Benzo[c]fused Isothiazoles. II. Synthesis of some Angular Isothiazolo[c]benzothiadiazoles. An Anomalous Amination Reaction

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The syntheses and pmr properties of the angular isothiazolo[*c*]-2,1,3-benzothiadiazoles (**1** and **2**) are described. An unusual electrophilic amination reaction with *N*-sulfinylmethanesulfonamide is discussed.

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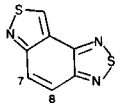
In Part I (1) we described the preparation of the angular benzobisisothiazoles and the symmetrical benzotrisisothiazole. We now discuss the preparation and properties of two mixed systems (**1** and **2**) containing both 1,2,5-thiadiazole and isothiazole moieties.



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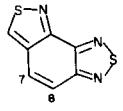

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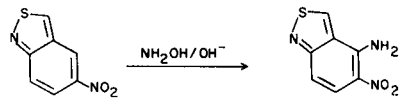
These heterocyclic systems are intermediate between our benzopolyisothiazoles (1) and the benzopolythiadiazoles described by Carmack and his co-workers (2), and are useful in providing information about the aromaticity (or lack of aromaticity) of the central benzenoid ring in such formally *o*-quinonoid compounds.

Isothiazolo[5,4-*c*]-2,1,3-benzothiadiazole (**1**) was prepared by two methods. In the first, 5-nitro-2,1-benzoisothiazole (**3**) (3) was aminated with hydroxylamine in basic solution to give the nitroamine (**4**); this was reduced by iron and acetic acid, and the *o*-diamino product (**5**)



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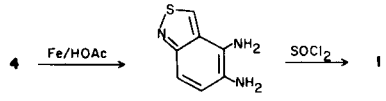

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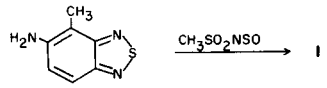
cyclised to the isothiazolobenzothiadiazole (**1**) with thionyl chloride. Compound **1** could also be made from 5-amino-4-methyl-2,1,3-benzothiadiazole (**6**) by treatment with *N*-sulfinylmethanesulfonamide.



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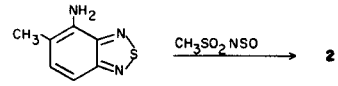
Isothiazolo[4,5-*c*]-2,1,3-benzothiadiazole (**2**) was synthesised from 4-amino-5-methyl-2,1,3-benzothiadiazole (**7**). The latter compound (**7**) has been reported (4), m.p. 125°, but we found that reduction of 5-methyl-4-nitro-2,1,3-benzothiadiazole yielded a product, m.p. 78-79°, the spectroscopic properties and analysis of which showed it was **7**. Treatment of **7** with *N*-sulfinylmethanesulfonamide afforded the isothiazolobenzothiadiazole (**2**).



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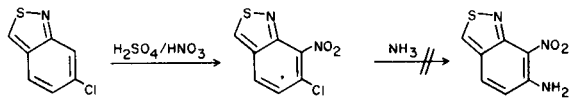
An attempt to prepare **2** by a benzisothiazole route was unsuccessful. Nitration of 6-chloro-2,1-benzisothiazole (**8**) yielded 6-chloro-7-nitro-2,1-benzisothiazole (**9**) which, although it is susceptible to nucleophilic displacement of the chlorine atom by hydrazine or dimethylamine (5), does not react readily with ammonia; 6-amino-7-nitro-2,1-benzisothiazole (**10**), although detected by mass spectrometry, was not obtained in isolable quantity.



8 **9** **10**

In the preceding paper (1) we described attempts to make "linear" benzobis-isothiazoles. We treated 1,3-diamino-4,6-dimethylbenzene (**11**) with *N*-sulfinylmethanesulfonamide; the product was not the expected linear benzobis-isothiazole but was 8-methylisothiazolo-[4,5-*c*]-2,1,3-benzothiadiazole (**12**). Although the yield of **12** is low, it cannot be accounted for by impurity (such as

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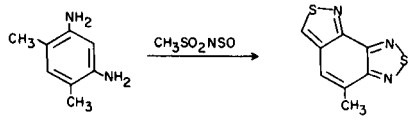

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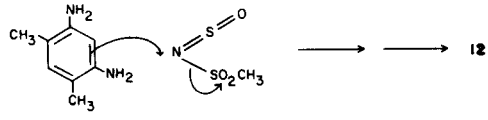
1,2,3-triamino-4,6-dimethylbenzene) in **11**, and we believe that this unusual reaction may involve an electrophilic amination as indicated in Scheme I. Of course, this



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amination may occur at a later stage of the various cyclisation reactions that ultimately produce **12**.

The pmr spectrum of **1** shows two sharp singlets only. The heterocyclic ring proton resonates at 9.40 ppm. The C-7 and C-8 protons give rise to a two-proton singlet at 7.50 ppm. Presumably, the immediate environments of these protons are sufficiently similar to render them magnetically equivalent. By contrast, the pmr spectrum of **2** displays a heterocyclic ring proton singlet at 9.40 ppm and and AB quartet as 7.70-8.05 ppm (J = 7 Hz) for the C-7 and C-8 protons. These values may be compared with the corresponding proton chemical shifts in the benzobisthiophen (**13**) (6.92 ppm) (6), in phenanthrene (7.56 ppm) and in the benzobisthiadiazole (**14**) (7.97 ppm) prepared by Carmack (2). It would appear that the "benzenoid" ring in **13** is distinctly more olefinic (and the compound

Scheme I

13 14

more reactive) than in phenanthrene or in any of the isothiazolo or thiadiazolo compounds discussed in this paper. In brief, the more nitrogen atoms the greater the "aromaticity" of the benzenoid ring.

EXPERIMENTAL

General.

See the preceding paper (1) for general notes and details of standard procedures for nitration (*A*), reduction (*B*) and cyclisation (*C*).

4-Amino-5-nitro-2,1-benzisothiazole (**4**).

Pesin's procedure (7) was employed. Hydroxylamine hydrochloride (15.78 g., 0.2271 mole) was added to a suspension of 5-nitro-2,1-benziso-thiazole (8.05 g., 0.0447 mole) (3) in methanol (1 l.). The mixture was cooled to −15° and a solution of potassium hydroxide (31.55 g., 0.5624 mole) in methanol (200 ml.) was added dropwise during 25 minutes. The mixture was stirred a further 40 minutes at room temperature and then poured onto ice (3 kg.). The yellow precipitate was filtered off and recrystallised from aqueous dimethylsulfoxide to yield the aminonitro compound **4** (5.98 g., 69%) as a fine yellow powder, m.p. 264-264.5°; pmr (DMSO-d_6): δ 6.4-7.8, AB quartet, J = 11 Hz, 2H, aromatic; 8.4-9.2, broad s, 2H, NH_2; 10.2, s, 1H, heterocyclic; ms: m/e (relative intensity): 197 (11), 196 (16), 195 (100, M^+), 165 (31), 149 (48), 138 (19), 122 (33), 105 (31), 95 (19), 78 (15), 52 (16), 45 (17).

Anal. Calcd. for $C_7H_5N_3O_2S$: C, 43.07; H, 2.59; N, 21.35; S, 16.4. Found: C, 42.92; H, 2.54; N, 21.35. S, 16.4.

4,5-Diamino-2,1-benzisothiazole (**5**).

Reduction of 4-amino-5-nitro-2,1-benzisothiazole (**4**) by general procedure *B* (1) afforded the diamine (**5**) in 21% yield as yellow crystals, m.p. 72-73°, pmr (deuteriochloroform): δ 3.0-4.0, broad s, 4H, NH_2; 7.0-7.5, AB quartet, J = 9 Hz, 2H, aromatic; 9.1, s, heterocyclic; ms: m/e (relative intensity): 167 (7), 166 (16), 165 (100, M^+), 164 (38), 138 (13), 137 (48), 105 (13), 84 (10), 82.5 (8, M^{2+}), 79 (12), 69 (7), 54 (13), 52 (30), 45 (13). Exact mass calcd for $C_7H_7N_3S$: 165.036. Found: 165.036. Other methods of reduction of **4** afforded no diamine.

Isothiazolo[5,4-*c*]-2,1,3-benzothiadiazole (**1**).

This was prepared by Komin and Carmack's (2) cyclisation procedure. 4,5-Diamino-2,1-benzisothiazole (4) (400 mg.), thionyl chloride (3.6 ml.) and pyridine (2 drops) were heated together under reflux for 90 minutes. The thionyl chloride and pyridine were evaporated and the residue was dissolved in dichloromethane (20 ml.) and washed with 2*M* hydrochloric acid. The organic layer was dried, reduced in volume and chromatographed on a 2 mm silica gel preparative tlc plate using dichloromethane as eluent. Extraction of the band with R_f of 0.48 afforded a solid which was recrystallised (carbon tetrachloride) to give isothiazolo[5,4-*c*]-2,1,3-benzisothiazole (**1**) (342 mg., 74%) as fine colorless needles, m.p. 112-113°; pmr (deuteriochloroform): δ 7.5, s, 2H, aromatic; 9.4 s, 1H, heterocyclic. Infrared spectrum (KBr): ν max 3120, 2970, 1540, 1425, 1340, 1200, 1140, 870, 830 and 790 cm^{-1}; ms: m/e (relative intensity): 195 (11), 194 (12), 193 (100, M^+), 192 (6), 166 (34), 160 (5), 149 (20), 96.5 (7, M^{2+}), 83 (12), 52 (9), 45 (12), 32 (10). Exact mass calcd. for $C_7H_3N_3S_2$: 192.977. Found: 192.978.

Anal. Calcd. for $C_7H_3N_3S_2$: C, 43.50; H, 1.57; N, 21.75; S, 33.2. Found: C, 43.11; H, 1.73; N, 22.00; S, 32.9.

Isothiazolo[5,4-*c*]-2,1,3-benzothiadiazole (**1**) was also prepared in 39% yield by cyclisation using general procedure *C* (1), of 5-amino-4-methyl-2,1,3-benzothiadiazole (4); the product was identical with that above.

4-Amino-5-methyl-2,1,3-benzothiadiazole (**7**).

5-Methyl-4-nitro-2,1,3-benzothiadiazole (4) (2.91 g.) was reduced by general procedure *B* (1) and afforded 4-amino-5-methyl-2,1,3-benzothiadiazole (1.50 g., 61%) as brown needles, from light petroleum, m.p. 78-79° (lit. m.p. 125°) (4); pmr (deuteriochloroform): δ ms: 2.3, s, 3H, CH_3; 4.5-5.2, s, 2H, NH_2; 7.3, s, 2H, aromatic; ms: m/e (relative intensity) 167 (6), 166 (17), 165 (85, M^+), 164 (100), 137 (8), 118 (11), 110 (11), 78 (48), 53 (23), 52 (29), 51 (32).

Anal. Calcd. for $C_7H_7N_3S$: C, 50.87; H, 4.28; N, 25.44. S, 19.4. Found: C, 50.91; H, 4.35; N, 25.63; S, 18.8.

Isothiazolo[4,5-*c*]-2,1,3-benzothiadiazole (**2**).

Cyclisation of 4-amino-5-methyl-2,1,3-benzothiadiazole (**7**) by general procedure *C* (1), followed by chromatographic separation on a silica column, afforded **2** in 40% yield as fine colorless needles, m.p. 117-118°, pmr (deuteriochloroform): δ 7.7-8.1, AB quartet, J = 7 Hz, 2H, aromatic; 9.4, s, 1H, heterocyclic; ir (potassium bromide): ν max 3100, 1610, 1550, 1425, 1395, 1265, 1070, 885, 845, 820 and 685 cm^{-1}; ms: (relative intensity) 195 (11), 194 (13), 193 (100, M^+), 166 (13), 149 (5), 142 (10), 134 (10), 109 (7), 96.5 (7, M^{2+}), 82 (13), 69 (11), 63 (26), 46 (14), 45 (41), 44 (12), 32 (20).

Anal. Calcd. for $C_7H_3N_3S_2$: C, 43.50; H, 1.57; N, 21.75; S, 33.2. Found: C, 43.25; H, 1.60; N, 21.37; S, 32.7.

6-Chloro-7-nitro-2,1-benzisothiazole (**9**).

Nitric acid (15 ml., d. 1.42) was added dropwise to a cold solution of 6-chloro-2,1-benzisothiazole (**8**) (4.60 g.) in sulfuric acid (25 ml.). The mixture was heated on a waterbath, cooled and poured into ice (500 g.). The product was recrystallised from ethanol, affording **9** (4.77 g., 82%) as pale yellow needles, m.p. 165°; pmr (deuteriochloroform): δ 7.3-8.1 AB quartet, J = 9 Hz, 2H, aromatic; 9.5, s, 1H, heterocyclic; ms: m/e (relative intensity) 216 (19), 214 (42), 186 (35), 184 (84), 168 (10), 158 (42), 156 (94), 133 (100), 124 (23), 88 (29), 69 (55), 45 (77).

Anal. Calcd. for $C_7H_3ClN_2O_2S$: C, 39.16; H, 1.41; N, 13.05. Found: C, 39.19; H, 1.41; N, 12.86%.

We were unable to prepare **10** by treatment of **9** with ammonia or with ammonium salts.

Cyclisation of 1,3-diamino-4,6-dimethylbenzene (**11**).

1,3-Diamino-4,6-dimethylbenzene (**11**) was prepared by hydrogenation of 1,3-dinitro-4,6-dimethylbenzene, m.p. 91-92°, (lit. m.p. 91-92°) (9). The product **11** formed pale yellow needles, m.p. 105-106° (lit. m.p. 104°) (9). This diamine **11** (4.00 g.) was cyclised by general procedure *C* (1), but using twice the quantity of *N*-sulfinylmethanesulfonamide. A mixture of products was obtained which on separation by preparative tlc on silica plates, using dichloromethane as eluent, afforded a product of R_f 0.37. This product was recrystallised from carbon tetrachloride, thus affording 8-methylisothiazolo[4,5-*c*]-2,1,3-benzothiadiazole (**12**) (0.86 g., 14%) as long colorless needles, m.p. 263-264°, pmr (deuteriochloroform): δ 2.7, s, 3H, CH_3; 7.40-7.55, s, 1H, aromatic; 9.1, s, 1H, heterocyclic; ir (potassium bromide): ν max 3100, 2910, 1510, 1400, 1360, 1150, 885, 860, 830, 770, 590 and 500 cm^{-1}; ms: m/e (relative intensity): 209 (13), 208 (17), 207 (100, M^+), 206 (40), 180 (5), 179 (6), 175 (6), 174 (10), 163 (5), 162 (5), 147 (12), 122 (7), 103.5 (7, M^{2+}), 69 (8), 45 (16).

Anal. Calcd. for $C_8H_5N_3S_2$: C, 46.35; H, 2.44; N, 20.28; S, 30.9. Found: C, 46.32; H, 2.41; N, 20.28; S, 30.7.

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