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THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—VIII[1]

THE STEREOCHEMISTRY OF ATRACTYLANIC ACID

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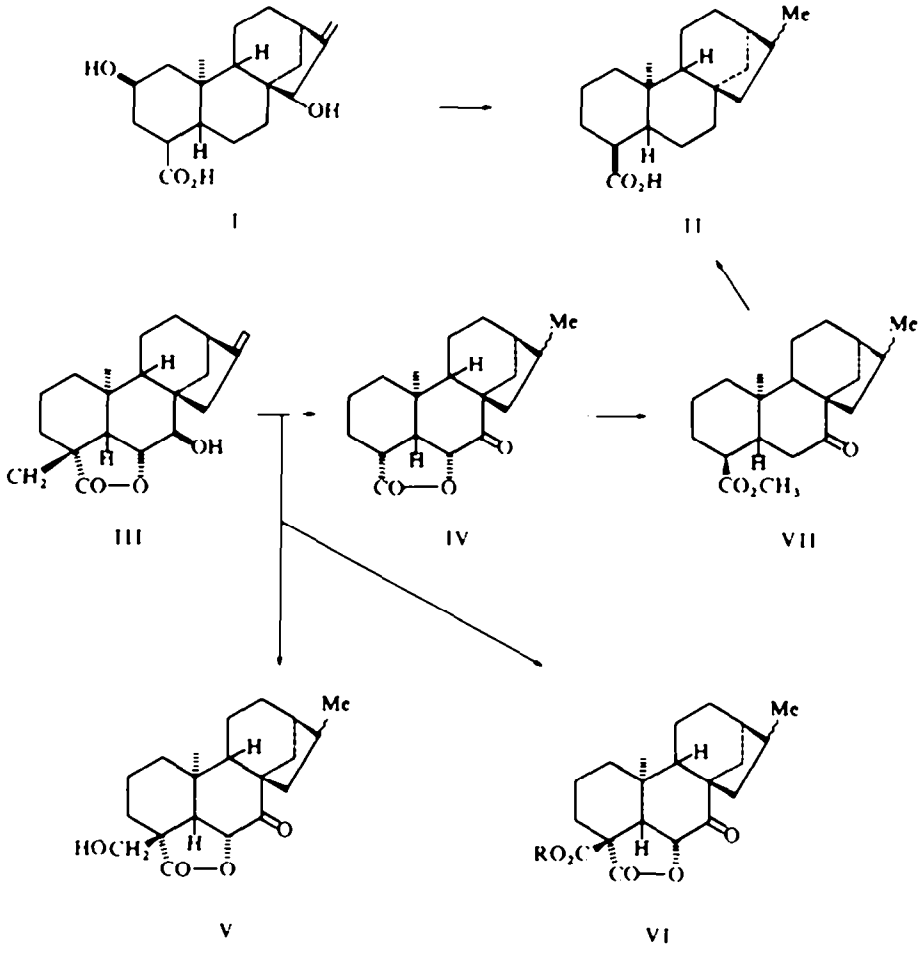
Abstract The stereochemistry of atractylanic acid particularly at C-9, is confirmed by a partial synthesis from 7,18-dihydroxykaurenolide

ATRACTYLIGENIN has been assigned the kauranoid stereochemistry (I).[2] At the outset of this work there was no link between atractyligenin and another member of the tetracyclic diterpenes. Such a link would be of value since the stereochemical evidence for atractyligenin whilst clearly defining an antipodal A/B ring fusion and a β-oriented ring D, is less secure with respect to C-9. Indeed the main evidence for the kauranoid *cis*-relationship of ring D and the C-9 hydrogen atom is the negative Cotton effect of a C-15 ketone. However C-15-ketones in both the (+)-phyllocladene and (−)-kaurene series (where ring D is β-oriented) show[3] negative Cotton effects. Although a 9β-hydrogen atom and 10α-methyl group are more reasonable on biogenetic grounds, a correlation with the kaurenolides which are of proven stereochemistry at C-9,[4] seemed desirable.

Atractylanic acid (II) has been formulated[2] as (−)-19-norkauran-18-oic acid. It was derived from atractyligenin by a sequence which precluded epimerization at any of the ring junctions and was assigned an equatorial carboxyl group at C-4. We now describe its partial synthesis from 7:18-dihydroxykaurenolide (III)[5] utilizing a similar route to that described earlier[6] for the preparation of (−)-kaur-16-en-19-oic acid from 7-hydroxykaurenolide.

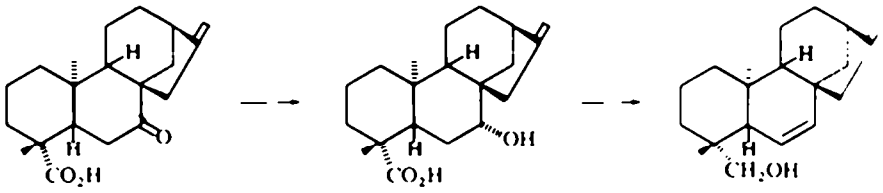
Hydrogenation of the kaurenolide gave the corresponding dihydro derivative. Oxidation with chromium trioxide which was accompanied by decarboxylation, led to the 18-nor-7-ketokauranolide (IV).[7] This was accompanied by a compound, $C_{20}H_{28}O_4$. The IR spectrum [ν_{max} 3210, 1753 and 1710 cm^{-1}] enabled the oxygen functions to be accounted for as hydroxyl, γ-lactone and ketone. The presence of a primary alcohol in this product was established by the NMR spectrum which showed a 2-proton resonance at τ 6·35. Hence it was assigned structure V. The keto-acid VI (R = H) was also isolated as its more stable methyl ester VI (R = Me). Hydrogenolysis of the keto-lactone IV with calcium in liquid ammonia followed by methylation with diazomethane gave the keto-ester VII. The identity of the 5:6 coupling constant (J = 6·0 c/s) with that of other kaurenolides of known stereochemistry[7] implied that the lactone IV retained the diaxial 19 → 6α-lactone ring. On the other hand the ester VII is formulated as the equatorial isomer since it was not epimerized by base.[2] Epimerization presumably occurred under the strongly



basic hydrogenolysis conditions. Wolff-Kishner reduction of the 7-ketone, although capricious, gave the required carboxylic acid II which was identical with a sample of atractylanic acid generously provided by Professor Piozzi and thus confirming the stereochemistry of atractyligenin at C-9.

(−)-Kaur-16-en-19-oic acid was required for biosynthetic work. In view of the capricious nature of the Wolff-Kishner reduction an alternative method of removing the 7-oxygen function was attempted. The 7-keto-acid VIII was prepared as before. It was reduced with sodium borohydride to form the 7α-alcohol IX. This is assigned the α-stereochemistry by analogy with the reduction of the related kaurenolides[8] in which attack of the reagent occurs from the less hindered β-face of the molecule. Furthermore this isomer was isolated as a by-product from the calcium in liquid ammonia hydrogenolysis of the parent keto-lactone. These reduction conditions would be expected to give the more stable equatorial epimer. It differed from the β-isomer which has been isolated from an *Echinocystis* extract.[9]

Conversion to the toluene-*p*-sulphonate with toluene-*p*-sulphonyl chloride in pyridine was slow. However vigorous reduction of the product with LAH gave an unsaturated alcohol. Its NMR spectrum included resonances assigned to the



VIII IX X

terminal methylene (τ 5·16) and a pair of doublets (τ 4·17 and 4·60; J = 10 c/s) assigned to a 6:7-olefin. It also contained a 2-proton hydroxymethyl resonance at τ 6·32. Hence the structure X was assigned to the alcohol. Elimination of the tosylate rather than reduction had occurred in its formation.

EXPERIMENTAL

General details are described in part I.[10]

Oxidation of 7,18-dihydroxykauranolide[7]

The kauranolide (1·47 g) in acetone (30 ml) was treated with the 8N CrO_3 reagent (2 ml) for 2 hr. MeOH was added, the soln concentrated, diluted with water (100 ml) and refluxed for 20 min. The product was recovered in AcOEt and separated into acidic (0·22 g) and neutral (1·19 g) fractions with $NaHCO_3$aq. Chromatography of the neutral fraction on silica gel and elution with 20% AcOEt–light petroleum gave the keto-lactone IV (270 mg). This compound was polymorphic crystallizing as prisms m.p. 162–163° or needles m.p. 206–208°, from AcOEt–light petroleum. Both forms showed identical solution spectra (IR and NMR). Further elution with 40% AcOEt–light petroleum gave the *hydroxy-ketolactone* V (567 mg) which crystallized from acetone light petroleum as needles, m.p. 237–240°. (Found: C, 72·8; H, 8·5. $C_{20}H_{28}O_4$ requires: C, 72·3; H, 8·5%); ν_{max} 3210, 1753, 1710 cm^{-1} τ 9·34, 9·03 (doublet, J = 6 c/s) 6·35, 5·06 (doublet, J = 6 c/s).

The acidic fraction was methylated with ethereal CH_2N_2 to give the *methyl ester* VI (R = Me) which crystallized from MeOH as prisms, m.p. 215°. (Found: C, 70·8; H, 7·8. $C_{21}H_{28}O_5$ requires: C, 70·0; H, 7·9%); ν_{max} 1775, 1713 (br) cm^{-1}.

Hydrogenolysis of the keto-lactone IV

Ca metal (2 g) was dissolved in liq. NH_3 (300 ml). The keto-lactone (1·13 g) was added and the soln refluxed for 4 hr. NH_4Cl (20 g) was added and the NH_3 evaporated. Water and dil HCl were added and the product recovered in AcOEt. The crude acid (1·1 g) was methylated with ethereal CH_2N_2. The *methyl ester* VII crystallized from light petroleum as needles, m.p. 132–135°. (Found: C, 75·6; H, 9·3. $C_{20}H_{30}O_3$ requires: C, 75·4; H, 9·5%); ν_{max} 1730 (br) cm^{-1} τ 9·12, 9·02 (J = 6 c/s), 6·4. The ester was recovered unchanged after standing with methanolic N KOH overnight.

Wolff-Kishner reduction of the ester VII

The methyl ester (300 mg) in dry diglyme (12 ml) and $N_2H_4 \cdot H_2O$ (2·1 ml) were stood overnight at room temp. The temp was raised to 150° for 5 hr and then refluxed for 3 hr. KOH pellets (2·5 g) were added and the soln heated at 235° for 8 hr. The soln was acidified and the product recovered in AcOEt. Chromatography on silica gel gave the carboxylic acid II (200 mg) which crystallized from AcOEt as needles, m.p. 190°. (Found: C, 78·8; H, 10·1. Calc. for $C_{19}H_{30}O_2$: C, 78·6; H, 10·4%) This showed an identical IR with a sample of atractylanic acid (m.p. 194°) provided by Professor Piozzi. The mixed m.p. was undepressed.

The methyl ester prepared with CH_2N_2 crystallized from MeOH as needles, m.p. 101° (lit. 60°). (Found: C, 79·2; H, 10·4. Calc. for $C_{20}H_{32}O_2$: C, 78·9; H, 10·6%.)

Reduction of the keto-acid VIII

The keto-acid[6] (100 mg) in MeOH THF (1:1; 3 ml) was treated with $NaBH_4$ (100 mg) for 90 min. The soln was concentrated, acidified with dil HCl and the product recovered in ether. Chromatography on silica gel gave the *7α-hydroxy-acid* IX (70 mg) which crystallized from AcOEt light petroleum as needles, m.p. 238°. (Found: C, 75·75; H, 9·4. $C_{20}H_{30}O_3$ requires: C, 75·4, H, 9·5%); ν_{max} 3450, 1695, 885 cm^{-1}. The *toluene-p-sulphonate* prepared with toluene-*p*-sulphonyl chloride crystallized from acetone–light petroleum as needles m.p. 150–152°; ν_{max} 1693, 1602, 886 cm^{-1} τ 9·15, 9·03, 7·65, 5·77, 5·32, 2·73, 2·24.

Reduction of the toluene-p-sulphonate

The above toluene-*p*-sulphonate (260 mg) in ether (100 ml) was heated under reflux with LAH (750 mg) for 12 hr. The soln was cautiously acidified and the product recovered in ether and chromatographed on silica. Elution with 5% AcOEt–light petroleum gave *kaur-6,16-dien-19-ol* (X) which crystallized from acetone: light petroleum as needles, m.p. 120–123°. (Found: C, 83·4; H, 10·9. $C_{20}H_{30}O$ requires: C, 83·9; H, 10·5%); ν_{max} 3400, 1660, 894 cm^{-1}.

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REFERENCES

[1] Previous part, J. R. Hanson and A. F. White, *Tetrahedron* **24**, 2527 (1968).
[2] F. Piozzi, A. Quilico, R. Mondelli, T. Ajello, V. Sprio and A. Melera, *Ibid.* Suppl. **8**, 515 (1966).
[3] R. Henderson and R. Hodges, *Ibid.* **11**, 226 (1960).
[4] B. E. Cross, R. H. B. Galt, J. R. Hanson and W. Klyne, *Tetrahedron Letters* 145 (1962).
[5] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 3783 (1963).
[6] R. H. B. Galt and J. R. Hanson, *Tetrahedron* **22**, 3185 (1966).
[7] J. R. Hanson, *Ibid.* **22**, 1701 (1966).
[8] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 2944 (1963).
[9] Professor C. A. West (private communication).
[10] J. R. Hanson, *Tetrahedron* **22**, 1453 (1966).