

**(R)-(+)-NORANICANINE  
A NEW TYPE OF TRIOXYGENATED  
BENZYLISOQUINOLINE  
ISOLATION AND SYNTHESIS**

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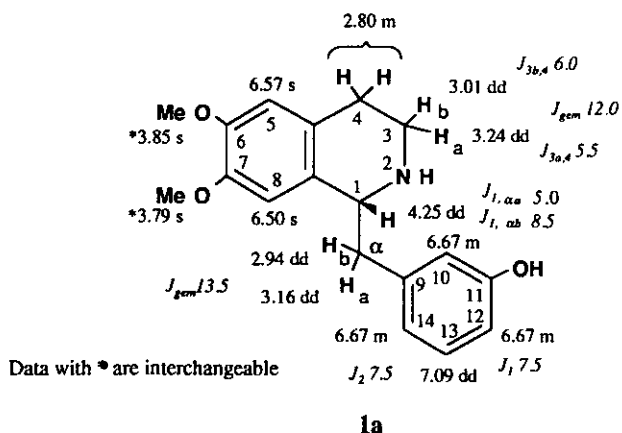
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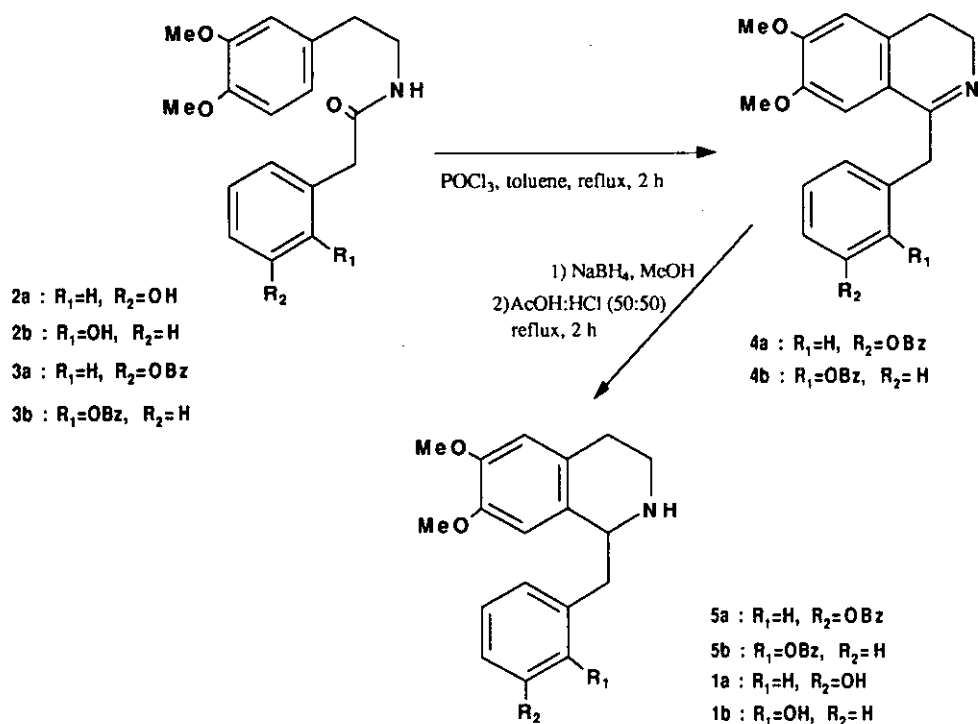
**Abstract** - (R)-(+)-Noranicanine (**1a**), a new type of benzylisoquinoline precursor was isolated from *Aniba canelilla* (Lauraceae) and its structure was determined by means of spectroscopic data as well as by synthesis.

1-Benzylisoquinolines and their derivatives represent one of the preeminent group of alkaloids in plants.<sup>1</sup> The benzylisoquinoline skeleton is known to be produced, *in vivo*, via cyclization of Schiff bases formed from condensation of dopamine with either 4-hydroxyphenylacetaldehyde or 3,4-dihydroxyphenylacetaldehyde.<sup>2</sup> Natural known 1-benzyltetrahydroisoquinolines with a monosubstituted benzyl group therefore always exhibit a *para* functionality in ring C. We now have isolated from a Bolivian Lauraceae, *Aniba canelilla*,<sup>3</sup> (+)-noranicanine (**1**), a trioxygenated benzyltetrahydroisoquinoline with a different substitution pattern in ring C, the oxygenated substituent being in the *meta* position. The structure of this new alkaloid has been firmly established by synthesis.

The EI mass spectrum of **1**, C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>, exhibited a typical benzyltetrahydroisoquinoline type fragmentation pattern<sup>4</sup> with a very weak molecular ion at m/z 299 and a base peak at m/z 192 representing the isoquinoline moiety. The nmr spectrum of (+)-noranicanine (CDCl<sub>3</sub>, 200 MHz, TMS=0) has been summarized around structure **1a**. Noteworthy were the absence of a *N*-methyl singlet and the presence of two methoxy singlets at  $\delta$  3.79 and 3.85 ppm and two aromatic singlets at  $\delta$  6.57 and 6.50 ppm for the isoquinoline moiety. Unlike coclaurine or other compounds monosubstituted in ring C, H-13 was there in evidence as a deshielded doublet of doublets at  $\delta$  7.09 ppm ( $J_{12,13}=J_{13,14}=7.5$  Hz). However, the unresolved multiplet centered at  $\delta$  6.67 ppm corresponding to the three remaining aromatic protons did not allow us to unambiguously establish the substitution pattern of the benzene ring.



Different assays of solvent effects failed in offering a better resolution than  $\text{CDCl}_3$ , however the hydroxyl substituent of ring C should be undoubtedly located either in the *meta* (**1a**) or in the *ortho* position (**1b**). We thus undertook the synthesis of both possible compounds *via* a classical route<sup>5,6</sup> in order to confirm the assigned structure **1** (Scheme 1).



Scheme 1

Condensation of 3,4-dimethoxyphenethylamine with *m*-hydroxyphenylacetic acid or *o*-hydroxyphenylacetic acid respectively led to amides (**2a**) (89%, mp 149-150 °C) and **2b** (97%, mp 108-109°C) which were benzylated to give **3a** (72%, mp 89-90 °C) and **3b** (85%, mp 112-113°C). A Bischler-Napieralski cyclization with **3a** and **3b** then provided 3,4-dihydroisoquinolines (**4a**) (71%, mp 79-80 °C) and (**4b**) (73%, mp 184-185°C) which were further reduced with sodium borohydride into **5a** (86%, mp 160-161°C) and **5b** (82%, mp 165-166°C), respectively. Debenzylation of **5a** and **5b** gave the corresponding phenol (**1a**) (61%, mp 155-156 °C) and (**1b**) (76%, mp 147-148 °C) as their hydrochlorides.<sup>7</sup> Compound (**1a**), in its base form, finally was spectroscopically identical with natural (+)-noranicanine.<sup>8</sup>

The 1-*R* configuration of the natural (+)-noranicanine is suggested by the positive optical rotation<sup>9</sup> and confirmed by the cd curve which presents a negative Cotton effect at 284 nm and a negative tail at 240 nm.<sup>10</sup>

To our knowledge, this is the first report of a natural benzyltetrahydroisoquinoline monosubstituted in ring C with the hydroxyl group being in the *meta* position. Due to the number of alkaloids derived from this basic skeleton, (+)-noranicanine may be therefore regarded as a new type of benzylisoquinoline precursor.

## REFERENCES AND NOTES

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- 2 R. Stadler and M. H. Zenk, *Liebig Ann. Chem.*, 1990, 555.
- 3 Plant collection, extraction and alkaloid isolation— The stem barks of *Aniba canelilla* (1.1 Kg) were collected in 1988 at Fatima de Chimanes, Bolivia. A voucher specimen (ref AF855) was deposited at the herbarium of ORSTOM-IBBA center of La Paz. The crude alkaloids (1.04%) were obtained from the powdered defatted stem barks following a classical procedure. Specific extraction was followed by MPLC (CHCl<sub>3</sub> gradually enriched with MeOH) and preparative TLC (CHCl<sub>3</sub>-MeOH 13%) on silica gel. This way, 16 mg of amorphous (+)-noranicanine were isolated.
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- 7 Eims data (70 eV) for compounds **2a**→**5a** and **2b**→**5b** : **2a** m/z : 315 (M<sup>+</sup>, C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>, 8.7%), 165 (10.4%), 164 (100%), 152 (4.8%), 151 (20%), 149 (8.8%), 108 (3.1%), 107 (14.8%), 91 (3.1%), 78 (4.8%), 77 (8.4%), 44 (3.4%) ; **3a** m/z : 405 (M<sup>+</sup>, C<sub>25</sub>H<sub>27</sub>NO<sub>4</sub>, 7.6%), 165 (12.3%), 164 (100%), 151 (12.5%), 149 (4.5%), 134 (3.9%), 107 (3%), 92 (3.8%), 91 (42.3%), 65 (5%) ; **4a** m/z : 387 (M<sup>+</sup>,

$C_{25}H_{25}NO_3$ , 5.7%), 386 (6.9%), 297 (22.3%), 296 (100%), 280 (4.6%), 268 (11.5%), 252 (3.5%), 192 (2.1%), 152 (1.7%), 92 (5.7%), 91 (53.1%), 77 (3.9%), 65 (7.4%), 38 (7%), 36 (18.9%), 35 (3.2%); **5a**  $m/z$ : 389 ( $M^+$ ,  $C_{25}H_{27}NO_3$ , 0.06%), 280 (1.3%), 193 (12.7%), 192 (100%), 176 (5.8%), 148 (3.5%), 147 (1.6%), 91 (9.5%); **2b**  $m/z$ : 315 ( $M^+$ ,  $C_{18}H_{21}NO_4$ , 9.6%), 165 (12.6%), 164 (100%), 152 (4.4%), 151 (15.6%), 107 (12.8%), 106 (3.2%), 91 (3.1%), 79 (3.9%), 78 (4.8%), 77 (8.6%); **3b**  $m/z$ : 405 ( $M^+$ ,  $C_{25}H_{27}NO_4$ , 0.8%), 165 (13.5%), 164 (100%), 151 (13.5%), 149 (5.4%), 107 (12.8%), 106 (4.4%), 92 (5.5%), 91 (62.0%), 79 (3.4%), 78 (8.0%), 77 (6.9%), 65 (13.0%); **4b**  $m/z$ : 387 ( $M^+$ ,  $C_{25}H_{25}NO_3$ , 0.4%), 377 (3.4%), 296 (6.7%), 281 (13.7%), 280 (71.9%), 264 (5.1%), 128 (5.6%), 126 (15.0%), 92 (8.1%), 91 (100%), 89 (7.5%), 65 (12.5%), 63 (7.1%), 52 (3.1%), 51 (4.7%), 50 (6.2%), 38 (3.2%), 36 (4.5%); **5b**  $m/z$ : 389 ( $M^+$ ,  $C_{25}H_{27}NO_3$ , 0.03%), 280 (3.0%), 193 (13.0%), 192 (100%), 176 (7.0%), 148 (3.0%), 91 (11.3%).

- 8 Spectral data for compounds **1a** and **1b**: **1a**:  $C_{18}H_{21}NO_3$ , uv  $\lambda$  max (MeOH) nm ( $\log \epsilon$ ): 207 (4.55), 229 sh (4.03), 282 (3.71),  $\lambda$  max (MeOH-KOH) nm ( $\log \epsilon$ ): 212 (4.66), 235 sh (3.96), 288 (3.61); ir v max (KBr): 3450, 3260, 1610, 1585  $cm^{-1}$ ; eims (70 eV)  $m/z$ : 299 ( $M^+$ , 0.2%), 193 (12.5%), 192 (100%), 177 (3.7%), 148 (4.0%), cims ( $NH_3$ )  $m/z$ : 300 ( $[MH]^+$ , 100%), 193 (3.1%), 192 (24.2%);  $^1H$ -nmr (200 MHz,  $CDCl_3$ ,  $\delta$  ppm): see **1a**,  $^{13}C$ -nmr (68 MHz,  $CDCl_3$ ,  $\delta$  ppm): 56.3 (C-1), 40.3 (C-3), 28.5 (C-4), 126.5 (C-4a), 111.7 (C-5), 147.1 and 147.7 (C-6 and C-7), 109.3 (C-8), 128.9 (C-8a), 41.9 (C- $\alpha$ ), 139.4 (C-9), 116.2 (C-10), 157.6 (C-11), 114.7 (C-12), 130.0 (C-13), 120.4 (C-14), 55.8 and 55.9 (2 OCH<sub>3</sub>); spectral data for natural (+)-noranicanine,  $[\alpha]_D^{+36}(c=1, CHCl_3)$ , cd (MeOH)  $\Delta\epsilon$  (nm) 0 (299), -0.15 (284), -0.04 (255), negative tail at 240 nm. **1b**:  $C_{18}H_{21}NO_3$ , uv  $\lambda$  max (MeOH) nm ( $\log \epsilon$ ): 206 (4.63), 230 sh (4.06), 281 (3.79),  $\lambda$  max (MeOH-KOH) nm ( $\log \epsilon$ ): 210 (4.76), 233 sh (4.11), 286 (3.80); ir v max (KBr): 3440, 3290, 1610, 1585  $cm^{-1}$ ; eims (70 eV)  $m/z$ : 299 ( $M^+$ , 0.2%), 193 (15.7%), 192 (100%), 178 (8.7%), 177 (4.0%), 176 (10.9%), 148 (5.7%), 131 (4.6%), 77 (7.8%), cims ( $NH_3$ )  $m/z$ : 300 ( $[MH]^+$ , 100%), 286 (6.7%), 193 (3.2%), 192 (23.9%), 178 (1.7%);  $^1H$ -nmr (200 MHz,  $CDCl_3$ ,  $\delta$  ppm): 2.83 and 3.35 (2m, 6H, 3 CH<sub>2</sub>), 3.83 and 3.85 (2s, 6H, 2 OCH<sub>3</sub>), 4.36 (dd, 1H,  $J=8.0, 1.0$  Hz, H-1), 6.54 (s, 1H, H-8), 6.60 (s, 1H, H-5), 6.73 (dd, 1H,  $J=7.0, 7.0$  Hz, H-13), 6.87 (d,  $J=7.0$  Hz, H-11), 7.03 (d,  $J=7.0$  Hz, H-14), 7.10 (dd,  $J=7.0, 7.0$  Hz, H-12);  $^{13}C$ -nmr (68 MHz,  $CDCl_3$ ,  $\delta$  ppm): 55.9 (C-1), 38.5 (C-3), 27.1 (C-4), 125.6 and 127.1 and 125.0 (C-4a and C-8a and C-9), 111.0 (C-5), 147.6 and 147.9 (C-6 and C-7), 109.9 (C-8), 40.3 (C- $\alpha$ ), 156.7 (C-10), 117.4 (C-11), 128.4 (C-12), 119.1 (C-13), 131.6 (C-14), 55.8 and 55.9 (2 OCH<sub>3</sub>).
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