. and t.l.c.) to be a mixture of 3β-acetoxy-5α-pregn-16-ene-11,20-dione 20-ethylene acetal (14a) and the corresponding 3-alcohol. Reacetylation with acetic anhydride (5 ml) and pyridine (10 ml) at room temperature for 5 h gave the acetal (13a) (4.8 g) (*ca.* 95% pure by g.l.c.).

TABLE 4

N.m.r. spectra of pregn-16-enes

Compound	60 MHz ^1H N.m.r. assignments (δ) (*J*/Hz) 10-CH_3	13-CH_3	Acetyl	Acetate	3-H	11-H	16-H
(1a; R = OAc)	1.05 (s)	0.83 (s)	2.25 (s)	2.00 (s)	4.65 (m, broad)		6.74
(2a; R = OAc)	1.18 (s)	0.83 (s)	2.26 (s)	2.00 (s)	4.72 (m, broad)		6.74
(3a; R = OAc)	0.99 (s)	0.81 (s)	2.26 (s)	2.01 (s)	4.67 (m, broad)	5.37 (m)	6.72
(4a; R = OAc)	1.09 (s)	0.80 (s)	2.26 (s)	1.99 (s)	4.74 (m, broad)	5.41 (m)	6.71
(5a; R = R′ = OAc)	0.96 (s)	0.90 (s)	2.22 (s)	2.03 (s) 2.09 (s)	4.63 (m, broad)	5.24 (m)	6.67
(6a; R = OAc)	1.15 (s)	1.08 (s)	2.22 (s)	2.00 (s)	4.62 (m, broad)	4.32 (m)	6.66
(7a; R = OAc)	1.23 (s)	1.15 (s)	2.24 (s)	2.01 (s)	4.76 (m, broad)	4.25 (m)	6.68
(8a; R = OAc)	0.92 (s)	1.06 (s)	2.22 (s)	1.99 (s) 2.01 (s)	4.63 (m, broad)	5.38 (m)	6.67
(9a; R = OAc)	1.05 (s)	1.05 (s)	2.21 (s)	2.00 (s, 6 H_2)	4.71 (m, broad)	5.27 (m)	6.67

3β,11β-Dihydroxy-5α-pregn-16-en-20-one 20-Ethylene Acetal (14a).—A stirred solution of the crude acetal (13a) in a mixture of methanol (100 ml), tetrahydrofuran (100 ml), and water (10 ml) at room temperature was treated portionwise with sodium borohydride (15 g). The solution became hot and was left to cool for 1.5 h. 4M-Sodium hydroxide (10 ml) was added to complete the hydrolysis and after a further 1.5 h excess of sodium borohydride was destroyed by careful addition of acetic acid. The reaction mixture was poured into water (2 l) to give a gum which solidified when stirred. The filtered and washed solid was dried *in vacuo* at 60 °C to give the crude *diol* (14a) (48.4 g). Crystallisation from acetone–diethyl ether gave a pure sample, m.p. 173—175 °C, $[\alpha]_D$ +31.7° (*c* 0.97), t_R 1.84, $\nu_{max.}$(CH_2Cl_2) 3 600 and 3 480 (OH), and 3 000 cm^{-1} (16-hydrogen); δ 1.10 (3 H, s, 13-Me), 1.21 (3 H, s, 10-Me), 1.50 (3 H, s, 20-Me), 3.65br (1 H, m, 3α-H), 3.87 (4 H, s, O–CH_2–CH_2–O), 4.32 (1 H, m, 11α-H), and 5.73 (1 H, m, 16-H) (Found: C, 73.15; H, 9.8. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.6%).

3β,11β-Dihydroxy-5α-pregn-16-en-20-one (6a; R = OH).—The crude acetal (14a) (48.2 g) was suspended in acetic acid (300 ml) and water (30 ml). The mixture was stirred for 1 h, poured into water (3 l), and the filtered product was washed with water and dried under reduced pressure at 60 °C to give the crude *diol* (6a; R = OH) (41 g). Recrystallisation from acetone gave pure diol, m.p. 214—225 °C, $[\alpha]_D$ +78.2° (*c* 1.03 in dimethyl sulphoxide), t_R 1.07,

$\lambda_{max.}$ 240 nm (ε 8 500); $\nu_{max.}$(KCl) 3 360, 3 400 (OH), 3 000 (16-H), 1 650 (20-ketone), and 1 589 cm^{-1} (16,17-C:C); δ[$(CD_3)_2SO$] 1.00 (3 H, s, 13-Me), 1.10 (3 H, s, 10-Me), 2.19 (3 H, s, acetyl-Me), 3.30br (1 H, m, 3α-H), 4.15 (1 H, m, 11α-H), and 6.81 (1 H, m, 16-H) (Found: C, 76.1; H, 9.9. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%).

3β,*Acetoxy*-11β-*hydroxy*-5α-*pregn*-16-*en*-20-*one* (6a; R = OAc).—A solution of the diol (6a; R = OH) (17 g) in pyridine (34 ml) was treated with acetic anhydride (17 ml) at room temperature for 17 h. Ice–water was added and filtration gave the crude monoacetate (6a; R = OAc) (19 g) which crystallised from acetone–diethyl ether, m.p. 176—184 °C, $[\alpha]_D$ +69.1° (*c* 0.96), t_R 1.48; $\lambda_{max.}$ 240 nm (ε 8 700); $\nu_{max.}$(CH_2Cl_2) 3 600 (OH), 1 725 (acetate), 1 662 (20-ketone), and 1 588 cm^{-1} (16,17-C:C); δ 1.08 (3 H, s, 13-Me), 1.15 (3 H, s, 10-Me), 2.00 (3 H, s, acetate-Me), 2.22 (3 H, s, Me of acetyl), 4.62br (1 H, m, 3α-H), 4.32br (1 H, m, 11α-H), and 6.66 (1 H, m, 16-H) (Found: C, 73.55; H, 9.2. $C_{23}H_{34}O_4$ requires C, 73.8; H, 9.15%).

3α-*Acetoxy*-5β-*pregn*-16-*ene*-11,20-*dione* 20-*Ethylene Acetal* (13b).—A vigorously stirred solution of the 11,20-dione (2a; R = OAc) (25 g) and toluene-*p*-sulphonic acid (1 g) in benzene (350 ml) and ethylene glycol (70 ml) was heated under reflux for 5 h using a Dean and Stark separator to remove water. The reaction was checked for completion (g.l.c.) and the cooled mixture was treated with an excess of solid potassium carbonate and the product extracted into benzene. The washed and dried extract was evaporated to dryness under reduced pressure to give a gum which by t.l.c. and g.l.c. was shown to be >98% 20-ethylene acetal and this was used for the subsequent experiment. A sample was crystallised several times from aqueous methanol containing a trace of pyridine to give the *acetal* (13b), m.p. 99—100 °C, $[\alpha]_D$ +71.4° (*c* 1.02), $\nu_{max.}$(KCl) 1 730 (acetate), 1 700 (11-ketone), and 1 627 cm^{-1} (C:C); δ 0.85 (3 H, s, 13-Me), 1.07 (3 H, s, 10 Me), 1.45 (3 H, s, 20-Me), 2.0 (3 H, s, acetate-Me), 2.54 (2 H, s, 12-H_2), 3.89 (4 H, narrow m, O–CH_2–CH_2–O), 4.72br (1 H, m, 3-H), and 5.82 (1 H, m, 16-H) (Found: C, 71.9; H, 8.7. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.7%).

3α-*Acetoxy*-11β-*hydroxy*-5β-*pregn*-16-*en*-20-*one* (7a; R = OAc).—A solution of the crude acetal (13b) in dry tetrahydrofuran (THF) (20 ml) was added dropwise during 15 min to a stirred suspension of sodium aluminium hydride (9.4 g; 8 mol equiv.) in dry THF (250 ml) the temperature being kept below 40 °C with external cooling. After the mixture had been stirred for a further 30 min, the excess of reagent was destroyed by careful addition of aqueous THF with ice cooling. Water (2 l) and dilute hydrochloric acid were then added to precipitate the product and render the mixture acid. The oily product was extracted with benzene and the dried extract was evaporated to give a gum which was dissolved in glacial acetic acid (200 ml) at *ca.* 40 °C and treated slowly with water (50 ml). After 10 min more water (2 l) was gradually added to give a partially solid gum which was extracted with benzene. The dried extract was evaporated to dryness under reduced pressure to give a solid which was acetylated in pyridine (100 ml) and acetic anhydride (50 ml) on a steam-bath for 1 h. The dried crude product (20.5 g) (*ca.* 92% pure by g.l.c.) was crystallised from acetone–hexane to give 3α-acetoxy-11β-hydroxy-5β-pregn-16-en-20-one (7a; R = OAc) (15.3 g), m.p. 158—159 °C, $\lambda_{max.}$ 240 nm (ε 8 500). Crystallisation from acetone–hexane gave a pure sample, m.p. 161—163 °C, $[\alpha]_D$ +115.7° (*c* 1.0), t_R 1.68; $\lambda_{max.}$ 240 nm (ε 8 900); $\nu_{max.}$(KCl) 3 500 (OH), 1 720 (acetate), 1 665 (20-ketone), and 1 585 cm^{-1} (16-C:C); δ 1.15 (3 H, s, 13-Me), 1.22 (3 H, s, 10-Me), 2.00 (3 H, s, acetate-Me), 2.24 (3 H, s, acetyl-Me), 4.25 (1 H, m, 11-H), 4.76br (1 H, m, 3-H), and 6.68 (1 H, m, 16-H) (lit.,[6] m.p. 160—161.5 °C).

3β-*Acetoxy*-5α-*pregn*-9(11),16-*dien*-20-*one* (3a; R = OAc).—A stirred solution of the diol monoacetate (6a; R = OAc) (20 g) in dimethylformamide (200 ml) was treated with collidine (40 ml) and the solution cooled to 0 °C. Methanesulphonyl chloride (12 ml) containing 5% sulphur dioxide was carefully added and the temperature allowed to rise to 25 °C during 1 h. During this time a complex precipitated and the final mixture had a thick consistency. The mixture was poured into ice–water (1 : 1) containing conc. hydrochloric acid (40 ml) and the solid was filtered off, washed with 2M-hydrochloric acid until free of collidine, and then with water and was finally dried under reduced pressure at 70 °C. Crystallisation from acetone gave the diene (3a; R = OAc) (18.2 g), m.p. 146—150 °C. An analytical sample had m.p. 167—170 °C, $[\alpha]_D$ +109° (*c* 1.2) (lit.,[11] m.p. 164—166 °C, $[\alpha]_D$ +67°,[11a] m.p. 171—173 °C, $[\alpha]_D$ +101° [11b]).

3α-*Acetoxy*-5β-*pregn*-9(11),16-*dien*-20-*one* (4a; R = OAc).—Using the method described above for the 5α-compound (3a; R = OAc), the diol monoacetate (7a; R = OAc) (97 g) gave the diene (4a; R = OAc) (83.5 g), m.p. 150—152 °C. Crystallisation from acetone–n-hexane gave a pure sample, m.p. 150—152 °C, $[\alpha]_D$ +172° (*c* 1.1) [lit.,[3] m.p. 151—153 °C, $[\alpha]_D$ +166° (acetone)].

3β,11β-*Diacetoxy*-5α-*pregn*-16-*en*-20-*one* (8a; R = OAc).—A suspension of the diol (6a; R = OH) (82.5 g) was dissolved by heating in a mixture of pyridine (82 ml), acetic anhydride (164 ml), and methylamine hydrochloride (4.1 g) and the solution was boiled for 3.5 h. The mixture was cooled, poured onto ice (2 kg), and the resultant solid filtered off, washed with water, and dried under reduced pressure at 70 °C. The crude product (109 g) in methylene chloride (150 ml) was passed through a short column of acid-washed alumina (100 g), washed through with ether (1l), and the combined eluates evaporated to dryness. The gummy residue solidified on addition of ether (200 ml). n-Hexane (400 ml) was then added, and the mixture cooled to 5 °C. The solid was filtered and washed with n-hexane to give the diacetate (8a; R = OAc) (79 g). Crystallisation from ether–n-hexane gave a pure sample, m.p. 157—159 °C, $[\alpha]_D$ +71.8° (*c* 1.0) (lit.,[11b] m.p. 111 and 148—156 °C).

3α,11β-*Diacetoxy*-5β-*pregn*-16-*en*-20-*one* (9a; R = OAc).—Using the same method as for the 5α-compound above, the 5β-diol (7a; R = OH) (23 g) with pyridine (23 ml), acetic anhydride (46 ml), and methylamine hydrochloride (0.5 g) gave the *diacetate* (9a; R = OAc) (28.8 g). Crystallisation from diethyl ether–n-hexane gave a pure sample, m.p. 150—154 °C, $[\alpha]_D$ +116° (*c* 1.0), t_R 1.73; $\lambda_{max.}$ 238 nm (ε 9 550); $\nu_{max.}$(CH_2Cl_2) 1 730 (2 × acetate), 1 668 (20-ketone), and 1 590 cm^{-1} (16-C:C); δ 1.05 (6 H, s, 10, and 13-Me), 2.00 (6 H, s, 2 × acetate-Me), 2.21 (3 H, s, acetyl-Me), 4.71br (1 H, m, 3 H), 5.27 (1 H, m, 11-H), and 6.67 (1 H, m, 16-H) (Found: C, 72.3; H, 9.0. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.7%).

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