Plakohypaphorines A−C, Iodine-Containing Alkaloids from the Caribbean Sponge *Plakortis simplex*[‡]

Claudio Campagnuolo,[a] Ernesto Fattorusso,*[a] and Orazio Taglialatela-Scafati[a]

Keywords: Natural products / Plakohypaphorine / Structure elucidation / Configuration determination / Iodoindole derivatives

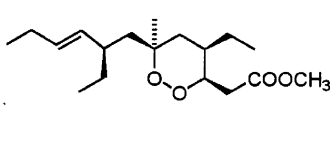
Investigation of the most polar fractions obtained from the organic extract of the Caribbean marine sponge *Plakortis simplex* has led to the isolation of three novel iodine-containing tryptophan betaines structurally related to the known hypaphorine (**5**), which have been named plakohypaphorine A (**2**), B (**3**) and C (**4**). Their structures have been determined by spectroscopic methods. Isolation of compounds **2**–**4** is particularly remarkable since it represents the first finding of iodoindole derivatives in a natural source, either marine or terrestrial.

Introduction

Plakortis simplex (Demospongiae, family Plakinidae, order Homosclerophorida) is a brown sponge commonly found as an encrusting species along the coasts of the Caribbean Sea. For several years our research group has been working on this organism and has managed to isolate a number of oxygenated polyketides, most of them possessing an unusual cycloperoxide moiety.[1−3] The most abundant of these molecules, plakortin (**1**), constituting approximately 20% of the entire organic extract, possesses a remarkable antimalarial activity.[4] In addition, many more bioactive glycolipids have been isolated from the same organism.[5]

During our investigation of the chemical composition of *P. simplex*, we have now analyzed the most polar fractions of the organic extract and obtained three new simple indole alkaloids (**2**−**4**), whose isolation and structural elucidation are the topic of this paper. To the best of our knowledge, the pyrrolidino-tyramine compound plakoridine A,[6] the pyrrolo-acridine plakinidines A−C,[7] and the cytotoxic β-carbolines plakortamines A−D[8] are the only *Plakortis* alkaloids hitherto known.

Compounds **2**−**4** are tryptophan betaines structurally related to hypaphorine (**5**), which has been found in several marine and terrestrial sources as a predator feeding deterrent.[9] In addition, a competitive antagonism against the auxin indole-3-acetic acid has been very recently disclosed for the same molecule.[10] Due to their structural similarity with hypaphorine, the novel compounds **2**−**4** have been named plakohypaphorines A−C, respectively.



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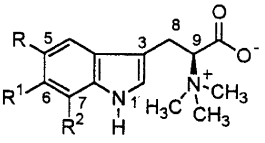

	2	3	4	5
R	H	H	I	H
R^1	H	I	H	H
R^2	I	I	I	H

Results and Discussion

A specimen of *P. simplex* was collected by hand during an expedition to the Caribbean Sea, and immediately frozen. After homogenization, the organism (57 g dry wt.) was exhaustively extracted first with methanol and then with chloroform. The methanol extract was partitioned between *n*BuOH and water, and then the organic phase, combined with the $CHCl_3$ extract, was subjected to chromatography over a column packed with reversed-phase silica gel (RP18) and eluted with a system of solvents from H_2O/MeOH (9:1) to H_2O/MeOH (1:9). Fractions eluted with H_2O/MeOH (4:6) were pooled and separated by medium-pressure liquid chromatography (MPLC) over silica gel. The most polar fractions thus obtained were finally purified by HPLC (eluent: H_2O/MeOH, 4:6) allowing the isolation of compounds **2**−**4** in a pure state.

The molecular formula $C_{14}H_{17}IN_2O_2$ was assigned to plakohypaphorine A (**2**) on the basis of HR-ESIMS data.

[‡] Metabolites from Plakortis simplex. Part V. For part IV see ref.[1]

[a] Dipartimento di Chimica delle Sostanze Naturali,
via D. Montesano, 49, 80131 Napoli, Italy
Phone: (internat.) +39-081/678-503
Fax: (internat.) +39-081/678-552
E-mail: fattoru@unina.it

Table 1. ^{1}H (500 MHz) NMR spectroscopic data of plakohypaphorine A (**2**), B (**3**) and C (**4**)

Position	**2** δ_H (J in Hz)	**3** δ_H (J in Hz)	**4** δ_H (J in Hz)
1-NH	10.82 (s, 1 H)	10.87 (s, 1 H)	10.85 (s, 1 H)
2	7.24 (s, 1 H,)	7.22 (s, 1 H)	7.24 (s, 1 H)
3			
3a			
4	7.60 (d, 1 H, 7.37)	7.47 (d, 1 H, 8.60)	8.02 (s, 1 H)
5	6.83 (t, 1 H, 7.37)	7.50 (d, 1 H, 8.60)	
6	7.48 (d, 1 H, 7.37)		7.68 (s, 1 H)
7			
7a			
8	3.21 (m, 2 H)	3.22 (m, 2 H)	3.22 (m, 2 H)
9	3.66 (dd, 1 H, 10.31, 3.44)	3.66 (dd, 1 H, 10.31, 3.44)	3.66 (dd, 1 H, 10.31, 3.44)
10			
$N(CH_3)_3$	3.19 (s, 9 H)	3.19 (s, 9 H)	3.19 (s, 9 H)

A monosubstituted iodoindole part structure for **2** was delineated from the following ^{1}H and ^{13}C NMR spectroscopic data: i) the ^{1}H NMR spectrum ([D$_6$]DMSO, Table 1) shows signals of a D_2O-exchangeable proton at δ = 10.88 ppm and four aromatic protons, one singlet at δ = 7.24 ppm, two doublets at δ = 7.60 (J = 7.37 Hz) and 7.48 ppm (J = 7.37 Hz), respectively, and a triplet at δ = 6.83 ppm (J = 7.37 Hz); ii) the last three protons are located on three adjacent carbons by the multiplicity and coupling constants of their ^{1}H NMR signals and by the correlations present in the COSY spectrum; iii) the above signals were easily associated with the relevant carbons through an HSQC experiment.[11] The ^{13}C NMR spectrum also contains signals for four non-protonated aromatic carbons at δ = 137.7, 127.9, 111.1, and 77.8. This last carbon was included among the aromatic ones in spite of its location in the mid-field region, assuming that it is linked to the strongly shielding iodine atom.

The nature of the second substituent on the iodoindole nucleus was delineated as $-CH_2-CHN^+(CH_3)_3-COO^-$ from the following spectral evidence: i) a singlet at δ = 3.18 ppm, integrating for nine equivalent protons, is present in the ^{1}H NMR spectrum; this was associated, by an HSQC experiment, to the carbon atom at δ = 51.3 ppm. Both carbon and proton chemical shift values are indicative of a trimethylammonium function. ii) The ^{1}H NMR spectrum also contains signals at δ = 3.66 (H-9) and 3.21 ppm (H_2-8), which were assigned to a $-CH_2-CH-$ moiety by correlations present in the COSY spectrum. iii) The carbon signal at δ = 168.8 ppm indicates the presence of a carboxylate group.

The iodine atom and the 2-trimethylammonium propionate residue are located on the indole moiety as indicated in formula **2** by the spatial proximity (evidenced through a ROESY correlation) of the methylene protons at position 8 (δ = 3.21 ppm) with both hydrogen atoms resonating as a singlet at δ = 7.24 ppm (H-2) and as a doublet at δ = 7.66 ppm. Therefore, this latter proton is located at C-4 and, taking into account that it is one of the termini of a spin system comprising three adjacent aromatic hydrogens, the iodine must be located at C-7. The correlations present in the HMBC spectrum (see Exp. Sect.), particularly the key HMBC cross-peaks of H_2-8 with C-2, C-3, C-3a, and C-10 and of H-1 with C-3, C-3a, C-7a, and with the high-field shifted iodine-binding C-7, fully corroborate the proposed structure **2**.

Several betaines, with different carbon frameworks, and most of them binding halogen atoms, have been isolated from marine invertebrates such as sponges and tunicates. In particular, the tryptophan-derived betaine 6-bromohypaphorine, found as a constituent of the marine sponges *Aplysina sp.* (as the D-stereoisomer)[12] and *Pachymatisma johnstoni* (as the L-stereoisomer)[13] is closely related to plakohypaphorine A (**2**). It should be noted that simple 5- or 6-halogen-substituted indole derivatives have been commonly found as spongal metabolites, while 7-haloindoles have been reported mostly as microbial metabolites.[14]

Plakohypaphorines B (**3**) and C (**4**) are diiodohypaphorines. They retain the iodine substitution at C-7 as in plakohypaphorine A, and they possess an additional iodine atom linked at C-6 and C-5, respectively.

Compound **3**, as indicated by HR-ESIMS, possesses the molecular formula $C_{14}H_{16}I_2N_2O_2$ which, compared to that of plakohypaphorine A, is in accordance with the replacement of a hydrogen atom with an iodine atom. Analysis of the ^{1}H and ^{13}C NMR spectra of plakohypaphorine B ([D$_6$]DMSO, Table 1 and 2) was carried out by inspection of the HSQC and HMBC spectra and by comparison with the parallel data obtained for plakohypaphorine A (**2**). The following considerations, arising from this analysis, allowed us to readily deduce the structure of plakohypaphorine B (**3**): i) the ^{1}H NMR spectrum of **3** shows a singlet (δ = 7.22 ppm) and two mutually coupled doublets (δ = 7.46 and 7.50 ppm) in the aromatic region in an *ortho*-relationship, as clearly indicated by the coupling constant J = 8.60 Hz; ii) the resonances of the aliphatic region are nearly superimposable with the same signals of plakohypaphorine A; iii) the singlet at δ = 7.22 ppm was confidently attributed to H-2 on the basis of its ^3J HMBC correlation peak with C-8; iv) the ROESY correlation peak of the doublet at δ = 7.46 ppm with the methylene at C-8 rules out the possibility of substitution at C-4, and consequently at C-5, unambiguously assigning plakohypaphorine B (**3**) as 6,7-diiodo-

N,*N*,*N*-trimethyltryptophan betaine. The whole series of HMBC cross-peaks (see Exp. Sect.) is in full agreement with this structure.

Table 2. ^{13}C (125 MHz) NMR spectroscopic data of plakohypaphorine A (**2**), B (**3**) and C (**4**)

Position	**2** δ_C (mult.)	**3** δ_C (mult.)	**4** δ_C (mult.)
1-NH			
2	124.5 (CH)	125.3 (CH)	125.5 (CH)
3	111.1 (C)	112.0 (C)	111.9 (C)
3a	127.9 (C)	128.1 (C)	129.7 (C)
4	119.0 (CH)	120.3 (CH)	126.9 (CH)
5	120.0 (CH)	128.9 (CH)	82.5 (C)
6	130.1 (CH)	100.5 (C)	135.4 (CH)
7	77.8 (C)	92.3 (C)	78.7 (C)
7a	137.7 (C)	138.5 (C)	139.1 (C)
8	25.2 (CH_2)	25.6 (CH_2)	25.5 (CH_2)
9	78.8 (CH)	77.9 (CH)	77.1 (CH)
10	168.8(C)	168.8 (C)	168.8 (C)
$N(CH_3)_3$	51.3 (CH_3)	50.9 (CH_3)	51.6 (CH_3)

HR-ESIMS data allowed us to assign the molecular formula $C_{14}H_{16}I_2N_2O_2$ to plakohypaphorine C (**4**), which is the same as plakohypaphorine B, thus suggesting that the two compounds must be positional isomers. The signals of the ammonium-linking three-carbon side chain in both the ^1H and ^{13}C NMR spectra of **5** ([D_6]DMSO, Table 1 and 2) are almost identical to the signals exhibited by the other two plakohypaphorines. On the other hand, in this case all the three aromatic resonances in the ^1H NMR spectrum appear as broad singlets, indicating the absence of any vicinal coupling between hydrogen atoms. Following the same reasoning as above, the proton at δ = 7.24 ppm was assigned to H-2, thus excluding the possibility of iodine substitution on ring A. Therefore, the absence of *ortho*-coupling between the remaining aromatic protons points to a 4,6-, a 5,6-, or a 5,7-diiodo substitution pattern.

The key ROESY correlation between the singlet at δ = 8.02 ppm (H-4) and the multiplet at δ = 3.20 ppm (H_2-8) rules out the first option. In order to discriminate between the remaining two possible disubstitutions we used information provided by evaluation of the intensities of the heteronuclear H−C coupling constants in the aromatic moiety. It is indeed well-known that in aromatic rings $^3J_{C,H}$ values are much larger than $^{2,4}J_{C,H}$.

The intensities of $J_{C,H}$ were estimated using PS-HMBC spectroscopy[15] as the key tool. This experiment does not supply the exact value of the heteronuclear coupling constants, but a simple comparison of the relative intensities of the cross-peaks is enough to distinguish between "small" and "large" $J_{C,H}$ couplings. The absolute lack of correlation is considered indicative of a small $J_{C,H}$ coupling

Accordingly, the singlet at δ = 8.02 ppm (H-4) shows large coupling constants with C-7a and with the protonated carbon at δ = 7.68 ppm, while small coupling constants are found to both C-3a and the two iodinated carbons (δ = 82.5 and 78.7 ppm). Analogously, the singlet at δ = 7.68 ppm shows large coupling constants with C-7a and with C-4, and small coupling constants with the two iodinated aromatic carbons (Table 3). The above pattern of heteronuclear coupling constants is only compatible with the 5,7-disubstitution. Therefore, plakohypaphorine C (**4**) was assigned as 5,7-diiodo-*N*,*N*,*N*-trimethyltryptophan betaine.

Table 3. Heteronuclear coupling constant pattern of Plakohipaphorine C (**4**)

	C-3a	C-4	C-5	C-6	C-7	C-7a
H-4	Small	–	Small	Large	Small	Large
H-6	Small	Large	Small	–	Small	Large

The $[\alpha]_D$ values obtained for plakohypaphorines A−C (**2**−**4**) are very similar to those reported for both L-hypaphorine and L-6-bromo-hypaforine[13] (in the same solvent CH_3OH/CF_3COOH, 8:1). Since the presence of a halogen atom (bromine) on the indole nucleus has been shown not to affect the sign of $[\alpha]_D$ for tryptophan derivatives,[12,13] we confidently assign the absolute configuration L (*S*) at C-9 of the three novel compounds.

Bromine and chlorine are, by far, the halogen atoms most frequently found in marine metabolites. On the contrary, iodine-containing secondary metabolites from marine organisms are extremely rare and this may be considered, to some extent, a consequence of the relatively low abundance of iodine in seawater (almost one thousand times less than bromine). To date, only very few examples of iodine-containing alkaloids — geodiamolide A from the sponge *Geodia sp.*,[16] dakaramine from the sponge *Ptilocaulis spiculifer*,[17] and its closely related analogue turbotoxin A from the gastropod *Turbo marmorata*[18] — have been reported from marine organisms. It should be noted that all these molecules belong to the class of tyrosine-derived alkaloids. To the best of our knowledge, there are no examples in the literature of iodine-containing indole alkaloids. In conclusion, isolation of plakohypaphorines A−C (**2**−**4**) appears particularly remarkable since it represents the first report of iodoindole compounds from either marine or terrestrial sources.

Experimental Section

General Methods: Optical rotations were measured in MeOH/trifluoroacetic acid on a Perkin−Elmer 192 polarimeter equipped with a sodium lamp (λ = 589 nm) and a 10-cm microcell. IR (KBr) spectra were recorded on a Bruker model IFS-48 spectrophotometer. UV spectra were obtained in MeOH using a Beckman DU70 spectrophotometer. Low and high resolution ESI-MS mass spectra were performed on a Finnigan MAT LCQ mass spectrometer. ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were measured on a Bruker AMX-500 spectrometer; chemical shifts are referenced to the residual solvent signal ([D_6]DMSO: δ_H = 2.49 ppm, δ_C = 39.5 ppm). Homonuclear ^1H connectivities were determined by COSY experiments. One bond heteronuclear ^1H-^{13}C connectivities were determined with the HSQC pulse sequence (interpulse delay set for $^1J_{CH}$ = 130 Hz). Two- and three-bond ^1H-^{13}C connectivities were determined by HMBC experiments optimized for a $^{2,3}J$ coupling

of 6.0 Hz. Heteronuclear coupling constants were measured using the PS-HMBC technique. NOE measurements were obtained with 2D ROESY experiments. Medium-pressure liquid chromatography (MPLC) was performed with a Büchi 861 apparatus with RP18 and SiO_2 (230−400 mesh) stationary phases. HPLC separations were achieved on a Waters apparatus equipped with an RI detector and LUNA reverse phase (C_{18}, 250 × 4 mm) columns.

Collection, Extraction and Purification: A specimen of *Plakortis simplex* was collected in Summer 1998 along the coasts of Berry Island (Bahamas), and identified by Prof. M. Pansini (Università di Genova). A voucher specimen has been deposited at the Istituto di Zoologia, Università di Genova, Italy with the ref. no. 2006. The organism was frozen immediately after collection and kept frozen until extraction, when the sponge (57 g, dry weight after extraction) was homogenized and extracted with methanol (4 × 500 mL) and with chloroform (4 × 500 mL). The methanol extract was initially partitioned between H_2O and *n*BuOH and then the organic phases were combined and concentrated in vacuo affording 29.3 g of a brown-colored viscous oil. This was subjected to chromatography on a column packed with RP18 silica gel and eluted with H_2O/MeOH (9:1; A_1), H_2O/MeOH (7:3; A_2), H_2O/MeOH (4:6; A_3), H_2O/MeOH (2:8; A_4), and H_2O/MeOH (1:9; A_5). Fraction A_3 (441.6 mg) was further chromatographed by MPLC [SiO_2 230−400 mesh; solvent gradient system of increasing polarity from *n*-hexane/EtOAc (7:3) to MeOH]. Fractions eluted with EtOAc/MeOH (1:1) to MeOH were rechromatographed by HPLC (eluent MeOH/H_2O 6:4, flow 0.8 mL/min) affording the novel plakohypaphorine A (**1**, 5.0 mg), B (**2**, 2.9 mg), and C (**3**, 2.7 mg) in a pure state.

Plakohypaphorine A (2): Pale yellow amorphous solid. $[\alpha]_D^{25}$ = +17.3 (*c* = 1.5 mg/mL in CH_3OH/CF_3COOH, 8:1). IR (KBr): $\tilde{\nu}_{max}$ = 3390, 1608, 1554 cm^{-1}. UV(CH_3OH): λ_{max} = 286.0 nm (ε = 3744), 224.0 nm (ε = 17211). LR-ESIMS: *m*/*z* = 373 [M + H^+], 395 [M + Na^+], 767 [2M + Na^+]. HR-ESIMS: observed *m*/*z* = 373.0458 [M + H]$^+$; calcd. for $C_{14}H_{17}IN_2O_2$, 373.0413. ^1H and ^{13}C NMR ([D_6]DMSO): see Table 1 and 2 respectively. HMBC correlations: C-2/H-1, C-2/H-8, C-3/H-1, C-3/H-8, C-3a/H-1, C-3a/H-5, C-3a/H-8, C-4/H-6, C-6/H-4, C-7/H-5, C-7a/H-1, C-7a/H-4, C-7a/H-6, C-9/H-8, C-9/$N(CH_3)_3$, C-10/H-8, C-10/H-9, $N(CH_3)_3$/H-9.

Plakohypaphorine B (4): Yellow amorphous solid. $[\alpha]_D^{25}$ = +30.4 (*c* = 1.2 mg/mL in CH_3OH/CF_3COOH, 8:1). IR (KBr): $\tilde{\nu}_{max}$ = 3390, 1608, 1554 cm^{-1}. UV (CH_3OH): λ_{max} = 290.0 nm (ε = 3686), 236.0 nm (ε = 18597). LR-ESIMS: *m*/*z* = 499 [M + H^+], 521 [M + Na^+]. HR-ESIMS: observed *m*/*z* = 498.9399 [M + H]$^+$; calcd. for $C_{14}H_{16}I_2N_2O_2$, 498.9379. ^1H and ^{13}C NMR ([D_6]DMSO): see Table 1 and 2, respectively. HMBC correlations: C-2/H-1, C-2/H-8, C-3/H-1, C-3/H-8, C-3a/H-1, C-3a/H-8, C-4/H-6, C-6/H-4, C-7a/H-1, C-7a/H-4, C-7a/H-6, C-9/H-8, C-9/$N(CH_3)_3$, C-10/H-8, C-10/H-9, $N(CH_3)_3$/H-9.

Plakohypaphorine C (3): Yellow amorphous solid. $[\alpha]_D^{25}$ = +29.1 (*c* = 1.0 mg/mL in CH_3OH/CF_3COOH, 8:1). IR (KBr): $\tilde{\nu}_{max}$ = 3390, 1608, 1554 cm^{-1}. UV (CH_3OH): λ_{max} = 284.0 nm (ε = 1211), 231.0 nm (ε = 8190). LR-ESIMS: *m*/*z* = 499 [M + H^+], 521 [M + Na^+]. HR-ESIMS: observed *m*/*z* = 498.9399 [M + H]$^+$ peak; calcd. for $C_{14}H_{16}I_2N_2O_2$, 498.9379. ^1H and ^{13}C NMR ([D_6]DMSO): see Table 1 and 2, respectively. HMBC correlations: C-2/H-1, C-2/H-8, C-3/H-1, C-3/H-8, C-3a/H-1, C-3a/H-5, C-3a/H-8, C-6/H-4, C-7/H-5, C-7a/H-1, C-7a/H-4, C-9/H-8, C-9/$N(CH_3)$, C-10/H-8, C-10/H-9, $N(CH_3)_3$/H-9; PS-HMBC correlations (in low field region): C-3a/H-4, C-4/H-6, C-5/H-6, C-6/H-4, C-7/H-6, C-7a/H-6.

Acknowledgments

This work is the result of a research programme sponsored by M.U.R.S.T., PRIN "Chimica dei Composti Organici di Interesse Biologico", Rome, Italy. We wish to thank Prof. Joseph R. Pawlik for giving us the opportunity to participate in an expedition to the Caribbean Sea, during which the sponge *Plakortis simplex* was collected, and Prof. M. Pansini (Istituto di Zoologia, Università di Genova, Italy) for identifying the organism. Mass, IR, and NMR experiments were performed at "Centro di Ricerca Interdipartimentale di Analisi Strumentale", Università di Napoli "Federico II". The assistance of the staff there is gratefully acknowledged.

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Received October 10, 2002
[O02561]