

### THREE NEW NORRISOLIDE RELATED REARRANGED SPONGIANS

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**Abstract:** Three new rearranged spongian-type diterpenes have been isolated from a Red Sea *Dysidea* species. All three compounds embody the substituted hydrindane portion as in norrisolide but differ in the hydrophilic part of the molecule. Compound 2 norrlandin, possesses the 2,7-dioxa-bicyclo[3.2.1]octane system and compounds 3, seco-norrisolide B, and 4, seco-norrisolide C, different substituted  $\gamma$ -lactones.

As part of a study on *Dysidea* metabolites<sup>1,2</sup> we have isolated from a brownish *Dysidea* sp. collected near Shaag Rock, the Gulf of Suez, The Red Sea, four diterpenes, compounds 1-4 in ca. 0.4, 0.3, 0.05, 0.01% (dry wt.) respectively.

Diterpenoids which are biogenetically assumed to be rearranged spongians, have been isolated from a variety of sponges<sup>3</sup> as well as from their nudibranch predators<sup>4-6</sup>. So far most of these diterpenes were found to embody one out of three carbobicyclic portions, that is, a bicyclo[4.4.0], [4.3.0] or [5.3.0] systems, linked to a mono or bicyclic hydrophilic, oxygenated heterocyclic component<sup>#</sup>. Most of these compounds have in common, in addition to the 14-carbon lipophilic part, the same branched six-carbon unit (C(11) to C(16) in the discussed compounds) originating from rings C and D of the spongian precursors. They differ in the oxygenation state, functionalities and the manner of cyclization(s) of this six-carbon appendix.

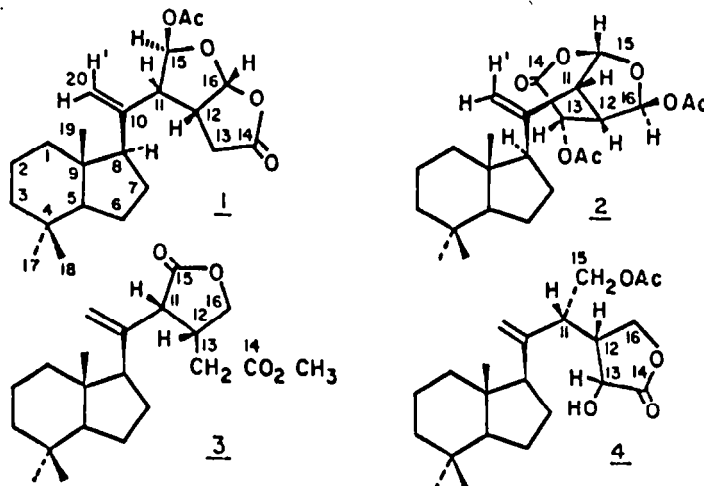


Figure 1

# The most recently reported spongialactone A<sup>7</sup> is an example for another type of spongian derived compounds in which ring A is oxygenated and transformed into a lactone.

Compounds 1-4 were obtained from the  $\text{CHCl}_3$  extract of the lyophilized sponge. The crude extract was chromatographed on silica-gel with hexane and with increasing percentage of EtOAc as eluants to yield the four compounds.

Compound 1 had the molecular formula  $\text{C}_{22}\text{H}_{32}\text{O}_5$  and its structure was determined by intensive 2D NMR experiments including COSY, one bond and long range CH-correlations as well as NOE measurements. Comparison of the spectral data of 1 with those of norrisolide<sup>5</sup>, established their identity. The above mentioned NMR studies enabled a complete  $^{13}\text{C}$  spectral assignment (Table 1) which was, in part, the basis for the structure determination of the other three compounds. Most characteristic also for the carbocyclic portion of the four compounds were the  $m/e$   $191[\text{C}_{14}\text{H}_{23}]^+$  and  $192[\text{C}_{14}\text{H}_{24}]^+$  fragments. NOE's between H-13 $\alpha$ , 15 $\alpha$  and -20' and between H-20, 20' and the methyl of the C(15) acetate group suggested that the relative conformation, in solution, of the two ring systems attached to the 10(20) double bond is the same as in the solid state (X-ray)<sup>5</sup>. Other NOE's between H-11, 12, 13, and 15 were in full agreement with the stereochemistry of norrisolide. The second compound (2) gave the molecular formula  $\text{C}_{24}\text{H}_{34}\text{O}_7$  from  $^{13}\text{C}$  NMR and mass measurements ( $m/e$  374,  $\text{M}^+$ -HOAc). Comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data for the lipophilic portion with those of 1 (Table 1, 2) indicated the presence of the same hydrindane system. IR absorptions at 1750 and  $1780\text{ cm}^{-1}$  suggested an acetate and a lactone functionality. Comprehensive  $^1\text{H}$  and  $^{13}\text{C}$  NMR studies of the oxygenated part of the molecule proposed a 2,7-dioxabicyclo[3.2.1]octane system, which was found to be identical to the heterocyclic part of macfarlandin E (= aplyviolacene) as well as shahamins I and J<sup>1</sup>. Compound 2, has therefore to be constructed from the lipophilic portion of norrisolide and the oxygenated part of macfarlandin E and it was designated norrlandin.

On the grounds of biogenetic considerations we assume that norrlandin (2) and compounds 3 and 4 possess the same relative configuration of the hydrindane portion as well as the chiral center at C-11 as in norrisolide(1). The relative configurations of the other chiral centers in the heterocyclic sites were determined relatively to C-11, in most cases independently, from NMR considerations (J-values and NOE's). As in previous cases (e.g. in case of macfarlandin E<sup>3b</sup> and the shahamins<sup>1</sup>) it could be suggested, on the basis of NOE measurements that compound 2 exists in one dominant C(10)-C(11) rotamer as shown, together with the relevant NOE's, in Figure 2.

The IR, mass and NMR spectra of compound 3 revealed the presence of the 10(20)exocyclic double bond, a methyl ester and a  $\gamma$ -lactone ( $1760\text{ cm}^{-1}$ ). As before comparison of the NMR data (Tables 1,2) confirmed the hydrindane portion of the molecule. A COSY experiment together with the measured coupling constants established unequivocally the structure of the hydrophilic portion of the molecule (Figure 1). It can be seen that one of the two heterocycles of

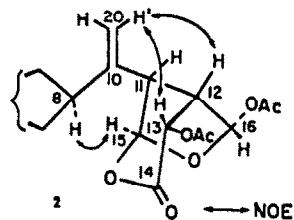


Figure 2

norrisolide (1) does not exist anymore in 3.

Compound 3, designated seco-norrisolide B is 16-deoxy-15-desacetyl-15-oxo-14,0(16)-seco-norrisolide 14-carboxylate. The cis relationship of the C(11) and C(12) substituents suggested on the grounds of biogenetic considerations agrees well with a coupling constant of 8.3Hz measured between H-11 and H-12 (a dihedral angle of ca. 0°).

The fourth isolated compound (4), obtained in minute amounts only, gave the molecular formula  $C_{22}H_{34}O_5$  from  $^{13}C$  NMR and mass measurements. The  $^{13}C$  NMR data for the non functionalized carbons of 4 were nearly identical with those of compounds 1-3 (Table 1), and hence the same hydrindane system was also inferred to 4. The IR, mass and NMR spectra revealed a secondary hydroxyl, a  $\gamma$ -lactone ( $1780\text{ cm}^{-1}$ ) and a primary acetate ( $1740\text{ cm}^{-1}$ ). A COSY experiment confirmed unequivocally the suggested  $\alpha$ -hydroxy- $\beta$ -substituted  $\gamma$ -lactone structure. From the formula of 4 (Figure 1) it can be seen that in this case the second THF ring of norrisolide stays open. Compound 4, designated seco-norrisolide C, is 15,16-dideoxy-13-hydroxy-15,16-seco-norrisolide. The stereochemistry of C-12 is tentatively suggested to be 12R\* on biogenetic considerations. A coupling constant of 10.3 Hz between H-12 and -13 suggested a trans relationship between the latter two protons.

All four compounds (1-4) have in common the same carbon backbone but differ in the manner of cyclization of the oxygenated six carbon appendix.

Compounds 1 and 2 have been shown to be cytotoxic ( $IC_{50}=1.5\mu\text{g/ml}$  and  $1.2\mu\text{g/ml}$  for 1 and 2 respectively).

#### EXPERIMENTAL

For general information see J. Org. Chem. 53, 4801 (1987). Correlations observed in the COSY experiments between  $H_i$  and  $H_j$  &  $H_m$  are given in the following manner:  $H_i$ - $H_j$ ,  $H_m$ ; etc.

The sponge specimens were collected at the southern part of the Gulf of Suez near Shaag Rock in October 1988. The samples were deep frozen immediately after collection, freeze-dried, and then extracted with ethylacetate and 10% methanol in chloroform. From the ethyl acetate extract we obtained in order of elution compounds 1,2,3,4.

Norrisolide (1): oil;  $[\alpha]_D^{25} +2.5$  (c, 0.1,  $CHCl_3$ ); IR( $CHCl_3$ ) 2950, 1780, 1760,  $1370\text{ cm}^{-1}$  mass spectra (CI), m/z (relative intensity) 316 ( $M^+$ -ACOH, 50), 192 ( $C_{14}H_{24}$ , 26), 150(20), 137(59), 123(100).  $^1H$  NMR( $C_6D_6$ )  $\delta$  4.90s, 4.78s, 1.62, 1.45(2H), 1.40(2H), 1.39, 1.38, 1.20(2H), 0.98, 0.83, 0.85(s, 3H), 0.80(s, 3H), 0.65, 0.47(s, 3H).

Norrlandin (2): oil;  $[\alpha]_D^{25} -5.4$  (c, 0.3,  $CHCl_3$ ); IR( $CHCl_3$ ) 2960, 1770, 1750, 1380, 1160,  $1000\text{ cm}^{-1}$  mass spectra (CI), m/z (relative intensity) 374 ( $M^+$ -60, 24) 341(20), 250(14), 192 ( $C_{14}H_{24}$ , 23), 191( $C_{14}H_{23}$ , 18.5), 150(25), 137(81), 136(96), 123(100).  $^1H$  NMR( $C_6D_6$ )  $\delta$  5.27(d, J=2.3), 4.98(bs), 1.94, 1.42, 1.40(2H), 1.35(2H), 1.34, 1.20(2H) 0.90, 0.89, 0.81(s, 3H), 0.78(s, 3H), 0.75, 0.47(s, 3H).

COSY measurements:  $H_{11}$ - $H_8$ ;  $H_{13}$ - $H_{11}$ ,  $H_{12}$ ,  $H_{15}$ ,  $H_{20}$ ;  $H_{15}$ - $H_{11}$ ,  $H_{12}$ ;  $H_{16}$ - $H_{11}$ ,  $H_{12}$ ;  $H_{20}$ - $H_8$ ,  $H_{11}$ ,  $H_{12}$ .

Seco-norrlandin B; (3): oil;  $[\alpha]_D^{25} +3.3$  (c, 0.15,  $CHCl_3$ ); IR( $CHCl_3$ ) 2960, 1760, 1730, 1380,  $980\text{ cm}^{-1}$  mass spectra (CI), m/z (relative intensity) 348( $M^+$ , 39), 238(12.5), 224(28),

191(13), 190(17), 150(60), 137(100).  $^1\text{H NMR}(\text{C}_6\text{D}_6)\delta$  5.02s, 4.91s, 0.85(s, 3H), 0.83(s, 3H), 0.68(s, 3H).

COSY measurements:  $\text{H}_{11}\text{-H}_{12}$ ;  $\text{H}_{12}\text{-H}_{13}$ ;  $\text{H}_{16}\text{-H}_{12}$ ,  $\text{H}_{13}$ ;  $\text{H}_{20}\text{-H}_8$ ,  $\text{H}_{11}$ ;  $\text{OCH}_3\text{-H}_{13}$ .

Seco-norrandin C(4); oil; IR( $\text{CHCl}_3$ ) 3060, 1780, 1740  $\text{cm}^{-1}$  mass spectra (CI), m/z (relative intensity) 378( $\text{M}^+$ , 12); 318(20), 194(44), 150(37), 137(63), 123(100).  $^1\text{H NMR}(\text{C}_6\text{D}_6)\delta$  4.71s, 4.59s, 2.33(ddd, J=18.5, 10.5, 8.0), 0.68(s, 3H), 0.84(s, 3H), 0.48(s, 3H). COSY measurements:  $\text{H}_{12}\text{-H}_{11}$ ;  $\text{H}_{13}\text{-H}_{12}$ ;  $\text{H}_{15}\text{-H}_{11}$ ;  $\text{H}_{16}\text{-H}_{13}$ ,  $\text{H}_{12}$ ;  $\text{H}_{20}\text{-H}_8$ .

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Table I -  $^{13}\text{C-NMR}$  Data of the Hydrindane and the Oxygenated Parts of Compounds 1-4 (in  $\text{C}_6\text{D}_6$ )

C	1	2	3	4	C	1	2	3	4
1	38.6	39.9	38.6	40.2	11	50.1	49.3	48.1	48.6
2	21.2	20.7	20.9	20.3	12	40.5	44.5	36.2	43.0
3	19.9	20.6	19.6	20.3	13	30.4	66.3	33.2	72.0
4	33.3	33.1	33.3	33.3	14	173.5	164.9	176.4	173.5
5	57.7	58.4	58.7	58.8	15	101.7	101.2	172.1	68.6
6	24.7	25.0	24.7	26.3	16	107.1	97.1	79.6	65.1
7	41.8	41.4	41.9	41.3	$\text{OCH}_3$			51.9	
8	58.7	56.1	58.0	57.2	Ac	168.5	169.2		176.1
9	45.0	43.4	44.9	44.5		20.4	19.7		20.5
10	143.5	139.9	141.0	145.5	Ac		168.5		
17	33.4	33.3	33.2	33.1			20.3		
18	20.6	19.7	20.5	19.2					
19	14.1	13.7	13.7	13.9					
20	116.8	116.7	118.6	113.7					

Table II - Partial Proton NMR Data of Compounds 1-4

H	1	2	3	4
11	2.65(dd, 9, 3, 3, 7)	3.30(bs)	3.05(d, 8, 3)	1.78(dd, 8, 6, 8, 4)
12	2.41(ddd, 10, 3, 9, 3, 4, 2)	3.05(dt, 4, 3, 1, 0)	2.65m	1.88(dt, 10, 4, 4, 5)
13 $\alpha$	2.12(dd, 8, 3, 4, 2)	6.31(d, 5, 2)	2.25(dd, 14, 0, 3, 9)	3.47(bd, 10, 3)
13 $\beta$	1.85(dd, 8, 3, 10, 3)		1.96(dd, 14, 0, 8, 1)	
15	6.63(d, 3, 7)	5.82(dd, 3, 0, 1, 0)	-	4.34(dd, 11, 3, 6, 4)
16	5.68(d, 5, 9)	6.90s	3.86(dd, 9, 7, 6, 1)	3.96(dd, 11, 3, 4, 2)
			3.68(dd, 9, 7, 3, 9)	3.86(dd, 9, 3, 8, 0)
$\text{OCH}_3$			3.25s	3.18(dd, 9, 3, 10, 7)
Ac	1.62s	1.64s 1.50s		1.69s

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