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A DIKETOPIPERAZINE DERIVED FROM TRICHLOROLEUCINE FROM THE SPONGE DYSIDEA HERBACEA

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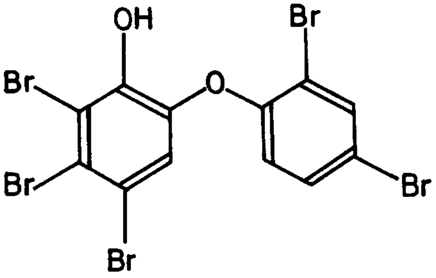
Dysidea herbacea is a Dictyoceratid sponge which is common throughout the Indo-Pacific region. Previous studies[1-3] have shown that the secondary metabolites derived from various collections of this sponge are diverse, ranging from polybromodiphenyl ethers, of which (1) is an example[1], to compounds derived from amino-acids and containing trichloromethyl-groups. Two examples dysidin (2) and dysidenin (3) have recently been reported[2,3]. We now report a further variant of this sponge, collected near Gladstone, Queensland, Australia, which has yielded a diketopiperazine derivative (4) of an N-methyltrichloroleucine.

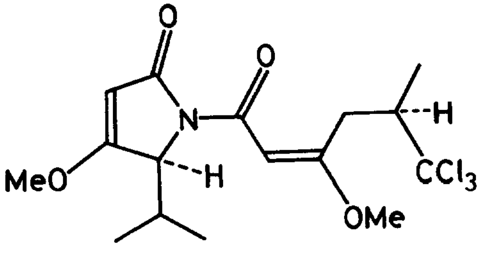
Extraction of a small freeze dried sample of D. herbacea with CH_2Cl_2 followed by p.l.c. separation of the extract on silica gel (CH_2Cl_2/EtOAc: 4/1) yielded (4) m.p. 106-107°, $[\alpha]_D^{20}$ -144° (c=0.5, $CHCl_3$) in 1% yield. The formula $C_{14}H_{18}Cl_6N_2O_2$ was established by high resolution mass spectrometry and the presence of two trichloro-methyl groups in the molecule was indicated by the ^{13}C n.m.r. spectrum which showed two singlets at 105.0 and 104.1 typical of this grouping[2,3]. The remainder of the ^{13}C n.m.r. consisted of resonances at 165.4 (2) and 159.7 (s) (2 x O=$\underline{C}$-N-); 131.6 (s) and 123.7 (d) (-CH=C-); 61.9 (d), 51.5 (d, 2C), 37.7 (t), 33.8 (q), 31.2 (q), 18.4 (q) and 17.6 (q). Compound (4) was therefore monocyclic with two carbonyl groups and one trisubstituted double bond.

The ^1H n.m.r. spectra of (4) in $CDCl_3$ and C_6D_6 is shown in Table 1. Extensive decoupling suggested partial structures (5) and (6) and the presence of two -N-Me singlets, together with i.r. and ^{13}C n.m.r. data, indicated the presence of two -CO-N-Me groups. The diketopiperazine structure (4) best fitted these data and the stereochemistry about the double bond was deduced from the unusually low field position of the C4 proton in the ^1H n.m.r. spectrum of (4) and (7) (see below), due to deshielding by the amide carbonyl group.

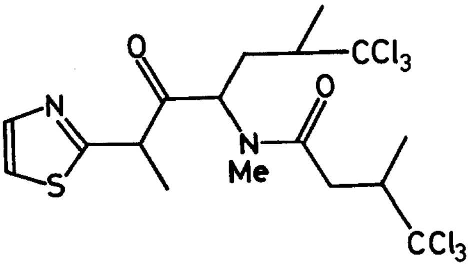
Reduction of (4) with zinc-acetic acid gave the dechlorinated analogue (7), m.p. 99-100° $[\alpha]_D^{20}$ -86° (c=0.5, $CHCl_3$), the ^1H n.m.r. spectrum of which (Table 1) was entirely consistent with the proposed structure. The mass spectrum showed a molecular ion at m/e 252 with the major fragment ion at m/e 195 (100%; $M^+-C_4H_9$). Hydrogenation of (7) gave the single optically active compound (8) m.p. 90-95° $[\alpha]_D^{20}$ +60° (c=0.6, $CHCl_3$).



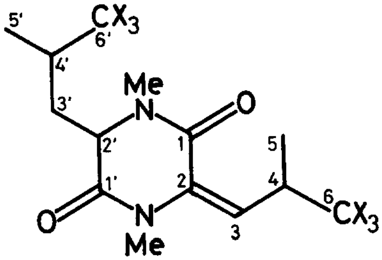
(1)



(2)

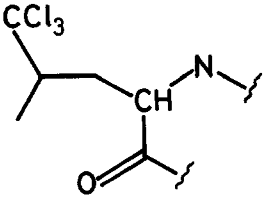


(3)

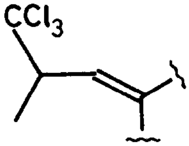


(4) X = Cl

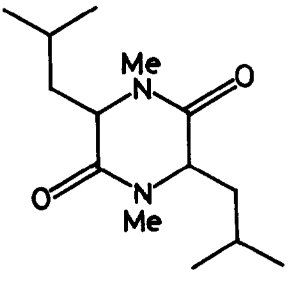
(7) X = H



(5)



(6)



(8)

The extreme variability of the secondary metabolites of *D. herbacea* is curious, particularly in view of the nature of these metabolites. The presence of either polybrominated diphenyl ethers[1] or polychlorinated amino acid derivatives[2,3] has been documented and the biosynthetic origin of both these classes of compounds contrasts markedly with isolates, usually terpenoid, reported from other members of the sponge Family Dysidideae.

A microscopic examination of various forms of *D. herbacea*, which is by habit a thin encrusting sponge, has revealed the presence of blue-green algae, at times representing half the cellular weight of the sample[4]. Amino acid derived metabolites have been reported from blue-green algae and the diverse secondary metabolites obtained from separate collections of *D. herbacea* are most readily rationalised as arising from different blue-green algal symbionts.

TABLE 1

Chemical shifts and coupling constants of the diketopiperazine (4) and some derivatives

	(4):- $CDCl_3$	(4):- benzene-d_6	(7):- benzene-d_6	(8):- CCl_4
C2'-H	4.04,1H,dd		3.62,1H,dd,J6,6Hz	2.70,2H,dd,J6,8Hz(+C2-H)
C3 -H	5.69,1H,d,J9Hz		5.00,1H,d,J9Hz	
C3'-H_A	1.76,1H,m	1.54,1H,m	1.44,2H,m	1.6,4H,m
C3'-H_B	2.47,1H,m	2.36,1H,m		
C4 -H	5.18,1H,dq,J6,9Hz	5.50,2H,m	3.96,H,m	1.9,2H,m
C4'-H	2.70,1H,m	2.64,1H,m	1.70,1H,m	
C5 -H	1.38,6H,d,J6Hz	1.12,3H,d,J6Hz	0.94,3H,d,J6Hz	0.98,6H,d,J6Hz
C5'-H		1.31,3H,d,J6Hz	0.69,3H,d,J6Hz	
C6 -H			1.15,3H,d,J6Hz	1.02,6H,d,J6Hz
C6'-H			0.79,3H,d,J6Hz	
N-CH_3	3.08,3H,s	2.56,3H,s	2.59,3H,s	2.96,6H,s
N-CH_3	3.22,3H,s	2.82,3H,s	2.78,3H,s	

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