Alkylated Steroids. Part 1. 16α-Substituted 17α-Methylpregnanes

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The sequential reaction of 3β-acetoxypregna-5,16-dien-20-one (1) with methylmagnesium bromide and then methyl iodide has been examined in detail. The major product (85%) was 3β-hydroxy-16α,17α-dimethylpregn-5-en-20-one (2). Other products identified were 3β-hydroxy-16α-methylpregn-5-en-20-one (4); the 21-methyl derivatives [(5) and (10)] of (2) and (4); the 21-(1-hydroxy-1-methylethyl) derivative (11) of (2); and a trace of the 21,21-dimethyl derivative (12) of (2). The scope of the reaction with regard to the range of substituents that can be introduced at positions 16 and 17 has been established by preparing a series of 16α-substituted 17α-methylpregnenolones with a variety of alkyl, aryl, and aralkyl groups. Some of these have been converted into the corresponding 16α,17α-disubstituted progesterones.

ALKYLATION at positions 16 and 17 in the steroid molecule has attracted considerable attention because of the widely different effects it can have on biological activity. Thus, whereas in progesterone a 16α-methyl substituent merely prolongs activity,[1] 16α- or 16β-methyl substituents in 9α-fluoroprednisolone have the unique effect of completely counteracting the potent salt-retaining effect of the 9α-fluorine atom and enhancing glucocorticoid activity. Alkylation at C-17, on the other hand, slightly increases the potency of progesterone [2] especially with regard to oral activity.[3] A 17-methyl group in 11-dehydrocorticosterone acetate substantially reduces activity in the liver glycogen test [4] and in another series of corticosterone derivatives [5] a 17-methyl substituent resulted in a similar reduction of activity. As a logical extension of these observations it was of interest to investigate the combined effect of introducing alkyl substituents at the adjacent positions C-16 and -17, and to this end a general reaction for preparing 16α,17α-dialkyl steroids from pregnadienolone acetate (1) is described herein. The course of the reaction and its scope have been investigated along with the nature and genesis of the major by-products.

The formation of 16α,17α-dimethyl steroids has been reported by several groups.[6] Schaub and Weiss [6c] employed a method similar to ours,[6a,b] involving the methylation of a 16α-methyl-17(20)-enolate salt with methyl iodide to elaborate the 16α,17α-dimethyl grouping in some corticosteroid analogues. A Russian group [6d,e] isolated 3β-hydroxy-16α,17α-dimethylpregn-5-en-20-one (2) in low yield from the reaction of 17-cyanoandrosta-5,16-dien-3β-yl acetate with methylmagnesium bromide, and the same compound was isolated [6f] as a minor product upon treatment of a reaction mixture consisting of a 16α-methyl-17(20)-enolate salt and an excess of Grignard reagent with halogen.‡

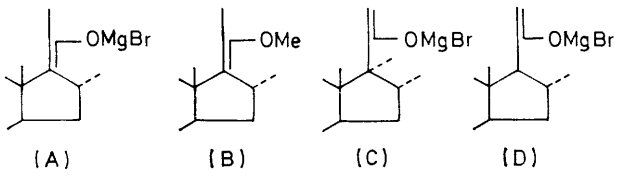
When the biological activity of the 16α,17α-dimethyl steroids was established [6a-c] it became of interest to study the reaction in greater depth, to discover its scope and limitations and to optimise the yield. The reaction is conducted in two stages without isolating the intermediate. The first stage involves the formation of a 17(20)-enolate salt of type (A) by conjugate addition of the Grignard reagent to the Δ^{16}-20-carbonyl grouping, and this is followed by heating with an excess of methyl iodide to complete the reaction. The reaction of methyl Grignard reagent with a Δ^{16}-20-ketone is known [7] to require a copper catalyst for optimal formation of the conjugate addition product. The role of copper in promoting conjugate addition of alkyl groups has been the subject of a recent review.[8] In our hands copper(I) bromide and copper(II) acetate are equally effective so

‡ Excess of methylmagnesium bromide reacted with iodine to give methyl iodide.

[1] H. van der Vies, Organon, Oss, personal communication.
[2] H. H. Gunthard, E. Beriger, C. R. Engel, and H. Heusser, *Helv. Chim. Acta*, 1952, **35**, 2437.
[3] R. Deghenghi, Y. Lefebvre, P. Mitchell, P. F. Morand, and R. Gaudry, *Tetrahedron*, 1963, **19**, 289.
[4] C. R. Engel, *J. Amer. Chem. Soc.*, 1956, **78**, 4727.
[5] C. R. Engel, *Canad. J. Chem.*, 1957, **35**, 131.
[6] (*a*) C. L. Hewett, G. F. Woods, and R. T. Logan, B.P. 1 105 013/1968; U.S.P. 3 520 908/1970; (*b*) G. F. Woods, C. L. Hewett, and W. R. Bucket, Abstracts Third Int. Congr. Horm. Steroids, 1970, Int. Cong. Ser. No. 210, Abstract No. 152; (*c*) R. E. Schaub and M. J. Weiss, *J. Medicin. Chem.*, 1967, **10**, 789; U.S.P. 3 483 236/1969; (*d*) V. I. Maksimov, B. M. Potopov, F. A. Lur'i, A. M. Muchnikova, S. L. Portnova, and L. S. Morozova, *Zhur. obshchei. Khim.*, 1967, **37**, 2651; (*e*) V. I. Maksimov, F. A. Lur'i, and L. A. Morozova, *ibid.*, 1963, **33**, 1666; (*f*) H. Reimann and O. Z. Sarre, *J. Org. Chem.*, 1967, **32**, 2321.
[7] K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1959, **42**, 2043.
[8] G. H. Posner, *Org. Reactions*, 1972, **19**, 1.

far as yield is concerned but the latter is preferable because it gives a cleaner product. We found that with all saturated alkyl Grignard reagents other than methyl, 1,4-addition takes place exclusively even in the absence of a copper catalyst.

Angular alkylation of 17(20)-enolate anions has been reported [9] to give 17α-alkyl derivatives, and as a general

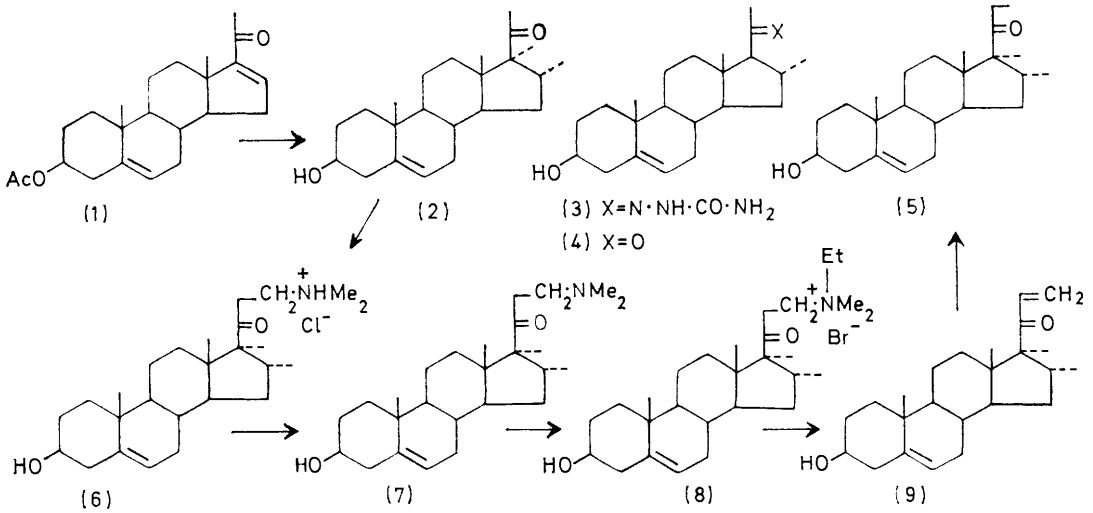


rule attack at C-16 and -17 in the pregnane series takes place from the rear side. It is not surprising therefore that the second methyl group at C-17 assumes the α-configuration. The evidence for this assignment is discussed later. Enolate salts formed from 9α-bromo-11-oxo-steroids by reaction with methyl Grignard reagent also undergo methylation at the angular position (C-9) on treatment with methyl iodide and furnish the 9α-methyl derivatives.[10] Similar reactions in which conjugate addition of a Grignard reagent is followed by α-alkylation of the enolate species have been reported outside the steroid field.[11]

Evidence that the second alkylation takes place exclusively on the enolate (A) or some form of it was provided when the reaction was carried out in the absence of copper catalyst. The yield of dimethylated product was much reduced and corresponded closely to the degree of conjugate addition occurring under these conditions (as deduced from the yield of 16α-methyl product formed when the reaction is worked up without addition of methyl iodide). The stereochemical course of the conjugate addition leading to 16α-substituted products is well established,[12] and the assignment of the 17α-configuration for the second methyl group is based on the following evidence. The signal at δ 0.72 for the 13-methyl protons in the n.m.r. spectrum of (2) is in excellent agreement with the calculated value [13] (δ 0.728). In 17α-acetyl steroids the 13-methyl protons resonate at a lower field (δ *ca.* 0.90—0.85).[14] A positive Cotton effect in the o.r.d. spectrum of (2) also supports the 17β-configuration of the acetyl side-chain.[15]

In order to optimise the reaction conditions it was decided to isolate and identify the main by-products. G.l.c. and t.l.c. did not achieve complete separation of all the components. Later it was found that high-pressure liquid chromatography (h.p.l.c.) effectively separates all except (11) from (2) and provides the best method of following the purification process. All components of the product detectable in more than trace amounts were isolated by a combination of crystallisation, chemical separation, and chromatography. The identity of each was established by physical measurements and, where possible, by unequivocal synthesis.

The fact that every product is alkylated at C-16α provides ample evidence for the high yield and stereospecificity of the conjugate addition reaction. The main by-product (3%) was isolated as the semicarbazone (3) and identified as 3β-hydroxy-16α-methylpregn-5-en-20-one (4). This product was originally thought to arise mainly,



[9] R. Deghenghi, C. Revesz, and R. Gaudry, *J. Medicin. Chem.*, 1963, **6**, 301; M. J. Weiss, R. E. Schaub, G. R. Allen, J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Cosica, *Tetrahedron*, 1964, **20**, 357.

[10] S. Binns, J. S. G. Cox, E. R. H. Jones, and B. Ketcheson, *J. Chem. Soc.*, 1964, 1161; R. E. Beyler, F. Hoffman, L. H. Sarrett, and M. Tishler, *J. Org. Chem.*, 1961, **26**, 2426.

[11] G. Stork, G. L. Nelson, F. Rouesac, and O. Gringore, *J. Amer. Chem. Soc.*, 1971, **93**, 3091; P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, 1973, **38**, 2100; R. K. Boeckman, *ibid.*, p.4550; F. Näf and R. Decoryant, *Helv. Chim. Acta*, 1974, **57**, 1317.

[12] G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooner, D. R. Hoff, and L. H. Sarrett, *J. Amer. Chem. Soc.*, 1958, **80**, 3160.

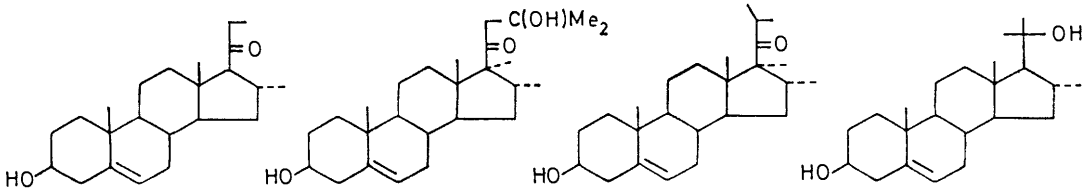
[13] W. Arnold, W. Meister, and G. Englert, *Helv. Chim. Acta*, 1974, **57**, 1559.

[14] J. E. Page, *Ann. Reports N.M.R. Spectroscopy*, 1970, **3**, 149.

[15] W. A. Struck and R. L. Houtman, *J. Org. Chem.*, 1961, **26**, 2883; P. Crabbé, *Tetrahedron*, 1963, **19**, 51.

if not exclusively, from the presence of moisture, possibly introduced with the methyl iodide. Since scrupulous exclusion of moisture failed to eliminate or reduce its formation, a small but constant amount of *O*-methylation probably takes place with the formation of the 20-enol methyl ether (B) which is hydrolysed to (4) during work-up. Despite several attempts, proof for the existence of this enol ether in the reaction mixture was not forthcoming. This also accounts for our failure to improve the 17-alkylation stage by increasing the concentration of methyl iodide or prolonging the reaction.

G.l.c. of the mother liquors after crystallising out most of the 16α,17α-dimethyl derivative (2) revealed two other products (t_R 0.82 and 1.26) in addition to the residues of (2) and (4). The component with t_R 1.26 (3%) was isolated by chromatography on alumina and shown to be 3β-hydroxy-16α,17α,21-trimethylpregn-5-en-20-one (5). N.m.r. was invaluable for establishing the structure of this compound because the characteristic signal for the acetyl side-chain was absent. Signals at δ 0.88 (d, *J* 7 Hz), 1.00 (s), and 1.03 (t, *J* 7 Hz) for the 16α-, 17α-, and 21-methyl groups respectively provided strong evidence for the proposed 16α,17α,21-trimethyl structure (5). This



(10) (11) (12) (13)

was confirmed by independent synthesis from (2) by Mannich condensation to form the 21-dimethylaminomethyl derivative (7); quaternisation to the ethobromide (8); degradation to the 21,21-methylene derivative (9); and finally catalytic reduction to (5).

The product (5) must arise by reaction of the 16α,17α-dimethyl product (2) with the excess of Grignard reagent (acting as base) to form the 20(21)-enolate (C), which is then methylated. This was confirmed by treating (2) with an excess of methylmagnesium bromide in tetrahydrofuran, followed by methyl iodide. Under these conditions it appeared from g.l.c. that along with (5) as the main product a small amount of the 16α,17α,21,21-tetramethyl derivative (12) was also formed. An authentic sample of (12) was then prepared by treating 16α,17α,21-trimethylpregnenolone (5) under the same conditions, working up the product, and repeating the process several times to improve the overall conversion. With the aid of this reference sample it was then possible to detect (12) in the crude dimethylation product.

The fourth product (t_R 0.82) (1%) isolated from the first mother liquors was identified as 3β-hydroxy-16α,21-dimethylpregn-5-en-20-one (10) by comparison with a sample prepared by treating 16α-methylpregnenolone (4) with methylmagnesium bromide and methyl iodide as described above for (2). Also formed in equal yield in this reaction was the 16α,20-dimethyl diol (13). The mother liquors from the dimethylation reaction were then investigated for the presence of the diol (13) but none was detected. We conclude, therefore, that (10) does not arise from 16α-methylpregnenolone by the same process which generates the 16α,17α,21-trimethyl derivative (5) from 16α,17α-dimethylpregnenolone (2). This also provides further indirect evidence for the formation of the 16α-methylpregnenolone (4) from an intermediate enol methyl ether (B), since any 16α-methylpregnenolone formed in the reaction by the ingress of moisture would lead to equal amounts of (10) and the 16α,20-dimethyl diol (13). Isomerisation of the enolate (A), formed initially by conjugate addition of methyl Grignard reagent to the Δ^{16}-20-oxo-grouping to give the enolate (D), would explain the formation of 16α,21-dimethylpregnenolone (10) in the complete absence of the diol (13).

T.l.c. of the first mother liquors revealed a further product (R_F 0.35) which was isolated by column chromatography and identified by mass spectral and n.m.r. evidence as 3β-hydroxy-21-(1-hydroxy-1-methylethyl)-16α,17α-dimethylpregn-5-en-20-one (11). The mass spectral parent ion (*m/e* 402) confirmed the molecular formula as $C_{26}H_{42}O_3$ and the ion at *m/e* 344 (loss of C_3H_6O) demonstrated the presence of the $Me_2C(OH)$ unit. N.m.r. signals at δ 0.87 (d, *J* 7 Hz), 1.02 (s), and 1.21 (6 H, s) were assigned to the methyl groups at positions 16α and 17α and in the $Me_2C(OH)$ substituent. Formation of this product requires the presence of a C_3 unit which can only arise by reaction of methyl Grignard reagent with acetate either from the steroid or from copper(II) acetate.

In an attempt to pin-point the origin of the C_3 unit the general dimethylation reaction was carried out on pregnadienolone with copper(II) acetate as catalyst and on pregnadienolone acetate with copper(I) bromide as catalyst. Only from the latter reaction was the 21-(1-hydroxy-1-methylethyl) derivative (11) detected, showing that the 21-substituent arises from acetate of the steroid.

Since formation of most of the unwanted products could be attributed to the presence of an excess of Grignard reagent, an attempt was made to control the quantity required by titrating a solution of the steroid (1) with methylmagnesium bromide, with phenylazodiphenylamine as indicator.[16] This achieved a slight reduction in the yield of 21-methylated products but did

[16] B. J. Magerlein and W. P. Schneider, *J. Org. Chem.*, 1969, **34**, 1179.

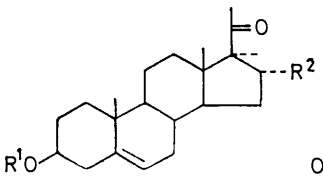
not eliminate them entirely. Attempts to decompose the excess of Grignard reagent with small quantities of ethyl acetate, acetone, or iodine before addition of the methyl iodide were without success. In every case the yield of 16α,17α-dimethylpregnenolone (2) was decreased. Replacement of methyl Grignard reagent by lithium dimethylcuprate was entirely effective, but after further reaction with methyl iodide, the yield and nature of the product was almost the same.

Replacement of methylmagnesium bromide by the appropriate saturated alkyl Grignard reagent in the general procedure furnished the 16α-alkyl-17α-methylpregnenolones (14) and (16)—(18). In every case the course of the reaction was unaffected by the presence or absence of copper catalyst, confirming that conjugate addition took place exclusively. In contrast 16α-phenyl-17α-methylpregnenolone (19) could only be isolated in the absence of catalyst, whereas the corresponding 16α-benzyl derivative (21) required the catalyst for its formation in acceptable yield.

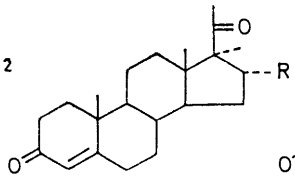
Allylmagnesium bromide on the other hand gave the 1,2-addition product (23) exclusively in the presence or absence of copper catalyst. Parker [17] similarly found that reaction of allylmagnesium bromide or allyllithium with cyclohexenone gave the 1,2-adduct as the sole product in the presence or absence of catalyst. According to House,[18] however, conjugate addition of an allyl group will take place with lithium diallylcuprate.

Although these 16α-substituted 17α-methylpregnenolones are generally formed in good yield, the rate of reaction with methyl iodide at C-17 decreases with increasing bulk of the 16-substituent. Despite a number of attempts to introduce other alkyl groups at C-17 no evidence was forthcoming that even with the 16α-methyl enolate intermediate replacement of methyl iodide by ethyl iodide or any other alkyl iodide would lead to another substituent at C-17.

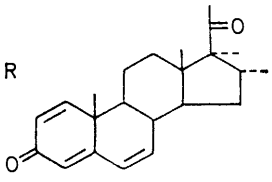
Four of the 16α,17α-disubstituted pregnenolones [(2), (15), (19), and (21)] were converted into the corresponding progesterone derivatives (24)—(27) by Oppenauer oxidation to provide a range of structures for biological investigation. 3β-Hydroxy-16α,17α-dimethylpregn-5-en-20-one (2) was also converted directly into the 1,4,6-triene (28) by treatment with dichlorodicyanobenzoquinone.[19]



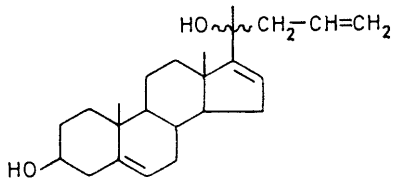
(14) R^1 = Ac, R^2 = Et
(15) R^1 = H, R^2 = Et
(16) R^1 = H, R^2 = Pr^n
(17) R^1 = Ac, R^2 = Pr^i
(18) R^1 = Ac, R^2 = Bu^i
(19) R^1 = H, R^2 = Ph
(20) R^1 = Ac, R^2 = Ph
(21) R^1 = H, R^2 = CH_2Ph
(22) R^1 = Ac, R^2 = CH_2Ph



(24) R = Me
(25) R = Et
(26) R = Ph
(27) R = CH_2Ph



(28)



(23)

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.

General Procedure for Dialkylation Reaction.—Solutions of alkylmagnesium halides were prepared in diethyl ether and the solvent was replaced by tetrahydrofuran by gradual distillation of the ether and addition of tetrahydrofuran until the temperature of the vapour reached 64 °C. The final solution should be *ca.* 1M with respect to Grignard reagent.

A stirred solution of alkylmagnesium halide (3.5 mol. equiv.) in tetrahydrofuran was treated under nitrogen with

[17] W. D. K. Macrossan, J. Martin, W. Parker, and A. B. Penrose, *J. Chem. Soc.* (*C*), 1968, 2323.

[18] H. O. House and W. F. Fischer, *J. Org. Chem.*, 1969, **34**, 3615.

[19] A. B. Turner, *J. Chem. Soc.* (*C*), 1968, 2568.

a solution of dry copper(II) acetate (0.09 mol. equiv.) in dry tetrahydrofuran (10 vol.) with the temperature kept below 20 °C. A solution of the steroid in dry tetrahydrofuran (3.2 vol.) was added over 30 min with the temperature kept at 20—25 °C. The mixture was stirred at room temperature until a sample showed no u.v. absorption at 240 nm (30 min). Dry methyl iodide (5 ml per g of steroid) was added and the mixture was heated to reflux with stirring for 16 h. The excess of methyl iodide was removed by distillation and the cooled mixture was poured into water (20 ml per g of steroid) containing 5% ammonium chloride and 2.5% sodium thiosulphate. The products were isolated by filtration or extraction with ether, and hydrolysis was completed by boiling a stirred solution of the crude product in methanol–tetrahydrofuran (3 : 2) with an excess of 10N-potassium hydroxide. After 1 h the cooled mixture was acidified with acetic acid and poured into water.

3β-*Hydroxy*-16α,17α-*dimethylpregn*-5-*en*-20-*one* (2).—3β-Acetoxypregna-5,16-dien-20-one (1) (470 g), alkylated as described above, gave a crude product which was filtered off, dried, and recrystallised from chloroform–methanol to afford 3β-hydroxy-16α,17α-dimethylpregn-5-en-20-one (2) (358 g), m.p. 192—196°. A pure sample had m.p. 204—207°, H_D^{20} −67.8 (*c* 1.05), *t*– 0.97, $[\theta]_{291.5}$ +6 800 (*c* 0.03% in MeOH) (*cf.* Maksimov *et al.*,[6e] who give m.p. 205—208°, $[\alpha]_D^{20}$ −62.5°).

The mother liquors from the first crop were evaporated to give further material (45 g) shown by g.l.c. to be mainly the 16α,17α-dimethyl compound (2) with an impurity (10%; t_R 0.66). This second crop, in ethanol (450 ml) was boiled under reflux overnight with semicarbazide acetate [from semicarbazide hydrochloride (22.6 g) and sodium acetate (22.6 g)]. The mixture was evaporated to dryness and extracted twice with hot toluene (1 l), and the combined extracts were concentrated and poured onto a short column of silica gel. The fraction eluted with toluene–ethyl acetate (3 : 1) was evaporated and the product was recrystallised from chloroform–methanol to furnish another crop of the 16α,17α-dimethyl compound (2) (26 g). The fraction eluted with chloroform–methanol (1 : 1) was concentrated (100 ml), diluted with methanol (50 ml), and distilled until crystallisation occurred. This gave 3β-hydroxy-16α-methylpregn-5-en-20-one semicarbazone (3) (4.3 g), m.p. 254—260°. A pure sample had m.p. 256—258°, $\lambda_{max.}$ 228 nm (ε 14 556) [lit.,[20] m.p. 245° (decomp.)].

The semicarbazone (3) (4.2 g) was heated under reflux for 2 h with methanol (40 ml) and 10% hydrochloric acid (40 ml). Removal of the methanol *in vacuo* and addition of water (250 ml) gave a solid which was filtered off, washed with water, dried, and recrystallised from methanol to yield 3β-hydroxy-16α-methylpregn-5-en-20-one (4), m.p. 181—185°, $[\alpha]_D$ +1.4 (*c* 1.26 in EtOH) [lit.,[7] m.p. 186—187°, $[\alpha]_D^{26}$ +9 ± 2° (in EtOH)].

The mother liquors from the main dimethylation reaction [total crude less two crops (358 and 45 g)] were examined. G.l.c. analysis detected four components: t_R 0.68 (18%, 16α-monomethyl), 0.82 (9%), 0.97 (63%, 16α,17α-dimethyl), and 1.26 (19%). T.l.c. in toluene–ethyl acetate (1 : 1) showed three spots: R_F 0.35, 0.45 (80%), and 0.51. The component with R_F 0.51, t_R 1.26 was isolated by chromatography on alumina and elution with benzene–ether (19 : 1) and shown to be identical with 3β-hydroxy-16α,17α,21-trimethylpregn-5-en-20-one (5) (see later). The component with R_F 0.35, t_R 0.97 was isolated by chromatography on silica gel and elution with toluene–ethyl acetate (6 : 1). Two recrystallisations from acetone–n-hexane gave 3β-*hydroxy*-21-(1-*hydroxy*-1-*methylethyl*)-16α,17α-*dimethylpregn*-5-*en*-20-*one* (11), m.p. 182—184°, $[\alpha]_D$ −59° (*c* 1.13), $\nu_{max.}$ (CH_2Cl_2) 3 600 (3-OH), 3 490 (side chain OH), and 1 678 cm^{-1} (20-ketone), δ 0.72 (3 H, s, 13-Me), 0.87 (3 H, d, *J* 7 Hz, 16α-Me), 0.98 and 1.02 (6 H, 2 s, 10- and 17-Me), 1.21 (6 H, s, Me_2C), 2.75—3.25 (1 H, m, 16β-H), 3.25—3.80 (1 H, m, 3α-H), 4.41 (1 H, s, OH), and 5.31 (1 H, d, *J* 4 Hz, 6-H) (Found: C, 77.3; H, 10.5. $C_{26}H_{42}O_3$ requires C, 77.6; H, 10.5%).

The component having t_R 0.82 appears to be the 16α,21-dimethyl derivative (10) by comparison (g.l.c. retention time) with an authentic sample (see later). This product could not be separated from the 16α,17α-dimethyl derivative (2) by column or thin-layer chromatography.

3β-*Hydroxy*-16α,17α,21-*trimethylpregn*-5-*en*-20-*one* (5).—3β-Hydroxy-16α,17α-dimethylpregn-5-ene-20-one (2) (25 g) in warm isopentyl alochol (500 ml) was treated with dimethylamine hydrochloride (50 g), paraformaldehyde (15 g), and 2N-hydrochloric acid (1.5 ml). The mixture was refluxed for 2½ h, cooled, treated with more paraformaldehyde (15 g), and heated under reflux for a further 1 h. The oil which separated on cooling was allowed to crystallise. The crystals (8.92 g), m.p. 204—212°, were isolated by filtration, and dried at room temperature (P_2O_5). A second crop (0.98 g), m.p. 198—204°, was obtained by washing the filtrate with saturated salt solution, concentrating the extract, and precipitating the product as a white solid with ether. The total product was stirred with methylene chloride (100 ml) for 30 min, filtered off, and washed with methylene chloride to give 3β-*hydroxy*-21-*dimethylaminomethyl*-16α,17α-*dimethylpregn*-5-*en*-20-*one hydrochloride* (6) (8.9 g), m.p. 222—232°, $\nu_{max.}$ (KCl) 3 230 (3-OH), 3 015 (6-H), 2 400—2 660 (several peaks) (tertiary amine salt), and 1 690 cm^{-1} (20-ketone) (Found: C, 71.0; H, 10.0; Cl, 7.9; N, 2.9. $C_{26}H_{44}ClNO_2$ requires C, 71.3; H, 10.1; Cl, 8.1; N, 3.2%).

The hydrochloride (6) (8.8 g) suspended in ether (900 ml) and methylene chloride (150 ml) was shaken for 40 min with N-potassium hydroxide (450 ml). The organic layer was separated, washed, dried, and evaporated to give the *amine* (7) (7.95 g), m.p. 130—148°, $\nu_{max.}$ (KCl) 3 100 (3-OH) and 1 687 cm^{-1} (20-ketone) (Found: M^+, 401.3281. $C_{26}H_{43}NO_2$ requires *M*, 401.3294).

The amine (7) (7.9 g) in methylene chloride (90 ml) was treated with ethyl bromide (18 ml) at room temperature overnight. The precipitated solid was filtered off, washed with methylene chloride, and dried *in vacuo* to give the *ethobromide* (8) (8.9 g), m.p. 242—248°, $\nu_{max.}$ (KCl) 3 300 (3-OH), 3 010 (6-H), and 1 695 cm^{-1} (20-ketone).

The ethobromide (8) (8.8 g) was dissolved in propan-2-ol–water (3 : 1; 2 l) and treated with saturated aqueous potassium carbonate (115 ml) to give a fine precipitate which was extracted into ether (500 ml). The extracts were washed, dried, and evaporated to give the 21-*methylene compound* (9) (6.4 g), m.p. 153—163°, $\lambda_{max.}$ 218 nm (ε 7 720), $\nu_{max.}$ (KCl) 3 300br (3-OH), 1 678 (20-ketone), and 1 606 cm^{-1} (C:CH_2) (Found: M^+, 356.2713. $C_{24}H_{36}O_2$ requires *M*, 356.2715).

The 21-methylene compound (9) (6.4 g) in propan-2-ol (320 ml) was hydrogenated over 10% palladium–charcoal (0.7 g) for 30 min. After removal of the catalyst, water (1 l) was added and the fine solid precipitated was extracted into methylene chloride (2 × 280 ml). The washed and

[20] R. E. Marker and H. M. Crooks, *J. Amer. Chem. Soc.*, 1942, **64**, 1280.

dried extract was run on to a short column of silica gel and washed through with methylene chloride (1 l). Evaporation of the total eluate and two crystallisations of the residue (6 g) from acetone–n-hexane gave 3β-*hydroxy*-16α,17α,21-*trimethylpregn*-5-*en*-20-*one* (5) (3.38 g), m.p. 174—178°, $[\alpha]_D$ −63.3° (*c* 1.1), R_F 0.45, t_R 1.26, $\nu_{max.}$ (CH_2Cl_2) 3 600 (3-OH) and 1 694 cm^{-1} (20-ketone), δ 0.68 (3 H, s, 13-Me), 0.88 (3 H, d, *J* 7 Hz, 16α-Me), 1.03 (3 H, t, *J* 7 Hz, 21-Me), 1.00 and 1.04 (6 H, 2 s, 10- and 17-Me), 2.73—3.33 (1 H, m, 16β-H), 3.33—3.82 (1 H, m, 3α-H), and 5.35 (1 H, d, *J* 4 Hz, 6-H) (Found: C, 80.7; H, 10.7. $C_{24}H_{38}O_2$ requires C, 80.4; H, 10.7%).

Treatment of 3β-*Hydroxy*-16α,17α-*dimethylpregn*-5-*en*-20-*one* (2) *with Methylmagnesium Bromide–Methyl Iodide*.—3β-Hydroxy-16α,17α-dimethylpregn-5-en-20-one (2) (4 g) was added to methylmagnesium bromide [from magnesium (2 g)] in tetrahydrofuran (50 ml). Methyl iodide (20 ml) was added and the mixture refluxed under nitrogen for 16 h. G.l.c. showed the product to be a mixture of starting material (2) (50%), the 16α,17α,21-trimethyl derivative (5) (40%), and a third component (10%) thought to be the 16α,17α,21,21-tetramethyl derivative (12) (see later) but which was not isolated.

3β-*Hydroxy*-16α,17α,21,21-*tetramethylpregn*-5-*en*-20-*one* (12).— 3β-Hydroxy-16α,17α,21-trimethylpregn-5-en-20-one (5) (2 g) in tetrahydrofuran (50 ml) was treated with methylmagnesium bromide [from magnesium (2 g)] followed by methyl iodide (20 ml) under the conditions of the dialkylation reaction. G.l.c. of the product detected two components: starting material (t_R 1.18; 90%) and a slower running component (t_R 1.33; 10%). This treatment was repeated seven times to give a final product (1.92 g) which contained 85% of the slower running component. Chromatography on silica gel (50 g) (elution with benzene) gave 3β-*hydroxy*-16α,17α,21,21-*tetramethylpregn*-5-*en*-20-*one* (12) (1.24 g). A sample purified from acetone–ether had m.p. 151—166°, $[\alpha]_D$ −40.3° (*c* 1.16), t_R 1.34, $\nu_{max.}$ (CH_2Cl_2) 3 610 (3 OH) and 1 697 cm^{-1} (20 ketone), δ 0.68 (3 H, s, 13-Me), 0.83 (3 H, d, *J* 7 Hz, 16α-Me), 0.98 (3 H, s, 17α-Me), 1.01 (6 H, d, *J* 7 Hz, Me_2C), 1.06 (3 H, s, 10-Me), 2.70—3.33 (2 H, m, 16β- and 21-H), 3.33—3.87 (1 H, m, 3α-H), and 5.38 (1 H, d, *J* 4 Hz, 6-H) (Found: C, 80.5; H, 10.6. $C_{25}H_{40}O_2$ requires C, 80.6; H, 10.8%).

Treatment of 3β-*Hydroxy*-16α-*methylpregn*-5-*en*-20-*one* (4) *with Methylmagnesium Bromide–Methyl Iodide*.—The 16α-methyl derivative (4) (5 g) in tetrahydrofuran (100 ml) was treated under the dimethylation conditions described above. The crude product (5 g) was treated with Girard P reagent (2 g) in ethanol (50 ml) containing acetic acid (5 ml) to remove 20% starting material as the water-soluble derivative. The product (4 g) was isolated by addition of water (200 ml) and filtration. Chromatography on silica gel (80 g) (elution with 2% ether in benzene) gave 3β-*hydroxy*-16α,21-*dimethylpregn*-5-*en*-20-*one* (10) (1.1 g), which after four recrystallisations from methanol had m.p. 174—178°, $[\alpha]_D$ +5.1° (*c* 1.0), t_R 0.82, $\nu_{max.}$ (CH_2Cl_2) 3 610 (3-OH) and 1 701 cm^{-1} (20 ketone), δ 0.63 (3 H, s, 13-Me), 0.92 (3 H, d, *J* 7 Hz, 16α-Me) 0.98 (3 H, s, 10-Me), 1.02 (3 H, t, *J* 7 Hz, 21-Me), 2.22 (2 H, q, *J* 7 Hz, 21-H_2), 2.22—3.08 (1 H, m, 16β-H), 3.18—3.93 (1 H, m, 3α-H), and 5.35 (1 H, d, *J* 4 Hz, 6-H) (Found: C, 80.2; H, 10.7. $C_{23}H_{36}O_2$ requires C, 80.2; H, 10.5%). Further elution with the same solvent gave 16α,20-*dimethylpregn*-5-*ene*-3β,20-*diol* (13) (1 g), which after one recrystallisation from acetone–n-hexane had m.p. 162—166°, $[\alpha]_D$ −67.8° (*c* 1.0), t_R 0.90, $\nu_{max.}$ 3 610 cm^{-1} (3- and 20-OH), δ 0.86 (3 H, s, 13-Me), 0.99 (3 H, s, 10-Me), 1.10 (3 H, d, *J* 7 Hz, 16α-Me), 1.25 (3 H, s, 20-Me), 1.30 (3 H, s, 20-Me), 1.63 (2 H, s, 3- and 20-OH), 3.18—3.80 (1 H, m, 3α-H), and 5.36 (1 H, d, *J* 4 Hz, 6-H) (Found: C, 80.0; H, 11.2. $C_{23}H_{38}O_2$ requires C, 79.7; H, 11.05%).

16α-*Substituted* 17α-*Methylpregnenolones* (*Table* 1).—3β-Acetoxypregna-5,16-diene-20-one (1) was treated with the appropriate Grignard reagent followed by methyl iodide under the general dialkylation conditions, but without the addition of copper salt [except in the case of the 16α-benzyl derivative (21)]. The product always contained some of the corresponding 16α-monoalkyl compound, which could be removed as the water-soluble Girard P derivative. The products were purified by crystallisation of the free hydroxy-compound or the acetate.

TABLE 1

Compd.	Yield (%)	M.p. (°C)	$[\alpha]_D$ (°) (*c*, %)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
(14)	49	156—158 *a*	−73.2 (1.0)	77.8	10.1	77.95	10.1
(16)	45	142—145 *b*	−70 (1.4)	80.8	10.85	80.6	10.8
(17)	35	171—175 *b*	−39 (2.0)	77.9	10.4	78.2	10.2
(18)	53	154.5—157 *b*	−76 (2.0)	78.7	10.6	78.45	10.35
(19)	38	197—200 *c*	+11.3 (1.0)	82.6	9.3	82.7	9.4
(20)		202—206 *b*	+2 (1.1)	80.3	9.0	80.3	9.0
(21)	43	200—202 *b*	−76.7 (1.0)	82.9	9.6	82.8	9.6
(22)		205—210 *c*	−78.5 (1.0)	80.35	9.3	80.5	9.15

a From MeOH. *b* From CH_2Cl_2–MeOH. *c* From Me_2CO–hexane.

Representative Oppenauer Oxidation.—3β-Hydroxy-16α,-17α-dimethylpregn-5-en-20-one (2) (30 g) in toluene (300 ml) and cyclohexanone (150 ml) was treated with aluminium isopropoxide (15 g) in toluene (75 ml). The mixture was heated under reflux for 45 min, cooled, treated with Rochelle salt (60 g), then steam-distilled until the distillate was clear. The product was filtered off, washed, and dried *in vacuo* to give, after three recrystallisations from acetone–n-hexane, 16α,17α-dimethylpregn-4-ene-3,20-dione (24) (22.75 g).

16α-*Substituted* 17α-*Methylprogesterones* (*Table* 2).—The 16α-substituted 17α-methyl progesterones were prepared from the corresponding pregnenolones by Oppenauer oxidation as described above.

TABLE 2

Compd.	Yield (%)	M.p. (°C)	[α] (°) (*c*)	λmax./nm(ε)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
(24)	76	160—162 *a*	+86.3 *a* (1.04)	240 (15 500)				
(25)	92	146 5—147.5 *b*	+62.5 (0.96)	240 (17 050)	80.6	9.9	80.85	10.2
(26)	78	257—260 *c*	+97.5 (1.0)	240 (16 970)	82.9	9.0	83.1	9.0
(27)	64	230—234 *c*	−9.63 (1.0)	242 (17 680)	83.2	9.1	83.2	9.15

a From Me_2CO–hexane; *cf.* Maksimov *et al.* [9c] who give m.p. 160—161.5, $[\alpha]_D$ + 84.8°. *b* From Et_2O. *c* From CH_2Cl_2–MeOH.

16α,17α-*Dimethylpregna*-1,4,6-*triene*-3,20-*dione* (28).—The 16α,17α-dimethyl compound (2) (5 g) was treated with dichlorodicyanobenzoquinone (10.89 g) in boiling toluene for 16 h. The cooled mixture was filtered and the filtrate diluted with ether (100 ml). The solution was washed with N-sodium hydroxide and water, then dried and evaporated. Crystallisation of the residue from ether–n-hexane gave starting material (0.92 g), and the contents of the mother liquors were chromatographed in benzene–petroleum (b.p. 60—80°) on acid-washed alumina (25 g). Elution with benzene–petroleum (b.p. 60—80°) gave a solid (2 g) which was further purified by crystallisation from ether and passage through a short column of alumina (10 g) in cyclohexane. Two crystallisations from ether–hexane then gave 16α,17α dimethylpregna-1,4,6-triene-3,20-dione (28) (1.1 g),

m.p. 139—141°, $[\alpha]_D$ −7.1° (*c* 1.0) (*cf.* Morozova *et al.*,[21] who give m.p. 141—142°, $[\alpha]_D$ −7.3°).

[21] L. S. Morozova, F. A. Lur'i, and V. I. Maksimov, *Khim-Farm. Zhur.*, 1972, **6**, 5.

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