Tetrahedron Letters, Vol.22, No.32, pp 3069 - 3070, 1981
Printed in Great Britain

0040-4039/81/323069-02$02.00/0

PAEONIFLORIGENONE, A NEW MONOTERPENE FROM PAEONY ROOTS

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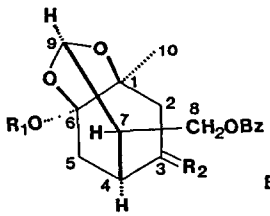
Summary: Paeoniflorigenone (1), a new monoterpene which produces a neuromuscular-blocking effect in mice, was isolated from paeony roots and its structure was elucidated.

In the course of our study on pharmacologically active principles of Paeoniae Radix, a new monoterpene, named paeoniflorigenone (PFG), was isolated from roots of *Paeonia albiflora* PALLAS in 0.04 % yield along with benzoic acid and paeoniflorin (5). PFG was found to produce a blocking effect on neuromuscular junction in phrenic nerve diaphragm preparations of mice.

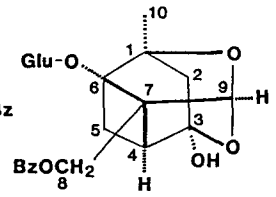
The ether-soluble fraction of the water extracts was chromatographed on silica gel with $CHCl_3$ to give PFG (1) as colorless viscous oil, $[\alpha]_D^{25}$+4.3°(c 0.69, MeOH); UV λ_{max}^{MeOH}nm(logε): 220(3.94), 258(sh), 263(2.90), 270(2.83); IR $\nu_{max}^{CHCl_3}$: 3400, 1725, 1605, 1272 cm^{-1}. The PMR spectrum ($CDCl_3$) of 1 showed the presence of methyl protons (δ1.32, s), methyleneoxy protons (4.14, 1H, dd, J=12, 9.6 Hz; 4.42, 1H, dd, J=12, 6 Hz, -O-C<u>H</u>$_2$CH-), an acetal proton (5.52, 1H, s, $\begin{matrix}-O\\-O\end{matrix}$>C<u>H</u>-), a hydroxyl proton (3.42) and aromatic protons (7.30-8.19, 5H). The CMR spectrum (pyridine-d_5) of 1 showed signals due to a ketonic carbonyl (δ210.2), an ester carbonyl (166.1), a methyl (22.2), three methylenes (35.6, 47.7, 63.5), three methines (43.7, 47.2, 100.0), two quaternary carbons (79.4, 102.4) and six aromatic carbons (128.8, 129.9, 130.6, 133.3).[1]

Acetylation of 1 with Ac_2O/pyridine gave an acetate (2) as colorless oil, $C_{19}H_{20}O_7$; $[\alpha]_D^{25}$-13.7° (c 1.24, MeOH); PMR ($CDCl_3$): δ2.16 (3H, s, -OAc). Methylation of 1 with CH_2N_2 yielded a methyl ether (3) as colorless prisms, $C_{18}H_{20}O_6$; mp 121-122°; $[\alpha]_D^{25}$-14.0°(c 1.0, MeOH); IR ν_{max}^{KBr}: 1730 cm^{-1} (ester), 1715 cm^{-1} (ketone); PMR (200 MHz, $CDCl_3$): δ1.26 (3H, s, -CH_3), 2.06 and 2.61 (each 1H, dd, J=12.8, 2.4 Hz; dd, J=12.8, 3.2 Hz, -C<u>H</u>$_2$CH-), 2.37 (1H, m, -O-CH_2C<u>H</u>-), 2.66 (2H, AB q, J=18 Hz), 2.95 (1H, m, -CH_2C<u>H</u>-), 3.56 (3H, s, -OCH_3), 4.08 and 4.42 (each 1H, dd, J=12, 9.6 Hz; dd, J=12, 6 Hz, -O-C<u>H</u>$_2$CH-), 5.55 (1H, s, $\begin{matrix}-O\\-O\end{matrix}$>C<u>H</u>-), 7.40-7.64 (3H, m), 8.08 (2H, dd, J=8.4, 2 Hz). On irradiation at δ2.37, both double doublets at δ4.08 and 4.42 changed to doublets (each J=12 Hz) and the multiplet at δ2.95 was sharpened. On irradiation at δ2.95, both double doublets at δ2.04 and 2.61 changed to doublets (each J=12.8 Hz).

Reduction of 3 with $NaBH_4$ in EtOH-CH_2Cl_2(2:1 v/v) afforded an alcoholic compound (4), $C_{18}H_{22}O_6$;

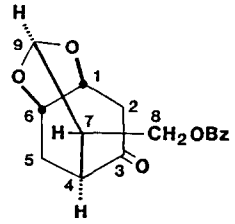


1 : R_1-H , R_2-O
2 : R_1-Ac, R_2-O
3 : R_1-Me, R_2-O
4 : R_1-Me, R_2-<OH H



5

Bz = C_6H_5CO



6

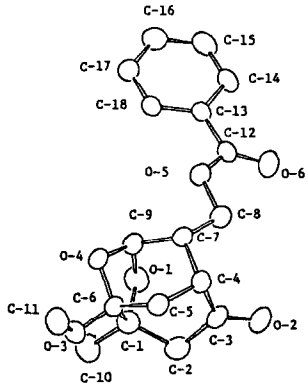


Fig.1

mp 102-103°; $[\alpha]_D^{25}$+64.6°(c 1.33, MeOH); PMR (200 MHz, $CDCl_3$): δ4.29 (1H, t, J=8 Hz, -CH-OH), 1.43 and 2.28 (each 1H, dd, J=12.8, 2.4 Hz; dd, J=12.8, 4.8 Hz, -CH_2CH-), 1.93 and 2.12 (each 1H, d, J=16 Hz; dd, J=16, 8 Hz, -CH(OH)-CH_2-), 2.38 (1H, m, -O-CH_2CH-), 2.81 (1H, m, -CH-CH(OH)-). The triplet at δ4.29 was changed to a doublet (J=8 Hz) by irradiation at δ2.12 or 2.81, whereas the double doublet at δ2.12 transformed to a doublet (J=16 Hz) and the multiplet at δ2.81 was sharpened by irradiation at δ4.29.

From these findings and the spectral similarity of PFG (1) to paeoniflorin (5),[1,2] the partial structure (6) was deduced for PFG. The remaining methyl and hydroxyl groups were supposed to locate at C-1 and C-6 or *vice versa*, respectively.

Finally, the X-ray crystallographical study of the methyl ether (3) confirmed the structure of PFG. Crystal data: $C_{18}H_{20}O_6$, M=332, orthorombic, space group $P2_12_12_1$; a=12.735(5), b=19.582(7), c=6.826(3) Å, Z=4, D_x=1.296 gm.cm^{-3}. A total of 1789 reflections were recorded in the θ-2θ scan mode using a Philips four-circle diffractometer (PW 1100) with graphite-monochromated Cu-Kα scan radiation. The structure was solved by the direct method with the aid of MULTAN. Block diagonal least-squares refinement with anisotropic temperature factors for non-hydrogen atoms, and isotropic temperature factors for hydrogen atoms converged to a conventional R value of 0.052. A computer generated perspective drawing of methyl ether (3) is shown in Fig. 1.

The absolute configuration of PFG and the detailed aspect of its pharmacological activity will be published elswhere.

Aknowledgement: We wish to thank to Dr. Y. Itatani and prof. Y. Yamamoto, Kanazawa university for the measurement of CMR spectra.

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(Received in Japan 31 March 1981)