Electrophilic and Nucleophilic Substitutions of 2-Amino- and 2-Hydroxy-1,3-diazaazulenes

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Synopsis. 2-Amino- (**2**) and 2-hydroxy-1, 3-diazaazulenes (**3**) underwent smoothly electrophilic bromination under basic conditions to give 2-amino-4,6,8-tribromo- (**4**) and 6-bromo-2-hydroxy-1,3-diazaazulenes (**7**), respectively. Bromo derivatives **4** and **7** underwent some nucleophilic substitutions, e.g., **4** reacted with ease with sodium methoxide to give 2-amino-4,6,8-trimethoxy-1,3-diazaazulene (**10**).

1,3-Diazaazulene (cycloheptimidazole) (**1**) and its derivatives are of theoretical interest in relation to the structural chemistry of nonbenzenoid aromatics and of biological interest in relation to naturally occurring cycloheptimidazole derivatives such as zoanthoxanthin[1a] epizoanthoxanthin,[1b] and paragracine.[1c]

1,3-Diazaazulene (**1**) would be difficult of undergoing an electrophilic substitution, because **1** has a large contribution of dipolar structure (**1a**) to the ground state[2] causing an enhanced diatropicity of the seven-membered ring and moreover the electron-rich 1- and 3-positions are blocked by nitrogen atoms. In fact it has been reported that, on treatment with bromine in chloroform or acetic acid, **1**,[3] 2-amino- (**2**),[4] and 6-amino-1,3-diazaazulene[5] give the corresponding diazaazulene-bromine molecular compounds which easily decompose regenerating respective starting diazaazulenes without giving any bromo-substituted product. There has appeared only one paper dealing with the electrophilic substitution in which 2-dimethylamino-1,3-diazaazulene affords brominated products in chloroform but in very poor yields.[6a] Most derivatives of **1**, therefore, have to be synthesized by condensation of the corresponding substituted 2-chloro- or 2-methoxytropones with guanidine or thiourea.[3,4,6-8] However, we have presumed that **2** and 2-hydroxy-1,3-diazaazulene (**3**),[3] carrying an electron-donating substituent at the 2-position and being in equilibrium with imino (**2a**) and keto (**3a**) forms,[9] respectively, may undergo effectively electrophilic substitutions at the seven-membered ring if any suitable reaction conditions are explored.[10] In order to clarify the fundamental reactivities of **2** and **3**, and to develop a new synthetic method for the preparation of 1,3-diazaazulene derivatives, we have now carried out a brief study on the electrophilic and nucleophilic substitution reactions of **2** and **3**, which is dealt with herein.

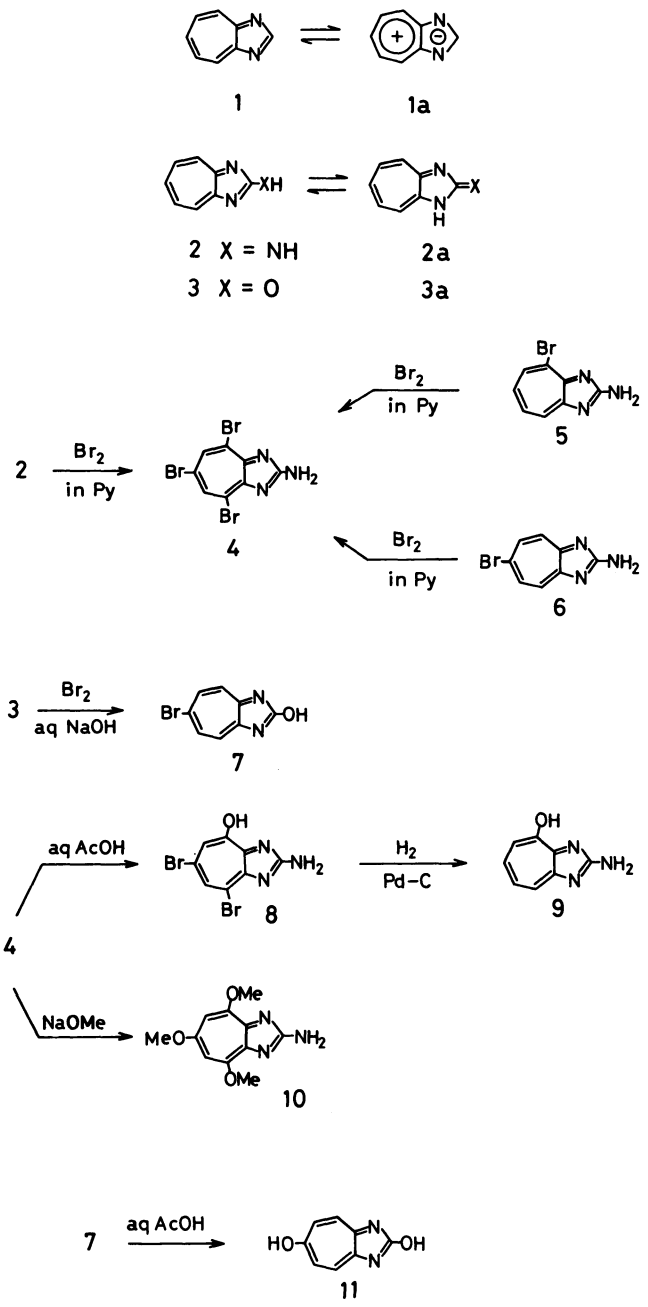
When 2-amino-1,3-diazaazulene (**2**) was allowed to react with an excess amount of bromine (4 molar equivalents) in pyridine solution at room temperature, 2-amino-4,6,8-tribromo-1,3-diazaazulene (**4**) was formed in good yield.[11] Even when a lesser amount of bromine was employed in this reaction, the same tribromo compound **4** was obtained in low yield, neither monobromo- nor dibromo-substituted product being obtained. The position of the bromo substituents of **4** is elucidated by the ^{1}H NMR spectrum which showed only one singlet in the region of the ring protons, and further by the formation of **4** on bromination of known compounds **5**[6b,12] and **6**[7] in pyridine.

The bromination of **3** in aq sodium hydroxide solution gave 6-bromo-2-hydroxy-1,3-diazaazulene (**7**) in moderate yield. Contrary to the case of **2**, neither dibromo- nor tribromo-substituted product of **3** was produced even when an excess amount of bromine was applied. The position of the bromo substituent of **7** was evidenced by the A_2B_2 type of signals in the ^{1}H NMR spectrum and by the fact that **7** was converted to known **11**[7] (vide post).

It has also been known that the substituent at the seven-membered ring of **5**[6b,12] and **6**[7] undergoes nucleophilic substitution, which is quite reasonable on considering the significant contribution of **1a** to the ground state of **1**. In order to obtain a further insight into the influence of an electron-donating amino or hydroxyl group on nucleophilic substitution, the solvolysis of **4** and **7** was then examined. When an aq acetic acid solution of **4** was heated to reflux, 2-amino-4,6-dibromo-8-hydroxy-1,3-diazaazuene (**8**) was formed in moderate yield. The ^{1}H NMR of **8** showed two unequivalent signals in the region of ring protons and the catalytic hydrogenation of **8** over Pd–C gave a known debrominated compound **9**,[6b,12] elucidating the structure of **8**. This fact indicates that **4** is attacked by a nucleophile first at the 4- (or 8-) position, presumably via the intermediate formation of a hydrogen-bonded chelate bridge among the nucleophile, protonated N-1 and electropositive C-8.[13] More interestingly when a methanolic solution of **4** was refluxed with sodium methoxide, 2-amino-4,6,8-trimethoxy-1,3-diazaazulene (**10**) was formed in good yield. The ^{1}H NMR spectrum of **10** showed only one singlet for the seven-membered ring protons (H-5,7). It is worthy of special notice that all the bromo substituents of **4** are easily replaced by the nucleophile even under the influence of the electron-donating 2-amino group. Similarly, reflux of an aq acetic acid solution of **7** afforded **11**.[7]

As a consequence, it has been proved that, although 1,3-diazaazulene (**1**) is electron-deficient at the seven-membered ring, the derivatives of **1** carrying an electron-donating amino or hydroxyl group at the 2-position, e.g., **2** and **3**, are reactive enough to undergo smooth electrophilic bromination under basic conditions, and that bromo-substituted 2-amino- and 2-

hydroxy-1,3-diazaazulenes, e.g., **4** and **7**, are capable of undergoing nucleophilc substitution with considerable ease under both acidic and basic conditions (despite the electron-donating influence of the 2-substituent).



Experimental

2-Amino-4,6,8-tribromo-1,3-diazaazulene (4). a) Bromination of 2-Amino-1,3-diazaazulene (2): Into a suspension of **2**[4] (1 g, 6.89 mmol) in pyridine (40 ml) was dropped a solution of bromine (6.9 g, 42 mmol) in pyridine (10 ml) at room temperature in a 10 min period, during which time the suspension went into solution and then a yellow powder precipitated again. After being diluted with water (20 ml), the precipitate was collected and washed with methanol to give crude **4**, yellow powder (2.1—2.3 g, 80—87% yield). An analytical sample of **4** was obtained by recrystallization from pyridine as yellow needles, mp>350°C. IR (KBr) 3340, 3130, 1685, 1522, 1508, 1362, 1010, 879 (m), 843, 830 cm^{-1}. ^1H NMR (CF_3COOH) δ=9.10 (2H, s, H-5,7), 7.6 (br. $\overset{+}{N}H_3$). Found: C, 25.05; H, 1.35; N, 10.75%. Calcd for $C_8H_4N_3Br_3$: C, 25.16; H, 1.06; N, 11.01%.

b) Bromination of 2-Amino-4-bromo-(5) and 2-Amino-6-bromo-1,3-diazaazulene (6): A suspension of **5**[6b,12] or **6**[7] (200 mg, 0.893 mmol) in pyridine (10 ml) was treated with a solution of bromine (430 mg, 2.7 mmol) in pyridine (1 ml). The same work-up as described in a) afforded **4** (240—260 mg, 70—75% yield).

6-Bromo-2-hydroxy-1,3-diazaazulene (7). Into a solution of **3**[3] (200 mg, 1.37 mmol) in 0.2 M sodium hydroxide (8 ml) (1 M=1 mol dm^{-3}) was dropped a solution of bromine (440 mg, 2.75 mmol) in 2 M sodium hydroxide (3 ml) at room temperature. Neutralization with dilute hydrochloric acid gave a precipitate, which was collected and recrystallized from saturated sodium hydrogencarbonate solution to give **7** (160 mg, 51.9% yield) as a yellow crystalline powder, mp>330 °C. Soluble in both dilute hydrochloric acid and dilute alkali. IR (KBr) 3450, 3020 2600, 1695, 1618, 1590, 1542 (m), 1467, 1430, 1387, 1355, 1322, 1295, 1055 (m), 955 848, 780 cm^{-1}. ^1H NMR (CF_3COOH) δ=8.98 (2H, d, J=10.5 Hz, H-5,7 or H-4,8), 8.51 (2H, d, J=10.5 Hz, H-4,8 or H-5,7). Found: C, 42.96; H, 2.29; N, 12.27%. Calcd for $C_8H_5ON_2Br$: C, 42.70; H, 2.24; N, 12.45%.

2-Amino-4,6-dibromo-8-hydroxy-1,3-diazaazulene (8). A suspension of **4** (500 mg, 1.31 mmol) in 95% acetic acid (50 ml) was refluxed for 3 h. The resulting solution was concentrated, diluted with water and a precipitate which separated was collected and recrystallized from glacial acetic acid (50 ml) to give **8**, yellow fibrous needles (260 mg, 62.2% yield), mp>320 °C. IR (KBr) 3430, 3095, 1978, 1580 (m), 1550, 1520 (m), 1490, 1393 (m), 1286, 913 (m) cm^{-1}. ^1H NMR (CF_3COOH) δ=8.31 (1H, d, J=1.3 Hz, H-5), 8.15 (1H, d, J=1.3 Hz, H-7), 7.6 (br. $\overset{+}{N}H_3$). Found: C, 30.21; H, 1.57; N, 13.30%. Calcd for $C_8H_5ON_3Br_2$: C, 30.12; H, 1.58; N, 13.18%.

Debromination of 8 to 2-Amino-4-hydroxy-1,3-diazaazulene (9). A solution of **8** (100 mg, 0.314 mmol) in 5% potassium hydroxide (20 ml) was shaken with hydrogen over 5% Pd–charcoal (50 mg) and 2 equivalents (14 ml) of hydrogen were uptaken. Usual work-up gave pale yellow needles of **9** (40 mg, 79% yield), identical in all respects with an authentic sample.[6b,12]

2-Amino-4,6,8-trimethoxy-1,3-diazaazulene (10). Compound **4** (500 mg, 1.31 mmol) was suspended in a sodium methoxide solution prepared from sodium (92 mg, 0.004 atom) and anhydrous methanol (40 ml) and then refluxed for 2.5 h. The methanol was evaporated and the residue was recrystallized from water (10 ml) to give **10** (250 mg, 66.0% yield), deep yellow needles, dp 240—245 °C. IR (KBr) 3370, 3300, 3120, 1643, 1610, 1563, 1515, 1458 (m), 1422 (m), 1378, 1250, 1208 (m), 1073 (m), 990, 839 (m), 778 (w) cm^{-1}. ^1H NMR (CF_3COOH) δ=4.34 (3H, s, OMe-6), 4.42 (6H, s, OMe-4,8), 7.40 (2H, s, H-5,7), 7.90 (br. $\overset{+}{N}H_3$). Found: C, 45.63; H, 6.39; N, 14.89%. Calcd for $C_{11}H_{13}O_3N_3 \cdot 3H_2O$: C, 45.63; H, 6.62; N, 14.53%.

2,6-Dihydroxy-1,3-diazaazulene (11). A suspension of **7** (200 mg, 0.889 mmol) in 95% acetic acid (20 ml) was refluxed for 3 h. Concentration of the resulting solution and recrystallization of a separated precipitate from water afforded **11** (110 mg, 68.7% yield) as yellow fibrous needles, entirely identical with an authentic sample.[7]

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