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APLYSINOPSIN, A NEW TRYPTOPHAN DERIVATIVE FROM A SPONGE

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We have previously reported the occurrence of two sesterterpene lactones (1 and 2) from two species of the sponge genus *Thorecta*[1]. Investigation of eight further species of this diffuse Indo-Pacific genus has revealed five species which do not elaborate sesterterpenes but contain the tryptophan derivative 3, for which we suggest the name aplysinopsin, as a major secondary metabolite.

Percolation of a freeze-dried sponge collection (nominally *Thorecta* sp.), collected on the Australian Great Barrier Reef, with dichloromethane followed by methanol produced a brownish yellow methanol extract which was fractionated on Sephadex LH20 to give the major metabolite 3 mp 232 - 233° as fine yellow needles from methanol λ_{max} (MeOH) 387 nm (ε 20,600); ν_{max} 3290, 1700, 1625 cm^{-1}. The same extraction procedure carried out under Soxhlet conditions produced a methanolic extract which gave 3 and a new compound 4 (probably an artefact) as the major products.

High resolution m.s. of 3 established the formula $C_{14}H_{14}N_4O$ with major fragment ions at m/e 169 and 155 whereas that of 4 indicated the molecular formula $C_{14}H_{13}N_3O_2$ with the same major fragment ions.

The 100 MHz ^1H n.m.r. spectra of both 3 and 4 were almost identical and 3 showed the following resonances ($DMSOd_6$):- δ11.45 (1H,bs,D_2O exchangeable), 8.75 (1H,bs), 7.87 (1H,m), 7.46 (1H,m), 7.30 - 7.00 (2H,m), 6.47 (1H,s), 4.2 - 3.2 (bs,D_2O exchangeable), 3.28 (3H,s) and 3.09 (3H,s). Zinc-acetic acid reduction of either 3 or 4 gave a mixture of products including *ca.* 10% 3-methylindole 5 which was probably produced from reduction of indole-3-aldehyde 6 formed by a retro-aldol of a compound incorporating the partial structure 7. The ^1H n.m.r. and u.v. spectra of 3 and 4 also supported this partial structure. The major m.s. spectral fragments at m/e 169 ($C_{11}H_9N_2$) and 155 ($C_{10}H_7N_2$) in both 3 and 4 could be rationalised as ions 8 and 9 and thus formulae 3 and 4 could be written.

Aplysinopsin (3) formed a diacetate mp 217 - 220° on acetylation with acetic anhydride-pyridine whereas 4 produced a monoacetate subliming at 220°. Reduction of the acetate of 4 with zinc-acetic acid gave a mixture of three products, 10, 11 and 12, in a ratio of 9 : 3.5 : 1, which was readily separated by p.l.c. The major product 10 was a gum. The structure followed from spectroscopic data (^{1}H n.m.r. ($CDCl_3$):- δ8.32 (1H,bd,J=7.5Hz), 7.60 - 6.94 (3H,m), 5.68 (1H,d of t, J=9, 3Hz), 4.86 (2H,m,J=16, 3Hz), 4.53 (1H,d, J=9Hz), 3.03 (3H,s), 2.97 (3H,s), 2.24 (3H,bs)) and the spontaneous conversion to the thermodynamically more stable isomer 12, the minor product of the reduction, with a half-life of *ca.* 14 days. The structure of the third product of the reduction 11 mp 190 - 191° was established by spectroscopic means and also a single crystal X-ray structure determination[2].

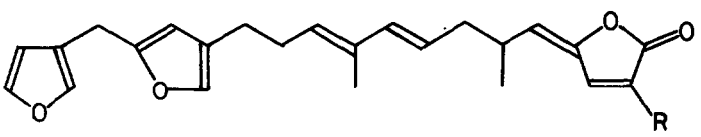
The structure 3 for aplysinopsin was confirmed by synthesis. Condensation of 6 with the creatinin derivative 13[3] in piperidine or sodium acetate-acetic acid gave 3 in good yield identical in all respects with the natural product. The alternative isomer formed by condensation of 6 and 14[3] gave 15 which was not identical with 3. 270 MHz ^{1}H n.m.r. suggested that natural and synthetic 3 exist as a mixture of double bond isomers (*ca.* 9:1) but the major isomer has not been elucidated[4].

Mass spectral data on crude natural 3 indicated the presence of a monobromo-analogue (*ca.* 5%) but attempts to separate this compound have failed.

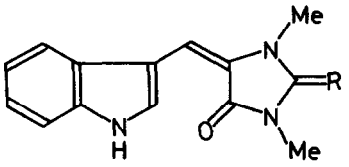
The genus *Thorecta* is a diffuse genus and many species have been incorporated. Lendenfeld[5] erected two genera, *Thorecta* and *Aplysinopsis*. The sponges which yielded aplysinopsin 3 fit Lendenfeld's description of *Aplysinopsis*, whereas three species which have yielded sesterterpenes 1 and 2 are more compatible with Lendenfeld's description of the genus *Thorecta*.

The occurrence of sesterterpenes (eg. 1 and 2) could prove to be chemotaxonomic markers for the genus *Thorecta*, whereas 3 has been detected in all species of *Aplysinopsis* studied to date.

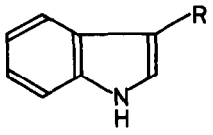
Recently 3 has been isolated from *Verongia spengelii*[6].



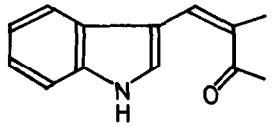
(1) R = Me
(2) R = CH_2OH



(3) R = NH
(4) R = O



(5) R = Me
(6) R = CHO



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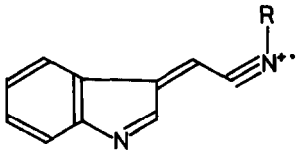
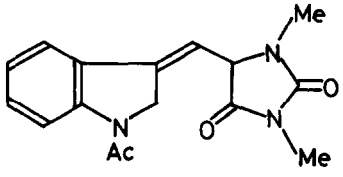


(8) R = Me
(9) R = H



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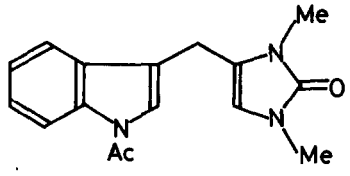

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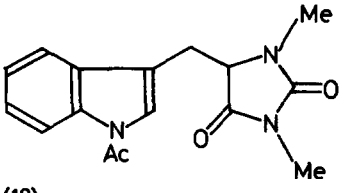

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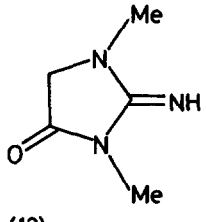

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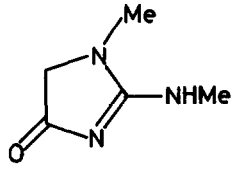

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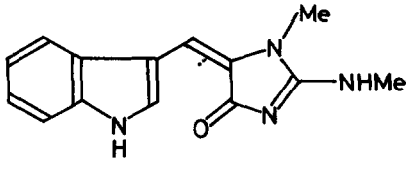

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REFERENCES

1. R. Kazlauskas, P.T. Murphy, R.J. Quinn and R.J. Wells, *Tetrahedron Letters*, 2635 (1976).

2. P. Schoenholzer, personal communication.

3. G.L. Kenyon and G.L. Rowley, *J. Amer. Chem. Soc.*, 93, 5552 (1971).

4. G. Englert, personal communication.

5. R. von Lendenfeld, "A Monograph of the Horny Sponges", Trübner and Co., London 1889.

6. F.J. Schmitz, personal communication. We thank Dr. Schmitz for prior communication of his results.