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THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—III

THE PARTIAL SYNTHESIS OF KAURENOLIDE[1]

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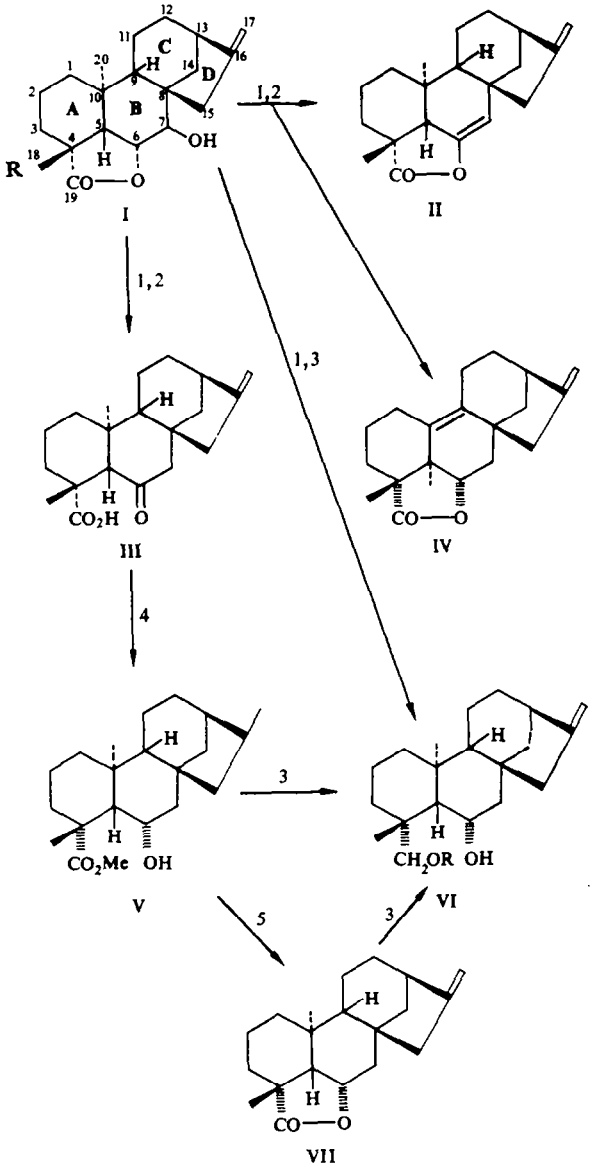
Abstract—Kaurenolide, 6α-hydroxy-(−)-kaur-16-en-19-oic acid 19 → 6α lactone (VII), has been prepared from 7-hydroxykaurenolide. Elimination and hydrolysis reactions formed 6-oxo-(−)-kaur-16-en-19-oic acid. The latter on reduction and relactonization, gave kaurenolide.

THE kaurenolides (I, R = Me, or CH_2OH) form the major kauranoid metabolites[2] of the fungus *Gibberella fujikuroi* ACC 917. However the parent kaurenolide (6α-hydroxy-(−)-kaur-16-en-19-oic acid 19 → 6 α-lactone, VII), has hitherto not been isolated from the fermentation. The possibility of its participation in the biosynthesis of the kaurenolides led us to prepare it from 7-hydroxykaurenolide (I, R = Me). This paper describes this partial synthesis and some details of the chemistry of the 6-position.

The elimination reactions of 7-hydroxykaurenolide and the NMR spectra of its derivatives were examined[2,3] in order to define the conformation of ring B. Since the fully substituted centre at C(8) formed part of a bridgehead, it precluded the ready formation of a trigonal carbonium ion at that position and thus the use of skeletal rearrangements to characterize the conformation of the 7-hydroxyl group in the manner applied to ring A of the triterpenes.[4] Thus the action of phosphorus pentachloride on both the 7β-(ax)- and 7α(eq)-hydroxykaurenolides led to the isolation of the Δ^6-enol-lactone (II), 6-oxokaur-16-en-19-oic acid (III) and a compound which had the formula $C_{20}H_{26}O_2$. This compound was also isolated as a by-product during the preparation of 6-oxokaur-16-en-19-oic acid (III) from the toluene-*p*-sulphonate of 7-hydroxykaurenolide by the action of dry lithium iodide in collidine.[2] The compound showed IR absorption at 1760 cm^{-1} characteristic of a saturated γ-lactone whilst apart from terminal methylene absorption (ν_{max} 1655 and 882 cm^{-1}), there was no further evidence of olefinic protons. In particular the NMR spectrum showed no proton resonances below $\tau = 5{\cdot}0$. However the UV spectrum showed high end absorption ($\varepsilon_{205} = 10{,}000$) and thus the molecule contained a further, presumably tetrasubstituted, double bond in addition to the terminal methylene group. The NMR spectrum also revealed a multiplet (partially obscured by the terminal methylene protons) at $\tau = 5{\cdot}1$ which is ascribed to the group C—CH(O·CO)—C together with two tertiary methyl groups at $\tau = 8{\cdot}8$ and a further seven allylic protons. A plausible

[1] Previous part, J. R. Hanson, *Tetrahedron* **22**, 1701 (1966).
[2] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 2944 (1963).
[3] J. R. Hanson, *Tetrahedron* **22**, 1453 (1966).
[4] (a) C. Doree, J. F. McGhie and F. Kurzer, *J. Chem. Soc.* 1467 (1947); (b) D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).



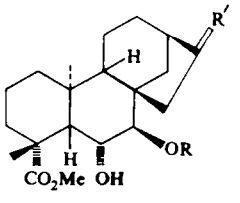
1. TsCl.pyr.; 2. LiI, collidine; 3. $LiAlH_4$; 4. $NaBH_4$, CH_2N_2; 5. Heat

structure to accommodate these results is (IV) arising through rearrangement of the Δ^6-enol lactone (II). During this rearrangement, which has a strong analogy in the formation of Westphalen's diol,[5] all the migrating groups possess a *trans* diaxial relationship to one another.

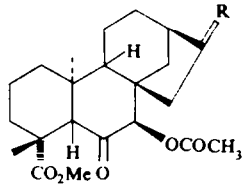
Hydrolysis of the Δ^6-enol-lactone with refluxing dilute hydrochloric acid has been reported[2] to give the 16-hydroxy-6-oxokaur-19-oic acid. Cleavage of the enol-lactone with boron trifluoride etherate led not only to hydrolysis and the formation of the keto acid but also to isomerization of the terminal methylene to the Δ^{15}-ene.

Reduction of the 6-keto-acid (III) with sodium borohydride followed by methylation with diazomethane gave a 6α-hydroxy-ester (V). The stereochemistry of the 6-hydroxy group was demonstrated by the further reduction of this hydroxy-ester with lithium aluminium hydride to give the known diol, 6α, 19-dihydroxykaurene (VI, R = H). This diol, which had been obtained by reduction of the toluene-*p*-sulphonate of 7-hydroxy-kaurenolide with lithium aluminium hydride, was also obtained by reduction of the 7,18-ditoluene-*p*-sulphonate[3] of 7,18-dihydroxy-kaurenolide. Thus typically,[6] reduction of the hindered 6-carbonyl group led to the axial alcohol. The 6(ax)-alcohol was inert to acetylation with acetic anhydride in pyridine. Thus acetylation of the 6α, 19-diol gave a monoacetate which from the change in NMR spectrum (2 protons shifted from $\tau = 6{\cdot}55$ to $\tau = 5{\cdot}55$) contained an axial primary acetate[7] (VI; R = $COCH_3$).

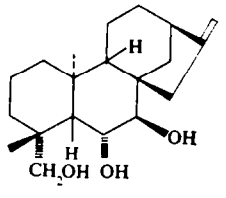
Acetylation of methyl 6α, 7β-dihydroxykaur-16-en-19-oate and its 17-norketone (VIII; R = H, R′ = CH_2 and O respectively) with acetic anhydride in pyridine led to the formation of monoacetates. Refluxing in acetic anhydride and sodium acetate brought about relactonization although the yield of the 7-acetate of 7-hydroxy-kaurenolide was poor. The monoacetyl derivatives could be oxidized with chromium



VIII



IX



X

trioxide to the corresponding α-keto-acetates (IX; R = CH_2 and O respectively). This oxidation was accompanied by some degradation of the 17-methylene to a 16-ketone.[8] The changes in the NMR spectra associated with this oxidation of the

[5] L. F. Fieser, *The Steroids*, p. 325, Reinhold, New York (1959).
[6] Ref. 5, p. 269.
[7] E. Wenkert and P. Beak, *Tetrahedron Letters* 358 (1961).
[8] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 3783 (1963).

free hydroxyl group enabled a distinction to be made between acetylation of the 6-axial and 7-axial hydroxyl groups. Oxidation of a 6-acyl derivative to a 7-ketone would be expected to lead to a doublet due to the 6-proton. On the other hand oxidation of a 7-acyl derivative to a 6-ketone should lead to singlets from the 5 and 7 protons. Singlets at τ 7·62 and τ 4·2 were observed corresponding to these protons and hence the acetyl derivative possessed structure (VII; R = $OCOCH_3$). Reduction of the keto-acetate (IX; R = CH_2) with lithium aluminium hydride led to the 6α, 7β, 19-triol (X) which was obtained also by direct reduction of 7-hydroxykaurenolide. Thus epimerization had not taken place at C-7 during oxidation. Treatment of both the 6α, 7β- and 6α, 7α-dihydroxy-19-methyl esters with toluene-*p*-sulphonyl chloride led to monotoluene-*p*-sulphonates. These were in turn oxidized to the corresponding 6-ketones again with some degradation of 17-methylene to a 16-ketone.

The partial synthesis of kaurenolide (VII) was completed by pyrolysis of the hydroxy-ester (VI) at 220°. Ozonolysis of the hydroxy-ester (VI) formed the 16-oxo-derivative, which underwent a similar relactonization to give the corresponding γ-lactone. The stereochemistry of this lactonization was demonstrated by reduction of kaurenolide to 6α, 19-dihydroxy-(−)-kaur-16-ene (VI).

EXPERIMENTAL

General experimental methods were as described in Part I.[8]

The action of PCl_5 *on 7β-hydroxykaurenolide* (I, R = Me). The kaurenolide (620 mg) suspended in ether (5 ml) was treated with PCl_5 (510 mg) at room temp for 2 hr. The soln was poured into dil. HCl and the organic material recovered in ether. Chromatography on silica gel in light pet. gave the enol-lactone (II; 115 mg), m.p. 202–204° followed by the *γ-lactone* (IV; 160 mg) which crystallized from light pet. as needles, m.p. 233–234° (Found: C, 80·1; H, 8·7. $C_{20}H_{36}O_3$ requires C, 80·5; H, 8·7%), ν_{max} 1760, 1655 and 882 cm^{-1}. NMR peaks at τ 8·8 (2-C(—CH_3)—), 7·8 (br. multiplet of 7 protons), 5·15 (multiplet 3 protons). Further elution with 10% AcOEt–light pet. gave 6-oxo-(−)-kaur-16-en-19-oic acid (III; 295 mg), m.p. 263–265°.

The action of PCl_5 *on 7α-hydroxykaurenolide.* The kaurenolide (250 mg) suspended in ether (5 ml) was treated with PCl_5 (210 mg) at room temp for 2 hr. The soln was diluted with ether, poured into dil. HCl and the organic material recovered in ether. Chromatography on silica gel gave successively the Δ^6-enol-lactone (II; 106 mg), the γ-lactone (IV; 29 mg) and the 6-keto acid (III; 93 mg) identified by their IR spectra.

Hydrolysis of the enol-lactone (II) *with* BF_3*-etherate.* The enol-lactone (61 mg) in ether (5 ml) was treated with BF_3-etherate (1 ml) for 5 hr. Dilution with water, followed by recovery of the organic material with ether gave 6-*oxo*-(−)-*kaur*-15-*en*-19-*oic acid* (30 mg) which crystallized from acetone as needles, m.p. 210–212°. (Found: C, 75·6; H, 9·3. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), ν_{max} 2750 (br.) 1740, 1659 (C=O and C=C) 825 cm^{-1}.

Reduction of the 6-keto acid (III) *with* $NaBH_4$. The keto acid (500 mg) in MeOH: tetrahydrofuran (1:1; 50 ml) was treated with $NaBH_4$ (500 mg) for 1 hr at room temp. The soln was concentrated, poured into water, acidified with dil. HCl and the organic product recovered in ether. Evaporation of the ether gave a semi-crystalline residue which was taken up in MeOH and methylated with diazomethane. The solvent was evaporated and the residue chromatographed on alumina. Elution with 10% AcOEt–light pet. gave *methyl 6α-hydroxy*-(−)-*kaur*-16-*en*-19-*oate* (V; 490 mg) which crystallized from light pet. as needles, m.p. 158–159°. (Found: C, 75·6; H, 9·7. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%), ν_{max} 3437, 1705, 1654 and 870 cm^{-1}.

Reduction of the hydroxy-ester (V). The hydroxy ester (45 mg) in dry ether (5 ml) was treated with LAH (49 mg) at room temp for 2 hr. The excess reagent was destroyed with AcOEt, the soln diluted with ether, washed with dil. HCl, water dried and evaporated to give 6α,19-dihydroxy-(−)-kaur-16-ene (71 mg) identified by its IR spectrum.[8]

Acetylation for 6α,19-*dihydroxy*-(−)-*kaur*-16-*ene* (VI). The diol (75 mg) in pyridine (5 ml) was treated with acetic anhydride (0·5 ml) for 2 days. The soln was poured into dil. HCl and extracted with ether. The extract was washed with $NaHCO_3$aq, dried and evaporated to give 19-*acetoxy*-6α-*hydroxy*-(−)-*kaur*-16-*ene* (VI; R = $COCH_3$) which crystallized from light pet. as needles, m.p. 134–135° (Found: C, 76·5; H, 9·4. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%), ν_{max} 3450, 1730, 1650, 880 cm^{-1} τ 9·00, 8·62, 7·90, 5·55, 5·20.

Acetylation of methyl 6α, 7β-*dihydroxy*-(−)-*kaur*-16-*en*-19-*oate* (VIII). The diol (325 mg) in pyridine (2 ml) was treated with acetic anhydride (0·5 ml) for 3 days. Isolation with AcOEt gave *methyl* 7β-*acetoxy*-6α-*hydroxy*-(−)-*kaur*-16-*en*-19-*oate* which crystallized from acetone–light pet. as needles, m.p. 190–192° (Found: C, 70·2; H, 8·9. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%), ν_{max} 3410, 1732, 1694, 1662 and 884 cm^{-1}.

Acetylation of methyl 6α,7β-*dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oate*. The diol (130 mg) in pyridine (2 ml) was treated with acetic anhydride (0·5 ml) for 2 days. Isolation with AcOEt gave *methyl* 7β-*acetoxy*-6α-*hydroxy*-16-*oxo*-17-*nor*-(−)-*kauren*-19-*oate* which crystallized from acetone–light pet. as needles, m.p. 196–198°. (Found: C, 67·8; H, 8·4. $C_{22}H_{32}O_6$ requires C, 67·3; H, 8·2%), ν_{max} 3382, 1752, 1734, 1696 cm^{-1}.

Action of acetic anhydride and AcONa *on methyl* 6α, 7β-*dihydroxy*-(−)-*kaur*-16-*en*-19-*oate*. The diol (125 mg) in acetic anhydride (5 ml) was heated under reflux with fused AcONa (500 mg) for 3 hr. The soln was poured into water, extracted with AcOEt, the extract washed with $NaHCO_3$aq dried and evaporated. The residue was chromatographed on alumina. Elution with 10% AcOEt–light pet. gave the acetate of 7-hydroxykaurenolide identified by its IR spectrum.[3]

Oxidation of the acetates (VIII, R = CH_3, and R = O). (a) The 7-acetyl derivative of the diol (VIII. R = CH_3) (200 mg) in acetone (5 ml) was treated with the 8N CrO_3 reagent 0·25 ml) for 4 hr. MeOH was added, the soln concentrated, diluted with water and the organic material recovered with AcOEt to give *methyl* 7β-*acetoxy*-6-*oxo*-(−)-*kaur*-16-*en*-19-*oate* (IX, R = CH_3; 85 mg) which crystallized from acetone–light pet. as needles, m.p. 120–121° (Found: C, 70·7; H, 8·5. $C_{22}H_{32}O_5$ requires C, 71·1; H, 8·3%), ν_{max} 1741, 1728, 1658, 895 and 885 cm^{-1}.

Chromatography of the mother-liquors on alumina gave in the fraction eluted with 40% AcOEt–light pet. the nor-ketone (IX, R = O; 21 mg) described below.

(b) Under similar conditions the acetyl derivative (VIII, R = $COCH_3$; R′ = O) gave *methyl* 7β-*acetoxy*-6,16-*dioxo*-17-*nor*-(−)-*kauran*-19-*oate* which crystallized from acetone–light pet. as needles, m.p. 174–175° (Found: C, 67·6; H, 7·7. $C_{22}H_{30}O_6$ requires C, 67·7; H, 7·7%), ν_{max} 1753, 1745, 1729 and 1721 cm^{-1}.

Preparation of the toluene-p-*sulphonates of the diols* (VIII, R = H; R′ = CH_3) and (VIII, R = H; R′ = O). The diol (VIII, R = H; R′ = CH_3) (750 mg) in dry pyridine (10 ml) was treated with toluene-*p*-sulphonyl chloride (1·1 g) for 2 days, at room temp. The soln was poured into dil. HCl and the organic material removed in ether. Chromatography on alumina gave the 7β-*toluene*-p-*sulphonate* of methyl 6α,7β-dihydroxy-(−)-kaur-16-en-19-oate which crystallized from light pet. as needles (720 mg), m.p. 144–145° (Found: C, 67·0; H, 7·3. $C_{28}H_{38}O_6S$ requires C, 67·2; H, 7·25%), ν_{max} 3400, 1690, 1655, 1600 cm^{-1}. The 7α-*toluene*-p-*sulphonate* of methyl 6α,7α-dihydroxy-(−)-kaur-16-en-19-oate prepared similarly had m.p. 190–192° (Found: C, 67·2; H, 7·4. $C_{28}H_{38}O_6$ requires C, 67·2; H, 7·25), ν_{max} 3410, 1695, 1654, 1590, 890 cm^{-1}.

Oxidation of the 6α-*hydroxy*-7α-*monotoluene*-p-*sulphonate*. The toluene-*p*-sulphonate (280 mg) in acetone (5 ml) was treated with the 8N CrO_3 reagent (0·25 ml) at room temp overnight. MeOH was added, the soln concentrated, diluted with water, extracted with AcOEt and the extract washed with $NaHCO_3$aq, water and dried. The solvent was evaporated and the residue chromatographed on alumina. Elution with 25% AcOEt in light pet. gave the *toluene*-p-*sulphonate* of methyl 7α-hydroxy-6-oxo-(−)-kaur-16-en-19-oate (45 mg) which crystallized from acetone–light pet. as thick needles m.p. 165–166° (Found: C, 67·7; H, 7·4. $C_{28}H_{36}O_6S$ requires C, 67·45; H, 6·9%), ν_{max} 1738, 1719, 1662, 1600 and 894 cm^{-1}.

Elution with 7·5% AcOEt in light pet. gave the *toluene*-p-*sulphonate* of methyl 7α-hydroxy-6,16-dioxo-17-nor-(−)-kauren-19-oate (109 mg) which crystallized from acetone–light pet. as needles, m.p. 194–195° (Found: C, 64·3; H, 6·9. $C_{27}H_{32}O_7S$ requires C, 64·8; H, 6·4%), ν_{max} 1747, 1722 and 1601 cm^{-1}.

Reduction of the acetate (VII; R = $COCH_3$, R′ = CH_3) *with* LAH. The acetate (54 mg) and LAH (73 mg) in ether (10 ml) were heated under reflux for 5·5 hr. Moist ether and dil. HCl were

cautiously added and the organic material recovered in ether to give 6α,7β,19-trihydroxy-(−)-kaur-16-ene (21 mg) which crystallized slowly from acetone–light pet. as needles, m.p. 207–209°, identified by the IR spectrum.[8]

Pyrolysis of the ester (V). The ester (30 mg) was heated on a metal block at 220° for 0·5 hr. The residue was extracted with acetone. On crystallization from acetone–light pet. it gave 6α-*hydroxy*-(−)-*kaur*-16-*en*-19-*oic acid* 19 → 6α-lactone (VII; 10 mg) m.p. 204–205° $[\alpha]_D^{20}$ −32° (*c*, 0·5 in EtOH) (Found: C, 79·5; H, 9·3 $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%), ν_{max} 1754, 1655 and 880 cm^{-1}.

Ozonolysis of methyl 6α-*hydroxy*-(−)-*kaur*-16-*en*-19-*oate* (V). A stream of ozonized oxygen (13–15 mg/min) was passed through a soln of the hydroxy ester (210 mg) in glacial AcOH (10 ml) for 5 min. After being left for 1 hr, the acetic acid was neutralized with $NaHCO_3$aq and the organic material recovered in ether. The residue crystallized from acetone–light pet. as needles, (195 mg) of *methyl* 6α-*hydroxy*-16-*oxo*-(−)-17-*norkauran*-19-*oate* m.p. 172–174° (Found: C, 71·6; H, 9·0. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%), ν_{max} 3406, 1735, and 1693 cm^{-1}.

Pyrolysis of the above ester. The nor-ketone (35 mg) from the above experiment was heated in a Pyrex tube at 250° for 0·75 hr. The residue was extracted with acetone and crystallized from acetone–light pet. to give needles (12 mg) of 6α-*hydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oic acid* 19 → 6α *lactone* m.p. 264–265° (Found: C, 74·9; H, 8·8. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·6%), ν_{max} 1755 and 1737 cm^{-1}.

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