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A BROMINATED QUINAZOLINEDIONE FROM THE MARINE TUNICATE *PYURA SACCIFORMIS*

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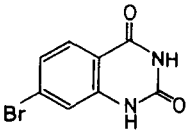
Various compounds of structural and medicinal interest have been isolated and characterized from marine tunicates in recent years (1,2). We have examined the constituents of the tunicate *Pyura sacciformis* (Drasche) (family Pyuridae) collected at Ago Bay, Mie Prefecture, Japan, and have isolated a new metabolite, a brominated quinazolinedione **1** together with 6-bromoindole-3-carbaldehyde previously isolated from a marine pseudomonad (3).

The EtOAc-soluble material from a MeOH extract of the tunicate *P. sacciformis* was chromatographed on Si gel with eluents of increasing polarity from C_6H_6 through C_6H_6-EtOAc (4:1 and 1:1) to EtOAc. The material obtained by elution with C_6H_6-EtOAc (1:1) was further separated by chromatography on Si gel. The fraction eluted with $CHCl_3$-Me_2CO (20:1) afforded 6-bromoindole-3-carbaldehyde, mp 201–203°, and the fraction eluted with $CHCl_3$-Me_2CO (5:1) yielded the brominated quinazolinedione **1**.



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The molecular formula, $C_8H_5BrN_2O_2$, of **1** was established by hrms. On the basis of the ^{1}H-nmr spectrum [δ 7.89 (1H, d, J=8.9 Hz), 7.39 (1H, d, J=2.0 Hz), 7.36 (1H, dd, J=2.0, 8.9 Hz)] the 1,2,4-trisubstituted C_6H_6 moiety in **1** was shown to be present. The ir spectrum of **1** revealed two strong bands at 1730 cm^{-1} and 1680 cm^{-1} due to two carbonyl groups. The uv absorption spectrum of **1** [λ max 310 nm (ε 4600) and 225 nm (ε 47000)] was similar to that of 2,4(1*H*,3*H*)-quinazolinedione (4). These spectral (^{1}H nmr, ir and uv) data suggested the possibility of a brominated quinazolinedione structure for **1**. This inference was supported by the mass spectrum of **1**, which showed a prominent fragment peak at *m/z* 197 $[M-HNCO]^+$, a characteristic peak of 2,4(1*H*,3*H*)-quinazolinedione resulting from the retro-Diels-Alder fragmentation (5). The position of the bromine atom at C-7 of 2,4(1*H*,3*H*)-quinazolinedione in **1** was deduced by the finding that the aromatic proton signal at δ 7.89 assignable to the proton on C-5 was observed as a doublet with a coupling constant of 8.9 Hz. This assignment was based on the ^{1}H-nmr spectral data of the known 1- or 3-alkyl-2,4(1*H*,3*H*)-quinazolinediones; the proton signal of C-5 was observed in the region δ 7.90–8.16, whereas the proton signal of C-8 appeared in the range δ 6.38–7.48 (6). Thus, the possibility of 6-bromo-2,4(1*H*,3*H*)-quinazolinedione for the natural product was excluded. The structure of 7-bromo-2,4(1*H*,3*H*)-quinazolinedione [**1**] was confirmed by synthesis. Reaction of 4-bromoanthranilic acid (7,8) with cyanic acid afforded the compound **1** in 44% yield. The synthetic compound **1** proved to be identical in all respects with the natural product.

The natural occurrence of 2,4(1*H*,3*H*)-quinazolinedione compounds is quite rare (9), although a considerable number of compounds with this heterocyclic skeleton are known synthetically (10). This represents the first isolation of a brominated quinazolinedione compound from a natural source.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The ir and uv spectra were recorded on a JASCO Model IR-810 spectrophotometer and a JASCO Model UVIDEC-510 spectrophotometer, respectively. ^{1}H-nmr spectra were obtained on a JEOL JNM-C675 (270 MHz) spectrometer using TMS as internal standard. Mass spectra were measured on a JEOL JMS-LG2000 instrument. For cc, Fuji-Davison Si gel BW-820-MH was used. Melting points are uncorrected.

COLLECTION AND ISOLATION PROCEDURES.—The specimens of the tunicate *P. sacciformis* (wet wt 8.5 kg, dry wt 680 g) were collected in March 1983, in Ago Bay, Mie Prefecture, Japan, and identified by Dr. T. Nishikawa, College of General Education, Nagoya University. A voucher specimen (no. KY-N-83) is deposited in the Laboratory of Organic Chemistry, Department of Chemistry, Faculty of Science, Nagoya University. The specimens of *P. sacciformis* were homogenized in MeOH (30 liters) in a blender. The resulting suspension was stored at room temperature for 10 days, filtered with suction, and washed with MeOH (15 liters). The combined MeOH extracts were evaporated to leave the aqueous residue (700 ml), which was extracted with EtOAc (3×700 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated to give a dark brown oil (28.5 g). A portion of the oil (7.85 g) was chromatographed on Si gel with C_6H_6, C_6H_6-EtOAc (4:1 and 1:1), and EtOAc, successively. Evaporation of the fraction eluted with C_6H_6-EtOAc (1:1) afforded an oily material (222 mg), which was further chromatographed on Si gel. The fraction eluted with $CHCl_3$-Me_2CO (20:1) on removal of the solvent provided 6-bromoindole-3-carbaldehyde, mp 201–203° (hexane-CH_2Cl_2), (17 mg, 0.0091% dry wt). Evaporation of the fraction eluted with $CHCl_3$-Me_2CO (5:1) gave a crystalline solid, which was washed with EtOAc to leave crystals of 7-bromo-2,4(1*H*,3*H*)-quinazolinedione [**1**], (0.6 mg, 0.00032% dry wt).

7-BROMO-2,4(1*H*,3*H*)-QUINAZOLINEDIONE [**1**].—Mp >330° (MeOH); ir ν max (KBr) 3300, 3160, 3040, 2830, 1730, 1680, 1610, 1590, 1430, 785 cm^{-1}; uv λ max (EtOH) 310 (ϵ 4600), 225 nm (ϵ 47000); ^{1}H nmr (270 MHz, CD_3OD) δ 7.89 (1H, d, J=8.9 Hz), 7.39 (1H, d, J=2.0 Hz), 7.36 (1H, dd, J=2.0, 8.9 Hz); eims *m/z* [M+2]$^+$ 242 (99%), [M]$^+$ 240 (100), 199 (70), 197 (69), 172 (41), 170 (48). Hrms calcd for $C_8H_5{}^{79}BrN_2O_2$ [M]$^+$ *m/z* 239.9534, found *m/z* 239.9539.

SYNTHESIS OF 7-BROMO-2,4(1*H*,3*H*)-QUINAZOLINEDIONE [**1**].—To a stirred solution of 4-bromoanthranilic acid (7,8) (97 mg, 0.45 mmol) in HOAc (14 ml)-H_2O (10 ml) was added a solution of NaOCN (65 mg, 1.00 mmol) in H_2O (2 ml) over 10 min. The mixture was stirred at 35° for 1 h, and a solution of NaOCN (105 mg, 1.62 mmol) in H_2O (6 ml) was added to the mixture. After being stirred at 35° for an additional 2 h, the mixture was evaporated to give a residue to which H_2O (10 ml) was added. To the suspension was added NaOH (1.0 g), and the mixture was stirred at room temperature for 20 min. During the stirring the mixture became clear, and crystals deposited gradually. After 15 h the crystals collected by filtration were dissolved in H_2O (10 ml) by heating, and the solution was neutralized by 1 N H_2SO_4 to precipitate crystals of **1**, mp >330° (MeOH), 47.6 mg (44%). The synthetic compound **1** was identical in all respects with natural **1**.

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