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PALBINONE, A POTENT INHIBITOR OF 3α-HYDROXY DEHYDROGENASE FROM PAEONIA ALBIFLORA

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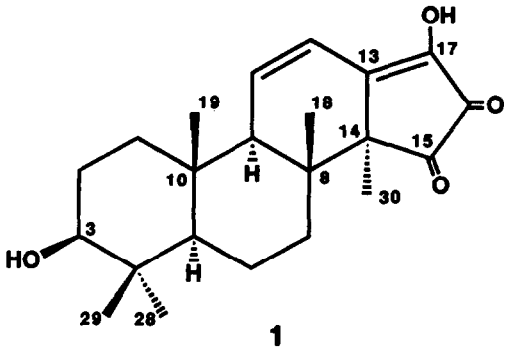
Summary: The structure of palbinone (1), isolated as potent inhibitor of 3α-hydroxy dehydrogenase from the roots of Paeonia albiflora PALLAS, was determined based on the 2D NMR spectroscopy.

Paeonia Radix, the roots of Paeonia albiflora, is one of the best known crude drugs in Japan, and has been the subjects of many investigators. Especially the monoterpenoids, which are the principal ingredients of Paeonia Radix, have been investigating as a major bioactive component of this crude drug.[1] In our search for biologically significant substances from P. albiflora, we have isolated a new terpenoid, named palbinone (1), and found that it has a potent inhibitory activity against 3α-hydroxy dehydrogenase.[2] This paper describes the isolation and structure elucidation of this new terpenoid.

The roots (5.0 kg) of P. albiflora were pulverized and extracted with chloroform at room temperature. The chloroform extract was roughly separated by silica gel column chromatography using $CHCl_3$ and 5% MeOH/$CHCl_3$. The $CHCl_3$ eluates were further separated by preparative TLC to give palbinone (1)(87 mg), along with paeonilactone B.[3]

Palbinone (1), red needles (from ether-hexane), mp 254-255°C, $[\alpha]_D$ -223.8° ($CHCl_3$), showed UV absorptions (MeOH) at 237 and 387 nm (log ε: 3.2 and 3.0)(α,β-γ,δ-unsaturated carbonyl groups) and IR absorptions ($CHCl_3$) at 3500(OH), 1750(ketone), 1700, 1690(unsaturated ketone), and 1605 cm^{-1}(double bond). It showed the molecular ion peak at m/z 358 in MS and its molecular formula was determined to be $C_{22}H_{30}O_4$ (M^+ 358.2137, calcd 358.2143) by high resolution MS. The ^1H- and ^{13}C-NMR[4] and ^1H-^1H and ^1H-^{13}C COSY[5] of 1



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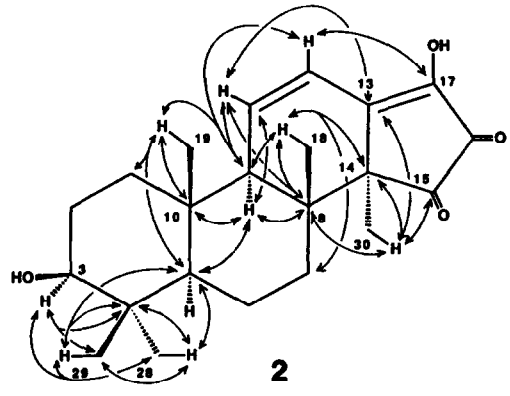

2

indicated the presence of two ketones (δ_C 201.26 and 180.89[6]), two double bonds (δ_H 6.40 and 6.90; δ_C 141.57, 120.29, 146.95, and 151.29), a hydroxymethine (δ_H 3.28; δ_C 78.64), five tert-methyl groups (δ_H 0.80, 0.82, 0.93, 1.02, and 1.20; δ_C 15.07, 19.02, 18.32, 27.79, and 19.44), and four quaternary sp^3 carbons (δ_C 37.20, 38.96, 40.02, and 50.74). The above data led us to suppose that the structure of palbinone might be 1.

At this stage, we measured the HMBC spectrum[7] of 1 in order to confirm the assumed structure (1). As shown in formula 2, the ^{13}C-signals at δ 146.95 (C-13) and at δ 56.08 (C-9) showed long-range correlations with the ^1H-signals at δ 1.20 (30-H_3) and 6.40 (11-H) and δ 0.82 (18-H_3), 0.93 (19-H_3), 6.40 (11-H), and 6.90 (12-H), respectively. In turn, the ^{13}C-signal at δ 37.20 (C-10) was correlated with the ^1H-signals at δ 0.93 (19-H_3) and 2.07 (9-H), and the signal at δ 54.87 (C-5) with the ^1H-signals at δ 0.80 (29-H_3), 0.93 (19-H_3), 1.02 (28-H_3), and 2.07 (9-H). Also some other significant long range correlations are shown by arrows. Thus the planar structure of 1 was proved.

The relative stereochemistry of 1 was determined on the basis of coupling constants of each protons and the results of NOE experiments. Irradiation at the 29-H_3 and 18-H_3 caused the increase of signal intensity of the 19-, 28-, 6α-, and 6β-protons and the 19-, 6β-, and 7β-protons, respectively, and irradiation at the 19-H_3 and 28-H_3 enhanced the increase of signal intensity of the 29-, 18-, 6β-, and 11-protons and the 29-, 5-, 6α-, and 3-protons, respectively. Also, irradiation at the 30-H_3 gave NOE enhancement of 7α- and 9-protons. Therefore the structure of palbinone was proved to be 1.

IC_{50} value (50% inhibitory concentration) of palbinone (1) against 3α-hydroxy dehydrogenase was 4.6 x 10^{-8}M. Palbinone (1) was more potent inhibitor of 3α-hydroxy dehydrogenase than indomethacin, which is known as one of the strongest inhibitors with an IC_{50} of 3.2 x 10^{-6}M under the same assay conditions.

References and Note

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4) 1: ^1H-NMR ($CDCl_3$) δ: 0.80 (3H, s, 29-H_3), 0.82 (3H, s, 18-H_3), 0.89 (1H, dd, J=12.0, 2.0 Hz, 5-H), 0.93 (3H, s, 19-H_3), 1.02 (3H, s, 28-H_3), 1.13 (1H, td, J=13.0, 4.5 Hz, 1β-H), 1.20 (3H, s, 30-H_3), 1.51 (1H, ddd, J=14.0, 11.5, 4.0 Hz, 6β-H), 1.66 (1H, m, 2β-H), 1.70 (1H, m, 7α-H), 1.72 (1H, m, 6α-H), 1.75 (1H, m, 2α-H), 1.95 (1H, dt, J=13.0, 4.0 Hz, 1α-H), 2.06 (1H, m, 7β-H), 2.07 (1H, br s, 9-H), 3.28 (1H, dd, J=12.5, 5.5 Hz, 3-H), 6.40 (1H, dd, J=10.0, 2.5 Hz, 11-H), 6.90 (1H, dd, J=10.0, 3.2 Hz, 12-H); ^{13}C-NMR ($CDCl_3$) δ: 15.07 (29-C), 17.92 (6-C), 18.32 (19-C), 19.02 (18-C), 19.44 (30-C), 26.72 (2-C), 27.79 (28-C), 33.31 (7-C), 37.20 (10-C), 38.11 (1-C), 38.96 (4-C), 40.02 (8-C), 50.74 (14-C), 54.87 (5-C), 56.08 (9-C), 78.64 (3-C), 120.29 (12-C), 141.57 (11-C), 146.95 (13-C), 151.29 (17-C), 180.89 (16-C)[6], 201.26 (15-C).
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