Electrophilic Addition to 24,25,26,27-Tetranorlanosta-8,22-dien-3β-yl Acetate

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Addition of the elements of hypobromous acid to the Δ^{22}-bond of the title compound (II) gives rise, after cyclisation, to the (22*S*)-epoxide (IIIa) in a highly selective manner. The two major bromohydrin intermediates have been shown to be the 23-bromo-22(*S*)-hydroxy- and 22(*R*)-bromo-23-hydroxy-isomers. A third, minor bromohydrin has the 23-bromo-22(*R*)-hydroxy-structure.

INOTODIOL (I) [1] is a reputedly cytotoxic principle [2] of the birch fungus *Inonotus obliquus*, which is the source of 'tchaga,' a Russian folk-lore medicine described [3] in Solzhenitsyn's novel 'Cancer Ward.' It has recently been synthesised in these laboratories [4] and demonstrated by Horeau's method [5] to possess the 22*R*-configuration. The synthesis proceeded by treatment of the lanosterol-derived Δ^{22}-olefin (II) [4] with *N*-bromosuccinimide in aqueous tetrahydrofuran, followed by base-induced cyclisation and saponification, to give in good yield an epoxy-alcohol, apparently homogeneous by t.l.c. and n.m.r. After several crystallisations of the epoxy-alcohol, treatment with the appropriate Grignard reagent gave inotodiol [(22*R*)-22-hydroxylanosterol] in 55% yield, identical with the natural product.

[1] (*a*) R. S. Ludwiczak and U. Wrzeciono, *Roczniki Chem.*, 1958, **32**, 39; (*b*) F. de Reinach Hirtzbach and G. Ourisson, *Tetrahedron*, 1972, **28**, 2259.

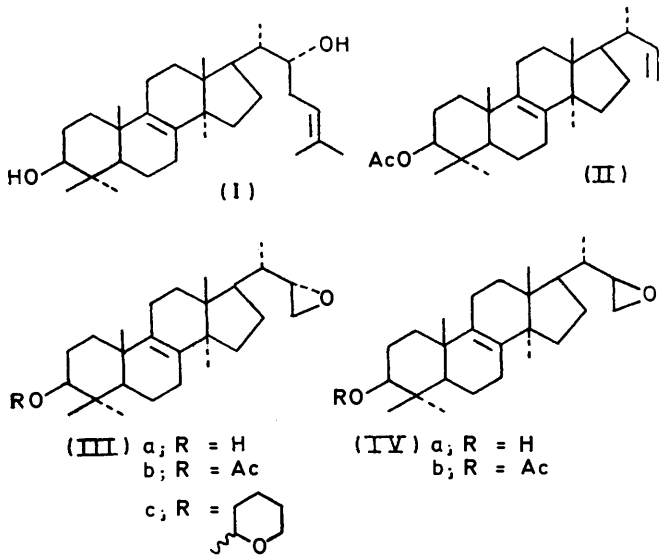
[2] E. V. Loviagina and A. N. Shivrina, *Biokhimiya*, 1962, **27**, 794.

[3] A. Solzhenitsyn, 'Cancer Ward,' Penguin, London, 1971, p. 147.

[4] J. P. Poyser, F. de Reinach Hirtzbach, and G. Ourisson, *Tetrahedron*, in the press.

[5] A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431, and references cited therein.

Further inspection (t.l.c.; eleven elutions in toluene) showed that the epoxy-alcohol prior to crystallisation was a 5 : 1 mixture of two epimers (R_F 0·12 and 0·09) in



which the less polar predominated. The recrystallised material contained *ca.* 90% of the less polar epimer (estimated by t.l.c.). From its relationship with inotodiol, it follows that this is the epoxy-alcohol of 22*S*-configuration (IIIa); the more polar, minor compound must be the 22*R*-epimer (IVa).

The mixture of epoxy-alcohols could be more readily resolved into its components after conversion into the corresponding 3β-acetates. The acetate mixture was obtained either by incomplete saponification of the bromohydrin intermediates or by direct acetylation of the epoxy-alcohols. T.l.c. (eight elutions in toluene) furnished the individual acetates [less polar (IIIb); more polar (IVb)], which on basic hydrolysis gave the pure epoxy-alcohols [(IIIa) and (IVa), respectively].

In the n.m.r. spectra of the 22*R*- and 22*S*-series, the signals due to the epoxide protons were distinct and characteristic for each. The members of the 22*S*-series, whether as the 3β-alcohol, 3β-acetate, or 3β-tetrahydropyranyl ether, showed a complex, two-proton n.m.r. multiplet at τ 7·3 (22-H and the 23-H '*trans*' to this) and a one-proton, four-peak signal at τ 7·6, as part of the A_2BX system. The (22*R*)-compounds (IVa and b) exhibited in contrast a three-proton multiplet at τ 7·3. Epimeric epoxides of this kind can therefore be easily distinguished, a fact which may prove a useful analytical tool for the assignment of the absolute stereochemistry to similar compounds. However, where the steroid bears polar substituents at C-20 and C-17, the foregoing observation cannot be applied (*e.g.* ref. 6).

Direct oxidation by peroxy-acid of the 22,23-double bond, which would be predicted to give the (22*R*)-epoxide preferentially,[7] is rendered impractical by competitive attack on the 8,9-double bond, even with ether as solvent.[8]

Electrophiles approach the monosubstituted Δ^{22}-system studied predominantly from the side of the 21-methyl group. Nickolson and Gut[6] observed a similarly favoured direction of attack on the same system bearing additional 17α- and 20(*S*)-hydroxy-groups. Barton *et al.* found an even more marked bias for approach from this side in derivatives of ergost-22-ene.[7] In contrast, using alkaline hydrogen peroxide, Sucrow *et al.*[9] obtained highly stereoselectively the 22(*S*),23(*R*)-epoxide from a 26-norcholest-22-en-24-one. A similar result was observed by Popplestone and Unrau[10] using the same reagent in the case of 3β-acetoxycholest-5,22-dien-24-one. However, these are examples of nucleophilic attack (Michael type). The stereoselectivity is equally interesting.

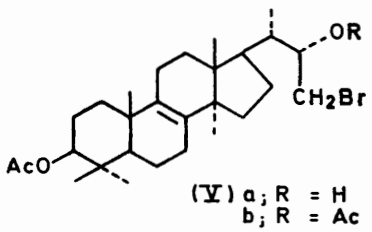
In the product from treatment of the olefin (II) with *N*-bromosuccinimide, three bromohydrins were detectable by t.l.c.: two isolable, major bromohydrins in approximately equal proportions, and a minor isomer of intermediate polarity, which could not be obtained pure. Basic cyclisation of either major bromohydrin gave the (22*S*)-epoxide (IIIa) as sole product. The n.m.r. spectrum of the least polar bromohydrin (Va) showed the presence of a methylene group bearing a bromine atom vicinal to a secondary alcohol function. This verifies the assigned structure, which is that of the Markownikoff product. The most polar bromohydrin exhibits n.m.r. signals for a primary alcohol function next to a secondary bromide group, in agreement with structure (VIa). Each of the derived acetates [(Vb) and (VIb)], on thermal equilibration at the m.p., afforded a mixture of both acetates in which the thermodynamically more stable (VIb) predominated (ratio 5 : 2).

The assigned structures were confirmed by use of tri-n-butyltin hydride,[11] which converted (Vb) into the diacetate (VIIa). Hydrolysis gave the diol (VIIb), and Jones oxidation[12] then furnished the dione (VIII), which showed a methyl ketone system as a singlet at τ 7·96 in its n.m.r. spectrum. Similarly, the bromohydrin (Va) gave the (22*R*)-22-hydroxy-3β-acetate (VIIc), separated with difficulty from the tetrahydrofuranyl ether by-product (VIId). Mild acidic treatment of the ether furnished a pure sample of (VIIc), which was more easily characterised as the benzoate (VIIe) or as the ketone (IX).

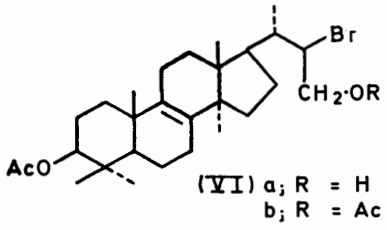
The methyl ketone (IX) provided a useful entry into the 22*S*-series, since it was reduced by hydride to give mainly 22*S*-epimer. This behaviour is similar to the hydride reduction of the 22-oxoergostane derivative (Xa)[7] and of several examples of 22-oxocholestanes,

[6] R. C. Nickolson and M. Gut, *J. Org. Chem.*, 1972, **37**, 2119.
[7] D. H. R. Barton, J. P. Poyser, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 53.
[8] G. Ponsinet and G. Ourisson, *Bull. Soc. chim. France*, 1967, **12**, 4452.
[9] W. Sucrow, B. Schubert, W. Richter, and M. Slopianka, *Chem. Ber.*, 1971, **104**, 3689.
[10] C. R. Popplestone and A. M. Unrau, *Canad. J. Chem.*, 1973, **51**, 1223.
[11] (*a*) H. G. Kuivila, L. W. Menapace, and C. R. Warne, *J. Amer. Chem. Soc.*, 1962, **84**, 3584; (*b*) H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, 1963, **28**, 2165.
[12] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. L. C. Weedon, *J. Chem. Soc.*, 1946, 39.

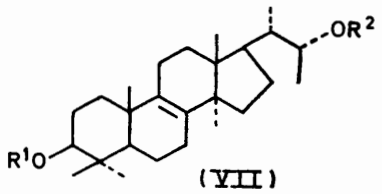
e.g. (Xb) [7] and (XI).[13] In these cases, the more polar, 22*S*-epimers which predominate are the 'anti-Cram' products.[14] In contrast, attack of Grignard reagent on a steroidal 22-aldehyde proceeds to give mainly the



(V) a; R = H
b; R = Ac

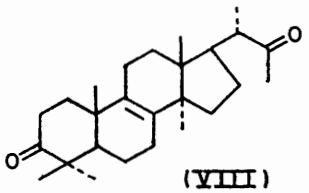


(VI) a; R = H
b; R = Ac

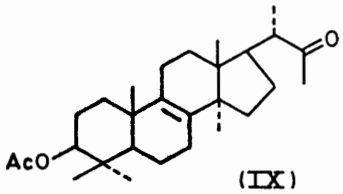


(VII)

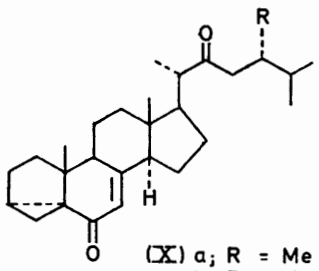
a; R^1 = Ac, R^2 = Ac
b; R^1 = H, R^2 = H
c; R^1 = Ac, R^2 = H
d; R^1 = Ac, R^2 = O·[CH_2]$_3$·CH
e; R^1 = Ac, R^2 = Bz



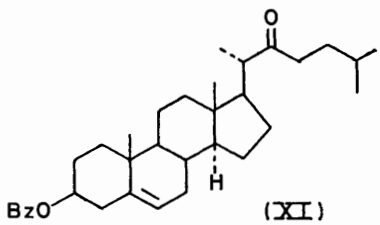
(VIII)



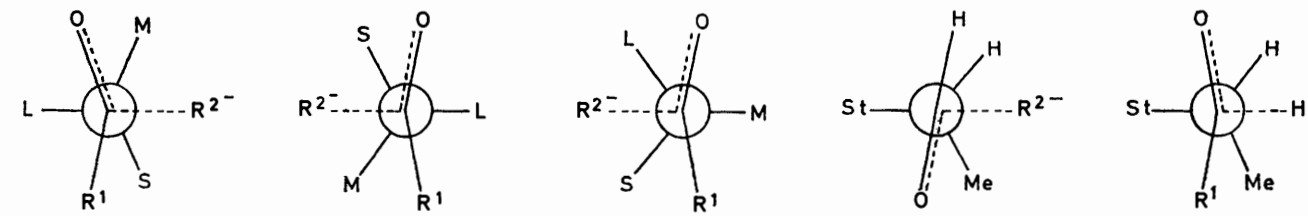
(IX)



(X) a; R = Me
b; R = H



(XI)



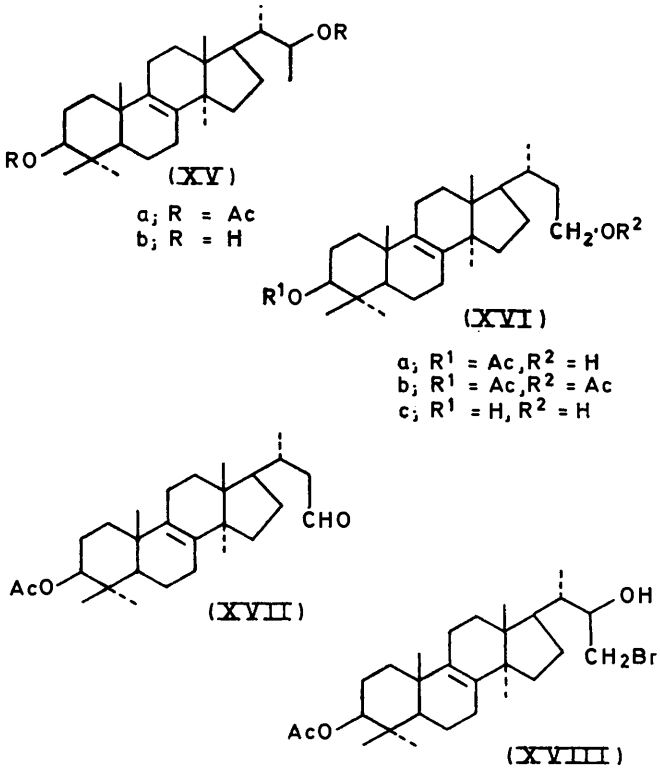
(XII)

epimer predicted by Cram's rule, as do hydride reductions of the 23-oxo-analogue of (Xa) [7] and of 23-oxolanosterol [15] (22*S*- and 23*S*-, respectively). The 22-ketones appear to behave in a similar manner to hindered cyclohexanones, the behaviour of which has been explained by Felkin *et al.*[16] in terms of the postulate that partial bonds in transition states can be the source of considerable torsional strain. Furthermore, the important steric interactions involve the incoming nucleophile R^{2-} and the group R^1 attached to the carbonyl group. The most stable transition state is thus (XIIa), followed by (XIIb) and then (XIIc). With Grignard reagents, the 22-aldehydes react mainly *via* the conformation (XIII), which corresponds to the transition state (XIIa). However, in the case of 22-ketones, the ratio of products obtained indicates that the preferred conformation for the transition state is (XIV) for hydride reductions. This is borne out by models, since steric interactions between the group R^1 and the 13β-methyl group or the 16β-proton (the positions γ to the carbonyl group) are the factors deciding the preferred conformation. In the absence of adjacent, polar directing groups, 22-oxo-steroids of the above type can therefore be assumed to give rise preferentially to the 22*S*-epimer, whether the reaction involved is that of an aldehyde with a saturated Grignard reagent, or that of a

[13] E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, 1969, **34**, 103.
[14] D. J. Cram and F. A. Abd-Elhafez, *J. Amer. Chem. Soc.*, 1959, **81**, 2748.
[15] N. Entwistle and A. D. Pratt, *Tetrahedron*, 1969, **25**, 1449.
[16] (*a*) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Letters*, 1968, 2199; (*b*) M. Chérest and H. Felkin, *ibid.*, p. 2205.

ketone with hydride. This may not be so where polar groups are present, or where acetylenic Grignard reagents are involved.[17]

In the present instance, the diol epimeric mixture resulting from hydride reduction of (IX) could only be



separated by multiple-elution t.l.c. (nine times) of the corresponding diacetates. The less polar component was the 3β,22(*R*)-diacetate (VIIa), obtained previously from (Vb). The more abundant, more polar product was the 22*S*-epimer (XVa). The ratio of the products was *ca.* 4 : 1 [*cf.* 7 : 1 for (Xa) and 3 : 1 for (Xb) [7] and for (XI) [13]]. In the n.m.r. spectrum of (XVa), the 22-proton appeared as a clear quartet showing only slight coupling with the C-20 proton. Compound (VIIa) exhibited a complex multiplet for the 22-proton. Hydrolysis of (XVa) gave the corresponding 3β,22(*S*)-diol (XVb). The most polar bromohydrin (VIa) could be transformed into the 3β-acetoxy-23-alcohol (XVIa), and thence into the diacetate (XVIb) and the diol (XVIc). Oxidation of (XVIa) with silver carbonate on Celite [18] in refluxing benzene furnished the aldehyde (XVII), which possessed the necessary aldehydic proton signal at τ 0·22 in the n.m.r. spectrum. The 2,4-dinitrophenylhydrazone was prepared by the method of Parrick and Rasburn.[19]

The bromohydrin of intermediate polarity [containing some (VIa)] gave a mixture of two monoacetate diols after exposure to tri-n-butyltin hydride. It was evident therefore that this was not the 22(*S*)-bromo-23-alcohol, which on similar treatment would give rise to the same alcohol (XVIa) as derived from (VIa). Hydrolysis of the monoacetate diol mixture yielded two separable diols, the more polar of which was (XVIc). The less polar compound was identical with the 3β,22(*S*)-diol (XVb), derived from (Va) *via* the lithium aluminium hydride reduction of the ketone (IX). Acetylation gave the 3β,22(*S*)-diacetate (XVa), identical with the material obtained as already described. The bromohydrin could therefore be assigned the structure (XVIII).

The molecular rotation difference for the tetranor-3β,22(*R*)- and -3β,22(*S*)-diols (VIIb) and (XVb) (Δ_{R-S} +71·4°) was consistent with previous findings [4,7] for pairs of epimeric 22-alcohols, and was comparable to that (+40°) for inotodiol and (22*S*)-22-hydroxylanosterol.*

Finally, it was found that the (22*S*)-epoxide, in the presence of bromide ions in tetrahydrofuran containing a trace of water, gave the bromohydrin alcohols corresponding to (Vb) and (VIb) in a ratio of 9 : 1, as demonstrated by t.l.c. comparison with these compounds after acetylation.

EXPERIMENTAL

For technical details see ref. 4. [$^2H_5$]Pyridine was used instead of [^{2}H]chloroform as solvent for n.m.r. spectra where indicated.

Epoxidation of 24,25,26,27-*Tetranorlanosta*-8,22-*diene*-3β-*yl Acetate* (II).—The 8,22-diene (II) (6·18 g, 15 mmol) in tetrahydrofuran–water (4 : 1; 130 ml) was treated with *N*-bromosuccinimide (2·84 g, 16·5 mmol) as described previously.[7] Chromatography of the crude product on silica gel (210 g) [elution with benzene and then with ethyl acetate–benzene (1 : 19)] gave three bromohydrins as a mixture (4·8 g), free of polar material. Heating under reflux for 4 h in methanol (210 ml) with sodium hydroxide (1·2 g), evaporation, and the usual work-up, followed by chromatography on silica gel (120 g) [hexane–ethyl acetate (19 : 1)] afforded a small amount of the epoxy-acetates (IIIb) and (IVb) (30 mg, 0·5%) as a 5 : 1 mixture. Further elution gave the epoxy-alcohols (IIIa) and (IVa) (3·36 g, 58%) as a 5 : 1 mixture.

The epoxy-acetates (196 mg) (obtained as above or by acetylation of the crude epoxy-alcohols with acetic anhydride and pyridine, and azeotropic removal of solvents by toluene) were separated by t.l.c. (seven elutions in toluene). The major, less polar component was (22*S*)-22,23-*epoxy*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*yl acetate* (IIIb) (101 mg), m.p. 161—163°, $[\alpha]_D^{20}$ +47° (*c* 1·1), $\nu_{max.}$ 1745, 1262, 1040, 917, and 841 cm^{-1}, τ 5·45br (1H, m, 3α-H), 7·3 (2H, m), 7·6 (1H, m), and 7·96, 8·99, 9·03, 9·10, 9·12, and 9·31 (methyls), *m/e* 428 (M^+), 413 (base peak), 353 (413 − AcOH), 341, 335, 323, 281, 187, 159, 135, 121, 119, and 107 (Found: C, 78·5; H, 10·3. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·35%).

The more polar component (22 mg) was the 22R-*epimer* (IVb), obtained as needles, m.p. 159—160·5°, $[\alpha]_D^{20}$ +37°

* We thank D. Arigoni and F. Marazza for a sample of synthetic (22*S*)-22-hydroxylanosterol, m.p. 150°, $[\alpha]_D^{25}$ +47°.

[17] (*a*) H. Mori and K. Shibata, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 1970; (*b*) P. G. Feakins, Ph.D. Thesis, London University, 1968; (*c*) J. P. Poyser, Ph.D. Thesis, London University, 1971, pp. 118—123.

[18] M. Fétizon, M. Golfier, and P. Morgues, *Tetrahedron Letters*, 1972, 4445.

[19] J. Parrick and W. Rasburn, *Canad. J. Chem.*, 1965, **43**, 3453.

(*c* 0·4), $\nu_{max.}$ 1738, 1395, 1250, 1033, 985, 908, and 822 cm^{-1}, τ 5·5br (1H, m, 3α-H), 7·3 (3H, m), and 7·97, 8·99, 9·12, and 9·32 (methyls), *m/e* 428 (M^+), 413 (base peak), 353, 341, (413 − side-chain from C-17), 335, 281 (341 − AcOH), 187, 159, 135, 121, 119, and 107 (Found: C, 78·7; H, 10·6. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·35%).

(22R)-22,23-*Epoxy*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*ol* (IVa).—The acetate (IVb) (19 mg) in methanol (4 ml) containing sodium hydroxide (10·5 mg) was heated under reflux for 2 h. Evaporation and the usual work-up gave, after chromatography on silica gel (4 g) [ethyl acetate–hexane (1 : 12)], the *alcohol* (14 mg, 80%), m.p. (microneedles) 148·5—151°, $[\alpha]_D^{17}$ +32° (*c* 0·1), $\nu_{max.}$ 3300, 1020, 905, and 820 cm^{-1}, τ 6·9br (1H, m, 3α-H), 7·35 (3H, m), and 9·02, 9·10, 9·20, and 9·32 (methyls), *m/e* 386 (M^+), 371 (base peak), 353, 299 (371 − side-chain from C-17), and 281 (Found: M^+, 386·3175. $C_{26}H_{42}O_2$ requires *M*, 386·3185).

(22S)-22,23-*Epoxy*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*ol* (IIIa).—The acetate (IIIb) (78 mg) was treated as above to give the *alcohol* (53 mg, 74%), m.p. (needles) 155—157°, $[\alpha]_D^{22}$ +45° (*c* 0·8), $\nu_{max.}$ 3280, 1035, 904, and 834 cm^{-1}, τ 6·76br (1H, m, 3α-H), 7·3 (2H, m), 7·6 (1H, m), and 9·01, 9·08, 9·19, and 9·31 (methyls), *m/e* as for (IVa) (Found: C, 80·5; H, 11·2. $C_{26}H_{42}O_2$ requires C, 80·8; H, 11·0%). Similar treatment of either of the bromohydrins (Va) and (VIa), and of either of the bromo-acetates (Vb) and (VIb) also furnished this single epoxy-alcohol, distinguishable from the epimeric (IVa) on t.l.c. by elution at least six times in toluene.

(22S)-22,23-*Epoxy*-3β-(*tetrahydropyran*-2-*yloxy*)-24,25,26,-27-*tetranorlanost*-8-*ene* (IIIc).—The epoxy-alcohol (IIIa) (200 mg) was dissolved in toluene (20 ml) and toluene-*p*-sulphonic acid (1 mg) was added. The volume of solution was reduced to a few ml, dihydropyran (0·5 ml) was added, and the mixture was kept at room temperature overnight. Filtration through silica gel (10 g) [elution with ethyl acetate–hexane (1 : 9)] gave a crystalline product (IIIc), the n.m.r. spectrum of which showed the same characteristic pattern of signals for the epoxide protons as those of the 3β-alcohol (IIIa) and the acetate (IIIb).

Oxidation of the Olefin (II) *by Peroxy-acid*.—The olefin (40 mg) in sodium-dried ether (5 ml) was stirred at 0° with *p*-nitroperbenzoic acid (19 mg).[8] A complex mixture of products resulted, and this approach was not further investigated.

(22S)-23-*Bromo*-22-*hydroxy*- *and* (22R)-22-*Bromo*-23-*hydroxy*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*yl Acetates* [(Va) *and* (VIa)].—The olefin (II) (4·12 g) was converted, as described above, into a mixture of three bromohydrins (3·1 g), which was chromatographed on silica gel (150 g) [ethyl acetate–hexane (1 : 9)]. The first bromohydrin to emerge was the (22S)-23-*bromo*-22-*hydroxy*-*isomer* (Va) (1·15 g, 23%), m.p. (dichloromethane–methanol; needles) 208·5—210·5°, $[\alpha]_D^{17}$ +34° (*c* 1·5), $\nu_{max.}$ 3480, 3320, 1730, and 1248 cm^{-1}, τ 5·48br (1H, t, 3α-H), 6·15br (1H, m, 22-H), 6·5 (2H, d, *J* 3 Hz), 7·7br (1H), and 7·97, 9·00, 9·12, and 9·28 (methyls), *m/e* 510, 508 (M^+), 495, 493, 435, 433 (M^+ − Me − AcOH, 94%), 428 (M^+ − HBr; 39%), 413 (base peak; M^+ − Me − HBr), 353 (86%), and 335 (Found: C, 66·3; H, 9·1; Br, 15·75. $C_{28}H_{45}BrO_3$ requires C, 66·0; H, 8·9; Br, 15·7%).

This was followed by a mixture (690 mg) of a minor, uncharacterised isomer [shown later to be the (22*R*)-23-bromo-22-ol (XVIII)] and the (22*R*)-22-bromo-23-hydroxy-compound (VIa). Continued elution gave the latter as *microneedles* (1·05 g, 21%), m.p. (dichloromethane–methanol) 192—194°, $[\alpha]_D^{17}$ +46° (*c* 1·1), $\nu_{max.}$ 3400, 1734, and 1265—1250 cm^{-1}, τ 5·48br (1H, t, 3α-H), 5·68 (1H, m, 22-H), 6·17br (2H, m), and 7·97, 8·99, 9·08, 9·12, and 9·27 (methyls), *m/e* 510, 508 (M^+), 495, 493, 435, 433 (20%), 428 (36%), 413 (74%), 353 (base peak), and 335 (Found: C, 65·5; H, 8·8; Br, 15·7%; M^+, 508·2548. $C_{28}H_{45}BrO_3$ requires C, 66·0; H, 8·9; Br, 15·7%; *M*, 508·2552).

Basic treatment (by the general procedure) of either (Va) or (VIa) gave rise to the (22*S*)-epoxy-alcohol (IIIa) only. The mixture of (XVIII) and (VIa) on the other hand led to a product containing mainly the (22*R*)-epoxy-alcohol (IVa) along with some (IIIa).

(22S)-23-*Bromo*-3β,22-*diacetoxy*- *and* (22R)-22-*Bromo*-3β,23-*diacetoxy*-24,25,26,27-*tetranorlanost*-8-*enes* [(Vb) *and* (VIb)].—The crude bromohydrin mixture [500 mg from olefin (II) (700 mg)] was acetylated with pyridine–acetic anhydride. Chromatography on silica gel (60 g) and elution with hexane containing increasing proportions of benzene furnished the (22S)-23-*bromo*-22-*acetate* (Vb) [135 mg; 14·4% based on (II)], m.p. (needles) 209—213·5°, $[\alpha]_D^{17}$ +37° (*c* 0·4), $\nu_{max.}$ 1739, 1726, 1260, 1249, 1241, 1229, and 1032 cm^{-1}, τ 4·77 (1H, m, 22-H), 5·66 (1H, m, 3α-H), 6·53 (2H, d, *J* 3·5 Hz), and 7·90, 7·96, 9·00, 9·13, and 9·32 (methyls), *m/e* 552, 550 (M^+), 537, 535, 477, 475, 417, 415, 335 (M^+ − Me − 2AcOH − HBr), and 43 (base peak) (Found: C, 65·1; H, 8·9. $C_{30}H_{47}BrO_4$ requires C, 65·3; H, 8·6%).

The acetate corresponding to the bromohydrin of intermediate polarity could not be obtained free of the other bromo-acetates.

Finally, the (22R)-22-*bromo*-23-*acetate* (IVb) was eluted and recrystallised to give plates, m.p. 198—201°, $[\alpha]_D^{17}$ +37° (*c* 0·3), $\nu_{max.}$ 1745, 1734, 1253, 1237, and 1037 cm^{-1}, τ 5·5 (1H, m, 3α-H), 5·65br (2H, s), 5·8 (1H, m, 22-H), and 7·93, 7·96, 8·98, 9·08, 9·12, and 9·27 (methyls), *m/e* as for (Vb) (Found: C, 65·4; H, 8·5. $C_{30}H_{47}BrO_4$ requires C, 65·3; H, 8·6%).

Thermal Isomerisation of the Bromo-acetates (Vb) *and* (VIb).—A crystalline sample of (Vb) or (VIb), heated at the m.p. for 10 min (either in a sealed capillary or between glass lamellae), underwent thermal equilibration to give a mixture of both isomers, in which (VIb) predominated by *ca.* 2 : 1 (t.l.c.), together with decomposition products.

(22R)-24,25,26,27-*Tetranorlanost*-8-*ene*-3β,22-*diyl Diacetate* (VIIa).—The bromo-acetate (Vb) (105 mg) was stirred for 72 h under nitrogen with tri-n-butyltin hydride as described.[7] Two chromatographic purifications on silica gel (10 g) and two crystallisations afforded the *diacetate* (VIIa) (55 mg, 61%), m.p. (plates) 227—228·5°, $[\alpha]_D^{17}$ +64° (*c* 0·3), $\nu_{max.}$ 1730, 1253, and 1023 cm^{-1}, τ 5·0 (1H, m, 22-H), 5·47br (1H, t, 3α-H), and 7·97, 8·00, 8·87, 8·99, 9·12, and 9·30 (methyls), *m/e* 472 (M^+), 457, 397 (base peak), 356 (M^+ − side-chain from C-17), 337 (M^+ − Me − 2AcOH), 289, and 281 (Found: C, 76·1; H, 10·2. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2%).

(22R)-24,25,26,27-*Tetranorlanost*-8-*ene*-3β,22-*diol* (VIIb).—The diacetate (VIIa) (50 mg) was hydrolysed in methanol (10 ml) containing sodium hydroxide (45 mg). Needles of the pure *diol* (25 mg, 61%) separated on cooling; m.p. 281—282° (unchanged on recrystallisation from tetrahydrofuran–methanol), $[\alpha]_D^{17}$ +50° (*c* 0·6 in tetrahydrofuran), $\nu_{max.}$ 3375 and 1029 cm^{-1}, τ ([$^2H_5$]pyridine) 5·72br (1H, m, 22-H), 6·41 (s, MeOH of crystallisation), 6·53br (1H, m,

3α-H), and 8·75, 8·92, 9·04, and 9·21 (methyls), *m/e* 388 (M^+), 373 (base peak), 355, 337 (M^+ — Me — $2H_2O$), 311, 283 (337 — side-chain from C-17), and 125 (base peak) (Found: C, 78·45; H, 11·8. $C_{26}H_{44}O_2$,0·5MeOH requires C, 78·7; H, 11·5%).

24,25,26,27-*Tetranorlanost*-8-*ene*-3,22-*dione* (VIII).—The diol (VIIb) (39 mg) was dissolved in the minimum of tetrahydrofuran (2 ml), acetone (25 ml) was added, and the mixture was oxidised with Jones reagent [12] at 0°. The crystalline residue from the extraction was chromatographed on silica gel (5 g), and eluted with ethyl acetate–hexane (1 : 19). Recrystallisation gave the *dione* (20 mg, 52%), m.p. (needles from methanol) 141—143° (resolidifying, and remelting at 152—155°), $[\alpha]_D^{17}$ +54° (*c* 0·8), $\nu_{max.}$ 1705 and 1700 cm^{-1}, τ 7·52 (2H, m), 7·90 (3H, s, 23-H_3), and 8·84, 8·88, 8·91, 8·94, 9·06, and 9·26 (methyls), *m/e* 384 (M^+), 369 (base peak), 351 (M^+ — Me — H_2O), 312, 297 (312 — Me), and 43 (Found: C, 81·3; H, 10·4. $C_{26}H_{40}O_2$ requires C, 81·2; H, 10·5%).

(22R)-22-*Hydroxy*- and (22R)-22-*Tetrahydro*-2-*furyloxy*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*yl Acetates* [(VIIc) *and* (VIId)].—The bromohydrin (Va) (808 mg) was debrominated with tri-n-butyltin hydride (5 g) as described [7] (reaction time 8 days). A mixture of two products (511 mg) was obtained even after two chromatographic purifications on silica gel [elution with ethyl acetate–hexane (1 : 19 to 1 : 9)], apparently owing to interconversion on the column. Further chromatography of the mixture (204 mg) [the remainder being converted into the ketone (IX); see later] gave the less polar compound, R_F equal to that of the diacetate (VIIa), which proved to be the (22R)-22-*tetrahydrofuryl ether* (VIId) (51 mg, 15·7%), m.p. (microneedles) 157—159°, $[\alpha]_D^{20}$ +59° (*c* 1·2), $\nu_{max.}$ 1729, 1260, 1250, and 1022 cm^{-1}, τ 4·75br (1H, t, H α to both ether linkages), 5·48br (1H, t, 3α-H), 6·16br (2H, t, CH_2 α to tetrahydrofuran oxygen), and 7·96, 8·99, 9·12, and 9·28 (methyls), *m/e* 500 (M^+), 485, 441, 415, 397 (M^+ — Me — dihydrofuran — H_2O), 355 (415 — AcOH), 337, and 71 (base peak, $C_4H_7O^+$) (Found: C, 75·95; H, 10·4%; M^+, 500·3852. $C_{32}H_{52}O_4$,0·5MeOH requires C, 75·5; H, 10·5%. $C_{32}H_{52}O_4$ requires *M*, 500·3865).

The more polar component (116 mg, 41·6%) was still slightly impure, but acidic hydrolysis with methanolic 0·05N-hydrochloric acid, according to the described procedure,[20] of either component afforded, after chromatography, the pure *monoacetate diol* (VIIc), m.p. (needles) 191—193°, $[\alpha]_D^{20}$ +52° (*c* 0·6), $\nu_{max.}$ 3620, 3520, 1738, 1720, 1646, 1265, 1248, and 1038 cm^{-1}, τ 5·5br (1H, t, 3α-H), 6·09 (1H, dq, 22-H), and 7·97, 8·93, 9·00, 9·03, 9·12, and 9·28 (methyls), *m/e* 430 (M^+), 415 (base peak), 397, 355, 337 (M^+ — Me — H_2O — AcOH), 311, 161, and 125 (Found: C, 76·4; H, 10·8. $C_{28}H_{46}O_3$,0·5MeOH requires C, 76·6; H, 10·8%. $C_{28}H_{46}O_3$,0·5H_2O requires C, 76·5; H, 10·8%).

Acetylation of (VIIc) gave the diacetate (VIIa), and basic hydrolysis of (VIIc) gave the diol (VIIb), identical with the compounds obtained as already described.

(22R)-24,25,26,27-*Tetranorlanost*-8-*ene*-3β,22-*diyl* 3β-*Acetate* 22-*Benzoate* (VIIe).—The monoacetate diol (VIIc) (57 mg) in pyridine (2 ml) containing benzoyl chloride (140 mg) was kept at room temperature overnight. Azeotropic removal of solvent with toluene and chromatography on silica gel (21 g) [ethyl acetate–hexane (1 : 39)] gave the *benzoate* (45 mg, 64%), m.p. (microneedles) 197—199°, $[\alpha]_D^{17}$ +41·5° (*c* 1·7), $\nu_{max.}$ 1733, 1717, 1601, 1584, 1286, 1253, and 708 cm^{-1}, $\lambda_{max.}$ (dioxan) 232 (ε 16,800), 272 (1800), and 280 nm (1500), τ 1·95 (2H, ddd, *J* 2, 3, and 7 Hz), 2·48 (3H, m), 4·71 (1H, m, 22-H), 5·49br (1H, t, 3α-H), 7·96 (3H, s), 8·79 (3H, d, *J* 7 Hz), 8·97 (3H, d, *J* 7 Hz), and 8·99, 9·11, and 9·28 (methyls), *m/e* 534 (M^+), 519, 459, 397 (base peak, M^+ — Me — BzOH), 356 (M^+ — Me — side-chain from C-17), 337, 105 ($PhCO^+$), and 43 (Found: C, 78·7; H, 9·6. $C_{35}H_{50}O_4$ requires C, 78·6; H, 9·4%).

22-*Oxo*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*yl Acetate* (IX).—The impure monoacetate diol (VIIc) (307 mg) in AnalaR acetone (40 ml) was oxidised at 0° with Jones reagent [12] to give, after work-up and chromatography on silica gel (20 g) [ethyl acetate–hexane (1 : 19)], the *ketone* (IX) (150 mg, 49%), m.p. (needles) 175—177°, $[\alpha]_D^{17}$ +32° (*c* 1·7), $\nu_{max.}$ 3580, 3505, 1735, 1720, 1700, 1650, 1270, 1250, 1175—1163, and 1039 cm^{-1}, τ 5·46br (1H, t, 3α-H), 6·53 (1H, m), 7·90 (3H, s), 7·96 (3H, s), 8·9 (3H, d, *J* 7 Hz), and 8·99, 9·08, 9·12, and 9·28 (methyls), *m/e* 428 (M^+), 413, 395, 353, 341 (M^+ — Me — side-chain from C-17, McLafferty), 335 (M^+ — Me — AcOH — H_2O), 281, and 43 (base peak) (Found: C, 76·8; H, 10·3. $C_{28}H_{44}O_3$,0·5MeOH requires C, 77·0; H, 10·4%; $C_{28}H_{44}O_3$,0·5H_2O requires C, 76·8; H, 10·4%).

Reduction of the Keto-acetate (IX).—To the keto-acetate (IX) (120 mg) in sodium-dried ether (60 ml) at 0° was added an excess of lithium aluminium hydride. After stirring for 3 h, the described procedure [7] and chromatography on silica gel (20 g) [ethyl acetate–hexane (1 : 4)] gave a product (79 mg) not resolvable on t.l.c., which the n.m.r. spectrum ([$^2H_5$]pyridine) showed to be a mixture of diols. Acetylation by the usual procedure gave a mixture of diacetates (VIIa) and (XVa), in which the more polar (XVa) predominated by *ca.* 7 : 3. Preparative t.l.c. in ethyl acetate–hexane (1 : 39) achieved separation after nine elutions. The less polar diacetate (VIIa) (20 mg, 15%) was identical with the material already described. The major, more polar product was (22S)-24,25,26,27-*tetranorlanost*-8-*ene*-3β,22-*diyl diacetate* (XVa) (43 mg, 33%), m.p. (plates) 147—149°, $[\alpha]_D^{20}$ +19° (*c* 1·2), $\nu_{max.}$ 1738, 1732, 1250—1240, and 1015 cm^{-1}, τ 5·0 (1H, 'dq,' 22-H), 5·53br (1H, t, 3α-H), 7·98 (3H, s), 8·00 (3H, s), 8·83 (3H, d, *J* 6·5 Hz), and 9·00, 9·12, and 9·32 (methyls), *m/e* as for (VIIa), with slight intensity differences (Found: C, 76·4; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2%).

(22S)-24,25,26,27-*Tetranorlanost*-8-*ene*-3β,22-*diol* (XVb).—Basic hydrolysis of the diacetate (XVa) (32 mg) by the usual procedure gave, after extraction and chromatography on silica gel (6·3 g) [ethyl acetate–hexane (1 : 4)], the *diol* (12 mg, 46%), m.p. (needles from ethyl acetate) 213—215°, $[\alpha]_D^{17}$ +32° (*c* 0·4), $\nu_{max.}$ 3400, 1099, 1030, 938, and 900 cm^{-1}, τ 6·1br (1H, m, 22-H), 6·75br (1H, m, 3α-H), and 8·74, 8·78, 8·90, 9·01, 9·09, 9·19, and 9·31 (methyls), *m/e* as for (VIIb) (Found: C, 80·3; H, 11·5. $C_{26}H_{44}O_2$ requires C, 80·35; H, 11·4%).

23-*Hydroxy*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*yl Acetate* (XVIa).—The most polar bromohydrin (VIa) (570 mg) was treated with tri-n-butyltin hydride (5 g) for 8 days as described previously.[7] Chromatography twice on silica gel (70 and 50 g) [ethyl acetate–hexane (1 : 19)] gave the *monoacetate diol* (230 mg, 48%), m.p. (plates from ethyl acetate–hexane) 147—149°, $[\alpha]_D^{20}$ +49° (*c* 0·7), $\nu_{max.}$ 3340, 1737, 1720, 1263, 1253, and 1036 cm^{-1}, τ 5·51br (1H, t, 3α-H), 6·32br (2H, t), and 7·97, 9·01, 9·13, and 9·31 (methyls), *m/e* 430 (M^+), 415, 401, 355 (base peak), 341 (M^+ — Me —

[20] D. H. R. Barton, P. G. Feakins, J. P. Poyser, and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 1583.

side-chain from C-17), and 337 (Found: C, 77·2; H, 10·7%; M^+, 430·3439. $C_{28}H_{46}O_3$,0·33MeOH requires C, 77·2; H, 10·8%; $C_{28}H_{46}O_3$ requires M, 430·3447).

24,25,26,27-*Tetranorlanost*-8-*ene*-3β,23-*diyl* *Diacetate* (XVIb).—The primary alcohol (XVIa) (32 mg) on acetylation in the usual manner and chromatography on silica gel (9 g) [ethyl acetate–hexane (1 : 24)] gave the *diacetate* (XVIb) (28 mg, 80%), m.p. (needles) 139·5—141·5°, $[\alpha]_D^{20}$ +53° (*c* 0·8), $\nu_{max.}$ 1739, 1245, and 1038 cm^{-1}, τ 5·49br (1H, t, 3α-H), 5·89br (2H, t), and 7·97 (6H, s), 8·99, 9·12, and 9·31 (methyls), *m/e* 472 (M^+), 467, 397 (base peak), 337, 275, and 43 (Found: C, 76·3; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2%).

24,25,26,27-*Tetranorlanost*-8-*ene*-3β,23-*diol* (XVIc).—Reductive cleavage of the ester function of the monoacetate diol (XVIa) (54 mg) by lithium aluminium hydride in the normal way afforded, after preparative t.l.c. [three elutions in ethyl acetate–hexane (1 : 3)], the *diol* (XVIc) (39 mg, 80%), m.p. (needles from ethyl acetate) 186—187°, $[\alpha]_D^{17}$ +58° (*c* 0·6), $\nu_{max.}$ 3330, 1104, 1072, and 1033 cm^{-1}, τ 6·3br (2H, t), 6·75br (1H, t, 3α-H), and 9·01, 9·12, 9·19, and 9·29 (methyls), *m/e* 388 (M^+), 373 (base peak), 355, and 95 (Found: C, 80·3; H, 11·4. $C_{26}H_{44}O_2$ requires C, 80·35; H, 11·4%).

23-*Oxo*-24,25,26,27-*tetranorlanost*-8-*en*-3β-*yl* *Acetate* (XVII).—The primary alcohol (XVIa) (58 mg) in benzene (40 ml) was refluxed for 12 h with silver carbonate on Celite (6 g).[18] Filtration through silica gel (9 g) [ethyl acetate–hexane (1 : 19)] gave the unstable *aldehyde* (39 mg, 67%), m.p. (without recrystallisation; chunks) 158—164°, $[\alpha]_D^{20}$ +40° (*c* 0·5), $\nu_{max.}$ 2710, 1738, 1726, and 1251 cm^{-1}, τ 0·25br (1H), 5·53br (1H, 3α-H), and 7·97, 8·99, 9·12, and 9·26 (methyls), *m/e* 428 (M^+), 413, 399 (M^+ — CHO), 369 (413 — side-chain from C-20), 353, 309, 187, 135, 121, 107, 69, and 43 (base peak) (Found: M^+, 428·3285. $C_{28}H_{44}O_3$ requires M, 428·3290).

2,4-*Dinitrophenylhydrazone of the Aldehyde* (XVII).—By the method of Parrick and Rasburn,[19] the aldehyde (XVIII) (25 mg) gave a yellow *hydrazone* (15 mg, 43%), m.p. (chloroform–methanol; needles) 236—237°, $[\alpha]_D^{20}$ +36° (*c* 0·7), $\nu_{max.}$ 3300, 1738, 1620, 1600, 1512, 1326, and 1270 cm^{-1}, $\lambda_{max.}$ (dioxan) 426 (ε 2400), 355 (22,100), 251 (11,500), and 222 nm (15,400), τ 0·81 (1H, d, *J* 4 Hz, 3′-H), 1·60 (1H, dd, *J* 4 and 14 Hz, 5′-H), 1·98 (1H, d, *J* 14 Hz, 6′-H), 2·34br (1H, t, *J* 10 Hz, 23-H), 5·38 (1H, m, 3α-H), and 7·96 8·99, 9·12, and 9·26 (methyls), *m/e* 608 (M^+), 593, 533, 413, 410, 369, 350, 309 (M^+ — Me — AcOH — side-chain from C-20), and 43 (base peak) (Found: M^+, 608·3547. $C_{34}H_{48}N_4O_6$ requires M, 608·3574).

Debromination of the Minor Bromohydrin (XVIII).—The bromohydrin of intermediate polarity (XVIII) [136 mg; containing *ca.* 25% of the most polar bromohydrin (VIa)] was debrominated as already described to give a mixture of two monoacetate diols (89 mg). Basic hydrolysis in the normal manner, followed by preparative t.l.c. [three elutions in ethyl acetate–hexane (1 : 3)], gave the more polar 3β,23-diol (XVIc) (18 mg, 17%), identical with that obtained from (VIa), and also the (22*S*)-3β,22-diol (XVb) (45 mg, 43%), identical with the major product from the hydride reduction of the ketone (IX). Acetylation gave the (22*S*)-3β,22-diacetate (XVa), indistinguishable from the material already described. The bromohydrin could therefore be assigned the structure (XVIII).

Ring Opening of the (22S)-22,23-*Epoxide* (IIIa) *by Bromide Ion.*—The epoxide (IIIa) (32 mg) treated for 60 h with isobutenylmagnesium bromide in tetrahydrofuran (5 ml; presumably containing a trace of moisture) gave, after chromatography, not inotodiol as expected, but a product of very similar R_F, shown to be a mixture of bromohydrin 3β-alcohols (21 mg, 54%) [by acetylation and comparison with the bromo-acetates (Vb) and (VIb)]. The bromohydrin 3β-alcohol corresponding to (Vb) predominated by *ca.* 9 : 1. The mixture of bromohydrin alcohols had m.p. (needles) 216—218·5°, $[\alpha]_D^{20}$ +35·5° (*c* 0·4), $\nu_{max.}$ 3330, 1054, and 1032 cm^{-1}, τ 6·08br (1H, m, 22-H), 6·52 (3H, s, MeOH of crystallisation), 6·69br (2H, d), 6·85br (1H, 3α-H), 7·7br (1H), and 9·01, 9·12, 9·19, and 9·28 (methyls), *m/e* 468, 466 (M^+), 453, 451, 435, 433, 386 (M^+ — HBr), 371, 353, 205, and 203 (base peak) (Found: C, 64·7; H, 9·3%; M^+, 468·2444/466·2451. $C_{26}H_{43}BrO_2$,MeOH requires C, 64·9; H, 9·5%; $C_{26}H_{43}BrO_2$ requires M, 468·2427/466·2447).

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