

3,5-Dibromo-2-methoxybenzoic acid from sea sponge *Didiscus sp.*

N. K. Utkina,^a S. A. Fedoreyev,^a S. G. Ilyin,^{a*} and M. Yu. Antipin^b

^aPacific Institute of Bioorganic Chemistry, Far Eastern Branch of the Russian Academy of Sciences, 159 prosp. 100-letya Vladivostoka, 690022 Vladivostok, Russian Federation.

Fax: +7 (423 2) 31 4050. E-mail: utkina@piboc.marine.su

^bA. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation.

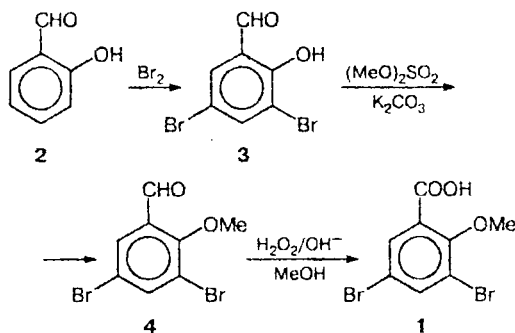
Fax: +7 (095) 135 5085

3,5-Dibromo-2-methoxybenzoic acid was isolated from sea sponge *Didiscus sp.* The structure of the title compound was established by spectral methods, by X-ray diffraction analysis, and by comparing with a synthetic sample prepared from salicylaldehyde.

Key words: sea sponge *Didiscus sp.*; 3,5-dibromo-2-methoxybenzoic acid; crystal and molecular structure; synthesis.

Sea sponges serve as a source of a large number of compounds with various structures.¹ When studying antioxidants of sea sponges, we isolated sesquiterpenophenols, namely, (+)-curcuphenol and (+)-curcudiol, from sea sponge *Didiscus sp.*² When studying an alcohol extract from this sponge, we isolated 3,5-dibromo-2-methoxybenzoic acid (**1**), which has not been detected previously in natural sources.

The molecular ion peaks in the mass spectrum of compound **1** (M^+ 308, 310, and 312) indicate that molecule **1** contains two bromine atoms. The IR spectrum of **1** has absorption bands of the carboxyl group at 1676 cm^{-1} (C=O) and 3068 cm^{-1} (OH). Analysis of the ^1H NMR spectrum demonstrated that compound **1** contains the methoxyl group and two aromatic protons (the spin-spin coupling constant is 2.4 Hz). Therefore, the structure of compound **1** is based on the 1,2,3,5-tetra-substituted aromatic ring. The arrangement of the substituents in the aromatic nucleus was established from the analysis of the ^{13}C NMR spectrum and was confirmed by the synthesis. Compound **1** was synthesized according to the following scheme:



Bromination of salicylaldehyde (**2**) afforded 3,5-dibromosalicylaldehyde (**3**). Methylation of **3** followed by oxidation of **4** with a 30% H_2O_2 solution in an alkaline medium in MeOH gave acid **1** in good yield. The spectral and physicochemical characteristics of the natural compound are identical to the corresponding parameters of the synthetic sample.

Single crystals of compound **1**, which were grown from a solution of the natural compound in CHCl_3 , were independently studied by X-ray diffraction analysis. In the crystal, molecules **1** are linked in centrosymmetric planar dimers through $\text{OH}\cdots\text{O}$ hydrogen bonds (Fig. 1). The distance between the oxygen atoms involved in the intermolecular hydrogen bond is $2.63(1)\text{ \AA}$.

Experimental

The IR spectra were recorded on a Specord-75 IR spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained on a Bruker WM-250 spectrometer with SiMe_4 as the internal standard. The mass spectra were measured on an LKB-9000S spectrometer with direct introduction of the sample into the ion source; the ionizing voltage was 70 eV.

Extraction and chromatography. Lyophilized sea sponge *Didiscus sp.* (120 g) was extracted successively with CHCl_3 and EtOH. The alcohol extract was concentrated. The resulting extract (1 g) was chromatographed on silica gel and then on Sephadex LH-20 using a 6 : 1 CHCl_3 —MeOH mixture as the solvent. TLC was carried out on Silufol plates using the same system of solvents. The chromatographic fractions containing compound **1** were concentrated and crystallized from EtOH (the yield was 40 mg).

Compound 1, m.p. 196–198 °C (EtOH). R_f 0.25. IR (KBr), ν/cm^{-1} : 1676 (C=O); 3068 (OH). ^1H NMR (DMSO- d_6). δ : 8.09 (d, 1 H, H-6, $J = 2.4$ Hz), 7.83 (d, 1 H, H-4, $J = 2.4$ Hz), 3.82 (s, 3 H, OMe). ^{13}C NMR (DMSO- d_6). δ : 164.6

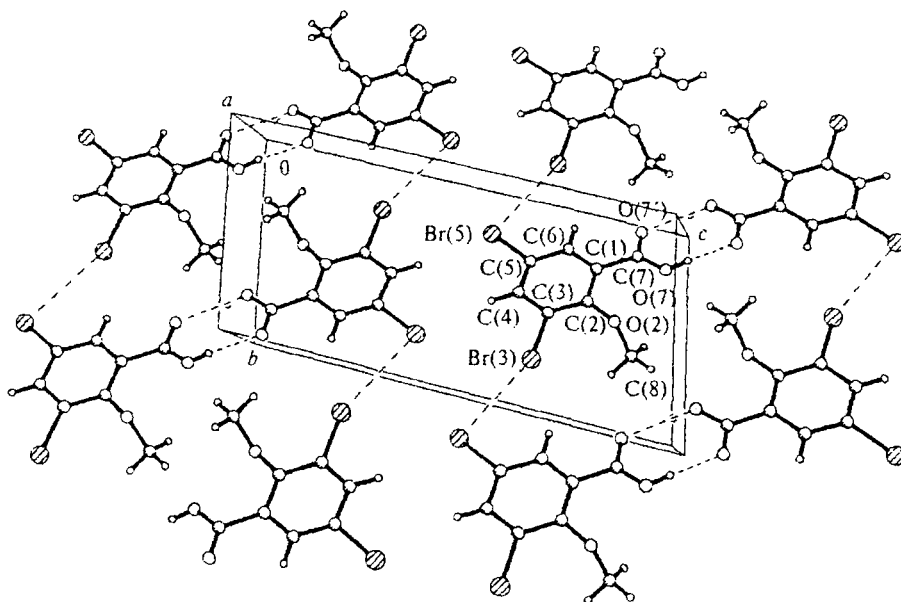


Fig. 1. The fragment of the crystal packing of compound 1. Hydrogen bonds and Br...Br contacts are indicated by dashed lines.

(s, CO), 154.8 (s, C-2), 137.7 (d, C-4), 132.3 (d, C-6), 129.3 (s, C-1), 119.1 (s, C-5), 115.8 (s, C-3), 61.6 (q, Me). MS, m/z : 308, 310, 312 [M^+].

Crystallographic data for compound 1, $C_9H_6O_3Br_2$, $M = 309.95$: $a = 4.061(4)$, $b = 7.412(7)$, $c = 15.943(16)$ Å; $\alpha = 76.56(8)$, $\beta = 88.67(8)$, $\gamma = 89.40(8)^\circ$; triclinic system, space group $P\bar{1}$; $V = 466(1)$ Å³; $Z = 2$; $d_{\text{calc}} = 2.206$ g cm⁻³; $F(000) = 296$; $\mu_{\text{Mo}} = 8.66$ mm⁻¹.

Crystals suitable for X-ray diffraction study were prepared from a solution in $CHCl_3$. The X-ray data were collected on a four-circle Siemens P3/PC diffractometer at -20°C using the $\theta/2\theta$ scanning technique to $2\theta = 50^\circ$ (graphite monochromator, Mo-K α radiation, $\lambda = 0.71073$ Å). A total of 1946 independent reflections were measured of which 1345 reflections with $I > 2\sigma(I)$ were used in the refinement. Corrections for the Lorentz and polarization factors and for absorption were applied.³ The structure was solved by the direct method and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms using the weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0002P)^2]$, where $P = (\max(F_o^2) + 2F_c^2)/3$. The positions of the hydrogen atoms of the hydroxyl and methyl groups were located from the difference synthesis and refined using restrictions imposed on the bond lengths and bond angles. The hydrogen atoms of the remaining groups were introduced in geometrically calculated positions. The refinement converged to the following R factors: $R = 0.076$ and $wR_2 = 0.155$. All calculations were carried out using the SHELX-86 and SHELXL-93 program packages.^{4,5} The coordinates of the nonhydrogen atoms and their equivalent isotropic thermal parameters are given in Table 1.

The bond lengths and bond angles in molecule 1 are close to the corresponding standard values. In the crystal, molecules are linked together both through intermolecular hydrogen bonds and intermolecular Br(3)...Br(5) contacts ($x+1, y+1, z$) (3.791 Å).

3,5-Dibromo-2-hydroxybenzaldehyde (3). Bromination of salicylaldehyde (2) was carried out according to a standard procedure.⁶ Crystallization from a $CHCl_3$ -EtOH mixture af-

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\times 10^3$)

Atom	x	y	z	$U/\text{Å}^2$
Br(5)	793(3)	2057(1)	-4434(1)	48(1)
Br(3)	6664(3)	7678(1)	-3157(1)	47(1)
O(2)	5172(17)	5020(8)	-1429(4)	38(2)
O(7)	2405(22)	1946(10)	-425(4)	61(2)
O(7')	-574(22)	220(9)	-1062(4)	57(2)
C(1)	2232(23)	2650(10)	-1960(5)	29(2)
C(2)	3957(22)	4342(10)	-2079(5)	29(2)
C(3)	4546(24)	5334(10)	-2934(6)	33(2)
C(4)	3644(24)	4668(12)	-3629(5)	33(2)
C(5)	2051(25)	2988(12)	-3477(6)	36(2)
C(6)	1328(24)	2020(12)	-2662(6)	34(2)
C(7)	1298(27)	1535(12)	-1085(6)	37(2)
C(8)	3022(30)	6252(15)	-1100(7)	58(2)

forded compound 3 in 97% yield, m.p. 82–83 °C (cf. Ref. 7: 85 °C).

3,5-Dibromo-2-methoxybenzaldehyde (4). Methylation of compound 3 was performed according to a known procedure.⁸ Crystallization from an acetone-ether mixture afforded compound 4 in 98% yield, m.p. 95–95.5 °C (cf. Ref. 9: 95 °C).

3,5-Dibromo-2-methoxybenzoic acid (1). A 30% H_2O_2 solution (5 mL) was added with stirring to a mixture of compound 4 (1.47 g, 0.005 mmol), MeOH (10 mL), and a 1 M NaOH solution (10 mL). The reaction mixture warmed up. After 15 h, MeOH was distilled off. The reaction mixture was neutralized with AcOH. The precipitate that formed was purified by recrystallization from EtOH. Compound 1 was obtained in a yield of 1.4 g (93%), R_f 0.25, m.p. 197–198 °C (cf. Ref. 10: 193–194 °C). The melting point of the mixed sample that contained the natural acid was 196–198 °C. The data of IR and 1H NMR spectroscopy and mass spectrometry for the samples are identical.

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