Marine Alkaloids. 9.* Synthesis of 6-Bromotryptamine

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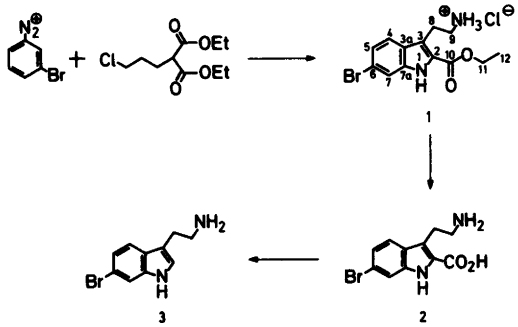
6-Bromotryptamine and related derivatives have been synthesized and characterized.

The marine bryozoan *Flustra foliacea* (L.) has given rise to the isolation and structure elucidation of a series of 6-bromo-substituted indole alkaloids derived from the tryptamine skeleton.[2] One of these, flustramine B, has been synthesized[3] as has the debromoanalogue.[4]

Synthetic strategies leading to these structures often imply 6-bromotryptamine as starting material. To our knowledge the latter compound has never been characterized.

In order to gain access to this key compound for pharmacological testing and further study of the derived alkaloids and in order to establish reference physical parameters for this and related systems we have undertaken the synthesis and characterization of 6-bromotryptamine as reported below. The synthesis is a modification of the method of Grandberg *et al.*[5] as developed by Szantay *et. al.*[6]



Results and discussion. The 3-bromophenyldiazonium ion was easily obtained by diazotation[6] of 3-bromoaniline prepared by reduction[7] of 3-bromonitrobenzene.[8] Japp-Klingemann reaction[9] of the diazonium ion with diethyl 3-chloropropylmalonate under basic conditions gave a 10 % yield of the indole *1* (Scheme 1) crystallizing with one molecule of ethanol. Saponification of *1* produces *2* in 80 % yield. Several attempts to decarboxylate *2* gave unsatisfactory results, however, a 80 % yield of 6-bromotryptamine (*3*) was finally obtained by careful acid catalysed decarboxylation. The overall yield of 6-bromotryptamine (*3*) from 3-bromoaniline was 6.4 %.

The *a priori* possibility of ring closure *ortho* to the bromo substituent, producing the 4-bromo isomer of *1*, was excluded by analysis of the ^{1}H–NMR data presented in Table 1. Evidence for the concommitant formation of the latter isomer was not encountered in any stage of the synthesis.

The assignment of the signals in the ^{13}C NMR spectra is based upon an estimation of the expected shift values using reported ^{13}C MR values[10,11] and reported or calculated substituent chemical shift values.[11,12]

The UV spectral data in Table 3 demonstrate the expected bathochromic shift in going from *3* to *2* and a further bathochromic shift from *2* to *1* as expected for the greater auxochromic effect of the ester function as compared to the carboxylate group. As seen from the table 6-bromotryptamine exhibits the expected bathochromic shift compared with tryptamine.

Experimental. NMR spectra were recorded at 90 MHz (^{1}H) and 22.5 MHz (^{13}C) on a Jeol-Fx-90Q instrument, UV spectra on a Unicam SP 8000 instrument, and IR spectra in KBr disc on a Perkin-Elmer 580 spectrometer. Melting points are uncorrected and determined on a Reichert apparatus.

6-Bromo-2-carbethoxytryptamine hydrochloride (1) was prepared by reaction of diazotized 3-bromoaniline (17.2 g),[6] obtained by reduction[7] of 3-bromonitrobenzene,[8] with 3-chloropropylmalonic acid diethylester (23.7 g)[13] in ethanolic potassium hydroxide. The resulting red oily product was refluxed in butanol (160 ml) with a few drops of water under nitrogen for 24 h. After cooling the product was isolated and recrystallized from ethanol (90 %) yielding 10 % of *1*·EtOH m.p. 192 °C (subl.). Anal. $C_{13}H_{15}N_2O_2Br \cdot HCl \cdot C_2H_5OH$: C, H, N, Br, Cl. IR (KBr): 2985(m), 1700(s), 1315(s), 1230(s) cm^{-1}. The mass spectrum exhibits the molecular ion at *m/z*: 310/312 indicating loss of ethanol and hydrogen chloride. Successive recrystallization from hydrochloric acid (0.1 M) or sublimation *in vacuo* (190 °C) gave analytically pure *1* m.p. 114–117 °C.

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Table 1. ^{1}H NMR Data of *1*, *2*, and *3*. The spectra are recorded of samples dissolved in DMSO-d_6. In parentheses are given the number of protons, the multiplicity, and the coupling constant in Hz. Signals from ethanol appear at δ 1.09(3H,t,7.33), 3.48(2H,q,7.32), and 3.83(1H,s,HO−)ppm. The ammonium protons appear at δ 8.41(3H,s,$H_3N^{\pm}$) ppm.[b] Signals from the ammonium protons appear at δ 8.83(3H,s) ppm.[c] The primary amino group gives signals at δ 1.8−2.0(2H,s) ppm.[d] The apparent discrepancy in the *J* value is due to the signal of a small impurity overlaying the signal at highest field and thus displacing this slightly.

Proton(s) at position	*1*·EtOH[a] δppm	*2*[b] δppm	*3*[c] δppm
1	11.94(1H,s)	11.19(1H,s)	11.15(1H,s)
2	–	–	7.18(1H,s)
4	7.86(1H,d,8.54)	7.53(1H,d,8.24)	7.48(1H,d,8.55)
5	7.23(1H,dd,8.55[d]/1.53)	7.08(1H,dd,8.54[d]/1.83)	7.11(1H,dd,8.55/1.52)
7	7.70(1H,d,1.52)	7.51(1H,d,1.52)	7.58(1H,d,1.52)
8	3.05(2H,s)	3.0−3.5(4H,m)	2.81(4H,s)
9	3.40−3.50(2H)		
11	4.40(2H,q,7.02)	–	–
12	1.41(3H,t,7.02)	–	–

Table 2. ^{13}C NMR Data of *1*, *2*, and *3*. The spectra of *1* and *3* are measured of DMSO-d_6 solutions, while the spectrum of *2* is recorded in D_2O made alkaline with solid KOH. The value of the signal from C-9 in *3* was obtained in $CDCl_3$ solution and corrected for solvent shift. In parenteses are shown the signal multiplicities as obtained from off-resonance decoupled spectra (s=singlet, d=doublet, t=triplet, q=quartet). Assignments for values marked with the same symbol may be interchanged.[a] Signals from ethanol appear at δ 18.5 (q) and 56.0 (t) ppm.

Carbon	*1*·EtOH[a] ppm	*2* ppm	*3* ppm
2	124.7(s)	129.2(s)	123.7(d)
3	118.0(s)	119.3(s)$^+$	112.9(s)*
3a	126.1(s)	133.2(s)	126.4(s)
4	122.8(d)*	124.7(d)*	120.1(d)$^+$
5	122.2(d)*	123.7(d)*	120.9(d)$^+$
6	117.0(s)	119.1(s)$^+$	113.6(s)*
7	115.0(d)	116.9(d)	113.8(d)
7a	136.9(s)	137.9(s)	137.1(s)
8	22.4(t)	29.4(t)	29.2(t)
9	n.o.	44.2(t)	41.1(t)
10	161.2(s)	172.1(s)	
11	60.6(t)		
12	14.3(q)		

Purification of the azo compound resulting from the coupling between the diazonium salt and the malonic acid ester by column chromatography (silica gel, hexane−methylene chloride) did not improve the yield of the ring closure reaction.

6-Bromo-2-carboxytryptamine (2) was obtained by saponification of *1* (2.0 g) by refluxing for 24 h in ethanolic sodium hydroxide (25 ml, 2 M plus 5 ml EtOH) under nitrogen. The precipitate formed by acidification (pH 5) with acetic acid at 0 °C was recrystallized from ethanol (90 %) to give 80 % *2*, m.p. 250−251 °C. Anal. $C_{11}H_{11}N_2O_2Br$: C, H, N, Br. IR (KBr) 3420(m), 3220(m), 2980(m), 1570(s), 1539(s) cm^{-1}.

6-Bromotryptamine (3) was prepared by reflux-

Table 3. UV-data of *1*, *2*, and *3*. The spectra are recorded in ethanol 96 %, (E) and ethanol 96 % saturated with HCl(g).

Compound	Solvent[a]	λ_{max}, nm	logε
1; EtOH	E	309, 231	4.18, 4.32
	E(HCl)	306, 228	4.18, 4.32
2	E	299, 229	4.05, 4.39
	E(HCl)	306, 229	4.15, 4.32
3	E	294, 289, 229	3.76, 3.81, 4.51
	E(HCl)	294, 287, 228	3.76, 3.81, 4.51
Tryptamine	E	292, 284, 276, 228	3.65, 3.73, 3.71, 4.53
	E(HCl)	292, 282, 276, 228	3.65, 3.73, 3.71, 4.53

ing for 7 h a solution of *2* (1.0 g) in sulfuric acid (20 ml, 4 N) under nitrogen. Cooling below 0 °C followed by basification with saturated sodium hydroxide solution, filtration and washing with water gave a product which after redissolving in sulfuric acid (20 ml, 4 N) and precipitation by addition of saturated sodium hydroxide solution gave 80 % pure *3* m.p. 120–120.5 °C. Anal. $C_{10}H_{11}N_2Br$: C, H, N, Br. IR (KBr): 3420(m), 2930(m), 2880(m), 1590(m), 1455(m), 920(s), 805(s) cm^{-1}.

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