Ring-c Aromatic Steroids. 17β-Methyl-18-norpregna-8,11,13-trienes

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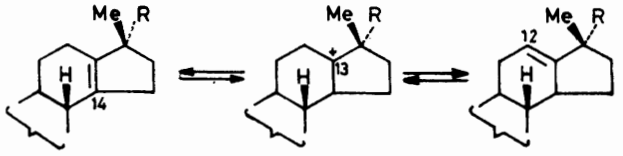
Boron trifluoride–diethyl ether converts 20α,21-diacetoxy-9α,11α-epoxy-17α-hydroxypregn-4-en-3-one (18) into 20α,21-diacetoxy-17β-methyl-18-norpregna-4,8,11,13-tetraen-3-one (19). An analogous c-aromatic steroid is similarly obtained from 9α,11α-epoxy-17α-methyltestosterone (9). From (19), by modifications of ring A and the 17α-side-chain, a series of 17β-methyl c-aromatic steroids has been prepared. The 5β configuration of the 3-ketone (21), obtained stereospecifically by hydrogenation of the Δ^4-3-ketone (19) is deduced from ^{13}C and ^1H n.m.r. data. Some acid-catalysed transformations of 17α-methyl-$\Delta^{9(11)}$-testosterone (1) are reported.

GENERAL routes to ring-c aromatic steroids have been explored by us in a programme to study the pharmacological properties of such substances. The impetus for such work comes in part from the isolation from fungi of viridin, a c-aromatic steroid,[1] and its related metabolites.[2] This paper records work based on Wagner–Meerwein migration of methyl from C-13 to C-17 upon elimination of a 17α-hydroxy. Before we commenced work, several other methods had been in use, *viz.* C-13→C-12 methyl migration,[3] total synthesis,[4] and transformation from c-aromatic diterpenes.[5]

In recent years Turner and his co-workers,[6] and Hewett *et al.*[7–9] have described work involving elimination–migration of 17-alcohols of the 17-methylandrostane group. We chose to work on pregnanes and corticoids to produce c-aromatic steroids of the 17β-pregnane series with oxygen functions on a 17α side-chain. The product. Where an 11-oxo-, 11β-hydroxy-, or 11β-acetoxy-function is present, thermodynamic factors tend to favour instead the $\Delta^{12(13)}$-product (Scheme 1). Our work (below) suggests that even in the presence of $\Delta^{9(11)}$-unsaturation, proton loss from the rearranged C-13 carbonium ion occurs initially from C-14.



SCHEME 1

17α-Methyl-$\Delta^{9(11)}$-testosterone (1) chosen as a model gave rise, on acid treatment, to a variety of products. With acetic acid–10M-hydrochloric acid (1 : 1), the rearranged trienone (4) was obtained after 5 h. This product has only two vinyl protons (Table 1) and, upon removal of the enone chromophore by sodium borohydride reduction, shows only end-absorption in the ultraviolet. Isomerisation of (4) took place on standing, and after 2 d, the main product was the fully conjugated trienone (6).[11] It appears that aerial oxidation also occurred, as the minor products isolated consisted of *ca.* 10% each of the aromatic Δ^4-ketone (7)[6b] and $\Delta^{4,6}$-ketone (8).[6b,12]

As the Δ^4-ketone (7) incorporates the c-aromatic system required, control of the degree of oxidation by choice of acid conditions was examined. No oxidation occurred in 10% trifluoroacetic acid in chloroform, the

TABLE 1

^1H Chemical shifts ($CDCl_3$ solutions; p.p.m. from $SiMe_4$; J and $W_{\frac{1}{2}}$ in Hz)

Compounds	H-4	H-11 (and H-12)	H-20	H-21a	H-21b	OAc
(2) [a]	5.8	5.6 (m)	1.70			
(3)	5.8	5.6 (m)	4.75 ($W_{\frac{1}{2}}$ 5)			
(4)	5.7	5.6 (m)				
(5)	5.8					
(9)	5.85	3.25 (J 1 and 5)				
(18)	5.85	3.25 (J 1 and 5)	5.3 (J 3 and 9)	4.6 (J 3 and 12)	4.0 (J 9 and 12)	2.0, 2.1
(17)	5.75	5.5 ($W_{\frac{1}{2}}$ 10)	5.35 (J 2.5 and 9)	4.55 (J 2.5, 12)	4.05 (J 9 and 12)	2.05, 2.1
(27)	5.75	5.5 ($W_{\frac{1}{2}}$ 12)	5.7 (J 2.5 and 9)	4.55 (J 2.5, 12)	3.95 (J 9 and 12)	2.05, 2.05, 2.1
(24) [b]	5.75	5.6 ($W_{\frac{1}{2}}$ 12)	5.45 (J 3 and 9)	4.6 (J 3, 12)	4.1 (J 9 and 12)	2.05, 2.15
(25) [c]	5.7	5.55 ($W_{\frac{1}{2}}$ 14)	5.6 (m)	4.1 [f,g]	4.3 [f,g]	2.05, 2.1
(26) [d]	5.75	5.55	5.6 (m)	4.1 [f]	4.3 [f]	2.05, 2.1
(19)	5.9	7.1 (AB q, J 9)	5.3 ($\Sigma J_{20.21}$ 12)	4.1 (m)	4.1 (m)	1.95, 2.05
(21)		7.1 (AB q, J 9)	5.3 ($\Sigma J_{20.21}$ 12)	4.05 (m)	4.05 (m)	1.95, 2.05
(23) [e]		7.05 (AB q, J 8)	5.35 ($\Sigma J_{20.21}$ 12)	4.1 (m)	4.1 (m)	1.95, 2.0, 2.1

[a] H-16 at δ 5.35 ($W_{\frac{1}{2}}$ 6). [b] H-6/7 at δ 6.2. [c] H-6/7 at δ 6.2; [h] H-16 at δ 5.85 ($W_{\frac{1}{2}}$ 5); H-8 at δ 3.1 (J 12). [d] H-16 at δ 5.8. [e] H-3 at δ 4.85 ($W_{\frac{1}{2}}$ 31). [f] AB of ABX. [g] Signal collapsed to AB q (J 12) on saturation of H-20. [h] Signal sharpened on saturation of H-8.

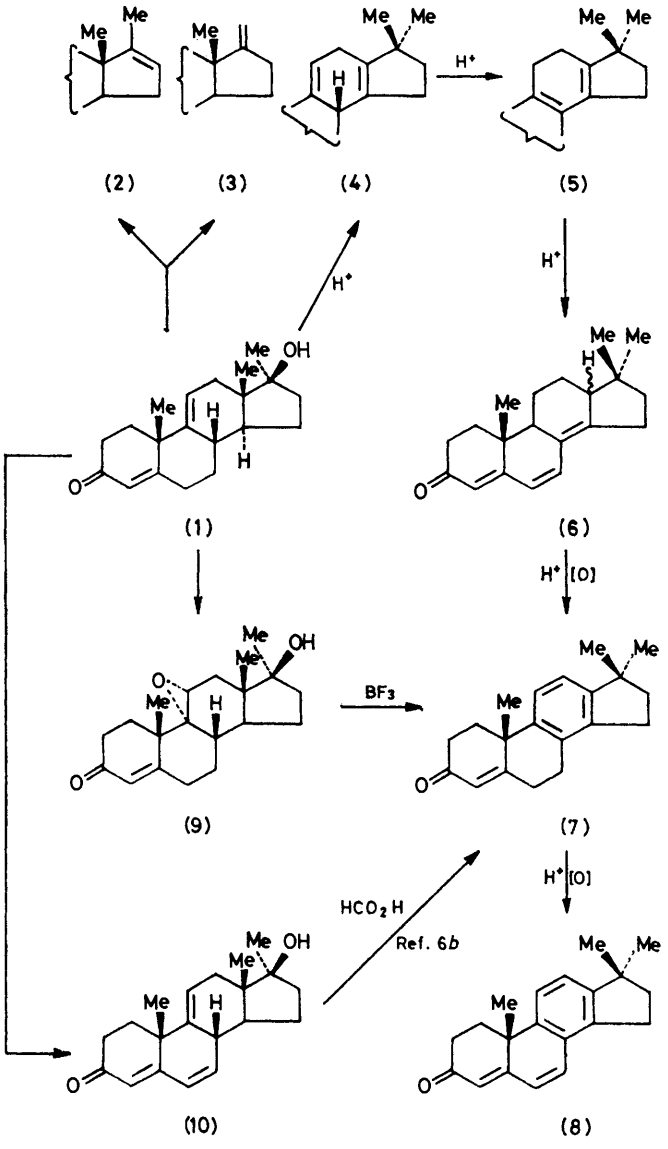
formation of such products requires two operations: (*i*) C-13→C-17 methyl migration, and (*ii*) generation of the required degree of unsaturation around ring c. We have examined strategies in which the two operations are carried out in the order listed or in the reverse order.

RESULTS AND DISCUSSION

We first studied the preparation of 18-nor-steroids having two double bonds in ring c, and the subsequent dehydrogenation reaction.

Formation of 18-nor-steroids by acid-induced C-13 methyl migration of 17-hydroxy-steroids is well documented.[10a] Generally there is proton loss from C-14 of the rearranged C-13 carbonium ion, leading to a $\Delta^{13(14)}$-

products being the trienones (4) and (6). With 100% trifluoroacetic acid the aromatic ketone (7) was obtained in 40% yield, other products being the conjugated



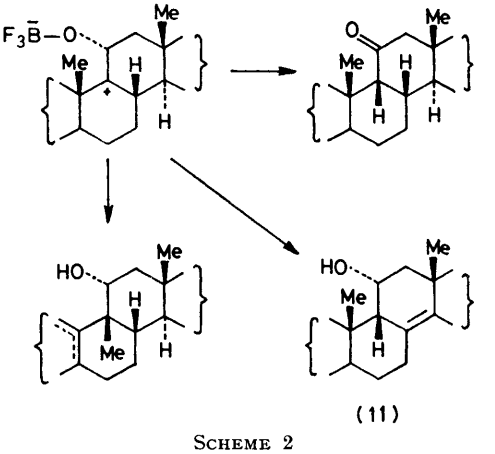
trienone (6), and a precursor of (6). The latter is tentatively given the structure (5) since it has only one vinyl proton (H-4, δ 5.8 p.p.m.). The sequential generation of products in the above reactions was followed by ^{1}H n.m.r. analyses at time intervals (see Experimental section).

Brown and Turner,[6a] in their work on steroidal phenanthrenes, postulated that where $\Delta^{9(11)}$-unsaturation was present in a 17-alcohol, C-13 methyl migration would be initiated by elimination to the Δ^{16}-olefin. However, we found no ^{1}H n.m.r. evidence for a transient Δ^{16}-intermediate in the migration reactions described above. As n.m.r. reference, the unrearranged Δ^{16}-olefin (2) was made [together with the $\Delta^{17(20)}$-isomer (3)] by simple elimination of the 17α-methanesulphonate of (1).

Aromatisation by catalytic dehydrogenation of 18-nor-steroids with one double-bond in ring c had been reported to be difficult.[8] Surprisingly the 1,4-dihydrobenzene system of (4) was also difficult to dehydrogenate, even in the presence of tetrahydropyran. Only in one experiment was the aromatic ketone (7) obtained free from other products.

In an alternative strategy the required degree of unsaturation around ring c is generated prior to the methyl migration step. Thus the Δ^6-analogue of (1) [*i.e.* (10)] was shown by Turner [6b] to yield the c-aromatic ketone (7) upon treatment with formic acid. The yield in this two-step process from (1) was 38%. We have raised the overall yield to over 80% by combining in a single reaction the generation of unsaturation and methyl migration. Thus the 9α,11α-epoxide (9) [obtained from (1) by *m*-chloroperbenzoic acid oxidation] smoothly yielded the c-aromatic product (7) on treatment with boron trifluoride–ether complex.

This experimental result is explicable in the context of the known behaviour of other 9α,11α-epoxides. Due to stereochemical strain, steroid 9α,11α-epoxides do not readily yield 9β(H)-11-ketones.[10c,13] Instead there is a tendency for methyl migration from C-10 to C-9,[14,15] or for hydride transfers to give a homoallylic alcohol (11) [14]

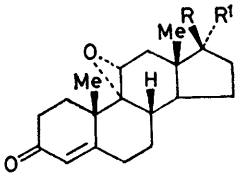


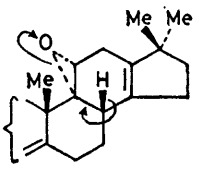
SCHEME 2

(Scheme 2). Since 9α,11α-epoxyprogesterone (12) (which lacks a 17-hydroxy) was recovered unchanged from boron trifluoride–ether under our conditions, we postulate a rearranged epoxide (13) as an intermediate in the formation of the c-aromatic steroid (7) from (9). The development of an allylic cation [see (13), arrows] would contribute to epoxide-opening in a similar manner to that postulated for the Δ^5-9α,11α-epoxide (14).[15]

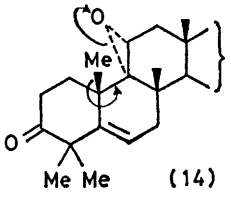
This procedure was next applied to corticoid starting materials. The 20,21-diacetate (16) of Reichstein's 'substance E' was dehydrated to the $\Delta^{4,9(11)}$-3-ketone (17) which was then converted to the 9α,11α-epoxide (18). The boron trifluoride-induced formation of an aromatic c-ring proceeded smoothly to yield (19) having ^{1}H and ^{13}C n.m.r. (Tables 1, 2, and 3) and mass-spectral data (Experimental section) in agreement with the structure. The aromatic product (19) was also prepared

by us (but in a lower yield) by refluxing in formic acid the $\Delta^{4,6,9(11)}$-3-ketone (24) (Turner's procedure,[6b] see above). In an attempt to reduce the severity of the





(12) R = Ac, R^1 = H
(13) R = R^1 = Me



(14)

conditions, use of toluene-*p*-sulphonic acid in refluxing benzene led only to an unrearranged Δ^{16}-compound (25) (^{1}H n.m.r., Tables 1 and 4). The $\Delta^{4,9(11)}$-ketone (17)

TABLE 2

^{1}H Chemical shifts (p.p.m.) of methyl groups of 17β-methyl C-aromatic steroids (in $CDCl_3$)

Compound	Ring A functions	17α-substituent	10β-Me	17-Me
(7)	Δ^4-3-oxo	Me	1.58	1.26, 1.26
(19)	Δ^4-3-oxo	$CH(OAc)CH_2OAc$	1.58	1.32
(20)	Δ^4-3-oxo	$CH(OH)CH_2OH$	1.60	1.33
(21)	3-oxo	$CH(OAc)CH_2OAc$	1.38	1.30
(22)	3-oxo	$CH(OH)CH_2OH$	1.40	1.32
(23)	3α-OAc	$CH(OAc)CH_2OAc$	1.19	1.29

also yielded a Δ^{16}-olefin (26) on similar treatment, but gave rise to a 17α-acetylated product (27) on reaction with boron trifluoride in acetic anhydride.

The C-aromatic 17β-methyl-18-nor-pregnane (19), prepared in three high-yielding steps from commercially available starting material, is a potentially important intermediate for a variety of other C-aromatic steroids. The Δ^4-3-oxo function provides ready access to A/B *trans* analogues by lithium–ammonia reduction [3] and to A/B *cis* compounds by hydrogenation (see below). Modification of the C-17 side-chain, including removal or migration of the 17β-methyl, is facilitated by the presence of oxygen functions at positions 20 and 21, and this is being studied at present.

Catalytic hydrogenation of a steroid Δ^4-3-ketone generally yields a mixture of 3-ketones with *cis* and *trans* A/B junctions.[10b,16] In contrast, the aromatic steroid (19) is hydrogenated stereospecifically from the β-face, when the reaction is carried out in neutral medium. The ^{13}C n.m.r. spectra of the resulting 3-keto-diacetate (21) and of the related 3-keto-diol (22) show that the shielding pattern of carbons on rings A and B is different from that [17] of the *trans*-A/B model compound (28) of synthetic origin. In particular, the C-19 methyl carbon is deshielded by 9.5 p.p.m. compared with (28) due to a decreased number of *γ-gauche* 'interactions'.[18] The ^{13}C n.m.r. spectra are further discussed below. Protons on the C-19 methyl group in (21) and (22) (δ 1.38 and 1.40 p.p.m., respectively) are also deshielded relative to those of the *trans*-A/B ketone (28) (δ 1.29 p.p.m.),[19] but have chemical shifts similar to those of the *cis*-A/B C-aromatic steroid (29) (δ 1.38) prepared from cholic acid by Stevenson.[3] For further characterisation as the 5β-series, the hydrogenation product (21) was converted by sodium borohydride reduction, followed by acetylation to the equatorial 3-acetate (23) (half-height width of H-3 ^{1}H n.m.r. signal, 31 Hz). The 10-methyl ^{1}H signal of the 3-acetate, and of the intermediate 3-

TABLE 3

^{13}C Chemical shifts (in p.p.m. relative to $SiMe_4$) in $CDCl_3$

Carbon	(19)	(21)	(22) [a]
C-1	37.1	37.9 [b]	37.9 [b]
C-2	34.8	38.4 [b]	38.4 [b]
C-3	198.7	212.2	213.6
C-4	124.1 [d]	43.4	43.5
C-5	169.5	42.4	42.5
C-6	30.6	24.0 [c]	24.0 [c]
C-7	28.3	23.7 [c]	23.7 [c]
C-8	130.9	131.4	131.3
C-9	143.0	140.6	139.8
C-10	39.2	36.7	36.8
C-11	124.8 [d]	124.3	124.1
C-12	121.9	121.3	121.7
C-13	144.4	144.2	145.8
C-14	141.3	142.3	142.5
C-15	29.2	29.2	29.4
C-16	34.8	34.9	34.8
C-17	50.0	49.9	50.6
C-18 [e]	24.8	24.5	24.3
C-19	27.8	30.5	30.5
C-20	76.4	76.3	78.8
C-21	63.8	63.9	63.5
CH_3CO	20.6, 21.0	20.7, 21.0	
CH_3CO	170.4, 170.6	170.5, 170.8	

[a] Traces of CD_3OD added to increase solubility. [b,c] Signals in any vertical column may be reversed. [d] C-11 is distinguished from C-4 by comparison of residual couplings in the single-frequency off-resonance decoupled spectra (E. Wenkert, H. T. A. Cheung, H. E. Gottlieb, M. C. Koch, A. Rabaron, and M. M. Plat, *J. Org. Chem.*, 1978, **43**, 1099). [e] *Viz.* 17-methyl carbon.

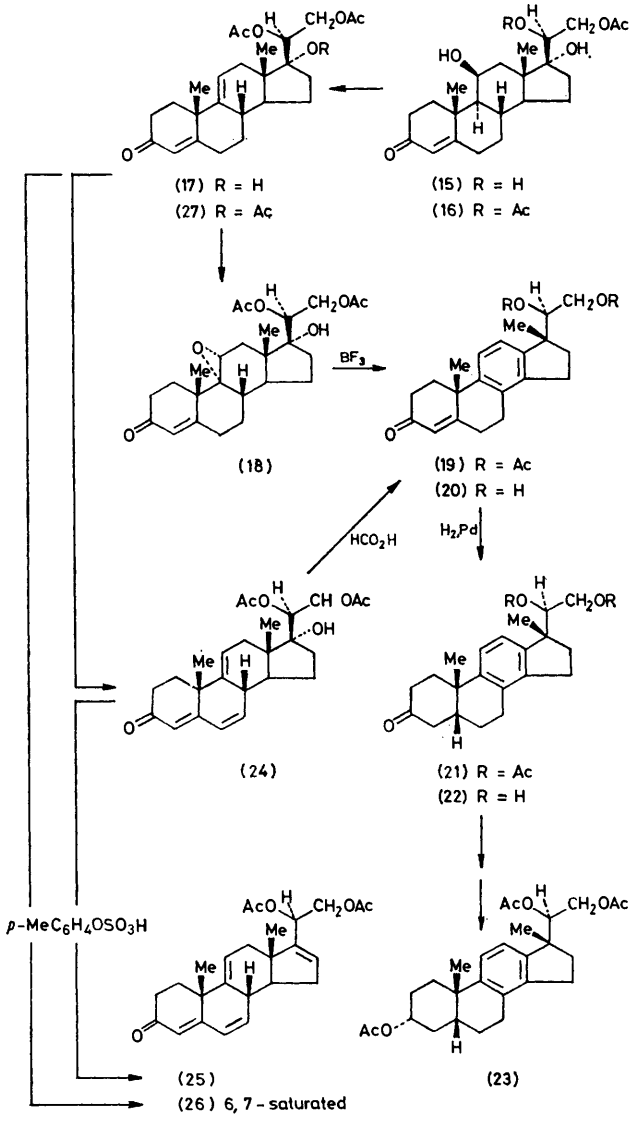
TABLE 4

^{1}H Chemical shifts (p.p.m.) of methyl groups of Δ^4-3-ketones (in $CDCl_3$)

Compound	Ring B/C functions	10β-Me	13β-Me	17-Me
(2)	$\Delta^{9(11)}$	1.38	0.73	1.70
(3)	$\Delta^{9(11)}$	1.38	0.82	
(17)	$\Delta^{9(11)}$	1.36	0.86	
(26)	$\Delta^{9(11)}$	1.36	0.85	
(27)	$\Delta^{9(11)}$	1.36	0.93	
(4)	$\Delta^{9(11),13}$	1.38		1.00, 1.03
(24)	$\Delta^{6,9(11)}$	1.33	0.93	
(25)	$\Delta^{6,9(11)}$	1.33	0.92	
(6)	$\Delta^{6,8(14)}$	1.10 *		0.68,* 1.00
(5)	$\Delta^{8,13}$	1.17		0.98, 0.98
(9)	9α,11α-epoxy	1.48	0.95	1.19
(18)	9α,11α-epoxy	1.47	0.94	

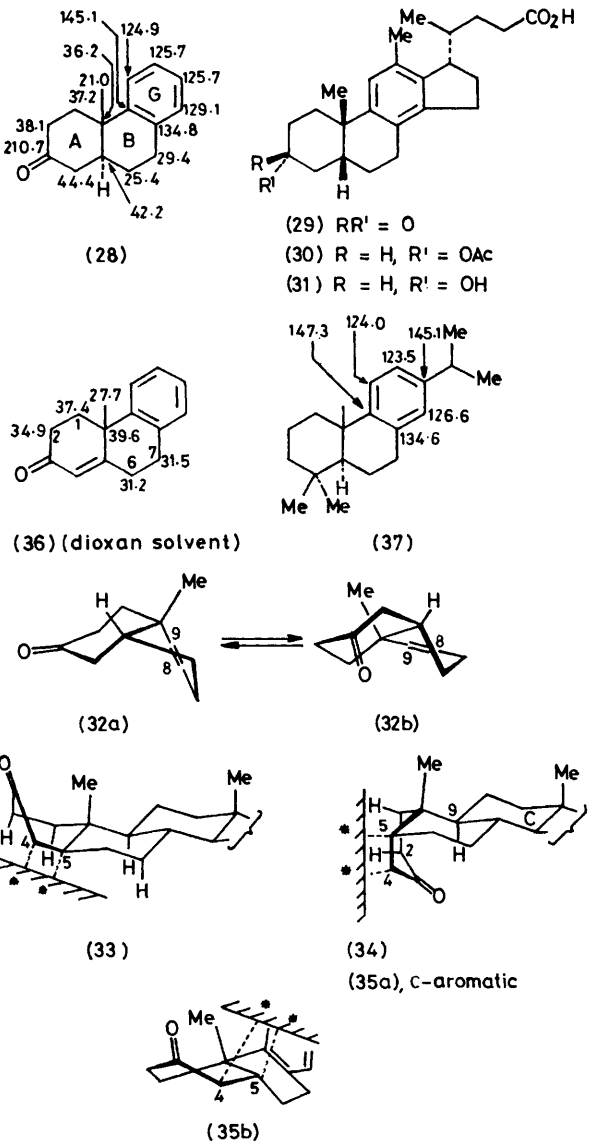
* Assignment of Sadée *et al.*[11]

alcohol, appears in each case at δ 1.19 p.p.m., a position identical to that found for the 3α-acetate (30) and 3α-alcohol (31) with *cis*-A/B fusion (δ 1.18 p.p.m.) prepared by Stevenson.[3]



The stereochemistry of hydrogenation of Δ^4-3-ketones, which is highly sensitive to structural features, has been discussed [10b] in terms of a delicate balance between the relative stability of catalyst–steroid complexes (33) and (34), with respectively 4α,5α, and 4β,5β attachment to the catalyst surface. In both, ring A has a boat-like conformation with parallel bonds from C-4 and C-5 to the catalyst surface. C-19 in complex (33) and C-9 in complex (34) occupy flagpole positions. The non-bonded interactions of these flagpole carbons with carbons 3, 2, and 4 are major destabilising factors. For a steroid with an aromatic C-ring and hence *no* hydrogen at C-9, those interactions involving C-9 are expected to be significantly reduced in the complex (35a) corresponding to β-hydrogenation. For such a compound, with trigonal C-8 and C-9, another complex for β-hydrogenation may be considered. This complex (35b), with a minimum of axial hydrogen atoms interacting with the catalyst, is formally related to the ' non-steroid ' form of *cis*-decalin. The observed addition of hydrogen solely from the β face of the C-aromatic Δ^4-3-ketone (19) is thus explicable in terms of the increased stability of the 4β,5β-bonded complex (35a) and/or (35b).

^{13}C *N.M.R. Spectra of* C-*Aromatic Steroids.*—The ^{13}C chemical shifts of the C-aromatic 3-ketones (21) and (22), and of the Δ^4-3-ketone (19) are collated in Table 3. Multiplicities in the off-resonance decoupled spectra and chemical-shift theory permit immediate shift designation for C-5, C-10, and C-17, as well as for the



low-field carbons, *i.e.* C-3 [and C-4 and C-5 for the Δ^4-3-ketone (19)], the acetate carbonyls, and those on the side-chain. Of the methyl signals, those of the acetate

groups are characterised by shifts of *ca.* 21 p.p.m., while those at 24.5 ± 0.3 p.p.m. are assigned to C-18 by virtue of the shift invariance in (19), (21), and (22). The remaining methyl signal is assigned to C-19 by elimination; 27.8 p.p.m. in the Δ^4-3-ketone (19) and 30.5 p.p.m. in the 3-ketones (21) and (22); the former shift is nearly identical to that in the model compound (36).[20,21a]

Of the six high-field methylenes in the Δ^4-3-ketone (19), carbons 1, 2, 6, and 7 are readily allocated chemical shifts by reference to the data for the model compound (36).[21a] The 3.2 p.p.m. shielding of C-7 in (19) compared with (36) is due to the *γ-gauche* effect of C-15. Assignment of the remaining two methylene signals to C-15 and C-16 is confirmed by the presence of a similarly shielded pair of signals in (21) and (22). Differentiation between these two signals comes from the recognition that C-16 is neopentyl and is more deshielded (34.8—34.9 p.p.m.) than is C-15 (29.2—29.4 p.p.m.). Allocation of methylene signals to carbons 1, 2, 4, 6, and 7 in the 3-ketones (21) and (22) is made difficult by uncertainty on the shape of the *cis*-fused A/B rings. Among the preferred conformations are the ' steroid ' (32a) and ' non-steroid ' (32b) forms, each with ring B as a half-chair. The relevant assignments in Table 3 are made assuming that the ' steroid ' conformation predominates, and noting expected small shift differences at C-2 and C-4 from 5β-cholestan-3-one.[22] Support for this assumption may be derived from the shieldings of aromatic carbons (see below).*

Of the two aromatic methine signals, that near 121.5 p.p.m. is assigned to C-12. Increased shielding relative to the model compound (37) [17] (2 p.p.m.) is consistent with C-12 having more *γ-gauche* ' interactions ' (with C-20 and the 17β-methyl carbon) than in (37). The other aromatic methine C-11, resonating near 124.5 p.p.m., appears to be little perturbed by changes in the A/B ring junction. [Compare (28) and (37) with 5α-H, (21) and (22) with 5β-H, and (19) with a Δ^4-3-oxo-function]. One of the four aromatic quaternary carbon signals from each of (19), (21), and (22) is at higher field (131 p.p.m.) than the other three (140—146 p.p.m.), and is assigned to C-8. The increased shielding of this carbon compared to that in the model compound (28) (*ca.* 3 p.p.m.) is analogous to that experienced by the α-carbon of indan relative to benzene (3.7 p.p.m.).[21b] The most deshielded of the four aromatic quaternary carbon signals is assigned to the neopentyl carbon C-13. This signal is, as expected, slightly more downfield in the 20,21-diol (22) (145.8 p.p.m.) than in the diacetates (19) and (21) (144.4 and 144.2 p.p.m., respectively). In contrast, changes on the side-chain have little effect on the more distant C-14, and for all three c-aromatic steroids this carbon is allocated a chemical shift near 142 p.p.m. The remaining carbon, C-9, is significantly more shielded in the 3-ketones (21) and (22) (140.6 and 139.8 p.p.m., respectively) than in the Δ^4-3-ketone (19) (143.0 p.p.m.); this is a consequence of the *γ-gauche* effect of C-2 and C-4 in the ' steroid ' form (32a) of the *cis*-A/B system (see above). These shift designations of the aromatic quaternary carbons are consistent with the observed lower signal intensity for C-9 and C-13 than for C-8 and C-14. The former pair of carbons each has fewer protons on adjacent carbons than the latter pair, and are expected to be less efficiently relaxed.[25]

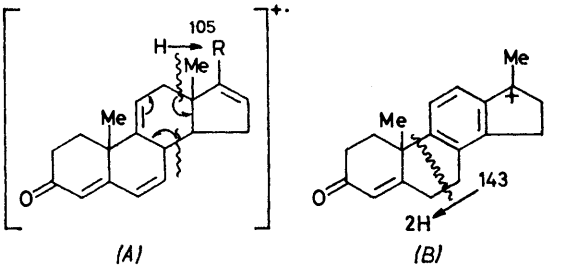
* The assumption is further justified by ^{1}H methyl shift data. The deshielding effect of a C-3 carbonyl on the protons of the C-10 methyl is expected to be smaller for conformer (32a) with the methyl equatorial (to ring A), than for conformer (32b) with the methyl axial. Data from ' Zürcher Tables ' indicate that the effects are respectively about 0.12 p.p.m. (*cf.* substituent effect of the 3-oxo-function for 5β-steroids [23]) and 0.24—0.28 p.p.m. (*cf.* effect of the 3-oxo-function for 5α-steroids,[23] of the 2-oxo-function for 10-methyl-*trans*-decalin,[24] and of the 7-oxo-function for steroids [23] and tricyclic diterpenes [19]). The C-3-carbonyl of the cis-A/B c-aromatic steroid (29) [3] has a small deshielding effect (0.15 p.p.m.) on the methyl at C-10, suggesting preponderance of the ' steroid ' form (32a).

EXPERIMENTAL

The phrase working-up constitutes addition of chloroform or dichloromethane, washing with 1M sodium carbonate and water, drying with anhydrous sodium sulphate, and evaporation to dryness *in vacuo*. U.v. spectra refer to methanol solutions. Mass spectra were determined with an AEI MS9 instrument operating at 70 eV with source temperature at *ca.* 180 °C. Hydrogen-1 and ^{13}C n.m.r. data are summarised in Tables 1—4; these were obtained on $CDCl_3$ solutions containing tetramethylsilane as internal reference.

The ^{13}C spectra were determined in the Fourier mode on a Varian CFT-20 (20 MHz) or a JEOL FX 60Q instrument (15 MHz). For proton-noise decoupling, respectively 7 and 4 μs pulses (corresponding to a tilt angle of *ca.* 26°), acquisition times of 0.54 s, and no pulse-delay were employed.

The letters *A* and *B* in mass-spectral data refer to the fragmentations shown below.



Dehydration of 17β-*Hydroxy*-17α-*methylandrosta*-4,9(11)-*dien*-3-*one*(1).—A solution of (1) (50 mg) and methanesulphonyl chloride (0.4 ml) in dimethylformamide (2 ml) and pyridine (0.5 ml) was stirred at 85 °C for 1 h. On working-up (including washing with 1M hydrochloric acid) there was obtained a 2 : 1 mixture (^{1}H n.m.r., Tables 1 and 4) of 17-methylandrosta-4,9(11),16-trien-3-one (2) and 17-methyleneandrosta-4,9(11)-dien-3-one (3). Mass spectrum of the mixture: *m/e* 282 (92%, $M^{+\cdot}$), 267 (100%, $[M - Me]^+$), 240 (10%, $[M - CH_2CO]^+$), and 225 (12%, $[M - Me - CH_2CO]^+$).

Rearrangement of 17β-*Hydroxy*-17α-*methylandrosta*-4,9(11)-*dien*-3-*one* (1).—(*a*) *With* 10M *hydrochloric acid and acetic acid* (1 : 1). (*i*) A solution of (1) (0.5 g) in the above acid mixture (3 ml) was worked-up after 5 h at room

temperature to give 17,17-dimethyl-18-norandrosta-4,9(11),-13-trien-3-one (4) as a colourless oil.

(*ii*) The product mixture from 35-h treatment was separated by preparative t.l.c. on silica gel (elution with 10% acetone in chloroform) to give two main fractions: the trienone (6) [11] [$\lambda_{max.}$ 351 nm (ε 21 000); *m/e* 282 ($M^{+\cdot}$) and 267] and a mixture of trienone (4) and the aromatic Δ^4-ketone (7).[6b]

(*iii*) Hydrogen-1 n.m.r. and u.v. spectra of product mixtures worked-up after various reactions times showed the presence of trienones (4) and (6), and of aromatic ketones (7) and (8) (the latter two with the same u.v. and ^{1}H n.m.r. spectra as those recorded [6b,12]) in percentage yields as shown below.

(*iv*) After treatment with a fully deuteriated version of the acid mixture (but with 7M DCl), ^{1}H n.m.r. analysis showed percentage composition as shown below.

	Products			
Time/h	(4)	(6)	(7)	(8)
12	65	25	10	0
24	45	45	10	0
48	0	80	10	10
72	0	70	15	15

	Products				
			unknown		
Time/h	(1)	(4)	component	(6)	(7)
1	58	15			
2	60	40			
4	40	60			
9	8	80	3	2	7
35	0	40	0	50	10

(b) *With trifluoroacetic acid.* The ^{1}H n.m.r. indicated the following percentage composition on treatment at room temperature with the acid shown.

	10% acid in $CDCl_3$			
			Unknown [a]	
Time/h	(1)	(4)	component	(6)
6	90	5	5	
8.5	60	30	2	3
24	25	70		5
53	5	80		15
72		70		30
85		60		40
126		50		50

	100% acid		
Time/h	(1) or (4)	(5) + (6) [b]	(7)
1	10	60	30
4.5		70	30
7		70	30
24		70	30
53		67	33
119		65	35
145		25 + 35	40
240 (and 2 h at 50 °C)		60	40

[a] Hydrogen-1 resonances (*inter alia*) at δ 0.74, 1.15 in $CDCl_3$; δ 0.74, and 1.19 p.p.m. in 10% $CDCl_3$–CF_3COOH for Me signals. [b] The amount of (5) decreasing with time.

9α,11α-*Epoxy*-17β-*hydroxy*-17α-*methylandrost*-4-*en*-3-*one* (9).—A solution of (1) (0.30 g) and *m*-chloroperbenzoic acid (0.24 g) in cold chloroform (6 ml) was stirred overnight at room temperature, washed with cold 10% sodium sulphite, and then worked-up to give the *epoxide* (9) (0.31 g) as needles from acetone, m.p. 194—196 °C; *m/e* 316.204 (20%, $M^{+\cdot}$) ($C_{20}H_{28}O_3$ requires 316.204), 301.181 (7%, [*M* — Me]$^+$), 298.191 (11%, [*M* — H_2O]$^+$), 283.170 (11%, [*M* — Me — H_2O]$^+$), 162 (23%), 161 (25%), 136 (27%), and (135 (100%).

17,17-*Dimethyl*-18-*norandrosta*-4,8,11,13-*tetraen*-3-*one* (7).—(*a*) The epoxide (9) (0.05 g) in dry toluene (2 ml) was treated with boron trifluoride–ether complex (0.15 ml). After 45 min at room temperature the mixture was diluted with saturated sodium bicarbonate and with ethyl acetate, and worked-up to yield (7) (90%) with a ^{1}H n.m.r. spectrum (Tables 1 and 2) and m.p. (104—105 °C) identical to those in the literature.[6b]

(*b*) A mixture of the trienones (4) and (6) [consisting mainly of (4)] (0.5 g) in ethanol (160 ml) was refluxed under nitrogen and in the presence of 10% palladium–charcoal (200 mg). Benzene (20 ml) was added and the reaction continued for 24 h. The c-aromatic ketone (7) was isolated upon removal of catalyst and solvent.

20α,21-*Diacetoxy*-17α-*hydroxypregna*-4,9(11)-*dien*-3-*one* (17).— 20α,21-Diacetoxy-11β,17α-dihydroxypregn-4-en-3-one (16) [26] (1.0 g) [m.p. 200—203 °C, prepared by monoacetylation of the triol acetate (15)] was stirred at 85 °C with dimethylformamide (20 ml), pyridine (0.5 ml), and methanesulphonyl chloride (0.85 mol). The precipitate formed was collected after 1 h, and crystallised (chloroform–methanol) to yield needles of the *diene* (17) (0.92 g), m.p. 283—285.5 °C; $\lambda_{max.}$ 248 nm (ε 14 300); *m/e* 430 (15%, $M^{+\cdot}$), 415 (20%, [*M* — Me]$^+$), 292 [15% (*A*), 6,7-saturated], 277 (25%, [292 — Me]$^+$), 267 (15%), and 227 (15%) (Found: C, 69.4; H, 7.9. $C_{15}H_{34}O_6$ requires C, 69.7; H, 8.0%).

17α,20α,21-*Triacetoxypregna*-4,9(11)-*dien*-3-*one* (27).—A solution of (17) (0.10 g), boron trifluoride–diethyl ether complex (1.0 ml), and acetic anhydride (0.5 ml) in dichloromethane, was set aside at room temperature for 8 min, then poured into ice–water, and worked-up after 15 min. The triacetate (27) was obtained as needles (0.08 g) from methanol, m.p. 170—175 °C; *m/e* 472 (2%, $M^{+\cdot}$), 430 (6%, [*M* — CH_2CO]$^+$), 415 (15%, [*M* — CH_2CO — Me]$^+$), 412 (15%, [*M* — HOAc]$^+$), 310 (12%, [430 — 2HOAc]$^+$), 292 [100%, (*A*) 6,7-saturated], 277 ([292 — Me]$^+$), and 267 (50%, [412 — $CHOAcCH_2OAc$]$^+$).

20α,21-*Diacetoxy*-9α,11α-*epoxy*-17α-*hydroxypregn*-4-*en*-3-*one* (18).—The epoxidation of (17), carried out as for (1), gave the 9α,11α-*epoxide* (18) as needles in 90% yield, m.p. 263—266 °C; *m/e* 446.229 (24%, $M^{+\cdot}$) ($C_{25}H_{34}O_7$ requires *M*, 446.230), 431.208 (9%, [*M* — Me]$^+$), 428.216 (6%, [*M* — H_2O]$^+$), 386.209 (11%, [*M* — HOAc]$^+$), 326.187 (16%, [*M* — 2HOAc]$^+$), 308.175 (10%, [326 — H_2O]$^+$), 301.180 (20%, [*M* — $CHOAcCH_2OAc$]$^+$), 293.156 (14%, [308 — Me]$^+$), 283 (36%), 162 (47%), 161 (47%), 138 (36%), and 137 (100%).

20α,21-*Diacetoxy*-17α-*hydroxypregna*-4,6,9(11)-*trien*-3-*one* (24).—Chloranil (2.5 g) and (17) (1.0 g) were refluxed in t-butanol (400 ml) for 49 h. Excess of chloranil (1.4 g) was removed by filtration, and the residue left on evaopration of t-butanol was dissolved in chloroform. The chloroform solution was washed repeatedly with water, 1M sodium hydroxide, and water again, dried, and evaporated to dryness. The residue was crystallised (chloroform–methanol) to give needles of the *triene* (24) (0.63 g), m.p. 273—275 °C; $\lambda_{max.}$ 286 nm (ε 23 200); *m/e* 428.220 (10%, $M^{+\cdot}$) ($C_{25}H_{32}O_6$ requires *M*, 428.220) and 283.170 (5%, [*M* — $CHOAcCH_2OAc$]$^+$), other ions (including base ion 275) being as for the dehydrated analogue (25).

20α,21-*Diacetoxypregna*-4,6,9(11),16-*tetraen*-3-*one* (25) *and* 20α,21-*Diacetoxypregna*-4,9(11),16-*trien*-3-*one* (26).—Treatment of (24) (0.5 g) with toluene-*p*-sulphonic acid (5 mg) in refluxing benzene for 100 h, gave on working-up a mixture which was acetylated and chromatographed to

give unreacted (24), m.p. 264—267 °C, and the Δ^{16}-*product* (25) as an oil (0.18 g) $\lambda_{max.}$ 284 nm (ε 21 200); *m/e* 410.210 (7%, $M^{+\cdot}$) ($C_{25}H_{30}O_5$ requires *M*, 410.209), 350.187 (44%, $[M - HOAc]^+$), 308 (12%, $[350 - CH_2CO]^+$), 307 (13%), 293 (18%, $[308 - Me]^+$), 291 (30%) ,290.166 [100%, (*A*)], 275.144 (57%, $[290 - Me]^+$),* 265 (28%, $[M - CHOAcCH_2OAc]^+$), and 105.070 [19%, from 290 as shown in (*A*)]. On similar treatment, (17) gave the corresponding Δ^{16}-product (26) (¹H n.m.r., Tables 1 and 4).

20α,21-*Diacetoxy*-17β-*methyl*-18-*norpregna*-4,8,11,13-*tetraen*-3-*one* (19) *and the Corresponding Diol* (20).—(*a*) A solution of the epoxide (18) (0.10 g) and boron trifluoride–ether complex (0.2 ml) in dry benzene (2.5 ml) was refluxed for 5 min. After being cooled to 0 °C, water and ethyl acetate were added. The mixture was worked-up to yield, after preparative thin-layer chromatography on silica gel using toluene–ethyl acetate (1 : 1), the c-*aromatic steroid* (19), forming needles (42 mg) from ether, m.p. 182—185 °C; $\lambda_{max.}$ 248 nm (ε 15 600); *m/e* 410 (3%, $M^{+\cdot}$), 290 (4%, $[M - 2HOAc]^+$), 265 (100%, $[M - CHOAcCH_2OAc]^+$), 250 (23%, $[265 - Me]^+$),* 237 (4%, $[265 - CO]^+$),* and 235 (5%, $[250 - Me]^+$) * (Found: C, 72.7; H, 7.5. $C_{25}H_{30}O_5$ requires C, 73.1; H, 7.4%). The ¹H n.m.r. spectrum of the crude reaction mixture indicated a yield of over 80%.

(*b*) A mixture of (24) (2.0 g) and 98% formic acid (50 ml) was refluxed for 3.5 h, cooled, and distributed between dichloromethane and water. The aqueous phase was neutralised (sodium bicarbonate) and extracted with dichloromethane. The combined dichloromethane solutions were worked-up to give needles of (19) (0.63 g).

The diacetate (19) was hydrolysed with 1% sodium hydroxide in water–ethanol (1 : 1) at room temperature for 30 min to give 20α,21-dihydroxy-17β-methyl-18-norpregna-4,8,11,13-tetraen-3-one (20) as an oil, *m/e* 265 (100%, $[M - CHOHCH_2OH]^+$) and 250 (10%, $[265 - Me]^+$).

20α,21-*Diacetoxy*-17β-*methyl*-18-*nor*-5β-*pregna*-8,11,13-*trien*-3-*one* (21) *and the Corresponding Diol* (22).—Hydrogenation of the Δ^4-3-ketone (19) in ethyl acetate over 10% palladium–charcoal gave the 5β(H)-3-*ketone* (21) as prisms (86%) from ethyl acetate, m.p. 168—170 °C; $\lambda_{max.}$ 269 nm (ε 470); *m/e* 412 (2%, $M^{+\cdot}$), 292 (2%, $[M - 2HOAc]^+$), 268 (30%), 267 (100%, $[M - CHOAcCH_2OAc]^+$), and 143 [20%, from 267 as shown in (*B*)] (Found: C, 72.1; H, 7.9. $C_{25}H_{32}O_5$ requires C, 72.8; H, 7.8%). The ¹H n.m.r. spectra indicated absence of the 5α-epimer in the crude hydrogenated product.

On mild alkaline hydrolysis, (21) was converted to the *diol* (22), forming prisms (82%) from ethyl acetate, m.p. 142.5—144.5 °C; $\lambda_{max.}$ 269 nm (ε 450); *m/e* 297 (2%, $[M - CH_2OH]^+$), 279 (1%, $[297 - H_2O]^+$), 268 (80%), 267 (100%, $[M - CHOHCH_2OH]^+$), 210 (2%, $[268 - C_3H_6O]^+$),* 209 (4%, $[267 - C_3H_6O]^+$),* 197 (4%, $[267 - C_4H_6O]^+$), 143 [18%, from 267 as shown in (*B*)],* and 128 (36%, $[143 - Me]^+$) * (Found: C, 76.1; H, 8.7. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6).

17β-*Methyl*-3α,20α,21-*triacetoxy*-18-*nor*-5β-*pregna*-8,11,13-*trien*-3-*one* (23).—To the 3-ketone (21) (0.10 g) in methanol (5 ml) maintained at 0 °C was added sodium borohydride (0.12 g) during 30 min. The mixture was set aside at 0 °C for 2 h and then at 25 °C for 2 h. After addition of glacial acetic acid, reduction of volume *in vacuo*, and addition of water, the mixture was worked-up to give a partially hydrolysed product. This was acetylated to give the 3α-acetate (23) (¹H n.m.r., Tables 1 and 2) as an oil in 50% overall yield after preparative t.l.c.

* Metastable transition observed.

Note added in proof: A transformation analogous to (18)→(19) can be carried out on the 20β-epimer of the epoxide (18) (our unpublished results). However, Campbell *et al.* (*J.C.S. Perkin I*, 1978, 163) were not successful in obtaining a c-aromatic product from 9α,11α-epoxy-5β-pregnane-3α,17α,20β-triol 3,20-di-acetate.

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