Pergamon

PII: S0031-9422(97)00106-4

Phytochemistry, Vol. 45, No. 6, pp. 1303–1305, 1997

0031-9422/97 $17.00+0.00

ALKALOIDS FROM *ALSTONIA SCHOLARIS*

TOH-SEOK KAM,* KOK-TIH NYEOH, KOOI-MOW SIM and K. YOGANATHAN

Department of Chemistry, University of Malaya, 59100 Kuala Lumpur, Malaysia

(*Received* 29 *November* 1996)

Key Word Index—*Alstonia species*; Apocynaceae; Leaves; indole alkaloids.

Abstract—Three new indole alkaloids, nareline ethyl ether, 5-*epi*-nareline ethyl ether and scholarine-*N*(4)-oxide, in addition to nareline methyl ether, picrinine and scholaricine were isolated from the leaf extract of *Alstonia scholaris*.

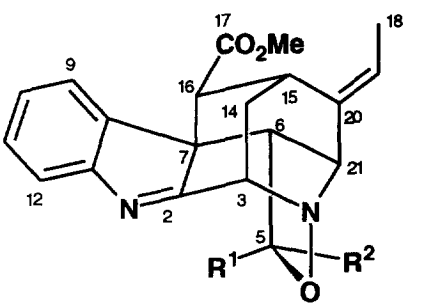
INTRODUCTION

Plants of the genus *Alstonia*, numbering about 38 species, are distributed in tropical areas including Africa, Indo-Malaya and Australia. Several species are used in traditional medicine throughout southeast Asia for the treatment of malaria and dysentery [1, 2]. *Alstonia scholaris* is usually a big tree growing up to *ca* 80–100 ft; in Malaysia, they are known by the local name, *Pulai*. Although representatives from India, Pakistan, the Phillipines, Taiwan and Thailand have received attention [3–9], the Malaysian species has not been previously investigated. We now report on the isolation of several new alkaloids from this source.

RESULTS AND DISCUSSION

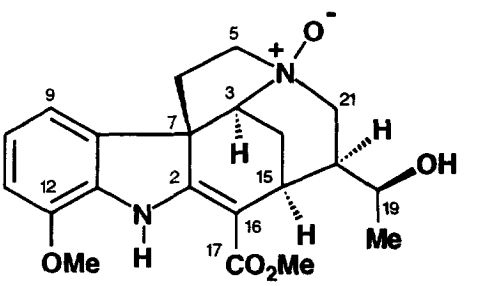
From the alkaloidal fraction of the leaf extract, the following alkaloids were isolated in order of their elution in column chromatography, *viz*., nareline methyl ether (**1**), nareline ethyl ether (**2**), 5-*epi*-nareline ethyl ether (**3**), picrinine (**4**), scholaricine (**5**) and scholarine-*N*(4)-oxide (**6**). The nareline-type alkaloids, **1** and **2**, constitute the major alkaloids, while compounds **2**, **3** and **6** are new.

Compound **2** was obtained as colourless needles and the UV spectrum showed absorption maxima at 216 and 256 nm, indicating the presence of an unsubstituted indolenine chromophore, which was confirmed by the resonance at δ 184.5 in ^{13}C NMR attributable to an imine carbon. The mass spectrum showed a $[M]^+$ at *m/z* 380 corresponding to the formula $C_{22}H_{24}N_2O_3$. Other major fragments were observed at *m/z* 350 $[M-CH_2O]^+$, 321 $[M-CO_2Me]^+$ and 306 $[M-CO_2Me-Me]^+$. The ^1H NMR spectral



2 $R^1 = H, R^2 = OEt$

3 $R^1 = OEt, R^2 = H$



6

* Author to whom correspondence should be addressed.

Table 1. ^1H and ^{13}C NMR spectral data for compounds **2**, **3** and **6***

Position	**2**		**3**		**6**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	184.5	—	185.6	—	167.8	—
3	62.9	4.66 *t* (3)	62.9	4.73 *t* (3)	74.6	4.30 *br s*
5	105.4	3.91 *s*	109.0	5.14 *d* (3)	68.4	3.64 *m*
		—		—		3.75 *m*
6	55.3	3.79 *d* (3)	51.3	3.91 *t* (3)	38.7	2.07 *dd* (14, 8)
		—		2.78 *td* (12, 6)		2.52 *m*
7	55.2	—	55.4	—	53.8	—
8	139.5	—	142.7	—	134.2	—
9	125.5	7.75 *br d* (7.5)	124.0	7.64 *br d* (7.5)	111.1	6.79 *dd* (7, 1)
10	125.8	7.26 *td* (7.5, 1)	125.5	7.17 *td* (7.5, 1)	123.0	6.95 *m*
11	128.9	7.43 *td* (7.5, 1)	128.0	7.34 *td* (7.5, 1)	111.9	6.90 *m*
12	121.0	7.72 *br d* (7.5)	120.5	7.59 *br d* (7.5)	144.6	—
13	157.5	—	156.8	—	132.0	—
14	35.2	2.10 *dt* (14, 3)	36.6	2.14 *m*	27.2	1.37 *br d* (13)
		2.37 *dt* (14, 3)		2.38 *dt* (14, 3)		2.56 *m*
15	31.6	3.35 *br d* (3)	31.7	3.31 *m*	27.8	3.49 *br s*
16	53.9	2.26 *d* (3)	56.4	2.13 *d* (3)	97.9	—
17	170.7	—	170.8	—	168.2	—
18	12.7	1.69 *d* (7)	12.6	1.67 *d* (7)	19.6	1.13 *d* (6.5)
19	122.9	5.81 *br q* (7)	122.9	5.72 *br q* (7)	67.2	3.27 *dd* (10, 6.5)
20	130.7	—	131.1	—	41.8	2.32 *m*
21	66.0	4.10 *d* (3)	68.3	4.02 *d* (3)	62.9	3.06 *br t* (10)
						3.45 *m*
$CO_2\underline{Me}$	51.8	3.71 *s*	51.8	3.68 *s*	52.2	3.88 *ms*
$OCH_2\underline{C}H_3$	14.9	1.02 *t* (7)	14.0	0.45 *t* (7)	—	—
$O\underline{C}H_2CH_3$	63.4	3.11 *m*	65.1	2.90 *dq* (14, 7)	—	—
$O\underline{C}H_2CH_3$	—	3.55 *dq* (14, 7)	—	3.31 *m*	—	—
12-OMe	—	—	—	—	55.5	3.87 *s*
NH	—	—	—	—	—	8.40 *br s*

* $CDCl_3$, 270 MHz; assignments based on COSY and HETCOR.

data (Table 1) showed the presence of four aromatic H from δ 7.26 to 7.75, an ethylidene group (δ 1.69, *d*, $J = 7$ Hz; 5.81, *br q*, $J = 7$ Hz), an ester methoxy (δ_H 3.71, *s*; δ_C 170.7) and an ethoxy group (δ 3.11, 1H, *m*; 3.55, 1H, *dq*, $J = 14, 7$ Hz; 1.02, 3H, *t*, $J = 7$ Hz). The spectrum could be assigned by the use of COSY and is similar to that of nareline methyl ether [3] obtained at 270 MHz, except for replacement of the 5-methoxy signal with signals due to the ethyl ether function (Table 1). The ^{13}C NMR spectrum accounted for a total of 22 carbons, in agreement with the molecular formula established from the mass spectral data, and is also similar to that of nareline methyl ether, except for replacement of signals due to methoxy by ethoxy. In the ^1H NMR, the signal due to H-5 is observed as a singlet (δ 3.91), which was also the case for the methyl ether derivative (δ 3.82), indicating the absence of vicinal coupling due to the H-5/H-6 dihedral angle of *ca* 90°, in agreement with the structure of nareline previously established by X-ray analysis [3]. Compound **2** is therefore nareline ethyl ether.

Compound **3** was obtained as a light yellow oil and its UV and mass spectral data were similar to those of compound **2**. The ^1H NMR spectral data were also similar to those of **2**, except for significant changes involving the H-5 and ethyl ether resonances, suggesting, in turn, a change in configuration at C-5. This was also reflected in the ^{13}C NMR spectral data which was similar to those of **2**, except for significant changes in the shifts associated with C-5 and C-6. The signal due to H-5 is now a doublet with $J = 3$ Hz and shifted to lower field at δ 5.14. This is consistent with the change in configuration of the C-5 ethoxy substituent resulting in a H-5/H-6 dihedral angle of *ca* 45°. The signal due to the methyl of the ethoxy group has also undergone a significant upfield shift to δ 0.45 as a result of anisotropy exerted by the aromatic ring due to the change in the stereochemistry of the ethyl ether substituent. Compound **3** is therefore 5-*epi*-narline ethyl ether.

Compound **6** was readily identified as the *N*(4)-oxide of scholarine from its spectra data, in particular the characteristic downfield shifts of the carbon resonances for C-3, C-5 and C-21, when compared with those of scholarine [4, 10].

EXPERIMENTAL

Plant material. Plant material was collected in Terengganu, Malaysia, and herbarium voucher speci-

mens are deposited at the Herbarium of the Forest Research Institute, Kuala Lumpur, Malaysia.

Extraction and isolation. Extraction of alkaloids was carried out in the usual manner, as described in detail elsewhere [11]. Alkaloids were isolated by CC and centrifugal TLC on silica gel. Solvent system used for CC was $CHCl_3$–MeOH. Solvent systems used for centrifugal TLC were hexane–Et_2O–NH_3, Et_2, Et_2O–NH_3, $CHCl_3$–MeOH and EtOAc–MeOH. The yields (g kg^{-1}) of alkaloids from the leaf extract were: **1** (0.083), **2** (0.148), **3** (0.0067), **4** (0.0011), **5** (0.0068) and **6** (0.019).

Nareline ethyl ether (**2**). Needles from $CHCl_3$–EtOAc, mp 225–227°. $[\alpha]_D$ −72° ($CHCl_3$, *c* 0.066). UV (EtOH), λ_{max} nm (log ε): 216 (3.93), 256 (3.45). EIMS (probe) 70 eV, *m/z* (rel. int.): 380 [M^+, $C_{22}H_{24}N_2O_3$] (91), 350 (100), 321 (22), 307 (90), 306 (35), 265 (50), 247 (42), 232 (44), 204 (38), 167 (28). ^1H and ^{13}C NMR: Table 1.

5-epi-*Nareline ethyl ether* (**3**). $[\alpha]_D$ −57° ($CHCl_3$, *c* 0.037). UV (EtOH), λ_{max} nm (log ε): 216 (4.07), 256 (3.58). EIMS (probe) 70 eV, *m/z* (rel. int.): 380 [M^+, $C_{22}H_{24}N_2O_3$] (100), 350 (75), 321 (15), 307 (22), 306 (25), 265 (15), 247 (16), 232 (14), 204 (15), 167 (10). ^1H and ^{13}C NMR: Table 1.

Scholarine N(4)-oxide (**6**). $[\alpha]_D$ −280° ($CHCl_3$, *c* 0.534). UV (EtOH), λ_{max} nm (log ε): 232 (3.95), 284 (3.51), 334 (3.78). EIMS (probe) 70 eV, *m/z* (rel. int.): 386 [M^+, $C_{21}H_{26}N_2O_5$] (6), 370 (30), 326 (5), 310 (15), 271 (100), 255 (20), 224 (10), 210 (6). ^1H and ^{13}C NMR: Table 1.

Acknowledgements—We thank the University of Malaya and IRPA for financial support of this work.

REFERENCES

1. Burkhill, I. M., *A Dictionary of Economic Products of the Malay Peninsula*. Ministry of Agriculture and Co-operatives, Kuala Lumpur, 1966.
2. Perry, L. M. and Metzger, J., *Medicinal Plants of East and Southeast Asia*. MIT Press, Cambridge, 1980.
3. Morita, Y., Hesse, M., Schmid, H., Banerji, A., Banerji, J., Chatterjee, A. and Oberhansli, W. E., *Helvetica Chimica Acta*, 1977, **60**, 1419.
4. Banerji, A. and Siddhanta, A. K., *Phytochemistry*, 1980, **20**, 540.
5. Atta-ur-Rahman, Asif, M., Ghazala, M., Fatima, J. and Alvi, K. A., *Phytochemistry*, 1985, **24**, 2771.
6. Atta-ur Rahman and Alvi, K. A., *Phytochemistry*, 1987, **26**, 2139.
7. Yamauchi, T., Abe, F., Padolina, W. G. and Dayrit, F. M., *Phytochemistry*, 1990, **29**, 3321.
8. Abe, F., Chen, R. F., Yamauchi, T., Marubayashi, N. and Ueda, I., *Chemical and Pharmaceutical Bulletin*, 1989, **37**, 887.
9. Yamauchi, T., Abe, F., Chen, R. F., Nonaka, G. I., Santisuk, T. and Padolina, W. G., *Phytochemistry*, 1990, **29**, 3547.
10. Keawpradub, N., Takayama, H., Aimi, N. and Sakai, S. I., *Phytochemistry*, 1994, **37**, 1745.
11. Kam, T. S. and Tan, P. S., *Phytochemistry*, 1990, **29** 2321.