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DITERPENOID TOTAL SYNTHESIS—V*

C-14 EPIMER OF (±)-7-DESOXOCASSAMIC ACID

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Abstract—The total synthesis of the title compound and its derivatives is described. The stereochemistry at C-14 of cassamic acid is briefly discussed.

CASSAMIC acid (I) is one of the diterpene acids obtained by hydrolysis of the total alkaloids from *Erythropleum guineense* barks. Its structure and stereochemistry together with those of its congeners were investigated by several workers.[1,2] Decisive evidence favouring the stereochemistry depicted in I for cassamic acid has recently been reported.[3] Thus Hauth *et al.* established the stereochemistry of cassain as II from the analysis of detailed NMR data.[3] Since cassamic acid has been chemically related to cassain (II) by Arya and Engel[2] it should be represented by I. At the beginning of the present work, the stereochemistry at C-18 was unknown and that at C-14 was ambiguous. Mathieson *et al.* favoured β-equatorial configuration for the C-14 methyl group[1] while the opposite was supported by Turner *et al.*[4] Therefore, it was decided to synthesize a racemic acid (IIIb) with the structure assigned to 7-desoxocassamic acid (IV) by Mathieson *et al.*[1,†] but now known to be its C-14 epimer. This paper describes the synthesis of IIIb‡ its dihydro derivative (VIIb) and two degradation products of cassamic acid in their racemic modifications.

Reductive methylation[6] of (±)-7-oxopodocarp-8-en-16-oic acid (V)[5] employing methyl iodide and lithium in liquid ammonia afforded an acid (VIa), m.p. 205–206°, in 47% yield. This was esterified to give methyl (±)-7-oxo-8β-methylpodocarpan-16-oate (VIb), m.p. 126–127°. The assigned β-equatorial configuration of the C-14 methyl group was supported by the fact that VIb was regenerated by base-catalysed equilibration. Since the reaction products of reductive alkylation were in many cases contaminated with the corresponding simple reduction products,[6] lithium-ammonia reduction[7] of the unsaturated keto acid (V) was tried to obtain a reference podocarpanone. Although the keto acid (IXa) could not be crystallized, the corresponding crystalline methyl ester, methyl (±)-7-oxopodocarpan-16-oate (IXb), m.p. 135–136°, was clearly different from the methylated ester (VIb).

The next stage was the application of the recently developed olefin synthesis with

* Part IV, K. Mori and M. Matsui, *Tetrahedron Letters* No. 2, 175 (1966).

† The stereochemistry at C-18 was unknown at that time.

‡ Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate in every case unless otherwise specified. Nomenclature used here for cassamic acid relatives is that of the English workers.[1] For podocarpanoids Klyne's nomenclature, *J. Chem. Soc.* 3072 (1953) is used.

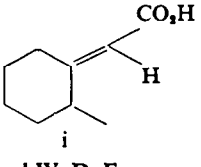
[1] G. T. Chapman, B. Jacques, D. W. Mathieson and V. P. Arya, *J. Chem. Soc.* 4010 (1963).
[2] V. P. Arya and B. G. Engel, *Helv. Chim. Acta* **44**, 1650 (1961).
[3] H. Hauth, D. Stauffacher, P. Niklaus and A. Melera, *Helv. Chim. Acta* **48**, 1087 (1965).
[4] R. B. Turner, E. G. Herzog, R. B. Morin and A. Riebel, *Tetrahedron Letters* No. 2, 7 (1959).
[5] K. Mori and M. Matsui, *Tetrahedron* **22**, 879 (1966).
[6] G. Stork, P. Rosen, N. Goldman, R. V. Coombs and J. Tsuji, *J. Amer. Chem. Soc.* **87**, 275 (1965).
[7] G. Stork and S. D. Darling, *J. Amer. Chem. Soc.* **86**, 1716 (1964).

a phosphonate carbanion.[8] Treatment of the keto ester (VIb) in tetrahydrofuran with diethyl carbomethoxymethylphosphonate and sodium hydride afforded the C-14 epimer of methyl (±)-7-desoxocassamate (IIIa) as an oil which was separated from the unchanged keto ester (VIb) by chromatography over alumina. Alkaline hydrolysis of the methyl ester (IIIa) gave a crystalline acid (IIIb), m.p. 199–200°. Assignment of the stereochemistry at C-18 of this acid as depicted in the formula (IIIb) was based on the assumption that the C-14 methyl group effectively controlled the steric course of the olefin synthesis.* The steric effect exerted by the C-14 methyl is such that some starting material could be recovered even after a prolonged reaction period and a large excess of phosphonate carbanion. As neither an authenic sample nor the IR spectrum of 7-desoxocassamic acid was available, a direct comparison of the synthetic IIIb with the natural product could not be made. Later it became clear that the synthetic acid is the C-14 epimer of (±)-7-desoxocassamic acid.

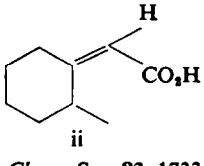
Catalytic hydrogenation of the oily unsaturated ester (IIIa) over Adams' platinum oxide afforded an oily ester (VIIa). This was treated with methanolic sodium hydroxide to give an acid (VIIb), m.p. 127–129°. The IR spectrum (in CCl_4) of this acid (VIIb) was almost superimposable on that of 7-desoxodihydrocassamic acid but careful comparison revealed a slight difference between them in 1130 cm^{-1} region. Since the stereochemistry at C-14 of the synthesized acid (VIIb) is β-equatorial, this spectral evidence implies that the correct structure of 7-desoxodihydrocassamic acid is not VIIb but VIII. In other words, the C-14 methyl group of cassamic acid is α-axial.†

* cf. Ref. 3.

† (1) Our synthetic isomer of 7-desoxocassamic acid has structure IIIb as discussed in the text. This means that the stereochemistry at C-18 of the synthetic acid is the same as that of the natural product as evidenced by Hauth *et al.*,[3] who prepared two model compounds, (i) and (ii), and compared their NMR spectra with that of a cassain derivative. The acid (i) was obtained from 2-methylcyclohexanone as the major product of a reaction with diethyl carbethoxymethylphosphonate—the same reaction which enabled us to prepare IIIb—and was shown to possess the same stereochemistry at C-18 as that of the natural product.[3] (2) Mathieson *et al.* employed Adams' platinum oxide in ethanol for the hydrogenation of the double bond in 7-desoxocassamic acid.[1] We also employed this catalyst and solvent and could, therefore, expect similar stereochemical results. (±)-7-Desoxodihydrocassamic acid could only be obtained if 7-desoxocassamic acid had the structure IIIb with β-equatorial C-14 methyl, but the product was not identical with the natural dihydro derivative. This implies that our acid with structure IIIb was not (±)-7-desoxocassamic acid but its C-14 epimer. (3) It is also possible that the synthesized acid (VIIb) possesses its two-carbon side chain at C-13 in the opposite configuration to that of the degradation product (VIII) in addition to the opposite stereochemistry at C-14. This does not affect our argument on C-14 stereochemistry, since the different stereochemical course during the hydrogenation was entirely due to the different stereochemistry at C-14 of the synthetic unsaturated acid (IIIb). If the stereoselectivity of the catalytic hydrogenation is reproducible, which seems to be a sound premise, non-identity of the synthetic and natural dihydro compound implies that they are isomeric at C-14 irrespective of the stereochemistry at C-13. The only way to settle this problem is to compare our synthetic acid (IIIb) with 7-desoxocassamic acid which is not available.



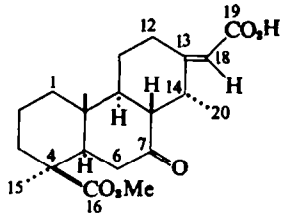
i



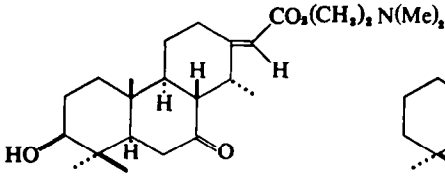
ii

[8] W. S. Wadsworth, Jr. and W. D. Emmons, *J. Amer. Chem. Soc.* **83**, 1733 (1961).

Formula IIIb assigned by the English workers to 7-desoxocassamic acid was based on the stereochemistry of its ozonolysis product (VIb) determined by ORD measurements.[1] Since our synthetic (±)-keto ester with stereochemistry VIb has an identical IR spectrum (in CCl_4) with that of the natural degradation product, epimerization at C-14 must take place during the ozonolysis of 7-desoxocassamic acid (IV).* In order to confirm this, the (±)-keto ester (VIb) was treated with ethanedithiol and boron trifluoride etherate to give a thioketal (Xa), m.p. 156–157°. This was



I



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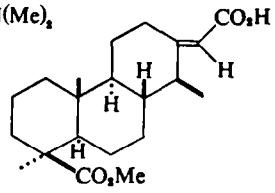
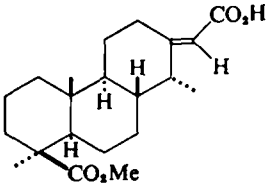
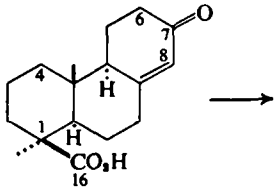


IIIb



IV



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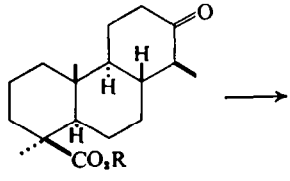
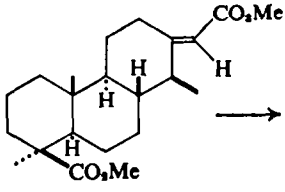
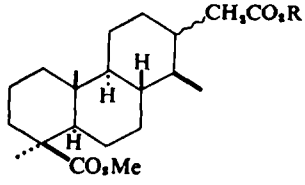


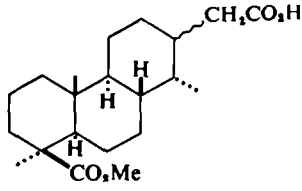
VIa R = H
b R = Me



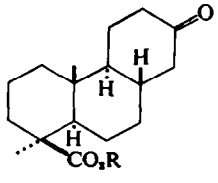
IIIa



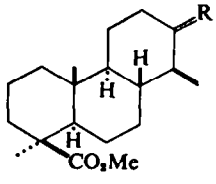
VIIa R = Me
b R = H

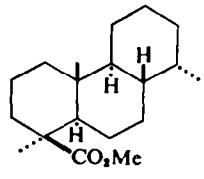


VIII

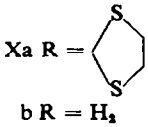


IXa R = H
b R = Me





XI

Xa R = 

b R = H_2

* Dr. Mathieson told in his private communication to one of us (K. M.) (11th November 1965) that he had realized prior to our work that epimerization at C-14 had taken place.

treated with Raney nickel in dioxan to yield methyl (±)-8β-methylpodocarpan-16-oate (Xb), m.p. 75–76°. Its IR spectrum (in CCl_4) was superimposable on that of a degradation product obtained by the Clemmensen reduction of the ozonolysis product of cassamic acid (I). The identity was also proved by gas chromatography. This clearly showed that epimerization at C-14 took place in this case, too. An incorrect structure (XI) with an α-axial C-14 methyl group had formerly been assigned to this degradation product, although the epimerization at C-14 during the ozonolysis of cassamic acid had correctly been recognized.[1]

In conclusion the α and axial stereochemistry at C-14 of cassamic acid and its congeners was indirectly supported by this synthetic work.

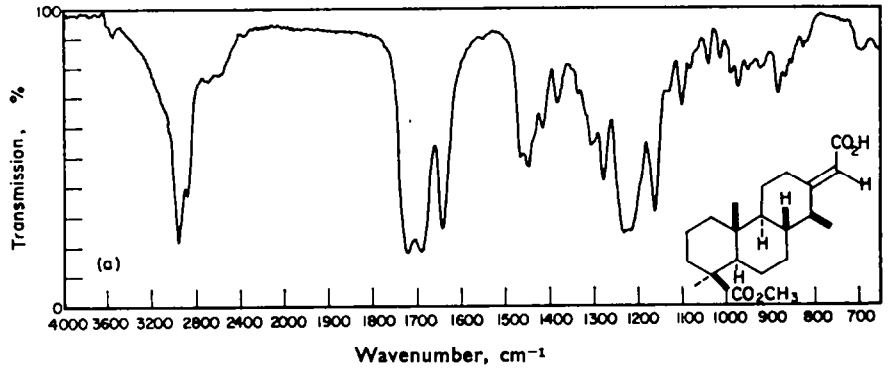


FIG. 1. IR spectrum (in CCl_4) of C-14 epimer of (±)-7-desoxocassamic acid (IIIb).

EXPERIMENTAL

All m.ps. are uncorrected. Pet. ether refers to the fraction, b.p. 30–50°.

(±)-7-*Oxo*-8β-*methylpodocarpan*-16-*oic acid* (VIa). To a stirred solution of Li (0·25 g) in liquid ammonia (150 ml), V, (3·0 g) in dry tetrahydrofuran (80 ml) was added with external cooling by a Dry ice–acetone bath. An additional small amount of Li (about 0·1 g) was added and the resulting blue solution stirred for 45 min. MeI (10 g) in dry tetrahydrofuran (20 ml) was then added dropwise. The medium turned white and stirring was continued for 30 min. The ammonia was allowed to evaporate overnight at room temp. Water (50 ml) was added and the mixture concentrated *in vacuo* to remove tetrahydrofuran. After acidification with HCl, the product was extracted with AcOEt. The extract was washed with water followed with saturated brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with AcOEt to give 1·5 g (47%) of VIa. The oily mother liquor weighed 1·25 g. The acid (VIa) separated from AcOEt–pet. ether as needles, m.p. 205–206°, ν_{max} (Nujol), 2600, 1710, 1695, 1252, 940 cm^{-1}. (Found: C, 74·55; H, 9·59. $C_{18}H_{30}O_3$ requires: C, 73·93; H, 9·65%.)

Methyl (±)-7-*oxo*-8β-*methylpodocarpan*-16-*oate* (VIb). The keto acid (VIa, 1·4 g) suspended in AcOEt (10 ml) was esterified with ethereal diazomethane yielding elongated prisms from AcOEt, m.p. 127–127°, ν_{max} (Nujol) 1728, 1712, 1230, 1163; (in CCl_4) 1728, 1718, 1154 cm^{-1}. The IR spectrum was superimposable on that of the natural degradation product; δ (60 Mc, in CCl_4, tetramethylsilane as internal standard), 0·63 (3H singlet), 0·89, 0·99 (3H doublet, J = 7 c/s), 1·15 (3H singlet), 3·55 (3H singlet) ppm. (Found: C, 74·29; H, 9·86. $C_{19}H_{30}O_3$ requires: C, 74·47; H, 9·87%.)

Attempted epimerization at C-14 *of the keto ester* (VIb). The keto ester (VIb, 50 mg) in MeOH (10 ml) was refluxed with MeONa (from 100 mg Na) for 1 hr. Then MeOH was removed *in vacuo*, the residue diluted with water and extracted with ether. The extract was washed with water and dried over Na_2SO_4. After evaporation of the ether, the unchanged VIb (45 mg) was recovered and identified by its IR spectrum and mixed m.p.

(±)-7-*Oxopodocarpan*-16-*oic acid* (IXa). Compound V, (0·3 g) in tetrahydrofuran (20 ml) was added to a stirred solution of Li (0·3 g) in liquid ammonia (50 ml). The blue solution was stirred for 30 min, abs EtOH (10 ml) added and the ammonia allowed to evaporate at room temp. The reaction mixture was diluted with water and concentrated *in vacuo* to remove tetrahydrofuran and EtOH. The aqueous solution was acidified with HCl and extracted with AcOEt. The extract was concentrated *in vacuo* and the residue in acetone (5 ml) oxidized with Jones' chromic acid reagent[9] (0·5 ml) for 10 min at room temp. The reaction mixture was diluted with water, extracted with AcOEt and worked up as usual to afford a gummy acid (IXa, 250 mg), ν_{max} (film) 1720, 1700 cm^{-1}.

Methyl (±)-7-*oxopodocarpan*-16-*oate* (IXb). The keto acid was esterified with excess ethereal diazomethane yielding IXb which crystallized from ether–pet. ether as leaflets, m.p. 135–136°, ν_{max} (Nujol) 1720, 1234, 1170, 1154, 1094 cm^{-1}. (Found: C, 74·55; H, 9·78. $C_{18}H_{28}O_3$ requires: C, 73·93; H, 9·65%.)

C-14 *Epimer of methyl* (±)-7-*desoxocassamate* (IIIa). Diethyl carbomethoxymethyl phosphonate (6·3 g, 30 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise to a stirred suspension of NaH (50% NaH in mineral oil, 1·8 g and the the mineral oil removed by washing with dry tetrahydrofuran) in dry tetrahydrofuran (20 ml) at 5–10°. The stirred mixture was kept at this temp for 30 min and then allowed to warm up to the room temp within 30 min. To the resulting gelatinous mixture, VIb (1·2 g, 4 mmoles) in dry tetrahydrofuran (20 ml) was added and the mixture stirred for an additional hr and the excess of phosphonate carbanion decomposed by adding cyclopentanone. After 1 hr, water was added to the reaction mixture, the organic layer separated, washed with water and dried over Na_2SO_4. The extract was concentrated *in vacuo* to remove tetrahydrofuran and methyl cyclopentylidene-acetate. The residue (1·5g) in ether (5ml) was chromatographed over alumina (25 × 1·6cm) in pet. ether to afford the following fractions (250 ml each). No. 1 (pet. ether), 250 mg, oil; No. 2 (pet. ether–ether, 20:1), 200 mg, oil; No. 3 (pet. ether–ether, 10:1), 430 mg, oil. These fractions yielded C-14 epimer of IIIa (880 mg, 63% yield, ν_{max} (film), 1735, 1650, 1160 cm^{-1}) contaminated with a small amount of VIb. Fractions No. 4–6 (pet. ether–ether, 10:1), yielded 400 mg which proved to be recovered VIb. Fractions 7 and 8 afforded a gum (100 mg). The diester (IIIa) was employed for the next step without further purification.

C-14 *Epimer of* (±)-7-*desoxocassamic acid* (IIIb). To IIIa (680 mg = fractions 1 and 3) in MeOH (20 ml) NaOH (1·8 g) in water (2 ml) was added. The mixture was refluxed for 3·5 hr and the resulting solution concentrated *in vacuo* leaving a residue which after addition of water was extracted with ether to remove the neutral fraction. The aqueous layer was acidified with HCl and extracted with ether. The ether layer was washed with saturated brine and dried over Na_2SO_4. Removal of the solvent gave 300 mg (43%) of crystalline IIIb which crystallized as needles from AcOEt–pet. ether, m.p. 199–200° (previous softening at 182°), ν_{max} (Nujol) 1726, 1685, 1638, 1240, 1160; (CCl_4) 1730, 1688, 1640, 1240, 1155 cm^{-1}. (Found: 72·06; H, 9·47. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26%.) The neutral fraction afforded VIb (80 mg).

A sterioisomer of dimethyl (±)-*cassane*-16,19-*dioate* (VIIa). IIIa (200 mg) in 99% EtOH (20 ml) was hydrogenated for 3 hr over Adams' PtO_2 (200 mg) at room temp under atm press. After filtering off the catalyst, EtOH was removed *in vacuo* leaving VIIa (200 mg, ν_{max} (film) 1738, 1160 cm^{-1}) as an oil used for the next step without purification.

A stereoisomer of (±)-7-*desoxodihydrocassamic acid* (16-*methyl hydrogen* (±)-*cassane*-16,19-*dioate*)(VIIb). To the hydrogenated VIIa (200 mg) in MeOH (10 ml) NaOH (1 g) in water (2 ml) was added and the mixture refluxed for 3 hr. The MeOH was removed *in vacuo* and the residue diluted with water. The aqueous solution was extracted with ether to remove neutral impurity. The aqueous layer was acidified with HCl and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford crystalline VIIb (150 mg, 76% yield. prisms from ether–pet. ether, m.p. 127–129°), ν_{max} (Nujol) 1725, 1705, 1160 cm^{-1}; (CCl_4) 1732, 1710, 1230, 1160 cm^{-1}. (Found: C, 71·70; H, 9·72. $C_{21}H_{34}O_4$ requires: C, 71·96; H, 9·78%.)

7-*Dithioethyleneketal of methyl* (±)-7-*oxo*-8β-*methylpodocarpan*-16-*oate* (Xa). To a solution of VIb (400 mg) in $CHCl_3$ (10 ml) ethanedithiol (0·5 ml) and BF_3-etherate (0·5 ml) was added and the mixture left overnight at room temp. The dark solution was poured into water and extracted with ether. The extract was washed with water and satutated brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 350 mg (70%) which crystallized in needles from MeOH, m.p. 156–157°, ν_{max} (Nujol)

[9] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953).

1726, 1152 cm^{-1}. (Found: C, 66·17; H, 9·12; S, 16·55; $C_{21}H_{34}O_3S_2$ requires C, 65·94; H, 8·96; S, 16·73%.)

Methyl (±)-8β-*methylpodocarpan*-16-*oate* (Xb). The above Xa (260 mg) in dioxan (30 ml) was boiled with Raney Ni W-7 (4 g) for 5 hr. Removal of the catalyst and solvent afforded an ester, 150 mg (75%) which crystallized as needles from MeOH m.p. 75–76°, ν_{max} (Nujol) 1726, 1155 (CCl_4) 1732, 1232, 1156 cm^{-1}. (Found: C, 77·96; H, 10·96. $C_{19}H_{32}O_2$ requires: C, 78·03; H, 11·03%). The IR spectrum was identical with that of the natural product. Gas chromatography; retention time, 8·3 min, Column: 1·0% SE-30 on Anachrom U (80 ~ 100 mesh) 180 cm × 4 mm i.d. Column temp 170°, N_2 flow rate 120 ml/min. The degradation product exhibited the same retention time as that of the synthesized compound.

Acknowledgment—We are indebted to Dr. D. W. Mathieson, School of Pharmacy, University of London, for kindly sending to us authentic samples of VIb and Xb and a copy of the IR spectrum of 7-desoxodihydrocassamic acid (VIII). Our thanks are also due to Dr. N. Ikekawa, Institute of Physical and Chemical Research, Tokyo, for gas chromatographic analysis.