Steroidal Analogues of Unnatural Configuration. Part IV.[1] Stereoselective Additions to the 5,6-Bond of 4,4,14α-Trimethyl-19(10 → 9β)-*abeo*-10α-pregn-5-enes and Correlation with the Related 19-Nor-10α-series

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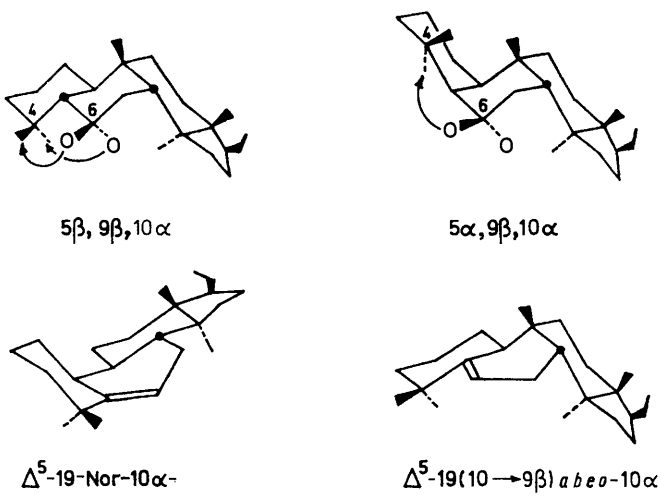
The hindered 5,6-double bond of 4,4,14α-trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-enes undergoes stereoselective *cis*-addition with peroxy-acid and osmium tetroxide to give 5β,6β-disubstituted products. A rigorous proof of the configurational assignments, by correlation with 5,6-disubstituted derivatives of 4,4,14α-trimethyl-19-nor-10α-pregn-5-enes, is presented.

An investigation [1] of the reactions of 4,4,14α-trimethyl-19-nor-10α-pregn-5-enes derived from cucurbitacin C [2] revealed that addition to the 5,6-double bond proceeds stereoselectively upon the α-face. The attempted utilisation of a 6-alkoxyl radical pathway [3] to functionalise and thereby degrade the 4,4-dimethyl system in this series has hitherto failed, and it was inferred that stereochemistry at the 5- and 6-positions predetermines the proclivity for such attack upon one of the methyl groups.

Parallel studies were initiated upon the related 4,4,14α-trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-enes.[2] An examination of Dreiding models of the derived 5β,9β,10α- and 5α,9β,10α-series delineates those 6-alkoxyl radicals which are suitably aligned for proton abstraction from 4-methyl groups (Figure). However, the former



FIGURE

series is subject to repulsive interactions between the 14α-methyl group and α-substituents on the C(9)–C(10) and C(6)–C(7) bonds, while the latter suffers severe steric compression due to the same interacting groups supplemented by the 4β-methyl group. It is conceivable that these factors could result in the adoption of non-chair conformations by the affected rings. The 6-alkoxyl radical approach to degradation of the 4,4-dimethyl system in the 4,4,14α-trimethyl-19(10 → 9β)-*abeo*-10α-series depends, therefore, upon determining the stereoselectivity of reagent attack upon the 5,6-bond and thence recognising ring deformations which would influence favourable alignments of the potential reaction sites.

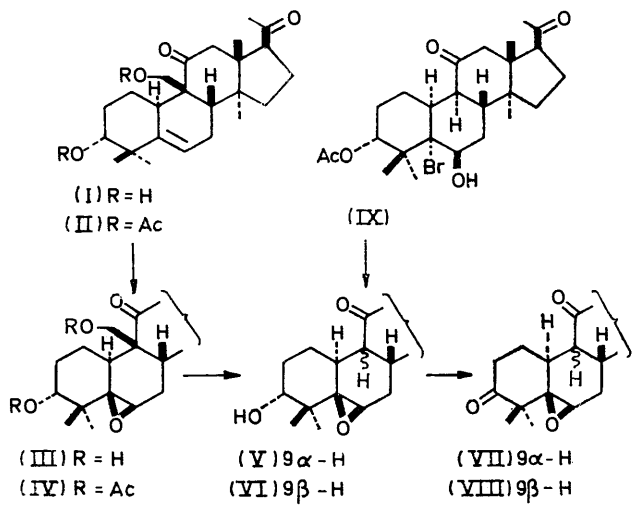
The Δ5-19-nor-10α-skeleton [1] has a relatively 'flat' shape (Figure) reminiscent of the natural (all-*trans*,*anti*-) steroids, and normal α-face reagent approach is favoured. In contrast, the α-face of the Δ5-19(10 → 9β)*abeo*-10α-skeleton is severely congested owing to concavity imposed by a BC-*cis* ring-junction. The contribution of the 9β-methyl group to steric hindrance upon the β-face is uncertain, but it may be concluded that the 5,6-bond in this series will be relatively unreactive and that such stereoselectivity as does prevail will be β-directed. It has been demonstrated [4,5] that the 5,6-double bond of cucurbitacins and skeletally related compounds is unaffected during hydrogenation of olefinic bonds situated upon terminal rings or in the side chain. Although certain *cis*-additions to this bond have been reported,[6] configurational assignments have not hitherto been rigorously defined. However, it is known that addition to B-ring olefinic bonds in lumisterol [7] and related 9β,10α-steroids [8] proceeds preferentially upon the β-face.

The conclusive assignment of configuration to 5,6-disubstituted products in the 4,4,14α-trimethyl-19-nor-10α-series [1] suggested a simple sequence of correlation reactions to establish the preferred direction of attack upon the olefinic bond of 4,4,14α-trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-enes. Thus, treatment of the Δ5-compound (I) with *m*-chloroperbenzoic acid led to a single epoxide (III). The possibility that the 19-hydroxy-group may have directed β-face epoxidation (albeit

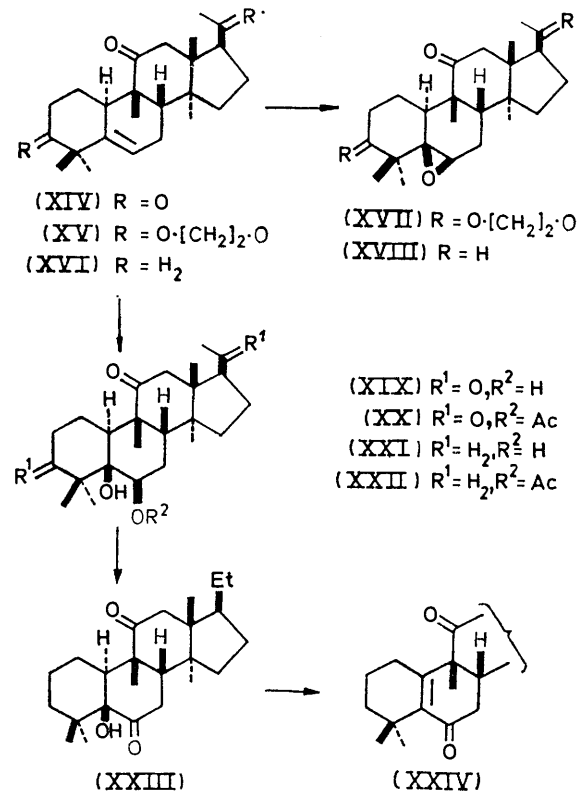
[1] Part III, J. R. Bull, P. R. Enslin, and H. H. Lachmann, *J. Chem. Soc.* (*C*), 1971, 3929.
[2] J. R. Bull and K. B. Norton, *J. Chem. Soc.* (*C*), 1970, 1592, and references cited therein.
[3] K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.
[4] D. Lavie and B. S. Benjaminov, *J. Org. Chem.*, 1965, **30**, 607.
[5] W. T. de Kock, P. R. Enslin, K. B. Norton, D. H. R. Barton, B. Sklarz, and A. A. Bothner-By, *J. Chem. Soc.*, 1963, 3828.
[6] D. Lavie, Y. Shvo, O. R. Gottlieb, and E. Glotter, *J. Org. Chem.*, 1962, **27**, 4546; R. Tschesche, G. Biernoth, and G. Snatzke, *Annalen*, 1964, **674**, 196; P. Tunmann, W. Gerner, and G. Stapel, *ibid.*, 1966, **694**, 162; T. R. Govindachari, N. Viswanathan, and P. A. Mohamed, *Chem. Comm.*, 1971, 665.
[7] P. A. Mayor and G. D. Meakins, *J. Chem. Soc.*, 1960, 2792.
[8] P. Westerhof and J. Hartog, *Rec. Trav. chim.*, 1965, **84**, 918.

more remotely situated than in known cases of steric predisposition due to allylic [9] and homoallylic [10] hydroxy-groups) was discounted, since acetylation of the epoxide (III) gave the diacetate (IV), which was also the only product obtained by direct epoxidation of the diacetate (II). Nevertheless, epoxidation of (I) proceeded much more rapidly than of (II), suggesting that participation by the 19-hydroxy-group does play an accelerating role.[9,10]

Alkaline treatment of epoxide (III) or (IV) in refluxing ethanol led, *via* retro-aldol loss of the 9β-hydroxymethyl group,[1] to a mixture of epoxides (V) and (VI). The isomers were separated and distinguished by characteristic differences in their c.d. spectra (Table 1), and by Jones oxidation at 0° to the known [1] epoxytriketones (VII) and (VIII), respectively. An identical mixture of (V) and (VI) was obtained by alkaline treatment of the bromohydrin (IX) of defined [1] configuration. As expected from the investigation of model substances,[1] direct epoxidation of the 19-nor-compound (X) afforded the α-epoxide (XII), which was further characterised by oxidation to the epoxytriketone (XIII). The α-epoxide (XII) was not detected in crude mixtures of (V) and (VI) obtained by the foregoing routes.



It follows that epoxidation of compounds (I) and (II) is highly stereoselective upon the β-face. Since the 19-oxygen function does not play a sterically directing role, it was expected that similar selectivity would obtain during e[illegible]ation of related 9β-methyl compounds [2] derived [illegible]0-bis(cucurbitacin B. The triketone [5] (XIV) was converted into the 3,20-bis(ethylenedioxy)-compound (XV), which gave the β-epoxide (XVII) upon treatment with *m*-chloroperbenzoic acid. Similarly, the Δ^5-11-ketone (XVI) obtained from (XIV) by selective Wolff–Kishner reduction, gave the epoxide (XVIII). No trace of an isomer was detected in either reaction.



Further evidence for the steric inhibition to α-face reagent approach was obtained from the failure of the Δ^5-11-ketone (XVI) to react with hypobromous acid. The simplest interpretation is that even in the event of 5β,6β-bromonium ion formation, subsequent *trans*-attack by OH^- is unable to proceed. A similar conclusion may be drawn from the failure of typical nucleophilic reagents [11] (*e.g.* HBr, H^+–H_2O, $LiAlH_4$) to cleave the β-epoxide (XVIII).

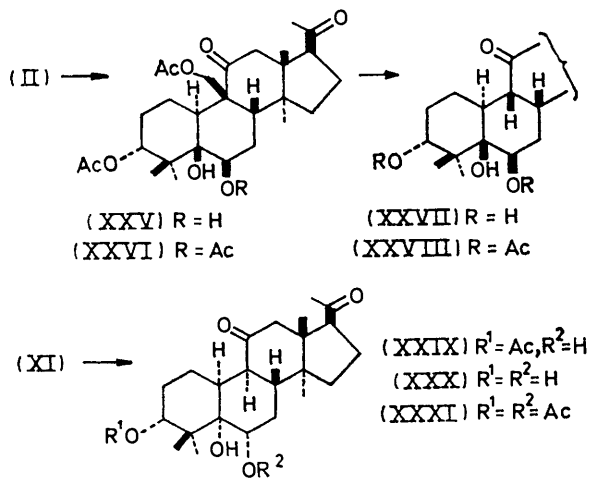
cis-Hydroxylation of the 5,6-double bond of cucurbitacin derivatives has been reported [6] without configurational assignments, and was accordingly re-investigated. Treatment of compounds (XIV) and (XVI) with osmium tetroxide in pyridine at 25° for several days afforded good yields of the respective diols (XIX) and (XXI). Careful g.l.c. and t.l.c. revealed that the products were

[9] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958; P. Chamberlain, M. L. Roberts, and G. H. Whitham, *J. Chem. Soc.* (*B*), 1970, 1374.

[10] M. Mousseron-Canet and J. C. Guileux, *Bull. Soc. chim. France*, 1966, 3853, 3858; M. Mousseron-Canet, B. Labeeuw, and J. Lanet, *ibid.*, 1968, 2125.

[11] J. G. Phillips and V. D. Parker in 'Steroid Reactions,' ed. C. Djerassi, Holden-Day, San Francisco, 1963, ch. 14.

homogeneous. The derived monoacetates (XX) and (XXII) displayed in their n.m.r. spectra, a complex seven-line multiplet at δ *ca.* 5·6 p.p.m. for the 6-proton. The signal was not amenable to first-order analysis but its width (*ca.* 20 Hz) must necessarily incorporate a diaxial coupling between the 6α- and 7β-protons. This was demonstrated by n.m.r. examination of (XXII) with successive additions of tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium [12] (0·15 mol.



equiv.). The appearance and multiplicity of the 6-proton signal altered with each addition and, with 0·9 mol. equiv. of the shift reagent, appeared as a broadened quartet (*J ca.* 11 and 6 Hz) at δ 9·74 p.p.m.† The expectation of β-face hydroxylation to give 5β,6β-diols was thus realised, since α-face attack would have given rise to an axial 6α-hydroxy-group.

Oxidation of the diol (XXI) afforded the 5β-hydroxy-6,11-dione (XXIII), which underwent smooth dehydration in thionyl chloride–pyridine at 0° to the $\Delta^{5(10)}$-compound (XXIV). Predictably,[13] the positive Cotton effect for the $n \longrightarrow \pi^*$ transition of the 11-ketone was weaker in (XXI) than in the Δ^5-compound (XVI) [Δε +6·34 (ref. 1)], while the c.d. spectrum of (XXIII) indicates that the 5β-hydroxy-6-ketone system makes a negative contribution to the overall Cotton effect (Table 1). The spectrum of the unsaturated diketone (XXIV) displayed substantial enhancement of the 11-ketone transition, presumably due to orbital overlap between this chromophore and the 5,10-double bond.[14]

Correlation of the Δ^5-19(10 $\longrightarrow$ 9β)*abeo*-10α- and Δ^5-19-nor-10α-derivatives *via cis*-hydroxylation of the olefinic bond provided further insight into the relative thermodynamic stabilities of the affected ring junctions. Thus, treatment of compound (II) with osmium tetroxide gave a single diol (XXV), which was converted into the 6-acetate (XXVI), the n.m.r. spectrum of which displayed a well defined quartet (*J* 11 and 6 Hz) at δ 5·63 p.p.m., for the 6α-proton. Treatment of compound (XXV) with alkali afforded the 19-nor-compound (XXVII). The strong positive Cotton effect observed

TABLE 1

C.d. spectra of ketones *

	9-Substituent	$\lambda_{max.}$/nm	Δε
Δ^5-3α-OAc-11,20-dione (II)	β-CH_2·OAc	294	+7·58
5β,6β-Epoxy-3α-OAc-11,20-dione (IV)	β-CH_2·OAc	294	+6·82
5β,6β-Epoxy-3α-OH-11,20-dione (V)	α-H	290	+3·03
5β,6β-Epoxy-3α-OH-11,20-dione (VI)	β-H	290	+5·58
Δ^5-3α-OH-11,20-dione (X)	α-H	286	+2·94
5α,6α-Epoxy-3α-OH-11,20-dione (XII)	α-H	291	+3·55
5α,6α-Epoxy-3,11,20-trione (XIII)	α-H	289	+3·9
5β,6β-$(OH)_2$-11-one (XXI)	β-Me	298	+5·45
5β-OH-6,11-dione (XXIII)	β-Me	298	+4·74
$\Delta^{5(10)}$-6,11-dione (XXIV)	β-Me	298	+13·7
5β,6β-$(OH)_2$-3α-OAc-11,20-dione (XXV)	β-CH_2·OAc	287	+7·52
3α,5β,6β-$(OH)_3$-11,20-dione (XXVII)	β-H	290	+5·4
3α,5α,6α-$(OH)_3$-11,20-dione (XXX)	α-H	291	+3·28

* Determined with a Jasco ORD/UV-5 instrument with c.d. attachment, for solutions in methanol. The compound (XXIV) also showed maxima at 345 (−2·01), 258 (−12·9), and 220 nm (+7·25).

for this compound (Table 1) is compatible with β-stereochemistry at C-9. This contrasts with the inversion which accompanies loss of the 9β-hydroxymethyl group in Δ^5-compounds.[1] That inversion did not occur confirms the assumption [1] based upon relative stabilities of *trans,syn,trans*- and *trans,anti,cis*-perhydrophenanthrenes,[15] that 5β,9β,10α-stereochemistry of the A-, B- and C-rings is energetically preferred to 5β,9α,10α-stereochemistry, since the latter ring fusion enforces a B-ring boat [15a] or twist-boat [15b] conformation. The result also provides compelling evidence for β-directed hydroxylation in the Δ^5-19(10 $\longrightarrow$ 9β)*abeo*-10α-series since the formation of a 5α,6α-diol from (II) would favour 9α-stereochemistry even more strongly than do the Δ^5-compounds.[1,15] This was readily proved: osmium tetroxide hydroxylation of the Δ^5-19-nor-compound (XI) gave the expected 5α,6α-diol (XXIX), which failed to undergo detectable isomerisation at C-9 despite prolonged treatment with alkali.

Corroborative evidence for the configurational assignments and aspects of stereochemistry was obtained from the n.m.r. spectra of the epoxides described here.

† Comprehensive analyses of the shift spectra of this derivative and related compounds will appear in a forthcoming publication.

[12] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.

[13] P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Francisco, 1965, pp. 125—128.

[14] M. Gorodetsky, A. Yogev, and Y. Mazur, *J. Org. Chem.*, 1966, **31**, 699; D. E. Bays, R. C. Cookson, and S. MacKenzie, *J. Chem. Soc.* (*B*), 1967, 215.

[15] (*a*) E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 282; (*b*) N. L. Allinger, B. J. Gordon, I. J. Tyminski, and M. T. Wuesthoff, *J. Org. Chem.*, 1971, **36**, 739.

The signal for the 6-proton of the epoxides (Table 2) varied not only with the configuration of the functional group, but with substitution and configuration at C-9. Thus, the epoxides (III), (IV), (XVII), and (XVIII) displayed between δ 3·23 and 3·39 p.p.m. a sharp doublet of unusually large splitting (*J* 5·5 Hz) for an epoxidic proton in a rigid six-membered ring.[16] The magnitude of this splitting appears to be characteristic of 5β,6β-epoxides with 9β-alkyl substitution since the stereochemically related 19-nor-9β,10α-compounds (VI) and (VIII) displayed quartets (*J* 3·5 and 1·8 Hz) for the 6α-proton.

TABLE 2

N.m.r. signals for the 6-proton of epoxides *

	Epoxide configuration	9-Substituent	6-H
(III)	β	β-CH_2·OH	3·39 (sh. d, 5·5)
(IV)	β	β-CH_2·OAc	3·34 (sh. d, 5·5)
(V)	β	α-H	3·4 (br. d, 3)
(VI)	β	β-H	3·23 (q, 3·5, 1·8)
(VII)	β	α-H	3·36 (br. d, 3)
(VIII)	β	β-H	3·19 (q, 3·5, 1·8)
(XII)	α	α-H	3·24 (br. d, 3·5)
(XIII)	α	α-H	3·22 (br. d, 3·5)
(XVII)	β	β-Me	3·23 (sh. d, 5·5)
(XVIII)	β	β-Me	3·30 (sh. d, 5·5)

* Recorded on a Varian HA-100 instrument for $CDCl_3$ solutions with Me_4Si as internal standard. The figure in the last column refers to chemical shift (p.p.m.) and the details in parentheses refer to multiplicity and observed splitting (Hz); sh. d = sharp doublet, br. d = doublet in which the distinct peaks are broadened relative to sharp doublets, q = quartet.

If the 5·5 Hz splitting is accommodated by a minimum-strain B-ring half-chair ($\phi_{6\alpha,7\beta}$ *ca.* 90° and $\phi_{6\alpha,7\alpha}$ *ca.* 30°) it follows that the B-ring of structures (VI) and (VIII) must be slightly deformed to permit a non-zero $J_{6\alpha,7\beta}$ value. Examination of Dreiding models reveals that although unilateral deformation of the B-ring is possible, there are no impelling steric factors present in the 9β-H series which are absent in the 9β-alkyl series. However, the energetically favourable increase in the 14α-Me/C(9)–C(10) distance by slight flattening of the C-ring [13,17a] results in sympathetic deformation of the B-ring half-chair. This process may occur freely in the 9β-H compounds, but be more inhibited when a 9β-alkyl substituent is present, owing to the competing energy demands of 9β-Me/8β-H eclipsing, and decrease in the 9β-Me/13β-Me distance, which ultimately result.

The C-ring of 11-oxo-steroids is prone to deformation [13,17] and, in compounds having 9β,10α-stereochemistry, the α-face interactions could greatly facilitate such changes. Further evidence for the existence of conformational anomalies between the 9β-H and 9β-alkyl series is obtained from n.m.r. examination of *cis*-diols. The spectra of acetates derived from the latter series clearly indicate that the 6β-substituent is equatorial and that the B-ring therefore enjoys a chair conformation. However, the 9β-H compound (XXVIII) displays a narrow quartet (*J* *ca.* 4 and 2 Hz) at δ 5·2 p.p.m. for the 6α-proton. This can only be accommodated by a B-ring deformation which does not occur in the 9β-alkyl series.

The epimeric 5,6-epoxides in the 9α-series cannot readily be distinguished by c.d. (Table 1) or n.m.r. (Table 2) data, but their marked dissimilarity in configurational preference at C-9 under equilibrating conditions suggests differences in their B-ring conformations. No conclusions can be drawn about the conformation of the C-ring in the 9α-series since severe α-face interactions are absent.

EXPERIMENTAL

For general directions see Part III.[1] N.m.r. data recorded in Table 2 are omitted from this section.

3α,19-*Diacetoxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-10α-*pregn*-5-*ene*-11,20-*dione* (II).—Treatment of the diol (I) with acetic anhydride–pyridine at 25° gave the *diacetate* (II), m.p. 195—197° (from chloroform–methanol), $[\alpha]_D$ +192° (*c* 0·9) (Found: C, 71·0; H, 8·4%; M^+, 472. $C_{28}H_{40}O_6$ requires C, 71·2; H, 8·5%; *M*, 472).

Epoxidation of Olefins.—All epoxidations were performed with *m*-chloroperbenzoic acid by use of similar procedures; only one detailed description is given.

(*a*) *m*-Chloroperbenzoic acid (85%; 0·29 g) was added to compound (I) (0·51 g) in chloroform (50 ml) at 25°, and the progress of the reaction was monitored by t.l.c. After 1·5 h no starting material remained, and the solution was washed with aqueous sodium carbonate (5%; 2 × 20 ml) and water (3 × 20 ml), dried (Na_2SO_4), and evaporated to dryness. The product was crystallised from acetone–ether to give 5,6β-*epoxy*-3α,19-*dihydroxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-5β,10α-*pregnane*-11,20-*dione* (III) (0·43 g), m.p. 218—221°, $[\alpha]_D$ +144° (*c* 1·0), δ 0·71, 0·84, 1·03, and 1·18 (4 × Me), 2·08 (COMe), 2·99 (1H, t, *J* 8 Hz, 17α-H), 3·47 (1H, q, *J* 10 and 5 Hz, 3β-H), and 3·68 and 3·89 p.p.m. (each 1H, d, *J* 12 Hz, 19-H) (Found: C, 70·95; H, 8·75%; M^+, 404. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%; *M*, 404).

Treatment of the epoxide (III) with acetic anhydride–pyridine at 25° gave the *diacetate* (IV), m.p. 216—218° (from acetone–methanol), $[\alpha]_D$ +122° (*c* 1·0), δ 0·70 (6H), 1·08, and 1·17 (4 × Me), 1·88 and 1·98 (2 × O·COMe), 2·06 (COMe), 2·99 (1H, t, *J* 8 Hz, 17α-H), 4·29 and 4·47 (each 1H, d, *J* 11 Hz, 19-H), and 4·66 p.p.m. (1H, m, *W* 16 Hz, 3β-H) (Found: C, 68·3; H, 8·5%; M^+, 488. $C_{28}H_{40}O_7$ requires C, 68·8; H, 8·25%; *M*, 488).

(*b*) Epoxidation of the diacetate (II) (0·1 g) in chloroform (12 ml) at 25° for 25 h gave compound (IV) (0·92 g), m.p. and mixed m.p. 216—218°.

(*c*) Epoxidation of the dione (X) (0·15 g) in chloroform (20 ml) at 25° for 3 h gave 5,6α-*epoxy*-3α-*hydroxy*-4,4,14α-*trimethyl*-19-*nor*-5α,10α-*pregnane*-11,20-*dione* (XII) (0·13 g), m.p. 228—232° (from acetone–ether), $[\alpha]_D$ +4° (*c* 1·0), δ 0·58, 0·83, 1·01, and 1·05 (4 × Me), 2·07 (COMe), 3·05 (1H, t, *J* 8·5 Hz, 17α-H), and 3·41 p.p.m. (1H, q, *J* 10 and 5 Hz, 3β-H) (Found: C, 73·9; H, 9·2%; M^+, 374. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%; *M*, 374).

(*d*) Epoxidation of (XV) (0·05 g) in benzene (10 ml)

[16] K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, 1964, **29**, 1136.

[17] (*a*) D. Lavie and B. S. Benjaminov, *Tetrahedron*, 1964, **20**, 2665; (*b*) P. Crabbé and A. Bowers, *J. Org. Chem.*, 1967, **32**, 2921.

at 25° for 22 h gave the 5β,6β-*epoxide* (XVII) (0·035 g), m.p. 238—243° (from ethyl acetate–methanol), $[\alpha]_D$ +117° (*c* 0·8), δ 0·81, 1·22 (6H), 1·24, and 1·31 (5 × Me), and 3·97 p.p.m. (8H, m, 2 × O·$[CH_2]_2$·O) (Found: C, 70·4; H, 8·8%; M^+, 474. $C_{28}H_{42}O_6$ requires C, 70·85; H, 8·9%; *M*, 474).

(*e*) Epoxidation of the ketone (XVI) (0·34 g) in benzene (25 ml) at 25° for 17 h gave 5,6β-*epoxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-5β,10α-*pregnan*-11-*one* (XVIII) (0·32 g), m.p. 113—115° (from acetone–methanol), $[\alpha]_D$ +98° (*c* 0·7), δ 0·56, 0·7, 1·06, 1·08, and 1·12 p.p.m. (5 × Me) (Found: C, 80·5; H, 10·5%; M^+, 358. $C_{24}H_{38}O_2$ requires C, 80·4; H, 10·7%; *M*, 358).

Osmium Tetroxide Hydroxylation of Olefins.—A similar procedure was used for all hydroxylations; only one detailed description is given.

(*a*) Osmium tetroxide (0·1 g) was added to compound (XIV) (0·13 g) in dry pyridine (15 ml) at 25°. Samples (0·2 ml) were withdrawn at 24 h intervals, treated with aqueous sodium disulphite (see later), and analysed by t.l.c. After 10 days at 25° no starting material remained. Aqueous sodium disulphite (10%; 15 ml) was added and the mixture was stirred for 1·5 h. Water was added and the product was extracted with chloroform (4 × 15 ml). The combined extracts were washed with water (3 × 20 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give 5,6β-*dihydroxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-5β,10α-*pregnane*-3,11,20-*trione* (XIX) (0·09 g), m.p. 168—171° (from acetone–hexane), $[\alpha]_D$ +163° (*c* 0·7) (Found: C, 71·2; H, 9·0%; M^+, 404. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%; *M*, 404).

Treatment of the trione (XIX) with acetic anhydride–pyridine at 25° afforded the 6-*acetate* (XX), m.p. 220—223° (from chloroform–methanol), $[\alpha]_D$ +167° (*c* 1·0), δ 0·6, 1·02, 1·18, 1·27, and 1·33 (5 × Me), 2·04 (O·COMe), 2·08 (COMe), 3·09 (1H, t, *J* 8 Hz, 17α-H), and 5·64 p.p.m. (1H, m, *W* 20 Hz, 6α-H) (Found: C, 69·9; H, 8·6%; M^+, 446. $C_{26}H_{38}O_6$ requires C, 69·9; H, 8·6%; *M*, 446).

(*b*) Hydroxylation of the ketone (XVI) (0·63 g) in pyridine (30 ml) at 25° for 10 days, and chromatography on alumina (3% deactivated; 30 g) with benzene afforded 5,6β-*dihydroxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-5β,10α-*pregnan*-11-*one* (XXI) (0·53 g), m.p. 138—140° (from aqueous acetone), $[\alpha]_D$ +136° (*c* 1·0) (Found: C, 76·4; H, 10·85%; M^+, 376. $C_{24}H_{40}O_3$ requires C, 76·55; H, 10·7%; *M*, 376).

Treatment of the product (XXI) with acetic anhydride–pyridine at 25° afforded the 6-*acetate* (XXII), m.p. 208—210° (from acetone–methanol), $[\alpha]_D$ +119° (*c* 1·2), δ 0·56, 0·84, 1·0, 1·26, and 1·33 (5 × Me), 2·03 (O·COMe), and 5·61 p.p.m. (1H, m, *W* 20 Hz, 6α-H) (Found: C, 74·3; H, 9·9%; M^+, 418. $C_{26}H_{42}O_4$ requires C, 74·6; H, 10·1%; *M*, 418).

(*c*) Hydroxylation of the diacetate (II) (0·5 g) in pyridine (15 ml) at 25° for 8 days gave 3α,19-*diacetoxy*-5,6β-*dihydroxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-5β,10α-*pregnane*-11,20-*dione* (XXV) (0·46 g), m.p. 270—273° (from chloroform–methanol), $[\alpha]_D$ +98° (*c* 1·2) (Found: C, 65·9; H, 8·1%; M^+, 506. $C_{28}H_{42}O_8$ requires C, 66·4; H, 8·35%; *M*, 506).

Treatment of the product (XXV) with acetic anhydride–pyridine at 25° afforded the *triacetate* (XXVI), double m.p. 262—265° and 269—272° (from chloroform–methanol), $[\alpha]_D$ +90° (*c* 0·8), δ 0·76, 0·83, 1·02, and 1·41 (4 × Me), 1·9, 2·0, and 2·05 (3 × O·COMe), 2·09 (COMe), 3·08 (1H, t, *J* 8 Hz, 17α-H), 4·49 and 4·92 (each 1H, d, *J* 12 Hz, 19-H), 4·95 (1H, q, *J* 12 and 5 Hz, 3β-H), and 5·63 p.p.m. (1H, q, *J* 11 and 6 Hz) (Found: C, 65·5; H, 8·1%; M^+ − 60, 488. $C_{30}H_{44}O_9$ requires C, 65·7; H, 8·1%; *M*, 548).

(*d*) Hydroxylation of the dione (XI) (0·25 g) in pyridine (10 ml) at 25° for 48 h gave 3α-*acetoxy*-5,6α-*dihydroxy*-4,4,14α-*trimethyl*-19-*nor*-5α,10α-*pregnane*-11,20-*dione* (XXIX) (0·23 g), m.p. 227—229° (from chloroform–methanol), $[\alpha]_D$ +33° (*c* 1·0), δ 0·58, 1·02, 1·04, and 1·1 (4 × Me), 2·01 (O·COMe), 2·06 (COMe), 3·05 (1H, t, *J* 8·5 Hz, 17α-H), 4·22 (1H, q, *J* 14 and 7 Hz, 6β-H), and 4·86 p.p.m. (1H, q, *J* 10 and 6 Hz, 3β-H) (Found: C, 69·1; H, 8·8%; M^+, 434. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%; *M* 434).

Treatment of the product (XXIX) with acetic anhydride–pyridine at 25° afforded the 3,6-*diacetate* (XXXI), m.p. 239—241° (from chloroform–hexane), $[\alpha]_D$ +23° (*c* 1·1), δ 0·6, 0·86, 1·07, and 1·1 (4 × Me), 2·0 and 2·02 (2 × O·COMe), 2·08 (COMe), 3·04 (1H, t, *J* 8 Hz, 17α-H), 4·77 (1H, q, *J* 10 and 5 Hz, 3β-H), and 5·32 p.p.m. (1H, t, *J* 8 Hz, 6β-H) (Found: C, 67·6; H, 8·1%; M^+, 476. $C_{27}H_{40}O_7$ requires C, 68·05; H, 8·45%; *M*, 476).

Treatment of the 5β,6β-*Epoxide* (IV) *with Alkali.*—Compound (IV) (1·6 g) in ethanol (135 ml) and aqueous N-sodium hydroxide (15 ml) was heated under reflux in nitrogen for 3 h. The mixture was neutralised with acetic acid, water was added, and the product was extracted with chloroform (3 × 30 ml). The usual work-up gave material (1·07 g) which was adsorbed on silica gel (200 g). Gradient elution with chloroform–methanol (98 : 2 to 97 : 3; 400 ml) gave unidentified oils (0·174 g), followed by material (0·156 g) which was crystallised from acetone–ether to give 5,6β-*epoxy*-3α-*hydroxy*-4,4,14α-*trimethyl*-19-*nor*-5β,10α-*pregnane*-11,20-*dione* (V), m.p. 187—189°, $[\alpha]_D$ −22°, (*c* 0·6), δ 0·63, 0·84, 0·98, and 1·04 (4 × Me), 2·08 (COMe), 3·02 (1H, t, *J* 8 Hz, 17α-H), and 3·62 p.p.m. (1H, q, *J* 10 and 5·5 Hz, 3β-H) (Found: C, 73·4; H, 8·9%; M^+, 374. $C_{23}H_{34}O_4$ requires C, 73·75; H, 9·15%; *M*, 374).

Further elution with chloroform–methanol (97 : 3; 450 ml) gave mixed fractions (0·22 g), followed by 5,6β-*epoxy*-3α-*hydroxy*-4,4,14α-*trimethyl*-19-*nor*-5β,9β,10α-*pregnane*-11,20-*dione* (VI) (0·3 g), m.p. 192—196° (from acetone–ether), $[\alpha]_D$ +139° (*c* 1·1), δ 0·85, 0·88, 0·93, and 1·03 (4 × Me), 2·08 (COMe), 2·98 (1H, t, *J* 8 Hz, 17α-H), and 3·56 p.p.m. (1H, q, *J* 10·5 and 5 Hz, 3β-H) (Found: C, 73·3; H, 9·0%; M^+, 374).

Oxidation of 5,6-*Epoxy*-3α-*hydroxy*-11,20-*diones.*—(*a*) Compound (V) (0·02 g) in acetone (5 ml) at 0° was treated with 8N-chromic acid. After 20 min at 0°, sodium disulphite was added and the product was isolated with ethyl acetate to give the epoxy-triketone (VII) (0·013 g), m.p. 187—190° (from chloroform–methanol), $[\alpha]_D$ −53° (*c* 0·4) (lit.,[1] m.p. 187—192°, $[\alpha]_D$ −57°).

(*b*) Oxidation of compound (VI) (0·03 g) as in the previous experiment, afforded the epoxy-triketone (VIII) (0·022 g), m.p. 220—225° (from acetone–methanol), $[\alpha]_D$ +170° (*c* 0·8), δ 0·87, 0·89, 0·98, and 1·28 (4 × Me), and 2·09 p.p.m. (COMe) (lit.,[1] m.p. 221—225°, $[\alpha]_D$ +173°).

(*c*) Oxidation of compound (XII) (0·05 g) as in the previous experiments afforded 5,6α-*epoxy*-4,4,14α-*trimethyl*-19-*nor*-5α,10α-*pregnane*-3,11,20-*trione* (XIII) (0·037 g), m.p. 260—263° (from ethyl acetate–methanol), $[\alpha]_D$ +16° (*c* 1·0), δ 0·58, 0·85, 1·07, and 1·28 (4 × Me), 2·07 (COMe), and 3·05 p.p.m. (1H, t, *J* 8 Hz, 17α-H) (Found: C, 74·1; H,

8·9%; M^+, 372. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%; M, 372).

Treatment of the Bromohydrin (IX) *with Alkali.*—N-Sodium hydroxide (1 ml) was added to compound (IX) (0·06 g) in ethanol (10 ml) at 25°. T.l.c. revealed that epoxide formation was complete within 5 min, and that after 4 h the 3-acetate had been hydrolysed to give a two-component mixture. Work-up followed by p.l.c. gave the epoxide (V) (0·008 g), m.p. and mixed m.p. 185—188°, and the epoxide (VI) (0·025 g), m.p. and mixed m.p. 191—196°.

3,20-*Bis*(*ethylenedioxy*)-4,4,14α-*trimethyl*-19(10 ⟶ 9β)-abeo-10α-*pregn*-5-*en*-11-*one* (XV).—Ethylene glycol (2 ml) was added to compound (XIV) (0·5 g) and toluene *p*-sulphonic acid (0·1 g) in dry benzene (60 ml). The mixture was heated under reflux with continuous return of the condensate through 4A molecular sieves for 20 h. The benzene solution was washed with water and evaporated to give *compound* (XV) (0·52 g), m.p. 203—207° (from acetone–methanol), $[\alpha]_D$ +171° (*c* 1·7) (Found: C, 73·5; H, 9·4%; M^+ 458. $C_{28}H_{42}O_5$ requires C, 73·3; H, 9·2%; M, 458).

4,4,14α-*Trimethyl*-19(10 ⟶ 9β)abeo-10α-*pregn*-5-*en*-11-*one* (XVI).—Potassium hydroxide (0·75 g) was added to compound (XIV) (1 g) and hydrazine hydrate (85%; 1 ml) in diethylene glycol (60 ml) and the mixture was heated under reflux for 2 h. The condenser was removed to allow the excess of hydrazine and water to escape and the mixture was heated under reflux at 220° for a further 3 h. The product was isolated with benzene and adsorbed on silica gel (50 g). Elution with benzene (200 ml) afforded the monoketone (XVI) (0·86 g), m.p. 158—160° (from acetone–methanol), $[\alpha]_D$ +244° (*c* 0·8), δ 0·62, 0·96, 1·0, 1·04, and 1·05 (5 × Me), and 5·56 p.p.m. (1H, m, 6-H) (lit.,[5] m.p. 150—151°, $[\alpha]_D$ +244°).

5-*Hydroxy*-4,4,14α-*trimethyl*-19(10 ⟶ 9β)abeo-5β,10α-*pregnane*-6,11-*dione* (XXIII).—Compound (XXI) (0·055 g) in acetone (15 ml) at 0°, was treated with 8N-chromic acid for 30 min. Aqueous sodium disulphite was added and the product was isolated with chloroform and adsorbed on alumina (3% deactivated; 10 g). Elution with benzene (30 ml) afforded the *diketone* (XXIII) (0·034 g), m.p. 148—150° (from acetone–methanol), $[\alpha]_D$ +31° (*c* 0·9), δ 0·68, 0·97, 1·11 (6H), and 1·23 p.p.m. (5 × Me) (Found: C, 77·2; H, 10·0%; M^+, 374. $C_{24}H_{38}O_3$ requires C, 76·95; H, 10·2%; M, 374).

4,4,14α-*Trimethyl*-19(10 ⟶ 9β)abeo-*pregn*-5(10)-*ene*-11,20-*dione* (XXIV).—Thionyl chloride (0·3 ml) was added dropwise to compound (XXIII) (0·065 g) in dry pyridine (1·5 ml) at 0°. After 1 h at 0° the solution was poured into cold water and the product was isolated by extraction with benzene to give *compound* (XXIV) (0·051 g), m.p. 143—146° (from acetone–methanol), $[\alpha]_D$ +144° (*c* 0·8), $\lambda_{max.}$ 263 nm (ε 7940) (Found: C, 80·7; H, 10·0%; M^+, 356. $C_{24}H_{36}O_2$ requires C, 80·85; H, 10·2%; M, 356).

Treatment of the 5β,6β-*Diol* (XXV) *with Alkali.*—Compound (XXV) (0·25 g) in ethanol (45 ml) and N-sodium hydroxide (5 ml) was heated under reflux in nitrogen for 3·5 h. Addition of water and extraction with chloroform afforded a product (0·19 g) which was adsorbed on silica gel (20 g). Elution with chloroform–methanol (97 : 3; 20 ml.) gave unidentified oils (0·04 g), and further elution with the same solvent (120 ml) gave 3α,5,6β-*trihydroxy*-4,4,14α-*trimethyl*-19-*nor*-5β,9β,10α-*pregnane*-11,20-*dione* (XXVII) (0·073 g), m.p. 285—288° (from acetone), $[\alpha]_D$ +107° (*c* 0·8 in C_5H_5N) (Found: C, 70·1; H, 9·0%; M^+, 392. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%; M, 392).

Treatment of the product (XXVII) with acetic anhydride–pyridine at 25° gave the amorphous 3,6-*diacetate* (XXVIII), $[\alpha]_D$ +87° (*c* 0·6), δ 0·7, 0·73, 0·98, and 1·18 (4 × Me), 2·01 and 2·08 (2 × O·COMe), 2·08 (COMe), 2·97 (1H, t, *J* 8 Hz, 17α-H), 5·03 (1H, q, *J* 10 and 5 Hz, 3β-H), and 5·2 p.p.m. (1H, q, *J* 4 and 2 Hz, 6α-H) (Found: C, 67·7; H, 8·2%; M^+, 476. $C_{27}H_{40}O_7$ requires C, 68·05; H, 8·45%; M, 476).

Treatment of the 5β,6β-*Diol* (XXIX) *with Alkali.*—Compound (XXIX) (0·08 g) in ethanol (27 ml) and aqueous N-sodium hydroxide (3 ml) was heated under reflux in nitrogen for 3 h. The usual work-up afforded 3α,5,6α-*trihydroxy*-4,4,14α-*trimethyl*-19-*nor*-5α,10α-*pregnane*-11,20-*dione* (XXX) (0·057 g), m.p. 297—300° (from acetone), $[\alpha]_D$ +81° (*c* 1·7 in C_5H_5N) (Found: C, 70·6; H, 9·0%; M^+, 392. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%; M, 392).

Treatment of the product (XXX) with acetic anhydride–pyridine at 25° afforded the 3,6-diacetate (XXXI), m.p. and mixed m.p. 239—241°.

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