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Pia B. Holst, Uffe Anthoni, Carsten Christophersen, and Per H. Nielsen

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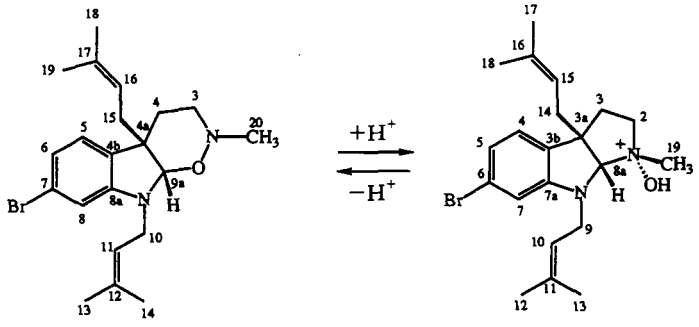
MARINE ALKALOIDS, 16.[1] REVERSIBLE CONVERSION OF FLUSTRAMINE B *N*-1-OXIDE TO FLUSTRARINE B

PIA B. HOLST, UFFE ANTHONI, CARSTEN CHRISTOPHERSEN,* and PER H. NIELSEN

Marine Chemistry, Section, The H.C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100, Copenhagen, Denmark

ABSTRACT.—Flustrarine B was quantitatively converted to flustramine B *N*-1-oxide by treatment with acid and the reverse reaction effected by treatment of flustramine B *N*-1-oxide with base.

Among the presently known 24 indole alkaloids (1–3) from marine bryozoans, three are *N*-oxides and one, flustrarine B [**1**], encompasses the hexahydro-1,2-oxazino[5,6-*b*]indole skeleton (4). The latter could be derived from the corresponding hexahydropyrrolo[2,3-*b*]indole *N*-1-oxide by ring expansion. We wish to report the facile conversion of flustrarine B [**1**] to flustramine B *N*-1-oxide hydrochloride [**2**] and vice versa.



1 **2**

Geneserine and geneseroline have been shown to participate in an acid-base catalyzed equilibrium to form physostigmine *N*-1-oxide and geneseroline *N*-1-oxide (5), respectively. Likewise, either **1** or **2** could be isolated depending on the acidicity of the solution. Flustramine B, isolated from the marine bryozoan *Flustra foliacea* (L.), by Likens-Nickerson gas phase extraction (1), yields partially racemized flustrarine B [**1**] on oxidation with H_2O_2 (4). On treatment of **1** with ethanolic hydrogen chloride the isomeric **2** was isolated in quantitative yield. In the eims the molecular ion *m/z* 406/404 attested to the isomeric nature of **2**. The main fragmentation pattern represents the loss, characteristic for *N*-oxides (6), of 16 mass units (O) from the molecular ion, while the corresponding pattern in the case of **1** displayed a loss of C_2H_5NO (*m/z* 347/345) and of C_2H_6NO (*m/z* 346/344) from the molecular ion. The structure of **2** otherwise revealed itself by comparison with nmr data from the flustramines, especially the highly indicative signal from C-8a and H-8a (Table 1).

The absolute configurations of the flustramines are unknown, but the relative stereochemistry has been shown in all cases investigated [including **1** (4)] to be cis with regard to the ring junction. The identity of the absolute configurations for **1** and **2** was established by comparison of cd data for the two compounds. The configurational assignment

[1]For Part 15, see Holst *et al.* (1).

TABLE 1. ^{1}H- and ^{13}C-Nmr Data of Flustramine B *N*-1-oxide [**2**].[a]

Position	δ_H (multiplicity, J_{HH}, Hz)	δ_C
2	4.16 (dd, 5.2, 12.4)	63.5
	2.93 (dt, 5.6, 12.8)	
3	2.79 (dt, 5.6, 12.8)	29.7
	2.22 (dd, 5.2, 12.4)	
3a.....		47.4
3b		132.9
4	6.96 (d, 8.1)	124.3
5	7.05 (dd, 8.0, 1.5)	117.2
6		124.2
7	5.75 (d, 1.5)	113.0
7a.....		151.5
8a.....	5.64 (s)	107.3
9	4.18 (dd, 6.8, 5.2)	37.3
10	5.08 (dd, 6.8, 5.2)	117.2
11		134.6[d]
12	1.79 (s)[b]	26.0[e]
13	1.74 (s)[b]	17.9[e]
14	2.54 (dd, 8.4, 6.8)	35.7
15	4.86 (dd, 8.4, 6.8)	117.5
16		135.5[d]
17	1.68 (s)[c]	25.8[f]
18	1.60 (s)[c]	17.7[f]
19	3.53 (s)	48.1

[a]Chemical shifts for the C-ring in the ring system of flustrarine B: δ_H=2.69 (Ha-3), 2.40 (Hb-3), 2.07 (H-2), 4.88 (H-9a), 2.49 (H-20); δ_C=53.8 (C-3), 29.3 (C-4), 44.9 (C-4a), 97.7 (C-9a), 46.1 (C-20).

[b-f]Signals bearing the same superscript may be interchanged.

of the new chiral center at *N*-1 in the *N*-1-oxide was derived from an nOe experiment where the signal originating from the *N*-1 methyl group (C-19) on saturation gave rise to an enhancement of 2% in the signal originating from the methylene protons at C-14 signifying a cis relationship between these groups. Since compounds related to natural physostigmine as shown with phenserine have a negative ellipticy at 250–260 nm, and compounds as shown with (+)-N^1-norphenserine belonging to the (3a*R*)-series have an opposite signal in this region (A. Brossi, personal communication) we concluded that **1** and **2** have the 1*S*,3a*S*,8a*S*-configuration.

In light of these investigations there is hardly any doubt that the two *N*-1-oxides described from a Canadian collection of *F. foliacea* (7), dihydroflustramine C *N*-1-oxide and flustramine D *N*-1-oxide, are capable of existing as hexahydro-1,2-oxazino[5,6-*b*]indole tautomers as well.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mass spectra originated from a JEOL JMS-HX/HX 110A tandem mass spectrometer. Nmr spectra were recorded on a Varian 400 Ft-nmr spectrometer at 400.0 MHz and 100.6 MHz for ^{1}H and ^{13}C nmr, respectively. Chemical shifts are in δ with TMS as internal standard. Cd and optical rotations were determined with a Jasco J-710 spectropolarimeter and the uv spectra on a Hewlett-Packard 8452A diode array spectrophotometer. Tlc were performed on Si gel 60 F_{254} Merck plates with EtOH-EtOAc (1:9) as eluent.

Flustrarine B [**1**].—Flustramine B (79.7 mg) obtained from *F. foliacea* was dissolved in Me_2CO (1 ml) and a solution of H_2O_2 (0.50 ml 3% diluted with 0.6 ml of H_2O followed by neutralization with $CaCO_3$ and filtration) was added (4). The reaction mixture was stirred at room temperature (11 days) until the presence of flustramine B was no longer detectable with tlc (R_f flustramine B, 0.43 and R_f [**1**], 0.63). Extraction with Et_2O (4×10 ml) and evaporation of the Et_2O extract left **1** (57.5 mg, 72%) as a yellow oil identified from mass spectra and nmr data (4). Cd (c=0.0078, EtOH) nm (Δε) 255 (−8.85), 304 (−3.48); $[\alpha]^{20}D$ −3.3° (c=0.078, EtOH); fabms (positive centroid) m/z $[M+H]^+$ 407/405.

Flustramine B N-1-oxide [**2**].—A solution of **1** (30.7 mg) in EtOH (1 ml) after acidification with ethanolic hydrogen chloride precipitated a red oil identified as **2** as described above. Cd (c=0.0071, EtOH) nm (Δε) 250 (−4.52), 300 (−3.20); fabms (positive centroid) m/z $[M+H+HCl]^+$ 443/441, $[M+H]^+$ 407/405; eims m/z $[M+H]^+$+HCl 443/441 (5), $[M+H]^+$ 407/405 (92), 391/389 (7), 389/387 (7), 360/358 (37), 347/345 (7), 346/344 (8), 292/290 (23), 279/277 (12), 278/276 (15), 224/222 (12), 210/208 (15), 143 (7), 130 (11), 69 (100). Uv λ max (EtOH) (log ε) 216 (4.47), 250 (3.94), 304 (3.56) nm. Nmr data are given in Table 1.

Neutralization of a solution of **2** (15.2 mg) in $CHCl_3$ (1 ml) with aqueous $NaHCO_3$, after drying ($MgSO_4$) and evaporation, afforded **1** (14.2 mg, 93%).

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