

Conversion of Shikonin Angelate into [2,2-Dimethyl-1-(2-methylcrotonoyloxy)cyclobutyl]-5,8-dihydroxy-1,4-naphthoquinone; a Novel Cyclisation of a 4-Methylpent-3-enyl Side Chain in a Natural Quinone

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During isolation of 5,8-dihydroxy-2-(4-methylpent-3-enyl)-1,4-naphthoquinone and shikonin angelate, the side chain of the latter cyclised to give an unusual four-membered ring system. The identification of this product and some of its reactions are described.

DURING an investigation of the nature of the pigments in *Alkanna hirsutissima* (Boraginaceae) we isolated ¹ 5,8-dihydroxy-2-(4-methylpent-3-enyl)-1,4-naphthoquinone (1) and shikonin angelate (6), by column chromatography on silica gel. Further elution of the column with chloroform-petroleum (3 : 2 v/v) gave dark red fractions showing a single spot on t.l.c.

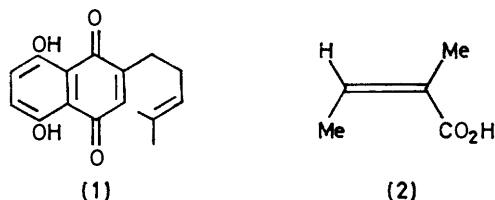
This product (A) showed u.v. and i.r. absorptions

similar to those of shikonin angelate (6), and the mass spectrum established the molecular formula as C₂₁H₂₂O₆, the same as that of shikonin angelate. However the ¹H n.m.r. spectra were significantly different (see Table). That the naphthazarin system was present was shown

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¹ M. Afzal and M. Tofeeq, *J.C.S. Perkin I*, 1975, 1334.

by the i.r. and n.m.r. data; we therefore inferred that the structural difference was in the side chain.



Saponification of the product (A) yielded angelic acid (2) and an alcohol (B), implying that the ester part of

Structure (8) was further confirmed by its fragmentation in the mass spectrum (Scheme 2). The presence of the abundant ion m/e 232 eliminated the possibility of a fused ring system. The simple α -fission ion at m/e 190 and other ions at m/e 219 and 69 also gave substantial support to structure (8). Thus the corresponding ester (A) must have structure (9).

The conversion (6) \rightarrow (9) formally corresponds to a photochemical 'di- π -ethane' rearrangement² and is one of the first such rearrangements to be found amongst natural products, although several other quinones with

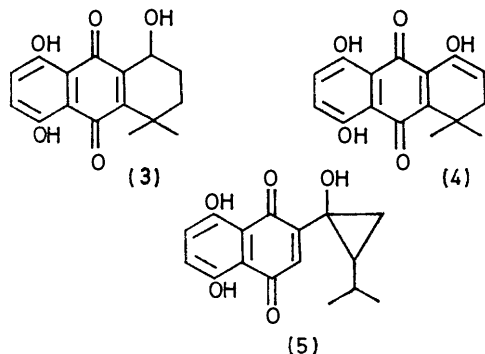
¹H N.m.r. data (τ values)

Compound	ArOH	ArH	Quinone H	CHOH CMe ₂	CMe: CHMe	CH: CMe ₂	CH ₂ CMe ₂	CMe: CHMe	:CMe ₂	>CMe ₂
Shikonin	-2.4 *	2.91	3.1	3.96br (2 H, q)	3.8	4.8	7.4-7.9	8.0	8.02	8.8
angelate	(1 H, s), -2.6 * (1 H, s)	(2 H, s)	(1 H, d, J 2 Hz)							
Compound (A)	-2.3 * (1 H, s), -2.4 * (1 H, s)	2.75 (2 H, s)	2.95 (1 H, s)		(1 H, q)		8.02 (4 H, m),	8.0 (6 H, s)		8.8 (6 H, s)
Alcohol (B)	-2.2 * (1 H, s), -2.3 * (1 H, s)	2.8 (2 H, s)	2.95 (1 H, s)				8.2 (4 H, m)			8.7 (6 H, 2s)

* Exchangeable with deuterium oxide.

shikonin angelate was not involved in the structural difference. This left a change in the 4-methylpent-3-enyl side chain of shikonin angelate as the only possibility.

The u.v. and i.r. data of the alcohol (B) indicated its definitive relationship with shikonin (7). The n.m.r. spectrum showed a quinone proton singlet at τ 2.95, and the absence of new benzylic and olefinic proton signals (compared with shikonin) precluded structures (3) and (4); a cyclopropane structure (5) was also eliminated by the observation of a singlet (6 H) for the CMe₂ group.

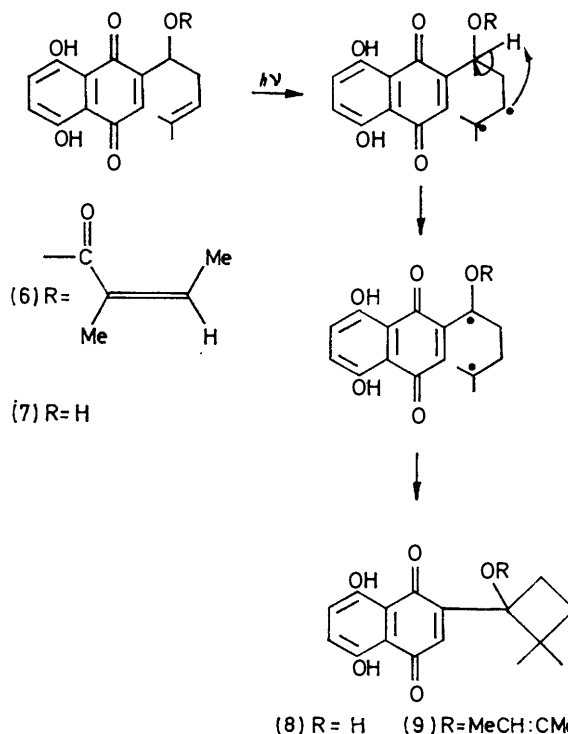


The only remaining possibility, the cyclobutane structure (8), is in complete agreement with the spectral data.

² S. S. Hixon, P. S. Marino, and H. E. Zimmerman, *Chem. Rev.*, 1973, **73**, 531.

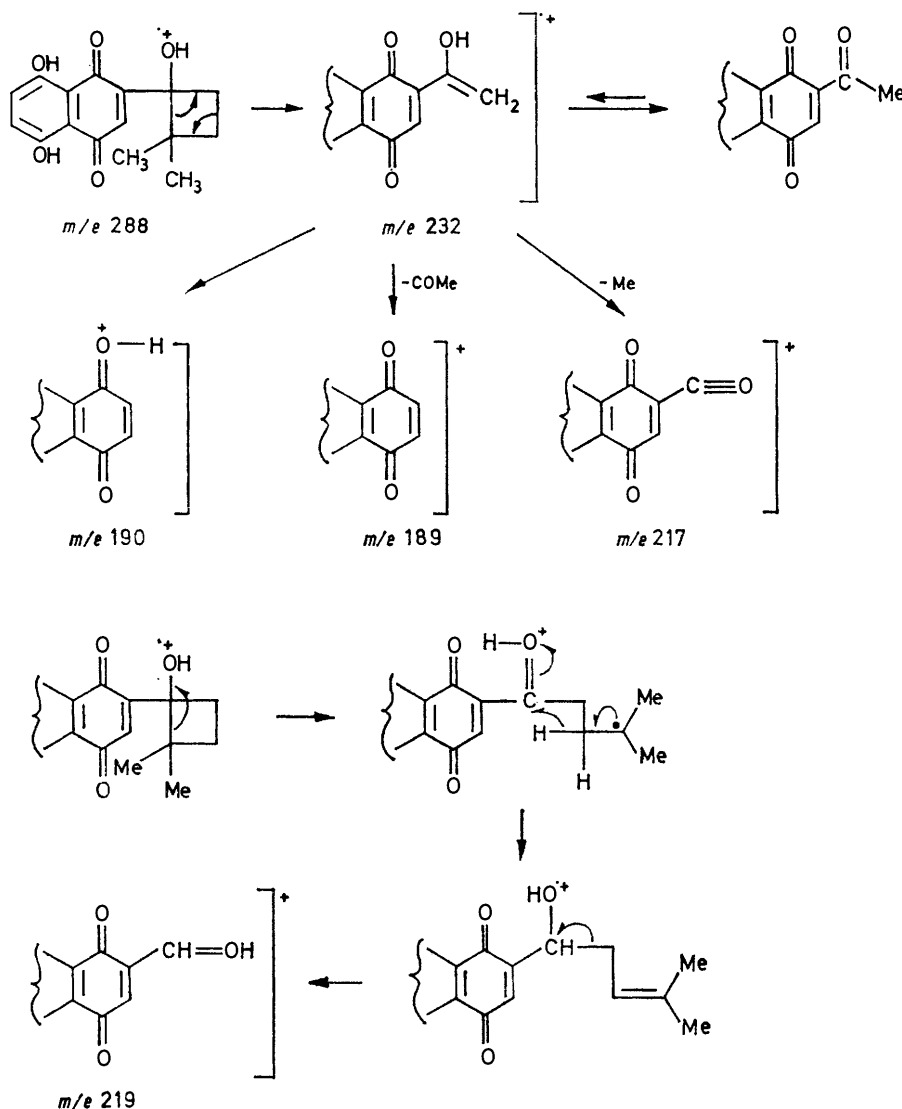
³ R. H. Thomson, 'Naturally Occurring Quinones,' Academic Press, London, 1971, p. 248.

methylpentenyl side chains have been isolated previously.³ This rearrangement is best rationalised in terms

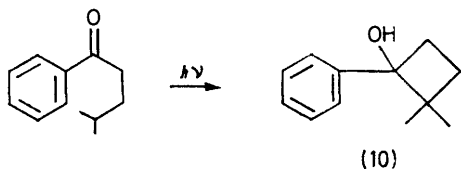


SCHEME 1

of H transfer followed by a collapse of a 1,4-diradical (Scheme 1). Collapse of such 1,4-diradicals to give a



cyclobutane ring has been demonstrated.⁴⁻⁶ A similar formation of a cyclobutanol (10) by collapse of a 1,4-diradical has been reported.⁷



The alcohol (8) underwent easy dehydration with methanolic hydrochloric acid to give the cyclobutene (11), and^c was converted by trifluoroacetic acid into the 1-hydroxy-4-methylpent-1-enyl derivative (12). Cyclo-

⁴ W. C. Agosta and D. K. Herron, *J. Amer. Chem. Soc.*, 1968, **90**, 7025.

⁵ A. B. Smith, tert., and W. C. Agosta, *J. Amer. Chem. Soc.*, 1973, **95**, 1961.

⁶ K. H. Schulte-Elte and G. Ohloff, *Tetrahedron Letters*, 1964, 1143.

butane and other small ring compounds are known to undergo ring fission with acids to give olefins.^{8,9}

The crude extract of *A. hirsutissima* showed no trace of compound (9) (t.l.c. in various solvent systems), which must therefore have been formed during the chromatographic purification of shikonin angelate. This was proved by an independent conversion of shikonin angelate (6) into compound (9) on an acid-washed silica gel column.

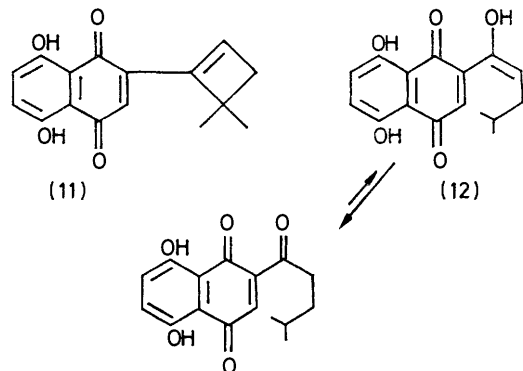
Proof for the formation of compound (9) by a radical mechanism was obtained by irradiation of shikonin angelate with a low-pressure mercury arc. T.l.c. of the crude product indicated the presence of compound (9), which was again isolated by chromatography on acid-

⁷ J. Grotewold, C. M. Previtali, and D. Soria, *J.C.S. Chem. Comm.*, 1973, 207.

⁸ J. M. Conia and P. Amice, *Bull. Soc. chim. France*, 1970, 2972.

⁹ J. K. Crandall and D. R. Paulson, *J. Org. Chem.*, 1971, **36**, 1184.

washed silica gel. Irradiation of shikonin (6) did not result in the alcohol (7). The cyclisation of shikonin angelate and not of shikonin itself could be due to a steric arrangement favourable for benzylic hydrogen



abstraction and allowing subsequent collapse of the 1,4-diradical to a cyclobutane.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. absorption spectra were measured for solutions in ethanol with a Unicam SP 800 spectrophotometer. I.r. spectra were determined with Perkin-Elmer 127 and 237 spectrophotometers, for potassium bromide discs, unless stated to the contrary. N.m.r. spectra were determined with Varian A60-D and HA 100 instruments (Me_4Si as internal reference). Mass spectra were measured with an A.E.I. MS9 spectrometer at University College, Swansea. Silica gel (200–300 mesh; Koch-Light) was acid-washed for column chromatography. Light petroleum had b.p. 40–60°. The usual t.l.c. solvent system was benzene-acetic acid-water (20 : 5 : 4; upper layer).

Isolation of Compound (9).—Powdered roots of *A. hirsutissima* were extracted and worked up as described previously.¹ Chromatographic purification of the crude extract (1.5 g) was carried out on an acid-washed silica gel column. After elution of the naphthoquinone (1) and shikonin angelate (6), the column was eluted with chloroform-petroleum (1 : 1 v/v), giving dark red solutions. The fractions containing compound (9), R_F 0.32 (dark red spot), were combined and concentrated under reduced pressure to give an uncrystallisable dark red oily material (150 mg), characterised as 2-[2,2-dimethyl-1-(2-methylcrotonoyloxy)cyclobutyl]-5,8-dihydroxy-1,4-naphthoquinone (Found: C, 68.2; H, 5.9%; M^+ , 370. $\text{C}_{21}\text{H}_{28}\text{O}_6$ requires C, 68.1; H, 5.9%; M , 370), ν_{max} (CHCl_3) 1 720, 1 650, and 1 610 cm^{-1} (conj. ester, C=C and H-bonded C=O, respectively).

Alkaline Hydrolysis of Compound (9).—Compound (9) (200 mg) was stirred in 2M-sodium hydroxide for 5 h at 25 °C. The blue solution was filtered, chilled in ice, and acidified with dilute, ice-cold sulphuric acid. The red mixture was extracted with chloroform (3 × 40 ml). The organic extract was washed with aqueous 5% sodium hydrogen carbonate (3 × 40 ml), dried, and concentrated under reduced pressure to yield 5,8-dihydroxy-2-(1-hydroxy-2,2-dimethylcyclobutyl)-1,4-naphthoquinone (8) as dark red needles (114 mg), R_F 0.27, m.p. 161–162° (from chloroform) (Found: C, 66.8; H, 5.7%; M^+ , 288. $\text{C}_{16}\text{H}_{16}\text{O}_5$ requires C, 66.7; H, 5.6%; M , 288), ν_{max} 1 640 and 1 610

cm^{-1} (quinonoid C=C and H-bonded C=O). Work-up of the alkaline extract yielded angelic acid, identical with an authentic sample.

Dehydration of the Alcohol (8).—The alcohol (8) (30 mg) was dissolved in methanol-hydrochloric acid (9 : 1 v/v) and set aside for 1 h. The mixture was diluted with ice-cold water and then extracted with chloroform (3 × 100 ml). The dried extract was concentrated under reduced pressure to give a red gum which crystallised from ether-hexane as dark red prisms of 2-(4,4-dimethylcyclobut-1-enyl)-5,8-dihydroxy-1,4-naphthoquinone (11) (20 mg), R_F 0.75, m.p. 120–121° (Found: C, 71.1; H, 5.3%; M^+ , 270. $\text{C}_{16}\text{H}_{14}\text{O}_4$ requires C, 71.2; H, 5.1%; M , 270), ν_{max} 1 650 and 1 610 cm^{-1} (olefinic C=C and H-bonded C=O), τ (CDCl_3) -2.3 (2 H, s, exchangeable with D_2O , chelated phenolic OH), 2.4 (1 H, s, quinonoid H), 2.55 (2 H, s, ArH), 4.6 (1 H, t, C=CH- CH_2), 7.8 (2 H, m, C=CH- CH_2), and 8.5 (6 H, s, CMe_2).

Treatment of the Alcohol (8) with Trifluoroacetic Acid.—The alcohol (8) (100 mg) was dissolved in trifluoroacetic acid (5 ml), and the reaction was followed by t.l.c. until all the starting material was consumed (1 h). The mixture was poured onto crushed ice and extracted with chloroform (3 × 80 ml). The dried extract was concentrated under reduced pressure to give a dark red gum, which crystallised from ether as red needles of 5,8-dihydroxy-2-(4-methyl-1-hydroxybut-1-enyl)-1,4-naphthoquinone (12) (80 mg), R_F 0.65, m.p. 85–86° (Found: C, 66.7; H, 5.3%; M^+ , 288. $\text{C}_{16}\text{H}_{16}\text{O}_5$ requires C, 66.6; H, 5.1%; M , 288), ν_{max} 1 640 and 1 610 cm^{-1} (olefinic C=C and H-bonded C=O), τ (CDCl_3) -2.3 (2 H, s, exchanged with D_2O , chelated phenolic OH), 2.5 (1 H, s, quinone H), 2.65 (2 H, s, ArH), 4.4 (1 H, t, CH_2 -CH=C-), 7.1 (1 H, m, CHMe_2), 7.8 (2 H, m, CH_2 -CH=C), and 8.3 and 8.4 (6 H, 2s, CMe_2).

Photochemical Conversion of Shikonin Angelate into Compound (9).—Shikonin angelate (470 mg) was irradiated in ethanol (400 ml) with a low-pressure mercury lamp under nitrogen for 90 h. Removal of the solvent under reduced pressure yielded a dark red gum of complex composition. T.l.c. in three solvent systems showed the presence of compound (9). Chromatographic separation on an acid-washed silica gel column [chloroform-petroleum (1 : 4 v/v)] removed most of the undesired material. Subsequent elutions with the same solvents (1 : 1 v/v) gave dark red fractions containing impure compound (9). The combined fractions were rechromatographed twice to give compound (9) as an uncrystallisable gum (43 mg), identical (i.r. and n.m.r.) with the compound isolated previously.

Conversion of Shikonin Angelate into Compound (9) on the Column.—Shikonin angelate (200 mg) was adsorbed on an acid-washed silica gel column. Elution was carried out with chloroform-petroleum (1 : 2 v/v) till the red band was half way through the column. Elution was discontinued and the column was left for 120 h. Continued elution with the same solvent system gave unchanged shikonin angelate (113 mg); elution with chloroform-ether (1 : 1 v/v) then gave compound (9) (12 mg), identical with that isolated previously.

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