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STEROIDAL ANALOGUES OF UNNATURAL CONFIGURATION—V

TRANSFORMATIONS OF 5,6β-EPOXY-4,4,14α-TRIMETHYL-19 (10 → 9β)*ABEO*-5β, 10α-PREGNAN-11-ONE

J. R. BULL and C. J. VAN ZYL

National Chemical Research Laboratory, South African Council for Scientific and Industrial Research, Pretoria, South Africa

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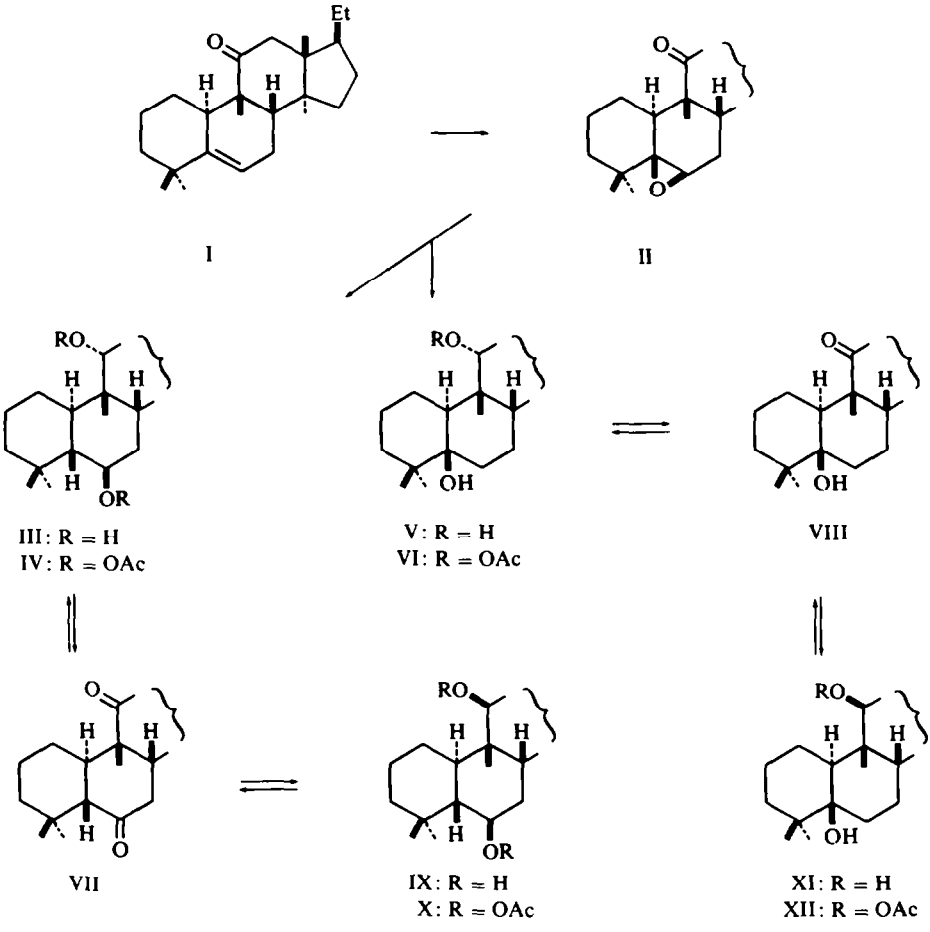
Abstract—Reductive cleavage of 5,6β-epoxy-4,4,14α-trimethyl-19(10 → 9β)*abeo*-5β,10α-pregnan-11-one (II) with lithium in ethylamine afforded products of C(5)-O and C(6)-O bond scission, the lack of selectivity being attributable to steric factors. The six possible 5,11- and 6,11-6β,11α-d-diols having 5β-stereochemistry, were prepared, and it was demonstrated that substantial deformations of the B- and C-rings occur in the series. Although attempted *trans*-cleavage of the epoxide (II) failed, a variety of rearrangement products was obtained by treatment with boron trifluoride-etherate or hydrogen bromide.

THE development of degradative routes to 4-bisdesmethyl derivatives[1,2] of cucurbitacins[3] is a challenging and potentially useful aspect of the study of this family of natural products, since this could lead to a variety of steriodal hormone analogues in which the unusual skeletal stereochemistry and substitution patterns are retained. A stratagem, which has been employed in related systems,[5] is functionalisation of one of the Me groups through 6-alkoxy-radical attack,[1,2] these intermediates being accessible by addition of oxygen-containing groups to the ubiquitous Δ^5-bond. Studies have hitherto shown that such additions are highly stereoselective in the 19-nor-10α-[2] and 19(10→9β)*abeo*-10α-series[1] of cucurbitacin derivatives, but that reactions of the latter series are circumscribed by severe steric hindrance. Furthermore, it was recognised[1] that the non-bonded interactions present in this skeleton could result in ring deformations which would disturb the alignment of potential reaction sites. We now present evidence that this is indeed so, and that the potential for exploiting the 6-alkoxy-radical pathway is likely to be limited.

Epoxidation of the model substance (I) leads exclusively to the β-epoxide (II)[1] which it was hoped could undergo *trans*-cleavage with suitable reagents to generate 6-hydroxy derivatives. In the event, treatment with aqueous perchloric acid[6] or lithium aluminium hydride[7] failed to open the epoxide (II), while treatment with halogen acids gave rearranged products (see below), but no halohydrins. It is evident that the steric factors which favour β-face epoxidation[1] of I, totally suppress reagent approach to the α-face of II.

The reduction of hindered epoxides has been achieved by treatment with lithium in anhydrous ethylamine[8] or ethylene diamine.[9] It is considered[8,10] that dianionic intermediates are involved and that the steric requirements of the attacking solvated electrons are considerably smaller than those of hydride ions.[7] Such cleavage of

* The preparation of 19 (10 → 9 β) *abeo* steroids *via* 9–carbonium ion processes has recently been reported.[4]

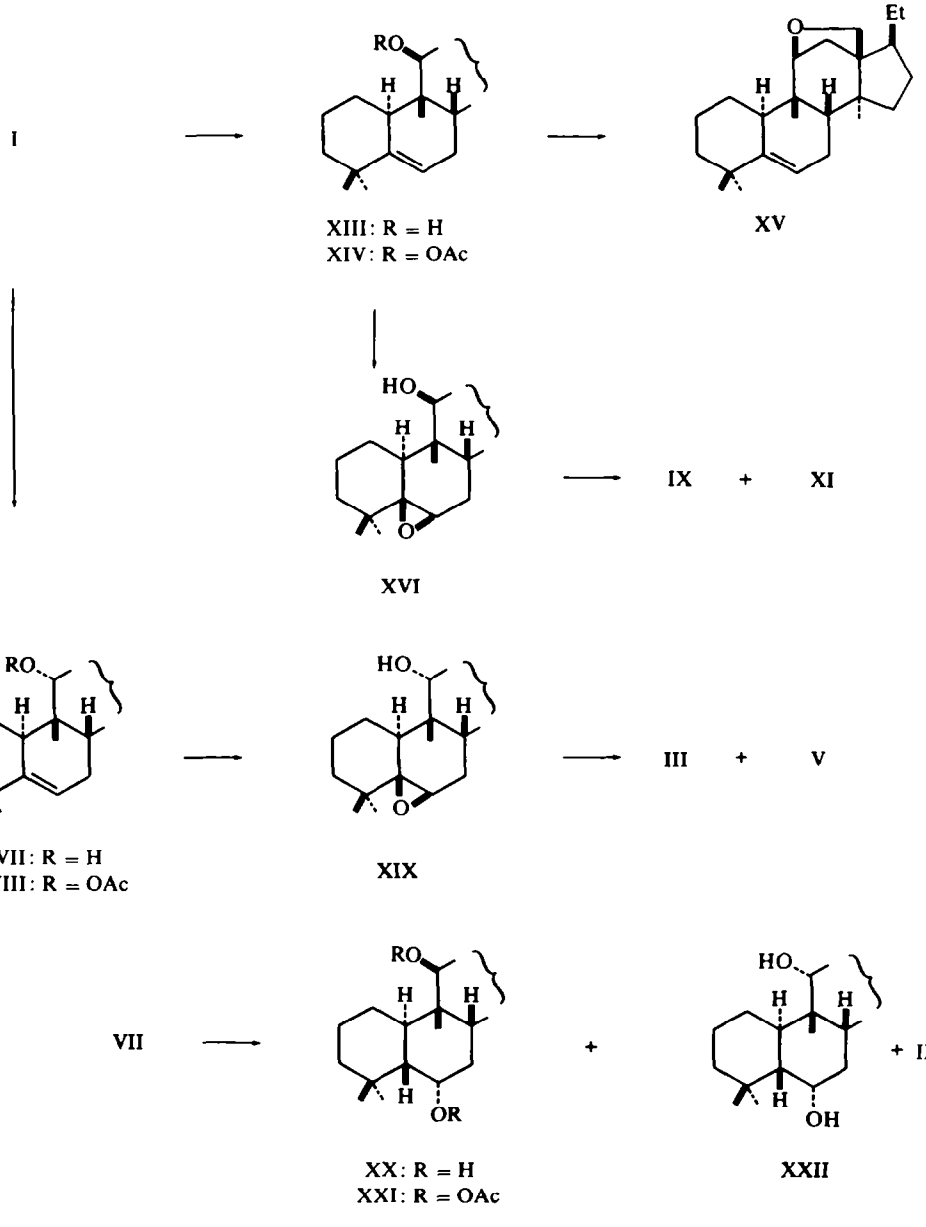


conformationally-rigid epoxides usually leads to products of diaxial opening.[8] However, treatment of II with Li-EtNH$_2$ afforded a mixture comprising two major products. Extensive chromatography gave the 6β,11α-diol (III), the 5β,11α-diol (V), and mixed fractions containing two minor components which were identified by comparative TLC as the 6β,11β-diol (IX) and the 5β,11β-diol (XI) (Table 1). Attempts to achieve better separation through prior acetylation of the reduction mixture failed, but Jones oxidation at 0° gave the readily-separated 6,11-diketone (VII) (59%) and 5β-hydroxy-11-ketone (VIII) (34%), together with traces of the Δ^5-11-ketone (I).[8] The isolated yields of the two products VII and VIII provided an estimate of the extent of C(5)-O and C(6)-O bond cleavage during reduction of the epoxide (II). The former cleavage, representing "equatorial" opening, is conspicuously predominant and suggests that stereoelectronic selection is inhibited by the hindered B-ring environment.

The assignment of 5β-stereochemistry to the 6β,11α-diol (III) implies a formal *cis*-cleavage of the epoxide (II) and is a reasonable consequence of C(5)—O bond

scission followed by protonation of the 5-carbanion on the less-hindered β-face. This stereochemistry is also thermodynamically favoured,[1,11] as was indicated by failure of the derived 6,11-diketone (VII) to undergo epimerisation at C(5) under equilibrating conditions.[12] The configuration of the 11-hydroxy-group follows from mechanistic considerations,[13] and was confirmed by correlation reactions (I → XVII → XIX → II + V, see below).

It was expected that reduction of the 6,11-diketone (VII) with Li-NH_3 would give the 6β,11α-diol (III) but remarkably, this was a minor component of the product



mixture, while the 6β,11β-diol (IX) was obtained in 85% yield (Table 1). This result was confirmed by a circuitous sequence of reactions. Thus, reduction of the Δ^5-11-ketone (I) with LAH afforded only the 11β-alcohol (XIII). NMR data (Table 2) showed that the 11-substituent is axial, but in view of a report[14] of reversed stereoselectivity upon LAH reduction of stereochemically-related 11-ketones, the assignment was confirmed by treatment of XIII with lead tetra-acetate and iodine in refluxing benzene. Crystallisation of the product afforded the 11β,18-epoxide (XV). The mother-liquor comprised labile iodine-containing material which was not examined.

The structure of XV was demonstrated by an NMR spectrum which displayed signals for four tertiary Me groups, a simple AB quartet (J 8 Hz) centred at δ 3·53 and 3·65 for the 18-protons, and a doublet (J 5·5 Hz) at δ 4·03 for the equatorial 11-proton. It is clear from models that only an axial 11β-OH group in a C-ring chair conformation is capable of undergoing alkoxy-radical attack upon a tertiary Me group in XIII.

The Δ^5-11β-ol (XIII) was treated with *m*-chloroperbenzoic acid to give the 5β,6β-epoxy-11β-ol (XVI) as the only product. The structure of XVI was confirmed by spectroscopic data (Table 2) and by Jones oxidation to the configurationally-defined[1] epoxyketone (II). Reduction of XVI with Li-EtNH_2 afforded a mixture of the 6β,11β-diol (IX) and the 5β,11β-diol (XI) (Table 1), in which products, configurations at the functionalised positions were now rigorously established. The former compound (IX) was identical to the major product of Li-NH_3 reduction of the 6,11-diketone (VII).

Reduction of the Δ^5-11-ketone (I) with Li-NH_3 afforded the Δ^5-11α-ol (XVII), in which the OH group is clearly equatorial (Table 2). Epoxidation of XVII yielded the 5β,6β-epoxy-11α-ol (XIX) which underwent cleavage with Li-EtNH_2 to give a mixture of the 6β,11α-diol (III) and the 5β,11α-diol (V) (Table 1).

The reduction of the 6,11-diketone (VII) with LAH was also examined, and led to the 6β,11β-diol (IX) as a minor component together with two new diols (XX and XXII) (Table 1). The major product (XX) was formulated as the 6α,11β-isomer on the basis of NMR evidence (Table 2) which showed that the chemical shift and splitting of the 11-proton is very similar to that of the 6β,11β-diol (IX). The minor product (XXII) could not be purified, but NMR data (Table 2) was obtained from a spectrum of material contaminated with XX, and the structure is assigned as the only outstanding 6,11-isomer in the 5β-series. Reduction of the 5β-hydroxy-11-ketone (VIII) with LAH afforded the 5β,11β-diol (XI) as the major product, together with the 5β,11α-isomer (V), but surprisingly, a similar product ratio was obtained upon Li-NH_3 reduction of VIII (Table 1).

Although the configurations of the diols were clearly established by the aforegoing sequences, the NMR data on the products and their respective acetates (Table 2) provide compelling evidence for ring deformations in the series. In all the compounds examined, the protons attached to the oxygen-bearing C atoms are clearly discernible. With one exception (*viz*, IX and its diacetate X), the 6- and 11-proton signals are mutually separated and can be unequivocally assigned. Since the respective vicinal protons are not distinguishable in the high-field methylene region, the observed splittings do not necessarily represent true coupling constants,[15] and caution was exercised in using these values. However, since all the signals displayed the expected multiplicities and symmetry it is clear that first-order treatment is not grossly inaccurate and accordingly, widths were used as a reliable measure of summed couplings with adjacent protons.

TABLE 1. PRODUCT DISTRIBUTION IN REDUCTIONS

Substrate	Method	Diol product % 6β,11α- III	5β,11α- V	6β,11β- IX	5β,11β- XI	6α,11β- XX	6α,11α- XXII
5β,6β-Epoxy-11-one (II)	(i)	60	30	<5[c]	<5[c]	—	—
6,11-Dione (VII)	(ii)	15	—	85	—	0	0
	(iii)	0	—	10	—	85	5[c]
5β-OH-11-one (VIII)	(ii)	—	20	—	80	—	—
	(iii)	—	10	—	90	—	—
5β,6β-Epoxy-11β-ol (XVI)	(i)	—	—	55	45	—	—
5β,6β-Epoxy-11α-ol (XIX)	(i)	60	40	—	—	—	—

[a] (i) Li-EtNH$_2$, EtOH (ii) Li-NH$_3$, EtOH (iii) LAH-THF

[b] In cases where only partial separation was achieved on column chromatography or PLC, the relative yields were estimated by TLC and GLC. Reproducible accuracy is therefore ≯5%.

[c] Not isolated pure.

A comparison of the epimeric Δ^5-11-ols (XIII and XVII), together with the chemical evidence, shows that the C-ring exists in a chair conformation. This also holds for the 5β,11α-diol (V), but in the 5β-11β-diol (XI) the 11-proton is more strongly coupled to 12-protons than in the Δ^5-11β-ol (XIII), suggesting a slightly flattened C-ring chair. This may be promoted by the 1,3-diaxial interaction between the 13β-Me and 11β-OH groups and has the added consequence that α-face interactions are also

TABLE 2. NMR SIGNALS FOR THE 6- AND 11-PROTONS[a]

Compound	11-H	6-H
6β,11α-(OH)$_2$ (III)	3·82 (t, 6) 12	4·07 (q., 5) 15
6β,11α-(OAc)$_2$ (IV)	4·90 (q., 7, 6) 13	5·21 (q., 5) 15
5β,11α-(OH)$_2$ (V)	3·85 (q., 10, 7) 17	—
5β,OH-11α-OAc (VI)	5·07 (q., 9, 7·5) 16·5	—
6β,11β-(OH)$_2$ (IX)	4·07 (q., 9·5, 7) 16·5	*ca* 4·06 (obsc.) ≯ 15
6β,11β-(OAc)$_2$ (X)	5·10 (q., 9, 6) 15	*ca* 5·16 (obsc.) ≯ 15
5β,11β-(OH)$_2$ (XI)	3·93 (q., 8, 3·5) 11·5	—
5β-OH-11β-OAc (XII)	5·16 (q., 6, 2) 8	—
Δ^5-11β-OH (XIII)	3·89 (q., 4, 2) 6	—
Δ^5-11β-OAc (XIV)	5·16 (q., 4, 2) 6	—
5β,6β-Epoxy-11β-OH (XVI)	3·81 (br.) 8[b]	3·29 (d., 5·5)
Δ^5-11α-OH (XVII)	3·89 (q., 11, 6) 17	—
Δ^5-11α-OAc (XVIII)	5·16 (q., 10·5, 6) 16·5	—
5β,6β-Epoxy-11α-OH (XIX)	3·76 (q., 11, 6) 17	3·30 (d., 5·5)
6α,11β-(OH)$_2$ (XX)	4·06 (q., 9·5, 7) 16·5	4·36 (br.) 18[b]
6α,11β-(OAc)$_2$ (XXI)	5·08 (q., 9, 6) 15	5·40 (br.t., 9) 18
6α,11α-(OH)$_2$ (XXII)	3·83 (q., 9, 6) 15	4·17 (br.) 14[b]

[a] NMR spectra were recorded on a Varian HA-100 instrument in CDCl$_3$ solutions with TMS as internal standard. The first figure in each column refers to chemical shift (p.p.m.) and the details in parentheses refer to multiplicity and observed splitting (Hz): t., triplet; q., quartet; br., unresolved signal. The last figure in each column refers to signal width.

[b] Half-height width.

slightly relieved. The latter factor could also account for evidence of C-ring flattening in the 6β,11α-diol (III) for which the 11-proton signal is distinctly narrower than for the Δ^5-11α-ol (XVII). Furthermore, the 6β-OH group in III is clearly ψ-axial since the 6α-proton is weakly coupled with those in the 5- and 7-positions. It is concluded that the B-ring adopts a twist-boat conformation in order to alleviate the eclipsing interaction between the 4β-Me and 6β-OH groups, and to further relieve α-face interactions between the 14α-Me group and the C(9)-C(10) and C(7)-C(6) bonds.

The postulated ring deformations are most graphically demonstrated by the 6β,11β-diol (IX) which contains a proven 11β-OH group lying in a ψ-equatorial orientation. This represents an extreme case of C-ring deformation to a twist-boat since a flattened chair cannot accommodate the observed 11-proton signal (Table 2). This also applies to the 6α,11β-diol (XX). The B-ring of both compounds must also adopt a twist-boat conformation.

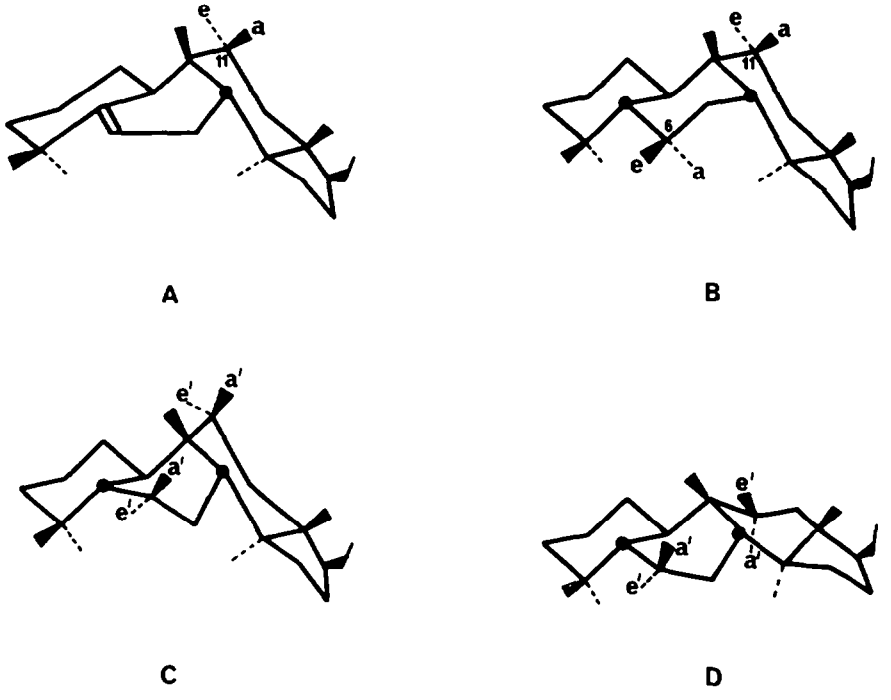


FIG. 1

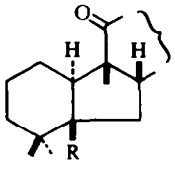
It is thus suggested that whereas strain-free Dreiding models represent the Δ^5-11-ols (as well as the 5β,6β-epoxy-11-ols) faithfully (Conformation A, Fig 1), the interactions present in an all-chair conformation (B) when the B-ring is saturated, are relieved by a B-ring twist-boat, C-ring flattened chair form (C) in the 6,11α-diols. The 6,11β-diols adopt a conformation (D) in which the B- and C-rings are twist-boats. While the C-ring of the 5β,11β-diol (XI) is demonstrably flattened, there is no direct evidence to suggest a B-ring deformation. The extent of these conformational changes cannot be precisely ascertained without more detailed analysis of the vicinal proton signals.

Attempts to clarify the NMR spectra using europium shift reagents[16] have not hitherto yielded the desired information since several protons suffer nearly-equivalent shifts. A study of model monofunctional systems is in progress.

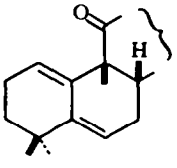
A mechanistic anomaly presents itself in the dissolving-metal reductions performed in this study. Thus, while the Δ^5-11-ketone (I) and the 5β,6β-epoxy-11-ketone (II) are reduced almost exclusively to 11α-OH compounds, the major products derived from reduction of the 6,11-diketone (VII) and the 5β-hydroxy-11-ketone (VIII) are 11β-isomers, albeit with ψ-equatorial orientation of the C-ring function, i.e. the 11β-OH group. This suggests that when the conformational restraint of an olefinic or epoxidic group is not present at C(5)-C(6), the C-ring has already assumed its deformed condition in the transition state, and that protonation of the 11-carbanion proceeds stereoselectively[17] or more rapidly[18] from the α-side. It is also possible that the C-ring of the starting 11-ketones (VII and VIII) (unlike I and II) is deformed, but direct evidence for this phenomenon is not available.

A variety of selective reactions was attempted on the 6,11-diketone (VII) in order to obtain further information about conformational changes, but it transpired that the 6-CO group reacts very sluggishly (selective reduction and protection) under conditions where the 11-function is unaffected. Similarly, attempts to attack the olefinic bond of the Δ^5-11-ketone (I) with diborane, without reducing the 11-function, failed. It has been reported[19] that hydroboration of a stereochemically-related system proceeds selectively on the β-face and that subsequent alkoxy-radical attack upon similarly-disposed Me groups is possible. Similar stereoselectivity prevails in I since prolonged *in situ* hydroboration afforded the 6β,11β-diol (IX) as the major product. There was some evidence of more rapid addition to the Δ^5-bond than reduction of the 11-CO group, but the preparative isolation of intermediates proved to be impractical. In any event, the conformational uncertainties associated with this series render it unlikely that the 6-alkoxy-radical pathway to 4,4-dimethyl degradation would be viable. The staggered disposition of the 4- and 6-functions (C and D, Fig 1) suggest that side-reactions might intervene, and even if the desired radical transfer were to take place it would be unselective.

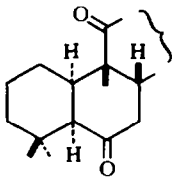
It was of interest to investigate the Lewis acid-catalysed rearrangement of the epoxyketone (II) in the hope that the 5α-isomer of the 6,11-diketone (VII) might be formed.[20] Brief treatment of II with BF_3-etherate afforded a mixture of products which was separated by chromatography on silica. The major product (75%) was formulated as the B-nor-5β-aldehyde (XXIII) on the basis of spectroscopic evidence, and is derived unexceptionally[20,21] by a 7(6→5)*abeo* rearrangement. A minor product (XXIV; *ca* 5%) is clearly an artefact of XXIII, and a third product, the $\Delta^{1(10),5}$-11-ketone (XXV; *ca* 5%) is derived from migration of the 10α-proton to the 5-position,



XXIII: R = CHO
XXIV: R = H



XXV



XXVI

and its subsequent elimination together with the formed 6β-OH group. Traces of further ill-defined products were encountered but could not be purified.

The abortive attempts to generate halohydrins by reacting the epoxide (II) with halogen acids yielded instead a mixture of halogen-free rearrangement products. Thus, treatment with 45% hydrogen bromide in acetic acid yielded the products (XXIII, XXIV), the isomeric 6,11-diketone (XXVI), and a minor dicarbonyl isomer which was not identified. The B-norcompound (XXIV) was obtained in 10% yield, but the respective yields of the remaining components (combined yield *ca* 65%) could not be accurately ascertained since they exhibited similar polarity and were only separated by fractional crystallisation. It is evident that in the HBr reaction, the suppression of nucleophilic attack by Br^- on the protonated epoxide due to α-face hindrance, creates the opportunity for neighbouring bonds to migrate in an analogous manner to the well-defined Lewis acid phenomena.[20] The respective product distributions in the two processes may be attributable to differing migratory propensities of the participating bonds, arising from conformational differences between a protonated and a Lewis acid co-ordinated epoxide.

The 6,11-diketone (XXVI), a product of simple 1,2-hydride shift,[21] was converted quantitatively to the 5β-isomer (VII) upon mild alkaline treatment,[12] thereby demonstrating that the assignment of 5β-stereochemistry to the 6β,11α-diol (III) and hence to all its derived products is correct.

EXPERIMENTAL

For general directions see Ref 2.

Lithium-ethylamine reduction of 5,6β-*epoxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregnan*-11-*one*(*II*). Li (0·4 g) was added in small, freshly-cut portions to a stirred soln of II (1·51 g) in anhyd ethylamine (100 ml). After development of a blue colour, EtOH (0·5 ml) was added and the soln was stirred for 1 hr. The excess of Li was destroyed with EtOH and the soln was evaporated to a small volume. Water was added and the product was extracted with chloroform (4 × 30 ml). The extract was washed with water, dried over $MgSO_4$ and evaporated to give semi-crystalline material (1·5 g).

A portion (0·2 g) of the product in chloroform was adsorbed on silica gel (20 g). Elution with chloroform-benzene (3:1, 110 ml) afforded 4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregnane*-6β,11α-*diol* (III: 0·056 g), m.p. 176–177° (from acetone-hexane), $[\alpha]_D$-9° (*c* 0·6) (Found: C, 79·2; H, 11·7%; M^+, 362. $C_{24}H_{42}O_2$ requires: C, 79·5; H, 11·7%; M, 362). Acetylation of III gave the 6,11-*diacetate* (IV), m.p. 153–154° (from MeOH), $[\alpha]_D$-13° (*c* 0·8) (Found: C, 75·3; H, 10·4%. M^+, 446. $C_{28}H_{46}O_4$ requires: C, 75·3; H, 10·4%; M, 446). Further elution with the same solvent mixture (30 ml) gave mixed fractions which were combined (0·14 g) and applied to PLC plates. Multiple development with chloroform-benzene (3:1) and separation of the bands afforded further III (0·055 g) and 4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregnane*-5,11α-*diol* (V: 0·052 g) as an amorphous product, $[\alpha]_D$-3° (*c* 0·9). (Found: C, 79·0; H, 11·3%; M^+, 362). Acetylation of V with Ac_2O-pyridine at 25° afforded the 11-*acetate* (VI), m.p. 161–164° (from acetone-MeOH), $[\alpha]_D$-5° (*c* 0·8) (Found: C, 76·8; H, 11·0%; M^+, 404. $C_{26}H_{44}O_3$ requires: C, 77·2; H, 11·0%; M, 404). Material (0·012 g) obtained from the intermediate and lower zones of the PLC plates revealed the presence of two minor components contaminated with the isolated products.

Oxidation of the diol mixture

The crude product (1·1 g) obtained in the previous experiment was dissolved in acetone (100 ml) and treated at 0° with 8N chromic acid. After 20 min, $NaHSO_3$aq was added and the product was isolated by extraction with chloroform, and adsorbed on silica gel (60 g). Elution with chloroform-benzene (1:1, 55 ml) afforded the Δ^5-11-one (I: 0·03 g), m.p. and mixed m.p. 155–157° (lit.,[1] m.p. 158–160°). Elution with chloroform gave 4,4,14α-*trimethyl*-19(10→9α)abeo-5β,10α-*pregnane*-6,11-*dione* (VII: 0·646 g), m.p. 216–218° (from acetone-MeOH), $[\alpha]_D$ + 131° (*c* 0·7), ν_{max} 1700 and 1692 cm^{-1}, δ 0·61, 1·02, 1·04, 1·16, and 1·28 (5 × Me) (Found: C, 80·7; H, 10·7%; M^+, 358. $C_{24}H_{38}O_2$ requires: C, 80·4; H, 10·7%; M, 358). Elution

with chloroform-MeOH (99:1, 60 ml) gave 5-*hydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregnan*-11-*one* (VIII: 0·37 g), m.p. 180–182° (from chloroform-MeOH). $[\alpha]_D$ + 152° (*c* 0·6), ν_{max} 1695 cm^{-1} (Found: C, 79·7; H, 11·1%; M^+, 360. $C_{24}H_{40}O_2$ requires: C, 79·9; H, 11·2%; M, 360).

Lithium-liquid ammonia reductions

(a) The diketone (VII; 0·16 g) in dry THF (6 ml) was added dropwise to a stirred mixture of Li (0·05 g) in liquid ammonia (freshly distilled from Na, *ca* 25 ml) and EtOH (0·1 ml). After 30 min, EtOH was added and the mixture was evaporated. Water was added and the product was isolated by extraction with chloroform, and adsorbed on silica gel (30 g). Elution with chloroform-MeOH (99·1, 180 ml) gave the 6β,11α-diol (III; 0·009 g), m.p. and mixed m.p. 172–175°, followed by mixed fractions (0·056 g), and 4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregnane*-6β,11β-*diol* (IX; 0·092 g), m.p. 169–174° (from acetone-hexane), $[\alpha]_D$ + 48° (*c* 0·8, C_5H_5N) (Found: C, 79·8; H, 11·7%; M^+, 362). The mixed fractions were combined and crystallised twice from acetone-hexane to give further IX (0·03 g), m.p. 167–172°. Acetylation of IX afforded the 6,11-*diacetate* (X) as an amorphous product, $[\alpha]_D$ + 34 (*c* 0·8) (Found: C, 75·8 H, 10·6%; M^+, 446).

(b) The hydroxy-ketone (VIII; 0·08 g) was reduced as described in the previous experiment. PLC of the product afforded V (0·009 g), identified by TLC and spectral analysis, and 4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-pregnane-5,11β-diol (XI; 0·052 g), double m.p. 118–120° and 142–144° (from acetone-hexane), $[\alpha]_D$-5° (*c* 0·4) (Found: C, 79·6; H, 11·6%; M^+, 362). Acetylation of XI afforded the 11-*acetate* (XII), m.p. 154–156° (from chloroform-MeOH), $[\alpha]_D$-13° (*c* 0·6) (Found: C, 77·0; H, 11·0%; M^+, 404).

(c) The Δ^5-11-one (I; 0·194 g) was reduced as described in the previous experiments. Chromatography of the product on silica gel (24 g) afforded 4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*en*-11α-*ol* (XVII; 0·173 g), m.p. 95–99° (from acetone), $[\alpha]_D$ + 66° (*c* 1·5) (Found: C, 83·4; H, 11·9%; M^+, 344. $C_{24}H_{40}O$ requires: C, 83·7; H, 11·7%; M, 344). Acetylation of XVII afforded the *acetate* (XVIII), m.p. 80–81° (from MeOH), $[\alpha]_D$ + 55° (*c* 0·9) (Found: C, 80·7; H, 11·0%; M^+, 386. $C_{26}H_{42}O_2$ requires: C, 80·8; H, 11·0%; M, 386).

Lithium aluminium hydride reductions

(a) A mixture of VII (0·15 g) and LAH (0·04 g) in dry THF (10 ml) was heated under reflux for 1·5 hr. The excess of reagent was destroyed and the product was isolated by extraction with chloroform, and adsorbed on silica gel (25 g). Elution with chloroform-MeOH (98:2, 140 ml) gave a mixed fraction (0·008 g) (M^+, 362) which comprised *ca* 80% (TLC) of XXII, followed by 4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregnane*-6α,11β-*diol* (XX; 0·125 g), m.p. 209–210° (from acetone-hexane), $[\alpha]_D$ + 33° (*c* 0·7, C_5H_5N) (Found: C, 79·4; H, 11·3% M^+, 362). Acetylation of XX afforded the 6,11-*diacetate* (XXI), m.p. 139–142° (from acetone), $[\alpha]_D$ + 58° (*c* 0·8) (Found: C, 75·25; H, 10·3%; M^+, 446). Further elution of the column with the same solvent (20 ml) afforded IX (0·011 g), m.p. and mixed m.p. 167–170°.

(b) The hydroxy-ketone (VIII; 0·09 g) was reduced as described in the previous experiment. PLC of the product gave V (0·007 g), identified by TLC and spectral analysis, and XI (0·074 g), m.p. and mixed m.p. 118–120° and 142–144°.

(c) The Δ^5-11-one (I; 0·199 g) was reduced as described in the previous experiments to give 4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*en*-11β-*ol* (XIII; 0·145 g) m.p. 129–131° (from aqueous acetone), $[\alpha]_D$ + 60° (*c* 1·1) (Found: C, 83·9; H, 11·7%; M^+, 344). Acetylation of XIII afforded the 11-*acetate* (XIV), m.p. 161–164° (from MeOH), $[\alpha]_D$ + 40° (*c* 1·1) (Found: C, 80·7; H, 11·2%; M^+, 386).

Lead tetra-acetate-iodine oxidation of the Δ^5-11β-*ol* (*XIII*)

Lead tetra-acetate (0·818 g) and I_2 (0·224 g) were added to XIII (0·16 g) in dry benzene (20 ml) and the mixture was heated under reflux for 1 hr. Aqueous KI was added, followed by $Na_2S_2O_3$, and the organic layer was separated, washed with water and evaporated. Crystallisation of the residue from MeOH afforded 11β,18-*epoxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*ene* (XV; 0·016 g), m.p. 171–173° $[\alpha]_D$ + 129° (*c* 1·0), δ 0·78, 0·93, 0·98, and 1·05 (4 × Me), 3·53 and 3·65 (each 1H, d, J 8 Hz, 18-H_2), 4·03 (1H, d, J 5·5 Hz, 11α-H), and 5·5 (1H, br., 6–H) (Found: C, 84·1; H, 11·2%; M^+, 342. $C_{24}H_{38}O$ requires: C, 84·2; H, 11·2%; M, 342). The residue derived from the mother-liquor contained iodinated material (MS) but attempted purification yielded dark, intractable gums.

Epoxidation and lithium-ethylamine reduction of the Δ^5-11-*ols*

(a) *m*-Chloroperbenzoic acid (85%, 0·07 g) was added to XIII (0·09 g) in chloroform (15 ml). The progress

of the reaction was followed by TLC. After 3 hr no starting material remained, and the chloroform soln was washed with Na_2CO_3aq and water, and evaporated to give XVI (0·09 g) as an oil, δ 0·68, 0·73, 0·76, 1·04, and 1·1 (5 × Me), 3·29 (1H, d, J 5·5 Hz, 6α-H[1]), and 3·81 (1H, br., $w_{\frac{1}{2}}$ 8 Hz, 11α-H) (Found: M^+, 360. $C_{24}H_{40}O_2$ requires: M, 360), which was homogeneous on TLC and GLC. The crude product (0·08 g) was dissolved in anhyd ethylamine (25 ml), and Li (0·03 g) was added in small part portions, followed by EtOH (2 drops). After 1·5 hr the mixture was worked up in the usual way and the product was separated by PLC to give IX (0·038 g), m.p. and mixed m.p. 168–172°, and XI (0·031 g), m.p. and mixed m.p. 118–120° and 141–143°.

(b) The Δ^5-11α-ol (XVII; 0·07 g) was treated with *m*-chloroperbenzoic acid as described in the previous experiment, to give XIX (0·07 g) as an oil, δ 0·68, 0·73, 0·86, 1·09, and 1·17 (5 × Me), 3·3 (1H, d, J 5·5 Hz, 6α-H[1]), and 3·76 (1H, q, J 11 and 6 Hz, 11β-H) (Found: M^+, 360). The total product was reduced with Li in anhyd ethylamine. The usual work-up followed by PLC of the product gave III (0·036 g), m.p. and mixed m.p. 175–177°, and V (0·023 g), identified by TLC and spectral analysis.

Acid-catalysed rearrangements of the epoxy-ketone (II)

(a) BF_3-etherate (0·1 ml) was added to II (0·12 g) in dry benzene (12 ml), and the progress of the reaction was followed by TLC. After 20 min the starting material had disappeared and the benzene soln was washed with $NaHCO_3$aq, water, and dried over Na_2SO_4. The solvent was evaporated and the residue in benzene was absorbed on silica gel (6 g). Elution with benzene (25 ml) afforded 4,4,14α-*trimethyl*-B-*nor*-19(10→9β)-abeo-5β,10α-*pregnan*-11-*one* (XXIV; 0·007 g), m.p. 129–132° (from chloroform-MeOH, $[\alpha]_D$ + 85° (*c* 0·6), ν_{max}1692 cm^{-1}, δ 0·76, 0·83, 0·89, 0·94, and 1·11 (5 × Me) (Found: C, 83·7; H, 11·6%; M^+, 330. $C_{23}H_{38}O$ requires: C, 83·6; H, 11·6%; M, 330), and further elution with the same solvent (10 ml) afforded 4,4,14α-*trimethyl*-19(10→9β)abeopregna-1(10),5-*dien*-11-*one* (XXV; 0·006 g), m.p. 138–141° (from acetone-MeOH), $[\alpha]_D$ + 253° (*c* 0·5), ν_{max}1693 cm^{-1}, λ_{max}240 nm (ε 12260), δ 0·61, 0·9, 0·96, 1·04 and 1·12 (5 × Me), 5·1 and 5.58 (each 1H, br., $w_{\frac{1}{2}}$ 8 Hz, 1- and 6-H) (Found: C, 84·9; H, 10·8%; M^+, 340. $C_{24}H_{36}O$ requires: C, 84·65; H, 10·65%, M, 340). Further elution with benzene (75 ml) gave 5-*formyl*-4,4,14α-*trimethyl*-B-*nor*-19(10→9β)abeo-5β,10α-*pregnan*-11-*one* (XXIII; 0·091 g), m.p. 147–150° (from acetone-MeOH), $[\alpha]_D$ + 77° (*c* 0·6), ν_{max}1706 and 1692 cm^{-1}, δ 0·72, 0·79, 1·0 (6H), and 1·04 (5 × Me), and 10·37 (1H, d, *J* 1·5 Hz, –CHO) (Found: C, 80·1; H, 10·4%; M^+, 358. $C_{24}H_{38}O_2$ requires: C, 80·4; H, 10·7%; M, 358). Further elution gave traces of unidentified crystalline mixtures (TLC).

(b) HBr (*ca* 45% w/v in AcOH, 0·3 ml) was added to II (0·2 g) in chloroform (30 ml), and the progress of the reaction was followed by TLC. After 2 hr no starting material remained, and the chloroform soln was washed with $NaHCO_3$ aq and water, and evaporated. The residue in benzene was adsorbed on silica gel (20 g). Elution with chloroform-benzene (1:1, 45 ml) afforded XXIV (0·018 g), m.p. and mixed m.p. 130–131°, and further elution with the same solvent (90 ml) afforded crystalline material (0·133 g). Fractional crystallisations from chloroform-MeOH gave 4,4,14α-*trimethyl*-19(10→9β)abeo-5α,10α-*pregnane*-6,11-*dione* (XXVI; 0·026 g), m.p. 186–188°, $[\alpha]_D$ + 143° (*c* 0·7), ν_{max} 1705 and 1692 cm^{-1}, δ 0·76, 1·02 (6H), 1·26, and 1·3 (5 × Me) (Found: C, 80·7; H, 10·9%; M^+, 358), and XXIII (0·021 g), m.p. and mixed m.p. 145–149°. Concentration of the mother-liquor afforded a compound (0·005 g), double m.p. 157–160° and 207–212°. ν_{max}1700 and 1692 cm^{-1}, δ 1·02, 1·23, 1·25, and 1·28 (6H) (5 × Me) (Found: M^+, 358).

Isomerisation of the 6,11-diketone (XXVI)

A solution of XXVI (0·006 g) in EtOH (2 ml) and 1N NaOH (1 drop) was kept at 25° for 24 hr. Water was added and the ppt was collected and dried to give VII (0·005 g), m.p. and mixed m.p. 214–218°.

REFERENCES

[1] J. R. Bull and J. C. S. Perkin I, in press (1972)

[2] J. R. Bull, P. R. Enslin and H. H. Lachmann, *J. Chem. Soc.* (*C*), 3929 (1971)

[3] J. R. Bull and K. B. Norton, *Ibid.* (*C*), 1592 (1970), and refs cited

[4] J. W. ApSimon, R. R. King and J. J. Rosenfeld, *Canad. J. Chem.* **47**, 1989 (1969); O. E. Edwards and T. Sano, *Ibid.* **47**, 3489 (1969); J. W. ApSimon and J. M. Rosenfeld, *Chem. Comm.* 1271 (1970) D. H R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia and M. M. Pechet, *Ibid.* 227 (1969)

[5] J. M. Midgley, J. E. Parkin and W. B. Whalley, *Chem. Comm.* 789 (1970); M. Fetizon and P. Foy, *Ibid.* 1005 (1967)

[6] J. M. Diggle, M. D. Halliday, A. Kasal, G. D. Meakins and M. S. Saltmarsh, *J. Chem. Soc.* (*C*), 2325 (1970)
[7] D. K. Murphy, R. L. Alumbaugh and B. Rickborn, *J. Am. Chem. Soc.* **91**, 2649 (1969), and refs cited
[8] A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.* 4604 (1957); *Ibid.* 3571 (1960); Y. Tsuda, T. Sano and Y. Inubushi, *Tetrahedron* **26**, 751 (1970)
[9] H. C. Brown, S. Ikegami and J. H. Kawakami, *J. Org. Chem.* **35**, 3243 (1970)
[10] E. M. Kaiser, C. G. Edmonds, S. D. Grubb, J. W. Smith and D. Tramp, *Ibid.* **36**, 330 (1971)
[11] N. L. Allinger, B. J. Gorden, I. J. Tyminski and M. T. Wuesthoff, *Ibid.* **36**, 739 (1971)
[12] N. L. Allinger, M. A. Darooge and R. B. Hermann, *Ibid.* **26**, 3626 (1961)
[13] D. N. Kirk and M. P. Hartshorn, *Steroid Reaction Mechanisms*, Ch. 4, Elsevier (1968)
[14] A. Smit and J. Bakker, *Rec. Trav. Chim.* **85**, 731 (1966)
[15] L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, ch. 2–3, Pergamon, Oxford (1969)
[16] J. K. M. Sanders and D. H. Williams, *Chem. Comm.* 422 (1970); R. E. Rondeau and R. E. Sievers, *J. Am. Chem. Soc.* **93**, 1522 (1971)
[17] J. W. Huffmann and J. T. Charles, *Ibid.* **90**, 6486 (1968); W. S. Murphy and D. F. Sullivan, *Tetrahedron Letters* 3707 (1971)
[18] D. A. H. Taylor, *Chem. Comm.* 476 (1969)
[19] R. E. Ireland and L. N. Mander, *J. Org. Chem.* **34**, 142 (1969)
[20] Ref. 13, ch. 8
[21] T. G. Halsall, Sir Ewart R. H. Jones, E. L. Tan and G. R. Chaudhry, *J. Chem. Soc.* (*C*), 1374 (1966); J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Ibid.* 635 (1968)