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Synthesis of 3,6-Bis(5'-bromo-3'-indolyl)-1,4-dimethypiperazine-2,5-dione

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Short Note

3,6-Bis(5'-bromo-3'-indolyl)-1,4-dimethypiperazine-2,5-dione

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Abstract: The one-pot synthesis of 3,6-bis(5'-bromo-3'-indolyl)-1,4-dimethylpiperazine-2,5-dione is reported. Sarcosine anhydride is brominated and immediately reacted with 5-bromoindole to produce the product, which is characterized by ^{1}H NMR, MS and microanalysis.

Keywords: 3,6-bis(5'-bromo-3'-indolyl)-1,4-dimethylpiperazine-2,5-dione; indole; bromination; dragmacidin

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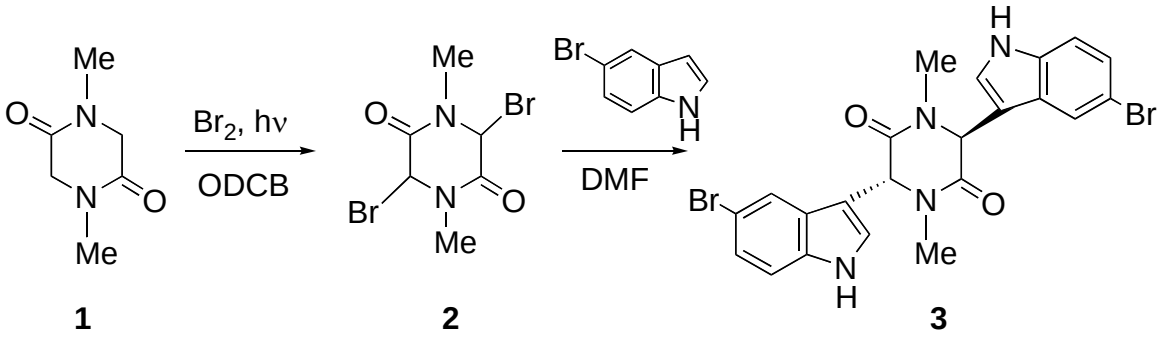
1. Introduction

Isolated from the marine sponge series *Dragmacidin, Hexadella,* and *Spongosorites*, unique bis-indolylpiperazine alkaloids have received significant attention in recent years for their antiviral, cytotoxic, and anti-inflammatory properties [1–10]. The dragmacidin series of alkaloids each contain a central piperazine ring with indole units attached at the 2- and 5- positions. The corresponding author successfully synthesized the first member of the dragmacidin series [11] and recently reported an improved procedure for preparing 1,4-dimethylpiperazine-2,5-dione, an important precursor [12]. We now report the synthesis of 3,6-bis(5'-bromo-3'-indolyl)-1,4-dimethylpiperazine-2,5-dione (**3**), a novel bis-indolylpiperazinedione utilizing the newly-developed procedure. This product will be utilized in the preparation of novel dragmacidin derivatives.

2. Results and Discussion

The synthesis of **3** is shown in Scheme 1. Bromine is directly added to **1** with heat and the illumination of a sun lamp. After one hour, the solution is cooled to provide the dibrominated product

as an unstable precipitate. This precipitate is then reacted with 5-bromoindole in DMF to produce **3**. In conclusion, an important precursor to a dragmacidin derivative has been prepared by efficient means.



3. Experimental Section

To a solution of sarcosine anhydride (**1**) (1.50 g, 10.6 mmol) in *o*-dichlorobenzene (15 mL), at 150°C, was added dropwise Br_2 (2.5 mL, 96.6 mmoL), under illumination of a sun lamp. The solution was heated for 1 h and then cooled to room temperature. The solution was decanted leaving beige crystals (**2**). To a solution of 5-bromoindole (2.21 g, 11.3 mmol) in DMF (20 mL) was slowly added **2** (1.50 g, 5.0 mmol), while the reaction temperature was maintained at room temperature with a water bath. The reaction mixture was stirred for 18 h, concentrated and diluted with methanol. The resulting solid was filtered to yield the product (**3**) as a white crystalline solid (1.92 g; 72.5%): mp > 250°C. ^{1}H NMR (d_6-DMSO): 2.67 (s, 3H), 5.64 (s, 1H), 7.25 (dd, 1H, *J* = 1.9, 8.6), 7.39 (d, 1H, *J* = 8.7), 7.49 (d, 1H, *J* = 2.5), 7.69 (d, 1H, *J* = 1.8), 9.67 (bs, 1H); MS: 532 (m^+, 17.3), 530 (54.5), 528 (51.3), 335 (100.0), 333 (99.9), 307 (31.9), 305 (30.7), 239 (47.9), 237 (91.8), 235 (68.0), 209 (30.6), 207 (30.9), 197 (30.2), 195 (29.7); Anal. Calcd. For $C_{22}H_{16}Br_2N_4O_2$: C, 48.84; H, 3.42; N, 10.57. Found: C, 49.80; H, 3.50; N, 10.64. Sarcosine anhydride (99.5%) was obtained from Acros Organics, and 5-bromoindole (99%) was obtained from Sigma-Aldrich, Inc.

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