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Structures of Biologically Active Minor Bases Related to Paragracine from *Parazoanthus gracilis* LWOWSKY[1)]

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Six biologically active minor bases (P-II—P-VII) related to paragracine (P-I) were isolated from *Parazoanthus gracilis* LWOWSKY and their structures were determined by spectral analyses as well as on the basis of chemical interconversions.

Keywords——*Parazoanthus gracilis*; paragracine; minor base; papaverine-like activity; 1,3,7,9-tetrazacyclopent[*e*]azulene; anthozoa; zoanthoxanthin; *Dentitheca habereri*; fluorescence

In previous papers[2)] we reported the isolation of paragracine, which shows papaverine-like activity, from the methanolic extract of an anthozoan, *Parazoanthus gracilis* LWOWSKY (Parazoanthidae, Japanese name: Sennari-sunaginchaku) which normally parasitizes *Dentitheca habereri* STECHOW (Plumulariidae, Japanese name: Sudare-gaya), and we also described some of the chemical properties of paragracine, which is an yellow-colored base and exhibits strong yellowish-green fluorescence in solution.

Next, an attempt was made to isolate biologically active minor components related to paragracine (P-I) contained in *P. gracilis*, and the six compounds designated as P-II, P-III, P-IV, P-V, P-VI and P-VII were isolated. In this paper we describe the isolation of these compounds and the determination of the structures on the basis of spectral analyses and chemical interconversions.

Isolation of Minor Components

The methanolic extract (M-1) obtained from 10 kg (wet weight) of *P. gracilis* was partitioned between water and ethyl acetate. The water layer was applied to an Amberlite XAD-2 column, which was washed with water and eluted with methanol. The results of thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) showed that the methanol-elutable material (M-2) contained paragracine (P-I) as a major component and several minor compounds (P-II—P-VII) which seemed to be structurally related to paragracine, since each spot in TLC showed a yellow color and characteristic fluorescence under an ultraviolet light. Further fractionation of M-2 was carried out to isolate six minor components as shown in Chart 1, guided by TLC and HPLC analyses.

The methanol-elutable material (M-2) was chromatographed to give fractions A-1, A-2 and A-3. Fraction A-1 was subjected to repeated column chromatography to afford fractions B-1, B-2 and B-3. Recrystallization of fraction B-1 gave paragracine (P-I, 13.15 g) and the mother liquor was further chromatographed to yield fractions C-1 and C-2. Fraction C-1 was recrystallized to provide additional P-I (0.65 g) and the mother liquor was purified by column chromatography to afford P-II (78 mg). Fraction C-2 was recrystallized to give P-III (100 mg). Fraction B-2 was purified by column chromatography to afford P-IV (36 mg). From fraction B-3, P-V (50 mg) was obtained after column chromatography, droplet counter current

chromatography (DCCC) and finally preparative TLC. Fraction A-2 was further chromatographed to give fractions D-1, D-2 and D-3. Recrystallization of fraction D-1 gave additional P-I (3.39 g). Fraction D-2 was purified by column chromatography and recrystallization to afford P-VI (358 mg). A mixture of fraction D-3 and the mother liquor of P-VI was purified by column chromatography, DCCC, preparative TLC and finally preparative HPLC to yield P-VII (100 mg).

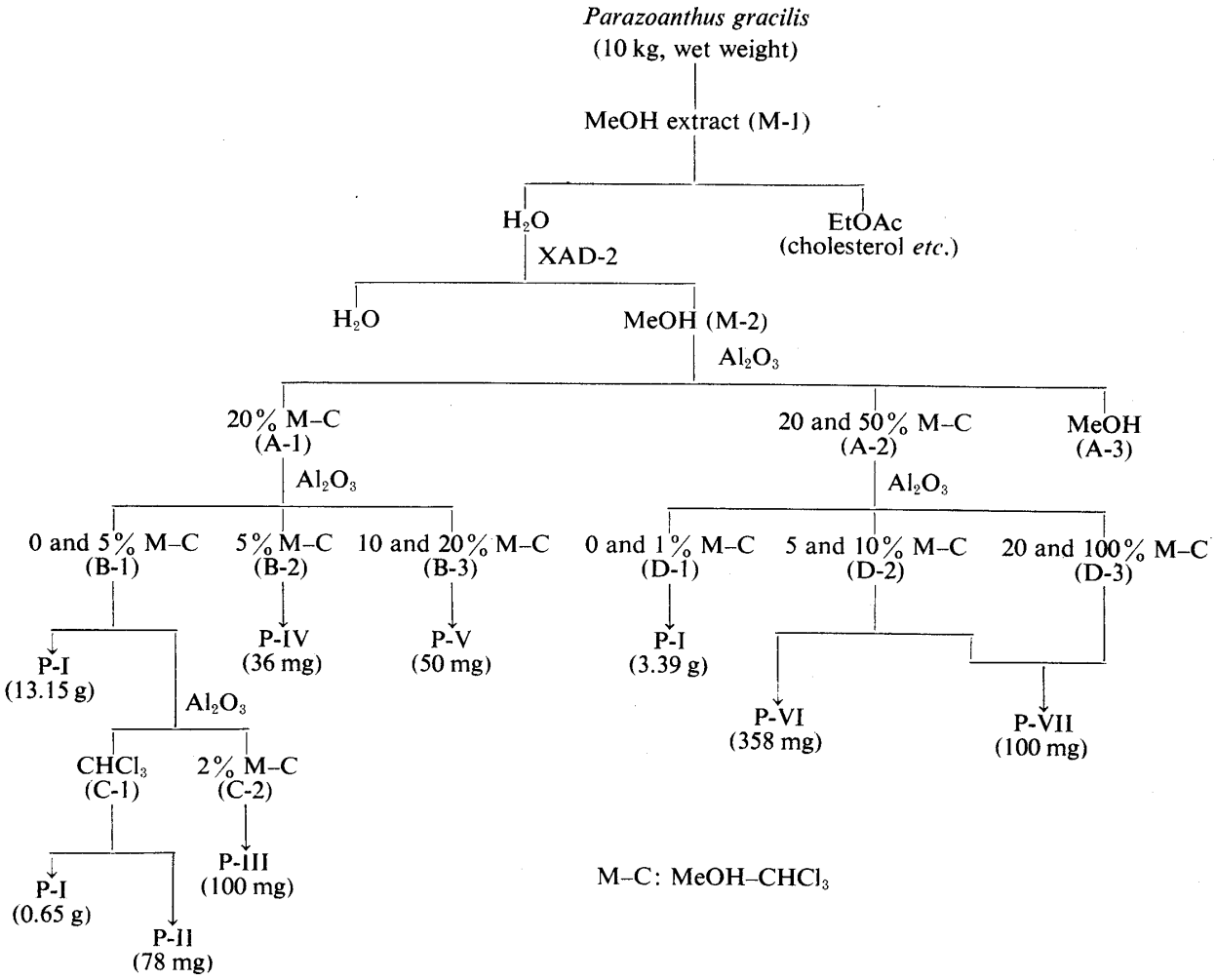

Chart 1

Structures of the Minor Components

All the minor components show similar fragmentation patterns in the mass spectra (MS) (Table I) and similar absorption maxima in the ultraviolet (UV) spectra (Table II) as compared with paragracine (P-I). It was found from the elemental analysis data and by high resolution mass spectrometry that they all have six nitrogens in the molecule. Furthermore, in the nuclear magnetic resonance (NMR) spectra (Table III) they all show one benzylic methyl group (2.95—3.07 ppm, 3H, s) and two aromatic protons (8.03—8.46 ppm, 2H, s or double d).

These findings indicate that all the minor components have the same basic skeleton, 2,8-diamino-6-methyl-1,3,7,9-tetrazacyclopent[*e*]azulene, as paragracine (P-I) and differ only in the numbers and positions of *N*-methyl groups. The positions of the *N*-methyl groups of each minor component can be deduced from the NMR spectra because the chemical shifts of the exocyclic *N*-methyl groups, the 1- or 9-methyl group and the 3-methyl group of P-I, its *N*-

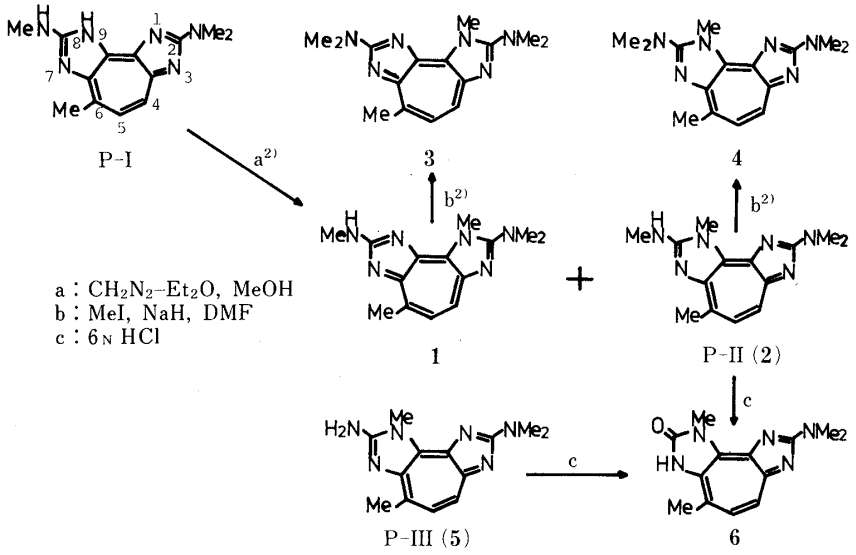

Chart 2

methyl derivatives (**1**—**4**)[2] and pseudozoanthoxanthin (**5**)[3] appear at 3.37—3.62, 4.51—4.61 and 4.05 ppm, respectively.

The NMR spectrum of P-II, mp 269—271 °C (dec.), $C_{14}H_{18}N_6$, shows the presence of one exocyclic *N*-dimethyl group and one *N*-methyl group (3.57 ppm, 9H, br s), and a 1- or 9-methyl group (4.63 ppm, 3H, s). From a comparison of the spectral data, it was concluded that P-II was identical with 9-methylparagracine (**2**).

P-III, mp >300 °C, $C_{13}H_{16}N_6$, has one exocyclic *N*-dimethyl group (3.53 ppm, 6H, s) and a 1- or 9-methyl group (4.62 ppm, 3H, s). Hydrolysis of P-III with 6 N hydrochloric acid gave the keto derivative (**6**) which was formed from **2** by the same treatment. Therefore, the exocyclic *N*-dimethyl group and the cyclic *N*-methyl group of P-III are located at the 2- and 9-positions, respectively. P-III was also isolated from a *Parazoanthus* sp. and its structure was determined by X-ray crystallographic analysis.[4]

P-IV, mp >300 °C, $C_{12}H_{14}N_6$ was suggested on the basis of the NMR spectrum to have two cyclic *N*-methyl groups of which one is a 1- or 9-methyl group (4.63 ppm, 3H, s) and the other is a 3- or 7-methyl group (4.06 ppm, 3H, s), and it was found to be identical with an authentic sample of pseudozoanthoxanthin (**5**).[3]

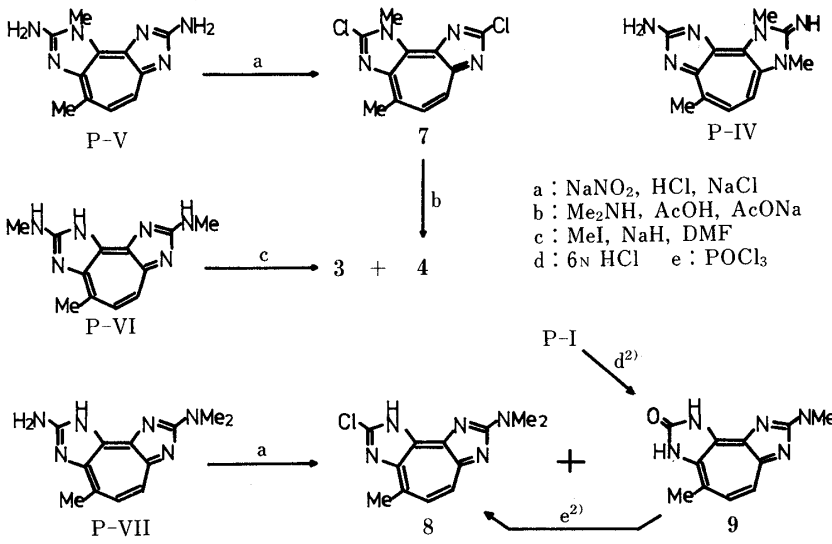

Chart 3

TABLE I. Mass Spectral Data

Compd.	*m/z* (Relative intensity)						
	M^+	M^+-CH_3	M^+-CH_2N	M^+-CH_3N	$M^+-C_2H_4N$	$M^+-C_2H_5N$	$M^+-C_2H_6N$
P-I	256 (100)	241 (58)	228 (7)	227 (36)	214 (3)	213 (4)	212 (6)
P-II	270 (100)	255 (85)	242 (9)	241 (47)	228 (3)	227 (3)	226 (6)
P-III	256 (90)	241 (100)	228 (9)	227 (55)	214 (4)	213 (5)	212 (8)
P-IV	242 (100)	227 (32)	214 (7)	213 (1)	200 (12)	199 (12)	198 (2)
P-V	228 (100)	213 (7)	200 (9)	199 (5)	186 (6)	185 (7)	184 (4)
P-VI	242 (100)	227 (10)	214 (18)	213 (12)	200 (3)	199 (3)	198 (3)
P-VII	242 (100)	227 (94)	214 (13)	213 (62)	200 (10)	199 (13)	198 (5)

TABLE II. UV Spectral Data

Compd.	λ_{max}^{MeOH} nm (log ε)	$\lambda_{max}^{MeOH-H^+}$ nm (log ε)
P-I	252 (4.08), 309 (sh, 4.69), 314 (4.72), 372 (4.10), 409 (4.11), 422 (sh, 3.82)	245 (4.13), 301 (4.74), 363 (3.84), 410 (4.33), 423 (sh, 4.12)
P-II	259 (3.90), 310 (4.77), 317 (4.66), 374 (3.94), 416 (4.27)	243 (sh, 3.84), 311 (4.80), 368 (3.90), 415 (4.35)
P-III	260 (4.31), 306 (4.69), 315 (sh, 4.60), 376 (4.26), 414 (4.38)	248 (4.37), 298 (4.68), 303 (sh, 4.64), 360 (4.18), 400 (sh, 4.35), 414 (4.45)
P-IV	248 (4.34), 274 (sh, 4.45), 282 (4.56), 308 (4.77), 368 (4.30), 406 (4.09), 422 (4.12)	248 (4.38), 289 (4.92), 350 (4.10), 388 (sh, 4.29), 400 (4.44)
P-V	252 (4.19), 298 (4.77), 362 (4.17), 401 (4.28)	241 (4.25), 287 (4.70), 292 (sh, 4.65), 348 (4.10), 390 (sh, 4.23), 401 (4.35)
P-VI	250 (4.06), 305 (sh, 4.71), 309 (4.72), 368 (4.07), 404 (4.04), 416 (sh, 3.81)	241 (4.12), 297 (4.76), 353 (3.84), 404 (4.31), 425 (sh, 3.63)
P-VII	250 (4.09), 303 (4.65), 369 (4.01), 407 (4.16), 420 (sh, 3.93)	244 (4.23), 294 (4.70), 352 (3.72), 410 (4.35)

TABLE III. NMR Spectral Data[a)]

Compd.	2-N–CH_3 (6H, s)	8-N–CH_3 (3H, s)	1-CH_3 (3H, s)	3-CH_3 (3H, s)	9-CH_3 (3H, s)	6-CH_3 (3H, s)	4-H or 5-H (1H, d, J=11)	4-H or 5-H (1H, d, J=11)
P-I	3.55	3.42	—	—	—	2.99	8.24[d)]	
P-II	3.57[c)]		—	—	4.63	3.00	8.07	8.30
P-III	3.53	—	—	—	4.62	2.95	8.03	8.26
P-IV	—	—	4.63	4.06	—	3.04	8.28[d)]	
P-V	—	—	—	—	4.53	2.97	8.05	8.30
P-VI	3.45[b)]	3.56	—	—	—	3.02	8.36[d)]	
P-VII	3.64	—	—	—	—	3.07	8.46[d)]	
1	3.53	3.37	4.51	—	—	2.90	7.99[d)]	
2	3.57[c)]		—	—	4.63	3.00	8.07	8.30
3	3.59[c)]		4.57	—	—	2.97	8.05	8.09
4	3.62[c)]		—	—	4.56	2.95	8.06	8.18
5[3)]	—	—	4.61	4.05	—	3.03	8.21[d)]	

a) Taken in CF_3COOH; s: singlet, d: doublet; coupling constants in Hz.
b) 3H, s. *c)* 9H, br s. *d)* 2H, s.

The NMR spectrum shows that P-V, mp >300 °C, $C_{11}H_{12}N_6$, possesses only one *N*-methyl group (4.53 ppm, 3H, s) which is located at the 1- or 9-position. Diazotization of P-V with sodium nitrite in 3 N hydrochloric acid in the presence of sodium chloride afforded the dichloride (**7**) and the monochloride. The dichloride (**7**) was transformed into 8-*N*,9-dimethylparagracine (**4**) by treatment with dimethylamine. Therefore, the cyclic *N*-methyl group of P-V is located at the 9-position.

It was considered from the NMR spectrum that P-VI, mp 190—192 °C (dec.), $C_{12}H_{14}N_6$, has only two exocyclic *N*-methyl groups (3.45 and 3.56 ppm, each 3H, s) and that P-VI is 2-*N*-desmethylparagracine. This was confirmed by permethylation of P-VI with sodium hydride and methyl iodide to give 1,8-*N*-dimethylparagracine (**3**) and 8-*N*,9-dimethylparagracine (**4**).

P-VII, mp >300 °C, $C_{12}H_{14}N_6$, has only one exocyclic *N*-dimethyl group (3.64 ppm, 6H, s). Diazotization of P-VII with sodium nitrite in 4 N hydrochloric acid in the presence of sodium chloride, yielded the monochloride (**8**) and the keto derivative (**9**), both of which were obtained from P-I.[2] Therefore, P-VII is 8-*N*-desmethylparagracine.

Thus, the structures of six minor components related to paragracine were determined. These minor components isolated from *P. gracilis* have papaverine-like activity similar to that of paragracine, and details of the biological activity will be reported elsewhere.

Experimental

All melting points were taken with a Yanagimoto microscope hot stage and are uncorrected. MS were obtained by the electron impact ionization method on a JEOL JMS-D300 mass spectrometer. Infrared (IR) spectra were measured on a Hitachi 285 spectrometer. UV spectra were taken on a Hitachi 323 spectrometer. NMR spectra were obtained using a JEOL JNM-C-60H spectrometer. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane, and the following abbreviations are used: s = singlet and d = doublet. Column chromatography was carried out using Al_2O_3 (neutral, Merck) and silica gel (Wako). TLC was performed on Al_2O_3 150 F_{254} and Silica gel 60 F_{254} plates (Merck). HPLC was carried out on a Waters Associates ALC/GPC 204 instrument employing a μBondapak C_{18} (4 mm × 30 cm) column with 80% CH_3CN–ammonium acetate buffer solution (0.1 M, pH 7.7) as the eluent.

Isolation (Chart 1)——Samples (10 kg, wet weight) of *Parazoanthus gracilis* LWOWSKY (Japanese name: Sennari-sunaginchaku) together with *Dentitheca habereri* STECHOW (Japanese name: Sudare-gaya) (the former is parasitic on the latter) were collected in June, 1975 at Shimoda, Sagami Bay. They were crushed in a mortar and extracted five times with MeOH for 24 h at room temperature. The mixture was filtered and the combined filtrate was concentrated *in vacuo* at 35—40 °C to give a methanol extract (M-1). Fraction M-1 was partitioned between EtOAc and H_2O. The combined EtOAc layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford EtOAc-soluble materials, from which cholesterol was isolated. The combined H_2O layer was passed through an Amberlite XAD-2 column (2 l). The column was washed with H_2O and then eluted with MeOH. The MeOH solution was concentrated *in vacuo* to give the XAD-2-adsorbed and MeOH-elutable materials (M-2, 118 g).

Fraction M-2 was suspended in 20% MeOH–$CHCl_3$ and applied to a column of Al_2O_3 (300 g), which was eluted with 20% MeOH–$CHCl_3$ to obtain fraction A-1 (42.0 g). The column was further eluted with 20%, then 50% MeOH–$CHCl_3$ (A-2, 22.9 g) and finally with MeOH (A-3, 1.37 g).

Fraction A-1, which contained P-I—P-V, was chromatographed on Al_2O_3 (300 g) to give fractions B-1 ($CHCl_3$ and 5% MeOH–$CHCl_3$, 17.1 g), B-2 (5% MeOH–$CHCl_3$, 2.67 g) and B-3 (10%, then 20% MeOH–$CHCl_3$, 2.24 g). Recrystallization of fraction B-1 yielded P-I (13.15 g) and the mother liquor was further chromatographed on Al_2O_3 (50 g) eluting with $CHCl_3$ (C-1, 2.05 g) and 2% MeOH–$CHCl_3$ (C-2, 152 mg). Fraction C-1 was recrystallized to afford additional P-I (0.65 g) and the mother liquor was purified by column chromatography (Al_2O_3, 30 g) using C_6H_6–$CHCl_3$ (3 : 1) as an eluent to provide P-II (78 mg) after recrystallization. P-III (100 mg) was obtained from fraction C-2 by recrystallization. Fraction B-2 was chromatographed on Al_2O_3 (50 g) with 2% MeOH–$CHCl_3$ and recrystallized to give P-IV (36 mg). Fraction B-3 was purified to afford P-V (50 mg) by successive column chromatography on Al_2O_3 (15 g, 5% MeOH–$CHCl_3$), DCCC ($CHCl_3$–MeOH–H_2O (35 : 65 : 40); stationary phase, lower layer; mobile phase, upper layer, 0.1 ml/min) and finally preparative TLC (silica gel, $CHCl_3$–MeOH–NH_4OH (80 : 20 : 2)).

Fraction A-2, which contained P-I, P-VI and P-VII, was further chromatographed on Al_2O_3 (180 g) to give fractions D-1 ($CHCl_3$, then 1% MeOH–$CHCl_3$, 5.05 g), D-2 (5%, then 10% MeOH–$CHCl_3$, 1.32 g) and D-3 (20%, then 100% MeOH–$CHCl_3$, 1.20 g). Recrystallization of fraction D-1 yielded additional P-I (3.39 g). Fraction D-2 was purified by column chromatography (Al_2O_3, 20 g, 5% MeOH–$CHCl_3$) and recrystallized to afford P-VI (358 mg). A

mixture of fraction D-3 and the mother liquor of P-VI was purified by the successive treatment as in the case of P-V to yield P-VII (100 mg).

P-II——Yellow prisms, mp 269—271 °C (dec., MeOH). MS *m/z*: 270.1592 (M^+, $C_{14}H_{18}N_6$=270.1592). *Anal.* Calcd for $C_{14}H_{18}N_6$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.15; H, 6.80; N, 31.03. P-II was identical with 9-methylparagracine (**2**)[2] on the basis of the MS, IR (KBr), UV and NMR spectra, and TLC and HPLC analyses.

P-III——Yellow needles, mp >300 °C (MeOH–$CHCl_3$). MS *m/z*: 256.1422 (M^+, $C_{13}H_{16}N_6$=256.1434). *Anal.* Calcd for $C_{13}H_{16}N_6$: C, 60.92; H, 6.29; N, 32.79. Found: C, 60.80; H, 6.43; N, 32.75.

P-IV——Yellow prisms, mp >300 °C (MeOH–CH_2Cl_2). MS *m/z*: 242.1238 (M^+, $C_{12}H_{14}N_6$=242.1278). *Anal.* Calcd for $C_{12}H_{14}N_6$: C, 59.48; H, 5.82; N, 34.69. Found: C, 59.32; H, 5.98; N, 34.51. P-IV was identical with pseudozoanthoxanthin (**5**)[3] on the basis of the MS, IR (KBr), UV and NMR spectra, and TLC and HPLC analyses.

P-V——Yellow needles, mp >300 °C (MeOH). MS *m/z*: 228.1116 (M^+, $C_{11}H_{12}N_6$=228.1121). *Anal.* Calcd for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.60; H, 5.52; N, 36.75.

P-VI——Yellow needles, mp 190—192 °C (dec., MeOH–CH_2Cl_2). MS *m/z*: 242.1261 (M^+, $C_{12}H_{14}N_6$= 242.1278). *Anal.* Calcd for $C_{12}H_{14}N_6$: C, 59.48; H, 5.82; N, 34.69. Found: C, 59.57; H, 5.85; N, 34.60.

P-VII——Yellow needles, mp >300 °C (MeOH). MS *m/z*: 242.1273 (M^+, $C_{12}H_{14}N_6$=242.1278). *Anal.* Calcd for $C_{12}H_{14}N_6$: C, 59.48; H, 5.82; N, 34.69. Found: C, 59.44; H, 6.01; N, 34.44.

Hydrolysis of 9-Methylparagracine (2)——A solution of **2** (26 mg) in 6 N HCl (1 ml) was heated in a sealed tube at 180 °C for 14 h. The reaction mixture was basified with 2 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to recover **2** (13 mg). The combined aqueous layer was neutralized with 2 N HCl and applied to an Amberlite XAD-2 column, which was washed with H_2O and eluted with MeOH. The MeOH-elutable product was purified by column chromatography (silica gel, 5% MeOH–$CHCl_3$) to afford the keto derivative (**6**, 4 mg), yellow needles, mp >300 °C (MeOH–CH_2Cl_2). MS *m/z* (%): 257 (76), 242 (100) and 228 (85). IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). UV λ_{max}^{MeOH} nm (log ε): 251 (4.25), 283 (sh, 4.39), 294 (4.62), 302 (sh, 4.48), 315 (sh, 4.24), 380 (4.17) and 420 (4.24). NMR (CF_3COOH) δ: 2.90 (3H, s), 3.50 (6H, s), 4.34 (3H, s), 7.98 (1H, d, J=11 Hz) and 8.09 (1H, d, J=11 Hz). *Anal.* Calcd for $C_{13}H_{15}N_5O$: C, 60.68; H, 5.88; N, 27.22. Found: C, 60.49; H, 5.93; N, 27.19.

Hydrolysis of P-III——A solution of P-III (6 mg) in 6 N HCl (1 ml) was heated in a sealed tube at 180 °C for 40 h. The reaction mixture was treated by the same procedures as described above to give the keto derivative (3 mg). This product was identical with **6** obtained above (MS, IR, UV, NMR, TLC and HPLC).

Conversion of P-V to 8-*N*,9-Dimethylparagracine (4)——Sodium nitrite (40 mg) and sodium chloride (20 mg) were added to a stirred solution of P-V (10 mg) in 3 N HCl (1.5 ml) under ice-cooling. The reaction mixture was stirred under ice-cooling for 1 h and allowed to stand in a refrigerator for 15 h. This solution was diluted with H_2O, neutralized with 2 N NaOH and extracted with *n*-butanol. The residue (16 mg) obtained after washing the *n*-butanol layer with H_2O and concentrating it *in vacuo* was fractionated by preparative TLC (silica gel, 10% MeOH–$CHCl_3$) to give two yellow products. The higher *Rf* band gave the dichloride (**7**, 5 mg), MS *m/z* (%): 270 (M^++4, 9), 268 (M^++2, 53), 266 (M^+, 83), 233 (M^++2−Cl, 31) and 231 (M^+−Cl, 100). The lower *Rf* band afforded the monochloride (1 mg), MS *m/z* (%): 249 (M^++2, 31), 247 (M^+, 100), 232 (M^+-CH_3, 11) and 219 (M^+-CH_2N, 13).

A solution of **7** (2 mg) and dimethylamine hydrochloride (48 mg) in MeOH (1 ml) and acetic acid (1 drop) in the presence of sodium acetate (49 mg) was heated in a sealed tube at 100 °C for 21 h. After removal of insoluble materials by filtration, the solvent was evaporated off *in vacuo* and the residue was applied to a short column of Al_2O_3 and eluted with $CHCl_3$. The product obtained was further purified by preparative TLC (silica gel, 10% MeOH–$CHCl_3$) to give yellow prisms (1 mg) which were identical with 8-*N*,9-dimethylparagracine (**4**) (MS, IR, TLC and HPLC).

Methylation of P-VI——A solution of P-VI (27 mg) in *N*,*N*-dimethylformamide (DMF, 2 ml) was stirred with sodium hydride (50% in mineral oil, 100 mg) for 15 min at room temperature and then a solution of methyl iodide (200 mg) in DMF (0.5 ml) was added. The reaction mixture was stirred for an additional 5 h at room temperature, then H_2O was added and the whole was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on a short column of Al_2O_3 (*n*-hexane, then EtOAc) and fractionated by preparative TLC (silica gel, 10% MeOH–$CHCl_3$) to yield two yellow products. The higher *Rf* (12 mg) and the lower *Rf* (7 mg) products were identical with 1,8-*N*-dimethylparagracine (**3**) and 8-*N*,9-dimethylparagracine (**4**), respectively (MS, IR, UV, NMR, TLC and HPLC).

Diazotization of P-VII——A solution of P-VII (10 mg) in 4 N HCl (1.5 ml) was treated with sodium nitrite (50 mg) and sodium chloride (20 mg) under ice-cooling. The reaction mixture was stirred for 2 h and allowed to stand in a refrigerator for 16 h. This solution was diluted with H_2O, neutralized with 2 N NaOH and extracted with $CHCl_3$. The aqueous layer was applied to an Amberlite XAD-2 column, which was washed with H_2O and eluted with MeOH. The MeOH-elutable material was fractionated by preparative TLC (silica gel, 10% MeOH–$CHCl_3$) to give two yellow products. The higher *Rf* (5 mg) and the lower *Rf* (3 mg) products were identical with the chloro (**8**) and the keto (**9**) derivatives of paragracine,[2] respectively (MS, IR, UV, TLC and HPLC).

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References and Notes

1) Parts of this work were presented at the 1st International Symposium on Marine Natural Products, Aberdeen, Scotland, September 1975, at the 19th Symposium on the Chemistry of Natural Products, Hiroshima, October 1975, at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976, and at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980.
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