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THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—V[1]

STEREOCHEMICAL STUDIES IN THE STACHENE SERIES

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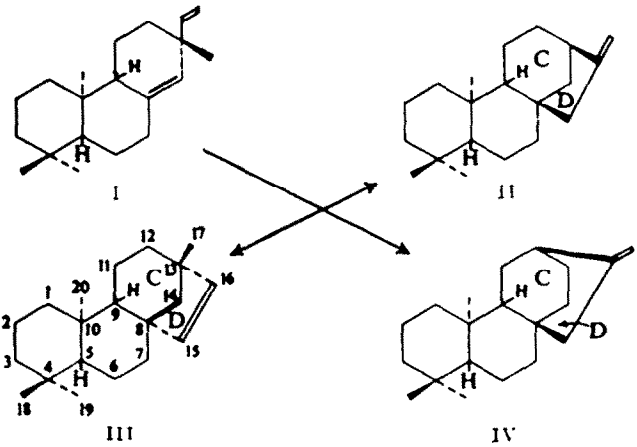
Abstract—Detailed evidence for the interrelationship between monogynol and steviol and the reverse conversion of the stachene skeleton to the kaurene skeleton is presented. The preparation of stach-15-en-2-one is also described.

THE classes of tetracyclic diterpenes may be distinguished on the basis of the fusion of their rings C and D. In particular the collapse of the carbonium ion arising by cyclization of the appropriate pimaradiene (I)[2] can lead to compounds of the kaurene (II), stachene (III), or atisine (IV) classes. At the outset of this work[3] the stereochemistry of compounds of the stachene series was the subject of some dispute. Evidence now available from NMR studies,[4,5] ORD and CD measurements together with chemical correlations[3,4] has resolved these discrepancies leading to the overall structure and stereochemistry III for stachene. In this paper we present in detail our evidence for the C/D stereochemistry. Part of this study forms the subject of a preliminary communication.[3]

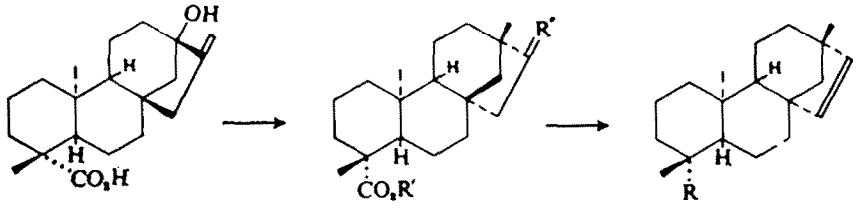
The alcohol monogynol, isolated[6,7] from *Erythroxylon monogynum* was assigned[6] the structure of 19-hydroxystach-15-ene on the basis of a relationship with stachene. On the other hand the Indian workers reported[7] the conversion of monogynol to the optical enantiomer of beyerane (identical[4] to isostevane and stachane). There was thus uncertainty as to which optical series monogynol belonged. Furthermore the original workers on stachenone proposed[8] a *syn* backbone containing a β-oriented ring D. On the basis of a biogenetic analysis Scott *et al.* predicted[9] (as was later substantiated) that stachenone would have the trans-*anti*-trans backbone although they retained the β-oriented ring D. However NMR spectra in this series revealed[4,5] a shielding effect by the ring D double bond on the angular C-10 methyl group. This indicated that in the stachene series these functions lay on the same side of the molecule. As stachenone had been assigned[8] an antipodal A/B fusion on the basis of ORD

[1] Previous part, R. H. B. Galt and J. R. Hanson, *Tetrahedron* **22**, 3185 (1966).
[2] E. Wenkert, *Chem. & Ind.*, 282 (1955).
[3] J. R. Hanson, *Chem. & Ind.*, 1579 (1964).
[4] P. R. Jefferies, R. S. Rosich and D. E. White, *Tetrahedron Letters* 1793 (1963).
[5] E. Wenkert, P. W. Jeffs and J. R. Mahajan, *J. Amer. Chem. Soc.* **86**, 2218 (1964).
[6] R. D. H. Murray and R. McCrindle, *Chem & Ind.* 500 (1964).
[7] A. H. Kapadi and Sukh Dev, *Tetrahedron Letters* 1171 (1964).
[8] W. H. Baarschers, D. H. S. Horn and LeRoy F. Johnson, *J. Chem. Soc.* 4046 (1962).
[9] A. I. Scott, F. McCapra, F. Comer, S. A. Sutherland, D. W. Young, G. A. Sim and G. Ferguson, *Tetrahedron* **20**, 1339 (1964).

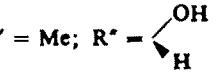
measurements this required an α-oriented ring D. In view of the conflicting proposals we sought a direct correlation between the stachene series and compounds of the kaurene series in which the stereochemistry rests on a secure foundation.[10]

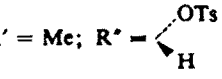


I II III IV



V VIa R′ = H; R* = O VIb R′ = Me; R* = O IX R = CO_2Me X R = CH_2OH

VII R′ = Me; R* = 

VIII R′ = Me; R* = 

Steviol (V), the aglycone of stevioside[11] was re-isolated *Stevia rebaudiana*. It has been related[10] to the kaurenolides and to (−)-kaurene and hence it is of known absolute stereochemistry. The acid-catalysed isomerization to isosteviol (VIa) involved the inversion of ring D which clearly parallelled the formation of 7α-gibbanes.[12] Reduction of the methyl ester of isosteviol with sodium in ethanol or with sodium borohydride gave the known 16-alcohol (VII). Since the same alcohol was formed by catalytic reduction of isosteviol methyl ester over Pt in acetic acid it was assigned the

[10] C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge and L. H. Briggs, *J. Amer. Chem. Soc.* **83**, 3720 (1961); B. E. Cross, R. H. B. Galt, J. R. Hanson and W. Klyne, *Tetrahedron Letters* 145 (1962).

[11] E. Mosettig and W. R. Nes, *J. Org. Chem.* **20**, 884 (1955).

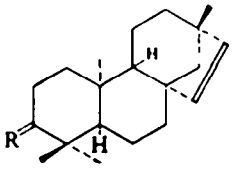
[12] B. E. Cross, *J. Chem. Soc.* 3022 (1960); J. F. Grove, *Quart. Rev.* **15**, 56 (1961).

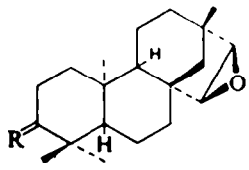
α-configuration in which catalytic attack was assumed to take place from the less-hindered face of the molecule. Treatment of the alcohol with phosphorus pentachloride gave intractable material(c.f.[18]) but conversion to its toluene-*p*-sulphonyl derivative (VIII) followed by smooth elimination with collidine led to the Δ^{15}-unsaturated ester IX. The NMR spectrum of this ester retained three tertiary C-methyl resonances and hence no rearrangement had taken place during this elimination. Reduction of the ester with LAH then gave the required 19-alcohol X, m.p. 119° $(\alpha)_D$ +27°, which was identical by mixed m.p. and IR spectrum with a sample of monogynol from *Erythroxylon monogynum* generously provided by Dr. R. D. K. Murray. This established the relationship between monogynol and steviol and confirmed the stereochemistry proposed[6] by Murray and McCrindle for monogynol.

An alternative solution lay in converting compounds of the stachene class to those of the kaurene skeleton. We have already described[13] a method of inverting the 7α-gibbane system to that of the gibberellins. Its application requires the generation of a leaving group at the 16 position which is *trans* antiparallel to the 12:13 bond. The alcohols which are readily accessible in this series from isosteviol possess the opposite configuration. However a 15:16 epoxide can provide such a group. Stachenone (XI) isolated[8] from Tambooti wood was reduced with sodium borohydride to the stachenol XII. This was acetylated and then treated with perbenzoic acid to give a single epoxide (XIV). The epoxide was relatively hindered. For example reduction with LAH led(c.f.[4]) to hydrolysis of the acetate and the formation of XV. This alcohol, which could be prepared by epoxidation of stachenol, was oxidized to the corresponding 3-ketone XVI.[8] However treatment of the epoxy-acetate XIV with BF_3-etherate, conditions[14] which are known to readily isomerize epoxides in this series, gave an unsaturated alcohol. The IR and the NMR spectra characterized the unsaturation as terminal methylene (ν_{max} 1650, 890 cm^{-1}; τ = 5·03) whilst the alcohol was secondary (1 proton at τ = 5·88). Furthermore the compound contained only three tertiary C-methyl resonances. Oxidation of the alcohol with chromium trioxide also led to cleavage of the terminal methylene and to the formation of a diketone containing cyclopentanone absorption [ν_{max} 1745 cm^{-1}]. The latter whilst lacking the terminal methylene resonances at τ = 5·0 contained a new resonance at τ = 6·92 associated[15] with the grouping CO·CH·CO in this environment. Hence the kauranoid structure XVII was assigned to the rearrangement product.

The α-ketol XVIII was also isolated from Tambooti wood.[8] This structure represents a further example of ring A tautomerism analogies to which are found in the lanostane series.[16] Further confirmation of this structure was provided in the following manner. The α-ketol and α-acetoxyketone showed resonances at τ = 6·10 (shifted to 5·07 in the acetate) and doublets at τ = 7·88 and 7·58 (J, 12 c/s) consistent with their 2-oxo formulation. Reduction of the toluene-*p*-sulphonate (XIX with LAH gave the alcohol XX which was in turn oxidized to a 2-ketone XXI. The latter showed four α-methylene proton resonances in the range τ = 7·5 to 8·0. The alcohol XX was assigned a 2α-(*axial*) stereochemistry by analogy with the comparable reaction[17] in the

[13] B. E. Cross, J. R. Hanson and R. N. Speake, *J. Chem. Soc.* 3555 (1965).
[14] A. H. Kapadi and Sukh Dev, *Tetrahedron Letters* 1255 (1965).
[15] J. R. Hanson, *J. Chem. Soc.* 5061 (1963).
[16] A. Lablache-Combier, B. Lacoume and J. Levisalles, *Bull. Soc. Chim.* 897 (1966).
[17] B. Lacoume and J. Levisalles, *Bull. Soc. Chim.* 2245 (1964).





XI R = O

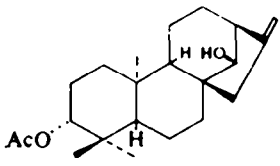
XII R = 

XIII R = 

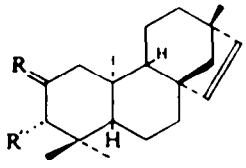
XIV R = 

XV R = 

XVI R = O



XVII



XVIII R = O; R′ = OH
XIX R = O; R′ = OTs

XX R =  ; R′ = H

XXI R = O; R′ = H

lanostane series and since the CH(OH) resonance appears as a quintuplet at $\tau = 5{\cdot}88$.

It was of interest in the light of the known antipodal A/B fusion of this skeleton to examine the ORD curves of these ring A ketones. As would be expected from octant projections stach-15-en-2-one (XXI) displayed a strong negative Cotton effect opposite in sign to the curves derived from ketomanoyl oxide and lanost-8-en-2-one. However the sign of the Cotton effect of the 3-ketones showed a dependence on ring D substituents. Thus whilst stach-15-en-3-one (XI) showed a weak positive effect both stachan-3-one and the corresponding 15:16-epoxide showed negative curves. It is possible that the conversion of C-15 to a tetragonal centre involves the introduction of a C-20 interaction which is sufficient to affect the geometry of ring A. Similar differences have been observed[16,18] between lanost-8-en-3-one and lanostan-3-one. The ORD curves of the 3-acetoxy and 3-tosyloxystach-15-en-2-ones showed negative Cotton effects in accord with the equatorial nature of these substituents.

Evidence for the conformation of ring A was sought in the measurements of 2:3 coupling constants in the epimeric diols[cf. 19] and their mono-acetates. Reduction of

[18] C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *J. Amer. Chem. Soc.* **80**, 4001 (1958).
[19] E. L. McGinnis, G. D. Meakins, J. E. Price and M. C. Styles, *J. Chem. Soc.* 4379 (1965).

the α-ketol with sodium borohydride gave the diequatorial 2β:3α-diol. However reduction of the α-acetoxy-ketone was more complex, the crude product showing major resonances at $\tau = 6{\cdot}75$ (doublet J, 5 c/s) and 4·88 (quintuplet) with minor resonances at 5·92 and 5·45 indicating some isomerization to a 2-acetoxy-3-hydroxy-stachene. An attempt was made to prepare the 3-epimeric diol. Stachenol was converted to its toluene-*p*-sulphonate and hydrogenated. The toluene-*p*-sulphonate underwent smooth elimination refluxing in collidine to form stach-2-ene [ν_{max} 765 cm^{-1}]. However osmylation proceeded in low yield and the only tractable product which could be identified was the diequatorial 2β:3α-diol. For satisfactory work epimers are required and since the spectra of this diol and the mono-acetate were not very well resolved, this approach was abandoned.

EXPERIMENTAL

General experimental details are described in part I. NMR spectra: a Varian Associates A60 and HA 100 spectrometers in $CDCl_3$ with TMS as an internal reference; ORD spectra a JASCO UV-ORD 5 spectrometer.

Reduction of iso-steviol methyl ester (VIb)

(a) *With sodium borohydride.* The ester[11] (500 mg) in MeOH (15 ml) was treated with $NaBH_4$ (300 mg) for 2 hr. The soln was acidified with dil. HCl, the organic solvents evaporated, and the product recovered in ether. Chromatography on alumina (Grade III) gave, in the fractions eluted with 25% ether:light petroleum, methyl 16α-hydroxystachan-19-oate (VII; 375 mg) which crystallized from acetone–light petroleum as needles, m.p. 164–165° (cf. lit.[11] m.p. 163–166°).

(b) *Catalytic reduction.* A soln of isosteviol methyl ester (71 mg) in glacial AcOH (5 ml) was added to a prereduced suspension of Adam's catalyst (50 mg) in glacial AcOH (5 ml) containing a trace of perchloric acid and hydrogenated until uptake ceased. The soln was poured into $NaHCO_3$aq. and the organic product recovered in ether. Crystallization from acetone–light petroleum gave the above alcohol VII identified by its IR spectrum. The *toluene-p-sulphonate* (VIII) of methyl 16α-hydroxystachan-19-oate, prepared with toluene-*p*-sulphonyl chloride in pyridine, crystallized from light petroleum as needles, m.p. 112–113°. (Found: C, 69·0; H, 8·7. $C_{35}H_{50}O_5S$ requires: C, 68·8; H, 8·3%.) ν_{max} 1710 and 1600 cm^{-1}.

Preparation of the unsaturated ester (IX)

The above toluene-*p*-sulphonate (240 mg) in collidine (5 ml) was heated under reflux for 4 hr. The soln was poured into dil. HCl and extracted with ether. The extract was washed with water, dried and evaporated. *Methyl stach-15-en-19-oate* (IX) (110 mg) crystallized from aqueous MeOH as plates, m.p. 107–109°. (Found: C, 79·0; H, 10·0. $C_{21}H_{32}O_3$ requires: C, 79·7; H, 10·2%.) ν_{max} 1710 cm^{-1}.

Reduction of the unsaturated ester (IX)

The above ester (75 mg) in ether (10 ml) was treated with LAH (100 mg) at room temp for 3 hr. Water followed by dil. HCl was cautiously added and the soln extracted with ether. The extract was washed with water, dried and evaporated to give 19-*hydroxystach-15-ene* (X; 44 mg) which crystallized from aqueous MeOH as needles, m.p. 120–121°. (Found: C, 82·7; H, 11·5. $C_{20}H_{32}O$ requires: C, 83·3; H, 11·2%.) $[\alpha]_D^{26}$ +27°, ν_{max} 3300 cm^{-1}. The sample was identical with a sample of the natural product generously provided by Dr. R. D. H. Murray.[6]

Epoxydation of the acetate of stachen-15-en-3α-ol. (XIII)

The acetate[8] (720 mg) was treated with 0·5 N perbenzoic acid in chf (30 ml) for 2 days at 0°. The soln was diluted with chf and washed successively with $FeSO_4$aq., dil. HCl, $NaHCO_3$aq., water and dried. Evaporation of the residue and chromatograph of the residue on alumina gave 3α-*acetoxy-15β,16β-epoxystachane* (XIV) which crystallized from acetone–light petroleum as needles, m.p. 164–165°. (Found: C, 76·2; H, 9·9. $C_{22}H_{34}O_3$ requires: C, 76·3; H, 9·9%.) ν_{max} 1728 cm^{-1}.

Rearrangement of 3α-acetoxy-15β,16β-epoxystachane (XIV)

The epoxide (275 mg) was treated with BF_3-etherate (5 ml) at 0° for 16 hr. The soln was poured into water, recovered with ether and the extract rinsed with $NaHCO_3$aq. Evaporation and chromatography on alumina in 10% AcOEt–light petroleum gave *3α-acetoxy-(−)-kaur-16-en-14β-ol* (XVII) (180 mg) which crystallized from acetone–light petroleum as needles, m.p. 102–103°. (Found: C, 75·2; H, 9·9 $C_{22}H_{36}O_3$ requires: C, 75·8; H, 10·4%.) ν_{max} 3500, 3440, 1720, 1650, 890 cm^{-1}.

Oxidation of the rearrangement product (XVII)

The alcohol (130 mg) in acetone (10 ml) was treated with the 8N CrO_3 reagent (0·25 ml) at room temp for 4 hr. MeOH was added and the soln worked up in ether to give *3α-acetoxy-(−)-17-norkauran-14,16-dione* which crystallized from acetone–light petroleum as needles, m.p. 189–190°. (Found: C, 73·2; H, 9·0. $C_{21}H_{30}O_4$ requires: C, 72·8; H, 8·7%.) ν_{max} 1748, 1725, 1720 cm^{-1}.

Reduction of 3-hydroxystach-15-en-2-one (XVIII).

The *toluene-p-sulphonate* of 3-hydroxystach-15-en-2-one, prepared with toluene-*p*-sulphonyl chloride in pyridine, crystallized from petrol as prisms, m.p. 172–173°. (Found: C, 70·5; H, 8·2. $C_{27}H_{36}O_4S$ requires: C, 71·0; H, 7·95%.) ν_{max} 1730, 1600 cm^{-1}, $[M]_{310}$ −2950°; $[M]_{280}$ +4220°.

The toluene-*p*-sulphonate (800 mg) and LAH (400 mg) were refluxed in dry THF (20 ml) for 2 hr. The soln was treated with dil. HCl and the organic product recovered in ether. Chromatography on alumina in 10% ether–light petroleum gave *stach-15-en-2α-ol* (XX) which crystallized from aqueous MeOH as needles, m.p. 89–90°. (Found: C, 83·2; H, 11·0. $C_{20}H_{32}O$ requires: C, 83·3; H, 11·2%.) ν_{max} 3310 (br) cm^{-1}.

Oxidation of stach-15-en-2α-ol (XX)

The alcohol (250 mg) in acetone (10 ml) was treated with the 8N CrO_3 reagent (0·25 ml) for 3 hr. MeOH was added, the soln concentrated, and the organic product recovered in ether. Chromatography on alumina in petrol gave *stach-15-en-2-one* (XXI) which crystallized from aqueous MeOH as needles, m.p. 119–120°. (Found: C, 83·3; H, 10·75. $C_{20}H_{30}O$ requires: C, 83·9; H, 10·6%.) ν_{max} 1695 cm^{-1}, $[M]^{25}_{310}$ −4090; $[M]^{25}_{270}$ +7770°.

Reduction of the epoxide (XIV)

The epoxide (210 mg) and LAH (400 mg) in dry ether were refluxed together for 4 hr. The soln was acidified and extracted with ether. Chromatography on alumina gave *15β,16β-epoxystachan-3α-ol* which crystallized from light petroleum as needles, m.p. 101–102° (Found: C, 78·8; H, 10·6. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%.) ν_{max} 3250 (br). The same alcohol could be prepared by epoxydation of stach-15-en-3-ol with *m*-chloroperbenzoic acid in chf. Acetylation with Ac_2O, in pyridine regenerated the acetoxy-epoxide, which was identified by its IR spectrum.

Oxidation of the epoxide (XV)

The epoxide (53 mg) in acetone (5 ml) was treated with the 8N CrO_3 reagent (0·1 ml) for 2 hr. MeOH was added, the soln concentrated, diluted with water and extracted with ether. The extract was evaporated and the residue chromatographed on alumina to give 15,16-epoxystachan-3-one, m.p. 113° [lit.[8] 114°], $[M]^{25}_{366}$ −960°; $[M]^{25}_{270}$ +850°.

Attempted preparation of stach 2β,3β-diol (cf. 16)

The *toluene-p-sulphonate* of stach-15-en-3α-ol, prepared with toluene-*p*-sulphonyl chloride in pyridine, crystallized from light petroleum as needles, m.p. 144–145° with dec. (Found: C, 73·6; H, 8·7. $C_{27}H_{38}SO_3$ requires: C, 73·3; H, 8·65%.) ν_{max} 1603, 754 cm^{-1}. The toluene-*p*-sulphonate (250 mg) in AcOEt (10 ml) was hydrogenated over 10% Pd–C (100 mg) to give *3-tosyloxystachane* which crystallized from light petroleum as prisms, m.p. 134–135° with dec. (Found: C, 72·2; H, 9·2. $C_{27}H_{40}O_3S$ requires: C, 72·9; H, 9·1%.) ν_{max} 1603 cm^{-1}.

3-Tosyloxystachane (200 mg) in collidine (10 ml) was refluxed for 6 hr. The soln was poured into dil. HCl extracted with ether, washed with water, dried and evaporated to give a gum (ν_{max} 765 cm^{-1}). This was treated with osmium tetroxide (200 mg) in pyridine (2 ml) and ether (8 ml) overnight.

The suspension was refluxed with KOH (2 g), mannitol (2 g) in aqueous EtOH (10 ml) for 3 hr. The product was recovered in ether and chromatographed on alumina. The sole tractable fraction (10 mg) crystallized as needles, m.p. 198–200° identified as stachan-2β,3α-diol by its IR spectrum. Authentic stachan-2β,3α-diol, m.p. 199–200° (lit. 200–205°) was prepared according to the literature[8] procedure.

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