Steroids. Part XV.[1] Rearrangements of 9- and 10-Hydroxy-5β-methyl-19-nor-steroids

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The backbone rearrangement of 10β-hydroxy-5β-methyl-19-nor-steroids is susceptible to changes in substituents at C(6) and to changes in the reaction medium. 9α-Hydroxy-5β-methyl-19-nor- and 10α-hydroxy-5β-methyl-19-nor-9β-steroids are simply dehydrated. The mechanisms of the backbone and the related Westphalen rearrangements are discussed. An anthrasteroid rearrangement of a 10β-hydroxy-5β-methyl-6-oxo-19-nor-steroid is reported.

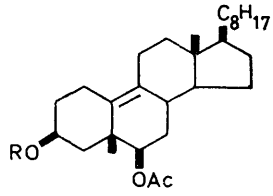
THE well known Westphalen rearrangement of 5α-hydroxy-steroids,[2] and the related boron trifluoride-catalysed rearrangements of 4,5- and 5,6-epoxy-steroids,[3] proceed nominally through C(5) and C(10) carbonium ions. The epoxide rearrangements are frequently more complex and extensive than those of the hydroxy-compounds and give backbone-rearranged products.

[1] Part XIV, I. G. Guest and B. A. Marples, *J. Chem. Soc.* (*C*), 1971, 1468.

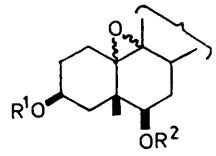
[2] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 257, and references cited there.

[3] (*a*) J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1966, **22**, 3195; (*b*) B. N. Blackett, J. M. Coxon, M. P. Hartshorn, and K. E. Richards, *ibid.*, 1969, **25**, 4999, and previous papers.

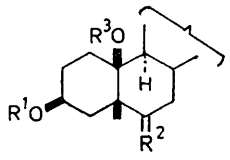
There appears to be considerable kinetic [4] and stereochemical [3,5] evidence which suggests that the epoxide rearrangements are non-concerted and involve discrete C(5) carbonium ion intermediates. We have presented evidence in support of a concerted first step in the Westphalen rearrangement,[6-8] whereas Coxon and Hartshorn and their co-workers favour a mechanism involving a discrete C(5) carbonium ion.[2,9] We undertook a study of the rearrangements of 9- and 10-hydroxy- and 9,10-epoxy-steroids to obtain more information about the

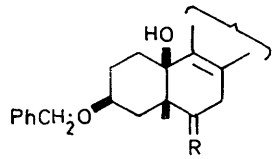


(1) R = $PhCH_2$
(2) R = Ac



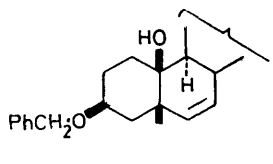
(3) R^1 = $PhCH_2$, R^2 = Ac, 9α,10α
(4) R^1 = $PhCH_2$, R^2 = Ac, 9β,10β
(5) R^1 = $PhCH_2$, R^2 = H, 9α,10α
(6) R^1 = $PhCH_2$, R^2 = H, 9β,10β
(7) R^1 = R^2 = H, 9α,10α





(8) R^1 = $PhCH_2$, R^2 = β-OH,H, R^3 = H
(9) R^1 = H, R^2 = β-OH,H, R^3 = H
(10) R^1 = $PhCH_2$, R^2 = β-OAc,H, R^3 = H
(11) R^1 = Ac, R^2 = β-OAc,H, R^3 = H
(12) R^1 = $PhCH_2$, R^2 = O, R^3 = H
(13) R^1 = $PhCH_2$, R^2 = β-OTs,H, R^3 = H
(14) R^1 = H, R^2 = H_2, R^3 = H
(15) R^1 = $PhCH_2$, R^2 = O, R^3 = Ac

(16) R = β-OH,H
(17) R = β-OAc,H
(18) R = O



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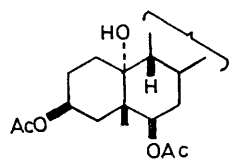


(20)

controlling factors in these rearrangements, with particular reference to the steps which follow methyl migration to C(5). We report here the backbone rearrangements of the 10β-hydroxy-compounds (8), (12), and (14), and the simple dehydration of the 10α-hydroxy-compound (20) and the 9α-hydroxy-compound (21).* The full details of our studies on the 9,10-epoxides [10] will be reported later.

The required 9- and 10-hydroxy-compounds were prepared from the Δ^9-compound (1).[11] Oxidation of compound (1) with monoperphthalic acid gave a mixture of the epoxides (3) (53%) and (4) (37%), which were separated by preparative t.l.c. The low chemical shift of the 5-methyl signal in the ^1H n.m.r. spectrum of the α-epoxide (3) (τ 8·80) relative to that of the β-epoxide (4) (τ 8·90) supports these assignments.[12] Also, the hydrolysed α-epoxide (5) shows no evidence for hydrogen-bonding in the i.r. spectrum, whereas the β-epoxide (6) is strongly hydrogen bonded.[13] Reduction of the β-epoxide (6) with lithium aluminium hydride afforded the 6β,10β-diol (8) (60%), the allylic alcohol (16) (13%), and the triol (9) (26%). The usual stereoelectronically controlled diaxial opening of epoxides [14] could lead to a 9β-hydroxy-10α-steroid, as an alternative to compound (8), if the epoxide (6) reacted in conformation (B) rather than conformation (A) (Figure 1). However, the ^1H

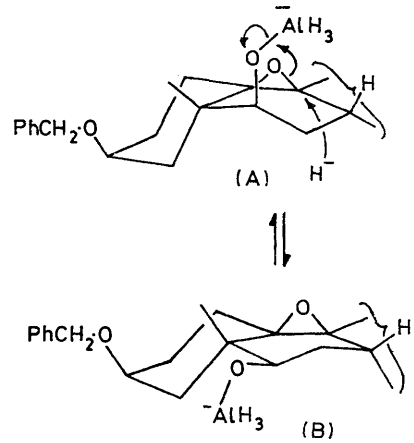


FIGURE 1

n.m.r. spectra of compound (8) and its monoacetate (10) show that in each case the 6-methine proton is equatorial ($W_{\frac{1}{2}}$ 8 and 6 Hz, respectively), and thus confirm the 9α,10β-stereochemistry. The preferred attack at C(9) may be assisted as shown in Figure 1, since the 6-hydroxy-group of the epoxide (6) would react rapidly with lithium aluminium hydride to give the $-O\bar{A}lH_3$ group.

Elemental analysis indicated that the allylic alcohol (16) was isomeric with the epoxide (6). Acetylation to the monoacetate (17) and oxidation with Jones reagent [15] to the ketol (18) confirmed the presence of the tertiary hydroxy-group. The high-field positions of the 5-methyl (τ 9·1) and 13-methyl (τ 9·35) signals in the ^1H n.m.r.

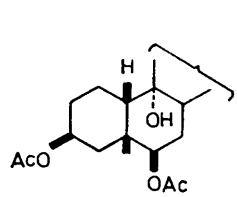
* For a preliminary account of some of this work, see J. G. Ll. Jones and B. A. Marples, *Chem. Comm.*, 1969, 689.

[4] H. W. Whitlock and A. H. Olson, *J. Amer. Chem. Soc.*, 1970, **92**, 5383.
[5] I. G. Guest and B. A. Marples, *J. Chem. Soc.* (*C*), 1971, 576.
[6] J. G. Ll. Jones and B. A. Marples, *Chem. Comm.*, 1970, 126.
[7] J. G. Ll. Jones and B. A. Marples, *J. Chem. Soc.* (*C*), 1970, 2273.
[8] J. G. Ll. Jones and B. A. Marples, *J. Chem. Soc.* (*C*), 1971, 572.
[9] J. M. Coxon, M. P. Hartshorn, and C. N. Muir, *Chem. Comm.*, 1970, 1591.
[10] I. G. Guest and B. A. Marples, *Tetrahedron Letters*, 1969, 3575.
[11] I. G. Guest, J. G. Ll. Jones, B. A. Marples, and M. J. Harrington, *J. Chem. Soc.* (*C*), 1969, 2360.
[12] A. D. Cross, *J. Amer. Chem. Soc.*, 1960, **82**, 3207.
[13] J.-C. Guilleux and M. Mousseron-Canet, *Bull. Soc. chim. France*, 1967, 24.
[14] Ref. 2, p. 112.
[15] C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

spectrum of compound (17) supported the $\Delta^{8(9)}$-structure.[16] The rearrangement of epoxides to allylic alcohols in the presence of lithium aluminium hydride has been previously observed.[17] The i.r. and ^{1}H n.m.r. spectra of the triol (9) show the absence of the benzyl group. Acetylation to the diacetate (11) confirmed the presence of the tertiary hydroxy-group ($\nu_{max.}$ 3635 cm^{-1}), and the ^{1}H n.m.r. spectrum of compound (11) confirmed the equatorial conformation of the 6-methine proton ($W_{\frac{1}{2}}$ *ca.* 5 Hz), and thus the 9α,10β-configuration. Jones oxidation of the 6β,10β-diol (8) gave the ketol (12). Treatment of the 6β,10β-diol (8) with toluene-*p*-sulphonyl chloride in pyridine gave the 6-tosylate (13) and the hydroxy-olefin (19). Attempted reduction of the 6-tosylate (13), in this mixture, with lithium aluminium hydride, afforded only the hydroxy-olefin (19), which was readily identified from its spectroscopic data [$\nu_{max.}$ 3640 cm^{-1} (OH); τ 4·5—5·0 (m, –CH=CH–)]. Hydrogenation of the hydroxy-olefin (19) gave the 3β,10β-hydroxy-compound (14).

The α-epoxide (5) resisted reduction by lithium aluminium hydride, presumably owing to β-face hindrance. Hydrogenolysis of the α-epoxide (5) over palladium gave the epoxy-diol (7). Reduction of the epoxy-diol (7) with lithium in ethylamine gave a mixture which, after acetylation and preparative t.l.c., afforded the diacetate (2) [2] (25%), and the hydroxy-diacetates (20) (25%) and (21) (41%). The i.r. spectra of the hydroxy-diacetates (20) and (21) show the presence of the tertiary hydroxy-groups ($\nu_{max.}$ 3640 cm^{-1}). The 6-methine proton signals in the ^{1}H n.m.r. spectra confirm the 10α-configuration for the compound (20) (axial H, $W_{\frac{1}{2}}$ *ca.* 16 Hz) and the 10β-configuration for the compound (21) (equatorial H, $W_{\frac{1}{2}}$ *ca.* 6 Hz). The 9β-configuration for compound (20) is assigned assuming the normal diaxial opening for epoxides.[14] The conformational mobility in the B-ring of the epoxide (7) is similar to that indicated for the β-epoxide (6) (Figure 1) and allows diaxial cleavage by attack at either C(9) or C(10).

Treatment of the 6β,10β-diol (8) and the 10-hydroxy-compound (14) with toluene-*p*-sulphonic acid in acetic anhydride at 100° gave high yields of the backbone-rearranged products (22) (77%) and (23) [18] (80%), respectively. The ^{1}H n.m.r. spectra of these compounds were characteristic of $\Delta^{13(17)}$-compounds. Double irradiation 88 Hz downfield from the C(21)H$_3$ doublet for each of the compounds caused its collapse to a singlet (τ *ca.* 9·07).[3] The mass spectrum of compound (22) showed an intense peak at *m/e* 421 due to the characteristic loss of the side chain.[19] Treatment of the hydroxy-ketone (12) with toluene-*p*-sulphonic acid in acetic anhydride at 100° gave the backbone-rearranged compound (24) (20%), the $\Delta^{1(10)}$-compound (26) (25%), and the acetate (15) (13%). The ketone (24) failed to isomerise with base to a Δ^7-6-ketone thus excluding the $\Delta^{8(9)}$- and $\Delta^{8(14)}$-structures. The ^{1}H n.m.r. spectrum of compound (24) was typical of a backbone-rearranged



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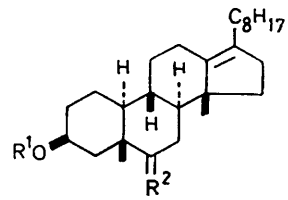
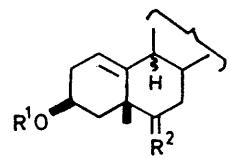
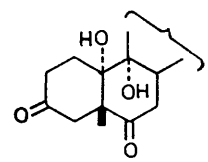


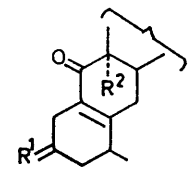
(22) R^1 = PhCH$_2$, R^2 = β-OAc,H
(23) R^1 = Ac, R^2 = H$_2$
(24) R^1 = PhCH$_2$, R^2 = O
(25) R^1 = PhCH$_2$, R^2 = β-OH,H



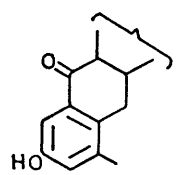
(26) R^1 = PhCH$_2$, R^2 = O, 9α
(27) R^1 = Ac, R^2 = β-OAc,H, 9β



(28)



(29) R^1 = O, R^2 = OH
(30) R^1 = β-O·CH$_2$Ph, R^2 = H



(31)

compound {τ 8·67 (s, 5β-Me), 9·03 [shoulder, lower branch of C(21)H$_3$ doublet], 9·04 (s, 14β-Me), and 9·12 [upper branch of C(21)H$_3$ doublet and lower branch of C(26)H$_3$ and C(27)H$_3$ doublets]}. Further confirmation of the structure (24) was obtained by its preparation by Jones [15] oxidation of the alcohol (25), which was obtained by hydrolysis of compound (22). The ^{1}H n.m.r. spectrum of compound (26) shows a vinyl proton signal (τ 4·4—4·7) and the chemical shifts of the 5β- and 13β-methyl groups (τ 8·78 and 9·33, respectively) suggest the $\Delta^{1(10)}$-structure rather than the alternative $\Delta^{9(11)}$-structure.[16,20] The i.r. spectrum of compound (15) shows ketone and ester carbonyl bands ($\nu_{max.}$ 1720 and 1740 cm^{-1}), and elemental analysis and the ^{1}H n.m.r. spectrum confirm that simple acetylation of compound (12) has occurred.

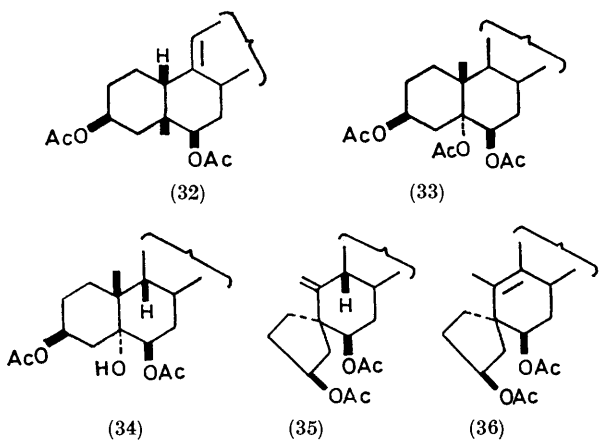
Slates and Wendler [21] have reported the base-catalysed rearrangement of the 9α,10α-dihydroxy-3,6-diketone (28) to the anthrasteroid (31). The proposed mechanism involves retroaldolisation of the ketone (28) and the intermediacy of the enone (29). The ketol (12) was

[16] N. S. Bhacca and D. H. Williams, ' Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, ch. 2.
[17] Y. Chretian-Bessiere, H. Desalbres, and P. Monthéard, *Bull. Soc. chim. France*, 1963, 2546.
[18] J. M. Coxon, M. P. Hartshorn, C. A. Lane, K. E. Richards, and U. M. Senanayake, *Steroids*, 1969, **14**, 441.
[19] (*a*) J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Letters*, 1966, 2125; (*b*) G. Snatzke and H. W. Fehlhaber, *Annalen*, 1964, **676**, 188.
[20] A. Fischer, M. J. Hardman, M. P. Hartshorn, D. N. Kirk, and A. R. Thawley, *Tetrahedron*, 1967, **23**, 159.
[21] H. L. Slates and N. L. Wendler, *Experientia*, 1961, **17**, 161.

converted in an analogous manner into the enone (30). The structure of compound (30) was supported by mass spectrometry (molecular formula $C_{34}H_{50}O_2$) and by its i.r. ($\nu_{max.}$ 1680 cm^{-1}) and u.v. ($\lambda_{max.}$ 248 nm) spectra. The ^1H n.m.r. spectrum of compound (30) showed a doublet, centred at τ 9·05, which is assigned to the A-ring methyl group.

Treatment of the 10α-hydroxy-compound (20) and the 9α-hydroxy-compound (21) with toluene-*p*-sulphonic acid in acetic anhydride at 100° resulted in simple dehydration and gave no appreciable quantities of backbone-rearranged products. Compound (20) afforded the Westphalen diacetate (2) [2] (50%) and the $\Delta^{1(10)}$-compound (27) (11%). The structure (27) is supported by the ^1H n.m.r. spectrum, which shows a vinyl proton signal (τ 4·5—4·7) and a characteristic chemical shift for the 13β-methyl group (τ 9·32).[16,20] Compound (21), under similar conditions, afforded the compound (2) [2] (6·5%) and the $\Delta^{9(11)}$-compound (32) (36%). Unchanged compound (21) (28%) was isolated. The structure (32) is supported by the ^1H n.m.r. spectrum, which shows a vinyl proton signal (τ 4·45—4·65) and the 13β-methyl signal at higher field (τ 9·39) than that in compound (26).[16]

The low yield of backbone-rearranged product obtained from the ketol (12), compared to that from the compounds (8) and (14), is probably due to the relatively



(32) (33) (34) (35) (36)

large $-I$ effect of the 6-oxo-group, which inhibits the migration of hydride ion from C(8) to C(9). Similar effects have recently been noted for 6- and 7-substituents in related rearrangements.[18,22,23] The smooth backbone rearrangements of compounds (8) and (14) are in marked contrast to the Westphalen rearrangement of 5α-hydroxy-steroids. The Δ^9-compounds are not intermediate in the formation of the $\Delta^{13(17)}$-compounds since the Westphalen derivative (1) was unchanged in acetic anhydride and toluene-*p*-sulphonic acid at 100°. The contrast in the extent of rearrangement is probably due, in part, to a difference in carbonium ion character at C(10). The backbone rearrangements of the 10β-hydroxy-compounds are facilitated by the *anti* and planar conformation of the 10β-OH and the 9α-H, which would allow a concerted hydride ion migration from C(9). In the Westphalen rearrangement, the 10-methyl group migrates across the face of the molecule to C(5). Thus, efficient overlap of the orbital of the hydride ion with the electron-deficient orbital at C(10) will be geometrically less favourable, and more carbonium ion character will be developed at C(10) (Figure 2). In this

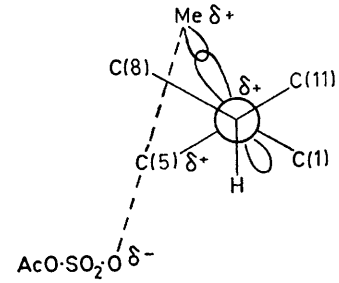


FIGURE 2 Westphalen migration of $C(19)H_3$ from C(10) to C(5)

situation, proton elimination competes very effectively with hydride migration. No account is taken in this argument of the different reagents and reaction conditions. The reaction of compound (8) under Westphalen rearrangement conditions (H_2SO_4–Ac_2O–AcOH) [2] gave the Westphalen compound (1) (60%) and the $\Delta^{13(17)}$-compound (22) (40%). Thus, it appears that the high yields of backbone-rearranged products from compounds (8) and (14) are due to the combination of favourable stereoelectronic arrangement and reaction medium. It is possible that the Westphalen reaction medium has a higher relative basicity or better dissociating and solvating properties than toluene-*p*-sulphonic acid in acetic anhydride. A similar product dependence on reaction medium has been reported by Coxon and Hartshorn and their co-workers in a study of the rearrangement of the triacetate (33).[18] Addition of acetic acid to the boron trifluoride–ether–acetic anhydride medium increased the yield of Δ^9-compounds relative to that of $\Delta^{13(17)}$-compounds.

The 10α-hydroxy-compound (20) gave a high Saytzeff : Hofmann product ratio (*ca.* 4·5 : 1), whereas the 9α-hydroxy-compound (21) gave the reverse (*ca.* 1 : 5·5). Under the reaction conditions employed, Saytzeff control would be expected to predominate since the transition states should have considerable cationic character (*E*1 or *E*2). The removal of the 10-H or the 8-H may be inhibited by the electron-withdrawing acetoxy-group at C(6). In principle, compounds (20) and (21) could undergo the backbone rearrangement to a 10β-epimer of the normal backbone-rearranged steroids. It is not possible to say whether the failure of compounds (20) and (21) to rearrange is due to thermodynamic or to kinetic control.

It is generally agreed that a fully concerted backbone

[22] J. M. Coxon and M. P. Hartshorn, *Tetrahedron Letters*, 1969, 105.

[23] J.-C. Jaquesy, R. Jacquesy, and M. Petit, *Tetrahedron Letters*, 1970, 2595.

rearrangement is unlikely.[3,4,24] However, the results described here and our earlier results [10] suggest that such rearrangements are facilitated when a synchronous mechanism is allowed by the geometry of the system. In these circumstances, and in the absence of other factors,[5] movement of the migrating group probably commences before complete ionisation. It appears also that the complete ionisation process requires very little more energy than the synchronous one.[3,4] It is clear that the nature of the reaction medium is important. In the reactions of epoxides with boron trifluoride–ether in benzene, the medium has no general base which may remove a proton (except the co-ordinated ether), and it is unlikely that the carbonium ion intermediates would be satisfactorily stabilised by solvation. Consequently, the rearrangements are allowed to proceed to yield largely the thermodynamically stable $\Delta^{13(17)}$-compounds.* [25] The Westphalen rearrangement medium is capable of rapid proton removal in the carbonium ion sequence. Thus the absence of appreciable quantities of Δ^4-compounds from the rearrangements of 5α-hydroxy-4-methylsteroids [8] militates against the intermediacy of C(5) carbonium ions. Inspection of models supports this since the C(10) carbonium ions derived from the 5α-hydroxy-4β-methyl compounds appear to be less stable than the appropriate C(5) carbonium ions. Also, it is likely that the 4-methyl-Δ^4-compounds would be of at least comparable thermodynamic stability to the corresponding Δ^9-compounds. We suggest therefore that the Westphalen rearrangement involves a concerted C(5)–O cleavage and methyl migration to give the C(10) carbonium ion, which rapidly loses a proton from C(9) or C(1).† The reaction is thus kinetically controlled. The small amount of Δ^4-compound isolated in the normal Westphalen rearrangement [2] may arise by an alternative *E*2-type mechanism. The proposed concerted rearrangement allows some relief of the essential diaxial interaction between the 6β-substituent [2] and the angular methyl group. This driving force is not required in the 4,5- and 5,6-epoxide rearrangements as the medium allows further rearrangement towards the thermodynamically stable products.

The recent observation [9] that the 5α-hydroxy-9β-compound rearranges *via* a C(5) carbonium ion, under Westphalen conditions, to the spiro-compounds (35) and (36) does not invalidate these arguments. The stereochemical features of compound (34) are different from those in 5α-hydroxy-9α-compounds, and the reaction course is also different. It is not surprising that the release of the 1,3-diaxial interaction between the 11-CH_2 and the 5α-O·SO_2·OAc group ‡ is not accompanied by a concerted methyl migration. Almost certainly the departing oxygen from C(5) will be pushed out of the C(19),C(10),C(5) plane, and overlap between the orbital of the migrating methyl group and the electron-deficient orbital at C(5) would be inefficient (Figure 3).

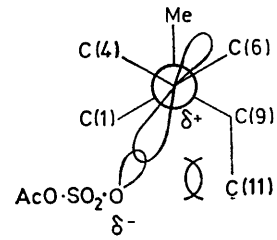


FIG. 3 H_2SO_4–Ac_2O-Catalysed C(5)–O bond cleavage for 5α-hydroxy-9β-steroids

EXPERIMENTAL

Solutions were dried over anhydrous sodium sulphate and solvents were removed *in vacuo* on a rotary evaporator. Plates (1 m × 0·5 mm thick) of Kieselgel PF254 (Merck) were used for preparative t.l.c. Deactivated (grade III) alumina (Camag) was used for column chromatography.

I.r. spectra were determined with Perkin-Elmer 237 and 257 spectrophotometers. U.v. spectra were determined for ethanolic solutions with a Unicam SP 800 spectrophotometer. ^{1}H N.m.r. spectra were determined, for solutions in carbon tetrachloride, at 60 MHz with a Perkin-Elmer R10 spectrometer, and mass spectra were recorded with A.E.I. MS 902 and MS 12 spectrometers. Rotations were measured for chloroform solutions at 22° with a Bendix polarimeter 143C.

6β-*Acetoxy*-3β-*benzyloxy*-9,10-*epoxy*-5-*methyl*-19-*nor*-5β,10α-*cholestane* (3) *and* 6β-*Acetoxy*-3β-*benzyloxy*-9,10-*epoxy*-5-*methyl*-19-*nor*-5β,9β-*cholestane* (4).—An ethereal solution of the olefin (1) [11] (300 mg) and an excess of monoperphthalic acid solution (70 ml) (60 g monoperphahtlic acid in 1 l of ether) was set aside at room temperature overnight. The solution was washed with sodium hydrogen carbonate solution until neutral and was then dried. Removal of solvent left the epoxide mixture. Separation was effected by column chromatography; elution with 5% ether–light petroleum (b.p. 60—80°), gave the α-*epoxide* (3) (160 mg), m.p. 88—90° (from methanol–water), $[\alpha]_D$ +13·3° (*c* 0·4), $\nu_{max.}$ 695 and 730 (Ph), and 1745 (C=O) cm^{-1}, τ 2·72 (s, Ph), 4·9—5·3 (m, 6-H), 5·52 (s, O·CH_2), 6·05—6·4 (m, 3-H, $W_{\frac{1}{2}}$ *ca.* 10 Hz), 8·05 (s, AcO), 8·80 (s, 5-Me), and 9·25 (s, 13-Me) (Found: C, 78·3; H, 9·95. $C_{36}H_{54}O_4$ requires C, 78·50; H, 9·9%); and the β-*epoxide* (4) (110 mg) (oil), $[\alpha]_D$ +43° (*c* 0·5), $\nu_{max.}$ 695 and 735 (Ph), and 1740 (C=O) cm^{-1}, τ 2·72 (s, Ph), 5·0—5·45 [q, *J* (apparent) *ca.* 6 and 14 Hz, 6-H], 5·5 (s, O·CH_2), 6·2—6·5 (m, $W_{\frac{1}{2}}$ *ca.* 18 Hz, 3-H), 8·0 (s, AcO), 8·90 (s, 5-Me), and 9·25 (s, 13-Me) (Found: C, 78·5; H, 10·2%).

3β-*Benzyloxy*-9,10-*epoxy*-5-*methyl*-19-*nor*-5β,10α-*cholestan*-6β-ol (5) *and* 3β-*Benzyloxy*-9,10-*epoxy*-5-*methyl*-19-*nor*-5β,9β-*cholestan*-6β-*ol* (6).—A 1% aqueous methanolic potassium hydroxide (10 ml) solution of the acetate (3) or (4) was heated under reflux for 15 min and was then poured into water. Extraction with ether gave the epoxy-alcohol. The epoxy-acetate (3) (60 mg) gave the *alcohol* (5) (49 mg), m.p. 126—127° (from methanol) $[\alpha]_D$ +25° (*c* 1·0), $\nu_{max.}$ 3620 cm^{-1} (sharp, OH), τ 2·68 (s, Ph), 5·45 (s, O·CH_2),

* The other modes of rearrangement which are commonly observed may be neglected for the purposes of this argument.

† The intermediacy of a protonated cyclopropane is also possible.

‡ Assuming the normal Westphalen-type intermediates.[2]

[24] J. M. Coxon, M. P. Hartshorn, and C. N. Muir, *Chem. Comm.*, 1971, 659.

[25] (*a*) J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1969, **25**, 149; (*b*) J. Bascoul, B. Cocton, and A. Crastes de Paulet, *Tetrahedron Letters*, 1969, 2401.

6·1—6·5 (m, 3- and 6-H), 8·95 (s, 5-Me), and 9·26 (s, 13-Me) (Found: C, 80·25, H, 10·2. $C_{34}H_{52}O_3$ requires C, 80·25; H, 10·3%). The epoxy-acetate (4) (60 mg) gave the *alcohol* (6) (43·5 mg) (oil), $[\alpha]_D$ +38·5° (*c* 0·9), $\nu_{max.}$ 3600—3300 (OH) cm^{-1}, τ 2·6 (s, Ph), 5·4 (s, O·CH_2), 6·1—6·4 (m, 6-H), 6·5—6·8 (m, 3-H), 8·7 (s, 5-Me), and 9·19 (s, 13-Me) (Found: C, 79·95; H, 10·5%).

Lithium Aluminium Hydride Reduction of 3β-*Benzyloxy*-9,10-*epoxy*-5-*methyl*-19-*nor*-5β,9β-*cholestan*-6β-*ol* (6).—A solution of the epoxy-alcohol (6) (250 mg) in dry tetrahydrofuran (25 ml) was treated with lithium aluminium hydride (250 mg) and the mixture was heated under reflux for 6 h. The excess of reducing agent was decomposed with methanol and the mixture was extracted with ether. The ethereal layer was washed with water and dried. Removal of the solvent gave a crude product. Preparative t.l.c. [elution (×1) with ethyl acetate–benzene (10 : 1)], gave 3β-*benzyloxy*-5-*methyl*-19-*nor*-5β-*cholestane*-6β,10-*diol* (8) (150 mg), an oil, $[\alpha]_D$ +12° (*c* 2·2), $\nu_{max.}$ (KBr) 700 and 735 (Ph) and 3400br (OH) cm^{-1}, τ 2·68 (s, Ph), 5·57 (s, O·CH_2), 6·3—6·5 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 6-H), 6·6—6·9 (m, [illegible] *ca.* 9 Hz, 3-H), 8·6 (s, 5-Me), and 9·28 (s, 13-Me) (Found: C, 80·2; H, 10·4. $C_{34}H_{54}O_3$ requires 79·95; H, 10·65%); 3β-*benzyloxy*-5-*methyl*-19-*nor*-5β-*cholest*-8-*ene*-6β,10-*diol* (16) (32 mg), m.p. 152—153° (from methanol), $[\alpha]_D$ +23° (*c* 1·3), $\nu_{max.}$ (KBr) 700 and 740 (Ph), and 3400br (OH) cm^{-1}, τ 2·55 (s, Ph), 5·38 (s, O·CH_2), 5·9—6·5 (m, 3- and 6-H), 9·01 (s, 5-Me), and 9·3 (s, 13-Me) (Found: C, 79·85; H, 10·35. $C_{34}H_{52}O_3$ requires C, 80·25; H, 10·3%); and 5-*methyl*-19-*nor*-5β-*cholestane*-3β,6β,10-*triol* (9) (64 mg), m.p. 245—248° (from methanol), $[\alpha]_D$ 0°, $\nu_{max.}$ (KBr) 3400br (OH) cm^{-1}, τ 8·52 (s, 5-Me) and 9·3 (s, 13-Me) (Found: C, 76·95; H, 11·35. $C_{27}H_{48}O_3$ requires C, 77·1; H, 11·5%).

6β-*Acetoxy*-3β-*benzyloxy*-5-*methyl*-19-*nor*-5β-*cholestan*-10-*ol* (10), 6β-*Acetoxy*-3β-*benzyloxy*-5-*methyl*-19-*nor*-5β-*cholest*-8-*en*-10-*ol* (17), *and* 3β,6β-*Diacetoxy*-5-*methyl*-19-*nor*-5β-*cholestan*-10-*ol* (11).—The hydroxy-steroids were acetylated with excess of acetic anhydride in pyridine in the usual manner.

The diol (8) (100 mg) gave the *acetate* (10) (80 mg), m.p. 135—136° (from methanol), $[\alpha]_D$ −3° (*c* 1·7), $\nu_{max.}$ (mull) 695 and 720 (Ph), 1745 (C=O), and 3600 (sharp, OH) cm^{-1}, τ 2·7 (s, Ph), 5·2—5·4 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 5·5 (s, CH_2·O), 6·2—6·5 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 3-H), 7·92 (s, AcO), 8·78 (s, 5-Me), and 9·29 (s, 13-Me) (Found: C, 78·2; H, 10·4. $C_{36}H_{56}O_4$ requires C, 78·2; H, 10·2%).

A crude sample of diol (16) (300 mg) gave the *acetate* (17) (225 mg) (an oil), $[\alpha]_D$ +4° (*c* 4·5), $\nu_{max.}$ 700 and 720 (Ph), 1745 (C=O), and 3640 (sharp, OH) cm^{-1}, τ 2·8 (s, Ph), 4·8—5·1 (m, $W_{\frac{1}{2}}$ *ca.* 14 Hz, 6-H), 5·6 (s, CH_2·O), 6·3—6·7 (m, 3-H), 8·05 (s, AcO), 9·1 (s, 5-Me), and 9·35 (s, 13-Me).

Triol (9) (150 mg) gave the *diacetate* (11) (101 mg), m.p. 124—125° (from methanol), $[\alpha]_D$ −7° (*c* 1·5), $\nu_{max.}$ 1750 (C=O) and 3635 (sharp, OH) cm^{-1}, τ 4·98—5·15 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 3-H), 5·2—5·45 (m, $W_{\frac{1}{2}}$ *ca.* 5 Hz, 6-H), 8·02 (s, AcO), 8·9 (s, 5-Me), and 9·3 (s, 13-Me) (Found: C, 73·8; H, 10·1. $C_{31}H_{52}O_5$ requires C, 73·5; 10·4%).

3β-*Benzyloxy*-10-*hydroxy*-5-*methyl*-19-*nor*-5β-*cholestan*-6-*one* (12) *and* 3β-*Benzyloxy*-10-*hydroxy*-5-*methyl*-19-*nor*-5β-*cholest*-8-*en*-6-*one* (18).—A solution of steroid in acetone at 0° was treated with chromic acid solution for 5 min.[15] The solution was diluted with water, and extracted with ether. The ether layer was washed with water, dried, and evaporated giving crude ketone.

The diol (8) (450 mg) gave the *ketol* (12) (400 mg), m.p. 111—112°, $[\alpha]_D$ −36° (*c* 2·3), $\nu_{max.}$ 1715 (C=O) and 3650 (sharp, OH) cm^{-1}, τ 2·75 (s, Ph), 5·4—5·8 (q, J_{AB} *ca.* 12 Hz, O·CH_2), 6·2—6·5 (m, 3-H), 8·75 (s, 5-Me), and 9·32 (s, 13-Me) (Found: C, 80·05; H, 9·9. $C_{34}H_{52}O_3$ requires C, 80·25; H, 10·3%).

The diol (16) (92 mg) gave the ketol (18) (24 mg), m.p. 167—170° (from methanol), $\nu_{max.}$ 1720 (C=O) and 3550 (sharp, OH) cm^{-1}, τ 2·65 (s, Ph), 5·4 (s, O·CH_2), 6·1—6·6 (m, 3-H), 8·88 (s, 5-Me), and 9·22 (s, 13-Me), *M* (mass spectrum), 506.

3β-*Benzyloxy*-5-*methyl*-19-*nor*-5β-*cholest*-6-*en*-10-*ol* (19).—A solution of diol (8) (200 mg) and toluene-*p*-sulphonyl chloride (200 mg) in pyridine (20 ml) was set aside at room temperature for 4 days. The mixture was poured into water, and extracted with ether, and the organic layer was dried. Evaporation left an oil which, after t.l.c. [elution with benzene–ethyl acetate (20 : 1)], gave a mixture of compounds (13) and (19) (150 mg), and starting material (8).

The mixture (150 mg) was then dissolved in dry tetrahydrofuran (25 ml) and treated with lithium aluminium hydride (100 mg) at room temperature for 1 h. After the addition of methanol (5 ml), the mixture was poured into water and extracted with ether. Evaporation of the extract gave an oil which, after t.l.c. [elution with benzene–ethyl acetate (20 : 1)], gave the *olefin* (19) (90 mg) as a gum, $[\alpha]_D$ −28° (*c* 1·8), $\nu_{max.}$ 3640 cm^{-1} (OH), τ 2·75 (s, Ph), 4·5—5·00 (m, 6- and 7-H), 5·57 (s, O·CH_2), 6·3—6·6 (m, 3-H), 8·82 (s, 5-Me), and 9·3 (s, 13-Me). The mass spectrum showed no molecular ion and an intense *M* − 4 peak at *m/e* 488·3638 ($C_{34}H_{48}O_2$ requires *M* − 4, 488·3654).

5-*Methyl*-19-*nor*-5β-*cholestane*-3β,10-*diol* (14).—An ethyl acetate solution (20 ml) of the alcohol (19) (80 mg) was stirred with 10% palladium–charcoal in hydrogen for ½ h. The solution was filtered and evaporated to give the saturated *diol* (14) (68 mg), m.p. 116—117°, $[\alpha]_D$ +27·5° (*c* 1·3), $\nu_{max.}$ 3650 cm^{-1} (OH), τ 5·85—6·1 (m, 3-H), 8·88 (s, 5-Me), and 9·35 (s, 13-Me) (Found: C, 79·85; H, 12·25. $C_{27}H_{48}O_2$ requires C, 80·1; H, 12·0%).

9,10-*Epoxy*-5-*methyl*-19-*nor*-5β,10α-*cholestane*-3β,6β-*diol* (7).—An ethyl acetate solution of the hydroxy-epoxide (5) (1·25 g) was shaken with 10% palladium–charcoal in hydrogen at room temperature until the uptake of hydrogen ceased. The solution was filtered and evaporated, giving the *diol* (7) (1·05 g), m.p. 173—174° (from aqueous methanol), $[\alpha]_D$ +26° (*c* 0·7), $\nu_{max.}$ (KBr) 3400br cm^{-1} (OH), τ 5·55—5·9 (m, 3-H), 6·0—6·4 (m, 6-H), 8·84 (s, 5-Me), and 9·25 (s, 13-Me) (Found: C, 76·85; H, 11·0. $C_{27}H_{46}O_3$ requires C, 77·45; H, 11·1%).

3β,6β-*Diacetoxy*-5-*methyl*-19-*nor*-5β,10α-*cholestan*-10-*ol* (20) *and* 3β,6β-*Diacetoxy*-5-*methyl*-19-*nor*-5β-*cholestan*-9α-*ol* (21).—A solution of epoxide (7) (1·2 g) in anhydrous ethylamine (50 ml) was treated with finely cut lithium metal (500 mg) at 0 °C, and the mixture was shaken until a permanent blue colour appeared. The solution was kept at room temperature for a further ½ h, after which water was carefully added. Extraction with ether gave an amorphous solid, which was acetylated with acetic anhydride in pyridine giving an oil. Preparative t.l.c. [elution (×2) with benzene–ethyl acetate (10 : 1)], gave the diacetate (2) (300 mg), m.p. 124—125°, $[\alpha]_D$ +80° (*c* 1·2) (lit.,[2] m.p. 128°, $[\alpha]_D$ +85°), the *alcohol* (21) (500 mg), m.p. 165—166° (from aqueous methanol), $[\alpha]_D$ +3·5° (*c* 2·8), $\nu_{max.}$ 1745 (C=O) and 3640 (sharp, OH) cm^{-1}, τ 4·7—5·00 (m, $W_{\frac{1}{2}}$ *ca.* 10 Hz, 3-H), 5·3—5·5 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 8·05 (s, AcO), 8·07 (s, AcO), 8·91 (s, 5-Me), and 9·3 (s, 13-Me) (Found: C, 73·8; H, 10·3.

$C_{31}H_{52}O_5$ requires C, 73·5; H, 10·4%), and the *alcohol* (20) (300 mg) as a gum, $[\alpha]_D$ +16·5° (*c* 3·0), $\nu_{max.}$ 1745 (C=O) and 3640 (sharp, OH) cm^{-1}, τ 4·9—5·4 (m, 3- and 6-H estimated $W_{\frac{1}{2}}$ *ca.* 8 and 16 Hz), 8·00 (s, AcO), 8·03 (s, AcO), 8·85 (s, 5-Me), and 9·35 (s, 13-Me).

Dehydration of Alcohols (8), (12), (14), (20), *and* (21).—An acetic anhydride solution of steroid (0·036M) and toluene-*p*-sulphonic acid (200 mg) was heated on a steam-bath for ½ h. The mixture was cooled, poured into water, and extracted with ether. The organic layer was dried and evaporated.

The diol (8) (900 mg), after t.l.c. [elution (×2) with benzene–ethyl acetate (20 : 1)], gave 6β-*acetoxy*-3β-*benzyloxy*-5,14-*dimethyl*-18,19-*bisnor*-5β,8α,9β,10α,14β-*cholest*-13(17)-*ene* (22) (700 mg), a gum, $[\alpha]_D$ +27° (*c* 1·3), $\nu_{max.}$ 1740 cm^{-1} (C=O), τ 2·75 (s, Ph), 5·4—5·8 (m, O·CH_2 and 3-H), 6·2—6·5 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 6 H), 8·02 (s, AcO), 8·88 (s, 5-Me), 9·02 and 9·11 [d, C(21)H_3], 9·11 [14-Me and lower branch of C(26)H_3 and C(27)H_3 doublets], and 9·21 [upper branch of C(26)H_3 and C(27)H_3 doublets] (Found: C, 80·7; H, 10·2. $C_{36}H_{54}O_3$ requires C, 80·85; H, 10·2%).

The ketol (12) (80 mg), after t.l.c. [elution with benzene–ethyl acetate (10 : 1)], gave a mixture (35 mg) and 10β-*acetoxy*-3β-*benzyloxy*-5-*methyl*-19-*nor*-5β-*cholestan*-6-*one* (15) (10 mg), a gum, $\nu_{max.}$ 1720 (C=O) and 1740 (acetate C=O) cm^{-1}, τ 2·78 (s, Ph), 5·4—5·7 (s, O·CH_2), 6·3—6·6 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 3-H), 8·08 (s, AcO), 8·68 (s, 5-Me), and 9·35 (s, 13-Me) (Found: C, 78·5; H, 10·0. $C_{36}H_{54}O_4$ requires C, 78·5; H, 9·9%). Further t.l.c. of the mixture [elution (×2) on silver nitrate-impregnated silica, with chloroform–light petroleum (b.p. 60—80°) (1 : 1)] gave 3β-*benzyloxy*-5-*methyl*-19-*nor*-5β-*cholest*-1(10)-*en*-6-*one* (26) (20 mg) as a gum, τ 2·78 (s, Ph), 4·4—4·65 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 1-H), 5·55 (s, O·CH_2), 6·1—6·4 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 3-H), 8·78 (s, 5-Me), and 9·33 (s, 13-Me), and 3β-*benzyloxy*-5,14-*dimethyl*-18,19-*bisnor*-5β,8α,9β,10α,14β-*cholest*-13(17)-*en*-6-*one* (24) (16 mg), a gum, $\nu_{max.}$ 1720 cm^{-1} (C=O), τ 2·75 (s, Ph), 5·55 (s, O·CH_2), 6·1—6·4 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 3-H), 8·67 (s, 5-Me), 9·03 (shoulder) and 9·12 [d, C(21)H_3], 9·04 (s, 14-Me), and 9·12 and 9·21 [C(26)H_3 and C(27)H_3 doublets], M^+ 490·3843 ($C_{34}H_{50}O_3$ requires *M*, 490·3811).

Hydrolysis of compound (22), in the usual manner with methanolic 1% potassium hydroxide, gave the alcohol (25), which on oxidation with Jones [15] reagent at 0° gave the ketone (24) (identical with an authentic sample).

The diol (14) (52 mg), after t.l.c. [elution with benzene–ethyl acetate (10 : 1)], gave 3β-acetoxy-5,14-dimethyl-18,19-bisnor-5β,8α,9β,10α,14β-cholest-13(17)-ene (23) [18] (40 mg), a gum, $[\alpha]_D$ +9° (*c* 0·8), τ 4·9—5·1 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 3-H), 8·05 (s, AcO), 9·04 and 9·12 (singlets, 5- and 14-Me), 9·02 and 9·12 [d, C(21)H_3], and 9·12 and 9·22 [C(26)H_3 and C(27)H_3 doublets].

The alcohol diacetate (21) (140 mg), after t.l.c. [elution with benzene–ethyl acetate (10 : 1)], gave the Westphalen diol diacetate (2) (9 mg), m.p. 123—124°, $[\alpha]_D$ +82° (lit.,[2] m.p. 127—128°, $[\alpha]_D$ +85°), 3β,6β-*diacetoxy*-5-*methyl*-19-*nor*-5β-*cholest*-9(11)-*ene* (32) (50 mg), m.p. 101—102° (from methanol), $[\alpha]_D$ −1·7° (*c* 0·8), τ 4·45—4·65 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 11-H), 4·9—5·15 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 3-H), 5·3—5·5 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 8·00 (s, AcO), 8·05 (s, OAc), 8·85 (s, 5-Me), and 9·38 (s, 13-Me) (Found: C, 76·4; H, 10·45. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·35%), and starting material (21) (40 mg).

The alcohol diacetate (20) (40 mg), after t.l.c. [elution with benzene–ethyl acetate (10 : 1)], gave the Westphalen diol diacetate (2) (20 mg), m.p. 126—127° (lit.,[2] m.p. 127—128°), and 3β,6β-*diacetoxy*-5-*methyl*-19-*nor*-5β,9β-*cholest*-1(10)-*ene* (27) (6 mg), a gum, $[\alpha]_D$ +10·5° (*c* 0·7), $\nu_{max.}$ 1745 (C=O) cm^{-1}, τ 4·5—4·75 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 1-H), 4·9—5·2 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 5·2—5·45 (m, $W_{\frac{1}{2}}$ *ca.* 13 Hz, 3-H), 8·00 (s, AcO), 8·05 (s, AcO), 8·95 (s, 5-Me), and 9·32 (s, 13-Me). The mass spectrum shows no molecular ion but a mass measurement on the *M* − AcOH peak gave *m/e* 426·3498 ($C_{29}H_{46}O_2$ requires 426·3498).

3β-*Benzyloxy*-1-*methyl*-19-*nor*-1(10 ⟶ 6)abeo-*cholest*-5-*en*-10-*one* (30).—A methanolic solution (5 ml) of steroid (12) (300 mg) was treated with 20% potassium hydroxide in methanol (30 ml) and the mixture was refluxed for 7 h. The solution was then poured into water and extracted with ether. The organic layer was separated, dried, and evaporated and gave an oil which, after t.l.c. [elution (×2) with benzene–ethyl acetate (10 : 1)], gave the *anthrasteroid* (30) (50 mg), a gum, $[\alpha]_D$ +115° (*c* 0·8), $\lambda_{max.}$ 284 (ε 10,800) nm, $\nu_{max.}$ 1640 (C=C) and 1680 (C=O) cm^{-1}, τ 2·75 (s, Ph), 5·35—5·55 (s, CH_2·O), 6·00—6·6 (m, 3-H), 9·00 and 9·10 (d, *J ca.* 6 Hz, 1-Me), and 9·22 (s, 13-Me), M^+ 490·3814 ($C_{34}H_{50}O_2$ requires 490·3811), and a mixture (50 mg) which was not investigated further.

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