Structure of Lithocarpic Lactone, a New Triterpenoid from Two *Lithocarpus* Species of Hong Kong

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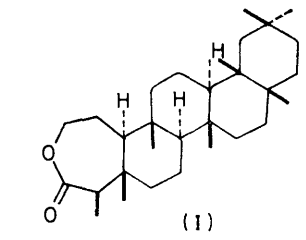
Lithocarpic lactone, a new triterpenoid isolated from the leaves of both *Lithocarpus litchioides* Chun and *L. irwinii* (Hance) Rehd. has been shown to be 2,3-secofriedelano-3,2-lactone (I).

THE light petroleum extracts of ten *Lithocarpus* species (Fagaceae) of Hong Kong contain various triterpenoids.[1] From the leaves of two of these, *L. litchioides* Chun and *L. irwinii* (Hance) Rehd., a new triterpene lactone, which we have named lithocarpic lactone, has been isolated together with some friedelane derivatives such as pachysandiol A (friedelane-2α,3β-diol) (II) from the former and pachysandiol-A and friedelane-2,3-dione (3-hydroxyfriedel-3-en-2-one) (III) from the latter. We now report chemical and spectroscopic studies which establish the structure (I) for this lactone.

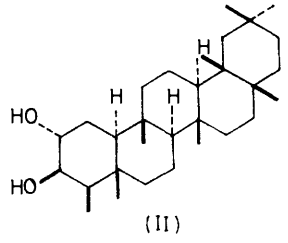
Lithocarpic lactone $C_{30}H_{50}O_2$ (M^+ 442), m.p. 319—320°, $[\alpha]_D$ +54·0°, gives a negative result in the tetranitromethane test. The presence of a δ- or ε-lactone ring is indicated by its i.r. spectrum ($\nu_{max.}$ 1745 and 1194 cm^{-1}). Its n.m.r. spectrum exhibits signals of seven tertiary Me groups at δ 0·88 (6H), 0·96 (3H), 1·01 (9H), and 1·42 (3H), and one secondary Me group at δ 1·05 (3H, d, *J* 7 Hz), suggesting that it is a derivative of friedelane or a related type of pentacyclic triterpene. A multiplet (2H) at δ 4·25 is probably due to two methylene protons adjacent to the oxygen function, and a quartet at δ 2·66 (1H, *J* 7 Hz) to a methine proton α both to the secondary Me group and to the carbonyl group of the lactone ring. Assuming the lactone function to be in ring A, the former can be assigned to the C-2 protons and the latter to the C-4 proton.

Two closely related compounds with an ε-lactone function in ring A of a friedelane-type skeleton have been reported. The first, apetalactone (28-hydroxy-3,4-secofriedelano-3,4-lactone) (IV),[2] isolated from two *Calophyllum* species, showed n.m.r. signals at δ 4·20 for the C-4 methine proton and δ 2·62 for the C-2 methylene protons. Thus, there is strong indication that the oxygen and carbonyl functions are reversed in the two compounds, as represented in (I) and (IV). The second, friedelalactone (3,4-secofriedelano-3,4-lactone) (V),[3] m.p. 230°, $[\alpha]_D$ 0°, prepared by Baeyer–Villiger oxidation of friedelin, is not identical with (I), but the mass spectral fragmentation behaviour of the latter is very similar to that reported for (V), as shown by peaks at *m/e* 318 (60%), 289 (31), 273 (5), 205 (100), and 189 (24). Other prominent fragments (*m/e* 371, 303, 290, 209, and 207) at 16 mass units higher than the corresponding peaks given by friedelin [4,5] also indicate that (I) is a friedelane-type compound with the lactone function in ring A.

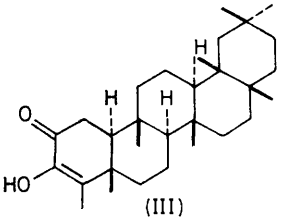
Alkaline hydrolysis of the lactone (I) gave a product which on attempted recrystallisation reverted to the



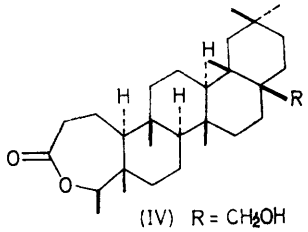
(I)



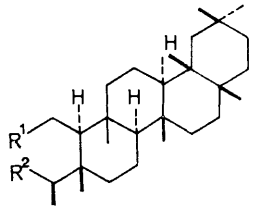
(II)



(III)



(IV) R = CH_2OH
(V) R = Me



(VI) R^1=CH_2OH; R^2=CO_2H
(VII) R^1=R^2=CH_2OH
(VIII) R^1=R^2=CHO
(IX) R^1=CHO, R^2=CO_2H

original lactone. However, on acidification of the filtrate after the reaction, a small quantity of the hydroxy-acid (VI), $\nu_{max.}$ 3520 (OH), 3000—2500, 1745, 1720, and 1200 cm^{-1} (CO_2H), was obtained. Attempted methylation of (VI) was unsuccessful; the lactone (I) was recovered almost quantitatively.

Reduction of the lactone (I) with sodium borohydride gave a diol (VII), $\nu_{max.}$ 3300 cm^{-1}. Periodate oxidation of pachysandiol-A (II) yielded the corresponding dial (VIII),[6] $\nu_{max.}$ 1720 cm^{-1}, which on reduction with sodium borohydride gave 2,3-secofriedelane-2,3-diol, identical

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with the diol (VII). The oxygen functions in the lactone (I) are therefore at C-2 and -3, and (I) is thus 2,3-secofriedelano-3,2-lactone.

Baeyer–Villiger oxidation of 3-oxo-compounds of the friedelane type leads to 3,4-seco-lactones (friedelalactone from friedelin [3] and apetalactone from canophyllol [2]), but it is conceivable that 2,3-seco-lactones are formed simultaneously as minor products through the less favourable migration of the C-2 methylene group, especially under strongly acid conditions.[7,8] We considered that 2,3-secofriedelano-3,2-lactone (I) might thus be synthesised from friedelin. We therefore attempted this oxidation with an excess of toluene-*p*-sulphonic acid as catalyst. The product was a mixture containing unchanged friedelin (60%) and two ε-lactones separable either by column or thin-layer chromatography. The one (3% yield) with lower R_F value was friedelalactone, and the other (0·04%), with higher R_F value was the lactone (I). The proposed structure (I) for lithocarpic lactone is thus confirmed.

Since friedelane-2,3-dione (III) and pachysandiol-A (II) are both friedelane-type compounds with oxygen functions at C-2 and -3, the co-occurrence of (I) with these compounds is not surprising. The biogenetic route to (I) might involve initial oxidation of (II) to (III), then partial oxidation of (III) to the 2-oxo-2,3-seco-3-oic acid (IX), which on reductive cyclisation would give (I).

Lithocarpic lactone (I) is the second isolated naturally occurring ε-lactone of the friedelane type. However, triterpenes with lactone ring structures similar to that of (I) have not been reported previously. The most closely related compound known appears to be putranjic acid [(2*S*)-hydroxy-3,4-secofriedelan-3-oic acid].[9–11] Two other pentacyclic 2,3-seco-triterpenoids isolated from plants are 2,3-seco-olean-12-ene-2,3,28-trioic acid [12] and 23-hydroxy-2,3-secours-12-ene-2,3,28-trioic acid (2 ⟶ 23)-lactone 3,28-dimethyl ester.[13]

EXPERIMENTAL

Mass spectra were recorded with a Hitachi–Perkin-Elmer RMU-6E spectrometer, n.m.r. spectra (for $CDCl_3$ solutions) with a Hitachi R-20 (60 MHz) instrument, i.r. spectra (KBr discs) with a Perkin-Elmer 337 spectrophotometer, u.v. spectra (for solutions in 95% ethanol) with a Unicam SP 800 spectrophotometer, and optical rotations (for $CHCl_3$ solutions) with a Bellingham and Stanley Pepol 60 spectropolarimeter. Alumina (B.D.H. analytical grade) was used for column and silica gel G (Merck) for thin-layer chromatography. Light petroleum had b.p. 60—80°.

Isolation of Lithocarpic Lactone (I).—(a) *From* Lithocarpus litchioides (with Y. C. Lee). Milled air-dried leaves (17 kg) of *Lithocarpus litchioides* were extracted twice, each time for 1 week, with cold light petroleum, and the combined extracts were concentrated and chromatographed on alumina (3 kg). After using less polar solvents to remove friedelin and monohydroxy-compounds,[1] elution with light petroleum–benzene (7 : 3) gave a solid (50 mg), which on crystallisation from chloroform yielded fine needles (I), m.p. 319—320°, M^+ 442, $\nu_{max.}$ 1745 and 1194 cm^{-1}. Elution with light petroleum–benzene (1 : 9) gave needles of pachysandiol-A (II) (0·15 g), m.p. 283—286° (from benzene), $\nu_{max.}$ 3500 cm^{-1}.

(b) *From* L. irwinii. Dried leaves (7 kg) were extracted and chromatographed on alumina (1·6 kg) as before. Elution with light petroleum–benzene (2 : 3) afforded a crystalline mass, which on several recrystallisations from chloroform gave 2,3-*secofriedelano*-3,2-*lactone* (I) as fine *needles* (60 mg), m.p. 319—320°, $[\alpha]_D$ +54·0° (*c* 0·33) (Found: C, 80·95; H, 11·6. $C_{30}H_{50}O_2$ requires C, 81·1; H, 11·6%), identical with the material from (a) (mixed m.p., i.r., n.m.r., and mass spectra, and t.l.c.). Elution with benzene yielded pachysandiol-A (II) (20 mg), m.p. 281—284°; further elution with chloroform afforded friedelane-2,3-dione (III) (25 mg), m.p. 271—273° (from ether), $[\alpha]_D$ +23·7° (*c* 0·4) M^+ 440, $\nu_{max.}$ 3340 (OH), 1675, and 1640 cm^{-1} [=C(OH)–C=O], $\lambda_{max.}$ 276 nm (ε 9700).

Hydrolysis of the Lactone (I).—The lactone (I) (70 mg) was boiled under reflux with 5% sodium hydroxide in ethanol (40 ml) for 4 h. The solution was distilled to a small volume and water was added. The precipitated product was filtered off and recrystallised from methanol to give needles (50 mg), m.p. 315—317°, of the starting lactone (I) (mixed m.p., i.r. spectrum, and t.l.c.). The filtrate, on acidification with dilute sulphuric acid, became turbid, and when heated on a steam-bath gave fine needles of the hydroxy-acid (VI) (10 mg), m.p. 307—308°, *m/e* 460 (M^+), 389, 371, 336, 321, 318, 308, 307, 303, 290, 289, 273, 227, 225, 209, 207, 205, 189, and 149, $\nu_{max.}$ 3520 (OH), 3000—2500, 1745, 1720, and 1200 cm^{-1} (CO_2H).

Attempted Methylation of the Hydroxy-acid (VI).—The hydroxy-acid (VI) (6 mg) was treated with diazomethane in ether. The product (5 mg), m.p. 316—318°, was identified as the lactone (I) (mixed m.p., i.r. spectrum, and t.l.c.).

Reduction of the Lactone (I).—Sodium borohydride (20 mg) was added to a solution of the lactone (I) (9 mg) in propan-2-ol (10 ml), and the mixture was boiled under reflux for 3 h. The precipitate obtained on acidification with acetic acid was extracted with ether, and recrystallised from methanol to give a solid diol (VII) (3 mg), m.p. 180—184°, *m/e* 446 (M^+) 322, 307, 304, 294, 293, 276, 275, 273, 213, 211, 205 (base peak), 195, 193, and 149, $\nu_{max.}$ 3300 cm^{-1} (OH).

Periodate Oxidation of Pachysandiol-A (II).—Mixed solutions of the diol (II) (25 mg) in ethanol (25 ml) and sodium periodate (0·1 g) in 0·5M-sulphuric acid (5 ml) were kept in the dark for 6 h. The excess of periodate was destroyed with ethylene glycol (1 drop). Water was added to dissolve the sodium sulphate formed, and the mixture was extracted with ether. Evaporation of the extract gave 2,3-secofriedelane-2,3-dial (VIII) [6] (8 mg), m.p. 168—172° (from light petroleum), $\nu_{max.}$ 1720 cm^{-1} (C=O).

Reduction of 2,3-*Secofriedelane*-2,3-*dial* (VIII). A solution of the dial (VIII) (7 mg) and sodium borohydride (20

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mg) in dry dioxan (15 ml) was kept at room temperature for 1 h. The product, 2,3-secofriedelane-2,3-diol (4 mg), m.p. 181—185° (from methanol), $\nu_{max.}$ 3300 cm^{-1} (OH), was identical with the diol (VII) (mixed m.p., i.r., and mass spectra, and t.l.c.).

Baeyer–Villiger Oxidation of Friedelin.—Friedelin (1 g) was added to a solution of *m*-chloroperbenzoic acid (5 g) in chloroform (150 ml) containing an excess of toluene-*p*-sulphonic acid. The solution was kept below 10° for 4 days, washed with aqueous 5% sodium hydroxide and water, dried (Na_2SO_4), and evaporated. The dry solid (1 g) obtained was chromatographed on alumina (80 g). Elution with light petroleum gave friedelin (0·6 g), m.p. 262—263°. Elution with light petroleum–benzene (1 : 1) yielded a solid, which on repeated recrystallisation from chloroform afforded fine needles of 2,3-secofriedelano-3,2-lactone (4 mg), m.p. 317—319°, M^+ 442, $\nu_{max.}$ 1745 and 1192 cm^{-1} (ε-lactone), identical with (I) (mixed m.p., i.r. and mass spectra, and t.l.c.). Further elution with the same solvent gave another solid, which showed two spots on t.l.c. [$CHCl_3$–EtOAc (9 : 1)] On preparative t.l.c., the compound with higher R_F value (trace) was shown to be the lactone (I), and the one with lower R_F value, on recrystallisation from chloroform–methanol afforded friedelalactone (V) (30 mg), m.p. 246—248°, $[\alpha]_D$ −7·0° (*c* 0·5) (lit.,[3] m.p. 230°, $[\alpha]_D$ 0°), M^+ 442, $\nu_{max.}$ 1745 cm^{-1}.

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