Aaptamines. Novel Benzo[*de*][1,6]naphthyridines from the Okinawan Marine Sponge *Aaptos aaptos*[1]†

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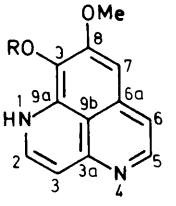
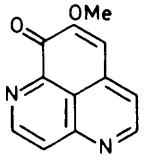
Two new aaptamine alkaloids, demethylaaptamine (**2**) and demethyl(oxy)aaptamine (**3**), have been isolated from the Okinawan marine sponge *Aaptos aaptos* as cytotoxic and antimicrobial substances. The structures of demethylaaptamine (**2**) and demethyl(oxy)aaptamine (**3**) were determined by interpretation of spectral data and results of chemical degradation experiments.

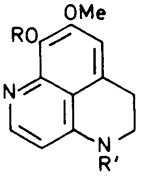
The yellow colour of the marine sponge *Aaptos aaptos* changes to dark brown after collection and the sponge contains a large amount of yellow compounds. The 70% ethanolic extract of the sponge showed α-adrenoceptor blocking, antimicrobial, and cardiotonic activity. We have previously reported the isolation and structural determination of aaptamine (**1**) which has α-adrenoceptor blocking activity.[2,3] Aaptamine (**1**) belongs to a new type of alkaloid having a 1*H*-benzo[*de*][1,6]naphthyridine skeleton. Recently, the structure of aaptamine (**1**) was confirmed by total syntheses.[4,5] We have now isolated two further aaptamine alkaloids from this sponge. In this paper, we describe the structural elucidation of demethylaaptamine (**2**) and demethyl(oxy)aaptamine (**3**).



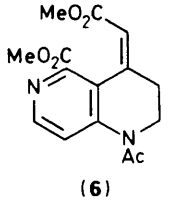
(**1**) R = Me
(**2**) R = H



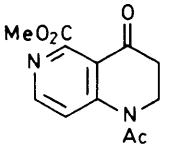
(**3**)



(**4**) R = Me, R' = H
(**5**) R = Me, R' = Ac
(**8**) R = R' = H
(**9**) R = R' = Ac



(**6**)



(**7**)

† Taken as Part 11 of the series 'Physiologically active marine natural products from Porifera.' Part 10: H. Wu, H. Nakamura, J. Kobayashi, Y. Ohizumi, and Y. Hirata, *Experientia*, in the press.

Specimens of *A. aaptos* were collected off Okinawa Island at a depth of 2 m in July 1981. The ethanol-soluble material of the methanolic extracts was chromatographed over silica gel with chloroform–methanol as eluant to give demethyl(oxy)-aaptamine (**3**), aaptamine (**1**) hydrochloride, and demethyl-aaptamine (**2**) hydrochloride in that order of elution.

High-resolution electron-impact mass spectral (h.r.m.s.) analysis of demethylaaptamine (**2**) established the molecular formula as $C_{12}H_{10}N_2O_2$, corresponding to a demethylated form of aaptamine (**1**). The ^{1}H n.m.r. spectrum of compound (**2**) showed one isolated proton signal at δ 7.14 (7-H) and two sets of coupled protons, at δ 7.78 and 6.36 (d, *J* 7.0 Hz, 2- and 3-H), and 7.27 and 6.83 (d, *J* 7.4 Hz, 5- and 6-H), which are similar to those of aaptamine (**1**) (Table 1). However, only one methyl signal was observed, at δ 4.01 (8-OMe), suggesting that compound (**2**) has the same skeleton as (**1**) but in which one of the two methoxy groups of aaptamine (**1**) is replaced by a hydroxy group.

In order to confirm the carbon framework of compound (**2**), it was converted into a diester (**6**), which was obtained from aaptamine (**1**) during its degradation to the keto ester (**7**). Hydrogenation of compound (**2**) over PtO_2 in a mixture of hydrochloric acid and acetic acid yielded a 5,6-dihydro compound (**8**), which was acetylated with acetic anhydride and pyridine to give a diacetyl compound (**9**). The diacetyl compound (**9**) was treated with ozone, followed by dimethyl sulphide and diazomethane, to furnish the diester (**6**), which was identical in all respects with that obtained from aaptamine (**1**) by the same sequence of reactions. These data established that compound (**2**) is a monodemethyl compound of aaptamine (**1**). The position of the remaining methoxy group in compound (**2**) was deduced on the basis of the 16% signal enhancement of 7-H on irradiation of the methoxy group, and the structural correlation with demethyl(oxy)aaptamine (**3**).

The molecular formula of demethyl(oxy)aaptamine (**3**), $C_{12}H_8N_2O_2$, was determined by its h.r.m.s. The molecular formula and one methoxy proton signal observed at δ 3.95 indicated structural similarities to demethylaaptamine (**2**). In the ^{1}H n.m.r. spectrum, four doublet aromatic proton signals assignable to 2-, 3-, 5-, and 6-H (δ 9.15 and 8.28, d, *J* 5.5 Hz, and 9.19 and 7.80, d, *J* 4.4 Hz) and a singlet proton signal due to 7-H (δ 7.21) were observed to lower field than those of compound (**2**). These data, and the i.r. band at 1 665 cm^{-1}, suggested that the hydroxy group of compound (**2**) was oxidised to form a carbonyl group. Aerial oxidation of compound (**2**) under basic conditions resulted in the formation of compound (**3**), which was identical with the natural product.

The ^{13}C n.m.r. data for aaptamine alkaloids are also useful for determining the structures (Table 2). Information regarding the skeletal network and the position of heteroatoms could be obtained from the data of direct and long-range ^{1}H–^{13}C

Table 1. ^{1}H N.m.r. data for aaptamine (**1**), demethylaaptamine (**2**), and demethyl(oxy)aaptamine (**3**) in $(CD_3)_2SO$[a]

Position	(1)	(2)	(3)
2	7.90 (d, *J* 6.5 Hz)	7.78 (d, *J* 7.0 Hz)	9.15 (d, *J* 5.5 Hz)
3	6.52 (d, *J* 6.5 Hz)	6.36 (d, *J* 7.0 Hz)	8.28 (d, *J* 5.5 Hz)
5	7.45 (d, *J* 7.3 Hz)	7.27 (d, *J* 7.4 Hz)	9.19 (d, *J* 4.4 Hz)
6	6.93 (d, *J* 7.3 Hz)	6.83 (d, *J* 7.4 Hz)	7.80 (d, *J* 4.4 Hz)
7	7.18 (s)	7.14 (s)	7.21 (s)
8-OMe	4.03 (s)	4.01 (s)	3.95 (s)
9-OMe	3.86 (s)		
NH	12.35, 13.10 (br s)	11.8 (br)	
OH		11.8 (br)	

[a] δ-Values in p.p.m.

Table 2. ^{13}C N.m.r. data for aaptamine (**1**), demethylaaptamine (**2**), demethyl(oxy)aaptamine (**3**), and dihydroaaptamine (**4**)[a]

	(1)			(2)			(3)			(4)		
Position	δ	m[b]	*J*[c]	δ	m[b]	*J*[c]	δ	m[b]	*J*[c]	δ	m[b]	*J*[c]
2	141.4	d/d	182/3	140.7	d/m	182	149.4	d/s	183	141.4	d/d	182/4
3	98.3	d/d	174/4	97.1	d/m	172	126.9	d/d	166/9	100.4	d/d	171/5
3a	149.4	s/t	/8	149.0	s/d	/7	156.3	s/m		156.8	s/dt	/8, 4
5	129.2	d/d	183/3	127.0	d/m	184	157.1	d/d	181/3	40.8	t/t	142/4
6	101.3	d/d	162/4	100.2	d/m	163	122.3	d/dd	167/10, 4	27.0	t/t	133/5
6a	132.6	s/d	/7	128.0	s/d	/8	137.1	s/d	/6	131.3	s/dt	/11, 5
7	113.5	d/d	170/4	113.4	d/m	172	108.7	d/d	163/6	112.0	d/t	162/4
8	157.1	s/m		151.2	s/m		149.2	s/m		156.0	s/m	
9	131.2	s/m		127.0	s/d	/7	177.9	s/d	/8	135.3	s/m	
9a	133.2	s/d	/7	128.9	s/d	/8	147.3	s/d	/11	133.7	s/d	/8
9b	115.9	s/m		115.4	s/m		118.2	s/m		109.2	s/m	
8-OMe	57.0	q/s	146	56.5	q/s	146	56.4	q/s	146	57.3	q/s	146
9-OMe	61.1	q/s	146							61.8	q/s	146

[a] δ-Values in p.p.m.; (**1**) and (**2**) in D_2O, (**3**) in $CDCl_3$–CD_3OD, and (**4**) in CD_3OD. [b] Multiplicity, direct coupling/long-range coupling. [c] Coupling constant in Hz, direct coupling/long-range coupling.

couplings, which were analysed by proton-selective decoupling and low-power proton-selective decoupling experiments, respectively. The position of the carbonyl functionality in compound (**3**) was clearly indicated by the ^{1}H–^{13}C long-range coupling between 7-H and C-9 (*J* 8 Hz).[6]

Aaptamine alkaloids represent a new type of alkaloid possessing potent pharmacological activity. Among these aaptamine alkaloids, aaptamine (**1**) showed the most powerful α-adrenoceptor blocking activity on vascular smooth muscle. On the other hand, demethyl(oxy)aaptamine (**3**) was the most cytotoxic to HeLa cells (50% effective dose 0.87 μg ml^{-1}) and exhibited the most potent antimicrobial activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* (minimum inhibitory concentration, MIC 3.13 μg ml^{-1}), *Bacillus subtilis* (MIC 6.25 μg ml^{-1}), and *Proteus vulgaris* (MIC 12.5 μg ml^{-1}). Cytotoxic and antimicrobial activities of demethylaaptamine (**2**) were approximately 0.5 times those of demethyl(oxy)aaptamine (**3**). Recently, necatrone, a pentacyclic alkaloid having strucutral similarities to demethyl(oxy)-aaptamine (**3**), has been isolated from the toadstool *Lactarius necator*.[7]

Experimental

All m.p.s were measured on a Yanagimoto micro-melting point apparatus and uncorrected. I.r. spectra were measured with a Hitachi 260-50 spectrophotometer. N.m.r. spectra were taken on a JEOL FX-90Q instrument, at 90 MHz and 22.5 MHz for ^{1}H and ^{13}C n.m.r. spectra, respectively. Tetramethylsilane was employed as internal standard in organic solvents, and dioxane as internal standard (δ_C 67.4 p.p.m.) in D_2O. U.v. spectra were recorded on a Varian Cary 17 spectrophotometer. High-resolution electron-impact mass spectra were obtained by using a Hitachi M-80A spectrometer. Silica gel (79—230 mesh) and preparative-layer silica gel and silica gel thin-layer chromatographic plates were obtained from E. Merk (Darmstadt). Hydrogenations were carried out at 1 atm. pressure.

Collection, Extraction, and Separation.—*Aaptos aaptos* was collected at Manza beach (average depth 2 m), Okinawa, and were then frozen, and shipped by air to Tokyo. The sponge (986 g, wet weight) stored at −20 °C was homogenised in methanol and extracted with methanol (3 × 2 l, and 1 l). After the solvent had been evaporated off under reduced pressure, the residue (86 g) was treated with ethanol. The ethanol-soluble portion (30 g) was adsorbed on a silica gel column (Merk Art 7734, 4.6 × 80 cm) and eluted with chloroform–methanol (5 l) (8:2) and then with chloroform–methanol (3 l) (7 : 3) to give three fractions, containing demethyl(oxy)aaptamine (500—1 000 ml), aaptamine (1—3 l), and demethylaaptamine (3—6 l), respectively.

The first fraction was separated on a silica gel column and by preparative t.l.c., both with chloroform–methanol (9:1) as mobile phase, to give *demethyl(oxy)aaptamine* (**3**) (235 mg) after crystallisation from methanol. The second fraction was chromatographed on a silica gel column with chloroform–methanol (8:2) as eluant to give crude aaptamine (6.23 g), which was crystallised from methanol by addition of acetone to afford bright yellow crystals of *aaptamine* (**1**) *hydrochloride* (1.72 g). The last fraction was dissolved in methanol, and acetone was added to the solution to yield *demethylaaptamine* (**2**) *hydrochloride* as a greenish yellow powder (3.53 g).

Demethyl(oxy)aaptamine (**3**). Yellow crystals, m.p. 198—

200 °C (decomp.); $\lambda_{max.}(H_2O)$ 235 (ε 10 600), 308 (1 740), 360sh (5 540), 373 (5 040), and 415sh nm (2 310); $\nu_{max.}$(KBr) 1 665, 1 620, 1 580, 1 275, and 1 100 cm^{-1}; *m/z* 212.0578 (M^+, $C_{12}H_8N_2O_2$ requires *M*, 212.0584) (Found: C, 64.2; H, 3.7; N, 12.9. $C_{12}H_8N_2O_2 \cdot \frac{3}{5}H_2O$ requires C, 64.63; H, 4.15; N, 12.56%. $C_{12}H_8N_2O_2$ requires C, 67.92; H, 3.80; N, 13.20%).*

Aaptamine (**1**) *Hydrochloride.* Bright yellow crystals, m.p. 110—113 °C; $\lambda_{max.}(H_2O)$ 214 (ε 13 700), 236 (14 700), 255 (17 900), 309 (3 640), 352 (3 750), 381 (5 000), and 394 nm (4 570); $\nu_{max.}$(KBr) 3 400, 3 020, 1 655, 1 605, 1 325, and 1 245 cm^{-1}; *m/z* 228.0885 (M^+, $C_{13}H_{12}N_2O_2$ requires *M*, 228.0896) (Found: C, 55.7; H, 4.8; N, 10.1; Cl, 12.7. $C_{13}H_{12}N_2O_2 \cdot HCl\frac{3}{4}H_2O$ requires C, 56.12; H, 5.25; N, 10.07; Cl, 12.74%. $C_{13}H_{12}N_2O_2 \cdot HCl$ requires C, 58.95; H, 4.95; N, 10.58; Cl, 13.39%).*

Demethylaaptamine (**2**) *Hydrochloride.* Greenish yellow powder, m.p. 248—251 °C (decomp. in sealed tube); $\lambda_{max.}(H_2O)$ 241 (ε 18 300), 313 (3 890), 370 (4 470), and 400 nm (4 130); $\nu_{max.}$(KBr) 3 300, 1 670, 1 640, 1 620, 1 560, 1 325, 1 250, and 1 100 cm^{-1}; *m/z* 214.0765 (M^+, $C_{12}H_{10}N_2O_2$ requires *M*, 214.0742) (Found: C, 51.7; H, 4.2; N, 9.9; Cl, 14.4. $C_{12}H_{10}N_2O_2 \cdot HCl \cdot \frac{3}{2}H_2O$ requires C, 51.90; H, 5.08; N, 10.09; Cl, 12.77%. $C_{12}H_{10}N_2O_2 \cdot HCl$ requires C, 57.50; H, 4.42; N, 11.17; Cl, 14.14%).*

Catalytic Hydrogenation of Aaptamine (**1**) *Hydrochloride.*—A solution of aaptamine (**1**) hydrochloride (342 mg, 1.30 mmol) in acetic acid (10 ml) and conc. hydrochloric acid (1 ml) was hydrogenated over PtO_2 (60 mg) overnight. The mixture was filtered and the filtrate was concentrated to dryness under reduced pressure to yield 240 mg of *dihydroaaptamine* (**4**) *hydrochloride* (240 mg, 70%) as pale yellow needles after crystallisation from acetone, m.p. 137—139 °C (sealed tube); $\lambda_{max.}(H_2O)$ 236 (ε 24 800), 242 (23 900), 272 (7 150), 282 (7 550), 323 (8 480), 333 (8 700), and 346 nm (7 380); $\nu_{max.}$(KBr) 3 420, 1 620, 1 350, 1 305, 1 120, 1 025, and 810 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 3.13 (2 H, t, *J* 7.1 Hz, 6-H_2), 3.64 (2 H, dt, *J* 1.6 and 7.1 Hz, 5-H_2), 3.88 (3 H, s, 9-OMe), 4.01 (3 H, s, 8-OMe), 6.63 (1 H, d, *J* 7.1 Hz, 3-H), 7.34 (1 H, s, 7-H), 8.13 (1 H, d, *J* 7.1 Hz, 2-H), and 9.17 (br s, exchangeable, NH); *m/z* 230.1064 (M^+, $C_{12}H_{12}N_2O_2$ requires *M*, 230.1054).

Acetylation of Dihydroaaptamine (**4**) *Hydrochloride.*—A solution of dihydroaaptamine (**4**) hydrochloride (100 mg, 0.38 mmol) in a mixture of pyridine (6 ml) and acetic anhydride (0.6 ml) was kept at 60 °C for 3 h. The resulting mixture was evaporated under reduced pressure and the residue was separated on a short column of silica gel to give the 4-*acetate* (**5**) (102 mg, 99%) as a powder, m.p. 122—124 °C (from diethyl ether); $\nu_{max.}$(KBr) 1 665, 1 610, 1 595, 1 505, 1 405, 1 290, and 1 115 cm^{-1}; $\delta_H(CD_3OD)$ 2.58 (3 H, s, NAc), 3.36 (2 H, t, *J* 6.2 Hz, 6-H_2), 4.06 (3 H, s, 9-OMe), 4.13 (3 H, s, 8-OMe), 4.25 (2 H, t, *J* 6.2 Hz, 5-H_2), 7.56 (1 H, s, 7-H), 8.27 (1 H, d, *J* 7.6 Hz, 3-H), and 8.70 (1 H, d, *J* 7.6 Hz, 2-H); $\delta_C(CDCl_3)$ 23.6 (q, NCO*Me*), 29.7 (t, C-6), 43.3 (t, C-5), 56.7 (q, 8-OMe), 61.5 (q, 9-OMe), 110.9 (d, C-3), 113.1 (d, C-7), 115.1 (s, C-9a), 127.8 (s, C-6a), 141.6 (s), 144.0 (s, 2 C), 150.1 (d, C-2), 151.3 (s, C-8), and 169.5 (s, NCOMe); *m/z* 272.1158 (M^+, $C_{15}H_{16}N_2O_3$ requires *M*, 272.1159).

Ozonolysis of Compound (**5**).—A solution of compound (**5**) (48.5 mg, 0.18 mmol) in methanol (5 ml) was saturated with ozone at −78 °C for 1 h and then dimethyl sulphide was added (200 mg) to the solution. The mixture was gradually warmed to room temperature. After the solvent had been removed under reduced pressure, the residue was chromatographed on a silica gel column with benzene–acetone (2 : 1) as eluant to give the *dimethyl ester* (**6**) as a powder, m.p. 109—110 °C; $\nu_{max.}$(KBr) 1 725, 1 705, 1 680, 1 310, and 1 210 cm^{-1}; $\delta_H(CDCl_3)$ 2.49 (3 H, s, NAc), 2.92 (2 H, br, 6-H_2), 3.62 (3 H, s, OMe), 3.80 (2 H, br, 5-H_2), 3.89 (3 H, s, OMe), 5.99 (1 H, t, *J* 1.1 Hz, 7-H), 7.50 (1 H, d, *J* 5.5 Hz, 3-H), and 8.54 (1 H, d, *J* 5.5 Hz, 2-H); $\delta_C(CDCl_3)$ 23.4 (q, NCO*Me*), 35.9 (t, C-6), 44.0 (t, C-5), 51.5 (q, OMe), 52.7 (q, OMe), 118.1 (d), 120.6 (d), 144.6 (s), 147.0 (s), 148.7 (d, C-2), 165.4 (s, C=O), 165.8 (s, C=O), and 170.0 (s, NCOMe); *m/z* 304.1081 (M^+, $C_{15}H_{16}N_2O_5$ requires *M*, 304.1058) (Found: C, 58.5; H, 5.4; N, 9.05. $C_{15}H_{16}N_2O_5 \cdot \frac{1}{5}H_2O$ requires C, 58.55; H, 5.37; N, 9.10%. $C_{15}H_{16}N_2O_5$ requires C, 59.20; H, 5.30; N, 9.21%).*

Ozonolysis of the Dimethyl Ester (**6**).—A solution of the dimethyl ester (**6**) (5 mg, 0.016 mmol) in methanol (1 ml) was treated with ozone for 4 h at −78 °C. Dimethyl sulphide reduction and then work-up furnished *compound* (**7**) (3 mg, 74%, after chromatography on silica gel t.l.c. with benzene–acetone (2:1), as rods, m.p. 172.5—173.5 °C (from methanol); $\lambda_{max.}(CH_3OH)$ 235 (ε 18 600), 262 (9 000), and 3.07 nm (3 050); $\nu_{max.}(CHCl_3)$ 3 030, 1 745, 1 705, 1 690, 1 580, 1 445, and 1 205 cm^{-1}; $\delta_H(CDCl_3)$ 2.42 (3 H, s, NAc), 2.83 (2 H, t, *J* 6.2 Hz, 6-H_2), 3.99 (3 H, s, OMe), 4.21 (2 H, t, *J* 6.2 Hz, 5-H_2), 7.74 (1 H, d, *J* 5.7 Hz, 3-H), and 8.57 (1 H, d, *J* 5.7 Hz, 2-H); *m/z* 248.0786 (M^+, $C_{12}H_{12}N_2O_4$ requires *M*, 248.0795).

Catalytic Hydrogenation of Demethylaaptamine (**2**) *Hydrochloride.*—A solution of demethylaaptamine (**2**) hydrochloride (407 mg, 1.63 mmol) in acetic acid (16 ml) and conc. hydrochloric acid (1.6 ml) was hydrogenated over PtO_2 (200 mg) overnight at 80 °C. The mixture was filtered and the filtrate was concentrated to dryness. The residue was dissolved in methanol and the solution was concentrated (after filtration) to give *dihydrodemethylaaptamine* (**8**) *hydrochloride* (380 mg, 93%) as a yellow powder (decomp. *ca.* 221 °C without melting); $\nu_{max.}$(KBr) 3 180, 2 920, 1 620, 1 590, 1 315, 1 250, and 1 110 cm^{-1}; $\delta_H(D_2O)$ 2.65 (2 H, t, *J* 6.9 Hz, 6-H_2), 3.34 (2 H, t, *J* 7.1 Hz, 5-H), 3.75 (3 H, s, 8-OMe), 7.07 (1 H, d, *J* 6.9 Hz, 3-H), 7.56 (1 H, s, 7-H), and 8.53 (1 H, d, *J* 6.9 Hz, 2-H); *m/z* 216.0919 (M^+, $C_{12}H_{12}N_2O_2$ requires *M*, 216.0897).

Acetylation of Dihydrodemethylaaptamine (**8**) *Hydrochloride.*—A solution of dihydrodemethylaaptamine (**8**) hydrochloride (43.2 mg, 0.17 mmol) in a mixture of pyridine (1 ml) and acetic anhydride (0.4 ml) was kept at 60 °C for 3 h. The mixture was evaporated under reduced pressure and the residue was separated on a short silica gel column with chloroform–methanol (95:5) as eluant to afford the *diacetyl compound* (**9**) (37.1 mg, 81%) as a powder, m.p. 202—203 °C (from benzene); $\nu_{max.}$ 1 755, 1 670, 1 620, 1 420, 1 210, 1 120, 1 020, and 865 cm^{-1}; $\delta_H(CDCl_3)$ 2.40 (3 H, s, Ac), 2.49 (3 H, s, Ac), 3.18 (2 H, t, *J* 5.7 Hz, 6-H_2), 3.96 (3 H, s, OMe), 4.15 (2 H, t, *J* 5.7 Hz, 5-H_2), 7.10 (1 H, s, 7-H), 7.26 (1 H, d, *J* 5.3 Hz, 3-H), and 8.77 (1 H, d, *J* 5.3 Hz, 2-H); *m/z* 300.1095 (M^+, $C_{16}H_{16}N_2O_4$ requires *M*, 300.1109).

Ozonolysis of the Diacetyl Compound (**9**).—A solution of the diacetyl compound (**9**) (10.2 mg, 0.034 mmol) in a mixture of chloroform (0.5 ml) and methanol (0.5 ml) was treated with ozone for 1.5 h at −78 °C. Dimethyl sulphide (50 mg) was added to the solution and the mixture was warmed to room temperature during 30 min. The resulting mixture was evaporated to dryness under reduced pressure and the residue was dissolved in methanol and treated with diazomethane. Chromatography of the product (silica gel t.l.c.) with benzene–

* We could not get satisfactory elemental analyses for the anhydrous compounds (**1**), (**2**), (**3**), and (**6**).

acetone (2:1) as developer yielded the dimethyl ester (**6**) (3.9 mg, 38%), which was identical with that derived from aaptamine (**1**).

Conversion of Demethylaaptamine (**2**) *Hydrochloride into Demethyl(oxy)aaptamine* (**3**).—A solution of demethylaaptamine (**2**) hydrochloride (49.4 mg, 0.20 mmol) in a mixture of methanol (0.5 ml) and 0.2M-Na_2CO_3 (0.5 ml) was stirred under oxygen (1 atm) at room temperature for 1 h. The mixture was concentrated to dryness under reduced pressure and the residue was separated on silica gel t.l.c. with chloroform–methanol (9:1) as developer to give demethyl(oxy)aaptamine (**3**) (30 mg, 71%), which was identical with the natural product.

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References

1 This work was presented at the Ninth International Congress of Heterocyclic Chemistry, Tokyo, Japan, July, 1983: Abstract G-66.
2 H. Nakamura, J. Kobayashi, Y. Ohizumi, and Y. Hirata, *Tetrahedron Lett.*, 1982, **23**, 5555.
3 Y. Ohizumi, A. Kajiwara, H. Nakamura, and J. Kobayashi, *J. Pharm. Pharmacol.*, 1984, **36**, 785.
4 J. C. Pelletier and M. P. Cava, *Tetrahedron Lett.*, 1985, **26**, 1259.
5 T. R. Kelly and M. P. Maguire, *Tetrahedron*, 1985, **41**, 3033.
6 J. L. Marshall, 'Carbon–Carbon and Carbon–Proton NMR Couplings,' Verlag Chemie International, Florida, 1983.
7 B. Fugmann, B. Steffan, and W. Steglich, *Tetrahedron Lett.*, 1984, **25**, 3575.

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