

The Structure of Fissinolide and Angustidienolide, Limonoids from Species of Meliaceae

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A recent paper has proposed revising the structure of fissinolide from methyl 3 β -acetoxy-1-oxomeliac-8(14)-enate (1a) to methyl 3 β -acetoxy-1-oxomeliac-8-enate (2a). Reasons are now presented for preferring the original formula. With *N*-bromosuccinimide, fissinolide gives the conjugated dienes methyl 3 β -acetoxy-1-oxomeliac-8,14-dienate (5a) and angustidienolide. The latter is shown to be methyl 3 β -acetoxy-1-oxomeliac-8(30),14-dienate (6a).

FISSINOLIDE is a limonoid first isolated as a natural product by Zelnik and Rosito in 1966 from the seed of *Cedrela fissilis*,¹ and under the name of grandifoliolin, by Adesogan and Taylor from the seed of *Khaya grandifoliola*.^{2,3} It was earlier obtained by Connolly *et al.* by reduction and acetylation of mexicanolide.^{4,5} The related isobutyrate, isolated from *Khaya senegalensis*, has been described under the name of khayasin,^{6,7} and some other esters have also been described as natural products.⁸

All three groups assigned to fissinolide the structure of methyl 3 β -acetoxy-1-oxomeliac-8(14)-enate (1a) (for nomenclature see ref. 8). As basis for this, Zelnik and Rosito cited the partial synthesis from mexicanolide (1c) by borohydride reduction to the alcohol (1b) followed by acetylation; while we used the transformation by methanolic sulphuric acid into the ether-ester (3a), which had been related to the corresponding iodoacetate (3d).⁷ The structure of (3d) was known from *X*-ray crystallography.⁹ Basic hydrolysis of fissinolide cannot be used to return to the alcohol (1b) as it leads to fragmentation of the molecule with the formation of the diene-lactone (4).^{5,7}

Swietenolide is the 6-hydroxy-derivative of the alcohol (1b). Its derivatives form a series parallel to those of fissinolide.^{10,11}

Recently, Lavie and his colleagues¹² have investigated the seed of the Brazilian *Cedrela angustifolia* and isolated fissinolide and two new compounds, angustidienolide and

2-hydroxyangustidienolide. They present evidence that angustidienolide has the structure (5a). Lavie *et al.* draw attention to the fact that angustidienolide and its 2-hydroxy-derivative and carapin (7c) and the related alcohol (7b) and acetate (7a), all of which have double bonds terminating at C-14, show 17-H resonating at δ ca. 5.2. In contrast, in related compounds known not to have double bonds terminating at C-14, such as swietenine (8e), 17-H resonates at δ ca. 5.6. Since mexicanolide shows a 17-H resonance at δ 5.3, while in fissinolide and the related alcohol it is at δ ca. 5.69, they deduce that the double bond is in different positions, and hence assign fissinolide and the related alcohol the structures (2a) and (2b). This new structure involves accepting a double bond shift in the borohydride reduction of mexicanolide, in the reverse oxidation of the alcohol to mexicanolide with chromic acid in acetone, and in the methanolysis of fissinolide to the ether-ester (3a). A similar revision would presumably apply to swietenolide, since the resonance shifts are parallel. Lavie also suggests that in view of the proposed revision of the structure, fissinolide should be renamed angustinolide.

In a preliminary communication, we have given reasons for rejecting this new name and structural revision.¹³

The anomaly of the resonance positions of 17-H pointed out by Lavie is certainly interesting. However,

⁷ E. K. Adesogan, C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor, *J. Chem. Soc. (C)*, 1966, 2127.

⁸ E. K. Adesogan and D. A. H. Taylor, *J. Chem. Soc. (C)*, 1968, 1974.

⁹ S. A. Adeoye and D. A. Bekoe, *Chem. Comm.*, 1965, 301.

¹⁰ T. Chakrabarty, J. D. Connolly, R. McCrindle, K. H. Overton, and J. P. Schwarz, *Tetrahedron*, 1968, **24**, 1503.

¹¹ J. D. Connolly, R. McCrindle, K. H. Overton, and W. A. C. Warnock, *Tetrahedron*, 1968, **24**, 1507.

¹² D. Lavie, E. C. Levy, C. M. Rosito, and R. Zelnik, *Tetrahedron*, 1970, **26**, 219.

¹³ D. A. H. Taylor, *Tetrahedron Letters*, 1970, 2797.

¹ R. Zelnik and C. M. Rosito, *Tetrahedron Letters*, 1966, 6441.

² E. K. Adesogan and D. A. H. Taylor, *Chem. Comm.*, 1967, 225.

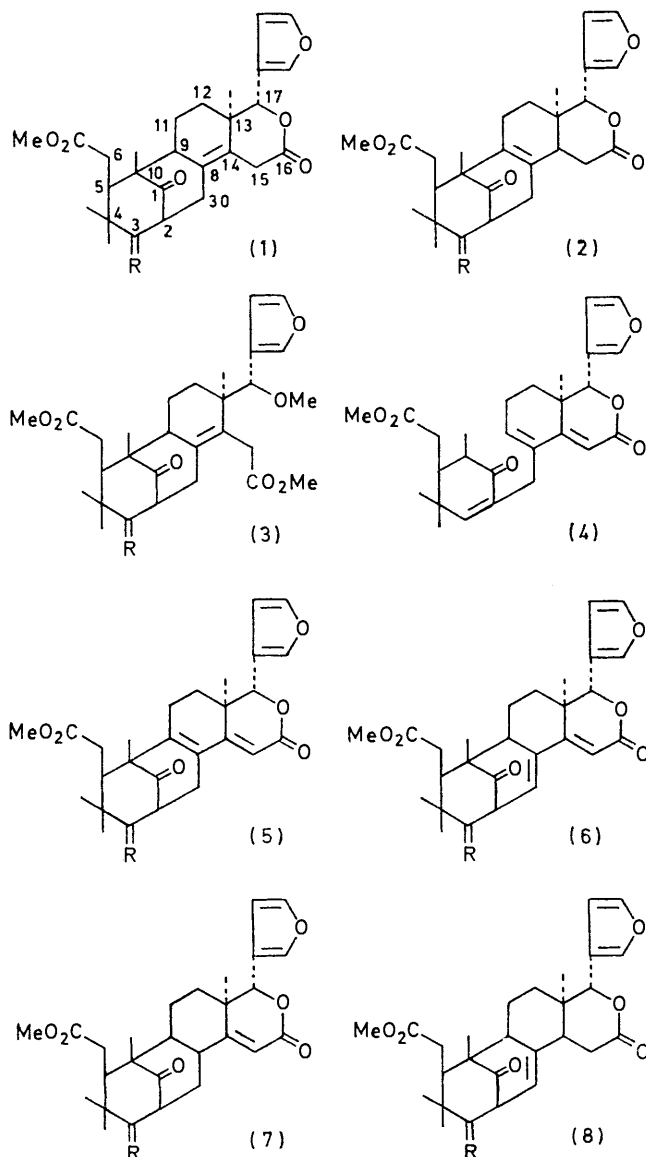
³ D. A. H. Taylor, *J. Chem. Soc. (C)*, 1970, 336.

⁴ J. D. Connolly, R. McCrindle, and K. H. Overton, *Chem. Comm.*, 1965, 162.

⁵ J. D. Connolly, R. McCrindle, and K. H. Overton, *Tetrahedron*, 1968, **24**, 1489.

⁶ E. K. Adesogan, C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor, *Chem. Comm.*, 1966, 27.

in ascribing it to anisotropic shielding of 17-H in mexicanolide by the 8(14)-double bond, and hence deducing the absence of a similar shielding in fissinolide, Lavie omits consideration of other possible shieldings. Fissinolide is a folded molecule, and we would suggest the possibility



- a; R = H, β -OAc
 b; R = H, β -OH
 c; R = O
 d; R = H, β -OCOCH₂I
 e; R = H, β -O-Tigloyl

of deshielding of 17-H by the 3 β -hydroxy- or -acetoxy-group, which in (1b) and (1a) are quite close to 17-H.

¹⁴ N. S. Ohochuku and D. A. H. Taylor, *J. Chem. Soc. (C)*, 1970, 421.

¹⁵ J. D. Connolly, R. McCrindle, and K. H. Overton, *Tetrahedron*, 1968, **24**, 1497.

¹⁶ J. D. Connolly, R. Henderson, R. McCrindle, K. H. Overton, and N. S. Bhacca, *J. Chem. Soc.*, 1965, 6935.

The observed shift of *ca.* 0.4 p.p.m. is comparable to that we have reported in similar cases.^{8,14}

A more reliable structural guide is the resonance position of 15-H₂, which in (1) are allylic, while in (2) they are not. In mexicanolide these two protons resonate at δ 3.47,¹⁵ in fissinolide at δ 3.58 and 3.68;³ the swietenolide derivatives are similar.¹¹ In compounds without an 8(14)-double bond, the resonance is, as expected, upfield; in swietenine (8e) and many derivatives at δ *ca.* 2.76,¹⁶ and in 2-hydroxydihydrofissinolide at δ 2.73 and 2.90.³ A small effect due to deshielding by the acetate is noticeable in the fissinolide derivatives, especially to one proton, presumably that on the β face.

It appears to us that the evidence summarised above is sufficient to prove the structure of fissinolide as (1a). However, we now wish to present some further considerations. In their paper¹² describing the isolation of angustidienolide, C₂₉H₃₄O₈, m.p. 248–254°, λ_{max} 282 nm (ϵ 8 \times 10³), Lavie and his colleagues stated that the n.m.r. spectrum, of which details were given, showed only one vinyl proton resonance, due to 15-H, at δ 6.24. Hydrolysis and oxidation of angustidienolide gave the corresponding ketone, supposed to be (5c), which had similar spectral properties.

Catalytic hydrogenation of angustidienolide gave fissinolide and a mixture which was not separated, but was said to contain the carapin derivative (7a), and a new compound identified as (1a). These were identified by n.m.r. spectroscopy of the mixture. Similarly, hydrogenation of the related ketone gave mexicanolide and, mostly, a new compound, m.p. 234–236°, which was identified as isomexicanolide (2c).

There seemed to us to be certain peculiar features about this work, notably the u.v. absorption maximum of angustidienolide. The extinction, 8 \times 10³, is far too weak for a transoid diene such as (5), which should be near 18 \times 10³, but might agree with a cisoid diene such as (6). The position of the maximum should be *ca.* 285 nm in both isomers.^{17–19}

In view of this we decided to re-investigate the chemistry of angustidienolide. Since we have not encountered it as a natural product, it was necessary to obtain it by partial synthesis. Fissinolide (1a) was treated with *N*-bromosuccinimide in boiling carbon tetrachloride under u.v. irradiation. Evolution of HBr was rapid, the main product crystallised readily, and was a new diene, isomeric with angustidienolide, m.p. 108° (loss of methanol of crystallisation), λ_{max} 285 nm (ϵ 1.8 \times 10⁴). The n.m.r. spectrum contained similar resonances to those described for angustidienolide, but in slightly different places. The new diene, dehydrofissinolide, was unstable to strong alkali, rapidly giving a bright red solution. Under sufficiently mild conditions it was hydrolysed to an amorphous alcohol which on

¹⁷ D. H. R. Barton, S. K. Pradhan, S. Sternhell, and J. F. Templeton, *J. Chem. Soc.*, 1961, 255.

¹⁸ J. C. Eck and E. W. Hollingsworth, *J. Amer. Chem. Soc.*, 1942, **64**, 140.

¹⁹ L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 17.

oxidation with chromic acid in acetone gave the corresponding ketone, dehydrocarapin, m.p. 238°, λ_{\max} 285 nm (ϵ 1.8×10^4). The properties of dehydrofissinolide correspond completely with those to be expected for methyl 3 β -acetoxy-1-oxomeliaca-8,14-dienate (5a).

Chromatography of the mother liquors gave the ether-ester (3a) and angustidienolide, identical with an authentic sample provided by Dr. R. Zelnik. Hydrolysis and oxidation of this then gave the corresponding alcohol and ketone. The properties of the alcohol correspond with those recorded,¹² but our sample of the ketone failed to crystallise. Examination of the n.m.r. spectrum of angustidienolide revealed a second vinyl proton resonance at δ 6.31, partly concealed by the resonance of 15-H. On the addition of a little hexadeuteriobenzene these resonances separated enough for the new one to be seen clearly upfield of that due to 15-H as a multiplet showing four lines (W 9 Hz).

The second vinyl proton must be at C-30 to give a conjugated diene lactone. This was confirmed by double resonance experiments. Irradiation of the 3-H resonance [δ 4.90 (d, J 9.5 Hz)] revealed that due to 2-H [δ 3.67 (m, more clearly seen after the addition of a little hexadeuteriobenzene)]. Irradiation of 2-H caused 3-H to collapse to a singlet, and the vinyl proton, which must therefore be 30-H, to a doublet (J_{2-30} 5.5 Hz). The third coupling of 2-H (1 Hz) and the second coupling of 30-H (3.5 Hz) are presumably both to 9-H.

This then proves that angustidienolide is methyl 3 β -acetoxy-1-oxomeliaca-8(30),14-dienate, as suggested by the u.v. absorption.

The hydrogenation product, 'isomexicanolide,' obtained from the ketone (6c) should then be the swietenine derivative (8c), and it was gratifying to note that its recorded properties corresponded with those of this compound. Repetition of the hydrogenation and comparison with an authentic sample⁸ confirmed the identity.

Since it is reported,¹² and we confirm, that the major hydrogenation product of angustidienolide (6a) is fissinolide, this confirms the structure of fissinolide as (1a). The isomer (2a) could not be produced in this way.

Compounds in the isomeric series (5) did not hydrogenate, and 'isomexicanolide' (2) and its derivatives remain unknown.

Further evidence supporting structure (1a) for fissinolide is provided by ¹³C n.m.r. spectroscopy. For this purpose proton noise as well as single frequency off-resonance decoupled spectra of both fissinolide and mexicanolide were recorded. Although a complete assignment of resonances with the aid of such arguments as residual splittings,²⁰ chemical shifts, and spectral comparison²¹ is not possible, the carbon atoms of interest could be designated. These comprise those α and β with respect to the olefinic carbon atoms, since it is known that upon introduction of a double bond into a six-membered

ring, the α -carbon atoms move upfield 1.8 p.p.m. and those β 4.2 p.p.m.²¹ The important resonances are therefore those due to C-9, -10, -11, -12, -13, -15, -30, and -17. From the multiplicity and magnitude of residual

Some ¹³C chemical shifts in fissinolide and mexicanolide

Carbon	Chemical shift *		Assignment criterion
	Fissin-olide	Mexican-olide	
9	40.85	40.19	Only high-field doublet, comparable chemical shift
10	52.90	54.27	Lowest field sp^3 carbon singlet in fissinolide
11	18.79	18.57	Highest field triplet, small residual splitting
12	29.24	28.84	Triplet, small residual splitting
13	38.10 or 38.22	37.99	Singlet, comparable chemical shift
15	33.40	32.93	Triplet, large residual splitting
17	80.63	80.63	Low-field, sp^3 carbon doublet
30	33.40	36.40	Triplet, large residual splitting

* In p.p.m. relative to internal tetramethylsilane.

splittings,²⁰ as well as empirical chemical shift increments,^{22,23} the resonances of these carbons could be assigned as listed in the Table. From this it can be seen that all carbons except two (C-10, -30) exhibit chemical shifts deviating by less than 1 p.p.m. in the two species. The larger deviations observed for C-10 and -30 is due to their close steric proximity to C-3, bearing a different substituent in the two compounds. If in fissinolide the double bond were between positions 8 and 9, the C-11 resonance should significantly move downfield, while a corresponding upfield shift would be expected for C-13. This, however, is obviously not the case.

EXPERIMENTAL

Dehydrogenation of fissinolide.—Fissinolide (1a) (5 g) and *N*-bromosuccinimide (2 g) were irradiated (260 nm) in boiling carbon tetrachloride (500 ml). After refluxing 5 min, the solution was concentrated to small bulk and washed with water. The organic layer was evaporated to dryness and the residue crystallised from methanol to give methyl 3 β -acetoxy-1-oxomeliaca-8,14-dienate (5a) (2.55 g) as prisms, m.p. 108° (decomp.) (Found: C, 66.0; H, 7.1. $C_{29}H_{34}O_8 \cdot CH_3OH$ requires C, 66.4; H, 7.1%), M^+ 510, $[\alpha]_D^{25} +212^\circ$, λ_{\max} (MeOH) 212 and 285 nm (ϵ 9×10^3 and 1.8×10^4), δ 0.9, 0.94, 1.09, and 1.11 (4 \times CMe), 5.13 (J 7.5 Hz, 3-H), 5.10 (17-H), and 5.85 (15-H).

The combined residues from fissinolide (22.5 g) were taken up in methylene chloride–light petroleum (b.p. 40–60°), and chromatographed over neutral alumina. Elution with the same solvent gave first the ether-ester (3a) (1.68 g), m.p. 194–196°, identical with an authentic sample,⁷ and then *angustidienolide* (6a) (1.18 g), m.p. 245–248°, $[\alpha]_D^{25} +141^\circ$, λ_{\max} (MeOH) 212 and 283 nm (ϵ 8×10^3 and 1.2×10^4), δ 0.80, 0.81, 1.06, and 1.21 (4 \times CMe), 4.89 (d, J 9.5 Hz, 3-H), 5.17 (17-H), 6.23 (15-H), and 6.31 (J_{30-2} 5.5, J_{30-9} 3.5 Hz, 30-H). The compound was identical with a sample supplied by Dr. R. Zelnik.

²² D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, 1964, **86**, 2984.

²³ D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1967, **89**, 6612.

²⁰ R. R. Ernst, *J. Chem. Phys.*, 1966, **45**, 3845.

²¹ H. J. Reich, M. Jautelat, M. T. Messe, F. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 7445.

Methyl 1,3-Dioxomeliaca-8,14-dienate (5c).—The diene acetate (5a) (1.0 g) was dissolved in methanol (300 ml) and treated with 10% methanolic potash (1 ml). After storing overnight the solution was acidified with hydrochloric acid and evaporated to small volume. The alcohol (5b), isolated with methylene chloride, remained amorphous, δ 0.99, 0.99, 1.09, and 1.15 (4 \times CMe), 5.10 (17-H), and 5.83 (15-H). Oxidation with chromic acid in acetone gave *methyl 1,3-dioxomeliaca-8,14-dienate* (5c), m.p. 236—237°, $[\alpha]_D +290^\circ$ (Found: C, 69.3; H, 6.45. $C_{27}H_{30}O_7$ requires C, 69.5; H, 6.5%), δ 0.95, 0.96, 1.16, and 1.16 (4 \times CMe), 5.11 (17-H), and 5.90 (15-H).

Hydrogenation of Methyl 1,3-Dioxomeliac-8(30),14-dienate (6c).—Hydrolysis of the acetate as described above for the isomer gave the alcohol, m.p. 128—130° (loss of methanol)/195—196°, $[\alpha]_D +287^\circ$, δ 0.71, 0.91, 1.03, and 1.19 (4 \times CMe), 5.19 (17-H), 6.31 (15-H), and 6.70 (*W* 9 Hz, 30-H).

Oxidation with chromic acid in acetone then gave the ketone, which did not crystallise, δ 0.86; 1.06, 1.06, and 1.31 (4 \times CMe), 3.93 (*J* 6, 1 Hz, 2-H), 5.19 (17-H), 6.23 (15-H), and 6.41 (*W* 9 Hz, 30-H). Hydrogenation of this (500 mg) in ethyl acetate over platinum oxide proceeded rapidly. The crystalline product, m.p. 210—225°, appeared (n.m.r.) to be a mixture of approximately equal parts of mexicanolide (1c) and the 8(30)-isomer (8c). No carapin was detected. Chromatography gave mexicanolide, identical with an authentic specimen, and the isomer (8c), m.p. 233—235°, $[\alpha]_D -240^\circ$, also identical with an authentic sample.⁸

Hydrogenation of Angustidienolide.—We confirm the report¹² that hydrogenation of angustidienolide yields principally fassinolide. The isomers (8a) and possibly (7a) were formed as well (n.m.r.), but were not isolated.

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