Pergamon

*Tetrahedron Letters*, Vol. 35, No. 27, pp. 4719-4722, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00917-1

# Revised Structure of Xestocyclamine A and Description of a New Analogue [1]

**Jaime Rodríguez and Phillip Crews***

Department of Chemistry and Biochemistry and Institute for Marine Sciences
University of California, Santa Cruz, Santa Cruz, CA 95064

***Abstract:*** The structure of xestocyclamine A (**1**) from the sponge *Xestospongia* sp. has been revised to **2**. The structure of a new two carbon homologue, xestocyclamine B (**3**), is also presented.

Recently, we described a new Protein Kinase C active alkaloid xestocyclamine A (**1**)[2] which is a member of an emerging group of unusual polycyclic diamine alkaloids. With only one exception[3] compounds having this framework appear to be restricted to Haplosclerid sponges.[4] The final step in our characterization of xestocyclamine A, whose aliphatic protons appeared as badly overlapping NMR multiplets (Figure 1), was to distinguish between structural candidates **1** and **2**. Both were reasonable from a biogenetic viewpoint and both seemed consistent with the NMR data. In our communication we explained that the TOCSY spectra of xestocyclamine A (Figure 1) contained a small correlation between δ 0.95 and 2.25 (#Aβ), which was interpreted as a 2D peak due to magnetization transfer from H1 to H18. The assignment of HC18 at δ 2.82/ 2.25/49.6 in turn allowed $^1$H resonances at 2.87/1.67 to be ascribed to H7 and C7 at 52.6 (revised assignments are shown in the $^1$H NMR of Figure 1). The proton H7' was used as the anchor point to explain the HMBC correlation from δ 1.67 (H7') to 54.1 (C19) which was then used to justify structure **1**. A subsequent reexamination of our HMQC-TOCSY spectrum (Figure 1) revealed faint correlations #B (between 33.4/1.67) and #C (between 52.6/2.80). According to our carbon and proton assignments,[2] these should correspond to magnetization transfer respectively between C2/H7 and C7/H2. but such data was not compatible with the avenues for $^1$H-$^1$H TOCSY coupling in **1**. Clearly, one of these faint, but pivotal TOCSY correlations, #Aβ or #B/#C, had to be an artifact because they were mutually inconsistent. Switching the carbon and proton shifts of atoms 7 with 18 in **1** to explain the HMQC-TOCSY peaks #B and #C would also require revision of the structure of xestocyclamine A to **2**. During the time frame when this ambiguity was realized we had also isolated a new xestocyclamine analogue, B. Its $^1$H NMR spectrum, though equally complicated (Figure 2), contained several resolved resonances including those of H2, H7', H18. The TOCSY and HMQC-TOCSY data that were subsequently obtained for B (Figure 2) were both in agreement as to how atoms 7 and 18 should be assigned. These data plus correlations in the HMBC spectra firmly allowed structure **3** to be proposed for xestocyclamine B and further indicated that the structure for xestocyclamine A should be revised from **1** to **2**.

Using an HPLC rather than a CCC separation protocol[2] was an enormous aid in the isolation of xestocyclamine B. The viscous oil obtained from extraction of a new collection of *Xestospongia* sp. was purified by normal phase HPLC (hexanes:acetone:$Et_2NH$, 84:16:2) to afford xestocyclamine B (60.0 mg), $[\alpha]_D$=+27.4 (c=0.02). The characterization of **3** commenced with establishing an APT formula, $C_{28}H_{43}$ (by HMQC NMR) and the molecular formula, $C_{28}H_{44}N_2O$ ( by HREIMS, m/z 424.3440, Δ=1.4 mmu of that calculated). The NMR shifts of xestocyclamine A ($C_{26}H_{40}N_2O$) and B were

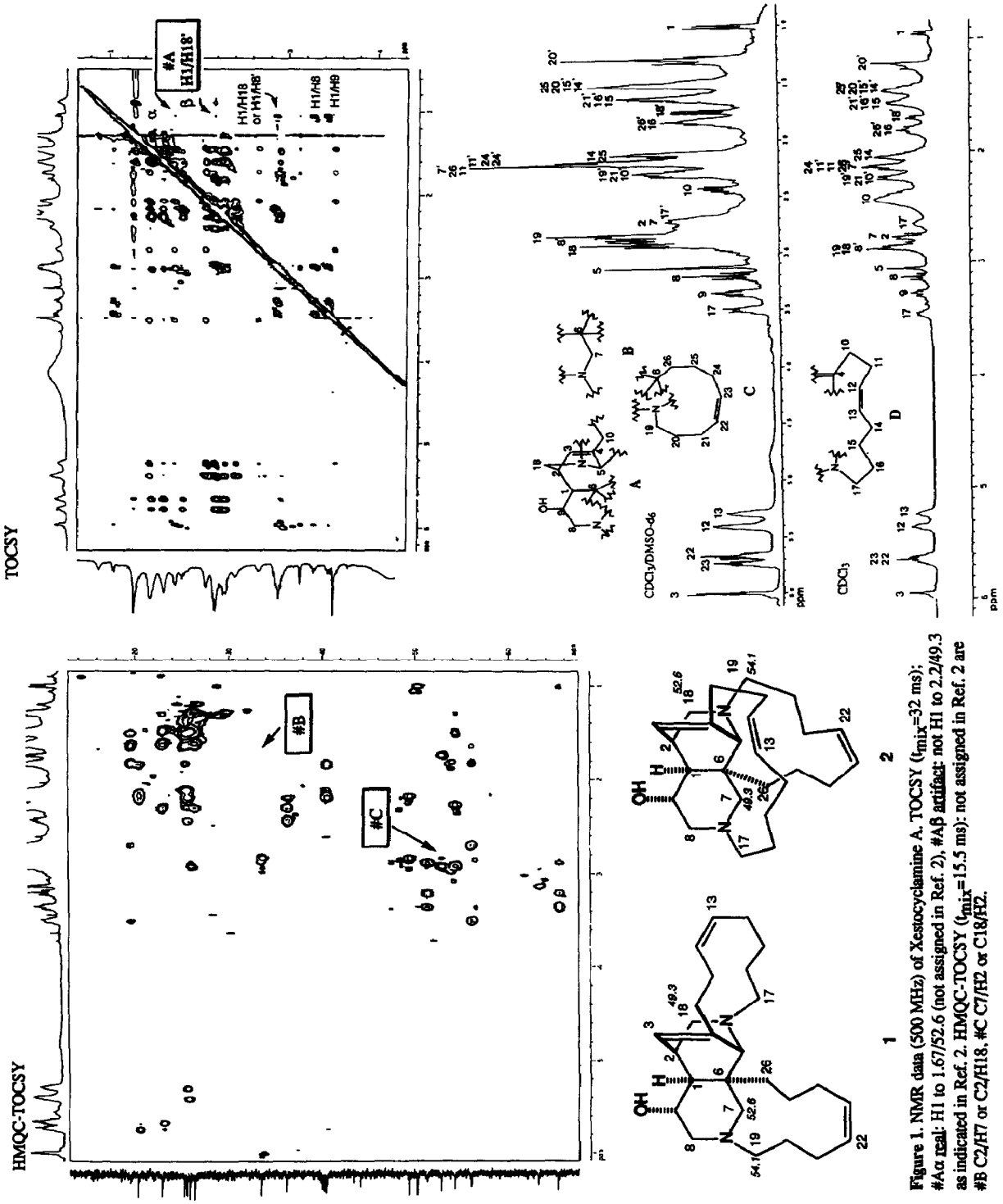


**Figure 1.** NMR data (500 MHz) of Xestocyclamine A. TOCSY ($t_{mix}$=32 ms); #Aα real: H1 to 1.67/52.6 (not assigned in Ref. 2), #Aβ artifact: not H1 to 2.2/49.3 as indicated in Ref. 2. HMQC-TOCSY ($t_{mix}$=15.5 ms): not assigned in Ref. 2 are #B C2/H7 or C2/H18, #C C7/H2 or C18/H2.

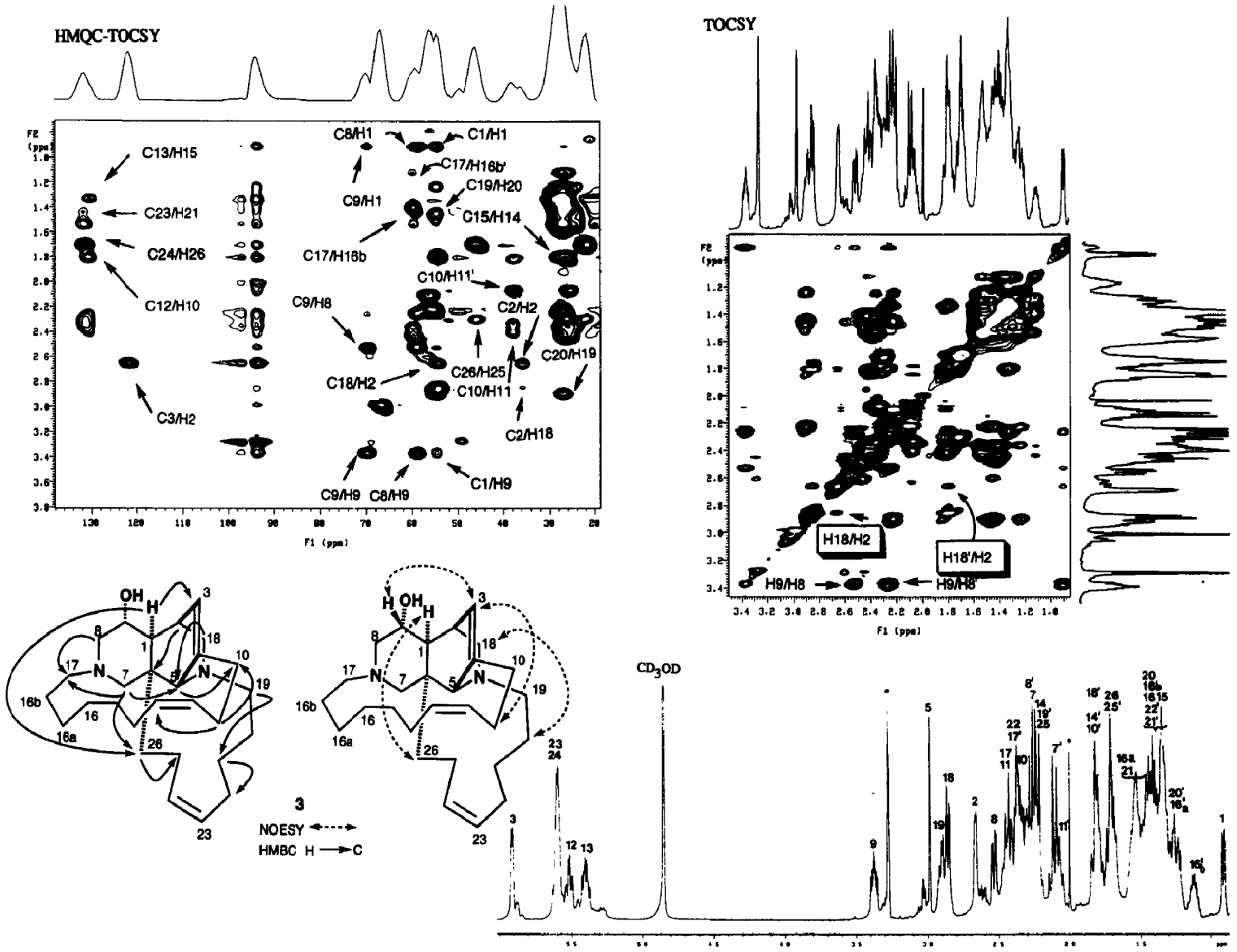


**Figure 2.** NMR data (500 MHz) of Xestocyclamine B. TOCSY ($t_{mix}$=30 ms), HMQC-TOCSY ($t_{mix}$=50 ms)

parallel (Table 1). The final NMR assignments for B as shown on the $^1H$ spectra in Figure 2 and in Table 1 were derived from side-by-side analysis of the 1D $^1H$ and $^{13}C$ spectra plus 2D COSY, TOCSY, HMBC and HMQC-TOCSY spectra.

For example, assignments of the congested upfield protons in the tricylic core came from the COSY correlations interrelating H3 to H2 and H3 to H18/18' (see H18/18' to H2 in the TOCSY, Figure 2). Two clear correlations in the HMBC interrelated H7' to C5 and H2 to C6. Assignments of atoms in the two long chains were begun by deciphering COSY correlations observed for the proton sets (beginning with the vinyl region) H13/H14, H12/H11, H20/H19, and H23/H22, H24/25 and H16b/H16a. The HMQC-TOCSY (Figure 2) spectrum provided many additional correlations such as H15 to C13, H13 to C11 and C14, H12 to C11, H11/11' to C10, H14 to C15, H16b to C17, H16b' to C17, H21 to C23, H24/23 to C22, C25, and C26. Interestingly, in 3 the HMQC TOCSY correlation between H18 and C2 or between H2 and C18 were very weak as was also the case in 2. That the vicinal coupling between H2/H18 is small in 3 (and also in 2) can be seen from the low intensity TOCSY correlations between H18,18'/2. A wealth of HMBC correlations were observed, as diagrammed on the structure in Figure 2, and were essential for completing the connections represented in 3. A high quality NOESY spectra provided the final justifcation for the stereochemistry at H's 9/1/2.

Table 1. NMR data of xestocyclamine A (2) and B (3).

| | (3) | | (2) | |
|---|---|---|---|---|
| | $^{13}C$ | $^1H$ (δ, m= Hz) | $^{13}C$ | $^1H$ (δ, m= Hz) |
| *1* | 54.8 d | 0.91 dd=8.0, 1.5 | 49.4 d | 0.95 dd=9.3, 0.8 |
| *2* | 36.1 d | 2.66 dd=6.0, 2.5 | 33.4 d | 2.80 m |
| *3* | 121.7 d | 5.91 dd=6.5, 2.5 | 125.3 d | 5.95 bd=7.0 |
| *4* | 146.1 s | - | 141.0 s | - |
| *5* | 67.0 d | 2.99 s | 63.1 d | 3.05 s |
| *6* | 47.7 s | - | 44.0 s | - |
| *7* | 56.4 t | 2.22 d=11.5/2.10 d=11.5 | 49.3 t | 2.82 m/2.25 m |
| *8* | 59.2 t | 2.53 dd=11.5, 4.5/2.25 m | 51.0 t | 3.10 t= 11.2/2.85 m |
| *9* | 69.9 d | 3.37 ddd=11.0, 8.5, 4.4 | 65.6 d | 3.20 dt=8.4, 4.1 |
| *10* | 38.1 t | 2.34 m/1.83 m | 36.1 t | 2.38 m/2.24 m |
| *11* | 25.4 t | 2.42 m/2.07 m | 25.8 t | 2.20 m |
| *12* | 131.3 d | 5.52 dt=10.5, 4.5 | 132.2 d | 5.32 m |
| *13* | 130.5 d | 5.40 dt=10.0, 6.0 | 131.6 d | 5.23 m |
| *14* | 26.7 t | 2.25 m/1.80 m | 25.2 t | 2.10 m/1.53 m |
| *15* | 28.9 t | 1.34 m | 26.3 t | 1.80 m/1.67 m |
| *16* | 25.2 t | 1.40 m | 19.4 t | 1.80 m/1.65 m |
| *16a* | 27.1 t | 1.54 m/1.27 m | | |
| *16b* | 26.6 t | 1.42 m/1.12 m | | |
| *17* | 60.0 t | 2.44 m/2.36 m | 55.9 t | 3.42 m/2.65 m |
| *18* | 54.3 t | 2.85 dd=9.0,1.5/2.23 m | 52.6 t | 2.87 m/1.67 bd=9.5 |
| *19* | 54.8 t | 2.90 m/1.83 m | 54.1 t | 2.75 m/2.12 m |
| *20* | 26.9 t | 1.44 m/1.24 m | 26.3 t | 1.50 m/1.28 m |
| *21* | 27.6 t | 1.54 m/1.34 m | 22.8 t | 1.79 m/1.53 m |
| *22* | 23.8 t | 2.36 m/1.54 m | 131.6 d | 5.55 dt= 11.0, 5.0 |
| *23* | 132.4 d | 5.59 m | 129.7 d | 5.57 m |
| *24* | 131.3 d | 5.59 m | 20.2 t | 2.20 m |
| *25* | 21.8 t | 2.30 m/1.70 m | 25.5 t | 2.10 m/1.53 m |
| *26* | 46.1 t | 1.71 m | 40.3 t | 2.17 m/1.80 m |

A revision of the structure of xestocyclamine to that shown in 2 brings it in line with that of 3. It is now clear that 2 and an isomeric compound, ingenamine, recently reported by Andersen[5] differ only in the placement of the double bonds. The former has a $\Delta^{22}$ while the latter has a $\Delta^{23}$ moiety.

**Acknowledgment**. Financial support was from NIH grants CA52955 and CA47135.

## REFERENCES AND NOTES


1 Part 7 in the series Novel Marine Sponge Alkaloids acids for part 6 see Ref 4h.

2 Rodríguez, J., Peters, B. M.; Kurz, L.; Schatzman, R. C.; McCarley, D.; Lou L.; Crews, P. *J. Am. Chem. Soc.* **1993**, *115*, 10436-10437.

3 The manzamines plus one alkaloid type of this group, the ircinals, come from a Dictyoceratida order sponge: Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J.Org. Chem* **1992**, *57*, 2480-2483.

4 There are eight other alkaloid types from Haplosclerida order sponges possessing these features: (a) Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hirota, H. *Tetrahedron Lett.* **1989**, *30*, 6891-6894. (b) Davies-Coleman, M. T.; Faulkner, D. J.; Dubowchik, G. M.; Roth, G. P.; Polson, C.; Fairchild, C. *J. Org. Chem.* **1993**, *58*, 5925-5930. (c) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863-3872; Cimino, G.; Fontana, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Mag. Reson. Chem.* **1991**, *29*, 327-322. (d) Braekman, J. C.; Daloze, D.; Macedo de Abreu, P.; Piccinni-Leopardi, C.; Germain, G.; van Meerssche, M. *Tetrahedron Lett.* **1982**, *23*, 4277-4280. (e) Nakagawa, N.; Endo, M.; Tanaka, N.; Gen-Pei, L. *Tetrahedron Lett.* **1984**, *25*, 3227-3230. (f) Baker, B. J.; Scheuer, P. J.; Shoolery, J. N. *J.Am. Chem. Soc.* **1988**, *110*, 965-966. (g) Ichiba, T.; Sakai, R.; Kohmoto, S.; Saucy, G.; Higa, T. *Tetrahedron Lett.* **1988**, *29*, 3083-3086. (h) Jaspars, M; Pasupathy, V.; Crews, P. *J. Org. Chem.* in press.

5 Kong, F.; Andersen, R. J.; Allen, T. M. *Tetrahedron Lett.* **1994**, *35*, 1643-1646.


(*Received in USA* 28 *March* 1994; *revised* 4 *May* 1994; *accepted* 6 *May* 1994)