The results from the DSC and NMR studies were compared to the outcome of a storage study of drug melts and drug/PVP co-melts for 5 weeks at 30 °C/< 10% RH and 30 °C/75% RH and, in the case of drug melts, −20 °C. The stability data (Table) indicates that amorphous indomethacin and indomethacin/PVP formulations are more stable than the respective nifedipine formulations.

The results of this study show that proton relaxation measurements, using variable temperature solid state NMR, are a valuable additional tool to thermal analytical methods for predicting the amorphous physical stability. For amorphous drug melts and drug/PVP co-melts $T_1\varrho$ measurements provide an insight into amorphous stability that is different to that of DSC Tg measurements. NMR relaxation measurements lead to an improved estimate of amorphous physical stability compared to DSC Tg determination.

In proton NMR all the proton relaxation rates are averaged. Future work will use ^{13}C NMR to measure the relaxation rate of different protons of the molecule to discover potential 'hotspots', which may be linked to the decreased physical stability of some amorphous compounds.

Experimental

1. Materials

Indomethacin, nifedipine and polyvinylpyrrolidone k30 (PVP) were purchased from Sigma Aldrich (Dorset, UK).

2. Methods

2.1. X-ray Powder Diffraction (XRPD)

To confirm that quench cooling resulted in an amorphous product, samples were melted in an X-ray sample holder and then quench cooled with liquid nitrogen. Following cooling the samples were analysed with a Philips X'Pert MPD (count time 1 s, step size 0.04 °2θ, Ni-filtered Cu-kα radiation, 30 kV, 40 mA, sample size: approx. 300 mg).

2.2. Differential Scanning Calorimetry (DSC)

Amorphous samples were prepared by melting either pure drug or drug/PVP (1 : 1 w/w) mixtures in crimped aluminium pans using a TA Instruments 2920 DSC at a heating rate of 10 K min^{-1} (nitrogen purge: 20 ml min^{-1}, sample size: approx. 5 mg, temperature and enthalpy calibration with an indium standard) and then quench cooling the melt using a stainless steel cylinder filled with liquid nitrogen placed over the DSC cell. To determine the Tg (onset) value the samples were then reheated in the DSC at 10 K min^{-1}.

2.3. Solid State NMR

Amorphous samples were prepared by melting approximately 500 mg of drug or drug/PVP in an oven in 1 cm long glass tubes. Molten samples were then plunged into liquid nitrogen. All cooled melts were transparent yellow solids. $T_1\varrho$ proton relaxation measurements were performed over a wide temperature range for all samples. Following preparation, the samples were placed in the NMR probe and cooled to −70 °C. Subsequent measurements were made by heating to various temperatures at 5 K min^{-1} and then measuring relaxation times isothermally. A Varian Unity plus NMR operating at 300 MHz was used for the proton measurements. For $T_1\varrho$ measurements a radio frequency field equivalent to 70 kHz was used.

Acknowledgement: The authors acknowledge the Vernon Tews scholarship for AF.

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A new picoline alkaloid from the pseudobulb of *Desmotrichum fimbriatum* Blume

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Received March 4, 2003, accepted April 5, 2003

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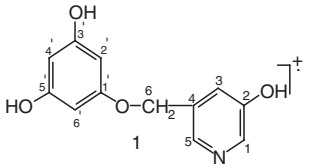
Pharmazie 58: 762–763 (2003)

Desmotrichum fimbriatum Blume (Orchidaceae), is an epiphytic orchid commonly known as Jivanti, distributed up to 2,700 m. It is an important Ayurvedic drug used as astringent, aphrodisiac, expectorant, stimulant, cardiotonic and to relieve asthma, bronchitis and throat infections [1, 2]. The earliest observation was the presence of traces an alkaloid, α- and β-jivantic acids [3] and 3-methyl octacosane, 9-methyl deca (15′-hydroxy-15-methyl-n-nonadeca-1-oate) and octacont-3-en-1,5-olide [4] from the stem and root of this plant. The present paper describes the isolation and characterization of a new alkaloid.

Compound **1**, named desmotrichinine was obtained as a yellow crystalline solid from chloroform fractions. It responded positively to Dragendorff's reagent and 5% ferric chloride solution. The HREIMS of **1** showed the molecular ions peak at m/z 233.0142 corresponding to the molecular formula established as $C_{12}H_{11}O_4N$. The positive ion FAB MS showed $[M]^+$ at m/z 233 and further significant fragments ion peak at m/z 138 [M-C_5H_5NO, C_4-C_6 fission]$^+$, 125 [M-C_6H_6NO, C_6-O fission]$^+$ and 108 [M-$C_6H_5O_3$]$^+$. Its IR spectrum showed characteristic absorptions for hydroxyl group (3300 cm^{-1}) and aromatic rings (1670, 1523 cm^{-1}). The UV spectrum also exhibited the absorption maximum at 335 nm and bathochromic shifts were observed with sodium acetate (418 nm) and boric acid (+ 18 nm) indicating the presence of an m-hydroxylated benzenoid nucleus [5].

The ^{1}H NMR spectrum of **1** displayed the presence of a two proton broad signal at δ 9.62 assigned to H-1 and H-5. A three proton-meta-coupled doublet at δ 7.21 (J = 3.6 Hz) was ascribed to H-2′, H-4′, H-6′. A one-proton double doublet at δ 6.58 with coupling interactions of 3.6 and 3.6 Hz was associated with H-3. A two-proton broad signal at δ 4.63 was due to oxygenated C-6 methylene protons. The ^{13}C NMR data showed signals at δ 177.7 (C-1, C-5), 111.9 (C-3) and 121.9 (C-4) supporting thereby that the compound **1** possessed a pyridine nucleus and carbon signals for oxygenated methylene carbons at δ 64.6 and aromatic carbons between δ 177.7- 111.6.

On the basis of the forgoing account the structure of **1** has been established as 2-hydroxy-6-pyrogalloloxy-β-picoline.



Experimental

1. General procedure

The m. p. was determined on a scientific apparatus and is uncorrected. The IR spectrum was recorded in KBr pallets on a Bio-rad 377 spectrophotometer. ^{1}H (300 MHz), ^{13}C (75 MHz) and 2D NMR spectra were screened by a Brucker Spectrospin NMR instrument in $CDCl_3$ using TMS as internal standard. HREI-MS was recorded on Varian MAT 731 and EIMS was run at 70 eV on a Joel D-300 spectrometer. Optical rotation was measured on a JASCO DIP-SL Polarimeter. CC was performed on silica gel (Merck, 60–120 mesh) and TLC on silica gel G (Merck).

2. Plant material

The pseudobulbs of *D. fimbriatum* Blume were purchased from the local market of Khari Baoli, Delhi, India, in October 1999. The specimen was identified by Dr. M.P. Sharma (taxonomist), in the Department of Botany, Jamia Hamdard. A voucher specimen No. Phytochem./03/2001 was deposited in the herbarium of the Phytochemistry Research Laboratory, Jamia Hamdard.

3. Extraction

The pseudobulbs of *D. fimbriatum* (2.5 kg) were extracted with petroleum ether, chloroform and then finally with MeOH. The chloroform fraction (40 g) was concentrated and chromatographed on silica gel (60–120 mesh). The column was eluted with petroleum ether and chloroform in order of increasing polarity.

4. Isolation and characterization of 1

Elution of the column with chloroform, fraction 130–50, afforded yellow crystals of **1,** recrystallized from chloroform-methanol (1 : 1), 40 mg (0.02%), m. p. 195–198 °C, R_f 0.25 (hexane-acetone-4 : 1). $[\alpha]^D_{20} + 25^0$ (c 0.1, MeOH); UV λ_{max} (MeOH) nm (log ε): 276 (5.2), 335 (6.92), 418 (7.2); IR ν_{max} (KBr): 3300, 2849, 1670, 1523, 1274, 1198, 1051, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.62 (2H, brs, H-1, H-6), 7.21 (3H, d, J = 3.6 Hz, H-2′, H-4′, H-6′), 6.58 (1H, dd, J = 3.6, 3.6 Hz, H-4), 4.63 (2H, brs, H2–6); ^{13}C NMR ($CDCl_3$): 177.7 (C-1), 157.2 (C-2), 111.9 (C-3), 121.9 (C-4), 177.7 (C-5), 64.6 (C-6), 152.8 (C-1′), 111.9 (C-2′), 157.2 (C-3′), 111.9 (C-4′), 152.8 (C-5′), 111.6 (C-6′); EIMS (rel. int): m/z 233 $[M]^+$ ($C_{12}H_{11}O_4N$) (9.2), 205 (25.9), 138 (36.6), 125 (52.4), 108 (100), 94 (15.6), 80 (81.3), 69 (19.5), 53 (65.8).

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