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THE ABSOLUTE CONFIGURATION OF BEYEROL

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We have already described (1) evidence for the structure of beyerol (I) and have allocated configurations at C-3, C-5, and C-10 as shown. Evidence for the configurations of the other asymmetric centres is now presented.

Support for the substitution pattern of the A and B rings has been obtained by the preparation of methyl 3-oxo-19-norbeyera-1,4,6-trien-17-oate (II), characterized as its 2,4-dinitrophenylhydrazone ($\lambda_{max.}^{CHCl_3}$ 414 mμ, ε,36300), by tribromination-dehydrobromination (2) of the saturated ketone. The U.V. spectrum of (II), $\lambda_{max.}^{EtOH}$ 227 (ε,10000), 258 (ε,5600) and 309 mμ (ε,6600), was in good agreement with related compounds (2). The N.M.R. spectrum* of (II) (CCl_4 soln.) showed a vinylic methyl group at 8.17 and vinyl absorption as two AB patterns with H_2, H_1 at 3.10, 4.23 (J, 10.5) and H_7, H_6 at 3.57, 3.88 (J, 10). No allylic splitting of either quartet was present, substantiating the quaternary nature of C-8 and C-10.

The configuration at C-4 is assigned on the following evidence.

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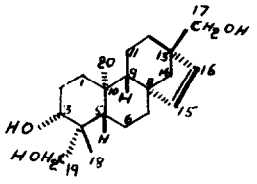
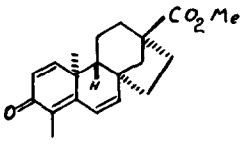
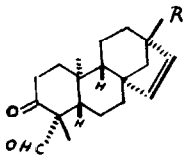
* N.M.R. spectra were measured on deuterochloroform or chloroform solution, unless otherwise indicated, with concentrations up to 20% w/v. Singlet positions and centres of multiplets are quoted on the τ scale and are believed to be within 0.3 p.p.m. Coupling constants (J) are in cycles/sec. to the nearest 0.5 c/s.



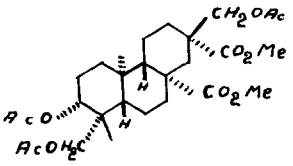
I



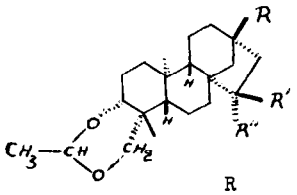
II



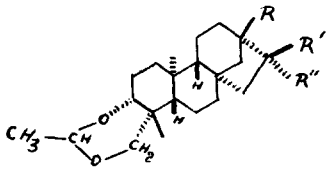
III R = CO_2H
IV R = CH_2OCOPh



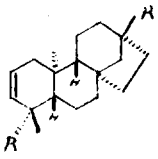
V



	R	R'	R''
VI	CH_2OH	OH	H
VII	CO_2Me	= O	
VIII	CH_2OH	H	OH
IX	CO_2Me	H	OH



	R	R'	R''
X	CO_2Me	H	OH
XI	CO_2Me	= O	
XII	CH_2OH	H	OH



XIII R = CH_2SCH_2Ph
XIV R = CH_3

3,19-Dioxobeyer-15-en-17-oic acid (III) and 3,19-dioxobeyer-15-en-17-yl benzoate (IV) show resonance of the aldehyde hydrogen at 0.31 and 0.30 respectively, values corresponding to an axial group (3). Further, beyeryl triacetate, 3α,19-diacetoxybeyer-15-en-17-oic acid and 17,19-diacetoxybeyerane show quartets arising from the methylene protons of the 4-acetoxymethyl group, at 5.74, 5.73 and 5.93 (J, 12, 12, and 11 respectively), consistent with an axial orientation of this group (4,5). The infrared spectrum of methyl 3α,19-dihydroxybeyer-15-en-17-oate shows free secondary hydroxyl at 3631 and intramolecularly hydrogen bonded hydroxyl at 3555 cm^{-1}. This result corresponds with values for analogous compounds in the triterpene series (6), contrary to an earlier suggestion (6). This, together with the fact that the 4-hydroxymethyl group is axial, confirms the equatorial disposition of the 3-hydroxyl, as does the formation of 3α,19-ethylidenedioxybeyer-15-en-17-ol (1).

Recent work by Ayer, McDonald, and Stothers (7) supports the view (8) that the carbonyl and olefinic groups have similar anisotropic effects, and in particular that a C-10 methyl group may be shielded by an olefinic centre attached to C-8. In a number of beyerene derivatives (Table I) similar shielding occurs and is removed by hydrogenation or epoxidation of the double bond. Although these effects are smaller than those observed by Ayer, McDonald, and Stothers, they are consistent with the different orientations of the interacting groups in the beyerene series. The spectra of various phyllocladene derivatives* show very similar effects to those of beyerol, whereas (-)-kaurene (9), (-)-isokaurene (9), and (-)-β-dihydrokaurene (5) all show the C-10 methyl absorption at the same position.

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* Samples of phyllocladene and isophyllocladene kindly supplied by Dr. R. Hodges.

TABLE I

Effect of 15(16)-Double Bond on C-10 Methyl Resonance

Compound	C-4 Methyl	C-10 Methyl
Methyl 3-oxo-19-norbeyer-15-en-17-oate	9.00*	9.02
Methyl 3-oxo-19-norbeyeran-17-oate	9.02*	8.87
Beyer-15-en-3α,17,19-triyl triacetate	8.98	9.21
Beyeran-3α,17,19-triyl triacetate	9.00	9.03
15β,16β-epoxybeyeran-3α,17,19-triyl triacetate	8.95	9.00
Dimethyl 3α,17,19-triacetoxy-15,16-secobeyeran-15,16-dioate (V)	9.01	9.26
Isophyllocladene	9.15,9.18	9.26
Phyllocladene	9.15,9.19	9.08
α-Dihydrophyllocladene**	9.15,9.19	9.11

* Doublet with J,6.5

** C-17 methyl, 9.02 (J,7)

Significant shielding requires that the methyl group be above or below the trigonal plane of the double bond and not more than ca. 3 Å from the olefinic centre. These conditions are met by the trans-anti-trans backbone for beyerol, but not by the trans-anti-cis (kaurene) or trans-syn-trans configurations. The most favourable conformation of the trans-syn-cis configuration has coordinates of the C-20 hydrogens with R of the order of 5 Å, θ ca. 20-40° (7), values which could result in slight deshielding.

Further evidence for the configurations at C-8 and C-9 has been obtained by preparation and study of the R.D. curves of the 15- and 16-ketones. Epoxidation of 3α,19-ethylidenedioxybeyer-15-en-17-ol

gave a single product, formulated as the β-epoxide, formed by attack from the less hindered (exo) side of the double bond. Reduction of the epoxide with lithium aluminium hydride gave the 15β,17-diol (VI), which was oxidised and methylated to the 15-keto ester (VII; $\nu_{max.}$ 1736 cm^{-1}). Reduction of the latter with lithium aluminium hydride gave the 15α, 17-diol (VIII) only, whereas sodium borohydride formed (VIII) and the 15α-hydroxy ester (IX). Oxygenation at C-15 was established by the fact that neither the diols (VI, VIII) nor the hydroxy ester (IX) showed any intramolecular hydrogen bonding in their I.R. spectra.

Hydroboration (10) of 3α,19-ethylidenedioxybeyer-15-en-17-ol gave a complex mixture of diols, which after oxidation, methylation, and crystallization gave some of the 15-keto ester (VII). Reduction of the mother liquors with sodium borohydride gave a mixture from which the 15α,17-diol (VIII), the 15α-hydroxy ester (IX) and the 16α-hydroxy ester (X) were obtained. Oxidation of (X) afforded the 16-ketone (XI; $\nu_{max.}$ 1757 and 1736 cm^{-1}). Reduction of either the 16α-hydroxy ester (X) or the 16-ketone (XI) with lithium aluminium hydride gave the 16α,17-diol (XII). The I.R. spectra of both the 16α-hydroxy ester (X; $\nu_{max.}$ 3630, 3605, 1735 and 1719 cm^{-1}) and the 16α,17-diol (XII; $\nu_{max.}$ 3641 and 3582 cm^{-1}) showed intramolecular hydrogen bonding, thus establishing the oxygenation at C-16.

The R.D. curve* of the 16-ketone (XI) showed a negative Cotton effect ([M] x 10^{-2}, -62°) similar in shape and magnitude to the 16-ketones derived from phyllocladene ($+108^{\circ}$, $+98^{\circ}$) (11,12), cafestol ($+115^{\circ}$) (11), kaurene ($+69^{\circ}$) (13), the Garrya alkaloids ($+134^{\circ}$) (14), and to isosteviol (-89°) (11). This requires that the olefinic bridge in beyerol have the α-configuration.

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* Measured through the kind cooperation of Professor C. Djerassi.

The R.D. curve* of the 15-ketone (VII) showed a positive Cotton effect. It is worth noting that published data (11) for analagous 15-ketones with a cis B/C ring junction show reduced amplitudes (-19°, -20°) and relatively unsymmetrical curves as compared with trans B/C ketones of the phyllocladene series (-96 to -113°) (12). This is consistent with the assignment of a trans B/C junction to beyerol.

The predominance of the trans-anti-cis stereochemistry among natural tetracyclic diterpenes substituted at C-16, coupled with Wenkert's (15) and Whalley's (16) biogenetic schemes suggests that most diterpenes of the beyerol type will have trans-anti-trans stereochemistry

Since isosteviol (17) appears to have the trans-anti-trans backbone (18) we have prepared beyerane for comparison with isostevane (17). Treatment of beyeran-3,17,19-triyl trimethanesulphonate with the sodium salt of benzyl thiol in dimethylformamide** proceeded with elimination to give the dithioether (XIII) whose N.M.R. spectrum showed a cis disubstituted olefin with the coupling expected for a 2-ene. Desulphurization with Raney nickel gave beyer-2-ene (XIV) which was hydrogenated to beyerane, m.p. $41.5 - 43.5^{\circ}$, undepressed by isostevane.***

A relationship with the diterpene stachenone (19) has been shown in the following way. Tosylation of beyeran-3,17,19-triol and chromatography gave the 17,19-ditosylate, formulated by analogy with the partial benzoylation products of beyerol and by oxidation to the ketone. The ditosylate was converted to the dibenzyl thioether, which after desulphurization with Raney nickel gave stachanol identical with a sample

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* Measured through the kind cooperation of Professor C. Djerassi.

** We are indebted to Dr. A.J. Parker for helpful discussions on this technique.

*** A sample kindly supplied from the collection of the late Dr. E. Mosettig.

derived from stachenol.*

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* A sample of stachenol kindly supplied by Dr. W.H. Baarschers.