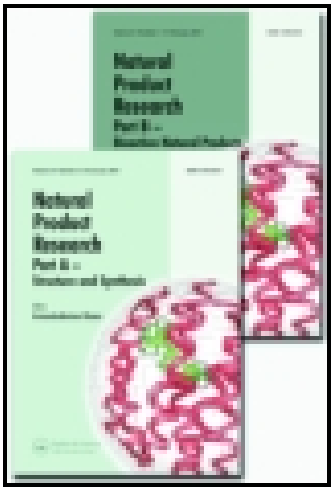

Natural Product Research: Formerly Natural Product Letters

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gnpl20

A new benzylisoquinoline alkaloid from Argemone mexicana

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Published online: 09 Dec 2009.

To cite this article: Sarita Singh, T.D. Singh, V.P. Singh & V.B. Pandey (2010) A new benzylisoquinoline alkaloid from Argemone mexicana, Natural Product Research: Formerly Natural Product Letters, 24:1, 63-67, DOI: 10.1080/14786410902800723

To link to this article: http://dx.doi.org/10.1080/14786410902800723

Natural Product Research
Vol. 24, No. 1, 10 January 2010, 63–67

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A new benzylisoquinoline alkaloid from *Argemone mexicana*

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(*Received 11 July 2008; final version received 2 February 2009*)

A new benzylisoquinoline alkaloid, argemexirine, together with two known protoberberine alkaloids, dl-tetrahydrocoptisine and dihydrocoptisine, have been isolated from the methanolic extract of the whole plant of *Argemone mexicana* L. The compounds were identified by spectral and chemical evidence. This is the first report of these alkaloids in this plant species.

Keywords: *Argemone mexicana*; Papaveraceae; alkaloids; argemexirine; dl-tetrahydrocoptisine; dihydrocoptisine

1. Introduction

Argemone mexicana L. (Papaveraceae) is a spiny herbaceous seasonal plant distributed throughout India. It generally grows in agricultural wastelands in the months of January–April. The plant is bitter, diuretic and purgative. It is used to destroy worms, and as cures for itching, leprosy, inflammations, bilious fevers, diarrhoea, dysentery and various skin diseases (Asolkar, Kakkar, & Chakre, 1992; CSIR, 1976). A number of protopine, berberine, benzophenanthridine and benzylisoquinoline alkaloids have been reported from this plant before (Chang et al., 2003; Chang, Chang, Khalil, Hsieh, & Wu, 2003; Doepke, Hess & Jimenez, 1976; Haisova, & Slavik, 1975; Hussain, Nakkady, Khan, & Shamma, 1983; Mishra, Bhakuni, Sharma, & Kaul, 1961; Nakkady & Sharma, 1988; Slavikova & Slavik, 1955). Here, we report the isolation of two known protoberberine alkaloids, dl-tetrahydrocoptisine (**1**) and dihydro-coptisine (**2**), and a new benzylisoquinoline alkaloid (**3**) from the methanolic extract of the whole plant of *A. mexicana*. The new alkaloid was designated with the trivial name argemexirine (**3**).

2. Results and discussion

Chromatographic resolution of the crude tertiary base fraction of the methanolic extract of the whole plant of *A. mexicana* furnished dl-tetrahydrocoptisine (**1**) (Pandey, Ray, & Dasgupta, 1974), dihydrocoptisine (**2**) (Tripathi & Pandey, 1987) and argemexirine (**3**).

Compound (**3**) was obtained as colourless amorphous powder. The HRMS data (Obsd. m/z 285.1368 for $[M^+]$) revealed the molecular formula to be $C_{17}H_{19}NO_3$. The compound gave a positive Dragendorff reaction for alkaloids. The appearance of a

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ISSN 1478–6419 print/ISSN 1029–2349 online

DOI: 10.1080/14786410902800723
http://www.informaworld.com

Table 1. ^{1}H NMR data of compound **3** and **5** and ^{13}C NMR data of **3** ($CDCl_3 + 20\%CD_3OD$).

Position	Compound **3** ^{1}H NMR, δ_H (multi., *J* in Hz)	Compound **3** ^{13}C NMR, δ_C	Compound **5** ^{1}H NMR, δ_H (multi., *J* in Hz)
1	4.45 (1H, dd, 3.10)	57.0	4.34 (1H, dd, 3, 10)
2	2.75 (1H, m)		2.54 (3H, s)
3	2.75 (1H, m) 3.35 (1H, m)	37.5	2.66 (1H, m) 3.24 (1H, m)
4	2.95 (2H, m)	28.6	2.86 (2H, m)
4a	–	125.0	–
5	6.80 (1H, s)	119.5	6.76 (1H, s)
6	–	144.0	–
7	–	142.3	–
8	6.75 (1H, s)	109.5	6.64 (1H, s)
8a	–	128.0	–
α	2.95 (1H, m) 3.35 (1H, m)	37.5	2.86 (1H, m) 3.24 (1H, m)
1′	–	132.0	–
2′	7.30 (1H, d, 8.5)	130.5	7.20 (1H, d, 8)
3′	7.00 (1H, d, 8.5)	114.0	6.89 (1H, d, 8)
4′	–	158.0	–
5′	7.00 (1H, d, 8.5)	114.0	6.89 (1H, d, 8)
6′	7.30 (1H, d, 8.5)	130.5	7.20 (1H, d, 8)
4′-OMe	3.85 (3H, s)	56.0	3.88 (3H, s)
6-OMe	–	–	3.70 (3H, s)
7-OMe	–	–	3.82 (3H, s)

blue colour with phosphomolybdic acid and ammonia vapour revealed the phenolic nature of the compound. Its UV spectrum showed absorption bands at λ_{max} 228 and 275 nm, characteristic of benzylisoquinoline alkaloids (Shamma, 1972). It showed an absorption band in its IR spectrum at 3300 cm^{-1} for hydroxyl and at 2820 cm^{-1} for methoxyl groups. Its ^{1}H NMR spectrum (Table 1) exhibited six proton multiplets (δ 2.75, 2.95 and 3.35) for three methylene protons, one –NH, two aromatic proton singlets (δ 6.75 and 6.80), four *ortho–meta* (δ 7.00 and 7.30) coupled aromatic protons, and one aromatic methoxyl group (δ 3.85), together with one proton double doublet (δ 4.45), which favoured the structure **3** as an alkaloid. The carbon signals of C-6 (144.0), C-7 (142.3) and C-4′ (158.0) in the ^{13}C NMR spectrum, which appeared downfield, indicated the attachments at these positions. The base peak at *m*/*z* 164 (ion **a**) and a strong peak at 121 (ion **b**) appeared in the mass spectrum due to the cleavage of C-1 to a C-α bond, which is characteristic of benzylisoquinoline alkaloids (Shamma, 1972) and suggested the presence of two hydroxy groups in ring A and one methoxy group in ring C. The structure **3** was thus proposed, and to which the trivial name argemexirine was designated. The chemical structure of argemexirine was further supported by methylation of **3** with HCHO and $NaBH_4$, which gave *N*-methylated product **4**. Compound **4**, upon methylation with CH_2N_2, furnished compound **5**, identical to *O*-methylarmepavine (Deulofeu, Comin, & Vernengo, 1968). Furthermore, argemexirine (**3**) on methylation with CH_2N_2 gave *N*-nor-*O*-methyl-armepavine (**6**) (Deulofeu et al., 1968), which on *N*-methylation furnished the compound **5** identical to *O*-methylarmepavine (Figure 1).

In ^{1}H–^{1}H COSY NMR, the chemical shift of protons of the aromatic region indicated that the proton of C-2′ couples with the protons of C-3′ and C-6′, whereas the C-3′ proton

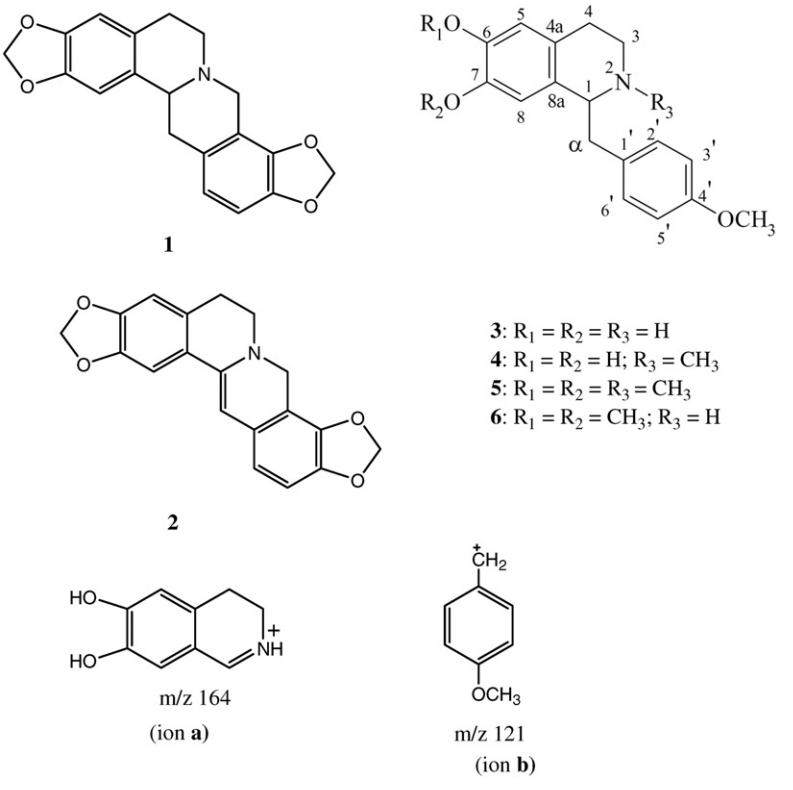

Figure 1. The chemical structures of compounds **1**–**6** and fragment ions **a** and **b**.

couples with the protons of C-2′ and C-5′. The chemical shift of protons of the aliphatic region indicated that protons of C-3 and C-4 couple with each other and the C-1 proton couples with two protons of C-α. ^{1}H and DEPT ^{13}C NMR (Table 1) and ^{1}H–^{1}H COSY data fits well with the structure **3** for argemexirine, a new benzylisoquinoline alkaloid.

Three benzylisoquinoline alkaloids, namely argenaxine, higenamine and reticuline, have earlier been reported from *A. mexicana* (Chang et al., 2003).

3. Experimental

3.1. *General experimental procedures*

Melting points are uncorrected. IR spectra, UV spectra and optical rotations were measured with a Perkin–Elmer spectrophotometer, a Carry-14 spectrophotometer and a Perkin–Elmer polarimeter 141, respectively. ^{1}H and ^{13}C NMR were run on a 500 MHz Bruker Hx-90 in $CDCl_3 + 20\%$ CD_3OD with TMS as an internal standard. MS were measured with a Kratos MS-50 mass spectrometer which was operated at 70 eV with evaporation of the sample in the ion source at 200°C. CC: silica gel column (BDH, 60–120 mesh); TLC: silica gel G (Merck); solvents for TLC: $CHCl_3$: MeOH (9 : 1). Analytical samples were dried routinely over P_2O_5 for 24 h *in vacuo*.

3.2. *Plant material*

The whole plant material of *A. mexicana* was collected in the first week of April 2006 from the Varanasi district, UP, India, and was identified by Prof. N.K. Dubey, Department of Botany, Banaras Hindu University, Varanasi, India. Specimen sample no. 221 is kept in the department.

3.3. *Extraction and isolation*

The air-dried, powdered, whole plant material of *A. mexicana* (3 kg) was extracted with MeOH in a Soxhlet extractor, and on evaporation of the solvent gave a brown coloured semi-solid (320 g). The MeOH extract was extracted with 7% aqueous citric acid and the acidic solution on basification and extraction with $CHCl_3$ furnished the crude base fraction (15.0 g). It was chromatographed over SiO_2 gel column eluting with solvents of increasing polarity. The eluants collected from C_6H_6 : $CHCl_3$ (1 : 1), (1 : 2) and (1 : 20) were crystallised separately from methanol, which furnished respectively the alkaloids dl-tetrahydrocoptisine (**1**) (25 mg), dihydrocoptisine (**2**) (18 mg) and argemexirine (**3**) (16 mg).

3.3.1. *Argemexirine (**3**)*

Compound **3** was crystallised from MeOH as colourless powder, m.p. 221–23°C, $[\alpha]_D^{25} \pm 0°$ (*c*, 0.45, $CHCl_3$) R_f 0.42 ($CHCl_3$: MeOH, 9 : 1). It exhibited UV (MeOH) λ_{max} (log ε): 228 (3.82), 275 (3.80) nm; IR (KBr) ν_{max}: 3300 (−OH), 2820 (−OMe), 1610 and 1560 (Ar − double bond) cm^{-1}; for ^1H and ^{13}C NMR data see Table 1; HRMS, *m*/*z* (relative intensity%): 285.1368 ($[M]^+$, $C_{17}H_{19}NO_3$, Calcd for 285.1365) (4), 164 (100), 163 (26), 121 (27), 106 (18), 67 (25).

3.3.2. *Methylation of argemexirine (**3**)*

Compound **3** (15 mg) was dissolved in MeOH and stirred magnetically with formaldehyde (10 drops) and a small amount of sodium borohydride for 8 h. The reaction mixture was poured over crushed ice, stirred for 1 h and then extracted with $CHCl_3$. The $CHCl_3$ extract was crystallised with MeOH, which gave compound **4** as amorphous solid. The mass spectrum of compound **4** exhibited a molecular ion peak at *m*/*z* 299.1525 ($[M]^+$, $C_{18}H_{21}NO_3$, Calcd for 299.1521) and other significant peaks at *m*/*z* 178 (base peak), 177, 121, 106. Compound **4** was dissolved in MeOH and treated with diazomethane in ether solution. The reaction mixture was allowed to stand overnight at room temperature, which furnished a colourless solid. It was crystallised from MeOH, which gave colourless granules of compound **5**, m.p. 91–92°C, $[\alpha]_D^{25} \pm 0°$ (*c*, 0.40, $CHCl_3$). For ^1H NMR see Table 1. It exhibited a molecular ion peak at *m*/*z* 327.1838 ($[M]^+$, $C_{20}H_{25}NO_3$ Calcd for 327.1834) and other fragment ion peaks at *m*/*z* 206 (base peak), 191, 176, 121, 106. ^1H NMR, MS and m.p. were identical to *O*-methylarmepavine.

Compound **3** (14 mg) was dissolved in MeOH, treated with diazomethane in ether solution, and the reaction mixture was allowed to stand for overnight. On evaporation, it gave a colourless solid, which on crystallisation from MeOH furnished the amorphous compound **6**. It exhibited a molecular ion peak at *m*/*z* 313.1685 ($[M]^+$ $C_{19}H_{23}NO_3$, Calcd for 313.1677) and other fragment ion peaks at *m*/*z* 192 (base peak), 177, 162, 121, 106, which were identical to *N*-nor-*O*-methylarmepavine. Compound **6** on methylation with

formaldehyde and sodium borohydride, as mentioned above, furnished *O*-methylarmepavine (**5**). m.p. = 91–92°C, $C_{20}H_{25}NO_3$ ($[M]^+$, *m/z* 327.1839, Calcd for 327.1834).

Acknowledgements

The authors are thankful to Prof. G. Rücker, Pharmazeutisches Institut der Universitat Bonn, Germany for spectral analysis and S. Singh is thankful to UGC for financial assistance.

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