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THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—VI[1]

THE STEREOCHEMISTRY OF SOME REACTIONS OF (−)-KAURENE

J. R. HANSON
The Chemical Laboratory, University of Sussex, Brighton

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Abstract—The stereochemistry of some reactions at C-16 in (−)-kaurene is clarified.

THE stereochemistry of the reactions of ring D of (−)-kaurene (I) reveal certain features which at first sight appear anomalous. The structure of the diterpene alcohol, (−)-kauran-16α-ol (II) which occurs in *Gibberella fujikuroi*,[2] rests on its preparation from (−)-kaurene hydrochloride[3], its dehydration to a mixture of (−)-kaurene and (−)-isokaurene[2] and on its partial synthesis[4,5] by reduction of (−)-kauran-16,17-epoxide.[3] A possible source of ambiguity in this relationship lies in the fact that treatment of (−)-kauren-16,17-epoxide (III) with acid also leads to the formation of a 16α,17-diol (IV) identical to the product of osmylation of (−)-kaurene. That is cleavage of the 16α-epoxide apparently takes place with retention of configuration at the tertiary centre C-16. Further evidence has therefore been provided for the stereochemistry of some reactions at C-16.

Treatment of (−)-kaurene with osmium tetraoxide in pyridine gave the known[4,6] 16,17-diol. This formed a monotoluene-*p*-sulphonate which underwent hydrogenolysis with LAH to give (−)-kauran-16α-ol identical to the natural product.[3] This relationship provides clear evidence for the identity of the stereochemistry of the two at C-16. The epimeric kauranol, (−)-kauran-16β-ol (VII), was prepared by the reaction of 17-norkauran-16-one (VI) with methyl magnesium iodide. The known 16,17-epoxide was prepared from (−)-kaurene with hydrogen peroxide and formic acid or *m*-chloroperbenzoic acid. The NMR spectrum which contained a two proton double-doublet at $\tau = 7{\cdot}2$ (J, 10 c/s) demonstrated that this compound was a 16,17-epoxide. It reproducibly gave both the 16α,17-diol on treatment with acid and (−)-kauran-16α-ol by reduction with LAH.[4,5]

The stereochemistry of hydroboronation of (−)-kaurene again reflected the attack of a reagent from the α-face of ring D. A primary alcohol (2 protons at $\tau = 6{\cdot}3$) was obtained. Reduction of the derived toluene-*p*-sulphonate with LAH afforded (−)-kaurene which is of known stereochemistry at C-16.[6,7] Hence the stereochemistry

[1] Previous part, J. R. Hanson, *Tetrahedron* **23**, 793 (1967).
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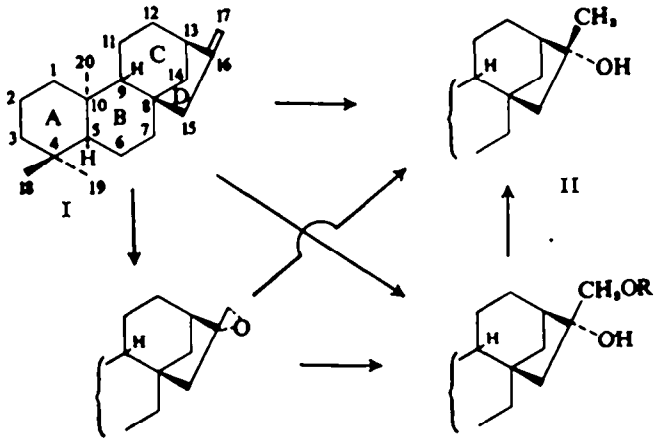
[3] J. K. McGimpsey and J. Murray, *J. Appl. Chem.* **10**, 340 (1960).
[4] J. R. Hanson, *J. Chem. Soc.* 5061 (1963).
[5] L. H. Briggs, R. C. Cambie and P. S. Rutledge, *J. Chem. Soc.* 5374 (1963).
[6] L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge and J. K. Wilmshurst, *J. Chem. Soc.* 1345 (1963).
[7] H. Vorbrueggen and C. Djerassi, *J. Amer. Chem. Soc.* **84**, 2990 (1962).

VIII was assigned to the alcohol. Oxidation of the alcohol with the 8N chromium trioxide reagent led to the corresponding carboxylic acid. Its epimer was prepared by rearrangement of (−)-kaurene epoxide with anhydrous magnesium bromide etherate. The gummy aldehyde so obtained was oxidized to the known[8] (—)-kauran-17-oic acid.



Attack from the less hindered face of the molecule is reflected in the reduction of the norketone. Thus reduction with $NaBH_4$ or LAH gave (−)-17-norkauran-16β-ol (IX).[4,6] However the same alcohol was produced both by catalytic reduction (Pt/HOAc) and by reduction with sodium in alcohol, processes which might be expected to lead to epimers at this centre. The stereochemistry of this alcohol was clarified by its NMR spectrum. The spectra of both the alcohol and its benzoate showed seven lines of an AX_3 system at $\tau = 5{\cdot}72$ and $\tau = 4{\cdot}76$ respectively, with coupling constants of 12, 6 and 4·5 c/s, corresponding to a proton coupled to two *cis* and one *trans* proton. Hence there must be a *cis* relationship to the bridgehead C-13 proton and thus the alcohol has the β-configuration.

EXPERIMENTAL

General details are described in Part I. The (−)-kaurene utilized in these experiments was isolated[9] from *Gibberella fujikuroi*. NMR spectra: in $CDCl_3$ on a Varian HA-100 spectrometer with TMS as an internal standard.

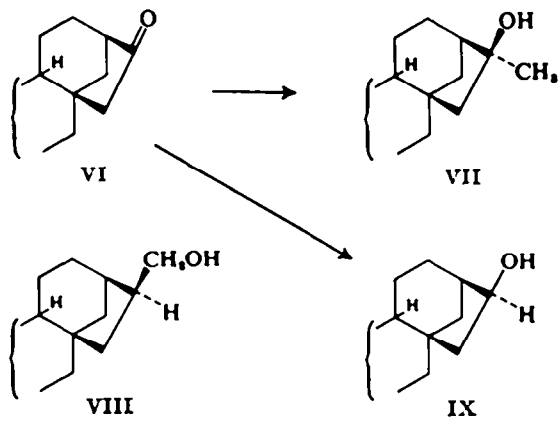
Toluene-p-sulphonate of (−)-*kauran*-16α,17-*diol* (IV)

The diol (510 mg) and toluene-*p*-sulphonyl chloride (750 mg) in pyridine (10 ml) were left at room temp for 36 hr. The soln was diluted with water, extracted with ether and the extract with dil. HCl, dried and evaporated. Chromatography on alumina in petrol gave the *mono-toluene-p-sulphonate* (V; 392 mg) which crystallized from acetone–light petroleum as needles m.p. 178–179°. (Found: C, 70·3; H, 8·8. $C_{27}H_{40}O_4S$ requires: C, 70·4; H, 8·7%.) ν_{max} 3540, 1603, 1170 cm^{-1}.

Kauran-16α-*ol* (II)

The above toluene-*p*-sulphonate (125 mg) and LAH (105 mg) in ether (10 ml) were heated under reflux for 2 hr. The soln was acidified and worked up in ether. Recovery gave kauran-16α-ol (65 mg) which crystallized from acetone as needles, m.p. 212–213° identical to the natural product.[8]

[9] C. A. Henrick and P. R. Jefferies, *Austr. J. Chem.* 17, 915 (1964).



Kauran-16β-*ol* (VII)

17-Norkauran-16-one (VI; 111 mg), Mg (1 g) and MeI (1 ml) in ether (10 ml) were heated under reflux for 2 hr. The soln was diluted with ether, acidified, washed, dried and evaporated to give *kauran*-16β-*ol* which crystallized from acetone as needles, m.p. 151–152°. (Found: C, 82·5; H, 11·6. $C_{20}H_{34}O$ requires: C, 82·7; H, 11·8%.) ν_{max} 3360 cm^{-1}.

Kauran-16,17-*epoxide* (III)

A soln of (−)-kaurane (I: 150 mg) in $CHCl_3$ (10 ml) was treated with H_2O_2 (5 ml) and formic acid (5 ml) at room temp for 5 hr. The soln was diluted with water, extracted with chf, the extract washed with $NaHCO_3$aq, dried and evaporated to give the epoxide (58 mg) which crystallized from MeOH as needles, m.p. 115–117° (lit.[4] m.p. 117°). NMR τ = 9·18; 9·13, 8·97, 7·26, 7·16 (doublets, J = 9 c/s).

Hydroboration of kaurene

Kaurene (500 mg) and BF_3-etherate (5 ml) in diglyme (25 ml) were treated with a soln of $NaBH_4$ (1·0 g) in diglyme (150 ml) over 1 hr. A 12% soln of NaOH in EtOH (20 ml) was added followed by the cautious addition of 30% H_2O_2 (30 ml). The soln was diluted with water and the product recovered in ether. Evaporation of the solvent and chromatography of the product on alumina gave 16β-*kauran*-17-*ol* (VIII; 210 mg) m.p. 158–160°. (Found: C, 82·2; H, 11·8. $C_{20}H_{34}O$ requires: C, 82·7; H, 11·8%.) ν_{max} 3330 cm^{-1}. NMR τ = 9·2; 9·15; 9·00; 6·3 (J = 7 c/s). The toluene-*p*-sulphonate, prepared with toluene-*p*-sulphonyl chloride in pyridine, had m.p. 146°, ν_{max} 1603, 1195, 1182 cm^{-1}.

Kaurane

Reduction of the toluene-*p*-sulphonate (15 mg) in ether (5 ml) with LAH (50 mg) under reflux for 2 hr, dilution with HCl and recovery of the organic product in ether gave a gum which was chromatographed on alumina. Elution with petrol gave kaurane (α-dihydrokaurane) (3 mg) as needles from MeOH, m.p. 81–82° identified by comparison with an authentic sample.[5]

Oxidation of 16β-*kauran*-17-*ol*

The alcohol (50 mg) in acetone (5 ml) was treated with the 8N CrO_3 reagent (0·25 ml) for 2 hr. MeOH (1 ml) was added and the soln concentrated. Dilution with water and extraction with ether gave 16β-*kauran*-17-*oic acid*, m.p. 189–190°. (Found: C, 76·7; H, 10·6. $C_{20}H_{32}O_3$, $\frac{1}{2}H_2O$ requires: C, 76·6; H, 10·6%.) ν_{max} 3603, 3350 (br), 1706, 1686 cm^{-1}.

Rearrangement of kaurene epoxide

The epoxide III (120 mg) in ether (10 ml) was treated soln of Mg (1 g) in ethylene dibromide (1·2 ml) in ether (50 ml) for 3 days at 0°. The soln was treated with the 8N CrO_3 reagent (0·25 ml) in acetone (5 ml). The usual isolation procedure gave 16α-(−)-kauran-17-oic acid (58 mg) which crystallized from light petroleum as needles, m.p. 217–218° (lit.[6] 217–219°) ν_{max} 3100 (br), 1695 cm^{-1}.

17-*Norkauran*-16β-*ol* (IX)

(a) *Catalytic hydrogenation.* 17-Norkauran-16-one (110 mg) was shaken with Adam's catalyst (50 mg) in glacial AcOH (10 ml) containing perchloric acid (5 drops) under H until rapid uptake ceased. The soln was poured into $NaHCO_3$aq, and the product recovered with ether. 17-*Norkauran*-16β-*ol* crystallized from light petroleum as needles, m.p. 156–158°. (Found: C, 82·05; H, 11·3. $C_{19}H_{36}O$ requires: C, 82·5; H, 11·7%.) ν_{max} 3306, 3239 (br) cm^{-1} NMR τ — 9·18, 9·13, 8·97, 5·72, (J — 12, 6, and 4·5 c/s).

(b) *Reduction with sodium borohydride.* The norketone (75 mg) in MeOH (10 ml) was treated with $NaBH_4$ (100 mg) for 1 hr. Dil. HCl was added and the product recovered with AcOEt. Evaporation of the solvent and chromatography of the product on alumina gave 17-norkauran-16β-ol (60 mg) which crystallized from light petroleum as needles, m.p. 159–160°. It was identified by its IR spectrum.

(c) *Reduction with sodium in ethanol.* The norketone (120 mg) in EtOH (50 ml) was heated under reflux. Na (1 g) was added in small portions over 3 hr. The soln was cooled, acidified and concentrated *in vacuo*. Recovery in ether and chromatography on alumina gave 17-norkauran-16β-ol (31 mg) which crystallized from light petroleum as needles, m.p. 156–157° identical to the products obtained above.

The *benzoate*, prepared with benzoyl chloride in pyridine, crystallized from benzene–light petroleum as needles, m.p. 181–182°. (Found: C, 81·7; H, 9·4. $C_{26}H_{40}O_2$ requires: C, 82·1; H, 9·5%.) ν_{max} 1710, 1600, 710 cm^{-1}, NMR τ — 9·18, 9·15, 8·98, 4·76 (J — 12, 6, 4·5 c/s) 2·6 and 2·0 (multiplets).

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