The Structure of Lividic Acid.  
A Depsidone from the Lichen  
Parmelia formosana

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Abstract

The depsidone, lividic acid [1'-carboxy-2',3-dihydroxy-4-methoxy-6-(2''-oxoheptyl)-6'-pentyldepsidone] (1) has been isolated from the lichen Parmelia formosana Zahlbr. The structure of this compound followed from a combination of spectroscopic properties and chemical interconversions. The overall substitution pattern of this depsidone was confirmed by methylation with excess diazomethane, whereupon methyl 3-methoxy-2',4',4''-tri-O-methylphysodysate was obtained. Further, lividic acid was synthesized from 3-hydroxyphysodic acid by methylation of the corresponding benzyl ester and subsequent hydrogenolysis.

Lividic acid (1) was first detected by Hale\(^1\) as an unknown metabolite of the lichen Parmelia livida Tayl. Subsequent large-scale extraction of this lichen\(^2\) yielded the common lichen products atranorin (5) and physodic acid (2), in addition to the unknown lividic acid and 4-O-methylphysodic acid (3).

An investigation of the structure of lividic acid followed\(^2\) but the results have yet to be published. During a chemotaxonomic survey of some lichens of eastern Australia\(^3\)\(^\text{--7}\) we observed that Parmelia formosana Zahlbr. produced a number of metabolites, the major component of which appeared to be lividic acid (1). Thin-layer chromatographic examination of this metabolite in three independent solvent systems\(^8\) confirmed that it had identical \(R_F\) values with lividic acid.

\(^1\) Hale, M. E., Jr, *Brittonia*, 1958, 10, 177.
\(^8\) Culberson, C. F., *J. Chromatogr.*, 1972, 72, 113.
The crude extract from this lichen was treated with excess ethereal phenyldiazo-methane, thereby converting the mixture of natural acids into the corresponding benzyl esters. The major component obtained on chromatographic separation of the benzyl esters was identified as benzyl lividate (6), and this ester was subsequently subjected to hydrogenolysis over palladium on carbon to regenerate the purified 'natural' acid. Thin-layer chromatographic and lichen mass spectrometric comparisons of the crude extract and the purified acid confirmed that no artefact formation had occurred.

The structure of lividic acid (1) and benzyl lividate (6) followed from the spectroscopic and microanalytical data. In particular the p.m.r. spectra were very similar to those of 3-hydroxyphysodic acid (4) and benzyl 3-hydroxyphysodate (7) respectively, but confirmed the presence of an O-methyl group. Further information regarding the structure of (1) was obtained from the mass spectral fragmentation pattern. Not only did this fragmentation substantiate the close relationship between (1) and 3-hydroxyphysodic acid (4), but it located the methoxyl substituent in ring A. The prominent daughter ions at m/e 279, 278 were the result of typical A-ring fragmentation (Scheme 1).

Scheme 1

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The Structure of Lividic Acid

To verify that the overall substitution pattern of lividic acid (1) was analogous to that of 3-hydroxyphysodic acid (4), this compound was treated with excess ethereal diazomethane whereupon it was converted into the known ester, methyl 3-methoxy-2',4,4'-tri-O-methylphysodisoylate (8). It only remained to establish whether the O-methyl substituent of lividic acid was present in the 3- or 4-position. This was achieved by acetylated benzyl lividate (6) with acetic anhydride and a trace of concentrated sulphuric acid. Isomerization through ring opening of the depsidone ring followed by the alternative ring closure (with the formation of an isocoumarin system) proceeded as well as concomitant acetylation to give benzyl 3-acetoxy-2',4'-di-O-acetyl-4-O-methylphysodisoylate (9).

The p.m.r. spectrum of this compound located the methoxy substituent at position 4, since O-acetylation had not appreciably affected the resonance of the aromatic proton at position 5. If the O-acetyl group had been adjacent to the aromatic proton, a downfield shift of the order of 0.2 ppm would have been expected. The corresponding deacetyl compound (10) was prepared by treating an acetone solution of benzyl lividate (6) with sodium hydrogen carbonate.

Lividic acid (1) was finally synthesized from 3-hydroxyphysodic acid (4) by methylation of benzyl 3-hydroxyphysodisoylate (7). Treatment of this ester with diazomethane at room temperature proceeded selectively at the 4-position to give, in the main, benzyl lividate (6) together with a small quantity of benzyl 3-methoxyphysodisoylate (11). Benzyl lividate (6) had previously been converted into lividic acid.

Finally benzyl 3-methoxyphysodisoylate (11) was acetylated by treatment with sulphuric acid and acetic anhydride to give benzyl 3-methoxy-2',4,4'-tri-O-acetylphysodisoylate (12). The p.m.r. spectrum of this compound neatly confirmed the former structural deductions. Not only did the ester (12) exhibit two low-field aromatic proton signals as a result of the adjacent O-acetyl groups, but in addition this compound exhibited methoxy resonances at significantly higher field ($\delta_{\text{OMe}}$ 3.50) than the isomeric ester.

Lividic acid (1) is thus the second biogenetically atypical depsidone known to have incorporated an additional nuclear hydroxyl group.

**Experimental**

The general experimental details have been published previously.

**Extraction of Parmelia formosana Zahlbr.**

The lichen material was collected on sandstone boulders, Brisbane Water National Park overlooking Woy-Woy, N.S.W. (JAE-776 (CANB)). The dried thallus (20 g) was extracted with anhydrous ether in a Soxhlet extractor for two days. The ethereal solution was then evaporated and the residue recrystallized from methanol to give atranorin (108 mg). The mother liquid was then evaporated to yield an orange solid (1.55 g).

A solution of this orange solid (190 mg) in acetone (25 ml) was treated with excess ethereal diazomethane overnight. The solvent was then evaporated and the residue adsorbed on two silica gel plates (100 by 20 by 0.1 cm) and eluted with 30% ethyl acetate-light petroleum. The major band was removed and rechromatographed on a similar plate with 50% ethyl acetate-light petroleum as eluent. The major band contained benzyl lividate (6) (40 mg, 0.2% of the dry weight) which crystallized from ether-cyclohexane as colourless plates, m.p. 161-162°C (Found: C, 68.9; H, 6.7. C22H30O9 requires C, 69.1; H, 6.5%. P.m.r. (CDCl3) δ 0.76-0.98 (6H, m, CH3CH2), 1.04-1.75 (12H, m, CH2(CH2)3CH3), 2.55 (2H, t, J 8 Hz, COCH2), 3.31 (2H, br t, ArCH2CH2), 3.90 (5H, s, ArCH2CO and OCH3), 5.38 (2H, s, OCH2), 6.53, 6.74 (each 1H, s, H5, H3'), 7.42 (5H, s, OCH2C6H5) and 11.12 (1H, br s, OH); mass spectrum m/e 590 (M+, 15%), 91 (100).

A slower moving band yielded benzyl 3-hydroxy-4-O-methylisophysodate (10) (13 mg, 0.07% of the dry weight) which crystallized from ether-cyclohexane as a colourless solid, m.p. 158-159°C (Found: mol. wt, 590-2513. C22H38O9 requires mol. wt, 590-2516). P.m.r. (CDCl3) δ 0.55-1.00 (6H, m, CH3CH2), 1.10-1.82 (12H, m, CH2(CH2)3CH3), 2.41-2.59 (2H, m, -OCCH2CH2), 2.90-3.11 (2H, m, ArCH2CH2), 3.92 (3H, s, OCH3), 5.43 (2H, s, OCH2), 6.17 (1H, s, CH=), 6.44, 6.53 (each 1H, s, H5, H3'), 7.40 (5H, s, OCH2C6H5) and 11.12 (1H, s, bonded OH); mass spectrum m/e 590 (M+, 28%), 278 (100).

**Lividic Acid (1)**

A mixture of benzyl lividate (68 mg), 10% palladium on carbon (25 mg) and ethyl acetate (5 ml) was stirred in an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was then filtered and the solvent evaporated. The residue (56 mg, 98%) was recrystallized from ethyl acetate-light petroleum to give lividic acid (1) as colourless plates, m.p. 158-159°C (Found: C, 63.0; H, 6.5. Calc. for C22H30O9H2O: C, 62.5; H, 6.6%). P.m.r. (CDCl3/CD3COCD3) δ 0.67-1.02 (6H, m, CH3CH2), 1.09-1.86 (12H, m, CH2(CH2)3CH2), 2.52 (2H, t, J 7 Hz, COCH2), 3.38-3.58 (2H, m, ArCH2CH2), 3.89 (5H, s, ArCH2CO and OCH3), 5.36, 6.68 (each 1H, s, ArH), 9.18 (1H, br H, OH or CO2H); mass spectrum m/e 500 (M+, <1%), 457 (5), 456 (16), 279 (13), 278 (66), 277 (12), 276 (10), 263 (7), 262 (32), 222 (7), 221 (26), 206 (12), 193 (21), 191 (5), 180 (9), 179 (5), 177 (9), 165 (5), 164 (18), 151 (13), 150 (5), 149 (5), 138 (9), 137 (9), 136 (5), 135 (8), 133 (5), 125 (8), 124 (100), 123 (26), 95 (7), 91 (8), 81 (7), 79 (7), 77 (13), 75 (7), 69 (8), 67 (9), 66 (6), 65 (10), 63 (5), 56 (15), 54 (10), 53 (6), 52 (10), 44 (43), 43 (15).

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Permethylation of Lividic Acid (1)

A solution of lividic acid (30 mg) in anhydrous ether (20 ml) was stirred with excess ethereal diazomethane at room temperature for 72 h. The solvent was then evaporated and the residue chromatographed on a silica gel plate, 50% ethyl acetate-light petroleum being used as eluent. The only major band which developed contained methyl 3-methoxy-2',4',4'-tri-O-methylisophysodate (8) (18 mg, 54%), identical with the authentic material.6

Benzyl 3-Hydroxy-4-O-methylisophysodate (10)

A mixture of benzyl lividate (24 mg), potassium hydrogen carbonate (100 mg) and acetone (10 ml) was stirred at room temperature for 7 h. The mixture was then poured into dilute hydrochloric acid and the suspension extracted with ether. The ethereal extract was dried (Na2SO4), concentrated and the residue applied to a silica gel plate (10 by 10 cm) and eluted with 40% ethyl acetate-light petroleum. Two major bands developed. The faster band yielded benzyl 3-hydroxy-4-O-methylisophysodate (10) (12 mg, 50%), identical with the material described above.

Methylation of Benzyl 3-Hydroxysphysodate (7)

A solution of benzyl 3-hydroxysphysodate (120 mg) in ethyl acetate (5 ml) was treated with ethereal diazomethane (1 equiv.) at room temperature for 1 h. The solvent was then evaporated and the residue applied to a silica gel plate. Elution with 50% ethyl acetate-light petroleum developed three bands. The initial band yielded benzyl 3-methylisophysodate (11) (14 mg, 11%) which from ether-cyclohexane gave colourless crystals, m.p. 124-125° (Found: mol. wt, 590-2513. C34H38O9 requires mol. wt, 590-2516). P.m.r. (CDCl3) δ 8 77-79 (6H, m, CH2CH3), 1.65-1.77 (12H, m, CH2(CH2)3CH3), 2.53 (2H, brt, -OCCH2CH2), 3.23 (2H, brt, ArCH2CH2), 3.92 (2H, s, ArCH2CO) 4.00 (3H, s, OCH3), 5.42 (2H, s, OCH2), 6.65, 6.81 (each 1H, s, H5, H3′), 7.45 (5H, s, OCH2CH2H3) and 11.24 (1H, s, OH); mass spectrum m/e 590 (M+ 22%), 91 (100). The second band yielded benzyl lividate (54 mg, 44%), identical with that obtained from the natural acid (m.p. and m.m.p., p.m.r., mass spec.). The final band contained unchanged benzyl 3-hydroxysphysodate (33 mg).

Benzyl 3-Acetoxy-2',4'-di-O-acetyl-4-O-methylisophysodate (9)

A mixture of benzyl lividate (9 mg), acetic anhydride (1 ml) and conc. H2SO4 (1 drop) was stirred at room temperature for 22 h. Water was then added and the resultant mixture was extracted with ether. The ether extract was washed several times with water, dried and evaporated. Benzyl 3-acetoxy-2',4'-di-O-acetyl-4-O-methylsphysodate (9) was obtained as a colourless oil (10 mg, 91%). The oil was adsorbed onto a small silica gel plate and eluted with 40% ethyl acetate-light petroleum. The major band contained the product and exhibited p.m.r. (CDCl3) δ 0 56-0-99 (6H, m, CH2CH3), 1.07-1.45 (12H, m, CH2(CH2)3CH3), 1.72, 1.92, 1.96 (each 3H, s, OCH3), 2.30-2.49 (2H, m, -OCCH2CH2), 2.63-2.81 (2H, m, ArCH2CH2), 3.87 (3H, s, OCH3), 5.31 (2H, s, OCH3), 6.10 (1H, s, CH=C), 6.51, 6.88 (each 1H, s, H5, H3′), 7.28-7.64 (5H, m, OCH2CH2H3); mass spectrum m/e 590 (M+ 22%), 91 (100).

Benzyl 3-Methoxy-2',4',4'-tri-O-acetylisophysodate (12)

Benzyl 3-methoxysphysodate (45 mg) was treated with acetic anhydride (5 ml) and conc. H2SO4 (1 drop) as described above. The oil obtained was chromatographed on a silica gel plate, 40% ethyl acetate-light petroleum being used as an eluent. The only major band which developed contained benzyl 3-methoxy-2',4',4'-tri-O-acetylisophysodate (12) (9 mg, 16%) (Found: mol. wt, 716.2872. C34H38O9 requires mol. wt, 716.2832). P.m.r. (CDCl3) δ 0 69-0.96 (6H, m, CH2CH3), 1.09-1.44 (12H, m, CH2(CH2)3CH3), 1.65, 1.93, 2.34 (each 3H, s, OCH3), 2.39-2.53 (2H, m, -OCCH2CH2), 2.73-2.89 (2H, m, ArCH2CH2), 3.50 (3H, s, OCH3), 5.38 (2H, s, OCH3), 6.11 (1H, s, CH=C), 6.81, 6.89 (each 1H, s, H5, H3′), 7.35-7.60 (5H, m, OCH2CH2H3); mass spectrum m/e 716 (M+, 10%), 632 (100), 91 (100).

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