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Synthesis of a piperidone model compound and revision of the structures of jenamidines A to C

Barry B. Snider,[a,*] Jeremy R. Duvall,[a] Isabel Sattler[b] and Xueshi Huang[b]

[a]*Department of Chemistry MS 015, Brandeis University, Waltham, MA 02454-9110, USA*
[b]*Hans-Knöll-Institute for Natural Products Research, Beutenbergstr. 11a, D-07745 Jena, Germany*

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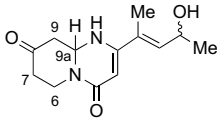
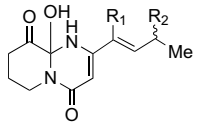
Abstract—Reaction of 2,3-dihydro-4-pyridone (**4**) with isatoic anhydride (**5**) provided the unstable product **6**, for which the NMR spectral data are quite different from those reported for the ring system of jenamidine A. This suggests that the proposed structures **1** to **3** of jenamidines A to C should be revised to **8** to **10**.

One of us recently reported the isolation of three bicyclic alkaloids, jenamidines A (**1**), B (**2**), and C (**3**), from the culture broth of *Streptomyces* sp. (strain HKI0297).[1] The structures were proposed as the best fit based on IR, UV, NMR, and mass spectral data. However, further consideration suggested that the aminal hydrogen H_{9a} of **1** should absorb further downfield than the observed value of δ 3.94 in jenamidine A, and that carbons C_7 and C_9 of **1**, which are adjacent to a ketone, should absorb further downfield than the observed values of δ 27.5 and 28.8, respectively.

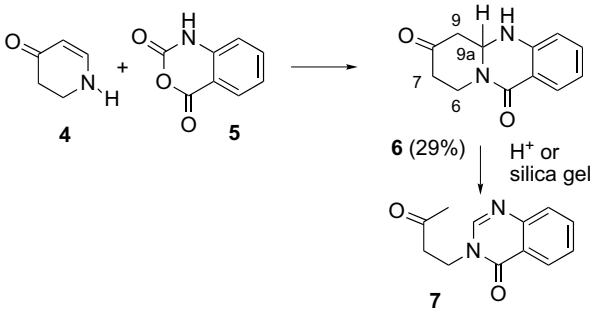


proposed structure for jenamidine A (**1**)



proposed structure for jenamidine B (**2**, R_1 = Me, R_2 = OH)
proposed structure for jenamidine C (**3**, R_1 = CH_2OH, R_2 = H)

These expectations were confirmed by the synthesis of tricycle **6** (see Scheme 1), which is a good model for the piperidone moiety of the proposed structure for jenamidine A (**1**). Reaction of 2,3-dihydro-4-pyridone



Scheme 1. Preparation and decomposition of tricyclic piperidone **6**.

(**4**)[2] with isatoic anhydride (**5**) and Et_3N in THF for 8 h in a sealed tube at 80 °C provided 29% (65% based on recovered **4**) of the surprisingly unstable tricyclic piperidone **6**.[3,4] Treatment of **6** with dilute acid resulted in a facile retro-Mannich reaction to give **7**[5] quantitatively.[6] Partial conversion of **6** to **7** occurred during flash chromatography on silica gel. The spectral data of **6** confirmed our earlier concerns about the proposed structure of jenamidine A (**1**). H_{9a} of **6** absorbs at δ 5.12 (dd, J = 3.7, 9.2 Hz) and the three CH_2 carbons absorb at δ 47.8, 40.9, and 39.7. All the absorptions and coupling constants are consistent with those expected for this structure.[3]

These observations suggested that the three methylene carbons of jenamidine A might be part of a pyrrolidine ring with the ketone elsewhere in the molecule. Eventually, we considered the unusual ketene aminals **8**, **9**, and

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* Corresponding author. Tel.: +1-781-736-2550; fax: +1-781-736-2516; e-mail: snider@brandeis.edu

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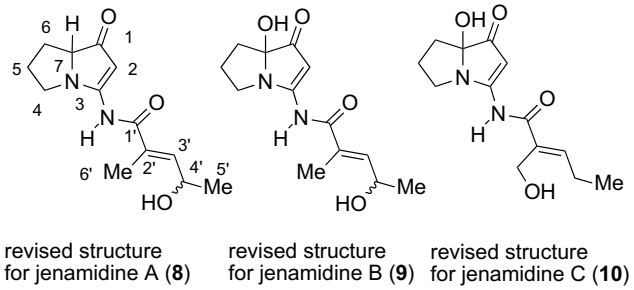
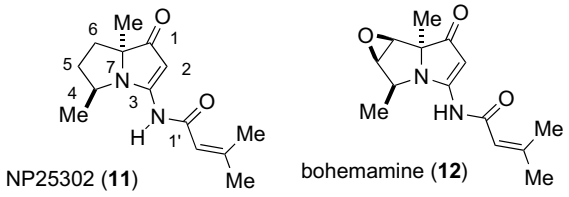


Figure 1. Revised structures for jenamidines A, B, and C.

10 as possible structures for jenamidines A, B, and C (Fig. 1). The ^{1}H and ^{13}C chemical shifts and HMBC correlations are consistent with this assignment.

A literature search indicated that bohemamine (**12**), whose structure was determined by X-ray crystallography,[7] and NP25302 (**11**), whose structure was very recently reported,[8] have the same ring system as **8**–**10**. The ^{13}C and ^{1}H NMR spectral data for the revised structures of jenamidines A (**8**), B (**9**), and C (**10**) correspond well to those of NP25302, except for the expected differences due to the two methyl groups and different side chain as shown in Tables 1 and 2 (the numbering system is that previously used for NP25302). It is noteworthy that the aminal carbon of the jenamidines absorbs from δ 171.5 to 173.5, a region more typical of an amide carbonyl than a double bond. The spectral data for the side chain of jenamidines A and B correspond well with those reported for ethyl 4-hydroxy-2-methylpent-2-enoate.[9]



Detailed analysis of the ^{13}C NMR data of the natural products revealed the occurrence of several doubled signals of similar intensity in samples of apparently chromatographically homogeneous jenamidines A (**8**) and B (**9**). In the case of jenamidine A (**8**), two signals with shift differences between 0.02 and 0.1 ppm were observed for all carbons except for C_4, C_5, and $C_{6'}$. A second set of proton signals for H_2, H_7, $H_{4'}$, and $H_{5'}$ cannot be fully assigned due to overlapping multiplets. For jenamidine B (**9**), additional carbon signals with shift differences between 0.02 and 0.09 ppm were detected for all carbons, except for C_4, C_5, C_6, $C_{2'}$, and $C_{6'}$. The absence of such doubled signals in jenamidine C (**10**) strongly suggests a mixture of two diastereomers for **8** and **9** with differing stereochemistry at $C_{4'}$. Therefore the compounds were renamed as jenamidines A_1/A_2 (**8**) and B_1/B_2 (**9**).

Strikingly, in jenamidines A_1/A_2 (**8**), the highest carbon shift differences are found for C_1 (0.106 ppm) and C_7 (0.107 ppm). The NOESY data suggest a possible explanation. Only one of the two diastereomers shows a correlation between H_2 and $H_{3'}$, which may indicate a folded side chain, possibly with hydrogen bonding between the 4′-OH and the C_1 carbonyl, which could be more preferred in one of the $C_{4'}$ configurations. In addition, the differing side chain conformations significantly affect H_2 resulting in a proton shift difference of 0.04 ppm.

Detailed reinvestigation of NMR data revealed another interesting feature of the jenamidines. The signal inten-

Table 1. ^{13}C NMR data in δ for compounds **8**–**11**

C	**8**[a,b]	**9**[a,b]	**10**[a]	**11**[c]
1	204.66 (C)	202.47(C)	202.4 (C)	205.7 (C)
	204.55 (C)	202.39 (C)		
2	93.83 (CH)	90.62 (CH)	90.4 (CH)	94.0 (CH)
	93.78 (CH)	90.60 (CH)		
3	173.47 (C)	172.29 (C)	171.5 (C)	167.7 (C)
	173.43 (C)	172.22 (C)		
4	49.30 (CH_2)	49.19 (CH_2)	48.5 (CH_2)	55.2 (CH)
5	28.75 (CH_2)	27.65 (CH_2)	27.8 (CH_2)	35.8 (CH_2)
6	27.49 (CH_2)	33.57 (CH_2)	33.6 (CH_2)	28.7 (CH_2)
	27.46 (CH_2)			
7	70.76 (CH)	97.22 (C)	97.0 (C)	75.1 (C)
	70.65 (CH)	97.14 (C)		
1′	169.82 (C)	170.20 (C)	168.4 (C)	164.6 (C)
	169.81 (C)	170.15 (C)		
2′	131.62 (C)	131.67 (C)	133.7 (C)	—
	131.60 (C)			
3′	143.66 (CH)	143.86 (CH)	146.9 (CH)	—
	143.63 (CH)	143.81 (CH)		
4′	65.30 (CH)	65.32 (CH)	22.4 (CH_2)	—
	65.25 (CH)	65.27 (CH)		
5′	22.69 (CH_3)	22.68 (CH_3)	13.6 (CH_3)	—
	22.66 (CH_3)	22.65 (CH_3)		
6′	12.92 (CH_3)	12.92 (CH_3)	57.0 (CH_2)	—

[a] Spectra recorded at 75 MHz in CD_3OD. Assignments made by 2-D NMR techniques (COSY, HSQC, HMBC).
[b] Doubled signals cannot be assigned to individual diastereomers.
[c] Spectral data (125 MHz, $CDCl_3$) from Ref. 8.

Table 2. ^{1}H NMR data in δ for compounds **8**–**11**

H	**8**[a]	**9**[a]	**10**[a]	**11**[b]
2	5.65 (1, s)[c]	5.56 (1, s)[c]	5.61 (1, s)	5.75 (1, s)
	5.61 (1, s)[c]	5.52 (1, s)[c]		
4	3.44 (1, m)	3.54 (1, m)	3.54 (1, m)	4.08 (1, m)
4	3.20 (1, m)	3.22 (1,m)	3.15 (1, m)	—
5	2.15 (1, m)	2.35 (1, m)	2.35 (1, m)	2.46 (1, m)
5	2.15 (1, m)	2.06 (1, m)	2.10 (1, m)	1.83 (1, m)
6	1.53 (1, m)	1.64 (1, m)	1.65 (1, m)	1.69 (1, m)
6	2.20 (1, m)	1.95 (1, m)	1.91 (1, m)	1.85 (1, m)
7	3.94 (1, m)[d]	—	—	—
3′	6.38 (1, br d)	6.35 (1, br d)	6.72 (2, t)	
	J = 7.9	J = 7.8	J = 7.6	
4′	4.65 (1, dq)[d]	4.62 (1, dq)	2.31 (2, dq)	
	J = 7.9, 6.5	J = 7.8, 6.4	J = 7.6, 7.6	
5′	1.29 (3, d)[d]	1.29 (3, d)	1.05 (3, t)	
	J = 6.5	J = 6.4	J = 7.6	
6′	1.91 (3, br s)	1.90 (3, br s)	4.45 (2, s)	

[a] Spectra recorded at 300 MHz in CD_3OD. Assignments made by 2-D NMR techniques (COSY, HSQC, HMBC).
[b] Spectral data (500 MHz, $CDCl_3$) from Ref. 8.
[c] Doubled signals could not be assigned to individual isomers.
[d] Doubled signals not fully resolved.

sity of the two H_2 singlets diminishes slowly, but significantly, over time in CD_3OD due to deuterium exchange. In jenamidine A_1/A_2 (**8**), about 20% of the signal intensity is lost in 3 days at an equal rate for both diastereomers. This exchange may be occurring by reversible protonation to give the amidinium cation. Alternatively, exchange could be initiated by deprotonation of the amide hydrogen. Lack of sufficient material did not allow us to further explore these observations.

In conclusion, structure determination of novel natural products with unusual skeletons from spectroscopic data alone remains a challenging problem. Synthesis can still play an important role as exemplified here by the preparation of model **6** for the proposed structure of jenamidine A (**1**). Differences between the spectral data of the two compounds indicated that the proposed structures **1** to **3** are incorrect. Revised structures **8** to **10** for jenamidines A to C fit the data well and have the same ring system as the natural products bohemamine and NP25302. Efforts are currently underway to confirm these reassignments by total synthesis.

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3. 5a,6,8,9-Tetrahydro-5*H*-pyrido[2,1-*b*]quinazoline-7,11-dione (**6**). A solution of 2,3-dihydro-4-pyridinone (**4**)[2] (100 mg, 1.09 mmol), isatoic anhydride (**5**) (178 mg, 1.09 mmol), and Et_3N (0.17 mL, 1.20 mmol) in 10 mL of dry THF was stirred in a sealed tube under N_2 for 8 h in an 80 °C oil bath. The mixture was cooled and concentrated to yield a mixture of **4**, anthranilic acid, tricycle **6** and **7**. Flash chromatography on silica gel (95:5 CH_2Cl_2–MeOH) yielded 150 mg of a mixture of **6** and **7** followed by 65 mg of recovered **4** (65%). The mixture of **6** and **7** was diluted with $CHCl_3$ and filtered. The filtrate was concentrated and the resulting oil was then taken up in minimal CH_2Cl_2. The solution was filtered and added dropwise to a solution of hexanes. The milky suspension was filtered and the precipitate was collected to give 67 mg of 90% pure **6** (29% yield, 65% based on recovered **4**) that decomposed to form **7** over time: mp 122–123 °C; ^{1}H NMR (CD_3OD) 7.71 (d, 1, J = 8.0), 7.25 (dd, 1, J = 8.0, 7.7), 6.73 (dd, 1, J = 8.0, 7.7), 6.65 (d, 1, J = 8.0), 5.12 (dd, 1, J = 3.7, 9.2, H_{9a}), 4.51 (ddd, 1, J = 4.3, 6.1, 13.4, H_6), 3.29 (ddd, 1, J = 4.3, 10.4, 13.4, H_6), 2.86 (dd, 1, J = 9.2, 15.3, H_9), 2.64 (dd, 1, J = 3.7, 15.3, H_9), 2.52 (ddd, 1, J = 6.1, 10.4, 15.9, H_7), 2.42 (ddd, 1, J = 4.3, 4.3, 15.9, H_7); ^{1}H NMR ($CDCl_3$) 7.91 (d, 1, J = 7.9), 7.31 (dd, 1, J = 7.9, 7.3), 6.86 (dd, 1, J = 7.9, 7.3), 6.67 (d, 1, J = 7.9), 5.17 (ddd, 1, J = 1.8, 3.8, 9.2, H_{9a}), 4.96 (br s, 1, NH), 4.73 (ddd, 1, J = 4.0, 6.1, 13.7, H_6), 3.24 (ddd, 1, J = 4.0, 10.7, 13.7, H_6), 2.92 (dd, 1, J = 9.2, 14.8, H_9), 2.72 (dd, 1, J = 3.8, 14.8, H_9), 2.62 (ddd, 1, J = 6.1, 10.7, 16.2, H_7), 2.49 (ddd, 1, J = 4.0, 4.0, 16.2, H_7); ^{13}C NMR (CD_3OD) 207.8, 165.4, 148.5, 135.2, 129.1, 119.5, 115.7, 115.2, 67.6, 47.8, 40.9, 39.7; ^{13}C NMR ($CDCl_3$) 205.7, 163.2, 145.5, 134.0, 128.5, 119.5, 114.7, 114.6, 66.5, 47.7, 40.2, 38.9; IR (KBr) 3303, 1720, 1640; HRMS (EI) Calcd for $C_{12}H_{12}N_2O_2$ (M^+) 216.0899, found 216.0903.
4. For the analogous compounds with the NH replaced by O or S see: Hamley, P.; Tinker, A. PCT Int. Appl. WO 00 06,576, 2000; *Chem. Abstr.* **2000**, *132*, 137406a.
5. 3-(3-Oxobutyl)-4(3*H*)-quinazolone (**7**). A solution of 10 mg of **6** in CH_2Cl_2 was washed three times with 5% aqueous HCl. The organic fraction was dried over magnesium sulfate and concentrated to give 8 mg of pure **7**: ^{1}H NMR ($CDCl_3$) 8.28 (d, 1, J = 6.7), 8.27 (s, 1), 7.76 (dd, 1, J = 7.9, 7.4), 7.71 (d, 1, J = 7.9), 7.50 (dd, 1, J = 7.4, 6.7), 4.22 (t, 2, J = 6.1), 3.07 (t, 2, J = 6.1), 2.16 (s, 3); ^{13}C NMR 206.2, 161.2, 148.0, 147.5, 134.2, 127.4, 127.1, 126.3, 121.9, 42.2, 41.4, 30.0; IR (neat) 1714, 1672; HRMS (EI) Calcd for $C_{12}H_{12}N_2O_2$ (M^+) 216.0899, found 216.0896. The spectral data are shifted considerably on addition of acid. The ^{1}H NMR spectral data are identical to those previously reported.[6]
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