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# NEW ALKALOIDS FROM *BANISTERIOPSIS CAAPI*

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**Key Word Index**—*Banisteriopsis caapi*; Malpighiaceae; alkaloids; harmic amide; acetyl norharmine; keto tetrahydro norharmine.

**Abstract**—Three new alkaloids isolated from *Banisteriopsis caapi*, were identified as harmic amide (1-carbamoyl-7-methoxy β-carboline), acetyl norharmine (1-acetyl-7-methoxy β-carboline) and ketotetrahydronorharmine (7-methoxy-1,2,3,4-tetrahydro-1-oxo-β-carboline)

## INTRODUCTION

*Banisteriopsis caapi* contains the β-carboline alkaloids, harmine (**1a**), harmaline (**2a**) and tetrahydroharmine (**3a**). In a previous paper [1], three new alkaloids from this plant were identified as harmine *N*-oxide (1-methyl-7-methoxy-β-carboline *N*-oxide (**1b**), harmic acid Me ester (1-methoxycarbonyl-7-methoxy-β-carboline) (**1d**) and harmalinic acid (1-carboxy-7-methoxy-3,4 dihydro-β-carboline) (**2b**). This paper reports the identification of three more new alkaloids which possess the β-carboline skeleton.

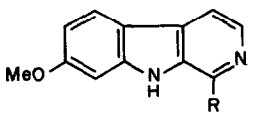
## RESULTS AND DISCUSSION

Solvent fractionations of aqueous methanol extracts were followed by column chromatography and preparative-TLC. Purified and identified alkaloids (**1e**), (**1f**) and (**3c**) corresponded with (**4**), (**6**) and (**7**) respectively in the previous report [1]. Compound (**5**) in this report has not yet been identified.

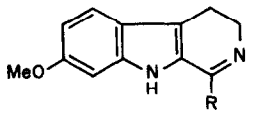
High resolution MS of (**1e**) gave the formula as $C_{13}H_{11}N_3O_2$. The UV spectrum showed the typical pattern of a β-carboline ($\lambda_{max}$ 255, 279 and 321 nm). The presence of an amide was indicated from IR analysis ($\nu$ 3420, 3390 and 1700 $cm^{-1}$). The PMR spectrum exhibited three aromatic proton signals at H-5 ($\delta$8.12), H-6 ($\delta$6.87) and H-8 ($\delta$7.34), ($J_{5,6}$ 8.6 Hz, $J_{5,8}$ 0.5 Hz and $J_{6,8}$ 2.1 Hz), AB splitting aromatic proton signals at H-3 ($\delta$8.34) and H-4 ($\delta$8.16, $J_{3,4}$ 5 Hz), an indolic NH proton signal at $\delta$11.44, an OMe proton signal at $\delta$3.87 and an amide proton signal at $\delta$7.67. Harmic acid (**1c**) when treated with $SOCl_2$ and $NH_3$ gave an amide which was identical with (**1e**) on the basis of UV, IR, MS and TLC comparison. Thus (**1e**) is harmic amide, 1-carbamoyl-7-methoxy β-carboline.

The second compound (**1f**), whose high resolution MS gave the formula as $C_{14}H_{12}N_2O_2$ also had a typical UV spectrum of β-carboline ($\lambda_{max}$ 260, 289 and 334 nm). The PMR spectrum was very similar to that of harmine (**1a**), namely three aromatic proton signals at H-5 ($\delta$8.12), H-6 ($\delta$6.92) and H-8 ($\delta$7.35), ($J_{5,6}$ 8.2 Hz, $J_{5,8}$ 0.5 Hz and $J_{6,8}$ 2.1 Hz), AB splitting aromatic proton signals at H-3 ($\delta$8.44) and H-4 ($\delta$8.24) ($J_{3,4}$ 5.0 Hz), an indolic NH proton signal at $\delta$11.65, and an OMe proton signal at $\delta$3.83. However, in place of the Me proton signal of harmine (**1a**), (**1f**) showed an acetyl proton signal at $\delta$2.78. The presence of the acetyl group was supported by its IR spectrum ($\nu$1670 $cm^{-1}$). Dehydration of amide (**1e**) with $P_2O_5$ gave the nitrile (**1g**), which showed CN absorption by IR ($\nu$2230 $cm^{-1}$). When treated with Grignard reagent (**1g**) yielded the acetyl compound (**1e**) which was identical to the natural product by UV, IR, MS and TLC comparison. (**1f**) is thus acetyl norharmine, 1-acetyl-7-methoxy β-carboline.

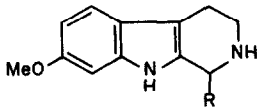
The third new alkaloid (**3c**) had the formula $C_{12}H_{12}N_2O_2$ as determined by high resolution MS. Its UV spectrum ($\lambda_{max}$ 249 and 314 nm) was different from those of harmine, harmaline and the other new alkaloids and its IR spectrum showed OH or amine absorption ($\nu$3100–3400 $cm^{-1}$) and carbonyl absorption ($\nu$1660 $cm^{-1}$). The PMR spectrum was remarkable similar to that of harmaline (**2a**), exhibiting three aromatic proton



**1a** R = Me (harmine)
**1b** R = Me, Nb oxide (harmine N-oxide)
**1c** R = $CO_2H$ (harmic acid)
**1d** R = $CO_2Me$
**1e** R = $CONH_2$
**1f** R = COMe
**1g** R = CN



**2a** R = Me (harmaline)
**2b** R = $CO_2H$ (harmalinic acid)
**2c** R = $CO_2Me$



**3a** R = Me (tetrahydroharmine)
**3b** R = $CO_2H$
**3c** R = O

signals at H-5 ($\delta$7.51), H-6($\delta$6.67) and H-8($\delta$6.92), ($J_{5,6}$ 8.8 Hz, $J_{5,8}$ 0.7 Hz and $J_{6,8}$ 2.1 Hz), ethylene proton signals at $\delta$2.76–3.08 (multiplet) and $\delta$3.39–3.73 (multiplet), an indolic NH proton signal at $\delta$11.38, and an OMe proton signal at $\delta$3.79. The broad signal at $\delta$7.39 suggested lactam absorption in agreement with the IR spectrum. Treatment of (**2a**) using the method of Nishikawa [2] yielded keto-tetrahydronorharmine, which was identical with the natural product (**3c**) by UV, IR, PMR, MS and TLC comparisons. (**3c**) is therefore ketotetrahydronorharmine, 7-methoxy-1,2,3,4-tetrahydro-1-oxo-$\beta$-carboline.

## EXPERIMENTAL

*Harmic amide* (**1e**). Needles from $CHCl_3$ and MeOH, yield 0.007%, mp 226–7°(dec) $C_{13}H_{12}N_3O_2$ ($M^+$ found: 241.086, calc: 241.085), UV: $\lambda_{max}^{CHCl_3}$ 255 (log $\epsilon$ 4.54), 279 (4.44) and 321 (4.35) nm IR: $\lambda_{max}^{Nujol}$ 3420, 3390, 3200, 1700, 1635, 1595, 1570 and 1480 $cm^{-1}$ PMR (DMSO-$d_6$): $\delta$3.87 (3-H, *s*, OMe), 6.87 (1-H, *q*, *J* 0.5 Hz; H-6), 7.34 (1-H, *d*, *J* 2.1 Hz; H-8), 8.12 (1-H, *q*, *J* 8.6 Hz; H-5), 8.26 (1-H, *q*, *J* 4.5 Hz; H-4), 8.34 (1-H, *q*, *J* 4.5 Hz; H-3), 7.67 (2-H, *b*, $CONH_2$) and 11.44 (1-H, *b*, indolic NH) MS: *m/e* 241 (100), 224 (16), 196 (81), 181 (14) and 153 (23).

*Preparation of* 1-*carbamyl*-7-*methoxy* $\beta$-*carboline.* Harmic acid (0.5 g) was suspended in excess $SOCl_2$, refluxed at 100° under dry conditions for 2 hr, followed by removal of excess solvent. The reaction mixture was treated with 15% aq. $NH_3$ (3 ml) at 50° for 1 hr and after cooling the amide was ppd, filtered and recrystallized from $CHCl_3$ and MeOH.

*Acetylnorharmine* (**1f**). Light yellow needles from $CHCl_3$, yield 0.0001%, mp 224–5°(dec.), $C_{14}H_{12}N_2O_2$ ($M^+$ found: 240.089, calc: 240.089), UV: $\lambda_{max}^{CHCl_3}$ 260 (log $\epsilon$ 4.18), 289 (4.37) and 334 (4.02) nm. IR: $\nu_{max}^{Nujol}$ 3370, 1670, 1630, 1595, 1585 and 1505 $cm^{-1}$ PMR (DMSO-$d_6$): $\delta$2.78 (3-H, *s*, COMe), 3.83 (3-H, *s*, OMe), 6.92 (1-H, *q*, *J* 0.5 Hz; H-6), 7.35 (1-H, *d*, *J* 2.1 Hz; H-8), 8.12 (1-H, *q*, *J* 8.2 Hz; H-5), 8.24 (1-H, q, *J* 5 Hz; H-4), 8.44 (1-H, *q*, *J* 5 Hz; H-3) and 11.65 (1-H, *b*, indolic NH) MS: *m/e* 240 (100), 225 (2), 212 (36), 198 (69), 197 (34) and 183 (16).

*Preparation of* 1-*acetyl* 7-*methoxy* $\beta$-*carboline.* Harmic amide (100 mg) was mixed with excess $P_2O_5$ and heated at 200° for 1 hr. The reaction mixture was cooled, $H_2O$ and aq. $NH_3$ added and the product extracted with $CHCl_3$. After drying and partial removal of solvent the nitrile compound crystallized. To this compound was added Mg (1 g), 20 ml anhydrous $Et_2O$ and excess $CH_3I$ and the mixture heated at 42–45° with stirring under reflux for 2 hr. The course of the reaction was followed using the qualitative colour test [3] for the Grignard reagent. The nitrile compound (48 mg) in $Et_2O$ was added to a soln of Grignard reagent and refluxed for 3 hr. After cooling at 0°, 1 ml cold 6N HCl was added with stirring and the mixture refluxed for 15 hr. The mixture cooled, the layers separated, the aq. layer treated with dil NaOH soln and the product extracted with $Et_2O$. The product was then purified by preparative TLC.

*Ketotetrahydronorharmine* (**3c**). White needles from $CHCl_3$ MeOH, yield 0.0005%, mp 197–8° (dec), $C_{12}H_{12}N_2O_2$ ($M^+$ found: 216.088, calc: 216.089), UV: $\lambda_{max}^{MeOH}$ 249 (log $\epsilon$ 4.41) and 314 (4.29) nm, IR: $\nu_{max}^{Nujol}$ 3100–3400, 1660, 1625, 1540, 1517, and 1513 $cm^{-1}$ PMR (DMSO-$d_6$): $\delta$2.76–3.08 (2-H, m, H-3 or H-4), 3.39–3.73 (2-H, m, H-4 or H-3), 3.79 (3-H, *s*, OMe), 6.76 (1-H, *q*, *J* 0.7 Hz; H-6), 6.92 (1-H, *d*, *J* 2.1 Hz; H-8), 7.51 (1-H, *q*, *J* 8.8 Hz; H-5), 7.39 (1-H, *b*, lactamic NH) and 11.38 (1-H, b, indolic NH) MS: *m/e* 216 (100), 201 (23), 187 (35) and 159 (90).

*Preparation of* 7-*methoxy*-1,2,3,4-*tetrahydro*-1-*oxo* $\beta$-*carboline.* Harmaline (1.8 g) was solved in 15 ml hot Py and 3 ml anhydrous HOAc added; the reaction mixture was maintained at room temp for 15 hr. The mixture was poured into ice $H_2O$ and the resultant white ppt. crystallized, washed with $H_2O$ and dried. The product (acetyl harmaline) (2 g) was dissolved in 120 ml of hot $Me_2CO$ and $KMnO_4$ powder (4 g) added with stirring at 0° over 5 hr. The reaction mixture was filtered and the precipitated $MnO_2$ washed with hot $Me_2CO$. After removing most of the solvent, $H_2O$ was added and the white crystalline ppt collected, dried and recrystallized again from $CHCl_3$. The final product acetyl ketotetrahydronorharmine was hydrolyzed with boiling alcoholic KOH for 2 hr. After cooling, $H_2O$ was added, and the white crystalline ppt filtered and dried.

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