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INTRAMOLECULAR OXIDATIVE CYCLIZATION ON *ORTHO*-PHENYLENEDIAMINES

SYNTHESIS OF 5,6-DIAMINOBENZTHIAZOLES†

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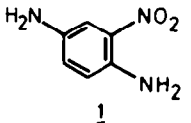
Abstract—A novel intramolecular oxidative cyclization of the 3,4-diaminophenyl thiourea (**3**) to the 5,6-diaminobenzthiazole (**4**) is reported. This conversion can be brought about by Pd/C in presence of atmospheric oxygen in acid solution. It is likely that the quinone-imine (**5**) is an intermediate in this transformation. Surprisingly, catalytic reduction (Pd/C, H_2) of the 4-amino-3-nitrophenyl thiourea (**2**) gave both **3** and **4**. A rational 'one-pot' reduction-oxidation sequence (iron/acid, ferric chloride) is described for the preparation of this and other such 5,6-diaminobenzthiazoles from the corresponding 4-amino-3-nitrophenyl thioureas.

In an earlier paper[1] we had described the reaction of 2-nitro-*p*-phenylenediamine (**1**) with methyl isothiocyanate the amine *meta* to the nitro group selectively reacted to produce the thiourea (**2**). As part of a routine synthetic programme, we planned to reduce this nitro-aniline (**2**) to an *ortho*-diamine and cyclize it to a benzimidazole. However, the reduction led to an unexpected product. We present below evidence to prove that this is the result of an intramolecular oxidative cyclization. The possible mechanism of this reaction is also discussed.

Catalytic reduction of the nitroaniline (**2**) in neutral solution was slow; after reduction, evaporation of the solvent and crystallization gave the base (**3**) in about 30% yield. Tlc (EtOAc, silica or alumina plates) indicated the presence of a different product in the mother liquor; this could be isolated as its hydrochloride (**4** .HCl). On the other hand, catalytic reduction of the nitroaniline (**2**) in acid solution gave exclusively (**4** .HCl). Iron/HCl reduction of the nitroaniline (**2**) gave a mixture of **3** and **4**. The proportion of **3** decreased and that of **4** increased as the reaction time was lengthened; after 16 hr at 90°, **4** was formed almost exclusively. The properties of **3** and **4** are listed in Table 1.

From the above data, it is obvious that **3** is the normal, expected reduction product of the nitroaniline (**2**)–(Mol. wt. 196; 3 aromatic protons of a typical 1,2,4-trisubstituted benzene). On the other hand, **4** has a mol. wt. which is two units less than that of **3**; of the two protons thus missing, one is an aromatic proton. The two remaining aromatic protons are not coupled to each other. The structure of **4** thus follows uniquely from this evidence.



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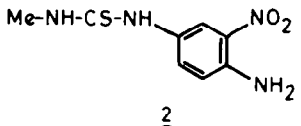

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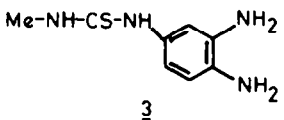

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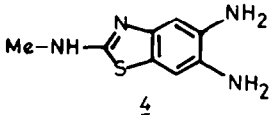

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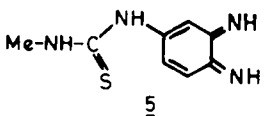

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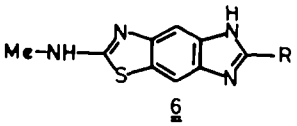

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a: R = H
b: R = CF_3
c: R = $NHCO_2Et$

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Table 1. Properties of 3 and 4

	Compound 3		Compound 4	
	Base	Hydrochloride	Base	Hydrochloride
m.p.	162-164°	240°	191-195°	327-330° (d)
Mass spec. (M^+)	196	-	194	-
^1H NMR: (aromatic region)	3 Ar-H (DMSO-d_6)	3 Ar-H; 8 lines characteristic of 1,2, 4-trisubstituted benzene (D_2O)	-	2 Ar-H; both sharp singlets. (D_2O)

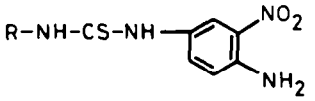
The UV absorption maxima of **3** and **4** are given in Table 2. As expected, the two pairs of spectra are widely different.

Mechanism. We postulate that under neutral conditions, in presence of catalyst, an oxidation/reduction equilibrium is set up between **3** and the quinone imine **5**. Protonation of the imine leads to a rapid, irreversible cyclization, with the ideally placed S atom acting as the nucleophile. A subsequent prototropic shift results in the formation of the benzthiazole (**4**). On this basis, it is also easy to understand the time-dependence of the **3**/**4** ratio during Fe/HCl reduction of the nitroaniline (**2**). The oxidation in this instance must be mediated through Fe^{3+}.

A deliberate oxidative cyclization of **3** to **4** would then be needed as proof of our hypothesis. This we have now achieved as follows. The thiourea (**3**) was dissolved in ethanol containing acid, and stirred in the presence of atmospheric oxygen with the same Pd/C catalyst. This resulted in the smooth conversion of **3** to **4** in about 50% yield. Omission of the catalyst alone from the above reaction system resulted only in the formation of (**3**.HCl). The same transformation could also be brought about in the same yield by means of ferric chloride in presence of hydrochloric acid.

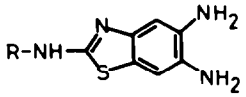
The fact that the benzthiazole (**4**) still retained the 1,2-diamino system was confirmed by cyclization with appropriate reagents to the imidazo [4,5-f]-benzthiazoles (**6**). Thus **6a**, **6b** and **6c** were respectively produced by reaction with formic acid, trifluoracetic acid and N-carbethoxy-S-methyl-pseudothiourea. In each case, ^1H NMR and mass spectra of the product confirmed the assigned structure.

Two other thioureas (**7** and **8**) have also been converted to the corresponding benzthiazoles (**9** and **10**). The procedure employed was a "one-pot"



7 : R = n-C_4H_9

8 : R = Ph-CH_2



9 : R = n-C_4H_9

10 : R = Ph-CH_2

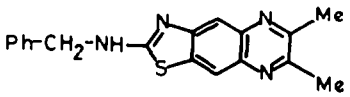


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Table 2. UV absorption maxima of 3 and 4

Compound	Neutral solution	Acid solution
3	$\lambda_{max.}$ 240.5 (21,250) $\lambda_{infl.}$ 302.5 (6,500)	$\lambda_{max.}$ 239 (22,900) $\lambda_{infl.}$ 265 (12,500)
4	$\lambda_{max.}$ 276 (10,300) $\lambda_{max.}$ 319 (9,000)	$\lambda_{max.}$ 308.5 (8,600)

Wavelengths in nm; ϵ values in brackets.

reduction-oxidation sequence, where first the nitro group was reduced by iron/acid, and then the mixture of open-chain and cyclized products was directly oxidized with ferric chloride, to yield exclusively the benzthiazole. The UV spectra of **9** and **10** were virtually superposable on that of **4**. In the ^{1}H NMR spectrum of **10**, the two singlet protons of the benzthiazole were submerged under the phenyl protons; they could however, be seen downfield in the tricyclic compound (**11**) obtained by condensation with diacetyl.

So far, to our knowledge, there has been only one report of the preparation of a 5,6-diaminobenzthiazole by a long and tedious route.[2]

EXPERIMENTAL

M.ps are uncorrected. ^{1}H NMR spectra were recorded on a Varian A-60 instrument; chemical shifts are expressed in δ values (ppm) TMS was the internal standard when the solvent was DMSO-d_6, or trifluoracetic acid (TFA). Mass spectra were determined on a Varian Mat CH 7 instrument at 70 eV utilizing direct insertion.

Catalytic reduction of the nitroaniline (**2**). Compound **2** (1.5 g) in MeOH (50 ml) was shaken with H_2 at 1 atm pressure in an Ente apparatus at 29° in presence of 10% Pd/C catalyst (0.7 g). The absorption of H_2 was very slow. After 3 hr, the soln was filtered, fresh catalyst (0.7 g) added and the hydrogenation re-started. After about 20 hr, the catalyst was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in aqueous acid and the non-basic material (starting material) removed. The soln was basified and extracted repeatedly with EtOAc. The extract was dried (Na_2SO_4) and the solvent removed. The residue was crystallized from MeOH–EtOAc to give **3** (0.4 g), m.p. 162–164°. (Found: C, 49.17; H, 6.40; N, 28.45. $C_8H_{12}N_4S$ requires: C, 48.97; H, 6.17; N, 28.56%). NMR (DMSO-d_6): 2.92 (d, J = 4; Me NH); 4.25 (br, 2 NH_2); 6.2–6.75 (3 Ar H); 6.95 (q, NH), 8.95 (s, NH). The mother liquor from the above crystallization was evaporated to dryness, the residue dissolved in MeOH and converted to the hydrochloride with alcoholic HCl. The hydrochloride was recrystallized from water–isopropanol to give **4**.HCl (0.3 g), m.p. 327–330° (d). (Found: C, 36.29; H, 4.69; N, 20.94. $C_8H_{10}N_4S$. 2HCl requires C, 35.97; H, 4.53; N, 20.98%) NMR (D_2O, no internal standard): 3.30 (s, Me); 7.20 (s, Ar–H); 7.75 (s, Ar H). The free base (**4**) obtained from this was crystallized from MeOH EtOAc, m.p. 191–195°.

Compound **3** obtained above was converted to the hydrochloride and crystallized from water isopropanol, m.p. 240° (d), after shrinking at 180–185°. NMR (D_2O, no internal standard): 3.20 (s, Me); 7.20–7.70 (8 line multiplet, typical of 1,2,4-trisubstituted benzene).

Conversion of **3** *to* **4**. (i) Compound **3** (0.1 g) in EtOH (10 ml) containing ethanolic HCl (4 drops) was treated with 10% Pd C catalyst (a pinch) and stirred at room temp for 18 hr in presence of atmospheric O_2. A little water was then added, warmed and filtered. The filtrate was concentrated *in vacuo*, treated with isopropanol and again evaporated. The solid was crystallized from water–isopropanol (most of the water was removed) to give the dihydrochloride of the benzthiazole (**4**. HCl) (50 mg), m.p. and mixed m.p. with the previous sample, 322–326° (d).

(ii) Compound **3** (0.2 g) in EtOH (10 ml) was warmed slightly, treated with a few drops of conc HCl, followed by a soln of $FeCl_3$ (0.1 g) in EtOH, and stirred at room temp for 2 hr The EtOH was then evaporated, the residue dissolved in water, basified with $NaHCO_3$ and extracted with EtOAc. The extract was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residual solid was converted to the hydrochloride in EtOH soln and crystallized from water–isopropanol (concentrated to remove most of the water) to give the dihydrochloride of the benzthiazole (**4**), m.p. and mixed m.p. 324–328° (d) (90 mg).

Synthesis of 2-alkylamino-5,6-diaminobenzthiazoles by "one-pot" reaction

(i) 5,6-*Diamino-2-methylaminobenzthiazole* (**4**). A mixture of Fe powder (30 g), water (200 ml) and conc HCl (5 ml) was stirred and heated to 60°. The nitroaniline **2** (20 g) was added to this and the mixture stirred and heated at 80–85° for 16 hr. The mixture was cooled, basified with Na_2CO_3 (10 g in 25 ml water) and filtered (hyflo supercel). The solid was extracted with boiling MeOH twice. Tlc of the MeOH extract showed that it was substantially pure product. The combined extract was concentrated *in vacuo*, the residue converted to the hydrochloride and crystallized from water isopropanol to give 5,6-diamino-2-methylaminobenzthiazole dihydrochloride (7.5 g), m.p. 325–329° (d). The compound was identical (mixed m.p., spectra) with that previously obtained.

(ii) 2-*n-Butylamino-5,6-diaminobenzthiazole* (**9**). 2-Nitro-*p*-phenylenediamine (15.3 g) and n-butyl isothiocyanate (11.5 g) were mixed in MeOH solution, stirred and refluxed for 3 hr. After cooling, the solid was filtered washed with MeOH and recrystallized from MeOH to give **7** (15.0 g), m.p. 196–199°. (Found: C, 49.58; H, 6.27; N, 21.20. $C_{11}H_{16}N_4O_2S$ requires: C, 49.25; H, 6.01; N, 20.89%).

Fe powder (4.5 g) in water (120 ml) and conc HCl (0.6 ml) was stirred and heated to 80°. The above **7** (3.0 g) was added in portions over 45 min. The mixture was further stirred and heated for 3 hr. It was then cooled, basified with Na_2CO_3 and filtered through hyflo. The residue was extracted thrice with boiling MeOH. The combined extract was evaporated *in vacuo*. The aqueous filtrate above was extracted twice with EtOAc and the extract evaporated. The two residues were combined. Tlc at this stage showed two spots (cyclized and uncyclized). The whole was dissolved in EtOH, treated with a few drops of conc HCl, and then with a soln of $FeCl_3$ (1.5 g) in EtOH. The mixture was left at room temp for ½ hr. It was then evaporated *in vacuo*, the residue treated with water, basified with $NaHCO_3$ and filtered through hyflo. The filtrate was extracted twice with EtOAc. The solid was extracted twice with boiling MeOH, the solvent evaporated and the residue extracted with EtOAc. The combined EtOAc extracts were dried (Na_2SO_4) and evaporated. The residue was passed through a short column of alumina in $CHCl_3$ soln The eluate was evaporated *in vacuo* and the residue was crystallized first from isopropanol-water and then again from water to give 2-n-butyl-amino-5,6-diaminobenzthiazole monohydrate as colourless needles (0.7 g), m.p 92–97°. (Found: C, 52.16; H, 7.35; N, 21.66 $C_{11}H_{16}N_4S.H_2O$ requires: C, 51.95; H, 7.14; N, 22.03%). MS: 236 (M^+). NMR ($CDCl_3$ + DMSO-d_6). 0.9 (t, Me); 1.1–1.8 (m, 2 CH_2); 3.3 (t, CH_2); 6.83 (s, Ar-H); 6.90 (s, Ar-H).

(iii) 2-*Benzylamino-5,6-diaminobenzthiazole* (**10**). The thiourea (**8**) was prepared by refluxing a methanolic soln of 2-nitro-*p*-phenylenediamine (15 g) and benzyl isothiocyanate (15 g) for 1 hr and recrystallizing the product (25 g) from EtOAc-hexane; m.p. 195–198 (Found: C, 56.00; H, 4.95; N, 18.58. $C_{14}H_{14}N_4O_2S$ requires: C, 55.62; H, 4.67; N, 18.54%). MS: 302 (M^+).

A suspension of Fe powder (40 g) in water (150 ml) and MeOH (600 ml) containing conc HCl (10 ml) was stirred and heated to 80–85°. To this was added the above **8** (20 g) in portions. The mixture was stirred and heated for 24 hr (tlc after 4 hr showed starting material to be present). The hot soln was then filtered through hyflo and the residue washed with hot MeOH. The combined filtrate was cooled, treated with a soln of $FeCl_3$ (6 g) in MeOH (20 ml) and left at room temp for ½ hr. The soln was then concentrated *in vacuo*, dissolved in water and basified with $NaHCO_3$. The mixture was filtered through hyflo, and the solid extracted thrice with boiling MeOH. The MeOH extract was evaporated and the residual solid crystallized from MeOH water to give **10** (8.5 g) m.p. 184–189° (d). (Found: C, 62.49; H, 5.48; N, 20.37).

$C_{14}H_{14}N_4S$ requires: C, 62.21; H, 5.22; N, 20.73%). MS: 270 (M^+).

Tricyclic derivatives

(i) 2-*Methylamino*-5*H*-*imidazo*[4,5-f] *benzthiazole* (**6a**). A soln of **4** .HCl (1.3 g) in water (20 ml) was treated with conc HCl (15 ml) and formic acid (4 ml) and refluxed for 2 hr. The soln was cooled and basified with ammonia. The solid was filtered, washed with water and crystallized from MeOH–water to give **6a** (0.5 g), m.p. 301–308°. (Found: C, 53.18; H, 4.30; N, 27.25. $C_9H_8N_4S$ requires: C, 52.94; H, 3.95; N, 27.44%). MS: 204 (M^+). NMR (DMSO-d_6): 3.00 (s, Me); 7.62, 7.88, 8.15 (3 Ar-H singlets).

(ii) 2-*Methylamino*-6-*trifluoromethyl*-5H-*imidazo* [4,5-f] *benzthiazole* (**6b**). A soln of **4** .HCl (2.0 g) in 5N HCl (15 ml) and trifluoracetic acid (4 ml) was heated at 100° for 4 hr and cooled. The hydrochloride of the product that separated was filtered and washed with isopropanol. It was converted to the base with ammonia and crystallized from EtOH–water to give **6b** (1.0 g), m.p. 335–337° (d). (Found: C, 44.14; H, 2.88; N, 20.72. $C_{10}H_7F_3N_4S$ requires: C, 44.12; H, 2.59; N, 20.59%). MS: 272 (M^+). NMR (DMSO-d_6): 3.03 (s, Me); 7.67 and 8.03 (Ar-H, singlets).

(iii) 2-*Methylamino*-5H-*imidazo* [4,5-f] *benzthiazole* 6-*carbamic acid ethyl ester* (**6c**). N-Carbethoxy-S-methylpseudothiourea was prepared from S-methylpseudothiourea sulfate (2.8 g) and ethyl chloroformate (2.16 g) as described before.[3] The dihydrochloride of **4** (2.6 g) in water (10 ml) was then added, followed by a soln of sodium acetate trihydrate (2.8 g) in water (7 ml). The mixture was stirred and refluxed for 1½ hr, then cooled and the solid filtered and washed with water to give **6c** (1.4 g), m.p. >350°. (Found: C, 49.34; H, 4.74; N, 23.78. $C_{12}H_{13}N_5O_2S$ requires: C, 49.48; H, 4.50; N, 24.05%). MS: 291 (M^+, 2%); 245 ($M^+ - 46$, 100%). NMR (TFA): 1.55 (t, Me); 3.45 (s, Me); 4.63 (q, CH_2); 8.05, 8.22 (2 Ar-H; singlets).

(iv) 2-*Benzylamino*-6,7-*dimethylthiazolo* [4,5-*g*] *quinoxaline* (**11**). A soln of **10** (2.7 g) in MeOH was treated with diacetyl (0.86 g) and refluxed for 2 hr. After evaporation of the MeOH, the residue was extracted with hot EtOAc and the product crystallized from MeOH–isopropanol to give **11** (1.0 g), m.p. 260 265°. (Found: C, 66.96; H, 5.53; N, 17.42. $C_{18}H_{16}N_4S$ requires: C, 67.48; H, 5.03; N, 17.49%). MS: 320 (M^+). NMR (DMSO-d_6): 2.6 (s, 2 Me); 4.75 (s, CH_2); 7.4 (5 Ar-H); 7.82, 8.19 (2 Ar-H, singlets).

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