Indian Journal of Chemistry
Vol. 33B, May 1994, pp. 432-435

Synthesis of (±)-6-hydroxy-3,4-dihydro-4,7-dimethylbenzo-1-pyran-2(*H*)-one, a tetranorsesquiterpenoid

K K Nadkarni, S P Kamat & S K Paknikar*
Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 203

Received 19 August 1993; revised and accepted 10 January 1994

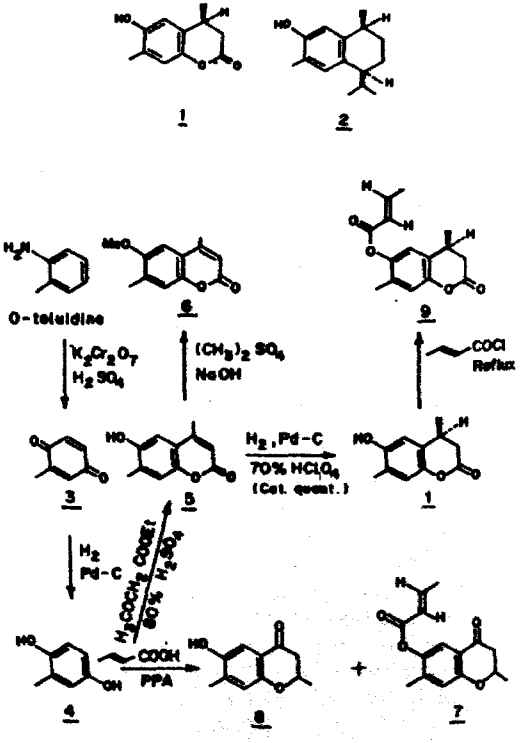
Synthesis of the title compound(1), a naturally occurring C_{11} coumarin, isolated from *Heritiera ornithocephala* Kosterm has been achieved. A probable biogenesis of 1 involving the mode of elimination of four carbon atoms of the sesquiterpenoid precursor 2 has been suggested. Preparation of benzo-1-pyran-4-ones 7 and 8 has also been reported.

Although 4-methylcoumarin and its derivatives have been synthetically known for over a century[1], very few of the naturally occurring coumarins are reported to possess a 4-methyl substituent[2]. The recent isolation of (−)-6-hydroxy-3, 4-dihydro-4,· 7-dimethylcoumarin (1) by Cambie and co-workers[3] from *Heritiera ornithocephala* Kosterm (Fam sterculiaceae) is perhaps the first representative of the naturally occurring 3,4-dihydrocoumarins and is likely to have a terpenoid biosynthetic origin rather than the customary biosynthetic derivation from a phenylpropanoid precursor[1(a)]. Herein, we report a synthetic confirmation of the assigned structure 1. We also propose a detailed biogenetic pathway which accounts for its co-occurrence with *cis*-7-hydroxycalamenene (2) and explains how four carbon atoms of the sesquiterpenoid precursor 2 are eliminated resulting in the formation of 1. Compound 1 represents the first member of the tetranorsesquiterpenoid group.

2-Methyl-*p*-benzoquinone (3), prepared by $K_2Cr_2O_7$ oxidation of *o*-toluidine[4], was converted into 2-methylhydroquinone (4) by catalytic hydrogenation over Pd-C in ethanol. The hydroquinone 4 was condensed with ethyl acetoacetate under Pechmann conditions[5] to yield 6-hydroxy-4,7-dimethylcoumarin (5) (**Scheme I**). The spectral data (MS and ^{1}H NMR) previously not recorded in the literature confirmed the identity of 5.

Saturation of the 3,4-double bond of 5 was found to be unusually difficult mainly because of its poor solubility in normal organic solvents and also the known inertness of the 3,4-double bond of coumarins towards hydrogenation[1(b)].

Methylative ring opening followed by hydrogenation, demethylation and ring closure was expected to yield 1. However, reaction of 5 with NaOH and dimethyl sulphate failed to give the ring opened product but gave a crystalline compound (m.p. 160°) which was identified as methyl ether (6) of 5 on the basis of ^{1}H NMR spectral data. Failure to get the ring opened *o*-methoxy-β-methylcinnamic acid



Scheme I

derivative is somewhat surprising as this method has been used earlier by other investigators[6,7].

The desired dihydro derivative **1** could be obtained as a crystalline solid (m.p. 142°) by carrying out the catalytic hydrogenation of **5** over 10% Pd-C at 90° in gl. acetic acid containing traces of perchloric acid[1(c),8]. The synthetic coumarin **1** was found to have identical spectral data when compared to those recorded on the natural sample.

Gupta *et al.*[9] reported the preparation of 5-, 6- and 7-hydroxy-3,4-dihydrocoumarins by reaction of the corresponding phenols with methyl acrylate in the presence of anhyd. aluminium chloride and dry HCl. These authors further observed that hydroquinone failed to react under these conditions. Our successful approach for the synthesis of coumarins with PPA[10] together with previous reports of condensation of phenol with crotonic acid[11] prompted us to investigate the reaction of 2-methylhydroquinone with crotonic acid in the presence of PPA at 70°. Under these conditions two compounds **7** and **8** having melting points 119° and 184°, respectively were obtained.

Examination of the ^{1}H NMR spectrum of compound **7** revealed the presence of vinyl methyl at δ 1.98 (3H, dd, J=7, 1.75 Hz), a vinyl proton at 6.05(1H, dq, J=15.5, 1.75 Hz) and another vinyl proton multiplet at 7.2(1H) clearly indicating the presence of a crotyl ester side chain. The presence of [−O−CH(CH$_3$)−CH$_2$−CO−Ar] grouping was evident from the secondary methyl doublet at δ 1.5 (3H, J=6.5 Hz), a two proton doublet at 2.64(2H) and a multiplet at 4.57(1H) corresponding to the C$_2$-hydrogen. The two aromatic protons appeared as singlets at δ 6.85 and 7.52 having a 1,4-relationship, and an aromatic methyl group appeared as a singlet at δ 2.17(3H). These chemical shifts were consistent with the structure 6-crotyloxy-2,3-dihydro-2,7-dimethylbenzo-1-pyran-4(*H*)-one (**7**). In order to support the assigned structure **7**, crotyl ester **9** of coumarin **1** was prepared. As anticipated, esters **7** and **9** were found to be different.

Compound **8** analysed for $C_{11}H_{12}O_3$. Its ^{1}H NMR spectrum (chemical shifts are given in experimental) lacked the signals due to the crotyl ester side chain, but showed the presence of [−O−CH(CH$_3$)−CH$_2$−CO−Ar] grouping, two aromatic protons in 1,4-position and a phenolic proton(singlet at δ 5.6). These facts are consistent with the structure 6-hydroxy-2, 3-dihydro-2, 7-dimethylbenzo-1-pyran-4(*H*)-one (**8**). Formation of benzo-1-pyran-4-one derivatives by reaction of 2,3- and 2,5-dimethylphenols with crotonic acid in the presence of PPA has been reported by Merchant and Joshi[11].

The biosynthesis of **1** is thought to involve 7-hydroxycalamenene (**2**) as an intermediate. The sequence of events leading finally to the loss of four carbon atoms most likely involves oxidative cleavage process (**Scheme II**). It is of interest to note that the compounds **A**, **B** and **C** have been reported to co-occur in the soft coral *Lemnalia cervicornis*[12].

Experimental Section

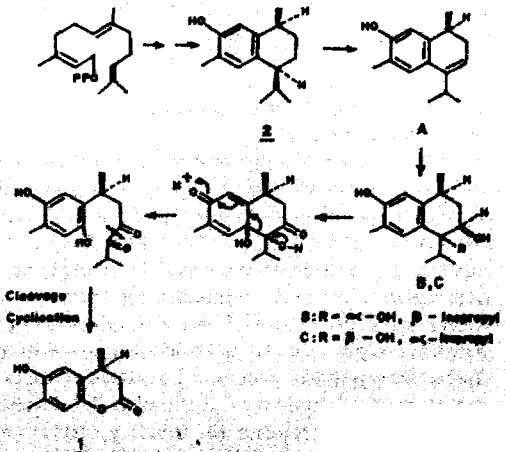
Melting points reported are uncorrected. Pet. ether refers to the fraction of b.p. 60-80°.

2-Methylhydroquinone (**4**)

2-Methyl-*p*-benzoquinone[4] (3; 0.61 g, 0.005 mole) was dissolved in EtOAc and hydrogenated using 5% Pd-C (0.065 g) at room temperature until absorption of H_2 ceased (4 hr). After filtration through a bed of charcoal, the catalyst and charcoal bed was washed with EtOAc (2 × 10 ml). The residue obtained after evaporation of the solvent was purified by crystallization from benzene to give **4** (yield 0.6 g, 96%), m.p. 126°.

6-Hydroxy-4,7-dimethylcoumarin (**5**)

To a thoroughly cooled and well stirred mixture of **4** (0.5 g, 0.004 mole) and ethyl acetoacetate (0.53 g, 0.004 mole) was added 80% H_2SO_4 (2.5 mL) over a period of 1 hr. The temperature was not allowed to rise above 5° during the addition and the mixture further stirred for 24 hr at room temperature. Usual work-up gave the crude **5** (0.55 g, 71.8%) which was



Scheme II

purified by crystallization from EtOH, m.p. 210° as reported[5]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.34(3H, s, $-CH_3$), 2.37(3H, s, $-CH_3$), 4.9(1H, s, C_3-H), 6.24(1H, bs, Ar−OH), 6.95(1H, s, Ar−H), 7.12(1H, s, Ar−H); MS: m/z 190(M^+·, 80%), 162(72), 161(100).

6-Methoxy-4,7-dimethylcoumarin (6)

The coumarin 5 (0.19 g, 0.001 mole) was dissolved in 1% NaOH (5 mL) by heating on a steam-bath. To the cooled solution was added dimethyl sulphate (0.126 g, 0.001 mole) while stirring over a period of 5 min, acidified with dil. HCl and the solid that precipitated out was chromatographed over silica gel. Elution with benzene-EtOAc (95:5) and crystallization from $CHCl_3$-pet. ether (1:1) gave 6 (0.062 g, 30%), m.p. 160°; IR (nujol): 2945, 1740(α,β-unsaturated lactone), 1570, 1470, 1420, 1390, 1250, 1180, 1090, 930, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 2.32(3H, s, C_4-CH_3), 2.44(3H, s, Ar−CH_3), 3.9(3H, s, $-OCH_3$), 6.2(1H, s, C_8-H), 7.1(1H, s, C_5-H).

6-Hydroxy-3,4-dihydro-4,7-dimethylbenzo-1-pyran-2(H)-one (1)

The coumarin 5 (0.304 g, 0.0016 mole) in AcOH(30 ml containing 10 drops of 70% $HClO_4$) was hydrogenated using 10% Pd-C (0.1 g) at 90° until absorption of H_2 ceased (3 hr). After filtration the catalyst was washed with AcOH (5 ml). After practically all AcOH was distilled out, the residue was neutralised with solid $NaHCO_3$, extracted with $CHCl_3$, washed with water and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was chromatographed over silica gel. Elution with benzene-EtOAc (95:5) gave 1 (0.19 g, 61.8%) m.p. 142°. IR and ^{1}H NMR were found to be identical with those recorded on natural 1[3].

Reaction of 2-methylhydroquinone (4) *with crotonic acid in presence of PPA*

An equimolar mixture of 4 (0.42 g, 0.0034 mole) and crotonic acid (0.29 g, 0.0034 mole) was stirred in PPA [prepared from P_2O_5 (7.0 g) and phosphoric acid (10 ml) at 110° for 1 hr] at 70° for 4 hr. The reaction mixture was poured over crushed ice (100 g) and left overnight. The solid obtained after filtration was found to be a mixture of two compounds (TLC). Addition of pet. ether to the concentrated solution of the two compounds, precipitated out the more polar component 6-hydroxy-2,3-dihydro-2,7-dimethylbenzo-1-pyran-4(*H*)-one (8; 0.062 g, 10%), m.p. 184°; IR (KBr): 3400(OH), 1685(CO), 1630, 1470, 1435, 1210, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz): δ 1.48(3H, d, $J=7$ Hz, C_2-CH_3), 2.24(3H, s, Ar−CH_3), 2.6(2H, d, $J=9$ Hz, C_3-H), 4.54(1H, m, C_2-H), 5.6(1H, s, Ar−OH), 6.76(1H, s, C_8-H), 7.28(1H, s, C_5-H) (Found: C, 68.48; H, 6.34. $C_{11}H_{12}O_3$ requires C, 68.75; H, 6.25%).

Concentration of the pet. ether soluble portion (mother liquor) containing compound 7 and chromatography over silica gel using benzene-EtOAc (99:1) as eluant, followed by crystallization with pet. ether gave 6-crotyloxy-2,3-dihydro-2,7-dimethylbenzo-1-pyran-4-(*H*)-one (7; 0.035 g, 4%), m.p. 119°; IR (KBr): 1745 (ester CO), 1695(CO), 1155, 1100, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.5 (3H, d, $J=7$ Hz, C_2-CH_3), 1.98(3H, dd, $J=7$, 1.75 Hz, vinyl $-CH_3$), 2.17 (3H, s, Ar−CH_3), 2.64(2H, d, $J=7$ Hz, C_3-H), 4.57(1H, m, C_2-H), 6.05(1H, dq, $J=15.5$, 1.75 Hz, vinyl H α- to CO), 6.85(1H, s, C_8-H), 7.2(1H, m, vinyl H β-to CO), 7.52(1H, s, C_5-H).

6-Crotyloxy-3,4-dihydro-4,7-dimethylbenzo-1-pyran-2(H)-one (9)

Coumarin 1 (0.096 g, 0.5 mmole) and crotonyl chloride (0.078 g, 0.75 mmole) were heated at 100° under reflux for 2 hr. The reaction product was extracted with $CHCl_3$. The extracts were washed with dil, NaOH, water and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a viscous liquid which was purified by passing through a column of silica gel to get 9 (0.125 g, 96%); ^{1}H NMR ($CDCl_3$, 90 MHz): δ 1.32(3H, d, $J=6.5$ Hz, C_4-CH_3), 2.04(3H, d, $J=6.5$ Hz, vinyl $-CH_3$), 2.18(3H, s, Ar−CH_3), 2.7(2H, m, C_3-H), 3.12(1H, m, C_4-H), 6.13(1H, s, vinyl H α- to CO), 6.32(1H, s, C_8-H), 7.1(1H, s, C_5-H), 7.4(1H, m, vinyl H β- to CO).

Acknowledgement

We thank Dr Ralf Mayer and (late) Dr Alan Thomas for spectral measurements, Prof. R C Cambie for the spectra of natural 1 and UGC, New Delhi for partial financial support to S P K under Minor Research Project.

References

1 Murray R D H, Mendoz J & Brown S A, *The natural coumarins* (John Wiley & Sons Ltd) 1982, p 440, 472, (a)163, (b)84, (c)86.

2 Murray R D H, *Naturally occurring plant coumarins* in: *Progress in the chemistry of organic natural products* 58 (Wien Springer Verlag, New York) 1991, p 84.

3 Cambie R C, Lal A R & Ahmad F, *Phytochemistry*, 29 (1990) 2329.

4 Cremlin R J W & Still R H, *Named and miscellaneous Reactions* in: *Practical organic chemistry*, (Heinemann Educational Books Ltd) 1967, p 187.

5 Desai R D & Mavani C K, *Proc Ind Acad Sci*, 15A (1942) 11.

6 Bickoff E M, Lyman R L, Livingston A L & Booth A N, *J Am Chem Soc*, 80 (1958) 3969.

7 Masahiro T, Yoshihiko M, Yoshiaki T & Takeyoshi T, *Tetrahedron Lett*, (1972) 5251.

8 Lemnich J, Pedersen P A & Nielsen B E, *Tetrahedron Lett*, (1969) 3365.

9 Das Gupta A K, Chatterjee R M & Das K R, *J Chem Soc (C)*, (1969) 29.

10 Bhattacharjee J & Paknikar S K, *Indian J Chem*, 28B (1989) 205.

11 Joshi V & Merchant J R, *Indian J Chem*, 15B (1977) 280.

12 Bowden B F, Coll J C, Engelhardt L M, Tapiolas D M & White A H, *Aust J Chem*, 39 (1986) 103.