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STEROIDAL ANALOGUES OF UNNATURAL CONFIGURATION—VI

A-RING TRANSFORMATIONS OF 4.4.14α-TRIMETHYL-19(10→9β)*ABEO*-10α-PREGN-5-ENE-3.11,20-TRIONE

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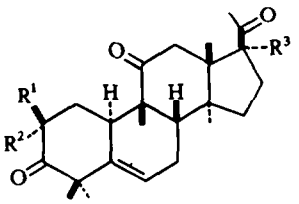
Abstract— Selective bromination of 4.4.14α-trimethyl-19(10→9β)*abeo*-10α-pregn-5-ene-3,11,20-trione (I) takes place almost exclusively at the 2-position, to give the mono-brominated isomers (III and IV). The respective configurations of the products were established by spectroscopic data, and by a series of chemical transformations in the A-ring. Lanthanide shift NMR spectroscopy of the equatorial 2β-bromo-compound (III) facilitated the configurational assignment and afforded information about the relative propensities of the 3-, 11-, and 20-CO groups for complexation with europium.

THE conformation of the A-ring in certain cucurbitacin derivatives has been the subject of speculation. During structural and degradative studies on naturally-occurring 2-OH-3-ketones (*e.g.* cucurbitacins A, B, and D), it was demonstrated[2] that the 2-OH group is equatorial, and it was reasonably assumed that the A-ring adopts a chair conformation, thus implying a β-configuration for the substituent. Subsequently, this assignment was rendered suspect since CD evidence[3] suggested that the A-ring of related 2-OH-3-ketones[4] adopts a twist conformation and that the ψ-equatorial 2-OH group has α-configuration. It has since transpired that such optical measurements are unreliable as a conformational probe since α-ketols and their acetates are prone to anti-octant behaviour.[5] The question of configuration at the 2-position in the natural 2-OH-3-ketones is therefore unresolved and consequently, the preferred conformation of the A-ring in these derivatives is uncertain.*

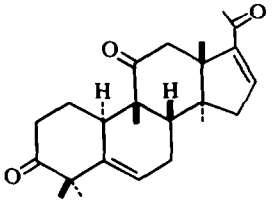
In an attempt to obtain chemical evidence to test the respective assignments, some reactions of the readily-available 3,11,20-triketone[6] (I) were studied. It is known that the 11-CO group is highly unreactive [7,8] and furthermore, that the 17-position in related 20-ketones appears to be subject to severe steric hindrance by the 14α-Me group.[9] If enolization of the 20-CO group occurs preferentially toward C(17), it was expected that electrophilic attack upon I might be induced to display selectivity toward the 2-position.

Controlled bromination of the triketone (I) with 0·8 mol pyridinium hydrobromide perbromide[10] afforded a mixture of products which was separated by column chromatography to give dibrominated material (MS; 7·7%), the 17-Br-compound (II; 5%), and the isomeric 2-Br-3-ketones (III; 23·5%) and (IV; 22·2%). Starting material (I; 40·5%) was also recovered. Experiments with an excess of reagent afforded in-

* A recent X-ray crystallographic analysis of the cucurbitacin glycoside, datiscoside, has proved that the 2-OH group has β-configuration.[27]



I: $R^1 = R^2 = R^3 = H$
II: $R^1 = R^2 = H$, $R^3 = Br$
III: $R^1 = Br$, $R^2 = R^3 = H$
IV: $R^1 = R^3 = H$, $R^2 = Br$



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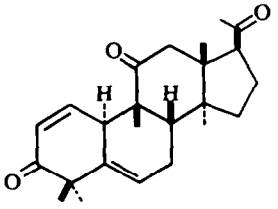

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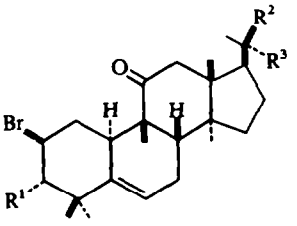
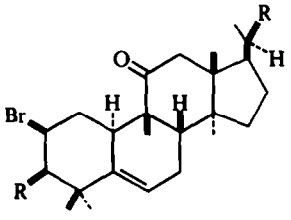
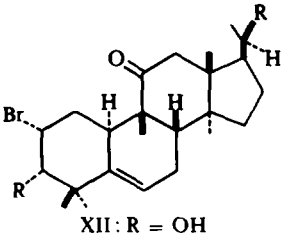


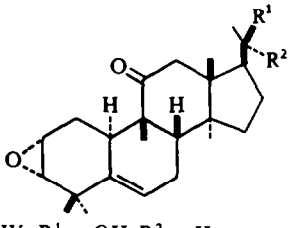
VII: $R^1 = R^2 = OH$, $R^3 = H$
VIII: $R^1 = R^2 = OAc$, $R^3 = H$
IX: $R^1 = R^3 = OH$, $R^2 = H$



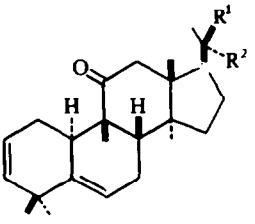
X: R = OH
XI: R = OAc



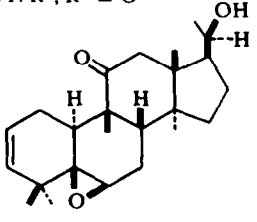
XII: R = OH
XIII: R = OAc



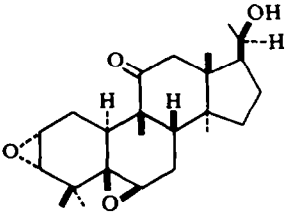
XIV: $R^1 = OH$, $R^2 = H$
XV: $R^1 = H$, $R^2 = OH$
XVI: R^1, $R^2 = O$



XVII: $R^1 = OH$, $R^2 = H$
XVII/XVIII: R', $R^2 = O$



XIX



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creasing proportions of dibrominated material. This product was not further examined since it was shown to be an inseparable mixture. Under the optimum conditions described, 90% of the monobromination occurred at the 2-position.

The structure of the minor Br-compound (II) was demonstrated by the absence in an NMR spectrum, of a low-field signal for a proton attached to a C-Br moiety; and by dehydrobromination to give the Δ^{16}-3,11,20-triketone (V) which exhibited the characteristic spectral properties for a Δ^{16}-20-CO chromophore.[11] The assignment of α-configuration to the 17-Br substituent is tentative because of the indeterminate steric influence of the 14α-Me group.[9] However, the NMR spectrum of II reveals that the 13β-Me group and the 12α-proton signals suffer downfield shifts (0·07 and 0·31 ppm resp) relative to the parent triketone (I). Such deshielding is compatible with the presence of a 17α-Br group.[12]

NMR examination of the isomeric 2-Br-3-ketones (III and IV) clearly indicated an equatorial-axial relationship in the respective dispositions of the Br-group. Thus, a spectrum of IV exhibited a triplet (J 5·5 Hz) at δ 4·49 for an equatorial 2-proton, while that of the other isomer (III) showed a quartet (14 and 5·5 Hz) at δ 4·86 for an axial 2-proton. The splitting pattern of the latter signal is very similar to those of the natural 2-OH-3-ketones and their derived acetates.[2,3] The relationship between the two isomers was further demonstrated by other spectroscopic data (Table 1). Although the expected band-shift characteristics of axial and equatorial α-Br-ketones[13] were partly obscured by multiple CO absorptions, comparison with the data obtained for the parent triketone (I) confirmed the NMR evidence for the respective conformational assignments.

The axial 2-Br-3-ketone (IV) was converted to the equatorial epimer (III) upon brief treatment with hydrogen bromide in acetic acid, and the positional assignment for the two isomers was established by dehydrobromination of III or IV, to give the Δ^1-compound (VI). NMR examination of VI revealed the presence of a disubstituted olefinic bond, a result which is possible only with 2-Br derivatives of I.

In view of the conformational uncertainties associated with the A-ring, evidence was sought to confirm the configurational assignments for III and IV. Examination of Dreiding models reveals that the observed NMR couplings may be accommodated by an A-ring chair (A) or twist (B) (Fig 1) in both of which cases, the C(1) and C(2) substituents are mutually staggered. In the former conformation (A), the β-substituent is equatorial and the α-substituent is axial, while in the latter (B), the respective assignments are reversed. A further possibility is that whereas the equatorial isomer may be represented by the chair conformation (A), the axial isomer could relieve the severe 1,3-diaxial interaction between the 2α-Br and 4α-Me groups by adopting a twist-boat conformation (C) or by existing in an indeterminate state of conformational equilibrium.[14] In conformation (C) the C(2)-C(1) projection would not alter significantly from that of the chair conformation (A). Other discrete conformers are incompatible with the NMR data, and furthermore, the ψ-axial isomer in conformation (B) can probably be discounted by inspection, since a severe interaction results between the 2β-Br and 9β-Me groups.

A comparison of the CD spectra (Table 1) provided indirect evidence for a non-chair conformation in the axial isomer (IV). It was recently shown [15] that an isolated Δ^5-3-ketone in this series gives rise to a negative Cotton effect ($\Delta\varepsilon$-1·79). Consequently, an axial α-Br group in conformation (A) should cause a strong negative maximum at

higher wavelength than the parent triketone (I),[16] with a residual, and more positive maximum below 300 nm for the 11- and 20-chromophores. The observed CD spectrum of IV is unsymmetrical about its maxima, clearly due to the predictable bathochromic shift of the 3-CO transition. However, the expected dominance exerted by an axial α-Br group is not evident, suggesting that an A-ring deformation, in which the 3-CO group contribution is not comparable to that of I, may be present. This is further evidenced by the absence in the CD spectrum of IV, of the strong positive end-absorption which is seen in the parent triketone (I).[5] This low-wavelength transition has tentatively been ascribed[5] to the $\pi \rightarrow \pi^*$ transition of the Δ^5-bond when favourably disposed for orbital overlap with the 3-CO group. Deformation of the A-ring would destroy the necessary spatial relationship[17] present in I.

TABLE 1. SPECTROSCOPIC DATA FOR TRIKETONES

	IR	UV	CD
	ν_{max} ($CHCl_3$)	λ_{max} (MeOH)	$\Delta\varepsilon$ (MeOH)
3,11,20-Trione (I)	1708 cm^{-1}	292 nm (ε 142)	+ 6·65 (295 nm)
2β-Br-3,11,20-Trione (III)	1735 cm^{-1}	291 nm (ε 179)	+ 5·49 (294 nm)
	1705 cm^{-1}		
2α-Br-3,11,20-Trione (IV)	1708 cm^{-1}	294 nm (ε 123)	+ 6·18 (292 nm)
		320 nm (infl., ε 71)	− 0·67 (332 nm)

By contrast, the CD spectrum of the equatorial isomer (III) shows the end-adsorption. Curiously the $n \rightarrow \pi^*$ band in III is weaker than in I. This could be a consequence of slight flattening of the A-ring chair, sufficient to increase the negative contribution of the 3-CO group, but insufficient to destroy the orbital interaction between that group and the Δ^5-bond.

The configuration of the Br-group in the equatorial isomer (III) was finally established by examining the influence of a lanthanide shift reagent[18] upon the NMR spectrum. It was reasoned that exposure of the signal due to the axial or ψ-axial 1-proton would permit measurement of the one geminal and two vicinal couplings expected. Conformation (A) would exhibit two large diaxial couplings ($\phi_{1\beta,2\alpha} \approx \phi_{1\beta,10\alpha} \approx 180°$), while conformation (B) would give rise to one large and one smaller vicinal coupling ($\phi_{1\alpha,2\beta} \approx 180°$, $\phi_{1\alpha,10\alpha} \not> 30°$). A difficulty could be presaged if equivalent complexation of the lanthanide occurred with the three available sites, since most of the signals for the β-removed protons would then be shifted at similar rates, and loss of resolution[19] might be expected before mutual separation. In the event, successive additions of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato europium (III)[18] [Eu(fod)$_3$] to a $CDCl_3$ solution of III showed that the 20- and 11-CO groups complex much more strongly than does the 3-CO group (Fig 2). Signals for protons in the environment of the C- and D-rings displayed apparently linear concentration-shift behaviour up to *ca* 0·5 mol Eu(fod)$_3$, whereafter their shift rates declined, while those of other protons increased. The increased shift rate of 2-H at higher Eu(fod)$_3$ concentrations (Fig 2) indicated stronger complexing participation by the 3-CO group, and at 0·7 mol of reagent, a broad, well-defined multiplet was partly visible. With 1·0 mol Eu(fod)$_3$ this signal appeared at δ 3·82 as a quartet-like

structure in which the broadened central lines indicated three large but slightly dissimilar couplings. Irradiation of the 2-H signal caused the multiplet at δ 3·82 to collapse to an ABX quartet (J 13 and 10 Hz), which couplings are ascribed to $J_{1\beta,1\alpha}$ and $J_{1\beta,10\alpha}$ respectively. It follows that the equatorial isomer (III) must necessarily be 2β-substituted in an A-ring chair conformation (A, Fig 1).

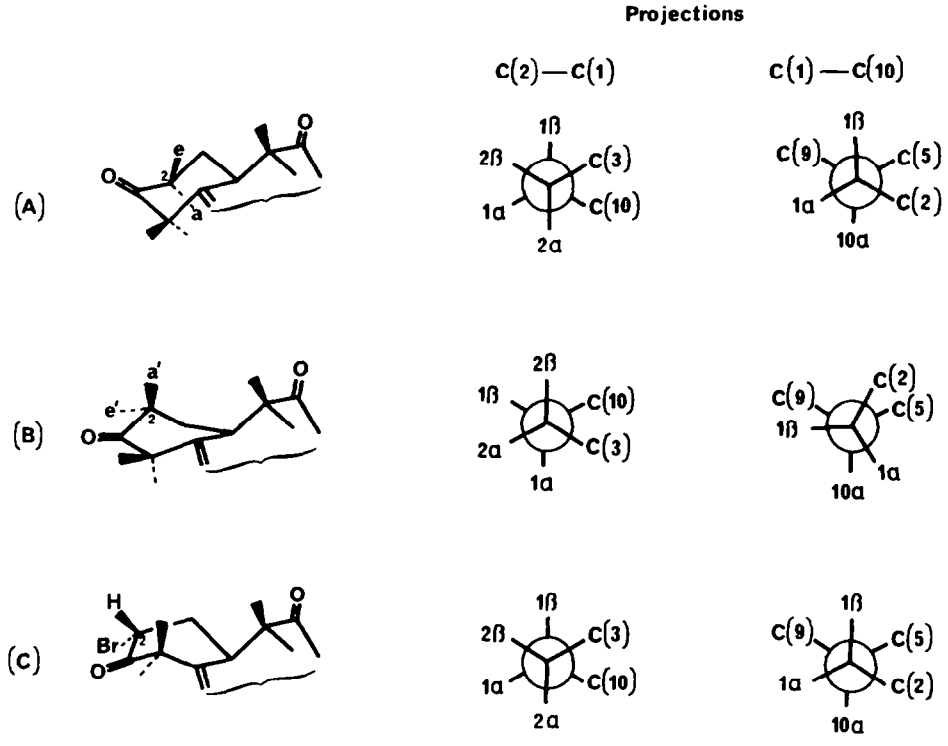

FIG. 1.

During this NMR examination, three one-proton multiplets (broken line, Fig 2) failed to resolve: these signals were assigned to 1α-, 10α- and 16ξ-H. It is known from model studies[20] that Eu-complexation with the 11-CO group causes strong downfield shifts of 1α-H, and it is clear that in this instance, the different shift rates of the 1-protons are not attributable to their axial-equatorial disposition to the 3-CO group alone. With the further exception of the 7- and 15-protons, which failed to shift sufficiently to be detected, the remaining protons in the molecule were unequivocally assigned (Fig 2). It is clear from this examination that polyfunctional systems are amenable to lanthanide shift analysis provided that differential complexation takes place.

An examination of models revealed that a similar experiment on the axial isomer (IV) would not distinguish between the conformations A and C (Fig 1). However, the firm configurational assignment based upon the aforegoing result, together with the CD evidence, suggests that the latter conformation C is the more likely.

Corroborative evidence for these conclusions were obtained through reduction of the 2-Br-3-ketones. Treatment of III with $NaBH_4$ afforded a mixture of bromohydrins, two of which, VII and X, were separated by chromatography. The presence of a third isomer (IX) in the mixed fractions was inferred from further transformations (*q.v.*). The major product (VII) was assumed to be the 2,3-diequatorial isomer since it has been shown[8] that similar reduction of the triketone (I) affords the 3α-OH compound. NMR data (Table 2) on VII and its derived diacetate (VIII) confirmed the assignment and demonstrated that the A-ring conformation undergoes little if any change during reduction of the 3-CO group. The *trans*-relationship between the 2- and 3-substituents was shown by smooth conversion of VII to the α-epoxide upon treatment with alkali.[21]

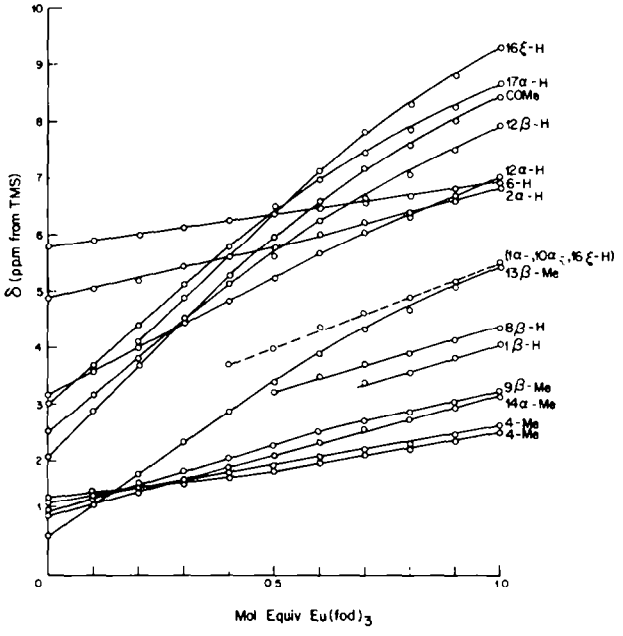

FIG. 2.

The minor isomer (X) exhibited the expected spectral properties for an axial 3β-OH derivative (Table 2), and failed to undergo loss of HBr despite prolonged treatment with alkali. The configuration of the 20-OH group in both products (VII and X) was assumed to be β- on the basis of precedent[8] and comparative NMR data[22] (Experimental).

A third product (IX) could not be cleanly separated from the major isomer (VII), but treatment of the mixed chromatographic fractions with alkali afforded a separable mixture of epoxides (XIV and XV). The NMR signals for their respective epoxidic protons were identical, but distinct differences in their 20-H signals indicated that the second component of the mixture was the 20α-OH compound (XV). This was confirmed by oxidation of XIV and XV to the same epoxy-diketone (XVI). The unisolable bromohydrin derived from $NaBH_4$ reduction of the 2β-Br-3-ketone (III) must therefore be the 2β-Br-3α,20α-diol (IX).

Reduction of the 2α-Br-3-ketone (IV) with $NaBH_4$ afforded a complex mixture, from which the major isomer (XII) was isolated pure. NMR examination (Table 2) revealed a clear doublet ($J_{3\beta,2\beta}$ 4 Hz) for 3-H, but the 2-H splittings were partly obscured by the 20-H signal and could not be accurately measured. The estimated half-height width (11 Hz) of the 2-H signal suggests that the magnitudes of $J_{2\beta,1\beta}$ and $J_{2\beta,1\alpha}$ are smaller in XII than in the 2α-Br-3-ketone (IV), but the evidence does not suffice to show that the A-ring underwent any conformational change during reduction. However, the *cis*-relationship between the 2- and 3-substituents was shown by failure of the compound XII to form an epoxide upon treatment with alkali.[21]

TABLE 2. NMR SIGNALS FOR 2- AND 3-PROTONS IN BROMOHYDRINS AND THEIR ACETATES[a]

Compound	2-H	3-H
2β-Br-3α,20β-$(OH)_2$ (VII)	4·44 (oct., 12·5, 10·5, 4)	3·48 (d., 10·5)
2β-Br-3α,20β-$(OAc)_2$ (VIII)	4·07 (oct., 12·5, 10·5, 4)	4·77 (d., 10·5)
2β-Br-3β,20β-$(OH)_2$ (X)	4·75 (br., 18[b])	3·75 (obsc., > 5[b])
2β-Br-3β,20β-$(OAc)_2$ (XI)	4·80 (br., 20[b])	5·08 (d., 2·5)
2α-Br-3α,20β-$(OH)_2$ (XII)	4·81 (m., 11[b])	3·49 (d., 4)
2α-Br-3α,20β-$(OAc)_2$ (XIII)	4·64 (m., 11[b])	4·46 (d., 4)

[a] NMR spectra were recorded on a Varian HA-100 instrument in C_5D_5N (diols) or $CDCl_3$ (diacetates) solutions with TMS as internal standard. The first figure in each column refers to chemical shift (ppm) and the details in parentheses refer to multiplicity and observed splitting (Hz): m., multiplet; d., doublet; q., quartet; oct., octet; br., unresolved signal.

[b] Half-height width.

It was of interest to examine some cleavage reactions of the α-epoxide (XIV) since the selective introduction of a protected oxygen function could provide routes[23] to the isomeric 2-OR-3- and 3-OR-2-ketones for comparison with the naturally-derived series. However, vigorous treatment of XIV with glacial acetic acid[23] failed to cleave the epoxy-group, while catalysis of the reaction with mineral acid gave no products derived from attack of OAc^-. However, brief treatment of XIV with hydrogen bromide in chloroform afforded the 2β-Br-3α-OH compound (VII). The exclusive formation of a diequatorial cleavage product must result from suppression of stereo-electronically favoured anti-parallel attack[24] by Br^- at C(2) due to the vicinal 4β-Me group.

The 2,5-diene (XVII) was prepared by zinc reduction[21] of VII (and X), in order to examine the stereochemistry of direct epoxidation of the Δ^2-bond. Surprisingly, treatment of XVII with 1 mol *m*-chloroperbenzoic acid afforded mixtures of the Δ^2-5β,6β-epoxide (XIX) and di-epoxide (XX). The stereochemistry of the A-ring epoxy-group in the latter product (XX) was established by treatment of the Δ^5-2α, 3α-epoxide (XIV) with *m*-chloroperbenzoic acid to give the same di-epoxide (XX). The configuration of the B-ring epoxy-group in XIX and XX was demonstrated by sharp NMR doublets of characteristically large splitting[7] (J 5·5 Hz) at δ 3·3 and 3·17 respectively.

The evident sequence of attack upon the Δ^5- and Δ^2-bonds in XVII is unexpected, since Δ^5-compounds in this series are known[7] to undergo epoxidation very slowly. It can be concluded that the Δ^2-bond in XVII is severely hindered by the 4,4-dimethyl group and furthermore, that the presence of this unsaturation in the A-ring alters the steric environment of the Δ^5-bond sufficiently to promote rapid and exclusive formation of XIX at the expense of XIV. Additionally no trace of 2β,3β-epoxides was detected in the epoxidation of XVII and it may be concluded that peracid attack on the Δ^2-bond is highly stereoselective. It was hoped that this preference could be exploited to prepare the 2β,3β-epoxide *via* the addition of HOBr to the Δ^2-bond, since either *trans*-adduct obtained by initial α-face attack (*viz.* 2α-Br-3β-OH or 2β-OH-3α-Br) could be converted to the desired product. However, treatment of the 2,5-diene-3,20-diketone (XVIII) with N-bromacetamide and $HClO_4$ in aqueous dioxan[25] afforded an ill-defined mixture of products which could not be separated. Treatment of the crude mixture with alkali afforded material which TLC examination revealed to contain the α-epoxide (XVI) as a major component, together with lesser amounts of a product of similar polarity. Although this latter product may be the β-epoxide, the route is not sufficiently stereoselective for preparing useful quantities of the isomer. The apparent anomaly between the peracid and HOBr results may arise through different steric demands by the respective reagents or more probably, through different transition state conformations in the A-ring.

EXPERIMENTAL

For general directions see Ref. 26.

Bromination of 4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*ene*-3,11,20-*trione* (*I*)

The triketone (I; 2·0 g) in chloroform (70 ml) and THF (70 ml) was treated with pyridinium hydrobromide perbromide (1·4 g) at 0° for 0·5 hr. Water was added and the product was extracted with chloroform. Evaporation of the solvent gave a residue which was adsorbed on silica gel (200 g). Elution with benzene-EtOAc (9:1, 2 1), gave unidentified oils (0·22 g), followed by 17α-*bromo*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*ene*-3,11,20-*trione* (II; 0·12 g), m.p. 165–167° (from chloroform-cyclohexane), $[\alpha]_D$ + 65° (*c* 1·2), δ 0·77, 1·08, 1·23, 1·23, and 1·54 (5 × Me), 2·41 (COMe), 3·44 (1H, m, *J* = 17, 9 and 2 Hz, 16ξ-H), and 5·75 (1H, m, 6-H) (Found: C, 63·9; H, 7·4%; M^+, 448 and 450. $C_{24}H_{33}BrO_3$ requires C, 64·1; H, 7·4%; M, 448 and 450).

Further elution gave 2α-*bromo*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*ene*-3,11,20-*trione* (IV; 0·54 g), m.p. 180–182° (from MeOH), $[\alpha]_D$ + 120° (*c* 1·0), δ 0·67, 1·08, 1·15, 1·29, and 1·39 (5 × Me), 2·09 (COMe), 3·05 (1H, t, *J* = 8·5 Hz, 17α-H), 4·49 (1H, t, *J* = 5·5 Hz, 2β-H), and 5·80 (1H, m, 6-H) (Found: C, 64·4; H, 7·4%; M^+, 448 and 450).

Further elution gave 2β-*bromo*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*ene*-3,11,20-*trione* (III; 0·57 g), m.p. 166–167° (from chloroform-hexane), $[\alpha]_D$ + 134° (*c* 1·0), δ 0·67, 1·06, 1·11, 1·26, and 1·36 (5 × Me), 2·09 (COMe), 3·03 (1H, t, *J* = 8·5 Hz, 17α-H), 4·86 (1H, q, *J* = 14 and 5·5 Hz, 2α-H), and 5·79 (1H, m, 6-H) (Found: C, 53·0; H, 6·0%; M^+, 448 and 450. $C_{24}H_{33}BrO_3.CHCl_3$ requires: C, 52·8; H, 6·1%; M, 448 and 450).

Starting material (I; 0·81 g) was recovered by further elution with the same solvent.

Isomerisation of the 2α-*bromo*-3,11,20-*triketone* (IV) *with acid*

The bromotriketone (IV; 0·011 g) in AcOH (0·8 ml) was treated with HBr (45% in AcOH; 0·2 ml) at 25°. After 1 hr chloroform was added and the soln was washed with water until neutral. Evaporation of the solvent gave a residue which was adsorbed on silica gel (2 g). Elution with benzene-EtOAc (9:1, 40 ml), gave III (0·003 g), m.p. and mixed m.p. 165–167° (from chloroform-hexane).

4,4,14α-*Trimethyl*-19(10→9β)abeo-10α-*pregna*-5,16-*diene*-3,11,20-*trione* (V)

A stirred mixture of II (0·06 g), Li_2CO_3 (0·09 g) and LiBr (0·06 g) in DMF (7 ml) was kept at 100° under

N_2 for 2·5 hr. Chloroform was added and the soln was acidified with AcOH then washed with water. Evaporation of the solvent gave a residue which was adsorbed on silica gel (15 g). Elution with benzene-EtOAc (9:1, 300 ml) gave an unidentified oil (0·008 g), followed by the *compound* (V; 0·038 g), m.p. 172–175° (from chloroform-cyclohexane), $[\alpha]_D$ + 192° (*c* 1·1), λ_{max}239 nm (ε 8500), δ 0·95, 1·13, 1·13, 1·18, and 1·23 (5 × Me), 2·25 (COMe), 5·73 (1H, m, 6-H), and 6·69 (1H, q, *J* = 3 and 2 Hz, 16-H) (Found: C, 78·1; H, 8·7%; M^+, 368. $C_{24}H_{32}O_3$ requires: C, 78·2; H, 8·75%; M, 368).

4,4,14α-*Trimethyl*-19(10→9β)abeo-10α-*pregna*-1,5-*diene*-3,11,20-*trione* (VI)

(a) A stirred mixture of III (0·42 g) Li_2CO_3 (0·35 g) and LiBr (0·35 g) in DMF (20 ml) was kept at 100° under N_2 for 4 hr. Chloroform was added, the soln was acidified with AcOH and washed with water. Evaporation of the solvent gave a residue which was adsorbed on silica gel (40 g). Elution with benzene-EtOAc (9:1, 1 1.), gave the *compound* (VI; 0·26 g), m.p. 217–220° (from chloroform-hexane, $[\alpha]_D$ + 116° (*c* 1·0), λ_{max}223 nm (ε 8400), δ 0·70, 0·98, 1·17, 1·18, and 1·26 (5 × Me), 2·09 (COMe), 3·03 (1H, t, *J* = 9 Hz, 17α-H), 3·33 (1H, m, $w_{\frac{1}{2}}$ 7 Hz, 10α-H), 5·76 (1H, m, 6-H), 5·94 (1H, q, *J* = 10·5 and 3 Hz, 2-H), and 6·63 (1H, q, *J* = 10·5 and 2·5 Hz, 1-H) (Found: C, 61·3; H, 6·8%; M^+, 368. $C_{24}H_{32}O_3 \cdot CHCl_3$ requires: C, 61·6; H, 6·8%; M, 368).

(b) Treatment of IV (0·42 g) with Li_2CO_3 (0·4 g), and LiBr (0·4 g) in DMF (30 ml), as in the previous experiment, and chromatography gave unreacted IV (0·04 g) followed by VI (0·2 g), m.p. and mixed m.p. 217–220° (from chloroform-hexane).

Reduction of bromotriketones

(a) The bromotriketone III (0·3 g) in MeOH (15 ml) at 0° was treated with $NaBH_4$ (0·6 g). After 45 min at 0° the mixture was acidified with AcOH, and the product was isolated by extraction with chloroform, and adsorbed on silica gel (60 g). Elution with benzene-EtOAc (3:1, 0·5 1), gave 2β-*bromo*-3β,20β-*dihydroxy*-4,4,14α-trimethyl-19(10 → 9β)abeo-10α-*pregn*-5-*en*-11-*one* (X; 0·04 g), m.p. 251–253° from chloroform-hexane), $[\alpha]_D$ + 93° (*c* 0·8), δ 0·94, 1·07, 1·07, 1·23, and 1·39 (5 × Me), 1·25 (3H, d, *J* = 6 Hz, 21-H), 3·75 (1H, obsc., $w_{\frac{1}{2}}$ ≯ 6, 3α-H), 3·80 (1H, obsc., 20α-H), 4·75 (1H, br., $w_{\frac{1}{2}}$ *ca* 18 Hz, 2α-H), and 5·70 (1H, m, 6-H) (Found: C, 63·7; H, 8·1%; M^+, 452 and 454. $C_{24}H_{37}BrO_3$ requires: C, 63·6; H, 8·2%; M, 452 and 454).

Treatment of X with Ac_2O-pyridine at 25° afforded the 3,20-*diacetate* (XI), m.p. 165–169° (from aqueous EtOH), $[\alpha]_D$ + 91° (*c* 1·4). δ 0·69, 1·03, 1·09, 1·09, and 1·13 (5 × Me), 2·03 and 2·08 (2 × OCOMe), 4·44 (1H, br., $w_{\frac{1}{2}}$ *ca* 20 Hz, 20α-H), 4·80 (1H, br., $w_{\frac{1}{2}}$ *ca* 20 Hz, 2α-H), 5·08 (1H, d, *J* = 2·5 Hz, 3α-H), and 5·64 (1H, m, 6-H) (Found: C, 62·3; H, 7·5%, M^+, 536 and 538. $C_{28}H_{41}BrO_5$ requires: C, 62·6; H, 7·7%; M, 536 and 538).

Further elution with the same solvent gave material (0·148 g) which was homogeneous on TLC but which was shown by subsequent treatment with alkali (*vide infra*) to be a mixture of two compounds. Fractional crystallisation of the mixture from chloroform-hexane afforded 2β-*bromo*-3α,20β-*dihydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*en*-11-*one* (VII; 0·11 g), m.p. 266–267°, $[\alpha]_D$ + 79° (*c* 1·1, C_5H_5N), δ 0·98, 1·07, 1·20, 1·21, and 1·44 (5 × Me), 1·28 (3H, d, *J* = 6 Hz, 21-H), 3·48 (1H, d, *J* = 10·5 Hz, 3β-H), 3·83 (1H, m, *J* = 9 and 6 Hz, 20α-H), 4·44 (1H, oct., *J* = 12·5, 10·5 and 4 Hz, 2α-H), and 5·74 (1H, m, 6-H) (Found: C, 63·4; H, 8·1%; M^+, 452 and 454). The mother liquor residues were retained for treatment with alkali.

Treatment of VII with Ac_2O-pyridine at 25° afforded the 3,20-*diacetate* (VIII), m.p. 221 223° (from MeOH), $[\alpha]_D$ + 119° (*c* 0·9), δ 0·68, 0·97, 1·01, 1·06 and 1·08 (5 × Me), 1·15 (3H, d, 6 Hz, 21-H), 2·00 and 2·09 (2 × OCOMe), 4·07 (1H, oct., *J* = 12·5, 10·5, and 4 Hz, 2α-H), 4·77 (1H, d, *J* = 10·5 Hz, 3β-H), 4·79 (1H, m, *J* = 10 and 6 Hz, 20α-H), and 5·74 (1H, m, 6-H) (Found: C, 62·7; H, 7·7%; M^+, 536 and 538).

(b) Reduction of IV (0·1 g) in MeOH (10 ml) at 0° for 0·5 hr gave unidentified minor products (0·01 g), and 2α-*bromo*-3α,20β-*dihydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*en*-11-*one* (XII; 0·068 g), m.p. 183–185° (from chloroform-hexane), $[\alpha]_D$ + 143° (*c* 1·0), δ 0·95, 1·09, 1·14, 1·34, and 1·45 (5 × Me), 1·26 (3H, d, *J* = 6 Hz, 21-H), 3·49 (1H, d, *J* = 4 Hz, 3β-H), 3·80 (1H, oct., *J* = 9 and 6 Hz, 20α-H), 4·81 (1H, m, $w_{\frac{1}{2}}$ 11 Hz, 2β-H), and 5·74 (1H, m, 6-H) (Found: C, 63·5; H, 8·1%; M^+, 452 and 454).

Treatment of XII with Ac_2O-pyridine at 25° afforded the 3,20-*diacetate* (XIII), m.p. 201–206° (from aqueous MeOH), $[\alpha]_D$ + 120° (*c* 1·2), δ 0·69, 1·04, 1·04, 1·10, and 1·24 (5 × Me), 1·15 (3H, d, *J* = 6 Hz, 21-H), 2·02 and 2·10 (2 × OCOMe), 4·46 (1H, d, *J* = 4 Hz, 3β-H), 4·64 (1H, m, $w_{\frac{1}{2}}$ 11 Hz, 2β-H), 4·85 (1H, oct., *J* = 10 and 6 Hz, 20α-H), and 5·75 (1H, m, 6-H) (Found: C, 62·5; H, 7·6%; M^+-60, 476 and 478).

Treatment of the bromohydrins with alkali

(a) 2N-NaOH (2 ml) was added to VII (0·05 g) in MeOH (15 ml) at 25°. After 16 hr at 25° chloroform was

added, and the soln was washed with water. The solvent was evaporated and the residue was adsorbed on alumina (3% deactivated; 15 g). Elution with benzene-chloroform (1:1, 200 ml) gave 2α,3α-*epoxy*-20β-*hydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*en*-11-*one* (XIV), m.p. 217–220° (from chloroform-hexane), $[\alpha]_D$ + 134° (*c* 1·1), δ 0·80, 1·01, 1·07, 1·13, and 1·22 (5 × Me), 1·15 (3H, d, *J* = 6 Hz, 21-H), 2·72 (1H, d, *J* = 4 Hz, 3β-H), 3·28 (1H, t, *J* = 4 Hz, 2β-H), 3·70 (1H, oct., *J* = 9 and 6 Hz, 20α-H), and 5·64 (1H, m, 6-H) (Found: C, 77·6; H, 9·7%; M^+, 372. $C_{24}H_{26}O_3$ requires: C, 77·4; H, 9·7%; M, 372).

(b) Treatment of the major chromatographically homogeneous fractions arising from reduction of III (0·07 g) in MeOH (20 ml) with 2N-NaOH (3 ml) at 25° as in the previous experiment gave 2α,3α-*epoxy*-20α-*hydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*en*-11-*one* (XV: 0·012 g), m.p. 227–230° (from chloroform-cyclohexane), $[\alpha]_D$ + 153° (*c* 1·0), δ 0·69, 1·01, 1·06, 1·13, and 1·22 (5 × Me), 1·19 (3H, d, *J* = 6 Hz, 21-H), 2·72 (1H, d, *J* = 4 Hz, 3β-H), 3·28 (1H, t, *J* = 4 Hz, 2β-H), 3·67 (1H, oct., *J* = 7·5 and 6 Hz, 20β-H), and 5·65 (1H, m, 6-H) (Found: C, 77·1; H, 9·7%; M^+, 372).

Further chromatography gave material (0·043 g) which was crystallised from chloroform-hexane to give XIV m.p. and mixed m.p. 217–220° (from chloroform-hexane).

(c) Treatment of X (0·01 g) in MeOH (10 ml) with 2N-NaOH (1 ml) at 25° as in the previous experiments gave unchanged X m.p. and mixed m.p. 251–253° (from chloroform-hexane).

2α,3α-*Epoxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregn*-5-*ene*-11,20-*dione* (XVI)

(a) Compound XIV (0·058 g) in acetone (20 ml) at 0° was treated with 8N-CrO_3. After 4 min at 0° MeOH was added and the product was isolated with chloroform. Evaporation of the solvent gave a residue which was adsorbed on silica gel (10 g). Elution with benzene–EtOAc (4:1, 200 ml), gave the *epoxy-diketone* (XVI; 0·047 g), m.p. 147–150° (from MeOH), $[\alpha]_D$ + 215° (*c* 1·1), δ 0·73, 1·02, 1·12, 1·15, and 1·23 (5 × Me), 2·09 (COMe), 2·74 (1H, d, *J* = 4 Hz, 3β-H), 3·05 (1H, t, *J* = 8·5 Hz, 17α-H), 3·30 (1H, t, *J* = 4 Hz, 2β-H), and 5·66 (1H, m, 6-H) (Found: C, 77·6; H, 9·1%; M^+, 370. $C_{24}H_{34}O_3$ requires: C, 77·8; H, 9·25%; M, 370).

(b) Oxidation of XV (0·01 g) in acetone (5 ml) as in the previous experiment, afforded XVI (0·008 g) m.p. and mixed m.p. 147–150° (from MeOH).

Treatment of the 2α,3α-*epoxy*-20β-*ol* (XIV) *with hydrogen bromide*

HBr was bubbled through a soln of XIV (0·034 g) in chloroform (10 ml, freshly distilled from P_2O_5) at 25°. After 5 min the soln was washed with water. Evaporation of the solvent gave a residue which was adsorbed on silica gel (10 g). Elution with chloroform–MeOH (97:3, 100 ml), gave VII (0·032 g), m.p. and mixed m.p. 265–267° (from chloroform–hexane).

20β-*Hydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregna*-2,5-*dien*-11-*one* (XVII)

(a) Zn (2 g) was added to VII (0·225 g) in AcOH (50 ml) and the mixture was heated under reflux for 1 hr. Chloroform was added and the soln was washed with water. Evaporation of the solvent gave the *dienone* (XVII; 0·17 g), m.p. 225–226° (from chloroform–hexane), $[\alpha]_D$ + 202° (*c* 1·2), δ0·82, 1·07, 1·07, 1·09, and 1·12 (5 × Me), 1·14 (3H, d, *J* = 6 Hz, 21-H), 3·72 (1H, oct., *J* = 9·5 and 6 Hz, 20α-H), 5·30 (1H, oct., *J* = 10, 2 and 1 H, 3-H), 5·58 (1H, oct., *J* = 10, 5 and 1 Hz, 2-H, and 5·72 (1H, m, 6-H) (Found: C, 80·8; H, 10·3%; M^+, 356. $C_{24}H_{36}O_2$ requires: C, 80·9; H, 10·2%; M, 356).

(b) Treatment of X (0·012 g) in AcOH (3 ml) with Zn (0·09 g) as in the previous experiment, afforded XVII (0·004 g) m.p. and mixed m.p. 223–226° (from chloroform–hexane).

4,4,14α-*Trimethyl*-19(10→9β)abeo-10α-*pregna*-2,5-*diene*-11,20-*dione* (XVIII)

Compound XVII (0·06 g) in acetone (30 ml) at 0° was treated with 8N-CrO_3. After 5 min at 0°, MeOH was added and the product was isolated with chloroform. Evaporation of the solvent gave a residue which was adsorbed on silica gel (15 g). Elution with benzene–EtOAc (9:1, 200 ml) gave the $\Delta^{2,5}$-*diketone* (XVIII; 0·028 g), m.p. 170–172° (from cyclohexane), $[\alpha]_D$ + 262° (*c* 0·9, δ 0·64, 1·08, 1·09, 1·12, and 1·12 (5 × Me), 2·07 (COMe), 3·03 (1H, t, *J* = 8·5 Hz, 17α-H), 5·30 (1H, oct., *J* = 10, 2 and 1 Hz, 3-H), 5·57 (1H, oct., *J* = 10, 4·5 and 1 Hz, 2-H), and 5·72 (1H, m, 6-H) (Found: C, 81·2; H, 9·6%; M^+, 354. $C_{24}H_{34}O_2$ requires: C, 81·3; H, 9·7%; M, 354).

Epoxidation of 20β-*hydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-10α-*pregna*-2,5-*dien*-11-*one* (XVII)

A soln of XVII (0·1 g) in benzene (20 ml) at 25° was treated with *m*-chloroperbenzoic acid (60%; 0·1 g). After 0·5 hr the soln was washed with $NaHCO_3$ aq and water. Evaporation of the solvent gave a residue which was adsorbed on silica gel (20 g). Elution with benzene–EtOAc (7:3, 400 ml), gave 5,6β-*epoxy*-20β-

hydroxy-4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregn*-2-*en*-11-*one* (XIX; 0·012 g), m.p. 198–202° (from benzene then aqueous MeOH), $[\alpha]_D$ + 151° (*c* 0·7), δ 0·76, 0·76, 1·10, 1·14, and 1·18 (5 × Me), 1·14 (1H, d, *J* = 6 Hz, 21-H), 3·30 (1H, d, *J* = 5·5 Hz, 6α-H), 3·71 (1H, oct., *J* = 9 and 6 Hz, 20α-H), 5·28 (1H, oct., *J* = 10, 2 and 1 Hz, 3-H), and 5·61 (1H, oct., *J* = 10, 5 and 2 Hz, 2-H) (Found: C, 77·1; H, 9·9%; M^+, 372. $C_{24}H_{36}O_3$ requires: C, 77·4; H, 9·7%; M, 372).

Further elution with the same solvent gave 2α,3α,5,6β-*diepoxy*-20β-*hydroxy*-4,4,14α-*trimethyl*-19(10→9β)abeo-5β,10α-*pregnan*-11-*one* (XX; 0·075 g), m.p. 184–188° (from benzene–cyclohexane), $[\alpha]_D$ + 105° (*c* 1·1), δ 0·75, 0·80, 1·09, 1·15, and 1·15 (5 × Me), 1·14 (3H, d, *J* = 6 Hz, 21-H), 2·73 (1H, d, *J* = 4 Hz, 3β-H), 3·17 (1H, d, *J* = 5·5 Hz, 6α-H), 3·31 (1H, q, *J* = 4 and 3 Hz, 2β-H), and 3·70 (1H, oct., *J* = 9 and 6 Hz, 20α-H) (Found: C, 74·2; H, 9·5%; M^+, 388. $C_{24}H_{36}O_4$ requires: C, 74·2; H, 9·3%; M, 388).

Epoxidation of the Δ^5-2α,3α-*epoxide* (XIV).

Compound XIV (0·025 g) in benzene (5 ml) was treated with *m*-chloroperbenzoic acid (60%; 0·03 g) at 25° for 24 hr. Work-up as in the previous experiment gave XX (0·015 g), m.p. and mixed m.p. 180–183° (from benzene cyclohexane).

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