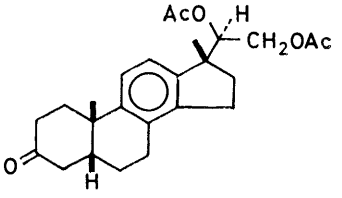
Ring c Aromatic Steroids. Part 2.[1] Rearrangement of 16α,17α-Epoxy- and 17α-Hydroxy-5,7-dienes

By Alan J. Bridgewater, H. T. Andrew Cheung,* Andrew Vadasz, and Thomas R. Watson,* Department of Pharmacy, University of Sydney, Sydney, Australia

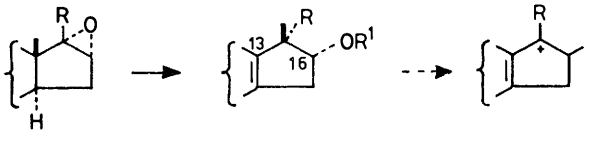
Epoxide-opening in 3β-acetoxy-16α,17α-epoxypregna-5,7-dien-20-one (3) and its $\Delta^{6,8(14)}$-isomer (7), as induced by boron trifluoride–acetic anhydride is accompanied by C-13 methyl migration. The product, 3β,16α-diacetoxy-17β-methyl-18-norpregna-5,7,13-trien-20-one (4) was converted in two steps into the c-aromatic steroid 3β,16α-diacetoxy-17β-methyl-18-norpregna-8,11,13-trien-20-one (6) as a mixture of C-5-epimers. A D-homo-product (17) resulted from acid-catalysed rearrangement of 3β,20ξ-diacetoxy-17α-hydroxypregna-5,7-diene (16).

In recent years several methods have been developed for the formation of ring c aromatic steroids.† In one, the methyl group at the c/D junction of a 17 hydroxy-steroid migrates to C-17, and the requisite degree of unsaturation in ring c is generated prior to, or after the Wagner–Meerwein rearrangement. In part 1,[1] we described the production by this method, of c-aromatic steroids of the 17β-methyl-18-norpregnane series [see *e.g.* (1)]. In this



(1)

paper we report on a related approach in which the methyl migration is initiated by the opening of a 16α,17α-epoxide [2,3] (see Scheme 1, first step). We were particularly attracted by this route since the resulting 17β-methyl-18-nor-steroid possesses a 16α-oxygen function which could provide the means for a second methyl migration to C-16. For the postulated methyl shift to C-16 (see Scheme 1, second step), the reaction centres are approximately anti-coplanar, and the process is expected to be stereoelectronically more favoured than the potentially competing processes of ring contraction and 17α-side-chain migration. Considerable therapeutic merit is associated with the 16-methyl or 16-methylene moiety in corticosteroids.[4]



Scheme 1

RESULTS AND DISCUSSION

The first example of acid-catalysed opening of 20-oxopregnane-16α,17α-epoxides with concurrent Wagner–Meerwein migration of the C-13 methyl, *viz.* (2) to (9), was reported by Heusler and Wettstein in 1954.[2] Among acid reagents used are hydrogen fluoride,[3] and toluene-*p*-sulphonic acid in conjunction with acetic anhydride [2] or with ethylene glycol.[3] It is now accepted [3] that the double-bond formed from the intermediate C-13 carbonium ion is usually located at position 13 (see Scheme 1, first step).

A c-aromatic product could be obtained if the epoxide-opening were carried out on a steroid possessing two double-bonds in the vicinity of ring c. The method has recently been explored by Hewett, Redpath and Savage.[5] From 16α,17β-epoxypregnenolone acetate (2) an appropriate homoannular 5,7-diene precursor (3) was prepared by us by allylic bromination followed by dehydrobromination with collidine. On treatment with boron trifluoride–diethyl ether complex in the presence of acetic anhydride, a good yield of 5,7,13-triene (4) was obtained.‡ The location of double-bonds is shown by a bathochromic shift of *ca.* 30 nm in the u.v. spectrum relative to the 5,7-diene precursor (3) (see Experimental section) and the presence of n.m.r. signals for only two vinyl protons (δ 5.6, see Table 1). Evidence that the 16α,17α-epoxide ring has been opened to give a 16α-acetate comes from ^{1}H n.m.r. data. A broad singlet near δ 3.7 characteristic of the 16β proton of a 16α,17α-epoxide [*cf.* (3), (7), and (8) on Table 1] is absent, and is replaced by an X of ABX signal at δ 5.2 identical to that of H-16β in the rearranged product (9) of Heusler and Wettstein.[2] Double-bond rearrangement of the 17β-methyl-18-norpregnatriene (4) to a c-aromatic product turned out to be difficult. Treatment with a variety of acid reagents (see Experimental section) produced in each case complex mixtures, presumably due to formation of products from anthrasteroid rearrangements and from participation of the 16α- and 20-functions.[6,7]

In further attempts to aromatise ring c, the homoannular 5,7-diene (3) was converted by toluene-*p*-sulphonic acid or sulphur dioxide [8] into the heteroannular 6,8(14)-diene (7).§ Treatment of the diene (7) with

† These methods are referred to in Part 1;[1] see also A. C. Campbell, M. S. Maidment, J. H. Pick, D. F. M. Stevenson, and G. F. Woods, *J.C.S. Perkin I*, 1978, 163.

‡ The similar use, with limited success, of Lewis acids such as zinc chloride in acetic anhydride has recently been reported by Redpath and his co-workers.[5] General applicability of the boron trifluoride–acetic anhydride reagent is shown by the formation of an analogous rearranged product (11) from 16α,17α-epoxyprogesterone (10) (see Experimental section).

§ Structural evidence is given at the end of this section.

boron trifluoride and acetic anhydride resulted in epoxide-opening and C-13 methyl migration, but with proton loss from C-5, yielding the triene (4), previously obtained from the diene (3) on similar treatment.

A good yield of a c-aromatic product was obtained nevertheless by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. This product, given structure (5), has u.v. absorption (see Experimental section) indicative of a polyunsaturated system. At 100 MHz, ^{1}H n.m.r. signals for *all* protons in the molecule are discerned (Table 1). Low-field AB quartets at δ 6.95 and 7.15 (J 8 Hz) and at δ 6.2 and 6.4 (J 9.5 Hz) are assigned to aromatic and vinyl protons at positions 11,12 and 6,7 respectively. Signals of benzylic protons at C-15 constitute the AB part of an ABX system at δ 3.0 (J_{AB} 17, J_{AX} 6 Hz) and δ 3.6 (J_{BX} 7.5 Hz). The X part which appeared at δ 5.4 collapsed to a singlet upon saturation of both C-15 protons, and is assigned to H-16β.

Hydrogenation of the 4,6-diene system in the c-aromatic pentaene (5) proceeded smoothly in the presence of palladium–charcoal, yielding the aromatic 8,11,13-triene (6) as a 6 : 4 mixture of 5α and 5β epimers. Configurational assignment at C-5 is based mainly on the relative shieldings of ^{1}H and ^{13}C nuclei on the angular methyl group at A/B junction as was discussed in Part 1.[1] Other features of the ^{1}H and ^{13}C n.m.r. data (Tables 1 and 2) substantiate the structure (6). Further trans-

TABLE 1

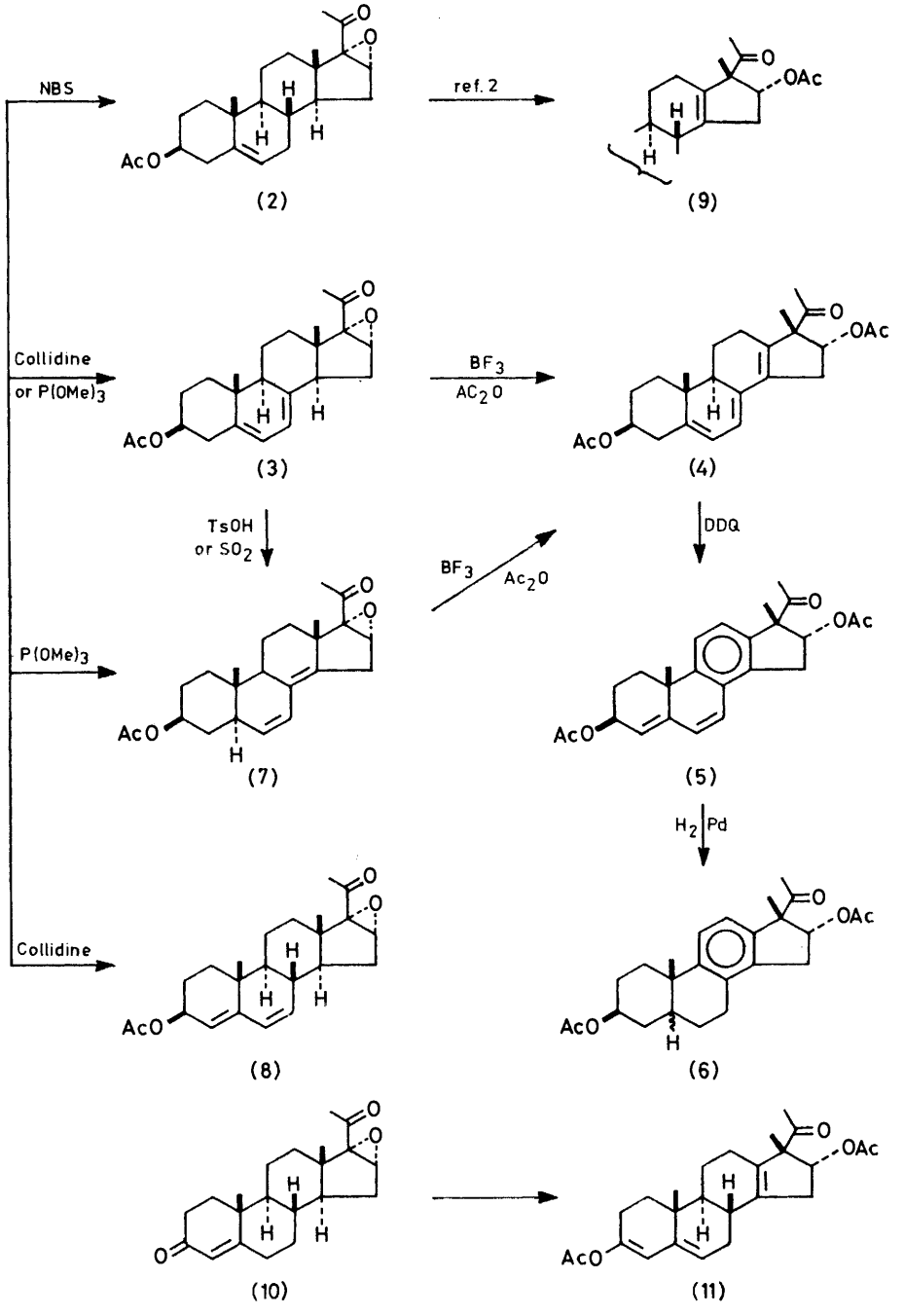
^{1}H N.m.r. data [a]

Compound	H-3α	H-4	H-6/H-7	H-14	H-15	H-16	H-18 (or 17-Me)	H-19	H-21/ OAc	Arom. H
(3)	4.6 ($W_{\frac{1}{2}}$ 19)		5.35 (J 6) 5.55 (J 6)			3.7 ($W_{\frac{1}{2}}$ 2.5)	1.00	0.96	2.02, 2.02	
(4)	4.64 ($W_{\frac{1}{2}}$ 21)		5.6 (m)			5.2 (t, J' 6.5)	1.39	0.86	2.02, 2.05, 2.08	
(11)		5.7 ($W_{\frac{1}{2}}$ 5)	5.6 ($W_{\frac{1}{2}}$ 6) (H-6)			5.2 (J 6, 8)	1.20	0.97	1.98, 2.10, 2.11	
(12) [d]	5.4 ($W_{\frac{1}{2}}$ 20)	3.25 (J 4.5, 13.5)	6.2 (J 8) 6.35 (J 8)	2.4 [b] (J 5.5, 11.5)	3.25 [b] (m)	3.75 ($W_{\frac{1}{2}}$ 2)	1.15	0.98	2.01, 2.03	
(13) [d]	5.4 [b] ($W_{\frac{1}{2}}$ 19)	3.2 [b] (J 5, 14)	6.25 (J 8.5) 6.45 (J 8.5)	2.9 [c] (J 6, 12.5)	4.7 [c] (J 6, 6.5, 14)	4.25 [c] (J 6.5, 8)	1.29	0.96	2.25 (H-21), 2.00	
(15) [e]	3.5—3.8 [f]		5.4 (J 6) 5.5 (J 6)				0.67	0.93	1.19 (J 6)	
(16) [g]	4.65 ($W_{\frac{1}{2}}$ 22)		5.45 (J 6) 5.55 (J 6)				0.74	0.97	1.19 (J 6.5), 2.05, 2.07	
(17) [h]	4.8 ($W_{\frac{1}{2}}$ 20)						2.45	1.20	2.57 (H-21), 2.05	7.45, 7.85 (J 9) 7.2, 7.75 (J 8.5)
(6) [k]	4.85 ($W_{\frac{1}{2}}$ 20) [k] 4.95 ($W_{\frac{1}{2}}$ 12) [k]				2.85 (J 6, 17) 3.4 (J 7.5, 17)	5.4 (J 6, 7.5)	1.47	1.12/ 1.30 [k]	2.0—2.1	6.9, 7.2 (J 9)
(5)	5.55 [i] (m)	5.55 [i] (m)	6.2 (J 9.5) 6.4 (J 9.5)		3.0 [b] (J 6, 17) 3.6 [b] (J 7.5, 17)	5.4 [b] (J 6, 7.5)	1.49	1.36	2.10, 2.03, 2.04	6.95, 7.15 (J 8)
(7)	4.75 ($W_{\frac{1}{2}}$ 17)		6.05 (J 3, 9.5) 5.30 (J 2, 9.5)		2.45 (broad d, J 17) 2.95 (J 17)	3.8 ($W_{\frac{1}{2}}$ 2.5)	1.30	0.65	2.02, 2.04	
(8)	5.35 (m)	5.35 (m)	5.55 (J 2, 10) 5.95 [a] J 3, 10) [j]			3.7 ($W_{\frac{1}{2}}$ 2.5)	1.10	1.00	2.05, 2.05	
(19a)						3.7 ($W_{\frac{1}{2}}$ 2.5)	1.04	2.20	2.04	6.9—7.2

[a] δ Values ($SiMe_4$ as interna' standard); J and $W_{\frac{1}{2}}$ in Hz; $CDCl_3$ solvent. [b,c] Signals inter-related by decoupling. [d] Entries in H-4 and H-15 columns are for α-protons. Signals for NPh at δ 7.4—7.5. [e] CD_3SOCD_3 (25%) added to increase solubility. [f] Overlaps with H-21 signals. [g] Signals for H-20 at δ 5.1 (q, J 6.5). [h] Signals for H-1β and H-7 appear near δ 3.2. [i] Signals sharpened on saturation of a multiplet (H-1 and H-2) near δ 2.2. [j] Signals for H-7; sharpened by 1.5 Hz on saturation of H-8 (near δ 2.4). [k] 6 : 4 Mixture of 5α- and 5β-epimers.

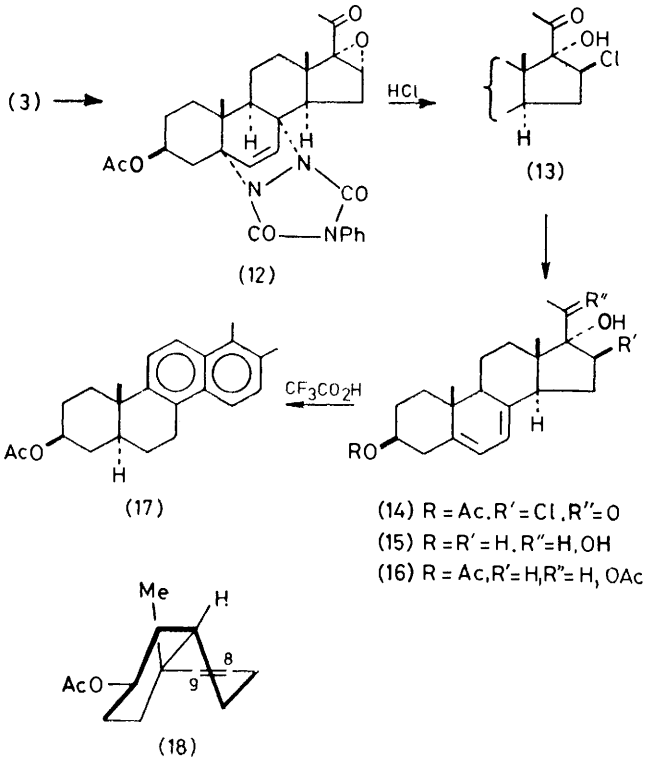
formations of the C-aromatic steroids (6) and (5), based on considerations discussed early in this paper, are in progress.

In attempts to obtain further C-aromatic products, the 5,7-diene (3) was protected by Diels–Alder addition [9] of the dienophile 4-phenyl-1,2,4-triazoline-3,5-dione. The epoxide-adduct (12) was then treated with acid to effect epoxide-opening. Toluene-*p*-sulphonic acid treatment gave complex products. Boron trifluoride–diethyl ether likewise is unsuitable; the formation of an anthrasteroid from a similar steroid adduct had been observed by Whalley and his co-workers.[10] With dry hydrogen chloride in chloroform, a good yield of a product was obtained which turned out to be the unrearranged chlorohydrin (13). The presence of chlorine is shown by the presence in the methane chemical ionisation mass spectrum of two isotopic quasi-molecular ions (*m/e* 407, 409) corresponding to the diene (14), formed by reverse Diels–Alder reaction in the ionisation chamber. For the 16α,17α-epoxides (2), (3), (7), (8) and (12), the H-16 ^{1}H n.m.r. signal is a broad singlet near δ 3.7. For the adduct-chlorohydrin (13), the signal consists of a doublet of doublets at δ 4.25, thus confirming that the epoxide ring has been opened. For both adducts (12) and (13),



the pronounced deshielding effects of the dioxotriazolidine moiety and of the Δ^6 double-bond on the 4α-, 14-, and 15α-protons are clearly seen in the ^{1}H n.m.r. spectra (Table 1).

Lithium aluminium hydride reduction of the adduct-chlorohydrin (13) caused reversion to a 5,7-diene,[11] accompanied by reduction of oxygen and chlorine functions at 3, 16, and 20, giving a quantitative yield pregna-5,7-diene-3β,17α,20ξ-triol (15) with u.v. absorption at 272, 282, and 294 nm. Since this triol forms a diacetate with acetic anhydride in pyridine at room temperature, one of the hydroxy-groups is tertiary and thus at 17 [see compound (15)]. The chlorine atom in the



chlorohydrin must then be attached to C-16. It thus appears that as for hydrogen bromide,[12] hydrogen chloride causes diaxial opening of the 16,17-epoxides. This is in contrast to other acid reagents including hydrogen fluoride (see above) which cause epoxide opening with methyl migration *via* an intermediate C-17 carbonium ion.[2,3] Both the triol (15) and its diacetate (16) show relatively small vicinal coupling (6 Hz) between the vinyl protons at C-6 and C-7. This feature, present also in the diene (3), is characteristic of homoannular 5,7-dienes, and reflects the low bond-order of the C-6/C-7 bond.

The diacetate (16), being a 17-alcohol with two unsaturations near ring C is, in fact, a potential precursor of C-aromatic 18-norsteroids. Exploitation of similar precursors had been studied by us [1] and others.[13] On treatment with trifluoroacetic acid at 70—75 °C, the diene (16) gave an aromatised product $C_{23}H_{28}O_2$, but in only 15% yield. U.v. absorption typical of a substituted naphthalene and ^{1}H n.m.r. spectrum showing signals due to two pairs of *ortho* aromatic protons and two aromatic methyl groups (Table 1) led us to consider the D-homo-C,D-aromatic structure (17). The 3β-acetoxy-group

TABLE 2

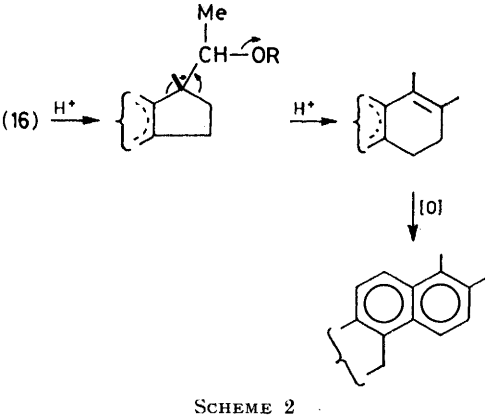
^{13}C Chemical shifts of (6) [a] (in p.p.m. relative to tetramethylsilane) in $CDCl_3$

	5α-Epimer	5β-Epimer		5α-Epimer	5β-Epimer
C(1)	36.0	32.3 [b]	C-13	146.7	146.7
C-2	27.0 [c]	27.1 [c]	C-14	141.0	141.0
C-3	73.1	70.2	C-15	36.8	36.8
C-4	34.1 [b]	33.5 [b]	C-16	82.4	82.4
C-5	39.8	37.4	C-17	63.2	63.2
C-6	25.0 [d]	24.8 [d]	C-18	22.5	22.5
C-7	27.7	23.8	C-19	28.2	30.8
C-8	132.0 [e]	132.3 [e]	C-20	207.4	207.4
C-9	143.0	138.9	C-21	22.5	22.5
C-10	36.8 [f]	36.2 [f]	CH_3CO	21.4, 21.8	21.4, 21.0
C-11	125.7	124.4	CH_3CO	170.4 [g]	170.6 [g]
C-12	121.2	121.5			

[a] 6 : 4 Mixture of 5-epimers. [b,c,d,e,f,g] Signals may be reversed.

remains equatorial since the half-height width of the H-3α signal (δ 4.8 p.p.m.) is 20 Hz. We favour a *trans*-A/B configuration for the product.*

The 1,2-relationship between the two aromatic methyl groups in the product indicates that the envisaged migration of the C-13 methyl did take place, but that an appropriate intermediate underwent expansion of ring-D, followed by aerial dehydrogenation (Scheme 2). Similar oxidation of steroid-polyenes in trifluoroacetic and other acids has been observed.[1,14]

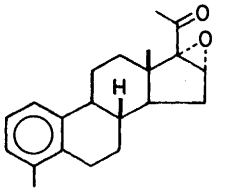


SCHEME 2

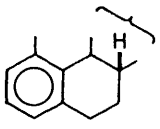
In the allylic bromination–dehydrobromination of 16α,17α-epoxypregnenolone acetate (2), a number of by-products were formed which are similar to those obtained by Hanson and Organ from 3β-hydroxy-5-pregnenes.[15] Using collidine as the dehydrobrominating reagent, besides the homoannular 5,7-diene (3), there was

* The 3β-acetoxy group of a *cis*-A/B C-aromatic steroid in a 'non-steroid' conformation would also be equatorial [see (18)]. However earlier work by us [1] indicated that for the C-aromatic steroid (1) the 'non-steroid' conformation is not the predominant one.

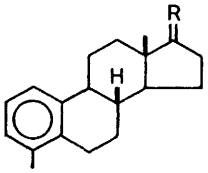
isolated by fractional crystallisation, minor amounts of the heteroannular 4,6-diene (8) with u.v. absorption at 232, 239, and 247 nm. Presence of unsaturation between C-6 and C-7 is shown by the relatively large vicinal coupling between the vinyl protons at these positions (10 Hz). As referred to earlier, where the 6,7-*bond* has low double-bond character the corresponding coupling is smaller (6 Hz). That the other double-bond is at position 4(5) is shown by the low-field position of the H-3α signal (δ 5.45) which overlaps with that due to H-4 [*cf.* the analogue (5), Table 1]. For the 16α,17α-epoxy-20-oxo-steroids (2) and (10), protons of C-13 methyl groups resonate at δ 1.06 and 1.08. The corresponding chemical shift for the 4,6-diene (8) is δ 1.10, which indicates that the B/C junction in (8) is the normal *trans* one.



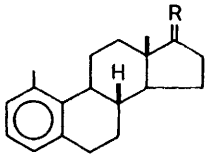
(19a)



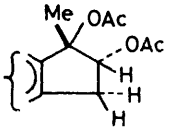
(19b)



(20a) R = H_2
(21a) R = O



(20b) R = H_2
(21b) R = O



(22)

With trimethyl phosphite as dehydrobrominating agent, by-products formed are an A-aromatic steroid (19a) and a second heteroannular diene, *viz.* the $\Delta^{6,8(14)}$-product (7). The latter with u.v. absorption at 245 nm has an ^{1}H n.m.r. spectrum showing signals for only two vinyl protons which are vicinal (see Table 1). The heteroannular diene system must then be placed at positions 6,8(14). The allylic protons at C-5, lying in the deshielding zone of the diene system, give rise to signals at δ 2.35 and 2.9 (AB quartet, J_{AB} 17 Hz). In contrast, the C-18 methyl protons are strongly shielded by the diene system, and resonate at δ 0.65. As the H-3α signal is similar in half-height width to those for the *trans*-A/B compounds (12) and (13), a 5α-configuration is indicated. The diene (7) is likely to have been formed from the thermodynamically less-stable homoannular diene (3) during treatment with trimethyl phosphite. The transformation of the diene (3) to the diene (7) by toluene-*p*-sulphonic acid and by sulphur dioxide has been referred to earlier in this paper.

The A-aromatic structure (19a) given to the other by-product from the trimethyl phosphite dehydrobromination is based on the u.v. (see Experimental section) and ^{1}H n.m.r. spectroscopic evidence (Table 1). The molecular weight (310, by mass spectrometry) corresponds to the loss of acetic acid from the dienes (3), (7), or (8). The formation of the A-aromatic product may be envisaged as a dienol-type rearrangement *via* a triene intermediate formed from, for example, (8) by elimination of acetic acid. We favour structure (19a) over structure (19b) on the basis of the ^{1}H chemical shifts of the aromatic methyl group. The observed shift (δ 2.20) is in accord with that of the 4-methyl model compounds (20a) and (21a) (δ 2.21), but not with that of the 1-methyl isomers (20b) and (21b) (δ 2.37).[16] The assumption of an 8β,9α-configuration for (19a), implicit in the above deduction, is justified by the observation that, similar to other 16α,17α-epoxy-20-oxopregnanes with the same configuration [*viz.* (2), (8), and (10)], the C-13 methyl resonates near δ 1.04 (see above).

EXPERIMENTAL

General procedures are as described in Part 1 [1] except that (unless otherwise specified) u.v. spectra refer to ethanol solutions. Mass spectrometry (m.s.) data given refer to electron impact (EI) unless otherwise stated; those marked † indicate that the exact mass was determined and * indicates that a metastable transition was observed. N.m.r. data for ^{1}H (100 MHz) and ^{13}C (20 MHz) are collated in Tables 1 and 2 respectively.

Bromination and Dehydrobromination of 3β-*Acetoxy*-16α,17α-*epoxypregn*-5-*en*-20-*one* (2).—(*a*) A mixture of *N*-bromosuccinimide (15 g) and compound (2) (30 g) in carbon tetrachloride (2 l) was heated under reflux for 20 min while being exposed to a 40-W tungsten lamp. The brominated steroid (obtained after removal of succinimide by filtration, and of carbon tetrachloride by evaporation) was dissolved in xylene (1 l) and heated under reflux with collidine (100 ml) for 45 min. After removal of collidine hydrobromide by filtration followed by washing with water, collidine, and xylene were evaporated under vacuum to give, on several crystallisations from methanol, needles of 3β-*acetoxy*-16α,-17α-*epoxypregn*-5,7-*dien*-20-*one* (3) (17 g), m.p. 174—177 °C, $\lambda_{max.}$ 271 (log ε 3.97), 282 (log ε 4.02), and 294 nm (log ε 3.76); *m/e* 370 (1%, $M^{+\bullet}$), 328 (3%, $[M - CH_2CO]^+$), 310 (15%, $[M - HOAc]^+$), 295 (24%, $[310 - Me]^+$), 268 (25%, $[310 - CH_2CO]^+$) *, 267 (100%, $[310 - Ac]^+$), 252, 251, 250, 249 (8% each), 81 (25%), and 43 (81%) (Found: C, 74.25; H, 8.1. $C_{23}H_{30}O_4$ requires C, 74.55; H, 8.15%).

In an experiment under identical conditions a 2 : 1 mixture (25 g) of the 5,7- and 4,6-dienes (3) and (8) was obtained and separated by fractional crystallisation from methanol. The more-soluble component, 3β-*acetoxy*-16α,-17α-*epoxy*-4,6-*pregnadien*-20-*one* (8), m.p. 170—172 °C, has $\lambda_{max.}$ (MeOH) 232 (log ε 4.16), 239 (log ε 4.20), and 247 nm (log ε 4.01) (Found: C, 74.05; H, 8.05. $C_{23}H_{30}O_4$ requires C, 74.55, H, 8.15%).

(*b*) *N*-Bromosuccinimide (5.5 g) and the pregn-5-ene (2) (10 g) were heated in refluxing carbon tetrachloride (170 ml) and light petroleum (60 ml) for 45 min. The brominated steroid, worked up as in (*a*), was heated with trimethyl phosphite (8.1 g) in xylene (50 ml) for 1½ h at 125 °C. Upon removal of most of the organic solvents under vacuum and

repeated crystallisation from methanol, the 5,7-diene (3) was obtained in 13% yield.

In an experiment in which the bromination step was prolonged to 9 h the dehydrobromination products, separated by chromatography over alumina, consisted of the 5,7-diene (3), the 6,8(14)-diene (7) (see below) (1.3 g), and 16α,17α-*epoxy*-4-*methyl*-19-*norpregna*-1,3,5(10)-*trien*-20-*one* (19a) (2.2 g), m.p. 174—175 °C, as needles from methanol, $\lambda_{max.}$ 285 nm (log ε 2.69); *m/e* 310 (38%, $M^{+\cdot}$) †, 267 (3%, $[M^+ - Ac]^+$), 266 (3%), 249 (8%, $[267 - H_2O]^+$) †, 43 (100%) (Found: *M* by m.s., 310.193 7. $C_{21}H_{26}O_2$ requires 310.193 2).

Reactions of 3β-*Acetoxy*-16α,17α-*epoxypregna*-5,7-*dien*-20-*one* (3) *with Acid Reagents*.—(*a*) A solution of the epoxy-5,7-diene (3) (0.5 g) and toluene-*p*-sulphonic acid (30 mg) in benzene (14 ml) was refluxed in a Dean-Stark apparatus. On work-up 3β-*acetoxy*-16α,17α-*epoxypregna*-6,8(14)-*dien*-20-*one* (7) (0.18 g) was obtained as needles from light petroleum, m.p. 208—210°, $\lambda_{max.}$ (MeOH) 245 nm (log ε 4.25); *m/e* 370 (42%, $M^{+\cdot}$) †, 310 (100%, $[M - HOAc]^+$) †, 295 (30%, $[310 - Me^+]$) †, 277 (12%, $[295 - H_2O]^+$) †, 267 (59%, $[310 - Ac]^+$) †, and 239 (43%) (Found: *M*, by m.s., 370.213 6. $C_{23}H_{30}O_4$ requires 370.214 4).

(*b*) To a solution of the diene (3) (1.7 g) and hydroquinone (0.1 g) in benzene (10 ml) and pyridine (2.5 ml) was added liquid sulphur dioxide (15 ml), and the solution was heated in a sealed tube for 16 h at 100 °C. The 6,8(14)-diene (7) (1.3 g) was obtained on evaporation of solvent and crystallisation from methanol.

Opening of 16α,17α-*Epoxide Rings with Boron Trifluoride–Acetic Anhydride*.—(*a*) A solution of 3β-acetoxy-16α,17α-epoxypregna-5,7-dien-20-one (3) (1.0 g) in a mixture of boron trifluoride–diethyl ether complex (0.1 ml), acetic anhydride (7 ml), and dry benzene (27 ml) was stirred under nitrogen and at room temperature for 70 min, and then poured into ice–water. The product obtained on work-up was chromatographed over alumina to give 3β,16α-*diacetoxy*-17β-*methyl*-18-*norpregna*-5,7,13-*trien*-20-*one* (4) (0.79 g) forming prisms from methanol, m.p. 192—194 °C; $\lambda_{max.}$ 304 (log ε 4.23), 319 (log ε 4.33), and 335 nm (log ε 4.26); *m/e* 412 (4%, $M^{+\cdot}$) †, 352 (7%, $[M - HOAC]^+$) *,†, 310 (21%), 309 (100%, $[352 - Ac]^+$) *,†, 251 (19%), 250 (17%), 249 (37%, $[309 - HOAc]^+$] *,†, 81 (18%), and 43 (59%) (Found: *M* by m.s., 412.223 2. $C_{25}H_{32}O_5$ requires 412.224 8).

(*b*) On similar treatment, 3β-acetoxy-16α,17α-epoxypregna-6,8(14)-dien-20-one (7) yielded the same rearranged triene (4).

(*c*) 16α,17α-Epoxypregn-4-ene-3,20-dione (10) on similar treatment overnight gave 3,16α-*diacetoxy*-17β-*methyl*-18-*norpregna*-3,5,13-*trien*-20-*one* (11) (70%), m.p. 178—181 °C, *m/e* (methane chemical ionisation) 441 (2%, $[M + C_2H_5]^+$), 413 (14%, MH^+), 371 (9%, $[MH - CH_2CO]^+$), 353 (32%, $[MH - HOAc]^+$), and 311 (20%, $[353—CH_2CO]^+$) (Found: C, 72.65; H, 7.6. $C_{25}H_{32}O_5$ requires C, 72.8; H, 7.8%). The same product was obtained in 35% yield from (10) using toluene-*p*-sulphonic acid and acetic anhydride as was described by Heusler and Wettstein for the corresponding reaction on epoxide (2).[2]

Reactions of 3β,16α-*Diacetoxy*-17β-*methyl*-18-*norpregna*-5,7,13-*trien*-20-*one* (4) *with Acid Reagents*.—(*a*) The triene (4) (60 mg) in chloroform (3 ml) saturated with hydrogen chloride was set aside for 72 h at room temperature. The main product, which failed to crystallise after purification by preparative t.l.c. (silica) has a ^1H n.m.r. spectrum characterised by signals near δ 7 due to aromatic protons, and those typical of protons shown on the partial structure (22) [*cf.* (5) and (6)]. A crude product with similar ^1H n.m.r. spectra was obtained when the triene (4) was treated with hydrogen chloride in acetic acid.

(*b*) To a solution of the crude triene (4) [prepared from 100 mg of diene (3)] in ethanol (5 ml) and benzene (0.6 ml) was added 0.2 ml of 10M hydrochloric acid, and the resulting solution was refluxed for 6 h. The mixture obtained on work-up was treated with potassium hydroxide (30 mg) in a mixture of methanol (5 ml), acetone (0.4 ml), and water (0.6 ml). After acidification, the product was worked-up, and chromatographed over silica (preparative t.l.c.) to give a crystalline fraction (20 mg), m.p. 170.5—172 °C, $\lambda_{max.}$ 224 (log ε 2.47) and 276 nm (log ε 4.34); *m/e* 292 (100%, $M^{+\cdot}$), 274 (15%, $[M - H_2O]^+$), 259 (15%, $[274 - CH_3]^+$), and 248 (15%); *m/e* (methane chemical ionisation) 321 (7%, $[M + C_2H_5]^+$), 293 (40%, MH^+), 292 (25%), 275 (100%, $[MH - H_2O]^+$), and 85 (100%); δ(CCl_4–$CDCl_3$) 2.2, 2.25, 2.35 (3 H singlets), 4.1 (1 H, $W_{h/2}$, 18 Hz), 7.1 and 7.5 (ABq, *J* 9 Hz), and 7.4 (1 H).

Formation of c-*Aromatic Steroids*.—A solution of the triene (3) (0.5 g) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.6 g) in dry dioxan (10 ml) was stirred at room temperature for 2 h. The resulting suspension was filtered and the filtrate filtered through a dry column of neutral alumina (20 g). Evaporation of the eluant (ethyl acetate) and crystallisation of the residue from methanol gave 3β,16α-*diacetoxy*-17β-*methyl*-18-*norpregna*-4,6,8,11,13-*pentaen*-20-*one* (5) (0.33 g) which on recrystallisation from acetone had m.p. 180—182 °C, $\lambda_{max.}$ 304 (log ε 4.21), 316 (log ε 4.27), and 332 nm (log ε 4.07); *m/e* (methane chemical ionisation) 437 (3%, $[M + C_2H_5]^+$), 409 (50%, MH^+), 349 (100%, $[MH - HOAc]^+$), 289 (15%, $[MH - 2HOAc]^+$), and 247 (27%, $[289 - CH_2CO]^+$) (Found: C, 73.45; H, 6.9; $C_{25}H_{28}O_5$ requires C, 73.5; H, 6.9%).

A solution of compound (5) (77 mg) in ethyl acetate (10 ml) was hydrogenated overnight in the presence of 10% palladium-on-charcoal (10 mg). On evaporation of the filtered reaction solution there was obtained a 6 : 4 mixture of 3β,16α-diacetoxy-17β-methyl-18-nor-5α-pregna-8,11,13-trien-20-one and its 5β-epimer (6) with ^1H and ^{13}C n.m.r. data as shown in Tables 1 and 2; *m/e* 369 (70%, $[M - CH_3CO]^+$), 327 (38%, $[369 - CH_2CO]^+$), 311 (52%), 310 (81%, $[369 - OAc]^+$), 309 (100%, $[369 - HOAc]^+$), 269 (29%), 267 (58%, $[327 - HOAc]^+$), 251 (65%), 185 (28%), 159 (30%), and 141 (57%); *m/e* (methane chemical ionisation) 413 (20%, MH^+) †, 353 (100%, $[MH - HOAc]^+$) †, 293 (18%, $[MH - 2HOAc]^+$) †, and 251 (28%) (Found: *M* of MH^+ in methane chemical ionisation m.s. 413.233 2; $C_{25}H_{33}O_5$ requires 413.232 8).

Diels–Alder Addition of 4-*Phenyl*-1,2,4-*triazoline*-3,5-*dione to* 3β-*Acetoxy*-16α,17α-*epoxypregna*-5,7-*dien*-20-*one* (3).—Following the procedure of Gillis and Hagarty [17] a dichloromethane solution (50 ml) of lead tetra-acetate (3.6 g) was added dropwise and with stirring to an anhydrous solution of 4-phenylurazole [18] (0.96 g) and the 5,7-diene (3) (2.0 g) in dichloromethane (50 ml) at 0 °C. After being stirred at room temperature for 2½ h, the solution was worked-up (including washing by 0.1M-hydrochloric acid and sodium hydroxide) to give, on addition of methanol, crystals of the *epoxy-adduct* (12) (2.25 g), m.p. 212—214 °C, *m/e* 545 (1%, $M^{+\cdot}$), 368 (6%, $[M$ — phenylurazole$]^+$), 310 (10%) †‡, 308 (16%, $[368 - HOAc]^+$)*†, 295 (20%, $[310 - Me]^+$) †‡, 293 (11%, $[308 - Me]^+$) †, 268 ‡, 267 (100%, [310 —

‡ Ions of same *m/e* as those given by the 5,7-diene (3).

Ac]$^+$) *†‡, 249—252 (*ca.* 25%) †, 177 (76%, [phenyl-urazole]$^+$) †, 119 (66%, [CONPh]$^+$, from 177) †*, 91 (25%, [119 − CO]$^+$) *†, 81 (20%) ‡, 77 (100%, Ph$^+$), 43 (100%) † (Found: C, 67.7; H, 6.45; N, 7.35. $C_{31}H_{35}N_3O_6$ requires C, 68.25; H, 6.45; N, 7.7%).

Opening of the Epoxide in the Epoxy-adduct (8).—A solution of the adduct (12) (2.0 g) in ethanol-free chloroform (35 ml) was saturated with dry hydrogen chloride. After 18 h the mixture was worked-up to give, upon addition of methanol, crystals of the 16,17-*chlorohydrin-adduct* (13) (1.48 g), m.p. 224—226 °C, *m/e* 408/406 [1/2%, $M^{+\bullet}$ of (10)], 406/404 (2/3%, [M − phenylurazole]$^+$), 348/346 (7/21%, [408/406 − HOAc]$^+$), 346/344 (21/10%, [406/404 − HOAc]$^+$), 310 (100%, [346/348 − HCl]$^+$), 295 (14%, [310 − Me]$^+$), 293 (25%), 267 (19%, [310 − Ac]$^+$), 239 (15%), 211 (15%), 209 (21%), 177 (70%, [phenylurazole]$^+$), 119 (82%, PhNCO$^+$), 91 (35%, NPh$^+$), 81 (30%), 77 (24%, Ph$^+$), and 43 (88%); *m/e* (methane chemical ionisation), 409/407 [1% each, MH$^+$ of (10)], 407/405 (1% each, [MH − phenylurazole]$^+$), 373 (1%, [409/407 − HCl]$^+$), 371 (1%, [407/405 − HCl]$^+$), 347/345 (12% each, [407/405 − HOAc]$^+$), 311 (17%, [371 − HOAc]$^+$), 205 (14%), 179 (65%), 178 (100%, MH$^+$ of phenylurazole), 120 (14%, PhNHCO$^+$) (Found: C, 62.6; H, 6.25; N, 6.85. $C_{31}H_{36}ClN_3O_6,CH_3OH$ requires C, 62.6; H, 6.55; N, 6.85%).

Reduction of the Chlorohydrin-adduct (13) *and Conversion into the* 5,7-*Dienes* (15) *and* (16).—A mixture of lithium aluminium hydride (0.24 g) and of the chlorohydrin-adduct (9) (0.20 g) in anhydrous tetrahydrofuran (15 ml) was heated under reflux for 18 h. Inorganic material formed upon destruction of excess of the reagent was removed by filtration of the dried (sodium sulphate) tetrahydrofuran solution. The residue obtained on evaporation of the filtrate was washed with chloroform to remove aromatic amines yielding 3β,17α,20ξ-*trihydroxypregna*-5,7-*diene* (15) (0.14 g) as needles from acetone, m.p. 228—230 °C, $\lambda_{max.}$ (MeOH) 272 (log ε 3.96), 282 (log ε 3.98), and 294 nm (log ε 3.73); *m/e* (methane chemical ionisation) 333 (3%, MH$^+$), 332 (5%, M^+), 315 (50%, [MH − H_2O]$^+$), 298 (23%), 297 (100%, [MH − 2H_2O]$^+$) (Found: C, 75.25; H, 9.5. $C_{21}H_{32}O_3$ requires C, 75.85; H, 9.7%). With standard work-up using acid, by-products were obtained.

On treatment overnight with acetic anhydride in pyridine at room temperature (15) (0.20 g) gave 3β,20ξ-*diacetoxy*-17α-*hydroxypregna*-5,7-*diene* (16) as needles (0.22 g) from acetone, m.p. 224—227°, $\lambda_{max.}$ (MeOH) 272 (log ε 3.97), 282 (log ε 4.00), and 294 nm (log ε 3.75) (Found: C, 71.5; H, 8.6. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.7%).

3β-*Acetoxy*-17,17a-*dimethyl*-D-*homo*-18-*norandrosta*-8,11,-13,15,17(17a)-*pentaene* (17).—A solution of the 17α-alcohol (12) (0.21 g) in trifluoroacetic acid (3 ml) was heated to 70—75 °C for 5 hr. The solid obtained on evaporation of the solvent was chromatographed twice on Kieselgel GF (eluant, 5% acetone in cyclohexane) to give the D-*homo steroid* (17) as needles (25 mg) from methanol, m.p. 165—167 °C, $\lambda_{max.}$ (EtOH) 284 (log ε 3.66), 313 (log ε 3.16), and 327 nm (log ε 3.13); *m/e* 336 (85%, $M^{+\bullet}$) †, 276 (3%, [M − HOAc]$^+$), 261 (100%, [M − Me − HOAc]$^+$) † (Found: M, by m.s., 336.209 4. $C_{23}H_{28}O_2$ requires 336.208 8).

We thank Professor S. Sternhell, Assoc. Professor A. V. Robertson, and Drs. J. L. E. Nemorin and I. R. Brown of the School of Chemistry of Sydney University for 100 MHz ^{1}H n.m.r. and high resolution m.s. data; Professor J. S. Shannon and Mr. Derek Nelson of the University of New South Wales, and Dr. J. Vine of this department for chemical ionisation mass spectra. The dehydrobromination reactions on compound (2) were initiated by Mr. T. C. Yan. The work was supported by a University Research Grant of the University of Sydney.

[8/2095 *Received, 5th December,* 1978]

REFERENCES

[1] Part 1, H. T. A. Cheung, R. G. McQueen, A. Vadasz, and T. R. Watson, *J.C.S. Perkin I*, 1979, 1048.
[2] K. Heusler and A. Wettstein, *Chem. Ber.*, 1954, **87**, 1301.
[3] H. L. Herzog, O. Gnoi, L. Mandell, G. G. Nathansohn, and A. Vigevani, *J. Org. Chem.*, 1967, **32**, 2907, and reference cited therein; V. Tortorella and A. Romeo, *Gazzetta*, 1962, **92**, 1118.
[4] L. H. Sarett, A. A. Patchett, and S. L. Steelman, *Progr. in Drug Research*, 1963, **5**, 11; D. Lednicer and L. A. Mitscher, 'The Organic Chemistry of Drug Synthesis,' Wiley, New York, 1977, pp. 195—200.
[5] C. L. Hewett, J. Redpath, and D. S. Savage, *J.C.S. Perkin I*, 1975, 1288.
[6] (*a*) D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanism,' Elsevier, Amsterdam, 1968, pp. 288—289; (*b*) *ibid.*, pp. 294—297.
[7] N. L. Wendler, 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, vol. 1, pp. 1114—1121.
[8] G. D. Laubach, E. C. Schreiber, E. J. Agnello, and K. J. Brunings, *J. Amer. Chem. Soc.*, 1956, **78**, 4743.
[9] R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Letters*, 1962, 615; S. S. H. Gilani and D. J. Triggle, *J. Org. Chem.*, 1966, **31**, 2397.
[10] N. Bosworth, A. Emke, J. M. Midgley, C. J. Moore, W. B. Whalley, G. Ferguson, and W. C. Marsh, *J.C.S. Perkin I*, 1977, 805.
[11] D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1971, 1968.
[12] B. Löken, S. Kaufmann, G. Rosenkranz, and F. Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 1738.
[13] C. L. Hewett, S. G. Gibson, I. M. Gilbert, J. Redpath, and D. S. Savage, *J.C.S. Perkin I*, 1973, 1967, and references cited therein.
[14] J. Torreilles and A. C. de Paulet, *Bull. Soc. chim. France*, 1968, 4886.
[15] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.
[16] E. Capsi, T. A. Wittstruck, and P. K. Grover, *Chem. and Ind.*, 1962, 1716.
[17] B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, 1967, **32**, 330.
[18] R. C. Cookson *et al.*, 'Organic Synthesis,' ed. R. E. Benson, Wiley, New York, vol. 51, pp. 121—126.