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Marine Alkaloids. 7. Synthesis of Debromoflustramine B and Related Compounds

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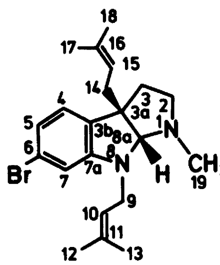
Debromoflustramine B has been synthesized and characterized. The synthesis and spectroscopic properties of a series of structurally related compounds are reported.

Recently a series of bromo-substituted alkaloids were isolated and identified from the marine bryozoan *Flustra foliacea* (L.). Most of the alkaloids are derived from the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole skeleton.[1] To establish a framework for the spectroscopic parameters of such compounds and also to study the chemistry and pharmacology of this interesting class of alkaloids, a synthetic study was undertaken. In this report we describe the synthesis and properties of debromoflustramine B (*5*) and related derivatives.

RESULTS AND DISCUSSION

Tryptophan derivatives with a protected N_b amino group are known to suffer electrophilic attack at the 3-position with concomitant attack of the N_b amine function at position 2 leading to derivatives of the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole ring system.[2]



Flustramine B

Reactions between N_b-trifluoroacetyl, N_b-acetyl, and N_b-ethoxycarbonyltryptamine (*1a, 1b* and *1c*, respectively) and γ,γ-dimethylallyl bromide (1-bromo-3-methyl-2-butene) were found to lead to the expected 1-acylated-3a-alkylated-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles (*2a, 2b* and *2c*) together with the 8-alkylated homologues (*3a, 3b* and *3c*). In all reactions the 1,2-dialkylated-N_b-acylated tryptamines (*6a, 6b* and *6c*) were always found as side products, presumably formed by acid-catalyzed rearrangement of *3*.[3]

On reaction with γ,γ-dimethylallyl bromide *2* could be alkylated to give *3*.

Hydrolysis of *3* to form *4* posed severe problems since *3* is sensitive to base. Acid hydrolysis only resulted in rearranged product (*6b, 6c*) and base-catalyzed as well as imidazole-mediated hydrolyses[4] gave unsatisfactory yields. Several attempts to hydrolyze *3b* and *3c* resulted only in a preparatively unacceptable yield of *4*. Finally, it was found that sodium borohydride reduction[5] of *3a* gave rise to a quantitative yield of *4*.

Several attempts to methylate *4* by standard procedures failed due to formation of large amounts of decomposition products.

However, reaction with formaldehyde and sodium cyanoborohydride[6] gave a fair yield of debromoflustramine B (*5*).

To prepare an *N*-1 methylated derivative (*7*) without *N*-8 substitution N_b-methyltryptamine

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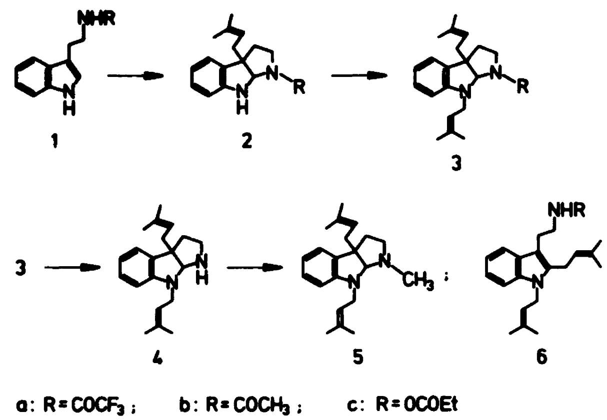

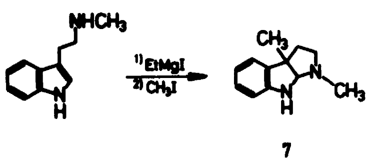

magnesium salt, prepared from the parent compound and ethylmagnesium iodide, was treated with methyliodide.[7] In our hands the analogous reaction with γ,γ-dimethylallyl bromide was not successful for the synthesis of *5*.

The ^{13}C NMR chemical shifts of the skeleton carbons of the compounds in Table 1 were assigned by comparison with the shifts of flustramine A and B,[1a,b] physostigmine[8] and related compounds. However, the aromatic carbons (particularly C-4, C-5 and C-6) were assigned partly by comparison with indoline and indoline derivatives and partly by comparison with the naturally occurring derivatives taking into account the bromo-substituent effect in the flustramines.[9,10] The latter compounds also proved to be valuable models for the assignment of the chemical shifts of the carbons in the isoprene units. All assignments, except for *2b*, were verified by off-resonance decoupling experiments.

EXPERIMENTAL

Mass spectra were recorded at 70 eV on an AEI-MS902 instrument; precise mass measurements were obtained by the peak matching method. UV spectra were recorded on a Unicam SP 18 instrument and IR spectra on a Perkin-Elmer 580 spectrometer. ^{13}C NMR spectra were recorded at 22.5 MHz and ^1H NMR at 90 MHz on a Jeol FX 90 Q instrument.

*N_b-Trifluoroacetyltryptamine (*1a*)* was prepared by a modified literature procedure (Ref. 11): Tryptamine (0.14 mol) was dissolved in dry CH_2Cl_2 (150 ml) and triethylamine (0.15 mol). Trifluoroacetic anhydride (20 ml) was added dropwise while the mixture was stirred and cooled in ice. After stirring for 2 h the reaction mixture was washed with Na_2CO_3 solution (200 ml) and water (200 ml). The aqueous phase was washed with CH_2Cl_2 and the combined CH_2Cl_2 phases after drying over $MgSO_4$ and evaporation left a residue which after recrystallization (MeOH: H_2O, 1:1) gave a colorless crystalline product in quantitative yield. M.p. 100–101 °C (lit. 99–100 °C).[11]

N_b-Acetyltryptamine and N_b-ethoxycarbonyltryptamine were prepared according to the literature.

*1-Trifluoroacetyl-3a,8-bis(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (*3a*).* To a solution of N_b-trifluoroacetyltryptamine (0.02 mol) in 117 ml acetate buffer (glacial acetic acid 200 ml, water 20 ml, and sodium acetate 8 g) γ,γ-dimethylallylbromide (0.06 mol) was added dropwise (30 min) with stirring in an N_2-atmosphere. After stirring for 3 h (under N_2) water (65 ml) was added and the reaction mixture was extracted with diethylether (150 ml) which after drying over $MgSO_4$ and evaporation left 11.4 g. Extraction with hexane–ethylacetate (3:1, 100 ml), left after filtration 28 % unreacted trifluoroacetyltryptamine. The filtrate on evaporation left a crude product which on purification by column chromatography (silica gel, Lobar, Merck) with ethylacetate–hexane (1:3) gave *2a* (353 mg, 5.6 %), *3a* (364 mg, 4.8 %) and *6a* (389 mg, 5.1 %). *3a* and *6a* may be purified by

Table 1. ^{13}*C NMR data of debromoflustramine B and related compounds*. Spectra measured at 22.5 MHz in $CDCl_3$ (40 mg ml^{-1}). Chemical shifts are given in parts per million relative to internal Me_4Si. Assignments for values marked with the same symbols may be interchanged. The ^{13}C signal multiplicities as obtained from the off-resonance decoupled spectra are shown in parenthesis (s=singlet, d=doublet, t=triplet, q=quartet).

Position	2b	2a	7	3b		3c		3a		4		5	
2	46.9	46.4(t)	52.5(t)	46.9(t)°		45.4(t)°		46.0(t)°		45.6(t)°		52.8(t)	
3	35.3°	35.1(t)°	41.0(t)	37.2(t)		37.0(t)		37.1(t)		40.9(t)°		39.0(t)°	
3a	56.1	55.9(s)	53.5(s)	55.8(s)		56.2(s)		55.4(s)		56.5(s)		57.1(s)	
3b	131.6	135.6(s)*	137.0(s)	133.0(s)$^{\Delta}$		133.2(s)$^{\Delta}$		132.4(s)$^{\Delta}$		133.7(s)$^{\Delta}$		133.3(s)*	
4	122.7	123.1(d)	122.7(d)	122.6(d)		122.6(d)		122.9(d)		123.1(d)		122.8(d)	
5	118.2*	118.7(d)	118.7(d)	119.3(d)		119.5(d)		118.7(d)		120.5(d)		120.8(d)	
6	127.9	128.7(d)	127.4(d)	128.2(d)		128.1(d)		128.6(d)		127.6(d)		127.5(d)	
7	108.8	109.3(d)	109.0(s)	106.6(d)		106.3(d)		106.9(d)		105.2(d)		105.2(d)	
7a	149.0	148.8(s)	149.5(d)	150.5(s)		150.1(s)		150.1(s)		151.0(s)		151.0(s)	
8a	79.4	81.5(d)	89.8(d)	82.7(d)		84.3(d)		84.5(d)		87.0(d)		87.0(d)	
Isoprene units				C-3a	N-8	C-3a	N-8	C-3a	N-8	C-3a	N-8	C-3a	N-8
1	34.3°	35.6°		37.2	44.6°	37.0	44.1°	37.1	44.6°	37.7°	43.1°	38.5°	46.8
2	118.9*	119.1		117.1	121.4	117.1	121.5	117.9	120.6	121.0	116.7	121.6	117.4
3	134.5	135.8*		134.6$^{\Delta}$	133.9$^{\Delta}$	133.7$^{\Delta}$	133.7$^{\Delta}$	135.5$^{\Delta}$	134.8$^{\Delta}$	134.7$^{\Delta}$	134.7$^{\Delta}$	135.7*	134.0*
4	25.6	25.9		25.8‡	25.9‡	25.7	25.7	25.9‡	25.7‡	25.9‡	25.7‡	25.9	25.9
5	17.6	17.9		18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
N-1 Substituent	C=O 169.3 –CH_3 22.2	C=O 156.2 –CF_3 n.o.	–CH_3 37.1	C=O 169.5 –CH_3 22.9		C=O 175.6 –CH_2 61.1 –CH_3 14.7		C=O 156.0 –CF_3 n.o.				–CH_3 38.1	

fractional recrystallization from hexane–ethylacetate (3:1 v/v). High resolution mass measurements gave: *2a* calc. for $C_{17}H_{19}F_3N_2O$ 324.145 found 324.144; *3a* calc. for $C_{22}H_{27}F_3N_2O$ 392.208 found 392.204; *6a* calc. for $C_{22}H_{27}F_3N_2O$ 392.208 found 392.202. UV (EtOH) *2a* λ_{max} 212 nm (ε 1.3×10^4), 236 (9.0×10^3), 296 (2.4×10^3); *3a* 213 (1.6×10^4), 252 (8.3×10^3), 304 (1.5×10^3). UV (0.5 N ethanolic HCl) *2a* 212 (1.3×10^4), 236 (9.1×10^3), 296 (2.5×10^3); *3a* 212 (1.5×10^4), 253 (8.1×10^3), 310 (1.6×10^3).

*1-Acetyl-3a-(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole* (2b). N_b-Acetyltryptamine (3 mmol) dissolved in 6 ml acetate buffer (glacial acetic acid 100 ml, water 20 ml and sodium acetate 8 g) was mixed with γ,γ-dimethylallylbromide, a slow stream of N_2 being passed through the solution. After 2 h at room temperature water (10 ml) was added. The reaction mixture was extracted with ether, which after drying ($MgSO_4$) and evaporation left 400 mg. Column chromatography (silica gel, Lobar, Merck, ethylacetate) gave *2b* (14.3 %). Calc. for $C_{17}H_{22}N_2O$ 270.173 found 270.174. UV(EtOH) λ_{max} 213 nm (ε 8.1×10^3), 244 (2.1×10^3), 294 (7.5×10^2). UV (0.5 N ethanolic HCl) 213 (5.5×10^3), 244 (1.1×10^3), 294 (3.7×10^2).

The same method was used for preparation of *2c* (yield 16 %).

*1-Acetyl-3a,8-bis(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole* (3b). To a mixture of *2b* (0.25 mmol) and K_2CO_3 (2 mmol) in acetone (2 ml) was added γ,γ-dimethylallylbromide (0.25 mmol) in acetone (1 ml) with a nitrogen stream being passed through the reaction mixture. Leaving overnight (with N_2), addition of water (2 ml) and extraction with CH_2Cl_2 left on evaporation of the CH_2Cl_2 solution 84.5 % of *3b*. Purification by column chromatography (silica gel, Lobar, Merck, ethylacetate) afforded 69 % pure *3b*, calc. for $C_{22}H_{30}N_2O$ 338.236 found 338.238. UV(EtOH) λ_{max} 216 nm (ε 1.4×10^4), 258 (7.6×10^3), 314 (1.9×10^3). UV (0.5 N ethanolic HCl) 212 (1.3×10^4), 254 (6.0×10^3), 308 (1.4×10^3).

Compound *3c* was prepared by the same method, yield 75 %, calc. for $C_{23}H_{32}N_2O_2$ 368.246 found 368.245. UV(EtOH) λ_{max} 212 nm (ε 1.6×10^4), 253 (8.8×10^3) 304 (2.9×10^3). UV (0.5 N ethanolic HCl) 212 (1.6×10^4), 255 (7.6×10^3), 304 (2.4×10^3).

*3a,8-Bis(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole* (4). a. Alkaline hydrolysis of *3a:* A solution of *3a* (0.12 mmol in an equimolar amount of ethanolic (40 %) 0.1 N NaOH (0.612 ml) was heated to 90 °C for 2.5 h. The reaction mixture was extracted with diethylether, which after drying ($MgSO_4$) and evaporation left a crude product. Column chromatography (silica gel, Lobar, Merck, MeOH:$CHCl_3$, 3.5:6.5) gave 3.3 % pure *4*. UV(EtOH) λ_{max} 212 nm (ε 1.1×10^4), 258 (6.8×10^3), 310 (1.4×10^3). UV (0.5 N ethanolic HCl) 212 (1.1×10^4), 248 (5.4×10^3), 304 (1.3×10^3).

b. Imidazole mediated hydrolysis of *3a:* To a solution of *3a* (0.1 mmol) and imidazole (0.1 mmol) in MeOH (2 ml) was added water (2 ml) dropwise. The resulting colloidal solution was cleared by addition of MeOH (7 ml). After 10 h at room temperature, 4 N NaOH was added to adjust to pH 11 followed by extraction with ether. Drying ($MgSO_4$) and evaporation gave a mixture of two products which after column chromatography (silica gel, Lobar, Merck, $CHCl_3$:MeOH, 6.5:3.5) gave 17 % of *4*.

c. $NaBH_4$ reduction: An initial cooled solution of *3a* (0.75 mmol) in abs. EtOH (375 ml) was treated with pulverized $NaBH_4$ (3 mmol). After stirring at room temperature for 1 h the excess $NaBH_4$ was removed by addition of acetone and the reaction mixture was stirred for an additional 15 min. Evaporation in vacuum left a crude product, which on purification by column chromatography (silica gel, Lobar, Merck, $CHCl_3$: ethylacetate, 6.5:3.5) gave a quantitative yield of *4*, calc. for $C_{20}H_{28}N_2$ 296.225 found 296.229.

d. Acid hydrolysis of *3b:* A solution of *3b* (3.52 mmol) in ethanol (119 ml) and 1 N HCl (119 ml) was kept at 60 °C for 1 h. After neutralization (Na_2CO_3), extraction with ether, drying over $MgSO_4$ and evaporation, the crude product was subjected to column chromatography (silica gel, Lobar, Merck, ethylacetate). A yield of 53 % *6b* was secured, calc. for $C_{22}H_{30}N_2O$ 338.236 found 338.234.

Compound *6c* was prepared analogously.

*1-Methyl-3a,8-bis(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole, debromoflustramine B* (5). To a stirred solution of *4* (0.39 mmol) and aqueous formaldehyde (37 %, 1.96 mmol) in CH_3CN (1.18 ml) $NaBH_3CN$ (0.63 mmol) was added. After the vigorous exothermic initial reaction had ceased, the mixture was stirred for 15 min and glacial acetic acid was added until neutral reaction. Stirring was continued for 1.45 h while the neutral reaction was maintained by addition of glacial acetic acid. After evaporation of the solvent in vacuum the residue was adjusted to pH 9 with 0.5 KOH. Extraction with ether (3×15 ml), washing with 0.02 N KOH, drying over K_2CO_3 and evaporation left a crude product which yielded to column chromatography (silica gel, Lobar, Merck, $CHCl_3$: ethylacetate, 6.5:3.5) to give *5* (57 %) calc. for $C_{21}H_{30}N_2$ 310.241 found 310.239; UV(EtOH) λ_{max} 211 nm (ε 1.1×10^4), 254

(2.0×10^3), 306 (5.4×10^2); UV (0.5 N ethanolic HCl) 211 (1.3×10^4), 246 (1.9×10^3), 295 (6.1×10^2); IR ($CHCl_3$) 2965 (s), 2940 (s), 2860 (s), 1605 (s), 1490 (s), 1460 cm^{-1} (s).

*1-Methyl-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (7).* Prepared according to Ref. 7. UV(EtOH) λ_{max} 214 nm (ε 8.5×10^3), 244 (1.0×10^4), 299 (3.7×10^3). UV (0.5 N ethanolic HCl) 210 (7.2×10^3), 238 (9.8×10^3), 193 (3.4×10^3).

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