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CHEMISTRY OF 2-BROMOLEPTOCLINIDINONE, STRUCTURE REVISION

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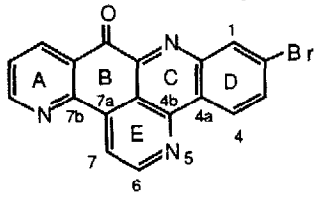
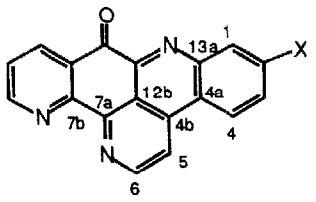
Summary: The structure of 2-bromoleptoclinidinone has been revised on the basis of selective long-range $^{1}H/^{13}C$ polarization transfer experiments and chemical correlation with ascididemin. Both alkaloids have the same pentacyclic aromatic skeleton.

Polycyclic aromatic alkaloids are emerging as a class of marine natural products having significant biological activities.[1-3] In 1987 we proposed structure **1** for 2-bromoleptoclinidinone, a cytotoxic metabolite isolated from an ascidian tentatively identified as a *Leptoclinides sp.*[1] Recently, Kobayashi *et al.* reported structure **2** for an antileukemic agent isolated from a *Didemnum* sp. of tunicate collected in Okinawa.[2] The skeletons for **1** and **2** differ only in the position of the nitrogen in ring E, and since structure **2** was one of the possible skeletons we had considered[1] for 2-bromoleptoclinidinone, we were prompted to reexamine our data to resolve whether these two natural products have the same or different skeletons. Several additional factors pointed to the need for a review. First, the long range H/C couplings used to help assign the structure of **1** had been ascertained using low power single frequency decoupling of fully coupled spectra taken in $CDCl_3$ and the similarity of chemical shifts of H-4 and H-7 (structure **1** numbering) 8.49, 8.45 ppm, respectively, made it impossible to get completely selective decoupling results. Hence minor differences in peak shape provided the basis for drawing conclusions. In a 2 D long range H/C experiment in $CDCl_3/CF_3CO_2H$, the 8.49 and 8.45 signals were coincident (8.55 ppm),rendering interpretation difficult. Finally, Kobayashi et al. reported[2] that **2** failed to exhibit the chelation with Fe(II) that could be expected for the 1,10-phenanthroline moiety present in this structure. We had interpreted a similar lack of chelation by **1** as an argument against assigning the skeleton of **2** to 2-bromoleptoclinidinone.[1]

1



2 X = H
3 X = Br



We have now reevaluated the crucial long range H/C couplings using the much more sensitive and definitive INAPT experiment[4] with $CDCl_3$ as solvent. Irradiation of H-4 (8.49 ppm) produced equally intense signals for the resonances assigned to C-4a and C-7a in structure **1**. Irradiation of the 8.45 ppm peak also induced signals of equal intensity for both these carbons. These results would be expected if each of these protons is long-range coupled to both of these carbons, but this requires interchanging C-7 and C-7a with the nitrogen and C-4b, respectively, in ring E of **1** to give the skeleton of **2**. That the separate irradiations of these two protons with similar chemical shifts produced noticeably selective results in the INAPT experiments was confirmed by the unequal intensities observed for the remaining carbon signals in the INAPT plots.[5]. Another important observation was that neither of these irradiations induced any signal for C-7b. All these results are more consistent with the ring E arrangement of **2** than **1**.

Direct comparison of the skeletons of 2-bromoleptoclinidinone and **2** was made by replacing the bromine in the former with hydrogen by hydrogenolysis (5% Pd, EtOH). The ^1H NMR spectrum of the reduced product[6] and ascididemin were identical.[7] Accordingly, 2-bromoleptoclinidinone (= 2-bromoascididemin) is now assigned structure **3**.[8]

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3. J. Kobayashi, J. Cheng, M. R. Walchli, H. Nakamura, Y. Hirata, T. Sasaki and Y. Ohizumi, *J. Org.Chem.*, **53**, 1800 (1988).
4. A Bax, J.A. Ferretti, N. Nashed, D.M. Jerina, *J. Org. Chem.*, ***50***, 3029 (1985).
5. Relative intensities are given in ( ). Irr. H-5, 8.45 ppm: C-12b (1.0), C-2 (0.53), C-13a(0.65); irr. H-6, 8.49 ppm: C-12b (0.63), C-2 (1.0), C-13a (0.93).
6. ^1H NMR ($CDCl_3$, 300 MHz, J in Hz): 7.69(dd, 4.8, 7.8, H-10), 7.98(br t, 7.2, H-3), 8.05(dt, 7.2, ~1, H-2), 8.59(d, 5.7, H-5), 8.67(br d, 8.1, H-1), 8.73(br d, 8.0, H-4), 8.82(dd, 7.8, 1.8, H-11), 9.20(dd, 4.8, 1.8, H-9), 9.32 (d, 5.7, H-6).
7. We thank Dr. J. Kobayashi, Mitsubishi-Kasei Institute of Life Sciences, Tokyo, Japan, for kindly providing a 500 MHz ^1H NMR spectrum ($CDCl_3$) and a sample of **2**.
8. Revised ^{13}C NMR shifts: C-4b, 137.7; C-5, 116.1; C-7a, 149.9 ppm; all other shifts as per ref. 1.

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