94. Novel Naamidine-Type Alkaloids and Mixed-Ligand Zinc(II) Complexes from a Calcareous Sponge, *Leucetta* sp., of the Coral Sea

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(16.III.95)

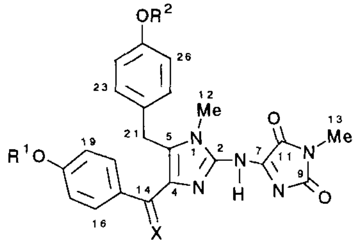
As compounds from a calcareous sponge, *Leucetta* sp., of the Coral Sea, we isolated a series of novel naamidine-type alkaloids, **6**–**10**, which are oxidized at a single benzylic position. We also report on the first marine, mixed-ligand metal complex **5** and on the first natural metal complexes **3** and **4** derived from classical naamidines, *i.e.*, **1** and **2**. The latter are also present in free form in the sponge.

1. Introduction. – In contrast with a wealth of chemical studies on demosponges, calcareous sponges were examined from this viewpoint for only a few spicular genera in the subclasses Calcinea and Calcaronea. From fatty acid [1a] and sterol [1b] composition, these sponges appear as a chemotaxonomically rather homogeneous group, well separated from the Demospongiae [1]. Also the alkaloids are peculiar: specimens in the genera *Leucetta* [2] and *Clathrina* [3] (Calcinea) yielded a series of closely interrelated 2-aminoimidazoles that embody one or two benzyl-substituted moieties. Examples include clathridines [2c, e, f] [3], isolated also from associated nudibranch molluscs [2e, f], naamidines [2a, e], isonaamidines [2a], naamines and isonaamines [2a], pyronamidine [2b, e], and leucettamidine and leucettamines [2d]. In naamidines E–F, the benzyl unit at C(5) has become a dimethoxyhydroquinone or a dimethoxyquinone system, respectively [2e]. Probably originated biogenetically from the intramolecular oxidative coupling of a highly oxygenated naamidine precursor, also a naphthoquinone bearing a fused imidazole ring, kealiiquinone, was isolated from *Leucetta* sp. [2b, e].

In this restricted scenario, Zn^{++} complexes for clathridine [2c, f] [3] and isonaamidine [2f] from these sponges stand among the few examples of metal complexes isolated from marine organisms [4]. To add to the keen interest towards such complexes [2c, f] [3] [4], we now report on the isolation from the calcareous sponge *Leucetta* sp. from the Coral Sea of the first naturally occurring mixed-ligand metal complex **5**, which also constitutes, together with the isolated complexes **3** and **4**, the first metal complexes of naamidine-type alkaloids. We also report on the isolation and characterization of the naamidine-type alkaloids **6**–**10** that are novel for being oxidized at a single benzyl position.

2. Results and Discussion. – 2.1. *Classical Naamidines A and G* (**1** and **2**, resp.) *and Their Zinc(II) Complexes* **3**–**5**. First in abundance besides the known naamidine A (**1**; *Scheme 1*) [2a, e], we found in this *Leucetta* sp. the new naamidine G (**2**), for which HR-EI-MS gave the composition $C_{24}H_{25}N_5O_4$. This suggested that, with respect to **1**, there is an additional Me group, which could be attributed to a 4-methoxybenzyl moiety on the basis of ^{13}C- and ^1H-NMR spectra (*s* at δ 3.75 coupled to a *q* at 55.27 ppm; *Tables 1* and *2*).

Scheme 1[a])[b])



1 R¹ = Me, R² = H, X = H,H
2 R¹ = R² = Me, X = H,H
6 R¹ = Me, R² = H, X = H,OH
a) → **6a** R¹ = Me, R² = Ac, X = H,OH
7 R¹ = R² = Me, X = H,OH
8 R¹ = Me, R² = H, X = H,MeO
9 R¹ = R² = Me, X = H,MeO
10 R¹ = R² = Me, X = O

[a]) Arbitrary numbering is for convenience; for systematic names, see *Exper. Part.*

[b]) The imino tautomeric form N(6)=C(7)–N(8) is also compatible with the data.

a) Ac_2O, MeOH, r.t., overnight.

Table 1. *^{13}C-NMR Data* (($(CD_3)_2CO$) *for the Isolated Naamidines* **1**, **2**, **6**, **7**, **9**, *and* **10** *and Their Zinc(II) Complexes* **3** *and* **4**[a]). Arbitrary numbering, see *Schemes 1* and *2*.

	1	**2**[b])	**6**	**7**[b])	**9**[b])	**10**[b])	**3**	**4**
C(2)	147.15 (*s*)	146.41 (*s*)	147.03 (*s*)	146.40 (*s*)	146.54 (*s*)	145.77 (*s*)	148.72 (*s*)	148.77 (*s*)
C(4)	136.60 (*s*)	135.37 (*s*)	140.46 (*s*)	139.22 (*s*)	137.38 (*s*)	135.46 (*s*)	133.26 (*s*)	133.34 (*s*)
C(5)	128.10 (*s*)	126.86 (*s*)	129.41 (*s*)	128.91 (*s*)[c])	128.87 (*s*)	139.04 (*s*)	128.97 (*s*)[c])	128.79 (*s*)
C(7)	145.46 (*s*)	145.29 (*s*)	145.44 (*s*)	not det.	142.69 (*s*)	141.84 (*s*)	154.96 (*s*)	155.00 (*s*)
C(9)=O	155.78 (*s*)	155.83 (*s*)	156.82 (*s*)	154.89 (*s*)	156.07 (*s*)	152.93 (*s*)	161.60 (*s*)	161.60 (*s*)
C(11)=O	162.50 (*s*)	162.35 (*s*)	162.44 (*s*)	162.12 (*s*)	not det.	160.94 (*s*)	164.83 (*s*)	164.81 (*s*)
Me(12)	29.95 (*q*)	29.93 (*q*)	29.80 (*q*)	29.89 (*q*)	29.84 (*q*)	30.06 (*q*)	31.41 (*q*)	31.42 (*q*)
Me(13)	24.52 (*q*)	24.68 (*q*)	24.52 (*q*)	24.72 (*q*)	24.69 (*q*)	24.81 (*q*)	24.34 (*q*)	24.35 (*q*)
CH_2(14)	32.58 (*t*)	32.12 (*t*)	69.56 (*d*)	69.54 (*d*)	78.75 (*d*)[d])	187.80 (*s*)	30.40 (*t*)	30.40 (*t*)
C(15)	133.13 (*s*)	128.92 (*s*)	137.82 (*s*)	135.01 (*s*)	132.47 (*s*)	130.95 (*s*)	131.11 (*s*)	131.07 (*s*)
CH(16), CH(20)	130.33 (*d*)	129.30 (*d*)	128.59 (*d*)	127.79 (*d*)	128.04 (*d*)	132.38 (*d*)	129.58 (*d*)	129.58 (*d*)
CH(17), CH(19)	114.47 (*d*)	113.97 (*d*)	114.11 (*d*)	113.86 (*d*)	113.80 (*d*)	113.45 (*d*)	114.03 (*d*)	114.04 (*d*)
C(18)	159.02 (*s*)	158.13 (*s*)	159.66 (*s*)	159.16 (*s*)	159.12 (*s*)	163.13 (*s*)	158.80 (*s*)	158.81 (*s*)
CH_2(21)	28.84 (*t*)	28.58 (*t*)	28.87 (*t*)	28.63 (*t*)	28.67 (*t*)	29.47 (*t*)	28.74 (*t*)	28.67 (*t*)
C(22)	129.45 (*s*)	131.33 (*s*)	127.69 (*s*)	128.83 (*s*)[c])	129.30 (*s*)	128.64 (*s*)	129.19 (*s*)[c])	130.45 (*s*)
CH(23), CH(27)	129.99 (*d*)	128.87 (*d*)	130.11 (*d*)	128.95 (*d*)	128.98 (*d*)	129.35 (*d*)	130.05 (*d*)	130.02 (*d*)
CH(24), CH(26)	116.23 (*d*)	114.18 (*d*)	116.13 (*d*)	114.17 (*d*)	114.12 (d)	114.20 (*d*)	116.37 (*d*)	114.94 (*d*)
C(25)	156.88 (*s*)	158.40 (*s*)	156.82 (*s*)	158.40 (*s*)	158.35 (*s*)	158.41 (*s*)	157.01 (*s*)	159.42 (*s*)
R^1	55.39 (*q*)	55.27 (*q*)	55.42 (*q*)	55.27 (*q*)	55.27 (*q*)	55.47 (*q*)	55.21 (*q*)	55.22 (*q*)
R^2	–	55.27 (*q*)	–	55.27 (*q*)	55.27 (*q*)	55.25 (*q*)	–	55.45 (*q*)

[a]) For compounds **5** and **8**, see *Exper. Part.* [b]) In $CDCl_3$. [c]) Interchangeable data within the same column. [d]) 56.87 (*q*, *Me*O–C(14)).

The NMR pattern for the benzylic protons of the isolated tetrahedral[1]) Zn^{++} complexes **3** and **4** (*Scheme 2*) differ markedly with respect to the corresponding free naamidines **1** and **2**, being isochronous in the latter (br. *s*) and diastereotopic in the former (*AB*

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[1]) Tetrahedral in analogy with the X-ray diffraction structure of the crystalline zinc complex of clathridine [3], where the N(3) and N(8) atoms of each clathridine unit are coordinated to a tetrahedral Zn^{++} ion.

Table 2. *^{1}H-NMR Data* ($(CD_3)_2CO$) *for the Isolated Naamidines* **1**, **2**, *and* **6–10** *and Their Zinc(II) Complexes* **3** *and* **4**[a]). Arbitrary numbering, see *Schemes 1* and *2*.

	1	**2**	**6**	**7**[b])	**8**[c])	**9**[b])	**10**[b])	**3**	**4**
Me(12)	3.50 (*s*)	3.50 (*s*)	3.47 (*s*)	3.47 (*s*)	3.48 (*s*)	3.44 (*s*)	3.62 (*s*)	3.66 (*s*)	3.66 (*s*)
Me(13)	3.06 (*s*)	3.06 (*s*)	3.06 (*s*)	3.15 (*s*)	3.06 (*s*)	3.16 (*s*)	3.18 (*s*)	2.87 (*s*)	2.87 (*s*)
2 H–C(14)	3.96 (br. *s*)	3.96 (br. *s*)	5.85 (br. *s*)	5.81 (br. *s*)	5.46 (br. *s*)	5.28 (br. *s*)	–	3.88, 3.44 (*AB*, *J* = 16.8)	3.88, 3.44 (*AB*, *J* = 16.8)
H–C(16), H–C(20)	7.22 (*d*, *J* = 8.7)	7.22 (*d*, *J* = 8.7)	7.40 (*d*, *J* = 8.7)	7.31 (*d*, *J* = 8.4)	7.40 (*d*, *J* = 8.7)	7.33 (*d*, *J* = 8.7)	8.11 (*d*, *J* = 8.7)	6.62 (*d*, *J* = 8.7)	6.63 (*d*, *J* = 8.7)
H–C(17), H–C(19)	6.82 (*d*, *J* = 8.7)	6.83 (*d*, *J* = 8.7)	6.84 (*d*, *J* = 8.7)	6.83 (*d*, *J* = 8.4)	6.89 (*d*, *J* = 8.7)	6.86 (*d*, *J* = 8.7)	6.97 (*d*, *J* = 8.7)	6.55 (*d*, *J* = 8.7)	6.55 (*d*, *J* = 8.7)
H–C(21)	4.01 (br. *s*)	4.05 (br. *s*)	4.00 (br. *s*)	3.87 (br. *s*)	4.08 (br. *s*)	3.97 (br. *s*)	4.39 (br. *s*)	4.05 (br. *s*)	4.11, 4.06 (*AB*, *J* = 16.8)
H–C(23), H–C(27)	6.94 (*d*, *J* = 8.7)	7.03 (*d*, *J* = 8.7)	6.94 (br. *d*, *J* = 8.4)	6.88 (*d*, *J* = 8.4)	6.94 (*d*, *J* = 8.7)	6.91 (*d*, *J* = 8.7)	7.14 (*d*, *J* = 8.7)	7.06 (*d*, *J* = 8.7)	7.15 (*d*, *J* = 8.7)
H–C(24), H–C(26)	6.74 (*d*, *J* = 8.7)	6.82 (*d*, *J* = 8.7)	6.72 (br. *d*, *J* = 8.4)	6.75 (*d*, *J* = 8.4)	6.74 (*d*, *J* = 8.7)	6.77 (*d*, *J* = 8.7)	6.81 (*d*, *J* = 8.7)	6.79 (*d*, *J* = 8.7)	6.88 (*d*, *J* = 8.7)
R^1	3.75 (*s*)	3.75 (*s*)	3.76 (*s*)	3.76 (*s*)[d])	3.78 (*s*)	3.78 (*s*)	3.89 (*s*)	3.70 (*s*)	3.70 (*s*)
R^2	–	3.75 (*s*)	–	3.75 (*s*)[d])	–	3.76 (*s*)	3.76 (*s*)	–	3.76 (*s*)
MeO–C(14)	–	–	–	–	3.32 (*s*)	3.34 (*s*)	–	–	–

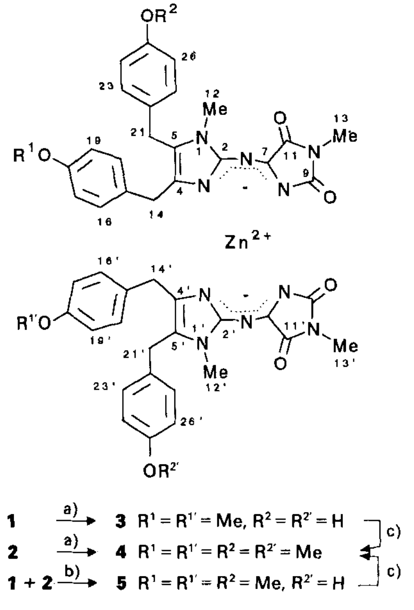
[a]) For compound **5**, see *Exper. Part*.

[b]) In $CDCl_3$.

[c]) In 12:88 mixture with **1**.

[d]) Interchangeable data within the same column.

Scheme 2[a]



[a] Arbitrary numbering is for convenience.

a) 0.1M aq. $ZnSO_4$, $MeOH/CH_2Cl_2$ 5:1, r.t., overnight.

b) 1. 0.1M aq. $ZnSO_4$, CH_2Cl_2, r.t., overnight; 2. *RP-8* HPLC separation.

c) MeI, KF·Al_2O_3, MeCN, r.t., overnight.

system; see *Table 2*). Moreover, the resonance for Me(13) of complexes **3** and **4** is displaced downfield by *ca.* 0.2 ppm with respect to **1** and **2**. Structure **4** is further supported by MS data and by small but significant NMR spectral differences with respect to the Cd^{++} complex obtained from naamidine G (**2**). The isolated complex **5** shows NMR spectra as for an equimolar mixture of **3** and **4**, although *RP-8* TLC and HPLC retention times are intermediate between the more polar **3** and the less polar **4**. This points to a mixed-ligand nature for **5**. Complexes **3** and **5**, having failed to give informative MS, were correlated to **4** *via* methylation by treatment with MeI and potassium fluoride–alumina (KF·Al_2O_3) [5] (*Scheme 2*). Structures **3**–**5** were definitely established by synthesis from the free naamidines A (**1**) and G (**2**) (*Scheme 2*).

These observations on the isolated Zn^{++} complexes **3**–**5** matched those on the sponge raw extracts, ruling out that these complexes may have been formed during the chromatographic workup [6].

2.2. *Naamidines Oxidized at a Benzyl Position.* The composition $C_{24}H_{25}N_5O_5$ for the new 14-hydroxynaamidine G (**7**) was obtained from FAB-MS, while neither 14-hydroxynaamidine A (**6**) nor its 25-*O*-acetyl derivative [2a] **6a** gave the molecular ion. Anyway, O-substitution at C(14) in both **6** and **7** was suggested by their NMR spectra (**6**: δ_H 5.85 (br. *s*) coupled to δ_c 69.56 (*d*); **7**: δ_H 5.81 (br. *s*) coupled to δ_c 69.54 (*d*); **6** and **7**: downfield shift for *H*–C(16) and *H*–C(20) with respect to **1** and **2**; see *Tables 1* and *2*).

The presence of a MeO group at C(14) in both 14-methoxynaamidine A (**8**) and 14-methoxynaamidine G (**9**) was established on the basis of evidence similar to the above (*Tables 1* and *2*) and was confirmed by HR-EI-MS data (*Exper. Part*).

Finally, the molecular formula $C_{24}H_{23}N_5O_5$ for 14-oxonaamidine G (**10**) was obtained by HR-EI-MS. Assignment of the carbonyl position to C(14) was mainly based on

^{1}H-NMR downfield shifts with respect to naamidine G (**2**; large $\Delta\delta$ for H–C(16) and H–C(20), smaller $\Delta\delta$ for H–C(17) and H–C(19); see *Table 2*).

3. Conclusions. – There are two the main messages from this work. The first is the selectivity of oxidation at a single benzylic position in naamidines **6**–**10**, which suggests enzymic routes, in accordance with the optical rotation displayed by the chiral compounds **6**–**9**. The second message concerns the Zn^{++} complex **5**, which is the first example of a mixed-ligand metal complex of marine origin. Complex **5** as well as **3** and **4** are also peculiar as they are the first natural metal complexes of naamidines. Previously, only the metal complex of a non-isolated isonaamidine C was known as a natural product in this area [2f].

While accumulation of Zn^{++} ions by these sponges occurs on a world distribution basis, from the Mediterranean Sea [3] to the Pacific basin, around the Fiji [2f] or in the Coral Sea as shown here, the role played by Zn^{++} trapped by these alkaloids is unknown. Any conjecture is hard to make since no well defined biological activity has been as yet discovered for these complexes. The marginal cytotoxicity on KB cells discovered here (*Exper. Part*) is irrelevant. However, Zn^{++} is a rare ion in the sea [4], and the metabolic cost of accumulating it in the sponges, and selectively with respect to other heavy metals, implies some role in the sponges the elucidation of which remains a challenge.

We thank Prof. *C. Lévi*, Musée National D'Histoire Naturelle, Paris, for the taxonomic identification and Mrs. *M. Rossi* and *A. Sterni* for technical contributions with product isolation and mass spectra, respectively. This work was carried out within the collaborative *ORSTOM-CNRS Program on Marine Substance of Biological Interest*. The work in Trento was supported by *MURST* (Progetti 40%) and *CNR*, Roma.

Experimental Part

1. *General*. All evaporations were carried out at reduced pressure. Yields are given on reacted compounds. M.p.: *Kofler* hot stage microscope; uncorrected. Flash-chromatography (FC): *Merck Si-60*, 15–25 μm. TLC: *Merck* silica gel *60 PF_{254}* plates. Reversed-phase HPLC: 25 × 1-cm columns filled with either *Merck LiChrospher RP18* (7 μm) or *Merck LiChrosorb RP-8* (7 μm); UV monitoring at λ 254 nm; solvent flux 5 ml min^{-1}. Polarimetric data; *JASCO-DIP-181* polarimeter; $[\alpha]_D$ values in 10^{-1} deg cm^3 g^{-1}. UV: *Perkin-Elmer-Lambda-3* spectrophotometer. IR: *Philips Pye Unicam SP3-200S* spectrometer; thin films from $CHCl_3$. NMR: *Varian-XL-300* spectrometer; ^{1}H at 300 MHz, ^{13}C at 75.4 MHz; in $CDCl_3$ or $(CD_3)_2CO$; δ in ppm rel. to internal $SiMe_4$ (= 0 ppm) and J in Hz; multiplicities from DEPT [7], assignments confirmed by selective decoupling irradiations, ^{1}H,^{13}C COSY [8] or ^{13}C,^{1}H-NMR by inverse detection shift correlation experiments [9a] on a special probe [9b]. Mass spectra: electron ionization (EI), unless otherwise stated with a *Kratos-MS80* mass spectrometer with home-built data system; fast-atom bombardment ionization (FAB) with the same apparatus equipped with a *Vacumetrics DIP* gun.

2. *Collection and Isolation*. The sponge (690M) was collected in March 1993 in shallow waters on the grand Passage reef, north from the lagoon of New Caledonia. It was determined taxonomically by Prof. *C. Lévi*, who retains a voucher specimen (R1523). The sponge was immediately frozen after collection and then freeze-dried (250 g dry weight). The freeze-dried powder was extracted with EtOH and the extract evaporated to give 0.96 g of residue, a small quantity of which (0.05 g) was subjected to *RP-8* HPLC ($MeCN/H_2O$ 62:38): pure Zn^{++} complexes **3** (2.1 mg; t_R 4.6 min), **5** (1.0 mg; t_R 6.6 min), and **4** (2.0 mg; t_R 10.6 min). The remaining residue was dissolved in H_2O/CH_2Cl_2 and the org. phase separated and evaporated to give a residue (0.8 g). The latter was mildly cytotoxic (KB) and antiyeast (*Candida albicans*), but neither **3** nor **4** possessed any anti-*Candida* activity and showed only marginal cytotoxicity toward KB cells. The residue from the CH_2Cl_2 extraction was subjected to FC (hexane/AcOEt, then $CHCl_3/MeOH$, gradient elution): *Fractions 1–23* (50 ml each). Compound **2** (36.0 mg) was obtained by precipitation from the partially evaporated *Fr. 9* and proved to be pure on *RP-8* HPLC ($MeCN/H_2O$ 6:4; t_R 8.1 min). *Frs. 8*, *10*, and *11* were subjected to *RP-8* HPLC ($MeCN/H_2O$ 1:1): yellow **6** (3.2 mg; t_R 5.3 min), **1**/**8** 88:12 (24.2 mg; t_R 8.0 min), **7** (4.3 mg; t_R 9.1 min), **9** (3.4 mg; t_R 15.4 min), **2** (2.2 mg; t_R 16.4 min), and **10** (t_R 16.8 min). The latter was further purified by *RP-18* HPLC ($MeCN/H_2O$ 1:1; 4.4 mg; t_R 7.0 min).

3. *Isolated Compounds. Naamidine A* (= *4-{{5-[(4-Hydroxyphenyl)methyl]-4-[(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazol-2-yl}amino}-1-methyl-1*H*-imidazole-2,5-dione*; **1**): UV (MeOH): 384 (10060), 276 (4800), 225 (21400). EI-MS: 433 (11, $M^{+\cdot}$), 418 (2), 326 (5), 121 (5), 107 (7). HR-EI-MS: 433.1746 ± 0.0030 ($C_{23}H_{23}N_5O_4^{+\cdot}$, calc. 433.1750).

Naamidine G (= *4-{{4,5-Bis[(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazol-2-yl}amino}-1-methyl-1*H*-imidazole-2,5-dione*; **2**): Yellow solid (AcOEt). M.p. 94°. UV (MeOH): 382 (9900), 276 (3400), 226 (18200). IR: 2915, 1794, 1734, 1715, 1615, 1448. EI-MS: 447 (59, $M^{+\cdot}$), 432 (10), 326 (22), 121 (26). HR-EI-MS: 447.1906 ± 0.0030 ($C_{24}H_{25}N_5O_4^{+\cdot}$, calc. 447.1906).

14-Hydroxynaamidine A (= *4-{{4-[Hydroxy(4-methoxyphenyl)methyl]-5-[(4-hydroxyphenyl)methyl]-1-methyl-1*H*-imidazol-2-yl}amino}-1-methyl-1*H*-imidazole-2,5-dione*; **6**): $[\alpha]_D^{25} = +6$ ($c = 0.3$, MeOH). UV (MeOH): 382 (4070), 276 (2900), 225 (10900). IR: 3600–3200 (br.), 1730, 1540, 1460. FAB-MS (glycerol, H^+ matrix): 434 (6).

14-Hydroxynaamidine G (= *4-{{4-[Hydroxy(4-methoxyphenyl)methyl]-5-[(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazol-2-yl}amino}-1-methyl-1*H*-imidazole-2,5-dione*; **7**): $[\alpha]_D^{25} = -8$ ($c = 0.2$, MeOH). UV (MeOH): 380 (5800), 275 (2900), 225 (11050). FAB-MS (glycerol, H^+ matrix): 464 (15, $[M + H]^+$), 446 (30).

14-Methoxynaamidine A (= *4-{{5-[(Hydroxyphenyl)methyl]-4-[methoxy(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazol-2-yl}amino}-1-methyl-1*H*-imidazole-2,5-dione*; **8**): isolated as a 12:88 mixture with **1**. ^{13}C-NMR ($(CD_3)_2CO$, only signals not superimposable to those of **1**): 79.27 (*d*, C(14)); 128.95 (*d*, C(16), C(20)); 114.22 (*d*, C(17), C(19)); 116.17 (*d*, C(24), C(26)); 56.67 (*q*, MeO–C(14)). EI-MS: 463 (0.6, $M^{+\cdot}$).

14-Methoxynaamidine G (= *4-{{4-[Methoxy(4-methoxyphenyl)methyl]-5-[(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazol-2-yl}amino}-1-methyl-1*H*-imidazole-2,5-dione*; **9**): $[\alpha]_D^{25} = +4$ ($c = 0.3$, MeOH). UV (MeOH): 380 (5900), 276 (2400), 225 (11500). IR: 3600–3100 (br.), 1685, 1610, 1540, 1495, 1350, 1260. EI-MS: 477 (1, $M^{+\cdot}$), 446 (2, $[M - \text{MeO}]^+$), 326 (1). HR-EI-MS: 477.2002 ± 0.0030 ($C_{25}H_{27}N_5O_5^{+\cdot}$, calc. 477.2012).

14-Oxonaamidine G (= *4-{{4-(4-Methoxybenzoyl)-5-[(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazol-2-yl}amino}-1-methyl-1*H*-imidazole-2,5-dione*; **10**): UV (MeOH): 370 (5900), 298 (6500), 223 (12400). IR: 3600 (br.), 3270 (br.), 2930, 1740, 1670, 1600, 1515, 1448, 1250, 1160, 1025. EI-MS: 461 (12, $M^{+\cdot}$), 447 (10), 432 (3), 326 (4), 135 (5), 121 (9). HR-EI-MS: 461.1700 ± 0.0030 ($C_{24}H_{23}N_5O_5^{+\cdot}$, calc. 461.1699).

Bis(naamidinato A)zinc(II) (**3**): Yellow amorphous solid. UV (MeOH): 380 (14500), 275 (12400), 222 (44600).

Bis(naamidinato G)zinc(II) (**4**): Yellow amorphous solid. UV (MeOH): 386 (19800), 273 (30200), 226 (56000). IR: 2930, 1768, 1720, 1615, 1448, 1180. ^{1}H-NMR ($CDCl_3$, for one of the two identical ligands): 3.58 (*s*, Me(12)); 2.94 (*s*, Me(13)); 3.73, 3.39 (*AB*, $J = 16.8$, 2 H–C(14)); 6.63 (*d*, $J = 8.7$, H–C(16), H–C(20)); 6.58 (*d*, $J = 8.7$, H–C(17), H–C(19)); 3.90, 3.86 (*AB*, $J = 16.8$, 2 H–C(21)); 6.97 (*d*, $J = 8.7$, H–C(23), H–C(27)); 6.81 (*d*, $J = 8.7$, H–C(24), H–C(26)); 3.71 (*s*, MeO–C(18)); 3.77 (*s*, MeO–C(25)). FAB-MS (3-nitrobenzyl alcohol matrix): 957 ($[M + H]^+$, most intense peak of a cluster typical for the presence of Zn isotopes).

(Naamidinato A)(naamidinato G)zinc(II) (**5**): Yellow amorphous solid. UV (MeOH): 390 (20100), 373 (20700), 278 (6300), 228 (43000). ^{1}H-NMR ($(CD_3)_2CO$): 3.66 (*s*, Me(12), Me(12′)); 2.87 (*s*, Me(13), Me(13′)); 3.88, 3.44 (*AB*, $J = 16.8$, 2 H–C(14), 2 H–C(14′)); 6.63 (*d*, $J = 8.7$, H–C(16), H–C(20)); 6.62 (*d*, $J = 8.7$, H–C(16′), H–C(20′)); 6.55 (*d*, $J = 8.7$, H–C(17), H–C(17′), H–C(19), H–C(19′)); 4.09 (br. *s*, 2 H–C(21)); 4.06 (br. *s*, 2 H–C(21′)); 7.15 (*d*, $J = 8.7$, H–C(23), H–C(27)); 7.06 (*d*, $J = 8.7$, H–C(23′), H–C(27′)); 6.88 (*d*, $J = 8.7$, H–C(24), H–C(26)); 6.80 (*d*, $J = 8.7$, H–C(24′), H–C(26′)); 3.70 (*s*, MeO–C(18), MeO–C(18′)); 3.76 (*s*, MeO–C(25)). ^{13}C-NMR ($(CD_3)_2CO$): 148.76 (*s*, C(2), C(2′)); 133.33 (*s*, C(4)); 133.26 (*s*, C(4′)); 128.78 (*s*, C(5)); 128.95 or 129.19 (*s*, C(5′)); 154.97 and 155.00 (*s*, C(7), C(7′)); 161.58 (*s*, C(9), C(9′)); 164.80 (*s*, C(11), C(11′)); 31.42 (*q*, C(12), C(12′)); 24.33 (*q*, C(13), C(13′)); 30.40 (*t*, C(14), C(14′)); 131.07 (*s*, C(15)); 131.11 (*s*, C(15′)); 129.58 (*d*, C(16), C(16′), C(20), C(20′)); 114.03 (*d*, C(17), C(17′), C(19), C(19′)); 158.80 (*s*, C(18), C(18′)); 28.68 (*t*, C(21)); 28.74 (*t*, C(21′)); 130.45 (*s*, C(22)); 129.19 or 128.95 (*s*, C(22′)); 130.05 (*d*, C(23), C(23′), C(27), C(27′)); 114.93 (*d*, C(24), C(26)); 116.36 (*d*, C(24′), C(26′)); 159.42 (*s*, C(25)); 156.99 (*s*, C(25′)); 55.21 (*q*, MeO–C(18), MeO–C(18′)); 55.45 (*q*, MeO–C(25)). EI-MS: 447 (6), 432 (1), 326 (2).

4. *Synthesis of Complexes* **3**–**5** *and of the* Cd^{++} *Complex of* **2**. To a soln. of **2** (12.0 mg, 0.027 mmol) in CH_2Cl_2 (1 ml) were added 0.1M aq. $ZnSO_4$ (5 ml) and MeOH (5 ml). The mixture was stirred vigorously at r.t. overnight, then partially evaporated, and finally extracted with AcOEt (3 × 10 ml). The combined org. phase was dried (Na_2SO_4) and evaporated to give pure **4** (12.5 mg, 98%), identical under every respect to the natural compound.

Under similar conditions, **1** (6.0 mg, 0.014 mmol) was treated with 0.1M $ZnSO_4$ to give pure **3** (6.3 mg, 98%), identical to the natural compound.

To a soln. of equimolar amounts of **1** (4.0 mg) and **2** (4.1 mg) in CH_2Cl_2 (1 ml) was added 0.1M $ZnSO_4$ (4 ml). The mixture was stirred vigorously overnight and then extracted with CH_2Cl_2 (3 × 10 ml). The combined org.

phase was evaporated and the residue subjected to *RP-8* HPLC (MeCN/H_2O 3:2): **3** (t_R 5.3 min; 2.5 mg, 29%), **5** (t_R 8.1 min; 2.4 mg, 28%), and **4** (t_R 14.0 min; 2.6 mg, 29%), identical to the natural complexes.

To a soln. of **2** (t_R 4.0 mg, 0.009 mmol) in CH_2Cl_2 (0.5 ml) were added 0.1M $CdSO_4$ (2 ml) and MeOH (2 ml). The mixture was stirred vigorously at r.t. overnight and, after workup as above, pure bis(naamidinato G)cadmium(II) was obtained (4.3 mg, 96%). UV (MeOH): 386 (1500), 270 (11900), 223 (12000). ^{1}H-NMR ($CDCl_3$): 7.00 (*d*, *J* = 8.7); 6.82 (*d*, *J* = 8.7); 6.64 (*d*, *J* = 8.7); 6.55 (*d*, *J* = 8.7); 3.95, 3.89 (*AB*, *J* = 16.9); 3.79, 3.47 (*AB*, *J* = 16.9); 3.77 (*s*); 3.67 (*s*); 3.59 (*s*); 3.00 (*s*). ^{13}C-NMR ($CDCl_3$): 165.38 (*s*); 162.19 (*s*); 158.53 (*s*); 158.18 (*s*); 154.32 (*s*); 148.20 (*s*); 132.88 (*s*); 129.31 (*s*); 129.27 (*s*); 129.03 (*d*); 128.86 (*d*); 126.87 (*s*); 114.33 (*d*); 113.78 (*d*); 55.30 (*q*); 55.05 (*q*); 31.43 (*q*); 30.39 (*t*); 28.57 (*t*); 24.56 (*q*).

5. *Acetylation of* **6**. A soln. of **6** (2.5 mg, 0.0056 mmol) and excess Ac_2O (0.05 ml) in MeOH (1 ml) was stirred at r.t. overnight, then evaporated, and purified by *RP-8* HPLC (MeCN/H_2O 1:1): **6** (t_R 5.0 min; 1.0 mg) and *25-O-acetyl-14-hydroxynaamidine A* (**6a**; t_R 7.4 min; 1.6 mg, 97%). ^{1}H-NMR ($(CD_3)_2CO$): 3.48 (*s*, Me(12)); 3.06 (*s*, Me(13)); 5.86 (*s*, H–C(14)); 7.40 (*d*, *J* = 8.7 H–C(16), H–C(20)); 3.76 (*s*, MeO–C(18)); 3.93 (br. *s*, 2 H–C(21)); 7.14 (*d*, *J* = 8.7 H–C(23), H–C(27)); 7.0 (*d*, *J* = 8.7 H–C(24), H–C(26)); 2.23 (*s*, AcO–C(25)).

6. *Methylation of Complexes* **3** *and* **5**. A suspension of **3** (2.8 mg, 0.003 mmol), MeI in excess (0.01 ml), and KF · Al_2O_3 (22 mg, class II; prepared from 0.2 mmol of KF impregnated on 0.1 g of alumina [5]) in MeCN (2 ml) was stirred at r.t. overnight. The mixture was filtered, the filtrate evaporated, and the residue subjected to prep. TLC ($CHCl_3$/MeOH 9:1): pure **4** (2.4 mg, 83%).

Under similar conditions, **5** was converted into **4**.

REFERENCES

[1] a) P. R. Bergquist, M. P. Lawson, A. Lavis, R. C. Cambie, *Biochem. Syst. Ecol.* **1984**, *12*, 63; M. P. Lawson, P. R. Bergquist, R. C. Cambie, *ibid.* **1984**, *12*, 375; b) P. R. Bergquist, A. Lavis, R. C. Cambie, *ibid.* **1986**, *14*, 101.

[2] a) S. Carmely, Y. Kashman, *Tetrahedron Lett.* **1987**, *26*, 3003; S. Carmely, M. Ilan, Y. Kashman, *Tetrahedron* **1989**, *45*, 2193; b) R. K. Akee, T. R. Carroll, W. Y. Yoshida, P. J. Scheuer, *J. Org. Chem.* **1990**, *55*, 1944; c) H. He, D. J. Faulkner, A. Y. Lee, J. Clardy, *ibid.* **1992**, *57*, 2176; d) G. W. Chan, S. Mong, M. E. Hemling, A. J. Freyer, P. H. Offen, C. W. DeBrosse, H. M. Sarau, J. W. Westley, *J. Nat. Prod.* **1993**, *56*, 116; e) A. R. Carroll, B. F. Bowden, J. C. Coll, *Aust. J. Chem.* **1993**, *46*, 1229; f) K. A. Alvi, B. M. Peters, L. M. Hunter, P. Crews, *Tetrahedron* **1993**, *49*, 329.

[3] P. Ciminiello, E. Fattorusso, S. Magno, A. Mangoni, *Tetrahedron* **1989**, *45*, 3873; P. Ciminiello, E. Fattorusso, A. Mangoni, B. Di Blasio, V. Pavone, *ibid.* **1990**, *46*, 4387.

[4] J. P. Michael, G. Pattenden, *Angew. Chem. Int. Ed.* **1993**, *32*, 1.

[5] T. Kawate, S. Sumi, T. Hanafusa, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2504.

[6] D. A. Cuppels, R. D. Stipanovic, A. Stoessl, J. B. Stothers, *Can. J. Chem.* **1987**, *65*, 2126.

[7] D. H. Doddrell, D. T. Pegg, H. R. Bendall, *J. Magn. Reson.* **1982**, *48*, 323; D. T. Pegg, D. M. Doddrell, M. R. Bendall, *J. Chem. Phys.* **1982**, *77*, 2745.

[8] A. Bax, *J. Magn. Reson.* **1983**, *53*, 517; H. Kessler, C. Criesinger, J. Zarbock, H. R. Loosli, *ibid.* **1984**, *57*, 331.

[9] a) L. Müller, *J. Am. Chem. Soc.* **1979**, *101*, 4481; b) G. Gray, *Magn. Moments* **1987**, *III*, 6.