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IODINATED PHENETHYLAMINE PRODUCTS FROM A DIDEMNID TUNICATE

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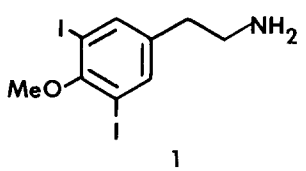
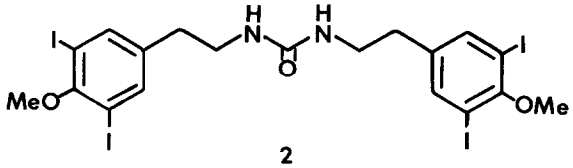
Summary: Two idodinated phenethylamine derivatives 1 and 2 were isolated from a didemnid tunicate.

Previously, we reported the isolation of novel amino acid derivatives from two didemnid tunicates Lissoclinum patella[1-2] and Didemnum ternatanum[3] both of which harbor unicellular prokaryotic algal symbionts. At the time it seemed probable that these symbionts were instrumental to the biosynthesis of these metabolites by virtue of the ability of prokaryotes to fix nitrogen. However, we now wish to report the isolation of iodinated tyramine derivatives 1 and 2 as metabolites of an unidentified Didemnum species, which is devoid of algal symbionts.



1



2

The tunicate collected on exposed rocks on the northwest end of Cocos Lagoon, Guam was freeze dried (116 G, dry weight) and exhaustively extracted with a regime of organic solvents. The 3,5-diiodo-4-methoxyphenethylamine 1 (453 mg, 0.39% dry weight) crystallized from the $CHCl_3$ extract as the hydrochloride mp 209-12°C (lit. 213°C).[4] Upon further

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standing, a second metabolite 2 (20 mg) also crystallized from the $CHCl_3$ extract (mp 224-25°C).

Compound 1 was assigned molecular formula $C_9H_{11}NOI_2$ (HRMS: obs. 402.8929, calc. 402.8941). The ^{13}C NMR spectrum contained resonances for six sp^2 carbons; at δ 157.1 s, 139.7 d (2C), 137.7 s, 91.5 s (2C); a methoxy at 60.1 and two methylene carbons at 39.4 and 30.8 ppm. The ^1H NMR spectrum of 1 hydrochloride (d_6DMSO) contained signals for two degenerate aromatic protons 7.76 (s, 2H), a methoxyl on a phenyl ring 3.73, and an A_2B_2 spin system [3.03 (t, 2H, J = 7 Hz), 2.86 (t, 2H, J = 7 Hz)] for a phenethylamine group and a singlet at 8.26 for the three protons on nitrogen. Finally, a synthetic sample of 1 prepared from N-acetyl tyramine[5] was identical in every respect to the natural product.

The minor component 2 had molecular formula $C_{19}H_{20}N_2O_3I_4$ (HRMS: obs. 831.7699, calc. 831.7675). 2 was a symmetrical urea derivative of 1 as indicated by the presence of resonances for only 10 carbons. Nine resonances [157.8 s, 140.2 d (2C), 139.6 s, 91.0 s (2C), 60.13 q, 40.4 t, 34.1 t] could be assigned to a 3,5-diiodo-4-methoxyphenethylamine unit, the remaining carbon at δ 156.6 s to a urea carbonyl. The ^1H NMR spectrum of 2 was also very similar to that of 1 [7.56 (s, 2H), 3.62 (s, 3H), 3.08 (dt, 2H, J = 7, 6 Hz), 2.49 (t, 2H, J = 7 Hz)] with addition of a triplet 5.78 (t, J = 6 Hz) for the NH proton of the urea.

Compound 1 has been synthesized previously[4], however, this represents the first report of either 1 or 2 as a natural product. Compound 1 showed *in vitro* activity against the yeast *Candida albicans* and was mildly cytotoxic, L1210 IC_{50} 20 μg/ml. Interestingly, we isolated the corresponding symmetrical phenethylamine urea from MeOH extracts of *D. ternatanum* indicating these substituted ureas are not artifacts.

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5. i ICI/HOAc; ii $(CH_3)_2SO_4$/NaH; iii HCl

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