Oxidative Dimerization of 2-Aminoimidazoles by Molecular Bromine. Synthesis of Parazoanthoxanthin A

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Zoanthoxanthins are a collective group of highly fluorescent marine pigments isolated from marine coelenterates which are closely related to sea anemones and stony corals.[1−3] The linear parazoanthoxanthin A (**1**) and angular pseudozoanthoxanthin A (**2**) form the basis of this group of tricyclic pigments in which a number of N-methylated derivatives have been identified to date. All contain a bis-fused 2-aminoimidazole (AI) nucleus that embodies a ten-electron azulene ring system. Both parazoanthoxanthin A (**1**) and pseudozoanthoxanthin A (**2**) have been previously synthesized.[4,5] The cleverly crafted synthesis by Büchi was the first to demonstrate that **1** and **2** can be obtained in a biomimetic fashion from the acid-promoted dimerization of various C_5N_3 precursors, namely AI derivatives **3**−**5**. From subsequent research in our lab,[5] a one-step synthesis of **1** and **2** was accomplished using the C_3N_3 metabolite, 2-aminoimidazole (AI). This forerunner served as an immediate precursor to the Büchi intermediate. The novel feature of the synthesis involved the facile addition of aldehydes to AI via an aldol or Mannich type process.[6] In this report, we describe the oxidative dimerization of 2-aminoimidazoles by molecular bromine. In particular, oxidative dimerization of a C_5N_3 precursor produced the tricyclic $C_{10}N_6$ marine pigment, parazoanthoxanthin A (**1**).

Early investigations on the oxidation of 2-aminoimidazoles by elemental bromine was first reported by Foley and Büchi in their elegant biomimetic synthesis of dibromophakellin.[7] The key step involved oxidation of dihydrooroidin to give a reactive diazafulvene intermediate that underwent cyclization to the natural product. More recently, investigations on the synthesis of a related class of $C_{11}N_5$ marine sponge alkaloids revealed that bromine generated *in situ* by a protodebromination/transbromination process leads to ipso oxidation of the AI nucleus to produce vinylogous AI products.[8] Based on this work, the oxidative dimerization of AI derivatives was investigated. For instance, ipso oxidation of AI derivative **6** would lead to diazafulvene intermediate **A** which, if in equilibrium with vinyl imidazole **B**, could undergo a possible intermolecular [4 + 6] cycloaddition to give the tricyclic pigments **1** and **2**.[4] Alternatively, if 0.5 equiv of oxidant is used, then equal quantities of diazafulvene **A** and unreacted **6** would be present and could undergo dimerization via a stepwise mechanism.

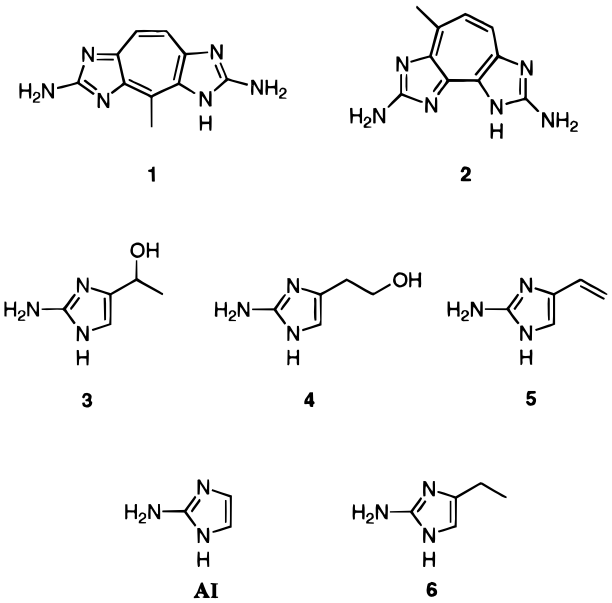
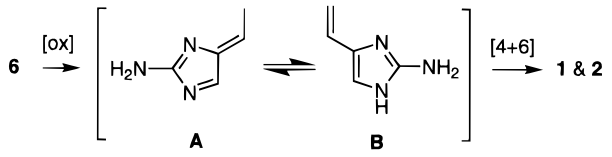


Figure 1.

Scheme 1



In experimenting with various reaction conditions for the dimerization, the one that worked best utilized methanesulfonic acid as the solvent, presumably, because of its low nucleophilicity. Treatment of **6** with 0.5 equiv of Br_2 (16 h, 23 °C) gave $C_{10}N_6$ dimer **7** as a colorless solid in excellent yield. The formation of dimer **7** results from initial ipso oxidation of **6** to produce diazafulvene **A** followed by the exocyclic addition of monomer **6**. No products resulting from endocyclic addition were detected. Further treatment of dimer **7** with 3 equiv of Br_2 (CH_3SO_3H, 23 °C) caused the oxidative cyclization to the 10e$^-$ azulene chromophore of pigment **1** in 73% yield. All spectral data of synthetic **1** were in complete agreement with those reported for the natural product. Parazoanthoxanthin A (**1**) was stable to oxidation by Br_2. In addition, the direct dimerization of **6** to **1** was attempted but achieved only moderate success. Generally, treatment of **6** with excess Br_2 (2 or 3 equiv) resulted in mixtures of products wherein **1** was produced in low yields. Using 1 equiv of Br_2, however, modest yields (25−35%) of **1** along with unreacted starting material were obtained as major isolates. While a number of reaction conditions was investigated in the oxidative dimerization

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(1) (a) Cariello, L.; Crescenzi, S.; Prota, G.; Giordano, F.; Mazzarella, L. *J. Chem. Soc., Chem. Commun.* **1973**, 99. (b) Cariello, L.; Crescenzi, S.; Prota, G.; Capasso, S.; Giordano, F.; Mazzarella, L. *Tetrahedron* **1974**, *30*, 3281. (c) Cariello, L.; Crescenzi, S.; Prota, G.; Zanetti, L. *Experientia* **1974**, *30*, 849. (d) Cariello, L.; Crescenzi, S.; Prota, G.; Zanetti, L. *Tetrahedron* **1974**, *30*, 3611. (e) Cariello, L.; Crescenzi, S.; Prota, G.; Zanetti, L. *Tetrahedron* **1974**, *30*, 4191. (f) Cariello, L.; Crescenzi, S.; Zanetti, L.; Prota, G. *Comp. Biochem. Physiol.* **1979**, *63B*, 77.

(2) (a) Schwartz, R. E.; Yunker, M. B.; Scheuer, P. J.; Ottersen, T. *Tetrahedron Lett.* **1978**, 2235. (b) Schwartz, R. E.; Yunker, M. B.; Scheuer, P. J.; Ottersen, T. *Can J. Chem.* **1979**, *57*, 1707.

(3) (a) Komoda, Y.; Kaneko, S.; Yamamoto, M.; Ishikawa, M.; Itai, A.; Iitaka, Y. *Chem. Pharm. Bull.* **1975**, *23*, 2464. (b) Komoda, Y.; Shimizu, M.; Kaneko, S.; Yamamoto, M.; Ishikawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 502.

(4) (a) Braun, M.; Büchi, G. *J. Am. Chem. Soc.* **1976**, *98*, 3049. (b) Braun, M.; Büchi, G.; Bushey, D. F. *J. Am. Chem. Soc.* **1978**, *100*, 4208.

(5) Xu, Y.-z.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **1992**, *33*, 4385.

(6) Xu, Y.-z.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **1993**, *34*, 6981.

(7) Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776.

(8) Xu, Y.-z.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* (in press).

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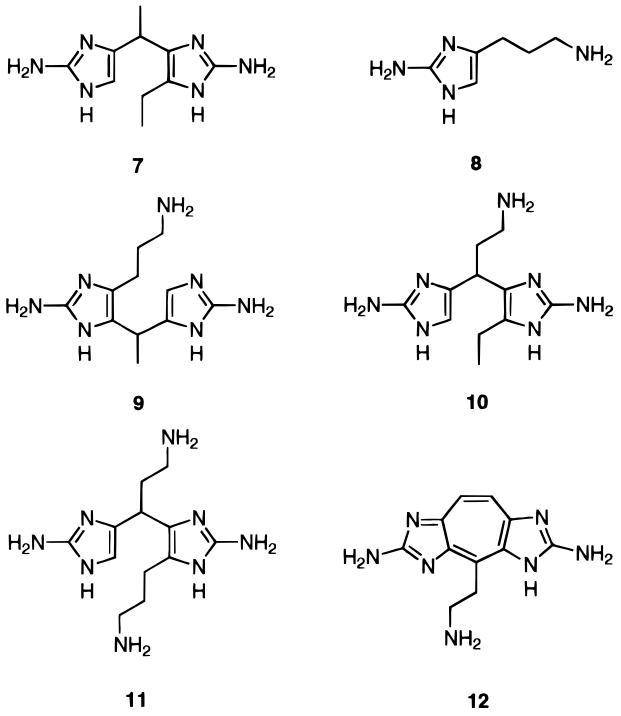

Figure 2.

of **6**, only trace amounts of pseudozoanthoxanthin A (**2**) could be detected by HPLC.

Next, the generality of the oxidative dimerization process was investigated using substrates that would lead to heterodimer formation. This was attempted using AI derivatives **6** and **8**. When **6** was treated with 0.5 equiv of Br_2 in methanesulfonic acid (10 min, 23 °C) followed by the addition of **8**, heterodimer **9** was cleanly obtained in good yield. Reversal of this process, however, resulted in a mixture of products. In addition to the anticipated formation of dimer **10**, cross dimerization products **7**, **9**, and **11** were produced. These results suggest that the Br_2 oxidation of **8** does not proceed as efficiently as **6**, and consequently, leads to a mixture of cross-coupled products. Treatment of **10** with 3 equiv of Br_2 produced a highly fluorescent material, which, after purification by HPLC, was identified as tetrazacyclopent-[*f*]azulene **12**.

One of the many unique aspects of marine natural products is the ubiquitous occurrence of halogenated metabolites. The incorporation of halogen is believed to take place by enzymatic oxidation of the corresponding halide to a reactive halonium ion species which then reacts with the organic substrate. Of the halogenated natural products isolated to date, brominated metabolites are the most common. A key issue pertaining to the biosynthesis of many brominated metabolites is whether or not the incorporation of bromine is simply adventitious, or does "Br^+" actually play an important role in crucial carbon−carbon or carbon−heteroatom bond forming processes. This is particularly true for metabolites that are devoid of halogens such as parazoanthoxanthin (A). The chemistry presented here, in conjunction with previous findings,[7] is suggestive of a common bromonium ion pathway in the biosynthesis of AI-containing metabolites. Finally, there are a number of AI-derived marine metabolites that appear to result from oxidative dimerization processes similar to the one at hand. These metabolites include the oroidin-based alkaloids ageliferins,[9] sceptrins,[10] and palau'amine.[11] The oxidative dimerization of **6** and related AI analogs seen in this report are the first examples illustrating the potential utility of this process. The method provides a rapid entry into a relatively complicated family of heterocycles without the use of protecting groups on nitrogen. Further studies involving the oxidation and oxidative dimerization of 2-aminoimidazole analogs are ongoing and will be the subject of future reports.

Experimental Section

General. Unless otherwise noted, materials were obtained from common commercial suppliers and used without further purification except solvents which were dried and distilled. AI derivatives **6** and **8** were prepared according to literature methods.[12] EM Science silica 60 (230−400 mesh) silica gel was used for chromatography. ^1H NMR spectra were measured on a Varian VXR 400 MHz spectrometer. Residual solvent signals were used as references. ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer at 75 MHz. For ^{13}C NMR, trace CD_3OD was added to each sample as an internal reference (48.8 ppm). Chemical ionization (CI) and electron impact (EI) mass spectra were obtained on a Nermag R-10-10-10 quadropole mass spectrometer. Chemical ionization was performed using either CH_4 or NH_3 gas. Fast atom bombardment (FAB) mass spectra were obtained on a JEOL DX303HF spectrometer. Combustion analyses were performed at the Analytical Facility, Columbia University.

Procedure for Oxidative Homodimerization of Monomers 6 and 8. To a stirred solution of AI derivative **6**·HCl or **8**·2HCl (5.0 mmol) in 5 mL of methanesulfonic acid was added Br_2 (2.5 mmol) at room temperature. The solution was stirred for 16 h, diluted with acetone, and decanted (30 mL × 3). Chromatography of the resulting residue using EtOAc/acetone/H_2O/HCOOH (5:3:1:1 for **7** and 5:3:2:2 for **11**) afforded dimer **7** or **11** as colorless solids.

5-[i-(4-Ethyl-2-aminoimidazol-5-yl)ethyl]-2-aminoimidazole (7). **7**·$2CH_3SO_3H$: 86% yield; ^1H NMR (D_2O) δ 1.13 (t, 3H, J = 7.5 Hz), 1.51 (d, 3H, J = 7.0 Hz), 2.48 (m, 2H), 2.18 (s, 6H), 4.13 (q, 1H, J = 7.0 Hz), 6.61 (s, 1H); ^{13}C NMR (D_2O) δ 14.0 (q), 17.3 (t), 18.4 (q), 26.7 (d), 39.4 (CH_3SO_3H), 110.4 (d), 121.8 (s), 125.8 (s), 129.3 (s), 147.0 (s), 148.0 (s); UV (CH_3OH) λ_{max} 217 nm; HRMS (FAB), calcd for $C_{10}H_{16}N_6$ 220.1436, found 221.1502 $(MH)^+$. Anal. calcd for $C_{10}H_{16}N_6$·$2CH_3SO_3H$: C, 34.94; H, 5.86; N, 20.37. Found: C, 35.15; H, 5.71; N, 20.22.

5-[1-[4-(3′-Aminopropyl)-2-aminoimidazol-5-yl]-3-aminopropyl]-2-aminoimidazole (11): 76% yield; **11**·4HCl: ^1H NMR (D_2O) δ 1.90 (m, 2H), 2.17 (m, 1H), 2.37 (m, 1H), 2.61 (m, 2H), 2.91 (m, 1H), 2.99 (t, 1H, J = 7.7 Hz), 3.05 (m, 1H), 4.17 (dd, 1H, J = 5.5, 9.9 Hz), 6.70 (s, 1H); ^{13}C NMR (D_2O) δ 21.0 (t), 27.3 (t), 30.0 (d), 30.1 (t), 38.1 (t), 39.7 (t), 111.1 (d), 119.8 (s), 124.3 (s), 126.5 (s), 148.0 (s), 148.3 (s); UV (CH_3OH) λ_{max} 218 nm; HRMS (FAB), calcd for $C_{12}H_{22}N_8$ 278.1971, found 279.2050 $(MH)^+$. Anal. Calcd for $C_{12}H_{22}N_8$·4HCl: C, 33.98; H, 6.18; N, 26.42. Found: C, 33.69; H, 5.98; N, 26.55.

Procedure for Oxidative Heterodimerization of Monomers 6 and 8. To a stirred solution of **6**·HCl (2.4 mmol) in 8 mL of methanesulfonic acid was added Br_2 (2.4 mmol) at room temperature. After 10 min, **8**·2HCl (2.4 mmol) was added and the resulting solution was stirred for 3 d. The reaction mixture was then diluted with acetone and decanted (35 mL × 3). Chromatography of the resulting residue using EtOAc/acetone/H_2O/HCOOH (5:3:1.5:1.5) afforded heterodimer **9** as a colorless solid in 70% yield. Reversal of the oxidation/addition steps for **6** and **8** afforded a mixture of dimers **7** (15%), **9** (20%), **10** (30%), and **11** (20%).

(9) Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772.

(10) (a) Rinehart, K. L. *Pure Appl. Chem.*, **1989**, *61*, 525. (b) Kobayashi, J.; Tsuda, M.; Murayama, H.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, T.; Ohta, T.; Nozoe, S. *Tetrahedron*, **1990**, *46*, 5579.

(11) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

(12) Lancini, G. C.; Lazzari, E *J. Heterocycl. Chem.* **1966**, *3*, 152. (b) Lancini, G. C.; Lazzari, E. Br. Patent 1,132,013 (1968).

4-[1(2-Aminoimidazol-4-yl)ethyl]-5-(3-aminopropyl)-2-aminoimidazole (9). **9**·3CH_3SO_3H: ^1H NMR (D_2O) δ 1.47 (d, 3H, J = 7.2 Hz), 1.88 (m, 2H), 2.58 (m, 2H), 2.76 (s, 6H), 2.95 (t, 2H, J = 7.7 Hz), 4.12 (q, 1H, J = 7.2 Hz), 6.59 (s, 1H); ^{13}C NMR (D_2O) δ 18.4 (q), 20.8 (t), 26.5 (t), 27.2 (d), 39.2 (t), 39.5 (CH_3SO_3H), 110.4 (d), 122.0 (s), 123.1 (s), 128.9 (s), 147.3 (s), 147.9 (s); UV (CH_3OH) λ_{max} 216 nm; HRMS (FAB), calcd for $C_{11}H_{19}N_7$ 249.1705, found 250.1784 $(MH)^+$. Anal. Calcd for $C_{11}H_{19}N_7$·3CH_3SO_3H: C, 31.28; H, 5.81; N, 18.24. Found: C, 31.15; H, 5.71; N, 18.22.

5-[1(2-aminoimidazol-5-yl)-3-aminopropyl]-2-amino-4-ethylimidazole (10). **10**·3CH_3SO_3H: ^1H NMR (D_2O) δ 1.11 (t, 3H, J = 7.6 Hz), 2.16 (m, 1H), 2.36 (m, 1H), 2.50 (q, 2H, J = 7.6 Hz), 2.77 (s, 4H), 2.91 (dt, 1H, J = 5.0, 11.9 Hz), 3.10 (dt, 1H, J = 5.0, 11.9 Hz), 4.13 (dd, 1H, J = 4.9, 10.0 Hz), 6.71 (s, 1H); ^{13}C NMR (D_2O) δ 13.9 (q), 17.3 (t), 29.9 (t), 29.9 (d), 38.1 (t), 39.5 (CH_3SO_3H), 111.0 (d), 118.3 (s), 126.6 (s), 127.6 (s), 147.6 (s), 148.1 (s); UV (CH_3OH) λ_{max} 217 nm; HRMS (FAB), calcd for $C_{11}H_{19}N_7$ 249.1705, found 250.1784 $(MH)^+$. Anal. Calcd for $C_{11}H_{19}N_7$·3CH_3SO_3H: C, 31.28; H, 5.81; N, 18.24. Found: C, 31.45; H, 5.68; N, 18.15.

Parazoanthoxanthin A (1). To a solution of **7**·2CH_3SO_3H (0.21 g, 0.5 mmol) in 3 mL of methanesulfonic acid was added Br_2 (0.073 mL, 1.5 mmol) at room temperature. The solution was stirred for 3 d and then diluted with acetone and decanted (25 mL × 3). Chromatography of the resulting residue using CH_2Cl_2/MeOH saturated with NH_3 (7:3) as the eluent afforded **1** (78 mg, 73%) as a yellow solid; ^{13}C NMR (D_2O, 1 drop of concd DCl in D_2O) δ 18.1, 126.0, 130.8, 142.9, 144.0, 154.9; UV (CH_3OH) λ_{max} 285 (sh), 295, 405; UV (·2HCl salt, CH_3OH) λ_{max} 293, 383; UV (concd HCl) λ_{max} 283, 388; UV (1 N NaOH) λ_{max} 294, 399; MS (CI), m/z 215 $(MH)^+$.

4-(2-Aminoethyl)-2,6-diamino-1,3,5,7-tetrazacyclopenten-[f]azulene (12). To a stirred solution of **10**·3CH_3SO_3H (0.16 g, 0.3 mmol) in 3 mL of methanesulfonic acid was added Br_2 (45 μL, 0.9 mmol) at room temperature. The solution was stirred for 10 d and then diluted with acetone and decanted (25 mL × 3). The resulting residue was purified by preparative TLC using CH_2Cl_2/MeOH saturated with NH_3 (7:3) as the eluent from which the intensely blue fluorescent band was excised. A small portion (10%) of the sample was subjected to reverse phase HPLC purification (0.1% TFA in H_2O/MeOH gradient), affording **12** as a yellow solid. Yield 41%. **12**·3HCl: ^1H NMR (D_2O) δ 3.42 (t, 2H, J = 7.0 Hz), 3.83 (t, 2H, J = 7.0 Hz), 8.14 (s, 2H); ^{13}C NMR (D_2O) δ 28.8 (t), 39.3 (t), 121.5 (d), 130.2 (s), 144.8 (s), 151.4 (s), 159.0 (s); ^{13}C NMR (D_2O, 1 drop of concd DCl in D_2O) δ 28.8 (t), 38.8 (t), 123.2 (d), 128.7 (s), 143.1 (s), 148.6 (s), 156.9 (s); UV (concd HCl) λ_{max} 285, 386; UV (1 N NaOH) λ_{max} 295, 400; HRMS (FAB), calcd for $C_{11}H_{13}N_7$ 243.1232, found 244.1310 $(MH)^+$. Anal. Calcd for $C_{11}H_{13}N_7$·3HCl: C, 37.46; H, 4.57; N, 27.80. Found: C, 37.27; H, 4.82; N, 27.60.

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