Oxidation of 1,2-Diaminobenzimidazoles to 3-Amino-1,2,4-benzotriazines

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Several substituted 1,2-diaminobenzimidazoles were synthesized via the cyclization of *o*-acylhydrazidoanilines with cyanogen bromide. A facile route to 1,2-diaminobenzimidazole and 1,2-diamino-5,6-dimethylbenzimidazole was also devised using the corresponding 2-aminobenzimidazoles and hydroxylamine-*O*-sulfonic acid as the aminating agent. Schiff bases of 1,2-diaminobenzimidazole were also prepared. The reaction of 1,2-diaminobenzimidazole with benzil provided 2,3-diphenyl-*as*-triazino[2,3-*a*]benzimidazole. Oxidation of the 1,2-diaminobenzimidazoles with lead tetraacetate afforded 3-amino-1,2,4-benzotriazines.

The purine antimetabolite behavior of the benzimidazole nucleus[1] coupled with the in vivo[2] and in vitro[3] utilization of preformed purines by malaria parasites prompted us to synthesize substituted 1,2-diaminobenzimidazoles as potential antimalarial agents. The substituents selected for this study, notably trifluoromethyl (−I, −R), chloro (−I, +R), and methyl (+I, +R) groups, represent specific electronic effects important in a wide variety of biologically active drugs.[4]

Synthesis. Our initial approach involved extension of the recent work of Ho and Day[5] to the synthesis of the 1,2-diaminobenzimidazole ring via the cyclization of *o*-acylhydrazidoanilines with cyanogen bromide. The required precursors were prepared from appropriate commercially available para-substituted anilines or *o*-nitroanilines, respectively. Thus, *p*-aminobenzotrifluoride (**1**) was acetylated in nearly quantitative yield with acetic anhydride. The resulting product (**2**) was nitrated with a 60:40 mixture of nitric and sulfuric acids and the intermediate (**3**) then saponified to give the desired substituted *o*-nitroaniline (**4a**).

Diazotization of *o*-nitroanilines (**4a–c**) followed by a sodium bisulfite reduction resulted in the formation of *o*-nitrophenylhydrazines (**5a–c**) which, in turn, were treated with acetic acid to afford the corresponding acetylated derivatives (**6a–c**).

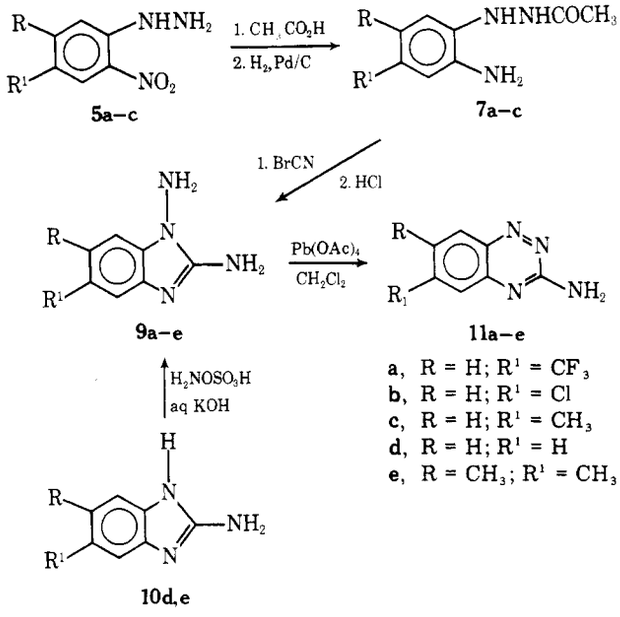
To avoid possible dehalogenation, **6b** was reduced with iron and water. Hydrogenation in a Parr apparatus using a platinum catalyst, although somewhat less effective than iron and water, was significantly faster and was used successfully for both **6a** and **6b.** The reduction of **6c** was accomplished in a Parr apparatus using palladium on carbon as the catalyst.

Cyclization of the reduced compounds was effected by addition of cyanogen bromide to an aqueous suspension of the substituted *o*-acylhydrazidoanilines (**7a–c**). The substituted 1,2-diaminobenzimidazoles (**9a–c**) were obtained by heating the monohydrobromides (**8a–c**) in hydrochloric acid, followed by neutralization with sodium bicarbonate.

Since the above synthesis was rather lengthy, we investigated possible methods of aminating 2-aminobenzimidazoles. After limited success with some of the newer aminating agents such as *O*-(2,4-dinitrophenyl)hydroxylamine,[6] we found hydroxylamine-*O*-sulfonic acid to be useful for this purpose.[7] When the reagent was added to an aqueous suspension of 2-aminobenzimidazole (**10d**) and potassium hydroxide, at ambient temperature, 1,2-diaminobenzimidazole (**9d**) was precipitated after 30 min. 2-Amino-5,6-dimethylbenzimidazole (**10e**) was aminated by the same procedure to afford **9e.** The reactions are summarized in Scheme I.

Reactions. 1,2-Diaminobenzimidazole (**9d**) was found to react preferentially with aldehydes at the 1-amino group. The reaction is catalyzed by a small amount of base. Schiff's bases **12** and **13** could be of considerable interest since the repository activity of antimalarial drugs has often been enhanced by Schiff base formation. Attempts to cyclize **12** to a five-membered ring with copper(II) acetate monohydrate and 2 equiv

Scheme I

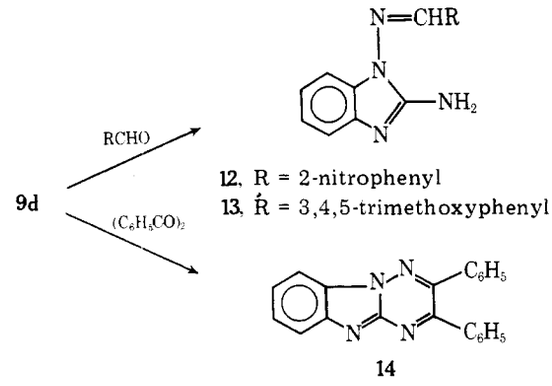


of hydrochloric acid or dilute sulfuric acid were unsuccessful. Only the corresponding salts were formed. The structures of **12** and **13,** as well as of the salts derived from **12,** were ascertained by infrared, ultraviolet, and nuclear magnetic resonance spectroscopy. ^{13}C nuclear magnetic resonance spectra of these compounds enabled us to unequivocally rule out the formation of a five-membered ring and identify the products of the cyclization attempts as the cited salts.

Although it had previously been shown by Ho and Day that 1,2-diaminobenzimidazole (**9d**) reacted with a number of α-dicarbonyl compounds including 2,3-butanedione, 2,3-pentanedione, pyruvic acid and benzoylformic acid, they could not obtain a condensation product with benzil.[8] We found that the desired compound (**14**) could, in fact, be generated in quantitative yield in the presence of potassium hydroxide as a catalyst. These reactions are summarized in Scheme II.

There are several examples in the literature of the synthesis of nitrogen heterocycles via the oxidation of *N*-amino compounds. Baumgarten et al.[9] obtained 3-cinnolinol by the lead tetracetate oxidation of *N*-aminooxindole. Rees et al.[10] synthesized 1,2,3-benzotriazines using either 1- or 2-aminoindazoles. Additional examples involve the formation of pyridazines from 1-amino-2-pyridones, upon loss of carbon monoxide,[11] and the preparation of 1,2,4-benzotriazines from 1-amino-2-quinoxalones.[12] The addition of lead tetraacetate to a solution of each of the 1,2-diaminobenzimidazoles (**9a–e**) in methylene chloride resulted in their oxidative conversion to the appropriately substituted 3-amino-1,2,4-benzotriazines (**11a–e**), thereby illustrating the versatility of the oxidation

Scheme II



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of *N*-amino compounds in synthetic heterocyclic chemistry.

3-Amino-6-chloro-1,2,4-benzotriazine (**11b**) was previously reported by Wolf et al.[13] In a subsequent publication,[14] these authors gave the melting point of the compound as 250–251 °C but did not analyze or further characterize their product. We found the melting point of **11b** to be 277.5–279 °C and both our analytical and spectral data support the postulated structure.

Although the reported mechanisms for the lead tetraacetate oxidation of *N*-amino compounds have invoked nitrene formation and subsequent ring expansion, we were unable to trap a nitrene intermediate either with olefins such as cyclohexene or trichloroethylene or with dimethyl sulfoxide.

Experimental Section

General. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., and Galbraith Laboratories, Knoxville, Tenn. IR spectra were obtained on a Perkin-Elmer 521 double beam grating spectrophotometer equipped with cesium bromide optics. ^{1}H NMR spectra were recorded with a Varian A-60A or JEOL-JNM-PS 100 instrument. ^{13}C NMR spectra were obtained on a JEOL-JNM-PS 100 spectrometer. Mass spectra were determined on a Perkin-Elmer 270-B, a Consolidated Electrodynamics Corp. CEC-110 (double focusing), and a Varian MAT CH-5 mass spectrometer. UV spectra were obtained on a Beckman DB spectrophotometer.

4-Trifluoromethylacetanilide (2). *p*-Aminobenzotrifluoride (10.0 g, 0.0621 mol) was added to 30 ml of acetic anhydride to give crude **2** which was then purified by recrystallization from benzene–chloroform (12 g, 95% yield): mp 151–152 °C (lit.[15a] mp 152 °C, lit.[15b] 150–151 °C); IR (KBr) 3400, 3375, 3200 (NH), 1670 cm^{-1} (CO); ^{1}H NMR (Me_2CO-d_6) δ 2.17 (s, 3 H, CH_3), 7.61 (d, 2 H, $J_{H\text{-}5,H\text{-}6}$ = 9 Hz, H-3 and H-5), 7.91 (d, 2 H, $J_{H\text{-}5,H\text{-}6}$ = 9 Hz, H-2 and H-6), and 9.55 (broad s, 1 H, NH).

2-Nitro-4-trifluoromethylacetanilide (3). Compound **2** (5.00 g, 0.0246 mol) was nitrated with a 60:40 mixture of nitric and sulfuric acids (50 ml). Recrystallization of the crude product from absolute ethanol gave 5.47 g (90% yield) of **3:** mp 110.5–112 °C (lit.[16] mp 112–113 °C); IR (KBr) 3400, 3300 (NH), 1715 (CO), 1525, and 1365 cm^{-1} (NO_2); ^{1}H NMR (Me_2CO-d_6) δ 2.28 (s, 3 H, CH_3), 7.87–9.10 (m, 3 H, aromatic H), and 10.27 (broad s, 1 H, NH).

2-Nitro-4-trifluoromethylaniline (4a). Compound **3** (5.00 g, 0.002 mol) was heated with potassium hydroxide in a minimum amount of aqueous ethanol for 30 min. The mixture was then added to 75 ml of cold water to afford a bright yellow precipitate. This solid was then chromatographed on silica gel using a 1:1 chloroform–benzene solution to yield 3.89 g (94% yield) of **4a:** mp 105–106.5 °C (lit.[16] mp 106–107 °C); IR (KBr) 3400, 3260, 3100 (NH), 1525, and 1348 cm^{-1} (NO_2); H^1 NMR (Me_2SO-d_6) δ 7.21 (d, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 9 Hz, H-6), 7.54 (dd, 1 H, $J_{H\text{-}2,H\text{-}6}$ = 2 Hz, H-5), 7.72 (broad s, 2 H, NH_2), and 8.27 (broad s, 1 H, H-3).

2-Nitro-4-trifluoromethylphenylhydrazine (5a). A solution of sodium nitrite (13.70 g, 0.198 mol) in 25 ml of water was added dropwise to a stirred mixture of **4a** (31.0 g, 0.150 mol) and 52.5 ml of concentrated hydrochloric acid at −7 °C. The reaction mixture was filtered and the filtrate added to a stirred solution of sodium sulfite (47.5 g, 0.377 mol) and sodium hydroxide (10.0 g, 0.25 mol) in 250 ml of water at −5 °C. Concentrated hydrochloric acid (37.5 ml) was added to the mixture and the temperature of the solution was then raised to 50 °C for 30 min. The yellow solid that formed on cooling was collected, added to 150 ml of concentrated hydrochloric acid, and heated on a steam bath until the yellow solid was converted to a brown precipitate. The brown precipitate was dissolved in a minimum amount of hot water. Insoluble tars were removed by filtration and the filtrate was made basic with a saturated aqueous sodium acetate solution. The free base was collected and recrystallized from benzene to give 13 g (39% yield) of bright orange needles: mp 115–116 °C (lit.[17] mp 112–113 °C); IR (KBr) 3450, 3300 (NH_2), 1560, and 1310 cm^{-1} (NO_2); ^{1}H NMR ($MeNO_2$-d_3) δ 4.28 (s, 2 H, NH_2), 7.66 (dd, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 9.5, $J_{H\text{-}3,H\text{-}5}$ = 2 Hz, H-5), 7.88 (dd, 1 H, $J_{H\text{-}3,H\text{-}6}$ = 1 Hz, H-6), 8.36 (dd, 1 H, H-3), and 9.23 (s, 1 H, NH).

4-Chloro-2-nitrophenylhydrazine (5b). This compound was prepared by the procedure described for **5a** using 25.50 g (0.148 mol) of 4-chloro-2-nitroaniline. The solid obtained was recrystallized from benzene to yield 20.6 g (74.3%) of brownish-red needles: mp 135–136 °C (lit.[18] mp 134 °C); IR (KBr) 3400, 3250 (NH_2), 1550 and 1340 cm^{-1} (NO_2); ^{1}H NMR (Me_2SO-d_6) δ 4.23 (broad s, 2 H, NH_2), 7.53 (dd, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 10, $J_{H\text{-}5,H\text{-}5}$ = 2 Hz, H-5), 7.73 (dd, 1 H, $J_{H\text{-}3,H\text{-}6}$ = 1 Hz, H-6), 7.98 (dd, 1 H, H-3), and 9.18 (broad s, 1 H, NH).

4-Methyl-2-nitrophenylhydrazine (5c). This compound was prepared via the procedure described for **5a** using 10.9 g (0.158 mol) of sodium nitrite in 20 ml of water and 18.0 g (0.118 mol) of 4-methyl-2-nitroaniline. The filtrate was added to a stirred solution of sodium sulfite (38.00 g, 0.3015 mol) and sodium hydroxide (8.0 g, 0.2 mol) in 200 ml of water at −5 °C. The resulting red product was recrystallized from benzene to give 13.0 g of **5c** (66% yield): mp 110–112 °C (lit.[19] mp 110 °C); IR (KBr) 3250 (NH_2), 1550 and 1340 cm^{-1} (NO_2); ^{1}H NMR ($MeNO_2$-d_3) δ 2.24 (s, 3 H, CH_3), 3.95 (broad s, 2 H, NH_2), 7.34 (dd, 1 H, $J_{H\text{-}5,H\text{-}6}$ = 9.5, $J_{H\text{-}3,H\text{-}5}$ = 2 Hz, H-5), 7.58 (dd, 1 H, $J_{H\text{-}3,H\text{-}6}$ = <1 Hz, H-6), 7.86 (dd, 1 H, H-3), and 8.73 (broad s, 1 H, NH).

2-Acethydrazido-5-trifluoromethylnitrobenzene (6a). A solution of **5a** (3.20 g, 0.0145 mol) in 10 ml of glacial acetic acid was heated on a steam bath for 1.5 h. Addition of 50 ml of cold water to this solution induced the precipitation of crude product which was purified by recrystallization from chloroform to give 3.00 g (79% yield) of **6a** as bright yellow needles: mp 186–187 °C; IR (KBr) 3280, 3180 (NH), 1655 (CO), 1535, and 1340 cm^{-1} (NO_2); ^{1}H NMR (Me_2CO-d_6) δ 2.05 (s, 3 H, CH_3), 5.17 (m, 1 H, NH), 7.44 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ = 9 Hz, H-3), 7.85 (d, 1 H, H-4), 8.48 (s, 1 H, H-6), and 9.43 (broad s, 1 H, NHCO).

Anal. Calcd for $C_9H_8F_3N_3O_3$: C, 41.07; H, 3.06; N, 15.97. Found: C, 40.89; H, 3.11; N, 16.09.

2-Acethydrazido-5-chloronitrobenzene (6b). A solution of **5b** (20.60 g, 0.110 mol) was acetylated with 85 ml of glacial acetic acid as described for **6a.** The product was recrystallized from chloroform to give 18.0 g (71% yield) of **6b** as orange needles: mp 164.5–165.5 °C; IR (KBr) 3280, 3190 (NH), 1650 (CO), 1535 and 1330 cm^{-1} (NO_2); ^{1}H NMR (Me_2SO-d_6) δ 2.00 (s, 3 H, CH_3), 3.51 (broad m, 1 H, NH), 7.20 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ = 9.5 Hz, H-3), 7.61 (dd, 1 H, $J_{H\text{-}4,H\text{-}6}$ = 2.5 Hz, H-4), 8.11 (d, 1 H, H-6), and 9.29 (broad s, 1 H, NHCO).

Anal. Calcd for $C_8H_8ClN_3O_3$: C, 41.82; H, 3.51; N, 18.31. Found: C, 41.62; H, 3.59; N, 18.21.

2-Acethydrazido-5-methylnitrobenzene (6c). A solution of **5c** (2.5 g, 0.015 mol) was acetylated with 9 ml of glacial acetic acid as described for **6a.** The product was recrystallized from chloroform to give 1.94 g (62% yield) of **6c** as orange needles: mp 168–169.5 °C; IR (KBr) 3250, 3200 (NH), 1650 (CO), 1515 and 1325 cm^{-1} (NO_2); ^{1}H NMR (Me_2SO-d_6) δ 2.00 (s, 3 H, $COCH_3$) 2.28 (s, 3 H, CH_3), 3.37 (broad s, 1 H, NH), 7.07 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ = 9 Hz, H-3), 7.46 (dd, 1 H, $J_{H\text{-}4,H\text{-}6}$ = 2 Hz, H-4), 7.93 (d, 1 H, H-6), and 9.03 (s, 1 H, NHCO).

Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.55; H, 5.18; N, 20.14.

2-Acethydrazido-5-trifluoromethylaniline (7a). A solution of **6a** (1.026 g, 0.0039 mol) in 50 ml of absolute ethanol was hydrogenated in a Parr apparatus for 30 min at 50 psi using 0.1 g of 5% platinum on carbon.

The product was recrystallized from ethyl acetate and ether to give 0.86 g (94% yield) of **7a** as a white solid: mp 166–167 °C; IR (KBr) 3300, 3150 (NH), and 1670 cm^{-1} (CO); ^{1}H NMR (Me_2SO-d_6) δ 1.92 (s, 3 H, CH_3), 5.02 (broad s, 2 H, NH_2), 6.50–7.28 (m, 4 H, aromatic H and NH), and 9.70 (s, 1 H, NHCO).

Anal. Calcd for $C_9H_{10}F_3N_3O$: C, 46.35; H, 4.32; N, 18.02. Found: C, 46.51; H, 4.43; N, 18.30.

2-Acethydrazido-5-chloroaniline (7b). This compound was obtained by the hydrogenation of a solution of **6b** (1.0 g, 0.004 mol) in 50 ml of ethanol as described for **7a.** The product was recrystallized

from benzene to give 0.48 g (55% yield) of **7b** as a white solid, mp 124–125 °C. Compound **6b** (7.34 g, 0.032 mol) in 200 ml of benzene was also reduced with activated iron (56.0 g, 1.0 mol) to give 3.9 g (61% yield) of **7b:** IR (KBr) 3300, 3250, 3200, 3175 (NH), and 1650 cm^{-1} (CO); ^1H NMR (Me_2CO-d_6) δ 1.95 (s, 3 H, CH_3), 3.03 (broad s, 1 H, NH_2), 4.58 (broad s, 1 H, NH_2), 6.38 (broad s, 1 H, NH), 6.38–6.95 (m, 3 H, aromatic H), and 9.05 (broad s, 1 H, NHCO).

Anal. Calcd for $C_8H_{10}ClN_3O$: C, 48.11; H, 5.05; N, 21.06. Found: C, 48.37; H, 4.93; N, 21.28.

2-Acethydrazido-5-methylaniline (7c). This compound was prepared by the hydrogenation of **6c** (4.00 g, 0.019 mol) in 150 ml of absolute ethanol using 0.2 g of 10% palladium on carbon (Parr apparatus, 1 h at 60 psi). The product was recrystallized from benzene to give 2.9 g (86% yield) of **7c** as orange-brown needles: mp 117.5–119 °C; IR (KBr) 3375, 3280, 3250, 3180 (NH), and 1650 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 1.88 (s, 3 H, $COCH_3$), 2.10 (s, 3 H, CH_3), 3.47 (broad s, 2 H, NH_2), 4.48 (broad s, 1 H, NH), 6.13–6.72 (m, 3 H, aromatic H), 9.53 (broad s, 1 H, NHCO).

Anal. Calcd for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.35; H, 7.32; N, 23.19.

1-Acetamido-2-amino-5-trifluoromethyl-1*H*-benzimidazole Hydrobromide Monohydrate (8a). Compound **7a** (0.440 g, 0.0019 mol) in 10 ml of water was added to a solution of cyanogen bromide (1.16 g, 0.011 mol) in 10 ml of water and the mixture stirred at room temperature for 2 h. The water was then removed under reduced pressure and the resulting solid was recrystallized from acetonitrile to give 0.41 g (60% yield) of **8a:** mp 249.5–251 °C; IR (KBr) 3350, 3200, 3125 (NH), and 1725 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 2.23 (s, 3 H, CH_3), 4.82 (broad s, HBr and H_2O), 7.30–8.00 (m, 3 H, aromatic H), 9.37 (broad s, 2 H, NH_2), and 11.60 (broad s, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}BrF_3N_4O \cdot H_2O$: C, 33.63; H, 3.39; N, 15.69. Found: C, 33.24; H, 3.23; N, 15.62.

1-Acetamido-2-amino-5-chloro-1*H*-benzimidazole Hydrobromide (8b). Compound **7b** (0.119 g, 0.0006 mol) in 10 ml of water was mixed with a solution of cyanogen bromide (0.291 g, 0.00275 mol) in 10 ml of water as described for **8a.** The product was recrystallized from absolute ethanol to give 0.16 g (87% yield) of **8b:** mp 306–308 °C; IR (KBr) 3400, 3200, 3150 (NH), and 1740 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 2.18 (s, 3 H, CH_3), 4.53 (broad s, HBr), 7.17–7.67 (m, 3 H, aromatic H), 9.23 (broad s, 2 H, NH_2), and 11.51 (broad s, 1 H, NH).

Anal. Calcd for $C_9H_{10}BrClN_4O$: C, 35.35; H, 3.30; N, 18.34. Found: C, 35.38; H, 3.58; N, 17.87.

1-Acetamido-2-amino-5-methyl-1*H*-benzimidazole Hydrobromide Monohydrate (8c). Compound **7c** (1.87 g, 0.0104 mol) in 50 ml of water was mixed with a solution of cyanogen bromide (1.10 g, 0.010 mol) in 10 ml of water as described for **8a.** The product was recrystallized from acetonitrile to give 2.17 g (69% yield) of **8c:** mp 254.5–255.5 °C; IR (KBr) 3400, 3350, 3200 (NH), and 1720 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 2.22 (s, 3 H, $COCH_3$), 2.40 (s, 3 H, CH_3), 5.15 (broad s, HBr and H_2O), 6.72–7.45 (m, 3 H, aromatic H), 8.97 (broad s, 2 H, NH_2), and 11.45 (broad s, 1 H, NH).

Anal. Calcd for $C_{10}H_{13}BrN_4O \cdot H_2O$: C, 39.61; H, 4.99; N, 18.48. Found: C, 39.58; H, 4.99; N, 18.37.

1,2-Diamino-5-trifluoromethyl-1*H*-benzimidazole (9a). A solution of **8a** (0.630 g, 0.0018 mol) in 4.5 ml of 4 N hydrochloric acid was refluxed for 1 h. The solution was cooled and then made basic with a saturated sodium bicarbonate solution. The precipitate that formed was recrystallized from absolute ethanol to give 0.35 g (93% yield) of **9a:** mp 250–251 °C; IR (KBr) 3400, 3275, and 3100 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 5.75 (s, 2 H, NNH_2), 6.67 (s, 2 H, NH_2), 7.30–7.48 (m, 3 H, aromatic H); UV λ_{max} (ethanol) (log ϵ) 285 (3.80), 256 sh (3.50), and 247 nm (3.64); λ_{max} (ethanol, H^+) (log ϵ) 282 (3.82), 276 (3.84), 243 (3.49), and 234 nm (3.75).

Anal. Calcd for $C_8H_7F_3N_4$: C, 44.45; H, 3.22; N, 25.92; F, 26.37. Found: C, 44.19; H, 3.11; N, 25.72; F, 26.59.

1,2-Diamino-5-chloro-1*H*-benzimidazole (9b). A solution of **8b** (0.500 g, 0.0016 mol) in 60 ml of 4 N hydrochloric acid was refluxed for 1 h and then treated as described for **9a.** The product was recrystallized from ethanol–benzene to afford 0.20 g (67% yield) of **9b:** mp 274–275 °C; IR (KBr) 3375, 3240, and 3140 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 5.55 (s, 2 H, NNH_2), 6.37 (s, 2 H, NH_2), 6.75–7.18 (m, 3 H, aromatic H); UV λ_{max} (ethanol) (log ϵ) 290 (3.53), 254 (3.34), and 249 nm (3.36); λ_{max} (ethanol, H^+) (log ϵ) 289 (3.48), 283 (3.53), 240 sh (3.28) and 232 nm sh (3.53).

Anal. Calcd for $C_7H_7ClN_4$: C, 46.02; H, 3.87; N, 30.69. Found: C, 45.95; H, 4.03; N, 30.48.

1,2-Diamino-5-methyl-1*H*-benzimidazole (9c). A solution of **8c** (1.00 g, 0.0033 mol) in 120 ml of 4 N hydrochloric acid was refluxed for 1 h and then treated as described for **9a.** The product was recrystallized from absolute ethanol to afford 0.50 g (94% yield) of **9c:** mp 296.5–298 °C; IR (KBr) 3340, 3200, and 3050 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 2.32 (s, 3 H, CH_3), 5.48 (s, 2 H, NNH_2), 6.08 (s, 2 H, NH_2), and 6.67–7.10 (m, 3 H, H-4, aromatic H); UV λ_{max} (ethanol) (log ϵ) 286 (4.18) and 248 nm (4.02); λ_{max} (ethanol, H^+) (log ϵ) 285 (4.17), 279 (4.23), 276 sh (4.18), and 231 nm sh (4.30).

Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.29; H, 6.01; N, 34.56.

Amination of 2-Aminobenzimidazole (10d). A. With *O*-(2,4-Dinitrophenyl)hydroxylamine. A solution of **10d** (1.33 g, 0.01 mol) in 50 ml of methanol was treated with sodium (0.23 g, 0.01 g-atom) in 30 ml of the same solvent. Evaporation of the solvent afforded a solid which was then dissolved in 100 ml of dry dimethylformamide and mixed with 1 equiv of *O*-(2,4-dinitrophenyl)hydroxylamine (1.99 g, 0.01 mol) at room temperature. After the solvent was removed under reduced pressure, the residue was then triturated with benzene, collected by filtration, and treated with aqueous sodium bicarbonate to afford 1,2-diaminobenzimidazole (**9d**) as an off-white solid (0.52 g, 35% yield), mp 248–252 °C (lit.[5] mp 256–259 °C).

B. With Hydroxylamine-*O*-sulfonic Acid. Hydroxylamine-*O*-sulfonic acid (9.30 g, 0.082 mol) was added to a solution of **10d** (10.0 g, 0.075 mol) and potassium hydroxide (9.82 g, 0.175 mol) in 200 ml of water at 25 °C. The reaction mixture was stirred at ambient temperature for 30 min. The solid that formed was collected and recrystallized from ethanol to afford 5.50 g (49.5% yield) of **9d,** mp 255–258 °C (lit.[5] mp 256–259 °C). The aqueous filtrate was evaporated and the remaining solid extracted with hot ethanol to give 3.5 g of **10d.** Based on recovered starting material, the yield of **9d** was 76%.

Amination of 2-Amino-5,6-dimethylbenzimidazole (10e). A solution of **10e** (1.61 g, 0.01 mol) in 100 ml of 0.85 N potassium hydroxide was treated overnight with hydroxylamine-*O*-sulfonic acid (1.24 g, 0.011 mol). The solid that formed was collected and recrystallized from ethanol to afford 0.44 g (25% yield) of **9e,** mp 292–294 °C. Evaporation of the ethanol filtrate gave 0.57 g (35% recovery) of **10e.** The corrected yield of **9e** was 38.5%: IR (KBr) 3330, 3200, and 3050 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 2.22 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 5.38 (broad s, 2 H, NNH_2), 5.88 (broad s, 2 H, NH_2), and 6.89 (s, 2 H, aromatic H); UV λ_{max} (ethanol) (log ϵ) 287 (4.01) and 243 nm (3.86); λ_{max} (ethanol, H^+) (log ϵ) 287 (4.03), 282 (4.06), 280 (4.04), and 232 nm (4.09).

Reactions of 1,2-Diaminobenzimidazole (9d). 1. With Aldehydes. 2-Amino-1-[(*o*-nitrobenzylidene)amino]benzimidazole (12). A mixture of 0.592 g (0.004 mol) of **9d** in 20 ml of ethanol and *o*-nitrobenzaldehyde (0.60 g, 0.004 mol) in 20 ml of ethanol was refluxed for 2 h to yield 0.84 g of **12a** (75% yield) as orange needles, mp 259–260 °C. This reaction was found to be catalyzed by base. When **9d** (1.18 g, 0.008 mol) and *o*-nitrobenzaldehyde (1.21 g, 0.008 mol) were heated in 40 ml of ethanol, addition of 2 drops of 2 N potassium hydroxide induced immediate precipitation of **12** as an orange solid (2.2 g, 98% yield): IR (KBr) 3350 (NH), 3000 (=CH), 1660 (C=C), 1510 (C=N), 1550, and 1360 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 6.85 (s, 2 H, NH_2), 6.93–8.66 (m, 8 H, aromatic H), and 9.45 (s, 1 H, N=CH); ^{13}C NMR 154.1 (C-2), 148.4 (C-NO_2), 144.1 (N=C), 142.5 (C-9), 133.6 (C-5′), 131.1 (C-4′), 129.3 (C-8), 128.9 (C-6′), 128.5 (C-1′), 124.6 (C-3′) 122.8 (C-5), 119.4 (C-6), 116.2 (C-4), and 109.9 ppm (C-7); UV λ_{max} (ethanol) (log ϵ) 332 (3.86), 311 (3.92), 268 (4.32), and 209 nm (4.53); λ_{max} (ethanol, H^+) (log ϵ) 327 (3.79), 260 (4.22), 225 (4.32) and 204 nm (4.72); MS *m/e* (%) 281 (97.5), 132 (100).

Anal. Calcd for $C_{14}H_{11}N_5O_2$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.98; H, 4.17; N, 24.94.

2-Amino-1-[(3,4,5-trimethoxybenzylidene)amino]benzimidazole (13). A solution of **9d** (1.48 g, 0.01 mol), 3,4,5-trimethoxybenzaldehyde (1.96 g, 0.01 mol), and 1 ml of 1.7 N KOH in 70 ml of ethanol was refluxed for 30 min. Evaporation of the solvent gave a solid which was recrystallized from ethanol to afford 2.9 g (89% yield) of **13:** mp 183–185 °C; IR (KBr) 3350 (NH), 2998 (=CH), 1650 (C=C), 1535 (C=N), 1565 and 1350 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) 3.79 (s, 3 H, *p*-OCH_3), 3.92 (s, 6 H, *m*-OCH_3), 6.88 (broad s, 2 H, NH_2), 6.92–8.03 (m, 6 H, aromatic H), and 9.03 (s, 1 H, =CH); ^{13}C NMR 154.3 (C-2), 153.1 (C-3′ and C-5′), 147.3 (N=C), 142.3 (C-9), 139.5 (C-4′), 129.6 (C-1′), 129.2 (C-8), 122.2 (C-5), 118.9 (C-6), 115.8 (C-4), 110.5 (C-7), 105.3 (C-2′ and C-6′), 60.1 (*p*-OCH_3), and 56.1 ppm (*m*-OCH_3); UV λ_{max} (ethanol) (log ϵ) 320 (4.11), 282 (4.23), and 228 nm (4.22); λ_{max} (ethanol, H^+) (log ϵ) 320 (4.06), 284 (3.87), 278 (3.87), 256 (3.68), and 222 nm (4.20).

Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.38; H, 5.61; N, 16.98.

Attempts to cyclize **12** by a variety of methods were unsuccessful. When **12** (0.50 g, 0.0018 mol) was refluxed in dilute sulfuric acid, a pale yellow solid formed and was recrystallized from ethanol, mp 233.5–235

°C. This compound was identified as 2-amino-1-[(*o*-nitrobenzylidene)amino]benzimidazole sulfate: IR (KBr) 3300 (NH), 3000 (=CH), 1690 (C=C), 1505 (C=N), 1530 and 1330 cm^{-1} (NO_2); ^1H NMR Me_2SO-d_6) δ 5.63 (broad s, 3 H, NH_2 and H_2SO_4), 7.02–8.72 (m, 8 H, aromatic H), and 9.57 (s, 1 H, =CH); ^{13}C NMR 148.8 (C-2, C-NO_2, and N=C), 135.6 (C-9), 133.9 (C-5′), 131.8 (C-4′), 129.2 (C-6′), 127.9 (C-1′), 125.0 (C-8), 124.7 (C-3′), 123.9 (C-5), 121.4 (C-6), 114.5 (C-4), and 110.5 ppm (C-7).

Anal. Calcd for $C_{28}H_{24}N_{10}O_8S$: C, 50.91; H, 3.66; N, 21.21; S, 4.84. Found: C, 50.42; H, 3.61; N, 20.97; S, 4.96.

2. With Benzil. 2,3-Diphenyl-*as*-triazino[2,3-*a*]benzimidazole (14). Addition of 3 drops of an aqueous 2 N potassium hydroxide solution to a heated solution of **9d** (0.296 g, 0.002 mol) and benzil (0.420 g, 0.002 mol) in 25 ml of ethanol produced immediate formation of a yellow precipitate. The reaction mixture was refluxed, with stirring, for 30 min to afford 0.64 g (94% yield) of **14**: mp 278–281 °C; IR (KBr) 3000 (=CH), 1540, 1500, and 1475 cm^{-1} (C=C); ^1H NMR δ 7.46 (s, 14 H, aromatic H); MS *m/e* (%) 322 (100); UV λ_{max} (ethanol) (log ϵ) 375 (4.01), 270 (4.38), and 202 nm (4.54).

Anal. Calcd for $C_{21}H_{14}N_4 \cdot H_2O$: C, 74.10; H, 4.74. Found: C, 74.40; H, 4.56.

3. With Lead Tetraacetate. 3-Amino-1,2,4-benzotriazine (11d). Lead tetraacetate (1.42 g, 0.003 mol) was added to a suspension of **9d** (0.30 g, 0.002 mol) in 25 ml of methylene chloride. The reaction mixture turned bright yellow and then brown. After 5 min, 3 ml of ethylene glycol was added to destroy any unreacted lead tetraacetate followed by 100 ml of water. The aqueous layer was extracted with methylene chloride; the extract was reduced in volume and then chromatographed on a silica gel column with methylene chloride–ethyl acetate. Elution of the resulting yellow band afforded 0.23 g (80% yield) of **11d**: mp 206–208 °C (lit.[20] mp 207 °C); IR (KBr) 3200, 3050 (NH), 1660 (C=C), and 1545 cm^{-1} (C=N); MS *m/e* (%) 146 (74) and 118 (100); ^1H NMR (Me_2SO-d_6) δ 7.25–8.45 (m, 6 H, aromatic H and NH_2).

Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14. Found: C, 57.29; H, 4.22.

3-Amino-6-trifluoromethyl-1,2,4-benzotriazine (11a). This compound was prepared as described for **11d** and isolated directly from the methylene chloride extracts without resort to column chromatography. Recrystallization of **11a** from ethanol afforded 0.10 g (95% yield): mp 230.5–232 °C; IR (KBr) 3240, 3100 (NH), 1650 (C=C), and 1540 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 280 (3.33), 252 sh (4.07), 236 (4.38), and 203 nm (4.28); ^1H NMR (Me_2SO-d_6) δ 7.53–8.63 (m, 3 H, aromatic H) and 7.92 (broad s, 2 H, NH_2).

Anal. Calcd for $C_8H_5F_3N_4$: C, 44.87; H, 2.35; N, 26.16. Found: C, 44.67; H, 2.24; N, 26.01.

3-Amino-6-chloro-1,2,4-benzotriazine (11b). Compound **11b** was prepared and purified as described for **11a.** The yield of **11b** was 0.06 g (48%): mp 277.5–279 °C; IR (KBr) 3200, 3095 (NH), 1675 (C=C), and 1550 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 303 (3.41), 242 (4.30), and 211 nm (4.25); ^1H NMR (Me_2SO-d_6) δ 7.33–8.35 (m, 3 H, aromatic H) and 7.75 (broad s, 2 H, NH_2).

Anal. Calcd for $C_7H_5ClN_4$: C, 46.55; H, 2.79; Cl, 19.63; N, 31.03. Found: C, 46.22; H, 2.65; Cl, 19.40; N, 30.99.

3-Amino-6-methyl-1,2,4-benzotriazine (11c). This compound was prepared as described for **11d** and purified by chromatography on a silica gel column with a 1:3 mixture of acetonitrile and ethyl acetate. Recrystallization of **11c** from ethanol afforded 0.09 g (57% yield) of a bright yellow solid: mp 242–244 °C; IR (KBr) 3200, 3080 (NH), 1650 (C=C), and 1540 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 308 (3.38), 237 (4.24), and 208 nm (4.22); ^1H NMR (Me_2SO-d_6) δ 2.48 (s, 3 H, CH_3), 7.13–8.23 (m, 3 H, aromatic H), and 7.44 (broad s, 2 H, NH_2).

Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03. Found: C, 59.78; H, 4.70.

3-Amino-6,7-dimethyl-1,2,4-benzotriazine (11e). Compound **11e** was prepared and purified as described for **11a.** The yield of **11e** was 0.06 g (73%): mp 286–288 °C (lit.[21] mp 286 °C); IR (KBr) 3200, 3140 (NH), 1650 (C=C), and 1520 cm^{-1} (C=N); UV λ_{max} (ethanol) (log ϵ) 308 (3.70), 238 (4.61), and 208 nm (4.53); ^1H NMR (Me_2SO-d_6) δ 2.40 (broad s, 6 H, CH_3), 7.28 (s, 1 H, H-5), 7.36 (s, 2 H, NH_2), and 8.78 (s, 1 H, H-8).

Registry No.—**1,** 455-14-1; **2,** 349-97-3; **3,** 396-12-3; **4a,** 400-98-6; **4b,** 89-63-4; **4c,** 89-62-3; **5a,** 1513-50-4; **5b,** 54454-57-8; **5c,** 50707-83-0; **6a,** 60882-61-3; **6b,** 60882-62-4; **6c,** 60882-63-5; **7a,** 60882-64-6; **7b,** 60882-65-7; **7c,** 60882-66-8; **8a,** 60882-67-9; **8b,** 60882-68-0; **8c,** 60882-69-1; **9a,** 60882-70-4; **9b,** 60882-71-5; **9c,** 60882-72-6; **9d,** 29540-87-2; **9e,** 60882-73-7; **10d,** 934-32-7; **10e,** 29096-75-1; **11a,** 60882-74-8; **11b,** 60882-75-9; **11c,** 60882-76-0; **11d,** 20028-80-2; **11e,** 27238-42-2; **12,** 60882-77-1; **12** sulfate, 60882-78-2; **13,** 60882-79-3; **14,** 60882-80-6; cyanogen bromide, 506-68-3; *o*-nitrobenzaldehyde, 552-89-6; 3,4,5-trimethoxybenzaldehyde, 86-81-7; acetic anhydride, 108-24-7; benzil, 134-81-6.

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