Alkylated Steroids. Part 4.[1] An Unusual Favorskii Rearrangement[2]

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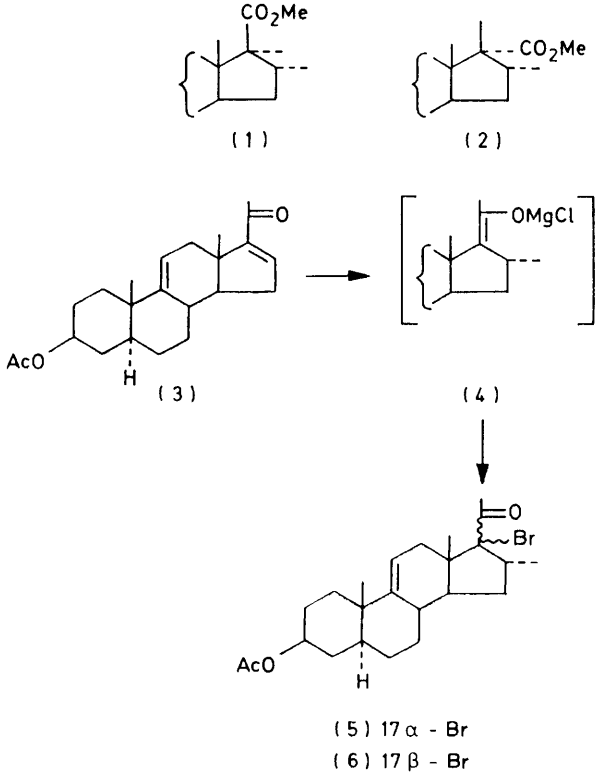
Favorskii rearrangement of the mixed 17ξ-bromo-16α-methyl-20-oxo-5α-pregn-9(11)-en-3β-yl acetates (5) and (6) (9 : 1) gives methyl 3β-hydroxy-16α,17α-dimethyl-5α-androst-9(11)-ene-17-carboxylate (7) and methyl 3β-hydroxy-16α-methyl-5α-pregn-9(11)-en-21-oate (9) as the major components. Only a small amount of the isomeric 16α,17β-dimethyl-17-carboxylate (8) is formed. The structures of the esters (7) and (9) are confirmed by synthesis, and an explanation for the unexpected formation of (9) is advanced.

THE Favorskii rearrangement of 17-bromo-20-oxo-pregnanes with methanolic base has been performed on a variety of substrates.[3-9] In all cases, the structure of the major product was formulated as a 17α-methyletianic ester. Generally, the corresponding 17β-methyl-17α-etianate was not identified, or was present in a small amount, although, in one instance[7] this isomer constituted 40% of the product. In connection with our work on 16α,17α-dimethylpregnanes,[10] we desired samples of 16α,17-dimethyletianates of types (1) and (2). We considered that the Favorskii rearrangement of the bromo-compound (5) under the conditions used by Wendler *et al.*[7] would afford a reasonable route to these compounds.



The 17-bromo-20-oxo starting material (5) was prepared from the diene (3) *via* the Grignard enolate (4) by a known route.[11,12] Minor impurities were removed by preparative h.p.l.c. to give the mixture of bromo-compounds (5) and (6) in a 9 : 1 ratio[11] (as measured by the relative heights of peaks due to the acetyl side-chains in the ^{1}H n.m.r. spectrum, and peak areas in the h.p.l.c. trace). An attempt to purify the 17α-bromo-isomer (5) by crystallisation from methanol resulted in enrichment of the 17β-bromo-isomer (6) in the crystals. A pure sample of the 17α-bromo-compound (5) was obtained by preparative h.p.l.c.

Favorskii reaction[7] on the mixed bromo-compounds (5) and (6) (9 : 1) followed by hydrolysis of the acetate group and re-esterification gave a product consisting of four components (g.l.c.) (see Table). Treatment of this

TABLE

Products formed in Favorskii Rearrangement

Starting material Solvent		(5) + (6) 9 : 1 MeOH	Pure (5) MeOH	Pure (5) MeO[CH$_2$]$_2$OMe
Product	Relative[a] retention	% Products (g.l.c.)		
Unknown	0.53			6.4
A(8)	1.0	6.9	6.5	8.3
B(7)	2.0	40.7	32.4	10.3
C(9)	2.33	49.0	51.0	70.0
D(25)	2.67	3.4	9.9	2.6

[a] Relative to cholestane on OV 210 at 230 °C.

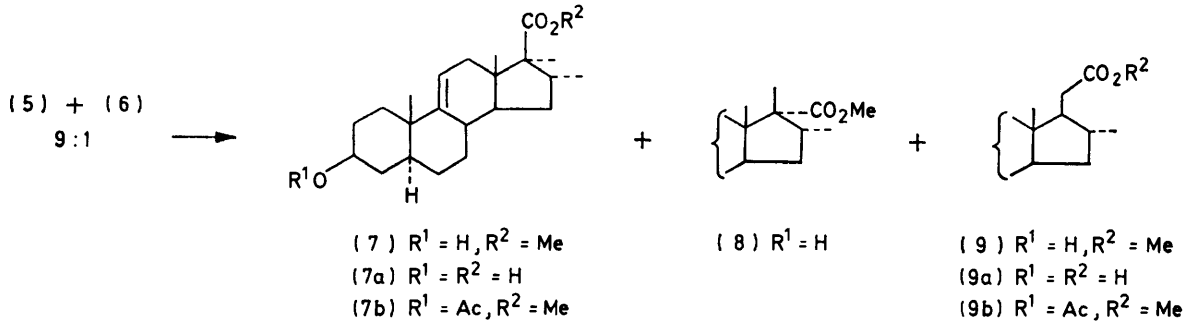
mixture with potassium hydroxide in methanol under reflux gave a neutral and an acidic fraction. Crystallisation of the neutral fraction [containing components A and B (g.l.c.)] gave component B which had an n.m.r. spectrum consistent with structure (7) or (8). Further, the mass spectrum displayed a stable parent ion at *m/e* 360 and a major fragmentation attributable to loss of $C_2H_3O_2$ (the carboxymethyl group). The assignment of structure (7) or (8) to component B is consistent with the known resistance to hydrolysis of 17β-methyletianic esters.[6,13]

Conclusive evidence that component B is the 17α-methyletianic ester (7) came from its synthesis. Thus, the 16α,17α-dimethylpregnenolone (10)[10] was converted *via* the 21-bromo- (11) and 21-acetoxy- (12) derivatives to the hydroxyketone (13). Side-chain cleavage with periodic acid gave the acid (7a), esterified to the etianic ester (7), identical with component B of the Favorskii reaction product.

A sample of the neutral fraction, enriched in component A (30%), showed by g.l.c.–mass spectrometry that component A was isomeric with component B (7), and displayed a similar breakdown pattern in the mass

spectrum. In view of this, and its resistance to hydrolysis, component A was tentatively assigned the 17β-methyletianate structure (8).

Crystallisation of the acidic fraction and re-esterification with diazomethane gave component C. The main evidence for the assignment of structure (9) to this material came from the proton n.m.r. spectrum which displayed a distorted doublet (non-first order) at δ 2.8 (*J* 6.5 Hz) attributable to the C-20 protons. Also, the ^{13}C n.m.r. spectrum was consistent with the proposed structure (9).

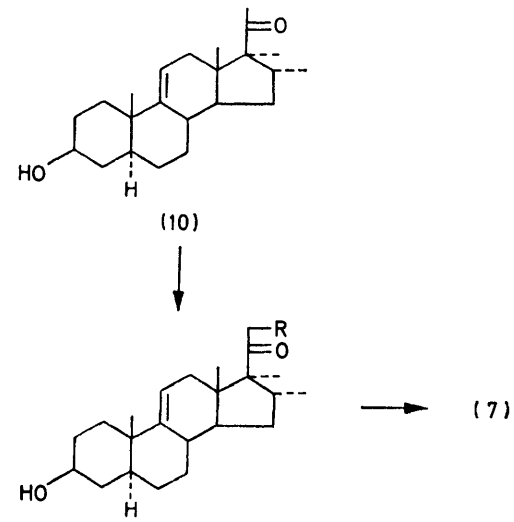


(7) $R^1 = H, R^2 = Me$
(7a) $R^1 = R^2 = H$
(7b) $R^1 = Ac, R^2 = Me$

(8) $R^1 = H$

(9) $R^1 = H, R^2 = Me$
(9a) $R^1 = R^2 = H$
(9b) $R^1 = Ac, R^2 = Me$

Confirmation that component C had structure (9) came from its conversion into a derivative (18) also prepared from the diene (3). Thus ester (9), as its tetrahydropyranyl ether (14), was reduced to the 21-hydroxy-compound (15), and hence converted *via* the toluene-*p*-sulphonate (16) into the 21-iodide (17), which was reduced with zinc–acetic acid to (18). The same compound (18)



(11) R = Br
(12) R = OAc
(13) R = OH

was prepared from the oxopregnadienyl acetate (3) by a 1,4-Grignard reaction to give (19) followed by Wolff–Kishner reduction of the 20-ketone. Component D was hydrolysed by the treatment with potassium hydroxide in methanol, and could be regenerated from the acidic fraction by diazomethane, but was only obtained as a mixture with component C. Although there is no direct evidence for the structure of component D, it is a readily hydrolysed ester, and is probably the 17α-isomer (25) of component C.

The polarity of the solvent used in the Favorskii rearrangement has an important influence on the products formed.[14,15] In particular, it has been suggested [15] that the reaction is stereospecific in non-polar solvents, and non-stereospecific in polar solvents. In an effort to gain additional evidence which would assist in determining the mechanism of formation of ester (9), pure samples of the 17α-bromo-20-ketone (5) (from preparative h.p.l.c.) were treated with sodium methoxide in methanol and in dimethoxyethane. The result was a considerable increase in the amount of the ester (9) at the expense of the etianate (7) in the reaction carried out in the non-polar solvent (see Table).

The mechanism of the Favorskii reaction is generally discussed in terms of the Aston [16]–Dewar [17] zwitterionic non-synchronous version of the Loftfield [18] cyclopropanone mechanism. The nature of the solvent,[14,15] the halide used,[19] and steric factors [20] are known to influence the structure of the products formed.

The rearrangement of the mixture of (5) and (6) (9 : 1) in methanol (see Table) will be considered first. From the known configuration of the major 17-bromo-isomer (5), the synchronous cyclopropanone mechanism would give mainly (23). However, an examination of the two major products (7) and (9) in which there has been retention of side-chain configuration, reveals that both products could not be formed from the same cyclopropanone. This leads to the conclusion that an equilibration process, such as zwitterion (22) formation, must be invoked, resulting in the generation of the isomeric cyclopropanone (24).

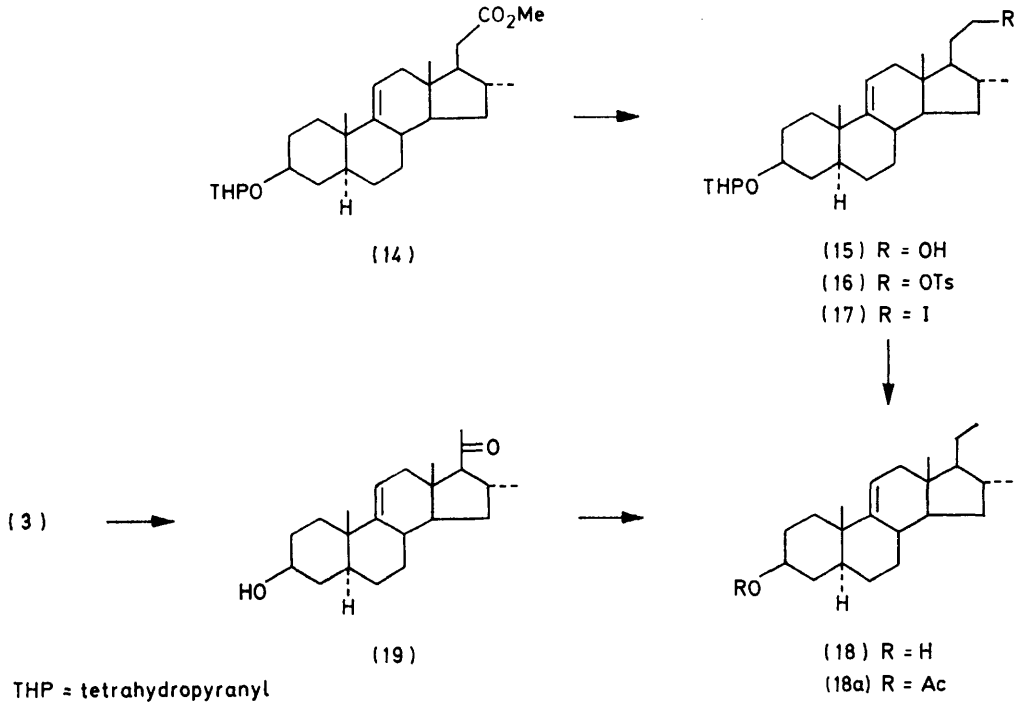
No attempt was made to determine whether (23) is formed by a synchronous attack from (20) or *via* the zwitterion (22). Certainly, the methylene group of the cyclopropanone in (24) is much less subjected to steric interactions with the 13-methyl group than that in (23), and this is a point in favour of (24) being the main product of cyclisation of the zwitterion (22). Thus it appears that both the synchronous [giving mainly (23)] and zwitterionic [giving mainly (24)] mechanisms are involved.

The preponderance of (9) in the reaction performed in

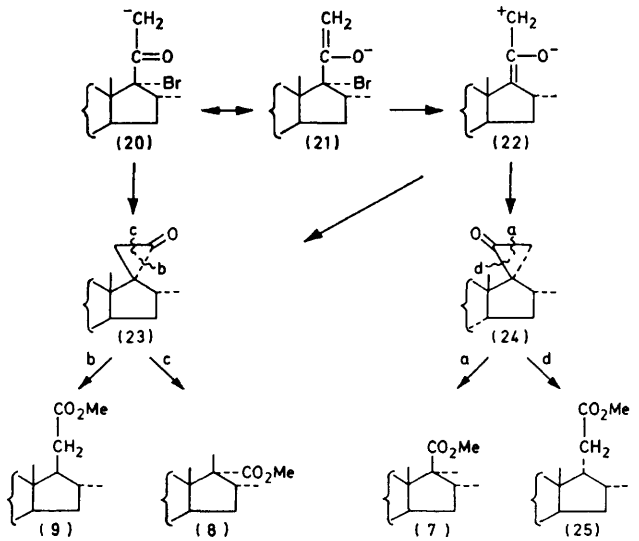
dimethoxyethane (see Table) suggests that the synchronous mechanism (20) ⟶ (23) is favoured in this case.[9] Certainly, there is a marked reduction in the formation of components B(7) and D(25) derived from cyclopropanone (24).

Thus the formation of (9) in preference to the 17β-methyletianate (8) appears to be the result of the additional steric compression on the cyclopropanone (23) from the presence of the 16α-methyl group.

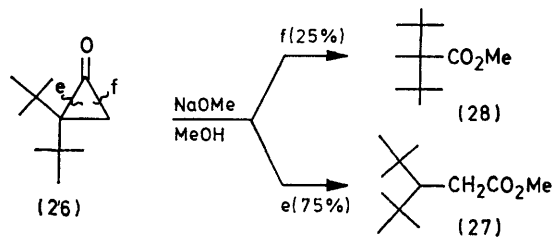
The formation of the two minor products, postulated as (8) and (25), can be envisaged as occurring *via* cleavage ' c ' of (23) and cleavage ' d ' of (24) respectively.



Attack by methoxide ion on the C-20,21 bond in (24) resulting in cleavage ' a ' gives rise to the expected product (7). That attack by methoxide ion on (23) causes cleavage ' b ' of the C-17,20 bond to give (9) may be due to the relief from steric interactions which results.



This view is supported by the cleavage of 2,2-di-t-butylcyclopropanone (26) with methoxide,[20] in which the predominant product (27) is derived from the cleavage ' e ' of the more highly congested bond.



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 unless otherwise stated. G.l.c. was performed with a Hewlett-Packard 5720 chromatograph and quoted retention times are relative to cholestane (R_t 1.0 on OV210 at 230 °C). ^1H N.m.r. spectra were recorded at 60 MHz with Perkin-Elmer R12B, and at 100 MHz with Varian Associates XL-100A-12FT spectrometers. Solutions of products were dried over anhydrous magnesium sulphate.

17α-Bromo-16α-methyl-20-oxo-5α-pregn-9(11)-en-3β-yl Acetate (5).—20-Oxo-5α-pregna-9(11),16-dien-3β-yl acetate (3) was converted into a mixture of the 17-bromo-isomers (5) and (6) (9 : 1) by a known method.[11] A pure sample of the 17α-bromo-derivative, isolated by preparative h.p.l.c. (Waters Associates System 500 h.p.l.c. instrument), had

m.p. 134—139 °C; $[\alpha]_D$ −96.8° (*c* 1.29 in dioxan); $\nu_{max.}$ (CH_2Cl_2) 1 725 (3-acetate) and 1 698 cm^{-1} (20-ketone); δ ($CDCl_3$) 0.75 (3 H, s, 13-Me), 0.93 (3 H, s, 10-Me), 1.06 (3 H, d, *J* 7 Hz, 16α-Me), 1.98 (3 H, s, OAc), 2.31 (3 H, s, COMe), 2.9 (1 H, m, 16β-H), 4.6 (1 H, m, 3α-H), and 5.28 (1 H, m, 11-H) {lit.,[11] m.p. 136—138 °C, $[\alpha]_D$ −82.5° (dioxan)}.

Favorskii Rearrangement of the Mixture of 17-*Bromo-compounds* (5) *and* (6) (9 : 1).—The mixture of 17-bromo-isomers (5) and (6) (9 : 1) (5 g) was added to a solution of sodium methoxide [from sodium (5 g) in methanol (150 ml)]. The resulting mixture was stirred and boiled under nitrogen for 2 h, then evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with water until neutral, dried, and evaporated to dryness. The combined aqueous washings were acidified (5M-HCl) and extracted with ethyl acetate. The organic extracts were washed with water, dried, combined with the product from the original extract, and evaporated to dryness. T.l.c. indicated incomplete hydrolysis of the 3-acetate, and the presence of acidic material. The crude product was dissolved in a saturated solution of potassium carbonate in methanol (100 ml) and left overnight at room temperature. The solution was acidified (5M-HCl), diluted to 600 ml with water, and the product extracted into ethyl acetate. The extracts were washed with water, dried, filtered, and evaporated to dryness. The resulting solid was dissolved in dichloromethane (250 ml) containing methanol (25 ml), and the solution was treated at room temperature with an excess of ethereal diazomethane. After 15 min the excess of diazomethane was destroyed by the addition of acetic acid (10% solution in dichloromethane) and the solution was evaporated to dryness. The residue was dissolved in toluene–ethyl acetate (2 : 1 v/v) and filtered through a layer of silica (3 × 1 in) to remove polar impurities. Evaporation of the filtrate gave a partially crystalline gum (4.05 g). G.l.c. showed the presence of four components: A, B, C, and D (see Table).

Hydrolysis of the Crude Product from the Favorskii Reaction.—A portion (2.6 g) of the crude product from the Favorskii reaction was dissolved in methanol (25 ml) and treated under nitrogen with potassium hydroxide (4 ml; 10M). The resulting suspension was stirred and refluxed for 3 h then cooled to room temperature. The precipitated solid was filtered off, washed with ethyl acetate, then water, and dried. This product was shown to be unhydrolysed ester (t.l.c.) containing a trace of acidic material. The filtrate was diluted with more water (150 ml) and the organic layer was separated, dried, and added to the solid material obtained from the reaction. The combined neutral products were dissolved in ethyl acetate (150 ml) containing dichloromethane (25 ml) and methanol (5 ml), and the solution was extracted with base (5% sodium carbonate solution), then washed with water, dried, and evaporated under reduced pressure. This neutral product (0.95 g) contained components A and B of the original Favorskii reaction (g.l.c.). The combined aqueous washings from the above isolation procedure were acidified (2M-HCl) and the precipitated material was filtered off and dried to give an acidic product (1.17 g).

Examination of the Neutral Product from the Hydrolysis Reaction.—The neutral product (0.95 g) from the hydrolysis reaction was crystallised from methanol–ethyl acetate then acetone–n-hexane to give *methyl* 3β-*hydroxy*-16α,17α-*dimethyl*-5α-*androst*-9(11)-*ene*-17-*carboxylate* (7) (component B), m.p. 152—157 °C; $[\alpha]_D$ −19.7° (*c*, 0.94); R_t 2.0; $\nu_{max.}$ (CH_2Cl_2) 3 680, 3 610 (hydroxy), and 1 724 cm^{-1} (ester); δ ($CDCl_3$ + 2 drops CD_3OD) 0.69 (3 H, s, 13-Me), 0.95 (3 H, s, 17-Me), 0.99 (3 H, d, *J* 7 Hz, 16α-Me), 1.06 (3 H, s, 10-Me), 3.66 (3 H, s, CO_2Me), 2.80 (1 H, m, 16β-H), 3.55 (1 H, m, 3α-H), and 5.37 (1 H, m, 11-H) (Found: C, 74.8; H, 10.2; H_2O, 1% (Karl Fischer). $C_{23}H_{36}O_3 \cdot \frac{1}{2}H_2O$ requires C, 74.8; H, 10.1%). This material was identical to a sample of the authentic ester (7) (see below).

Treatment of (7) with acetic anhydride–pyridine gave the 3-*acetate* (7b) (from aqueous acetone), m.p. 135—139 °C; $[\alpha]_D$ −23° (*c*, 1.01); $\nu_{max.}$ 1 724 (3-acetate and 17-ester), and 1 245 cm^{-1} (3-acetate); δ ($CDCl_3$) 0.68 (3 H, s, 13-Me), 0.94 (3 H, s, 17-Me), 0.97 (3 H, d, *J* 7 Hz, 16α-Me, 1.04 (3 H, s, 10-Me), 2.01 (3 H, s, OAc), 2.88 (1 H, m, 16β-H), 3.66 (3 H, s, CO_2Me), 4.69 (1 H, m, 3α-H), and 5.37 (1 H, m, 11-H) (Found: C, 74.9; H, 9.5. $C_{25}H_{38}O_4$ requires C, 74.6; H, 9.5%). An attempt to obtain a sample of component A by preparative h.p.l.c. gave a fraction containing 70% component B and 30% component A. G.l.c.–mass spectrometry of this fraction displayed a molecular ion and a breakdown pattern for component A which was almost identical with the mass spectrum of component B.

Examination of the Acidic Product from the Hydrolysis Reaction.—Crystallisation of the acidic product (1.17 g) from the hydrolysis reaction from methanol gave 3β-*hydroxy*-16α-*methyl*-5α-*pregn*-9(11)-*en*-21-*oic acid* (9a), m.p. 249—250 °C; $[\alpha]_D$ −18.0° [*c*, 0.98 in $CHCl_3$–MeOH (1 : 1)]; $\nu_{max.}$ (KCl) a series of broad bands 3420–2 550 (3-hydroxy and carboxylic acid), and 1 690 cm^{-1} (carboxylic acid); δ ($CDCl_3$ + 2 drops CD_3OD) 0.62 (3 H, s, 13-Me), 0.95 (3 H, s, 10-Me), 1.03 (3 H, d, *J* 7 Hz, 16α-Me), 2.27 (2 H, distorted d, *J* 6.5 Hz, 20-CH_2), 3.58 (1 H, m, 3α-H), and 5.28 (1 H, m, 11-H) (Found: C, 77.0; H, 9.8. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%).

Esterification with diazomethane in ether gave the *methyl ester* (9) (component C), m.p. 124—125 °C; $[\alpha]_D$ −19.6° (*c*, 1.4); R_t 2.33; $\nu_{max.}$ (CH_2Cl_2) 3 600 (3-hydroxy), 3 040 (11-H), and 1 728 cm^{-1} (ester); δ ($CDCl_3$) 0.62 (3 H, s, 13-Me), 0.95 (3 H, s, 10-Me), 0.99 (3 H, d, *J* 7 Hz, 16α-Me), 2.28 (2 H, distorted d, *J* 6.5 Hz, 20-CH_2), 3.5 (1 H, m, 3α-H), 3.64 (3 H, s, CO_2Me), and 5.26 (1 H, m, 11-H) (Found: C, 76.6; H, 10.1. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%).

Methyl 3β-*Acetoxy*-16α-*methyl*-5α-*pregn*-9(11)-*en*-21-*oate* (9b).—Treatment of the ester (9) (0.35 g) with acetic anhydride (3 ml) in pyridine (3 ml) gave the *acetate* (9b) (0.25 g), m.p. 102—103 °C from ether–n-hexane, $[\alpha]_D$ −18° (*c*, 1.14), R_t 1.28; $\nu_{max.}$ (CH_2Cl_2) 3 050 (olefinic H) and 1 728 (3-acetate and 21-ester); δ ($CDCl_3$) 0.60 (3 H, s, 13-Me), 0.92 (3 H, s, 10-Me), 0.95 (3 H, d, *J* 6 Hz, 16α-Me), 2.0 (3 H, s, OAc), 2.26 (2 H, d, *J* 7 Hz, 20-CH_2), 3.62 (3 H, s, CO_2Me), 4.72 (1 H, m, 3α-H), and 5.3 (1 H, m, 11-H) (Found: C, 74.75; H, 9.4. $C_{25}H_{38}O_4$ requires C, 74.6; H, 9.5%).

21-*Bromo*-3β-*hydroxy*-16α,17α-*dimethyl*-5α-*pregn*-9(11)-*en*-20-*one* (11).—3β-Hydroxy-16α,17α-dimethyl-5α-pregn-9(11)-en-20-one [10] (10) (3.37 g) as a solution in dry tetrahydrofuran (THF) (68 ml) was treated with copper(II) bromide (5.64 g) and the stirred solution was refluxed for 16 h. The reaction mixture was cooled and filtered to remove copper(I) bromide and the filtrate was diluted with water. The resulting gum was extracted into ether and the ether extracts were washed with water, dried, and evaporated to give the product (11) as a gum (*cf.* Schaub and Weiss [21] who obtained an amorphous solid *via* the 21-ethoxalyl derivative).

3β,21-*Dihydroxy*-16α,17α-*dimethyl*-5α-*pregn*-9(11)-*en*-20-

one (13).—The bromo-compound (11), prepared as described above, was dissolved in dimethylformamide (DMF) (50 ml) and treated with sodium acetate (6 g). The mixture was refluxed under nitrogen for 1½ h, then cooled and poured into water. The resulting brown solid (12) was filtered off, dried, and dissolved in methanol (50 ml) saturated with potassium carbonate. After 1½ h at room temperature the reaction was neutralised (2M-HCl), diluted with water (250 ml), and the brown product was filtered off. Preparative h.p.l.c. and crystallisation from dichloromethane–methanol gave the *diol* (13) (1.1 g) m.p. 190—193 °C; $[\alpha]_D$ −27.4° (*c*, 1.2); $\nu_{max.}$ (CH_2Cl_2) 3 600 and 3 470 (hydroxy), and 1 694 cm^{-1} (20-ketone); δ ($CDCl_3$) 0.60 (3 H, s, 13-Me), 0.89 (3 H, d, *J* 7 Hz, 16α-Me), 0.92 (3 H, s, 17-Me), 1.01 (3 H, s, 10-Me) 3.0 (1 H, m, 16β-H), 3.42 (1 H, m, 3α-H), 4.19 (2 H, d, *J* 4 Hz, 21-CH_2), and 5.26 (1 H, m, 11-H) (Found: C, 76.8; H, 10.3. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%).

3β-Hydroxy-16α,17α-dimethyl-5α-androst-9(11)-ene-17β-carboxylic Acid (7a).—The diol (13) (0.64 g), prepared as described above, was dissolved in methanol (45 ml) and treated at room temperature with a solution of periodic acid (0.96 g) in water (9.6 ml). After 2 d the mixture was diluted with water (200 ml) and the resulting solid was filtered off. Extraction of this solid with ethyl acetate at 20 °C gave a small amount of the ester (7) (0.17 g) (see below). Further successive extractions with boiling ethyl acetate, 9 : 1 (v/v) dichloromethane–methanol, and 1 : 1 (v/v) dichloromethane–methanol gave the required *carboxylic acid* (7a) (0.48 g), m.p. 255—258 °C (from dichloromethane–methanol); $[\alpha]_D$ −44.9° (*c*, 1.34 in pyridine); $\nu_{max.}$ (KCl) a series of broad bands at 3 490—2 580 (hydroxy and carboxylic acid), and 1 692 cm^{-1} (carboxylic acid); δ (C_5D_5N) 0.95 (6 H, s, 17- and 18-Me), 1.08 (3 H, d, *J* 7 Hz, 16α-Me), 1.20 (3 H, s, 10-Me), 3.10 (1 H, m, 16β-H), 3.70 (1 H, m, 3α-H), and 5.39 (1 H, m, 11-H) (Found: C, 76.1; H, 10.0. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%).

Methyl 3β-Hydroxy-16α,17α-dimethyl-5α-androst-9(11)-ene-17-carboxylate (7).—The acid (7a) (0.38 g), suspended in dichloromethane–methanol (9 : 1 v/v) (250 ml), was treated with a solution of diazomethane in ether for 5 h. The excess of diazomethane was destroyed with dichloromethane–acetic acid (9 : 1 v/v) and the reaction mixture was evaporated to dryness. The residue was dissolved in acetone and boiled with charcoal for 10 min, then the solution was filtered and the filtrate was concentrated to give the *ester* (7) (0.15 g), m.p. 157—160 °C, identical with component B of the Favorskii reaction (mixed m.p., t.l.c., g.l.c., and i.r. and n.m.r. spectra).

16α-Methyl-5α-pregn-9(11)-en-3β-ol (18).—(a) *From Component C* (9) *of the Favorskii Reaction.* A solution of the ester (9) (1.21 g) in benzene (36 ml) was treated with dihydropyran (2.4 ml) and toluene-*p*-sulphonic acid (60 ml) for 1½ h. The reaction was worked up by the addition of potassium carbonate, followed by washing the benzene solution with sodium carbonate solution, then with water until neutral. The organic solution was dried and evapated under reduced pressure to give the tetrahydropyranyl ether (14) as an oil (2.42 g), R_t 3.79 (on SE30 at 225 °C), contaminated with dihydropyran. This crude ether (14) (2.42 g) was dissolved in dry THF (20 ml) and treated with a solution of sodium aluminium hydride (0.6 g) in dry tetrahydrofuran (25 ml) at room temperature. After 2 h the excess of hydride was destroyed by the addition of wet THF and the reaction mixture was filtered. The residue was washed with ethyl acetate, and the combined organic solutions were evaporated to dryness to give the hydroxy-compound (15) (1.87 g), R_t 3.65 (on SE 30 at 225 °C). A solution of the 21-hydroxy-compound (15) (1.87 g) in dry pyridine (25 ml) containing toluene-*p*-sulphonyl chloride (1.8 g) was kept at 3 °C for 20 h. The reaction was poured onto ice–water (150 ml) and the product was extracted into diethyl ether. The combined extracts were washed well with water, dried, and evaporated to give the toluene-*p*-sulphonate (16) (2.55 g). A solution of the toluene-*p*-sulphonate (16) (2.43 g) in acetone (30 ml) containing sodium iodide (3.6 g) was refluxed under nitrogen for 2 h. The cooled reaction was diluted with water (100 ml) to give a white emulsion. The product was extracted into ether, and the extract was washed with sodium hydrogensulphite solution, then water (×3), dried, and evaporated to give the iodide (17) (1.98 g). A solution of the iodide (17) (1.98 g) in glacial acetic acid (25 ml) was treated with zinc dust (4.0 g) and the mixture was stirred at 70 °C for 16 h. The zinc was removed by filtration and water (100 ml) was added to the filtrate to precipitate the product. The oil which formed was extracted into ether and the extracts were washed with water, dried, and evaporated. The residue was dissolved in methanol (20 ml) containing hydrochloric acid (3 ml; 5M) and the solution was boiled for 30 min. Addition of water (100 ml) yielded a gum which was extracted into ether. The ether extracts were washed with water, dried, and evaporated to a gum (2.15 g). Column chromatography on silica (100 g), eluting with benzene–ethyl acetate (20 : 1 v/v) afforded 16α-methyl-5α-pregn-9(11)-en-3β-ol (18) (0.37 g), m.p. 145—148 °C (from dichloromethane–methane), identical with an authentic sample prepared as below (mixed m.p., g.l.c., and i.r. and n.m.r. spectra).

(b) *From 20-Oxo-5α-pregna-9(11),16-dien-3β-yl Acetate* (3) A solution of methylmagnesium bromide (from 2.4 g magnesium) in THF (50 ml) was cooled to 0 °C and treated with copper(II) acetate (0.25 g). After 10 min, the diene (3) (5 g) in dry tetrahydrofuran (20 ml) was added, and within 5 min no αβ-unsaturated ketone remained (u.v. spectrum). The mixture was poured into water (500 ml) containing ammonium chloride (10 g) and the resultant white solid was filtered off, washed with water, and dried. The last of the 3-acetate was hydrolysed by boiling the product in methanol (50 ml) saturated with potassium carbonate for 30 min. The reaction was cooled, acidified (acetic acid), and diluted with water (200 ml). The white crystalline product was filtered off and dried (4.41 g). Crystallisation from acetone–n-hexane gave the 16α-methyl compound (19) (3.12 g), m.p. 192—195 °C (lit.,[10] 189—191 °C). A solution of the 16α-methyl compound (19) (2.0 g) in ethanol (50 ml) containing hydrazine hydrate (5 ml) was refluxed for 1½ h. The solvent was then replaced with butane-1,4-diol (60 ml) and solid potassium hydroxide (1.36 g) was added carefully to the hot solution. The temperature was raised to 200 °C and the solution was heated at this temperature for 2½ h. The cooled reaction mixture was poured into ice–water (200 ml) and neutralised with acetic acid. The resulting brown solid was filtered off and dried. Column chromatography on alumina and elution with ether containing 1—3% methanol gave the required product (18) (1.71 g) which was still coloured. A solution of the product (18) (1.71 g) in methanol (50 ml) was treated with charcoal and the mixture was refluxed for 30 min. The charcoal was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in toluene–ether (1 : 1 v/v) and passed through a short column of silica (50 g). Evaporation of

the solvent and recrystallisation from dichloromethane–methanol afforded 16α-*methyl*-5α-*pregn*-9(11)-*en*-3β-*ol* (18) (0.6 g), m.p. 146—149 °C; $[\alpha]_D$ −11.3° (*c*, 1.05); R_t 0.4; $\nu_{max.}$ (CH_2Cl_2) 3 615 cm^{-1} (hydroxy); δ ($CDCl_3$) 0.55 (3 H, s, 13-Me), 0.98 (3 H, d, *J* 7 Hz, 16α-Me), 0.90 (3 H, s, 10-Me), 3.55 (1 H, m, 3α-H), and 5.23 (1 H, m, 11-H) (Found: M^+, 316.2766. $C_{22}H_{36}O$ requires *M*, 316.2766).

16α-*Methyl*-5α-*pregn*-9(11)-*en*-3β-*yl Acetate* (18a).—The hydroxy-compound (18) (0.1 g) was acetylated overnight at room temperature with acetic anhydride (2 ml) in pyridine (2 ml). The reaction mixture was poured onto crushed ice (25 g) and the mixture was brought to room temperature. The product was filtered off and dried over phosphorus pentaoxide at 60 °C *in vacuo* to give the *acetate* (18a) (0.11 g), m.p. 75.5—80 °C; R_t 0.59 (on SE30 at 225 °C); $\nu_{max.}$ (CH_2Cl_2) 1 730 cm^{-1} (acetate); δ ($CDCl_3$) 0.58 (3 H, s, 13-Me), 0.95 (3 H, s, 10-Me), 1.01 (3 H, d, *J* 7 Hz, 16α-Me), 2.0 (3 H, s, OAc), 4.65 (1 H, m, 3α-H), and 5.28 (3 H, m, 11-H) (Found: M^+, 358.2864. $C_{24}H_{38}O_2$ requires *M*, 358.2872).

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