Colpol, a New Cytotoxic C-C-C Metabolite from the Alga Colpomenia sinuosa

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COLPOL, A NEW CYTOTOXIC C_6-C_4-C_6 METABOLITE FROM THE ALGA *COLPOMENIA SINUOSA*

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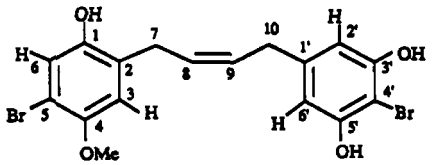
ABSTRACT.—A new dibromo C_6-C_4-C_6 metabolite **1** from the Red Sea alga *Colpomenia sinuosa* has been isolated. The structure was elucidated based on mass and nmr spectroscopic methods.

As part of our continuing search for biologically active secondary metabolites from marine sources (1) we have isolated a novel cytotoxic dibromo metabolite **1** from the alga *Colpomenia sinuosa* Derbes and Solier (order Punctariales, family Scytosiphonaceae). Bioactivity-directed fractionation of the MeOH-CH_2Cl_2 (1:1) extract of this alga, using Sephadex LH-20 cc and silica vlc, afforded pure **1** which was responsible for the cytotoxicity of the crude extract (IC_{50} 20 μg/ml). The structure of the new metabolite **1**, designated colpol, was determined by its 1D and 2D nmr and ms as well as its chemical transformation to its dihydro derivative **2**.

Dcims provided *m/z* 443, 445, 447 (1:2:1, 100%, $[MH]^+$) in the positive mode and 521, 523, 525, 527 (1:3:3:1, 45%, $[M+Br]^-$) and 442, 444, 446 (1:2:1, 100%, $[M]^-$) in the negative mode for $C_{17}H_{16}Br_2O_4$. The ^1H- and ^{13}C-nmr spectra (Table 1) suggested **1** to be a substituted 1,4-diphenylbut-2-ene. The ^1H- and ^{13}C-nmr line assignment based on the δ_c values and mainly HMQC, HMBC, and nOe measurements is given in Table 1. The three phenolic groups were confirmed by microacetylation of **1** to its three-acetate derivative [δ_H 7.24 s (1H), 6.87 s (2H), 6.69 s (1H), 2.35 s (6H), and 2.27 s (3H)].



1
2 8,9-dihydro

Hydrogenation of colpol [**1**] gave the expected 8,9-dihydro-derivative **2**. The mass spectrum of **2** confirmed unequivocally the suggested structure: the eims gave the molecular ion as the parent peak, *m/z* 444, 446, 448 (1:2:1, 100%), the two benzylic ends of the molecule, *m/z* 201, 203 (1:1, 17%, $C_7H_6O_2Br$, C-1′–C-6′, C-10), and *m/z* 215, 217 (1:1, 20%, $C_8H_8O_2Br$, C-1–C-7) as well as 366, 368 (1:1, 42%, $[M-Br]^+$), 136 (20%, $C_8H_8O_2$) and 124 (34%, $C_7H_6O_2$).

Colpol was found to exhibit in vitro cytotoxicity towards P388, A549, HT-29, and CV-1 tumor cells, with IC_{50}'s of 10 μg/ml for all four.

Biogenetically, colpol belongs to the rare C_6-C_4-C_6 natural products (2,3). Whether it is a polyketide or of a mixed polyketide-shikimate origin has to be proven. To the best of our knowledge, colpol is the first reported dibromodiphenylbutane marine product, and it represents a new class of compounds (4).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—*C. sinuosa* was collected in April 1992 in the Gulf of Eilat. A specimen is deposited at the Aquarium of Eilat, Israel.

Colpol [**1**].—The MeOH-CH_2Cl_2 (1:1) extract of *C. sinuosa* (250 g dry wt) in aqueous MeOH was successively partitioned between hexane, CCl_4, $CHCl_3$, and EtOAc. The latter extract (150 mg)

TABLE 1. Nmr Data of Colpol [**1**] in Me_2CO-d_6.[a]

Position	δ_c	δ_H	HMBC correlation	nOe's (%)
1	150.9 s		H-3, H-6	
2	129.2 s		H-7, H-6	
3	115.8 d	6.84 s	H-7	H-8 (0.8), H-7 (0.8), OMe (2.4)
4	151.1 s		H-7, OMe	
5	109.6 s		H-6, H-3	
6	120.9 d	7.05 s	H-3	1-OH (0.5)
7	29.0 t	3.45 dd (7,1.5)[c]	H-8, H-9	H-3 (3.5), H-9 (3)
8	130.1 d	5.69 dtt (10.5,7,1.5)		H-3 (0.9), H-2′ (−)[b], H-7 (1.5), 1-OH (0.4)
9	130.0 d	5.62 dtt (10.5,7,1.5)		H-2′ (0.8), H-10 (0.7)
10	34.2 t	3.40 dd (7,1.5)	H-9, H-8, H-6′	H-3 (1), H-2′ (3), H-8 (1.4)
4-OMe	57.7 q	3.75 s		H-3 (6)
1′	143.2 s		H-10, H-9	
2′	109.1 d	6.44 s		H-7 (0.3), H-9 (1.1), H-10 (1.8), 3′- OH (3)
3′	156.7 s		H-2′, H-6′	
4′	97.2 s		H-2′, H-6′	
5′	156.7 s		H-2′, H-6′	
6′	109.1 d	6.44 s		
1-*OH*		8.40		H-6 (4.5), H-2′ (4.5)[c]
3′- *OH*		8.59		
5′- *OH*		8.59		

[a]The nmr spectra were recorded on a Bruker ARX 500 MHz instrument. Chemical shifts are in δ (ppm). *J* values reported in Hz.

[b](−) is a negative nOe.

[c]Due to the exchange between the phenolic protons, the same nOe's were observed from 1-O*H* or 3′-,5′-O*H* irradiations.

contained crude **1**. Sephadex LH-20 chromatography eluted with hexane-MeOH-EtOAc (2:1:1) followed by silica vlc [hexane-EtOAc (7:3)] afforded pure **1** (12 mg) as the only metabolite obtained in large enough quantities for structure determination: hrcims 444.9460 (calcd for $C_{17}H_{16}Br^{79}Br^{81}O_4$ 444.9468); optically inactive glass; ν max ($CHCl_3$) 3424, 3017, 2952, 1592, 1499, 1443, 1401, 1200, 1040 cm^{-1}; λ max (MeOH) 216 (4200), 298 nm (800); ^1H and ^{13}C nmr see Table 1.

Dihydrocolpol [**2**].—Colpol (2 mg) in EtOH was hydrogenated at 30 psi over Pt for 2 h. Evaporation gave the dihydro derivative **2**: an oil; cims *m/z* 446 (100%), 366, 368 (42%), 202, 204 (17%), 215, 217 (20%), 136 (20%), 124 (34%); ^1H nmr ($CDCl_3$) 6.97 s (1H), 6.65 s (1H), 6.44 s (2H), 3.62 s (OMe), 2.55 m (2H), 2.10 m (2H), 1.62 m (4H).

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