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NEOSIPHONIAMOLIDE A, A NOVEL CYCLODEPSIPEPTIDE, WITH ANTIFUNGAL ACTIVITY FROM THE MARINE SPONGE *NEOSIPHONIA SUPERSTES*

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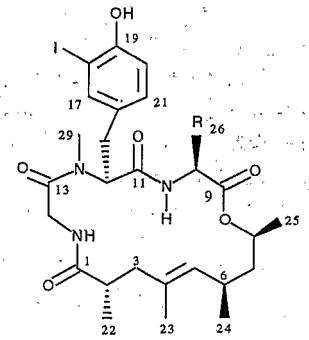
ABSTRACT.—A novel cyclodepsipeptide, neosiphoniamolide A [**1**], has been isolated from the sponge *Neosiphonia superstes*. The structure of **1**, which contains a 12-carbon hydroxy acid, glycine, valine, and a halogenated tyrosine residue in an 18-membered ring, is related to jaspamide and the geodiamolides, previously isolated from sponges. The structure was solved by spectroscopic analysis.

Marine sponges are a well-established source of unique and biologically active peptides (1,2). Jaspamide from *Jaspis* sp. (order Choristida) (3,4) and the geodiamolides from *Geodia* sp. (order Choristida) (5) and also from *Pseudoaxinissa* sp. (6), belonging to the order Axinellida (which is taxonomically distant from *Geodia*), are recent examples. They are four-residue cyclic depsipeptides, which contain a common 12-carbon polypropionate residue and three amino acid residues found in the tripeptide portion of the 18-membered macrocycle. All these metabolites were reported to exhibit potent antimicrobial and cytotoxic activities (3,6); jaspamide was also reported to be insecticidal (3). As a part of an ongoing study of biologically active metabolites from New Caledonian marine invertebrates, we have been working on the bioactive extracts of the sponge *Neosiphonia superstes*, from which we have isolated sphinxolides, potent cytotoxic 26-membered macrolides (7). We now report the isolation and structure determination of a new cyclodepsipeptide, neosiphoniamolide A [**1**], which is related to the previously known jaspamide and the geodiamolides.



1 R=$CH(CH_3)_2$
2 R=CH_3

The CH_2Cl_2-MeOH (8:2) extract of the sponge was chromatographed by Si gel mplc (MeOH: $CHCl_3$, 2:98) followed by reversed-phase C-18 μ-Bondapak hplc with 73% aqueous MeOH to give neosiphoniamolide A (**1**, 2 mg, colorless glass) and major amounts of the previously isolated sphinxolides. The fabms of **1** gave a pseudomolecular ion at *m/z* 656 $[M+H]^+$. Resonances in the ^1H- and ^{13}C-nmr spectra could be assigned to a 12-carbon polypropionate unit (C-1 to C-8 and attached methyls) identical to that found in jaspamide (3) and the geodiamolides (5,6). Additional ^1H- and ^{13}C-nmr resonances could be assigned to an *N*-methyl-3-iodotyrosine residue and

one glycine residue by comparison of their chemical shifts and coupling constants to those reported for the resonances assigned to the same residues in geodiamolide D [**2**] (6). Uv absorptions at λ max 219, 284, and 292 (ε13270, 4000, 3000) supported the presence of a 3-iodotyrosine residue (5). The remaining resonances in the ^{1}H-nmr spectrum of neosiphoniamolide A [**1**] could be readily assigned to a valine residue [δ 0.75 and 0.79 (3H each, d, J=6.5 Hz); 1.99 m; 4.33 (dd, J=7.0 and 8.8 Hz)] supported by decoupling experiments, which allowed the doublet at δ 6.42 (J=8.8 Hz) to be assigned to NH-Val and by the ^{13}C-nmr shifts at 18.1 (×2), 31.5, and 58.4 ppm. The above fragments identified by the nmr data accounted for the mol wt of neosiphoniamolide A [**1**]. It was apparent, therefore, that **1** was a valine analogue of geodiamolide D [**2**] (6) in which the alanyl residue is replaced in **1** by a valine residue, and what remained to be determined was the sequence. An intense nOe between the glycine NH proton resonating at δ 6.46 t and H-2 at 2.47 m revealed that the glycine was attached via an amide linkage to the polypropionate fragment. In addition, an intense nOe between the valine NH resonating at δ 6.42 d and the iodotyrosine methine signal H-12 at δ

tion and confirmed that 3-iodotyrosine had the unusual D configuration.

Neosiphoniamolide A [**1**] inhibited the growth of the fungi *Piricularia oryzae* and *Helminthosporium gramineum* with IC_{90} values of 5 ppm, but exhibited weaker activity against a panel of fungi used by Rhône-Poulenc in their in vitro primary screening search for antifungal compounds. More potent activities were exhibited by the co-occurring macrolides, the sphinxolides (see Experimental).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Nmr measurements were performed on a Bruker AMX-500 instrument interfaced with a Bruker X-32 computer. The neosiphoniamolide A [**1**] samples were prepared by dissolving 2 mg in 0.4 ml of $CDCl_3$. The optical rotation was measured on a Perkin-Elmer 141 polarimeter using a sodium lamp operating at 589 nm. Fabms were recorded in a glycerol/thioglycerol matrix in the positive-ion mode on a VG ZAB instrument (argon atoms of energy 2–6 kV). Uv spectra were obtained on a Beckmann DU 70 spectrophotometer.

ANIMAL MATERIAL.—*Neosiphonia superstes* Sollas (Demospongiae, Lithistida, Phymatellidae) was collected during the dredging campaigns (1987, 1989) of the ORSTOM-CNRS Programme "Substances Marines d'Intéret Biologique (SMIB)," in the South of New Caledonia (Banc Eponge region) at a depth of 500–515 m. Taxonomic identification was performed by Lévi and Lévi of the Museum Nationale d'Histoire Naturelle, Paris, France; reference specimens are on file at ORSTOM Centre de Nouméa (reference 1408).