

THE RHAZIMANINE-BHIMBERINE ENIGMA

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ABSTRACT.—Evidence is presented to support the view that rhazimanine and bhimberine, two indole alkaloid samples isolated in 1986 from *Rhazya stricta* and claimed to be identical with (16*R*)-3-*epi-E*-isositsirikine [**1**] and (16*S*)-3-*epi-E*-isositsirikine [**2**], respectively, consist mainly of one and the same compound, (16*R*)-*E*-isositsirikine [**3**].

In 1986, Atta-ur-Rahman and collaborators reported the isolation of two alkaloids, named rhazimanine and bhimberine, from *Rhazya stricta* (Apocynaceae) (1,2). Mainly on the basis of extensive nmr measurements, structures **1** and **2** were proposed. Thus, rhazimanine and bhimberine were identified as the two possible C-16 epimers of 3-*epi-E*-isositsirikine [**1** and **2**].

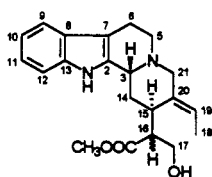
The structures presented have intrigued other researchers and doubts have been cast over the proposals, based on a comparison of the ¹H-nmr data of rhazimanine and bhimberine with those of synthetically prepared **1** and **2** (3–6). Although these results indicated the non-identity of rhazimanine and bhimberine with structures **1** and **2**, they did not resolve the rhazimanine-bhimberine enigma.

During our recent studies on the isomers of isositsirikine (7), the complete ¹H- and ¹³C-nmr data of all eight possible isomers became available. Comparison of the ¹H- and ¹³C-nmr data indicated for rhazimanine (1) and bhimberine (2) with those of the eight isositsirikine isomers, led to the conclusion that neither rhazimanine nor bhimberine is identical

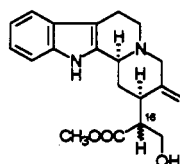
with any of the eight isomers. On the other hand, the C-6 signals at 18.0 ppm [17.96 ppm (**1**)] and 18.1 ppm [18.10 ppm (**2**)] in the ¹³C-nmr spectra and the H-3 signals at 4.36 ppm and 4.29 ppm in the ¹H-nmr spectra, respectively, indicated that, if rhazimanine and bhimberine are isositsirikines at all, and this is supported by their molecular peaks at *m/z* 354 (1,2), they must belong to the *E*-isositsirikine, not to the 3-*epi-E*-isositsirikine, series.

With this new information we considered the possibility that the ¹H- and ¹³C-nmr signals of rhazimanine [**1**] and bhimberine [**2**] might have been erroneously assigned. To explore this, we set out to reassign the signals, respecting as far as possible the earlier multiplicity assignments of the ¹³C-nmr signals made by DEPT experiments (1,2), and compared the new assignments with those of compounds **3** and **4** (7). A very good similarity was found with the spectral data of compound **3**, especially in the case of **1** (Tables 1 and 2).

Because the *R_f* values of 0.19 (1) and 0.20 (2) [silica, petroleum ether (40–60°)-Me₂CO-Et₂NH (16:4:1)] indicated for rhazimanine and bhimberine are very



1 C-16-H β (16*R*)
2 C-16-H α (16*S*)



3 C-16-H β (16*R*)
4 C-16-H α (16*S*)

TABLE 1. ¹H-Nmr Data (taken in CDCl₃) of Rhazimanine, Bhimberine, Rhazimanine/Bhimberine Hybrid, and Structure 3' (=mirror image of compound 3; *vide infra*).

Proton(s)	Rhazimanine ^a		Rhazimanine/ bhimberine hybrid ^{a,b} reassigned	Structure 3' ^c	Bhimberine ^b	
	original	reassigned			reassigned	original
H-3 . . .	4.36 br s	4.36 br s	4.36 br s	4.31 br s	4.29 dd	4.29 dd
H-5α . .	2.70 ddd	3.30 ddd	3.28 m	3.27 dd	3.28 m	2.62 m
H-5β . .	2.97 m	3.19 m	3.16 m	3.15 ddd	3.16 m	2.94 m
H-6α . .	3.30 ddd	2.97 m	2.97 m	3.00 m	2.94 m	3.37 m
H-6β . .	3.19 m	2.70 ddd	2.62 m	2.65 br d	2.62 m	3.28 m
H-14α . .	1.72 m	1.72 m ^d	1.72 m ^d	2.22 m	1.53 m ^d	1.53 m
H-14β . .	2.25 m	2.25 m	2.25 m	2.26 m	2.32 m	2.32 m
H-15 . .	3.12 m	3.12 m	3.12 m	3.10 m	3.37 m	3.16 m
H-16 . .	2.52 m	2.52 m	2.52 m	2.52 m	2.46 m	2.46 m
H-17a . .	3.50 m	3.50 m	3.50 m	3.50 br dd	3.68 m	3.68 m
H-17b . .	3.62 m	3.62 m	3.62 m	3.55 br dd	3.83 m	3.83 m
H-18 . .	1.62 m	1.62 m	1.62 m	1.67 d	1.60 br d	1.60 br d
H-19 . .	5.66 br q	5.66 br q	5.66 br q	5.64 br q	5.78 br q	5.78 br q
H-21α . .	3.56 m	3.56 m	3.56 m	3.54 br d	3.62 m	3.62 m
H-21β . .	3.03 br d	3.03 br d	2.99 m	2.93 br d	2.99 m	2.99 m
COOCH ₃	3.81 s	3.81 s	3.81 s	3.82 s	3.76 s	3.76 s

^aValues taken from Atta-ur-Rahman *et al.* (1).

^bValues taken from Atta-ur-Rahman *et al.* (2).

^cValues taken from Lounasmaa *et al.* (7). N.B. To facilitate direct comparison with the data in different lines, the data of compound 3 are presented as corresponding to its mirror image (called structure 3'). As a consequence, the configurational indications α and β, given earlier for the same compound [cf. Lounasmaa *et al.* (7); Table 1; compound 7], have been interchanged.

^dThe H-14 signals of compound 3 appear at 2.26 ppm and 2.22 ppm. It is plausible that the multiplets at 2.25 ppm and 2.32 ppm, originally assigned only for H-14β in 1 and 2, respectively, in reality represent both H-14 signals. If this is accepted, the signals at δ 1.72 ppm and δ 1.53 ppm assigned originally for H-14α in 1 and 2, respectively, are due to impurities.

similar, it could be that the sample separation was incomplete. Moreover, both samples may have contained some, and not necessarily the same, impurities, which slightly influenced the chemical shifts of the different signals. For this reason, we considered it justified not only to compare the reassigned rhazimanine and bhimberine signals with those of compound 3, but also the combined reassigned data of rhazimanine and bhimberine (rhazimanine/bhimberine hybrid signals; a combination incorporating those reassigned rhazimanine and bhimberine signals best fitting with the signals of compound 3; Tables 1 and 2). The similarity of these data with those of compound 3 is striking.

We therefore conclude that the rhazimanine sample, and to a lesser ex-

tent the bhimberine sample, consist of (16*R*)-*E*-isositsirikine [3]. Both original samples seem to have been contaminated by some impurities. In the case of the bhimberine sample, one of the impurities may have been (16*R*)-*E*-isositsirikine acetate (*vide supra*), whose presence in *Rhazya stricta* has been claimed (8).

Our proposal for the rhazimanine structure is mainly in agreement with the nOe difference measurements presented for 1. Because of the impurities present, the case of 2 is less clear.

With these proposals, we suggest that the nearly decade-long enigma concerning the rhazimanine and bhimberine structures has been solved.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Our

TABLE 2. ¹³C-Nmr Data (taken in CDCl₃) of Rhazimanine, Bhimberine, Rhazimanine/Bhimberine Hybrid, and (16*R*)-*E*-Isositsirikine [3].

Carbon	Rhazimanine ^a		Rhazimanine/ bhimberine hybrid ^{a,b} reassigned	(16 <i>R</i>)- <i>E</i> -Iso- sitsirikine ^c [3]	Bhimberine ^b	
	original	reassigned			reassigned	original
C-2 ...	131.4	131.4	132.4	132.5	132.4	132.5
C-3 ...	49.6	53.2	52.9	52.7	52.9	49.4
C-5 ...	50.2	50.2	50.2	50.8	49.9	49.9
C-6 ...	18.0	18.0	18.0	17.6	18.1	18.1
C-7 ...	107.0	107.0	107.0	107.4	106.4	106.4
C-8 ...	126.9	127.2	127.2	127.4	129.2	124.9
C-9 ...	118.1	118.1	118.1	118.0	118.2	118.2
C-10 ..	119.7	119.7	119.7	119.5	119.8	119.8
C-11 ..	122.1	122.1	122.1	121.7	122.8	122.8
C-12 ..	111.6	111.6	111.6	111.4	111.9	111.9
C-13 ..	136.6	136.6	136.6	136.3	136.8	136.8
C-14 ..	29.7	29.7	29.7	29.6	31.9	31.9
C-15 ..	32.8	32.8	32.8	32.5	33.0	33.0
C-16 ..	53.2	49.6	49.4	49.4	49.4	52.9
C-17 ..	61.6	61.6	61.6	61.6	63.8 ^d	63.8 ^d
C-18 ..	13.5	13.5	13.5	13.4	14.1	14.1
C-19 ..	127.2	126.9	124.9	124.9	124.9	129.2
C-20 ..	131.3	131.3	132.5	132.7	132.4	132.5
C-21 ..	53.8	53.8	51.9	52.3	51.9	51.9
C-22 ..	174.7	174.7	174.7	175.2	173.4	173.4
MeO ..	52.2	52.2	52.2	52.2	52.5	52.5

^aValues taken from Atta-ur-Rahman *et al.* (1).

^bValues taken from Atta-ur-Rahman *et al.* (2).

^cValues taken from Lounasmaa *et al.* (7).

^dIn the spectrum of (16*R*)-*E*-isositsirikine acetate the corresponding signal is indicated at δ 63.6 ppm (8).

¹H-nmr spectra were measured with a Varian Unity-400 NMR spectrometer operating at 399.952 MHz and ¹³C-nmr spectra with a Varian Gemini-200 spectrometer working at 50.289 MHz using CDCl₃ as solvent. Chemical shifts are given in ppm by reference to TMS (¹H nmr; δ_H 0.00 ppm) and CDCl₃ (¹³C nmr; δ_C 77.00 ppm).

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Received 15 July 1994