# Diterpenoids of *Leonotis* Species.    Part IV.[1]    Dubiin, a Furanoid Labdane Derivative from *L. dubia* E. Mey

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The furanoid $\delta$-lactone dubiin, $C_{22}H_{30}O_6$, isolated from *Leonotis dubia* E. Mey, is identified as 6$\beta$-acetoxy-15,16-epoxy-9-hydroxylabda-13(16),14-dien-19,20-olactone (1).

THE gum obtained on extraction of *L. dubia* leaves with acetone afforded (from ethyl acetate) a crystalline solid, which was shown by t.l.c. to consist almost entirely of a single compound, dubiin, $C_{21}H_{30}O_6$, m.p. 187—188°. The proposed structure (1) is supported by the following spectroscopic evidence. The i.r. spectrum revealed the presence of a hydroxy-group (3640 cm⁻¹), ester carbonyl and $\delta$-lactone groups (1730 cm⁻¹), and a furan ring (1560, 1500, and 872 cm⁻¹). The presence of a $\beta$-substituted furan ring[2] was confirmed by a positive Ehrlich test, a u.v. band at 213 nm ($\varepsilon$ 5000), by one-proton n.m.r. peaks at $\delta$ 7·52, 7·42, and 6·38, and by the fragments *m/e* 81 and 95 (cleavage of 11,12- and 9,11-bonds, respectively) in the mass spectrum. The n.m.r. spectrum also had three-proton signals at $\delta$ 0·87(d), 0·97(s), and 1·90(s), one-proton signals at $\delta$ 4·20(s) and 5·02(q), and an AB quartet ($J$ 12 Hz) centred at $\delta$ 4·46 due to a methylene group close to an oxygen atom. The peak at $\delta$ 4·20 disappeared on addition of $D_2O$ and must therefore be due to an hydroxy-proton, which is tertiary, since it resists acetylation. The signal at $\delta$ 5·02 is diagnostic for a proton adjacent to an acetate group, the width of the peak ($W_{\frac{1}{2}}$ 8 Hz) being indicative of an equatorial orientation.

Dehydrogenation with palladium–charcoal of either dubiin or of the derivative obtained by reduction with lithium aluminium hydride failed to give 1,2,5-trimethylnaphthalene, readily obtained by similar treatment of marrubiin and of the labdane diterpenoids from *L. leonurus*.[3] On catalytic reduction dubiin afforded a tetrahydro-derivative which presumably consists of a

mixture of C-13 epimers.[4,5] Dubiin absorbed 2 mol. equiv. of alkali to give the diol (2), m.p. 187—188°, which resisted tosylation and acetylation with acetyl chloride–pyridine at room temperature, but gave the parent ester (1) with refluxing acetic anhydride–pyridine. The n.m.r. spectrum of the diol is similar to that of the ester (1) except that the one-proton quartet has moved upfield to $\delta$ 3·92 ($W_{\frac{1}{2}}$ 8 Hz)[6] and the three-proton singlet at $\delta$ 1·90 is absent as expected.

Oxidation of saponified dubiin with Jones,[7] Sarett,[8] and Collins[9] reagents and with chromic acid–ether[10] afforded the ketone (3), m.p. 157—159°, $\nu_{max.}$ 1725 cm⁻¹. The keto-group is hindered and, as expected[11] for a 6-ketone, did not form any of the usual ketone derivatives. The mass spectrum showed that a maximum of three deuterium atoms could be incorporated into the ketone (3). The presence of a 7-oxo-group would also result in incorporation of three deuterium atoms, but this would cause the n.m.r. doublet due to the 8-methyl group to collapse to a singlet. This was not observed. In addition, the mass spectrum of the ketone had a strong peak at *m/e* 193 arising from $\alpha$-cleavage to form the fragment (4). On deuteriation this peak appeared at *m/e* 195 as expected. In the n.m.r. spectrum of the ketone (3) the two doublets of the quartet present in the spectra of dubiin (1) and the diol (2) overlap to form a triplet ($J$ 13 Hz) at $\delta$ 4·28. This observation indicates that the methylene protons have similar magnetic environments and supports the proposed structure (1) for dubiin in which the lactone carbonyl group is at C-19 rather than at C-20. For the latter, Dreiding models show that in the expected half-chair conformation of

[1] Part III, E. R. Kaplan, K. Naidu, and D. E. A. Rivett, *J. Chem. Soc. (C)*, 1970, 1656.
[2] T. Kubota in 'Cyclopentanoid Terpene Derivatives,' eds. W. I. Taylor and A. R. Battersby, Marcel Dekker, New York, 1969, p. 279.
[3] E. R. Kaplan and D. E. A. Rivett, *J. Chem. Soc. (C)*, 1968, 262.
[4] P. H. Boyle, *Chem. and Ind.*, 1966, 33.
[5] D. M. S. Wheeler, M. M. Wheeler, M. Fetizon, and W. H. Castine, *Tetrahedron*, 1967, **23**, 3909.
[6] N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 77.

[7] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.
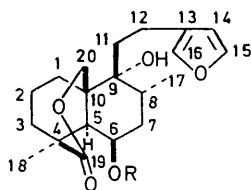[8] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, 1953, **75**. 422.
[9] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.
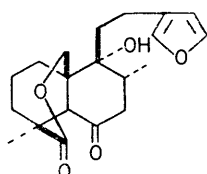[10] H. C. Brown, C. P. Garg, and K. T. Liu, *J. Org. Chem.*, 1971, **36**, 387.
[11] T. Anthonsen, P. H. McCabe, R. McCrindle, and R. D. H. Murray, *Tetrahedron*, 1969, **25**, 2233.
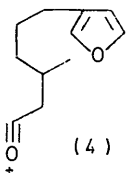
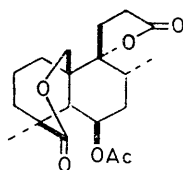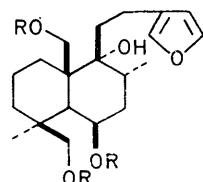the lactone ring [12] the C-19 methylene protons of the 6-ketone would not be magnetically equivalent.
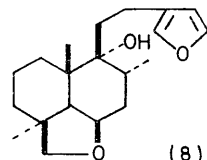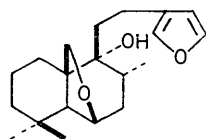


(1) R = Ac
(2) R = H

(3)

(4)

(5)
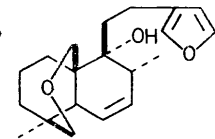
(6) R = H
(7) R = Ac
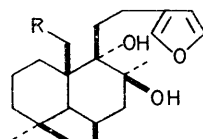
(8)

(9)

(10)

(11) R = OH
(12) R = H

Dubiin was oxidised by chromic acid in acetic acid to the γδ-dilactone (5), m.p. 219—220°, $\nu_{max.}$ 1770 (γ-lactone) and 1730 (δ-lactone) cm$^{-1}$, thus showing that the hydroxy-group in dubiin is attached to C-9.

Reduction of dubiin with lithium aluminium hydride afforded a tetraol (6) which formed a triacetate (7). In an effort to confirm the structure of dubiin we attempted to convert the tetraol into the known ether (8) [13] by treatment with tosyl chloride in pyridine and reducing the resulting tosylate with lithium aluminium hydride. The unstable tosylate obtained gave unsatisfactory analytical results but was reduced to a compound, $C_{20}H_{30}O_3$, m.p. 115—117°, isomeric but not identical with the epoxide (8), m.p. 124°. In the n.m.r. spectrum of our compound there was evidence for one secondary and two tertiary methyl groups and three low-field protons and

this material is considered to be the epoxide (9). In agreement with this structure the i.r. spectrum exhibited bands at 1497 and 861 cm$^{-1}$ expected [14] for a 6β,20-oxide as well as a doublet at 1380 and 1368 cm$^{-1}$ characteristic of a *gem*-dimethyl group. The mother liquors from the crystalline tosylate were also reduced with lithium aluminium hydride, to afford the 19,20-epoxide (10), $C_{20}H_{28}O_3$, m.p. 76—77°, whose n.m.r. spectrum revealed the presence of one secondary (δ 1·02, $J$ 6 Hz) and one tertiary (δ 0·80) methyl group, two low-field methylene groups at δ 3·24 (t, $J$ 12 Hz) and 3·53 (t, $J$ 12 Hz), and two olefinic protons resonating as a quartet centred at δ 5·41 ($J$ 10 Hz). In agreement with structures (9) and (10), these ethers on catalytic hydrogenation absorbed 2 and 3 mol. equiv. of hydrogen, respectively.

The formation of the ethers (9) and (10) from the tetraol (6) is at variance with the recent report by White and Manchand [15] of the conversion of the closely related pentaol (11) into 8β-hydroxymarrubenol (12) by tosylation and hydrogenolysis with lithium aluminium hydride.
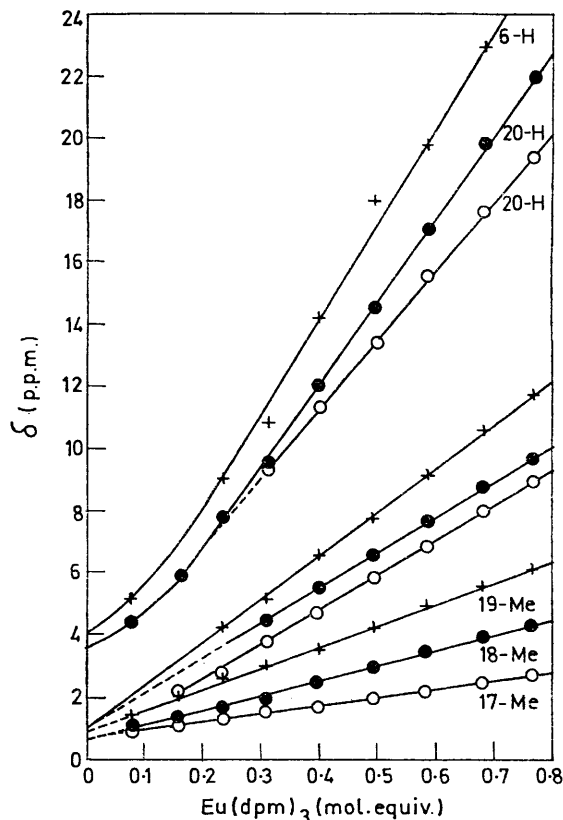


The 60 MHz n.m.r. spectra of the epoxide (9) containing various amounts of tris(dipivaloylmethanato)europium(III)

This difference in behaviour between the alcohols (6) and (11) is presumably due to the influence of the 8β-hydroxy-group. This is also responsible for the formation of a monotosylate on tosylation of 8β-hydroxy-

[12] K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Comm.*, 1965, 634.
[13] R. A. Appleton, J. W. B. Fulke, M. S. Henderson, and R. McCrindle, *J. Chem. Soc.* (*C*), 1967, 1943; E. R. Kaplan, Ph.D. Thesis, Rhodes University, 1968.

[14] J. F. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, 1963, **28**, 1207.
[15] J. D. White and P. S. Manchand, *J. Amer. Chem. Soc.*, 1970, **92**, 5527; *J. Org. Chem.*, 1973, **38**, 720.

marrubenol (12);[1] marrubenol on similar treatment is converted into the ether (8).[13]

The Figure shows the relationship between the concentration of Eu(dpm)$_3$ and the chemical shifts of various protons in the 60 MHz spectrum of the ether (9). Clearly the europium complexes preferentially with the ether oxygen atom rather than with that of the hydroxy-group [16] since the change in chemical shift is greatest for the three low-field protons and least (except for the furan protons, whose signals are hardly shifted) for the 17-methyl protons. The ether (8) showed the same tendency. This is surprising since models indicate that the tertiary hydroxy-group is not particularly hindered.

## EXPERIMENTAL

For general experimental details see ref. 1. Unless stated otherwise all i.r. spectra and specific rotations were determined for solutions in chloroform; n.m.r. spectra were determined with Varian HA100 and Perkin-Elmer R12 (60 MHz) spectrometers.

*Isolation.*—Air-dried leaves of *L. dubia* (2·7 kg), collected in the Belmont Valley near Grahamstown during April 1969 (a specimen is preserved in the University Herbarium), were extracted with acetone. The extract was decolourised with charcoal and evaporated, and the residue was crystallised from ethanol (150 ml). The crystalline product (42 g, 1·55%) showed only one spot on t.l.c. in ethyl acetate–hexane (1 : 1), and was dissolved in chloroform and washed with water (a chloroform solution of the gum obtained from the acetone extract gave emulsions on washing with water). Evaporation and crystallisation afforded *dubiin* [6β-*acetoxy*-15,16-*epoxy*-9-*hydroxylabda*-13(16),14-*dien*-19,20-*olactone*] (20 g, 0·75%), m.p. 187—188°, [α]$_D$ −17° (*c* 1·1), λ$_{max.}$ 213 nm (ε 5000), ν$_{max.}$ 3640, 1730, 1560, 1500, and 872 cm$^{-1}$, δ [(CD$_3$)$_2$SO; 100 MHz] 7·52 (1H, t, *J* 1 Hz, 15-H), 7·42 (1H, s, 16-H), 6·38 (1H, t, *J* 1 Hz, 14-H), 5·02 (1H, q, *J* 3 Hz, 6-H), 4·46 (2H, ABq, *J* 12 Hz, 20-H$_2$), 4·20 (1H, s, disappears on addition of D$_2$O, 9-OH), 1·90 (3H, s, OAc), 0·97 (3H, s, 18-H$_3$), and 0·87 (3H, d, *J* 6 Hz, 17-H$_3$) (Found: C, 67·85; H, 7·8%; *M*$^+$, 390. C$_{22}$H$_{30}$O$_6$ requires C, 67·7; H, 7·75%; *M*, 390).

*Saponification of Dubiin.*—Saponification of dubiin (2·0 g) in refluxing ethanolic 0·7M-potassium hydroxide for 1 h afforded 15,16-*epoxy*-6β,9-*dihydroxylabda*-13(16),14-*dien*-19,20-*olactone* (2) (1·7 g), needles (from aqueous ethanol), m.p. 187—188°, [α]$_D$ +13° (*c* 1·2 ), ν$_{max.}$ 3640, 1715, 1560, 1500, and 872 cm$^{-1}$, δ [(CD$_3$)$_2$SO; 100 MHz] 7·50 (1H, t, *J* 1 Hz, 15-H), 7·41 (1H, s, 16-H), 6·37 (1H, t, *J* 1 Hz, 14-H), 4·66 (1H, s, 6-OH, disappears on addition of D$_2$O), 4·40 (2H, ABq, *J* 11 Hz, 20-H$_2$), 3·92 (2H, s, 6-H and 9-OH; latter disappears on shaking with D$_2$O), 1·13 (3H, s, 18-H$_3$), and 0·89 (3H, d, *J* 6 Hz, 17-H$_3$) (Found: C, 68·9; H, 8·2. C$_{20}$H$_{28}$O$_5$ requires C, 68·95; H, 8·1%).

*Acetylation of the Diol* (2).—Saponified dubiin (20 mg) was refluxed in acetic anhydride (1·5 ml) and pyridine (0·1 ml) for 1 h to give dubiin (m.p., mixed m.p., and i.r. spectra).

*Hydrogenation of Dubiin.*—Dubiin (460 mg) in ethanol (200 ml) was hydrogenated over 10% palladium–barium sulphate (0·9 g) (uptake 1·78 mol. equiv. during 15 min). The resulting *tetrahydrodubiin* (208 mg) crystallised from ethyl acetate–hexane as needles, m.p. 156·5—158°, [α]$_D$ −11° (*c* 1·0), ν$_{max.}$ 3630 and 1725 cm$^{-1}$ (Found: C, 66·9; H, 8·7. C$_{22}$H$_{34}$O$_6$ requires C, 67·0; H, 8·7%).

*Oxidation of the Diol* (2) *with Collins' Reagent.*—Chromium trioxide (3·5 g, 35 mmol) was added in one portion at room temperature to a stirred solution of pyridine (5·5 g) in redistilled methylene chloride (100 ml).[17] The mixture was stirred for 15 min and a solution of saponified dubiin (2·0 g, 5·8 mmol) in methylene chloride (20 ml) was added. Stirring was continued for a further 15 min; the solution was decanted and the residue washed with ether (15 ml). The combined organic solutions were washed successively with aqueous 5% sodium hydroxide (3 × 50 ml), 5% hydrochloric acid (3 × 50 ml), 5% aqueous sodium hydrogen carbonate (50 ml), saturated aqueous sodium chloride (50 ml), and water (2 × 50 ml), and dried (Na$_2$SO$_4$). Evaporation gave the 6-*ketone* (3) (1·76 g, 88%), m.p. 157—159° (needles from ethyl acetate–hexane), [α]$_D$ −51° (*c* 1·5), ν$_{max.}$ 1725, 1560, 1500, and 872 cm$^{-1}$, δ [(CD$_3$)$_2$SO; 100 MHz] 7·52 (1H, t, *J* 1 Hz, 15-H), 7·42 (1H, s, 16-H), 6·38 (1H, t, *J* 1 Hz, 14-H), 4·28 (2H, t, *J* 13 Hz, 20-H$_2$), 3·07 (1H, s, 5-H), 1·14 (3H, s, 18-H$_3$), and 0·99 (3H, d, *J* 6 Hz, 17-H$_3$) (Found: C, 68·95; H, 7·55%; *M*$^+$, 346. C$_{20}$H$_{26}$O$_5$ requires C, 69·35; H, 7·55%; *M*, 346). Oxidation of the diol (2) with Jones[7] and Sarett[8] reagents, and with chromic acid–ether,[10] gave the ketone (3) in 55, 69, and 86% yields, respectively.

*Deuteriation of the Ketone* (3).—A solution of the ketone (3) (58 mg) and potassium hydroxide (85 mg) in deuterium oxide (2 ml) was refluxed with exclusion of moisture for 8 h and acidified. The precipitate was dissolved in ethanol (1·5 ml) to back-exchange −OD for −OH, and the product was crystallised from aqueous ethanol; m.p. 161—164°, *M*$^+$ 349.

*Oxidation of Dubiin with Chromium Trioxide–Acetic Acid.*—Chromium trioxide (3·7 g) in water (6 ml) and acetic acid (20 ml) was slowly added to an ice-cooled solution of dubiin (1·5 g) in acetic acid (10 ml) and the mixture was left at room temperature for 4 days. The acetic acid was removed under reduced pressure, water was added, and the product was extracted with chloroform. The extract was washed with aqueous sodium carbonate and evaporated. Crystalisation of the residue from benzene–hexane furnished the γδ-*dilactone* (5) as needles (0·84 g), m.p. 219—220°, [α]$_D$ +3° (*c* 1·4), ν$_{max.}$ 1770 and 1730 cm$^{-1}$, δ [(CD$_3$)$_2$SO; 60 MHz], 6·06 (1H, q, *J* 3 Hz, 6-H), 4·40 (2H, ABq, *J* 12 Hz, 20-H$_2$), 1·90 (3H, s, OAc), 1·00 (3H, s, 18-H$_3$), and 0·82 (3H, d, *J* 6 Hz, 17-H$_3$) (Found: C, 65·25; H, 7·5. C$_{19}$H$_{26}$O$_6$ requires C, 65·1; H, 7·5%).

*Reduction of Dubiin with Lithium Aluminium Hydride.*—Dubiin (10·0 g) was refluxed with lithium aluminium hydride (5·0 g) in tetrahydrofuran (400 ml) for 24 h to afford the *tetraol* (6) as prisms (8·3 g) (from ethanol), m.p. 221—222°, [α]$_D$ −17° (*c* 0·9 in EtOH), δ [(CD$_3$)$_2$SO; 100 MHz], 7·50 (1H, t, *J* 1 Hz, 15-H), 7·36 (1H, s, 16-H), 6·34 (1H, m), 6·04 (1H, d, *J* 4 Hz), 5·36 (2H, m), 0·96 (3H, s, 18-H$_3$), and 0·85 (3H, d, *J* 6 Hz, 17-H$_3$) (signals at δ 6·34, 6·04, and 5·36 disappeared on shaking with D$_2$O) (Found: C, 68·1; H, 9·1. C$_{20}$H$_{32}$O$_5$ requires C, 68·15; H, 9·15%).

The derived *triacetate* (7), prepared in refluxing acetic anhydride–pyridine, crystallised from ethyl acetate–hexane as needles, m.p. 127—128°, [α]$_D$ −40° (*c* 1·0) (Found: C, 64·8; H, 7·8. C$_{26}$H$_{38}$O$_8$ requires C, 65·25; H, 7·95%).

*Conversion of the Tetraol* (6) *into the Epoxides* (9) *and* (10). —A solution of the tetraol (5·0 g) and toluene-*p*-sulphonyl

[16] J. K. M. Saunders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641; H. Hart and G. M. Love, *Tetrahedron Letters*, 1971, 625.

[17] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000.

chloride (24·0 g) in dry pyridine (130 ml) was left at −30° for 3 days. Ice was added, the solution was extracted with ether, and the extract was washed with dilute hydrochloric acid and water, dried, and evaporated to give a gum. Crystallisation from methanol afforded a *tosylate* (1·8 g), m.p. 63—66° (raised by recrystallisation to 79—83°) (Found: C, 64·7; H, 7·8%). The crude tosylate (1·8 g) was refluxed with lithium aluminium hydride (2·0 g) in tetrahydrofuran (150 ml) for 16 h to afford the *epoxide* (9) as needles (0·64 g) (from benzene–hexane), m.p. 115—117°, $[\alpha]_D$ +19° (c 1·0), $\nu_{max.}$ 3630, 1497, 1380, 1368, 872, and 861 cm⁻¹, δ (CDCl₃; 60 MHz), 7·04 (1H, t, J 1 Hz, 15-H), 6·92 (1H, s, 16-H), 5·99 (1H, t, J 1 Hz, 14-H), 3·93 (1H, q, J 4 Hz, 6-H), 3·57 (2H, ABq, J 9 Hz, 20-H₂), 0·90 (6H, s, 18-H₃ and 19-H₃), and 0·86 (3H, d, J 6 Hz, 17-H₃) (Found: C, 75·2; H, 9·45%; M⁺, 318. C₂₀H₃₀O₃ requires C, 75·4; H, 9·5%; M, 318).

The mother liquors from the crude tosylate were evaporated and reduced as before with lithium aluminium hydride (10 g) in tetrahydrofuran (500 ml) and the product was purified by chromatography (alumina–benzene) to furnish the *epoxide* (10) as needles (0·50 g) (from hexane), m.p. 76—77°, $[\alpha]_D$ −67° (c 1·1), $\nu_{max.}$ 3620 and 872 cm⁻¹, δ (CDCl₃; 60 MHz), 7·04 (1H, t, J 1 Hz, 15-H), 6·93 (1H, s, 16-H), 6·01 (1H, t, J 1 Hz, 14-H), 5·58 and 5·24 (2H, olefinic ABq, J 10 Hz), 3·53 (2H, t, J 12 Hz, 20-H₂), 3·24 (2H, t, J 12 Hz, 19-H₂), 1·02 (3H, d, J 6 Hz, 17-H₃), and 0·80 (3H, s, 18-H₃) (Found: C, 76·0; H, 9·0%; M⁺, 316. C₂₀H₂₈O₃ requires C, 75·9; H, 8·9%; M, 316).

*Hydrogenation of the Epoxides* (9) *and* (10).—The epoxides (20 mg) in ethanol (10 ml) were hydrogenated over 10% palladium–barium sulphate. Oxides (9) and (10) absorbed 2·00 and 2·94 mol. equiv. of hydrogen, respectively, during 10 min. Only the *tetrahydro-derivative* of (9) could be crystallised; it formed needles (from benzene–hexane), m.p. 111—112°, $[\alpha]_D$ +24° (c 1·0) (Found: C, 74·5; H, 10·65. C₂₀H₃₄O₃ requires C, 74·5; H, 10·65%).