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NEW ALKYLATED SCALARINS FROM THE SPONGE DYSIDEA HERBACEA

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Abstract

Six new biogenetically interesting alkylated scalarins, scalardysin-A and B, scalarherbacin-A and B and the latter's acetates were isolated from Dysidea-herbacea. Structures are suggested for the various compounds based on their spectral data.

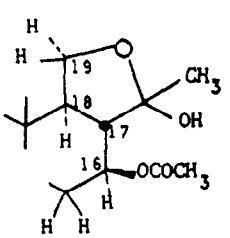
The scalarins are tetracarbocyclic sesterterpens which were isolated from several sponges[1]. Heteronemin for example, is one of this group members which was isolated from Heteronema erecta (Inodes erecta), collected either in Australia[2] or in the Gulf of Eilat (Red Sea)[3]. Recently, from the same sponge, we have also isolated small amounts of another compound of the scalarins namely, scalaradial[1] (one or more isomers, vide infra)[4].

This report describes the structure of several new compounds, closely related to the scalarins, which were isolated from the sponge Dysidea herbacea (Keller) collected in the Gulf of Suez (Red Sea).

The extraction of the freeze-dried sponge (petrol ether 1.6% dry weight) and subsequent repeated chromatographies (LH-20 and Silica gel) gave, among other materials, 3 pairs of compounds named in order of polarity scalardysin-A and B, scalarherbacin-A and B and scalarherbacin-A and B acetates (1, 2, 3a, 4a and 3b, 4b respectively)[5].

The mass and ^{1}H-NMR spectra[6] showed clearly that each pair consists of two homologues possessing exactly the same functionalities, differing in the methyls. Partial separation between the two homologues was achieved on a RP-18 reverse-phase HPLC column (up to ca. 80% enrichment of each one of the counterparts) or on a reverse-phase TLC plate[7]. The spectral properties of the first pair (1 & 2) indicated the presence of a ketone (ν_{max}1700 cm^{-1}), an acetate (ν_{max}1730 cm^{-1}) and a tert. hydroxyl group (ν_{max}3400 cm^{-1}, no CHOH was observable in the ^{1}H-NMR spectrum neither does the pair undergo acetylation). According to the ^{13}C-NMR spectrum (δ,$CDCl_3$, 22.63 MHz) which confirmed the CO(δ214.7), and the acetate (δ170.4 and 21.2) three additional oxygen bearing carbons do exist in 1 & 2: δ72.3d(C-16), 67.4t(C-19) and 101.8s(C-20). The low field resonance of the last carbon is characteristic for a ketal (or acetal), a group which was further supported by the δ1.44 singlet attributed to a O-C(CH$_3$) OH group. The mutual position of the various functional groups in 1 (and 2) as well as the stereochemistry of C-16, 17 and 18, was determined on the basis of the ^{1}H-NMR spectrum to be[8]:

H-16	δ	4.84 dt	(J=5.5 and 11 Hz)
H-17	δ	1.97 m	(J=10 and 11 Hz)
H-18	δ	2.36 brq	(J=10 Hz)
H-19	δ	3.61 t	(J=10 Hz)[1b]
H-19'	δ	4.41 t	(J=10 Hz)



The only differences between the ^{1}H-NMR spectra of 1 and 2 are in the methyl group signals:

CH_3	21	22	23	24	25	26	27
1(R=Me)	0.81	0.85	0.80	1.13	1.04	1.44	—
2(R=Et)	——	0.87	0.80	1.13	1.04	1.44	0.74t (J=6.9)
Heteronemin	0.82	0.88	0.80	1.15	1.00	12-oxo-scalarin derivative.	

From these δ values it is clear that one of compound's 1 methyls (δ0.81) is replaced by an ethyl in 2 (δ0.74t J=6.9Hz). While the ^{1}H-NMR data was most informative concerning the functionalities, the mass spectrum of 1 suggested the existence of the scalarins' AB ring system in this molecule (m/e 191, $C_{14}H_{23}^+$, 12%)[9]. In compound 2, on the other hand, the m/e 191 fragment was missing, and instead a similar fragment in intensity appeared at m/e 205 ($C_{15}H_{25}^+$, 15%) pointing on the same AB ring system except that one of the methyls was replaced by an ethyl group.

The above data together with the ^{13}C-NMR values vide infra, suggested for scalardysin-A and B (1 and 2) the same tetracarbocyclic skeleton as in the scalarins.

The location of the extra carbonyl function which, according to the above data, must be in ring C has to be at C-12 for the following reasons:

a) An α-to-carbonyl proton seen in the ^{1}H-NMR of 1 (and 2) at δ2.58t (J=13 Hz) is the A part of an ABX system, the X part appearing at δ2.32brdd (J=13 and 3 Hz). Only a 12-keto group can explain such an ABX system, furthermore the $J_{9,11}$ value of 13 Hz defines the stereochemistry at C-9 (see fig. 1).

b) The chemical shifts of the C_8-Me (24) and C_{13}-Me (25) at δ1.13 and 1.04 ppm respectively, are in good agreement with the expected values according to a 12-keto model compound[1b]. As for the Me/Et replacing site, C-4 seems to be the preferred choice[10].

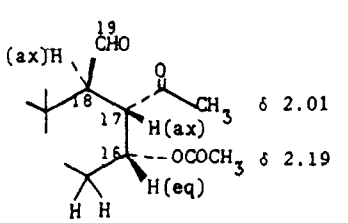
The differences observed in the high field region of the ^{1}H-NMR spectra of 1 and 2 are in two of compounds' 1 Me-signals, meaning that the 0.81s resonance line disappears (the 0.80s remains unchanged) and the 0.85s is most likely the one to be shifted to δ0.87 in 2, the fact that two Me-signals change, prefer C-4 to C-10[11]. An all trans-anti-trans stereochemistry is suggested for 1 and 2, as well as for the two other pairs discussed below, based on the good agreement found while comparing the chemical shifts of rings' A-C carbon atoms, of these compounds, with those of the hither-to known scalarins[12].

Formally, compounds 1 and 2 can be looked at as scalarins which underwent methylations at the methyl group of one or two of the terminal isoprenoid units respectively. Whether such a methylation occurs before or after ring cyclisation cannot be determined yet.

The two other isolated pairs of compounds (3a, 4a and 3b, 4b) are closely related to each other; 3b and 4b being the acetylation products of 3a and 4a respectively[13].

The IR, ^{1}H-NMR and ^{13}C-NMR data suggest for the crystalline pair 3a, 4a the following functional groups[14]: a secondary alcohol (the one which underwent acetylation to give 3b and 4b), a secondary acetate, an aldehyde and a methyl ketone (confirmed by a positive iodoform test) in the following sequence[8]:

H-16 δ 5.62q (J≈2 Hz) C-16 δ 72.3
H-17 δ 3.13dd (J=10.8 and 2.7 Hz)
H-18 δ 3.54brd (J=10.8 Hz)
H-19 δ 9.75d (J=2 Hz) C-19 δ 205.8
C-20 δ 205.7



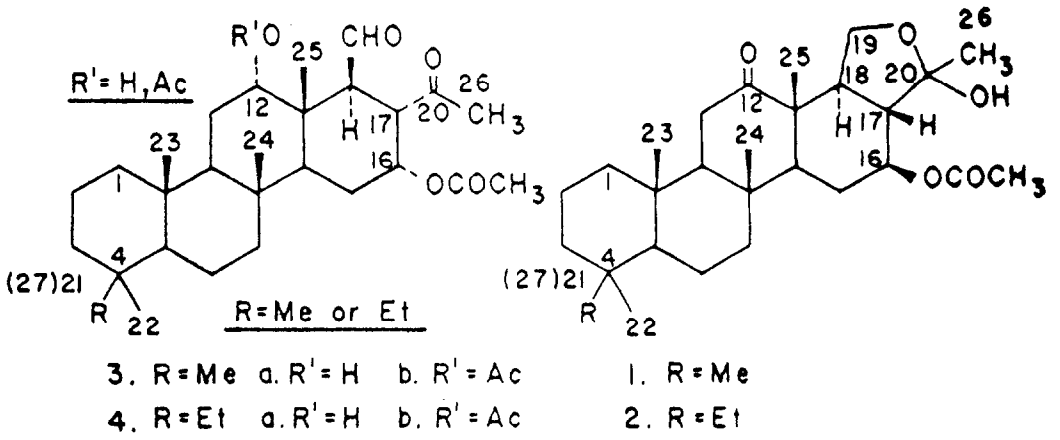


Figure 1

In similar arguments to theones applied in the structure elucidation of 1 and 2, the scalarin skeleton is also suggested for scalarherbacin-A and B (3 and 4) (see Fig. 1)[11]. In the absence of the 12-keto group in the latter compounds, all the methyls contract to a narrow range (0.81 - 0.87) thus avoiding, as yet, conclusions about the ethyl location which is suggested to be at C-4 on biogenetic reasons only.

Compounds 3 and 4 can easily undergo epimerization at C-17 and 18, nevertheless they do not seem to be artifacts as their specific proton signals appear already in the ^{1}H-NMR spectrum of the crude extract.

However, other epimers do also exist, as was the case with the above mentioned scalaradial. It is interesting to note the absence of the above compounds from Dysidea herbacea collected at other places over the world[15]. However, in Dysidea pallescens was found a scalarin derivative named dysidenin[1a]. Dysidenin is an arylation product of scalarin or one of its precursors. However, as a phenol group is involved in this case, another biogenesis can be suggested, which differs from the one leading to the above compounds.

We are presently working on the structure elucidation of minor compounds which are found in the sponge.

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References and Notes

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2. R. Kazlauskas, P.T. Murphy, R.J. Quinn and R.J. Wells, Tetrahedron Letters, 2631(1976).

3. Y. Kashman and A. Rudi, Tetrahedron 33, 2997 (1977).

4. Long chain amides of α-methylene-β-alanine methyl ester, were also isolated from Heteronema erecta; see Y. Kashman, L. Fishelson and I. Neeman, Tetrahedron 29, 3655(1973).

5. TLC was performed on silica gel with: a) toluene-ethyl acetate 1:1 and b) ether, as eluents.

6. The ^{1}H-NMR spectra were recorded on a Bruker 270 MHz instrument. δ-values ($CDCl_3$) are in ppm from TMS.

7. The RP-18 reverse phase TLC plate was eluted with acetonitrile (Rf=0.27 and 0.35 for 2 and 1 respectively); although both compounds are crystalline, their m.p. and α_D are meaningless as 1 and 2 were obtained only in ca. 80% purity.

8. The vicinity of the various protons was confirmed by a double irradiation experiment.

9. Other significant fragments in the mass spectrum are: m/e 382 (M^+-H_2O-HOAc, 30%), 147 (31%), 148 (20%), 149 (18%) - resulting from rings D and E, and 123 ($C_9H_{15}^+$, -ring A, 17%). The corresponding fragments in the spectrum of 2 are found to be shifted by 14 m.u.

10. Methyls 24 and 25 were excluded both because of their δ-values (discussed before); Methyl 23 however, has to be considered.

11. Similar conclusions could be arrived at, according to the ^{13}C-NMR data however, because the individual scalardysins were only 80% pure the data was not completely unambiguous.

12. The angular carbon atoms serve particularly as good stereochemical probes, see discussions in references 1b and 3; δ(C): 56.5(5),37.7(10),36.4(8),58.6(9),38.2(13),47.5(14)±0.3 ppm.

13. Acetylation of pair 3a, 4a with Ac_2O/Pyridine at r.t. over night yielded compounds 3b and 4b, respectively. The H-12 signal of 3b & 4b appearing at δ4.95 brs is the only one to be shifted

14. The m.p. and α_D are meaningless as we dealt with only ca 80% pure compounds (each one mixed with its counterpart); $\nu_{max}^{CHCl_3}$ 3500,1735 and 1710cm^{-1}, m/e(CI) 475(12%) for 3a and 461(10%) for 4a ($M+1^+$).

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