N_b-Methyl Strictamine – A New Alkaloid from the Leaves of *Rhazya stricta*

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Continuing studies on the leaves of *Rhazya stricta* have resulted in the isolation of a new Picralima alkaloid, N_b-methyl strictamine **2**.

Introduction

Rhazya stricta (Decaisne) is a small glabrous erect shrub which grows abundantly in various parts of Pakistan [1, 2]. It is well known in the indigenous system of medicine as a bitter tonic, as a curative for chronic rheumatism, sore throat and in fever [3, 4]. It is especially reputed for its antitumour activity and a number of cytotoxic alkaloids have been reported from the plant [5, 6].

Results and Discussion

The crude alkaloidal material isolated by conventional procedures [4, 7] was subjected to column chromatography over neutral alumina. Elution with chloroform:methanol (97:3) afforded a new crystalline alkaloid, named N_b-methylstrictamine **2**, m.p. 176–178 °C, $[\alpha]_D = -65$. It was very polar but homogeneous on TLC, having a distinctly different R_f value to the other alkaloids isolated from *R. stricta*. The UV spectrum exhibited a characteristic indoleninic absorption with $\lambda_{\max}$ MeOH 222, 265 nm and $\lambda_{\min}$ MeOH 242 nm. The IR spectrum showed a strong absorption at 1740 cm⁻¹ indicating the presence of ester group in the molecule. The HRMS afforded M⁺ at m/z 337.1932 corresponding to the formula C₂₁H₂₅N₂O₂, and a prominent peak due to loss of hydrogen at m/z 336.1852 corresponding to the formula C₂₁H₂₄N₂O₂ indicating the presence of eleven double bond equivalents in the molecule. Other important fragments were present at m/z 322.1689 (C₂₀H₂₂N₂O₂), 308.1524 (C₁₉H₂₀N₂O₂) and 263.1549 (C₁₈H₁₉N₂). The remaining fragmentation pattern was found to be very similar to that of strictamine [9].

¹H NMR spectrum (300 MHz, CDCl₃) provided considerable information on the structure, and this was further supported from two-dimensional measurements (COSY 45°, 2D–J resolved). A doublet at δ 1.56 was assigned to the ethylidene methyl group, with the corresponding quartet for the olefinic proton of the ethylidene group resonating at δ 5.89. The presence of an ester methyl and a quaternary N–Me were apparent by signals at δ 3.68 and δ 3.80 respectively.

Extensive NOE difference studies were carried out to establish the structure and relative stereochemistry. Irradiation at δ 1.56 (18-Me) resulted in 5% NOE at δ 5.89 (19-H) while irradiation at δ 5.89 (19-H) resulted in a corresponding 6.2% NOE at δ 1.56 (18-Me). Irradiation at δ 3.72 (15-H α) resulted 5.6% NOE at δ 1.56 (18-Me), 6.8% NOE at δ 2.08 (14-H α), and 6.8% at δ 2.15 (16-H). These NOE effects established the configuration of ethylidine group in N_b-methyl strictamine as being E. Irradiation at δ 1.93 (14-H β) resulted 5.2% NOE at δ 2.08 (14-H α), while irradiation at δ 4.28 (5-H α) resulted 3.7% NOE at δ 5.06 (21-H α) and 3.7% at δ 2.71 (C₆–H α). Similar irradiations in the aromatic region established the chemical shifts of the aromatic protons. The NOE effects are presented in Fig. 1.

The ¹³C NMR (CDCl₃) (75 MHz) showed 21 signals. The multiplicities were established by using polarization transfer (DEPT) experiments. The substance showed a downfield signal at δ 170.1 which was assigned to the carboxyl carbon atom of ester group. Another downfield signal at δ 177.70 was assigned to the C-2 carbon. Three signals corresponding to CH₃ groups appeared at δ 58.3, δ 52.0 and δ 13.47 and were assigned to N_b methyl, ester methyl and ethylidine methyl groups respectively. Two methylene groups resonated at δ 63.2 and δ 63.66 and were assigned to C-5 and C-21 carbons respec-

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Table I. ¹³C NMR (CDCl₃).

Carbon	N _b -Methyl strictamine		Strictamine
	Chemical shift (ppm)	Multiplicity	Chemical shift
2	177.70	—C—	190.98
3	68.41	—HC	55.15
5	63.25	—H ₂ C	51.98
6	34.38	—H ₂ C	36.13
7	53.37	—C—	58.40
8	144.29	—C—	138.15
9	123.03	—HC	123.47
10	127.80	—HC	125.47
11	127.12	—HC	125.61
12	129.23	—HC	128.19
13	154.46	—C—	119.93
14	25.07	—H ₂ C	156.10
15	29.95	—HC	33.62
16	53.99	—HC	32.50
18	13.47	—H ₃ C	12.90
19	122.30	—HC	121.02
20	127.32	—C—	146.35
21	63.66	—H ₂ C	53.68
ester CH ₃	52.09	—CH ₃	51.55
N _b —CH ₃	58.38	—CH ₃	—
ester C=O	170.1	—C=O	171.68

tively. A lowfield aliphatic carbon at δ 68.41, which was due to a CH group, was assigned to the C-3 carbon atom. The C-16 carbon atom (CH) resonated at δ 53.99. The other carbon signals are presented in Table I along with those of strictamine.

On the basis of above spectroscopic studies and the highly polar nature of the compound it was concluded that the alkaloid was N_b-methyl strictamine. This was confirmed by methylation of strictamine [8] in EtOAc with CH₃I at room temperature, and comparison of the reaction product by co-chromatography and spectroscopy with the isolated compound.

Experimental

A portion (600 g) of the ethanol extract (1.3 kg) of fresh leaves of *R. stricta* was Soxhlet extracted with petroleum ether to afford the crude alkaloidal material (1.11 g). Chromatography over neutral alumina (BDH, 300 g) and elution with CHCl₃–MeOH (47:3) yielded a new crystalline base (0.22 g) m.p. 176–178 °C, no colouration with Ce(SO₄)₂·4H₂O solution; $[\alpha]_D^{25}$ CHCl₃ = –65°, UV spectrum $\lambda_{\max}$ MeOH 222 nm, 263 nm, $\lambda_{\min}$ MeOH 242. IR: $\lambda_{\max}$ CHCl₃ 1740 cm^{–1} (ester C=O). HRMS: m/z 337.1932 (C₂₁H₂₅N₂O₂), 336.1852 (C₂₁H₂₄N₂O₂), 322.1689 (C₂₀H₂₂N₂O₂), 308.1524 (C₁₉H₂₀N₂O₂), 263.1549 (C₁₈H₁₉N₂). ¹H NMR spectrum (CDCl₃, 300 MHz): δ 1.56 (3H, d, $J_{18,19}$ = 6.9 Hz), δ 1.93 (d, 1H, 14-H β , $J_{14\beta,14\alpha}$ = 14.5 Hz), δ 2.08 (1H, dd, 14-H α , $J_{14\alpha,15\alpha}$ = 5.2, $J_{14\alpha,14\beta}$ = 15.0 Hz), δ 2.15 (1H, s, 16-H, $J_{16,15}$ = 3.4 Hz), δ 3.60 (1H, m, 5-H β), δ 2.71 (1H, dd, 6-H α , $J_{6\alpha,5\alpha}$ = 5.0 Hz, $J_{6\alpha,6\beta}$ = 13.0 Hz), δ 3.60 (1H, m, 6-H β), δ 3.72 (1H, m, 15-H α), δ 3.68 (3H, s, ester-CH₃), δ 3.80 (3H, s, N_b–CH₃), δ 4.28 (1H, dd, 5-H α , $J_{5\alpha,6\alpha}$ = 5.0, $J_{5\alpha,5\beta}$ = 13.00 Hz), δ 4.98 (1H, m, 3-H α), δ 4.92 (1H, d, 21-H β , $J_{21\beta,21\alpha}$ = 15 Hz), δ 5.06 (1H, d, 21-H α , $J_{21\alpha,21\beta}$ = 15 Hz), δ 7.41 (1H, d, 9-H, $J_{9,10}$ = 7.8 Hz), δ 7.20 (1H, m, 10-H), δ 7.34 (1H, m, 11-H), δ 7.63 (1H, d, 12-H, $J_{12,11}$ = 7.6 Hz). ¹³C NMR spectra (CDCl₃) (Table I).

Alkylation of strictamine 1

Strictamine (50 mg) was dissolved in EtOAc (5 ml), CH₃I (0.5 ml) was added to the solution. The reaction mixture was stirred at 30 °C for 30 min, and the solution evaporated to dryness. The reaction product was co-chromatographed over silica gel (Merck F₂₅₄) with N_b-methyl strictamine in H₂O:butanol (9.5:0.5). The product was found to be identical to the isolated compound by co-chromatography and spectral comparison.

- [1] J. D. Hooker and B. D. Jackson, *Index Kewensis*, Vol. 4, p. 705 and Supplement 8 (1926–1930), Clarendon press, Oxford 1865.
- [2] J. D. Hooker, *Flora of British India*, Vol. 3, p. 540, Reeve and Company 1875.
- [3] Anon, *Curtis Botanical Magazine* **152**, 9119 (1926).
- [4] Y. Ahmad, K. Fatima, P. W. LeQuesne, and Atta-ur-Rahman, *Phytochemistry* **22**, 1017 (1983).
- [5] S. Mukhopadhyay, G. A. Handy, S. Funayama, and G. A. Cordell, *J. Nat. Prod.* **44**, 896 (1981).
- [6] S. Siddiqui and A. Q. S. Bukhari, *Nature* **235**, 393 (1972).
- [7] Y. Ahmad, K. Fatima, Atta-ur-Rahman, J. L. Ocolowitz, B. A. Solheim, J. Clardy, R. L. Garnick, and P. W. LeQuesne, *J. Am. Chem. Soc.* **99**, 1943 (1977).
- [8] H. K. Schnoes, K. Biemann, J. Mokry, I. Kompis, A. Chatterjee, and G. Ganguli, *J. Org. Chem.* **31**, 1641 (1966).