# First synthesis of 6,7-diaminoindole and 1,2,5-selenadiazolo[3,4-*g*]indole

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## Abstract

5-Methyl-4-nitro-2,1,3-benzoselenadiazole (**1**) was converted into 1,2,5-selenadiazolo[3,4-*g*]indole (**3**) by the Batcho-Leimgruber indole synthesis. Subsequent deselenation afforded 6,7-diaminoindole (**4**) which on treatment with biacetyl afforded 2,3-dimethylpyrrolo[2,3-*f*]quinoxaline (**5**) in 80% yield from **3**.

**Keywords:** Benzoselenadiazole, diaminoindole, deselenation, quinoxaline

## Introduction

Aromatic amines represent an important class of compounds for a wide variety of pharmaceuticals, pesticides, additives and dyes. In recent years, mutagenic aminoimidazo-quinoxalines, -quinolines and -naphthyridines have been prepared[1] for analytical purposes and for structure-biological activity studies related to food carcinogens.[2] Retrosynthetic analysis of some needed bioisosteric pyrroloquinoxalines led to 6,7-diaminoindole (**4**). Surprisingly, although derivatives of **4** are known,[3] the unsubstituted indole **4** has not been reported. Moreover, neither has the possible precursor 6,7-dinitroindole nor any suitable amino-nitro(so)indole. On the other hand, deselenation of 2,1,3-benzoselenadiazoles (bsd) has previously afforded *ortho*-benzenediamines which have then been conveniently converted into, *eg*, less accessible 4-nitrobenzimidazoles[4] and elusive 5-nitroquinoxalines.[5] Thus, we thought that the unsubstituted indole **4** might be obtained from the readily available **1**[6] via the novel 1,2,5-selenadiazolo[3,4-*g*]indole (**3**).

This paper communicates the first preparation of selenadiazoloindole **3** and diaminoindole **4**, together with an illustration of their synthetic use en route to nitrogen heterocycles.
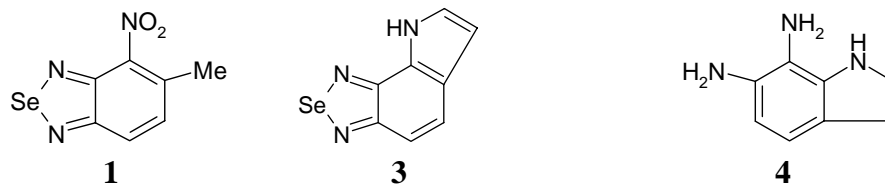
Batcho-Leimgruber indole synthesis[7] on bsd **1**, using *N,N*-dimethylformamide dimethyl acetal (DMFDMA) in acetonitrile or DMF gave the *trans* isomer ($J$ = 13.1 Hz) of enamine **2** in 84% isolated yield. The reductive cyclization is usually done with hydrogen over a palladium catalyst or with Raney nickel and hydrazine.[7] Attempts to transform **2** into **3** by hydrogenation over 10% Pd-C in THF, at ambient conditions and up to 50 psi, gave only intact **2**. Further, no traces of **3** were detected in the dark reaction mixtures produced when hydrogen and Raney nickel in THF and/or alcohols were employed at various temperatures. Heating **2** with hydrazine hydrate and Raney nickel in THF and/or alcohols gave the desired **3** in less than 10% yield. However, more efficient ring closure to **3** was eventually achieved by heating **2** with iron powder in acetic acid and ethanol, conditions known to convert 4-nitro-bsd into the amino compound without substantial deselenation.[8]
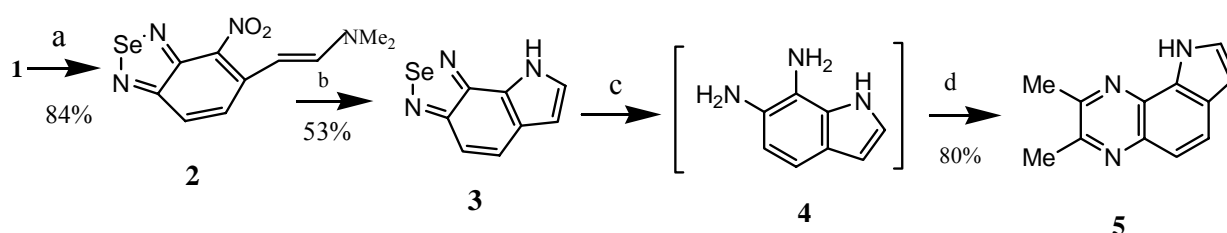


Reagents and conditions: (a) DMFDMA, DMF, 60 °C, 3 h or MeCN, reflux, 2 h; (b) Fe, AcOH:EtOH 1:1, reflux, 30 min; (c) 80% $N_2H_4$, Raney nickel, MeOH, reflux, 4 h; (d) $Ac_2$, MeOH, 56 °C, 2.5 h.

Deselenation of bsd is usually accomplished by, *eg*, hydrogen iodide in hydrochloric acid,[4,5] stannous chloride and hydrochloric acid,[9] zinc and hydrochloric acid[10] or by ammonium sulfide.[1a,4,5a] Because of the potential oligomerization of the 2-unsubstituted indole **3** in acid,[11] we first attempted deselenation by ammonium sulfide in ethanol. In contrast to previous efficient deselenations with this reagent,[1a,4,5a] only a small amount of **3** was deselenated even in higher boiling alcohols. However, the desired diaminoindole **4**[12] could be obtained in high yield by heating **3** with hydrazine hydrate and Raney nickel. Treating crude **4** with selenium dioxide gave selenadiazoloindole **3**, quantitatively and spontaneously as indicated by TLC. Furthermore, crude **4** was treated with diacetyl to provide the apparently unknown pyrroloquinoxaline **5** in 80% isolated yield from **3**. Other pyrrolo[2,3-*f*]quinoxalines have been prepared and tested for biological activity.[13] Derivatives of the sulfur analogue of **3** have been obtained via Fisher indole synthesis on 4-amino-benzothiadiazole.[3,14]

In conclusion, the Batcho-Leimgruber indole synthesis has been successfully applied to **1** for the

synthesis of unsubstituted 6,7-diaminoindole. Since the indole unit occurs widely in nature, and its chemistry is one of the most active areas of heterocyclic chemistry, we believe that access to *ortho*-diaminoindoles will find many applications. *ortho*-Diamines are easily transformed into, *eg*, benzimidazoles, quinoxalines and benzodiazepines which are often found in numerous pharmaceuticals. Work is in progress on the preparation of the isomeric 5,6- and 4,5-diaminoindoles.

## Experimental Section

**General Procedures.** Yields are not optimized. Evaporations were performed under reduced pressure at 40 $^o$C. All reactions and purifications were monitored by thin layer chromatography (UV detection and Van Urk's reagent[15]) on aluminium sheets coated with silica gel 60 $F_{254}$ plates (Merck). 'Flash' and 'dry flash' column chromatography was performed on silica gel 60 (35-70 $\mu$, Grace). Melting points (uncorrected) were determined on a Büchi Melting Point B-545. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX 300 spectrometer at 25 $^o$C, and referenced to the solvent (Me$_2$SO $\delta_H$ 2.50 and $\delta_C$ 39.5 or CHCl$_3$ $\delta_H$ 7.26 and $\delta_C$ 77.0). Gradient HMBC experiments were used for the assignments. Coupling constants $J$ are given in Hz and without sign. The infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 instrument. The electrospray mass spectra were taken on a Perkin-Elmer API 150Ex spectrometer and the EI (70 eV, direct insertion) mass spectrum of **1** was taken on a Micromass Platform spectrometer. Ions containing isotopes other than $^{80}$Se are not listed.

**Materials.** Unless otherwise stated, these were commercial samples. All organic solvents were either freshly distilled or of *pa* quality. Solvent mixtures are defined by volume ratios (v/v). Petrol refers to petroleum ether, bp 60-70 $^o$C.

**5-Methyl-4-nitro-2,1,3-benzoselenadiazole (1).** Prepared as in the lit.[6a] Mp: 196-8 $^o$C [lit.[6a] 192-4 $^o$C; lit.[6b] 194-5 $^o$C]. $^1$H NMR (DMSO-$d_6$) $\delta$ 7.98 (1H, d, $J$ = 9.2, 7-H), 7.60 (1H, d, $J$ = 9.2, 6-H), 2.44 (3H, s, Me); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 158.25 (7a-C), 150.63 (3a-C), 141.69 (4-C), 131.92 (7-C), 131.61 (5-C), 125.46 (6-C), 16.99 (Me); IR (KBr, *cf* lit.[6c]) 3084, 1617, 1527, 1504, 1493, 1381, 1359, 1343, 1323, 1276, 823, 733 cm$^{-1}$; MS *m/z*: 243 (M$^+$, 32), 226 (42, M-OH, *ortho*-effect), 213 (5, M-NO), 197 (5, M-NO$_2$), 117 (100).

**(*E*)-5-[2-(Dimethylamino)ethenyl]-4-nitro-2,1,3-benzoselenadiazole (2).** Oven-dried and septum-capped flasks were used. DMFDMA (2.8 mL, 21 mmol) was added dropwise from a syringe, at rt, to a stirred slurry of benzoselenadiazole **1** (2.2 g, 9 mmol) in acetonitrile (30 mL) under a nitrogen atmosphere. The mixture darkened during the addition. Heating at reflux for **2** h (TLC: petrol/EtOAc 1:1) gave a dark red solution which was concentrated to give 2.2 g of **2** (84%). This was converted into **3** without further purification. An analytical sample was obtained by crystallization from isopropanol: mp 186-7$^o$C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.99 (1H, d, $J$ = 9.8, 7-

H), 7.92 (1H, d, $J$ = 13.1, 2′-H), 7.68 (1H, dd, $J$ = 9.85, 0.5, 6-H), 5.41 (1H, d, $J$ = 13.1, 1′-H), 3.01 (6H, s, $N$-Me); ^{13}C NMR (DMSO-$d_6$) δ 157.08 (7a-C), 152.82 (3a-C), 149.93 (2′-C), 135.39 (5-C), 132.84 (4-C), 127.11 (6-C), 124.77 (7-C), 88.09 (1′-C), 41.35 ($N$-Me); IR (KBr) 2919, 2802, 1620, 1599, 1484, 1394, 1238, 1115, 976, 814, 750 cm$^{-1}$; MS $m/z$: 299 (MH$^+$).

**1,2,5-Selenadiazolo[3,4-$g$]indole (3).** A mechanically stirred mixture of **2** (1.5 g, 5.0 mmol) and iron powder (3.0 g, 53.7 mmol) in absolute ethanol/glacial acetic acid 1:1 (60 mL) was cautiously heated to reflux under a nitrogen atmosphere. After 30 min (TLC: petrol/EtOAc 1:1) the mixture was allowed to reach rt, poured into water (130 mL) and filtered through Celite. The pad was washed with Et$_2$O (150 mL). After separating the ether, the aqueous layer was further extracted with Et$_2$O (2x). The organic layer was washed with water and saturated Na$_2$CO$_3$ solution until the aqueous layer reached pH 8. The ether layer was washed with brine, filtered and concentrated onto silica. 'Dry flash' chromatography (petrol/EtOAc 1:1) and collection of the yellow band gave 590 mg (53%) of **3**. An analytical sample was obtained by sublimation under vacuum: mp 190-2 $^o$C; ^{1}H NMR (CDCl$_3$) δ 9.6 (1H, br s, 8-H), 7.70 (1H, dd, $J$ = 9.3, 0.4, 5-H), 7.42 (1H, d, $J$ = 9.3, 4-H), 7.27 (1H, dd, $J$ = 3.1, 2.3, 7-H), 6.61 (1H, dd, $J$ = 2.8, 2.3, 6-H); ^{1}H NMR (DMSO-$d_6$) δ 12.5 (1H, br s, 8-H), 7.73 (1H, d, $J$ = 9.2, 5-H), 7.36 (1H, app t, $J$ = 2.7, 7-H), 7.31 (1H, d, $J$ = 9.2, 4-H), 6.57 (1H, dd, $J$ = 2.6, 2.0, 6-H); ^{13}C NMR (DMSO-$d_6$) δ 159.53 (3a-C), 150.72 (8b-C), 126.80 (5-C), 125.72 (5a-C), 124.63 (8a-C), 124.57 (7-C), 115.09 (4-C), 104.57 (6-C); IR (KBr) 3157, 3089, 2996, 2900, 1606, 1539, 1496, 1410, 1365, 1329, 1276, 1248, 1028, 775, 653 cm$^{-1}$; MS $m/z$: 224 (MH$^+$).

**2,3-Dimethylpyrrolo[2,3-$f$]quinoxaline (5).** To a stirred solution of **3** (160 mg, 0.7 mmol) and 80% hydrazine hydrate (82 µL, 2.1 mmol) in MeOH (40 mL), at rt, was added a spatulatip of Raney nickel (W-2) under a nitrogen atmosphere. Evolution of gas took place. The reaction mixture was heated to reflux and an additional 82 µL of 80% hydrazine hydrate was added after 3 h at reflux. After 45 min (TLC: EtOAc) the mixture was allowed to cool to rt, filtered through Celite, and the pad was washed with MeOH (40 mL). The light yellow filtrate containing **4**[12] (which turned red upon exposure to air) was placed under a nitrogen atmosphere, and diacetyl (123 µL, 1.4 mmol) was added. The solution was stirred at 56 $^o$C for 2 h. TLC (EtOAc) indicated some unreacted **4**. An additional portion of diacetyl (61 µL) was added and after another 30 min TLC indicated complete consumption of **4**. The reaction mixture was diluted with water (10 mL) and evaporated to about half of the original volume, whereupon crystals formed. The mixture was cooled, the precipitate was collected and dried in a vacuum desiccator to give 65 mg of **5**. The mother liquor was diluted with CH$_2$Cl$_2$ and brine. The aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic phases were washed with water and brine. Drying (Na$_2$SO$_4$) and evaporation of the solvent afforded another 48 mg of **5**. Yield: 80%. An analytical sample was obtained by sublimation under vacuum: mp 243-4 $^o$C; ^{1}H NMR (CDCl$_3$) δ 9.8 (1H, br s, 9-H), 7.89 (1H, d, $J$ = 8.8, 6-H), 7.63 (1H, d, $J$ = 8.8, 5-H), 7.37 (1H, dd, $J$ = 3.0, 2.5, 8-H), 6.72 (1H, dd, $J$ = 3.0, 2.2, 7-H), 2.74 (6H, s, 2- and 3-Me); ^{13}C NMR (CDCl$_3$) δ 150.61 (3- or 2-C), 150.23 (2- or 3-C), 138.66 (4a-C), 130.81 (9b-C), 129.67 (9a-C), 126.09 (6a-C), 123.91 (8-C), 123.65 (6-C), 120.06 (5-C), 104.11 (7-C), 22.89 (3- or 2-Me), 22.77 (2- or 3-Me); IR (KBr)

3175, 1498, 1379, 1360, 1348, 1167, 796 cm$^{-1}$; MS *m/z*: 198 (MH$^+$).

## Acknowledgments

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