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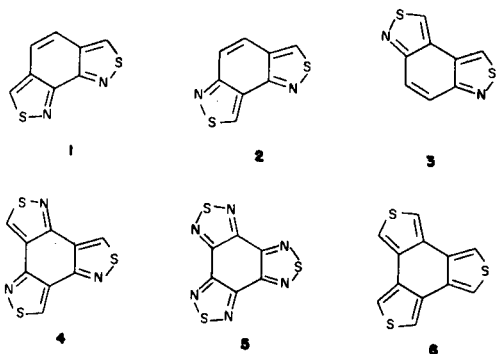
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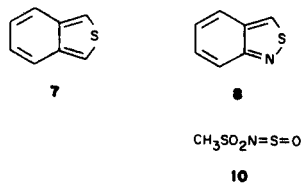
The synthesis of all the possible angular benzo[*c*]bisothiazoles (**1**, **2** and **3**), and of the symmetrical benzo[*c*]trisothiazole (**4**) are described. The pmr properties of these compounds are compared with analogous thiophenes and thiadiazoles

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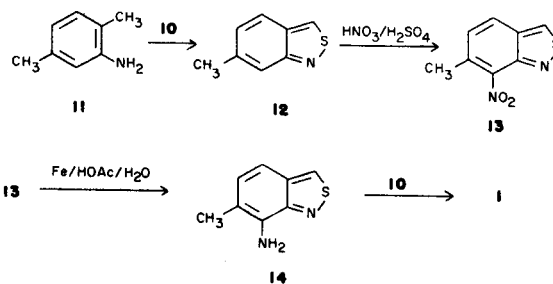
We have synthesized all three possible angular benzo[*c*]bisothiazoles (**1**, **2** and **3**) and the symmetrical benzo[*c*]trisothiazole (**4**). This compound **4** is formally a "hexaradialene" analogous to the benzotrithiadiazole (**5**) described by Komin and Carmack (1) and the benzotrithiophene (**6**) of Hart and Sasaoka (2). It has been suggested by the latter authors that hexaradialenes such as **6** may have chemical properties different from those of the parent bicyclic compound **7** as a result of the loss of electron density from the central six-membered ring. 2,1-Benzisothiazole (**8**) and 2,1,3-benzothiadiazole (**9**) are also, formally, *o*-quinonoid compounds analogous to benzo[*c*]thiophene (**7**) and it was of interest, therefore, to compare the properties of all the compounds in the series **1** through **9**.



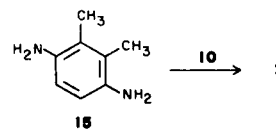
The key reaction we used for the construction of the isothiazole rings is that described by Singerman (3) in which an aromatic methyl group and an adjacent amino group are cyclized to an isothiazole by the action of *N*-sulfinylmethanesulfonamide (**10**). For such cyclisations this is much better than our earlier reagent, thionyl chloride (4), as no chlorinated by-products are formed and yields are higher.



The starting materials for the syntheses of **1** and **2** were readily available dimethylanilines (xylidines). For example, 2,5-dimethylaniline (**11**) is readily cyclized to 6-methyl-2,1-benzisothiazole (**12**) which on nitration with a mixture of nitric and sulfuric acids at 0-5° affords 6-methyl-7-nitro-2,1-benzisothiazole (**13**). Reduction of **13** with iron filings and dilute acetic acid on a steam bath yields 7-amino-6-methyl-2,1-benzisothiazole (**14**) which, treated with *N*-sulfinylmethanesulfonamide (**10**) affords benzo[2,1-c:3,4-c']bisothiazole (**1**). Benzo[1,2-c:3,4-c']bisothiazole (**2**) was prepared by an analogous sequence from 2,4-dimethylaniline.



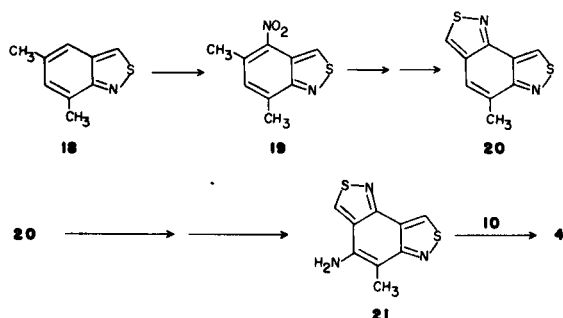
Nitration of 4-methyl-2,1-benzisothiazole affords a 7-nitro derivative (**5**); none of the 5-nitro isomer needed for the synthesis of benzo[1,2-c:4,3-c']bisothiazole (**3**) is formed. We found, however, that **3** is easily prepared by a one-pot double cyclisation of 1,4-diamino-2,3-dimethylbenzene (**15**).



We have also attempted to make the linear benzobisothiazoles (**16** and **17**) by similar reactions of the appropriate diaminodimethylbenzenes but without success. An anomalous reaction occurring in one such attempt is described in the following paper (6).



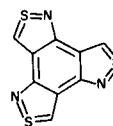
The benzotris-isothiazole (4) was prepared from 5,7-dimethyl-2,1-benzisothiazole (18) by a simple extension of the sequence used to prepare the bis-compounds (1 and 2). Nitration of 18 affords 5,7-dimethyl-4-nitro-2,1-benzisothiazole (19) which on reduction and cyclisation yields 8-methylbenzo[1,2-c:3,4-c']bisisothiazole (20). Nitration of 20, and reduction of the product affords the amino compound (21); cyclisation of 21 yields benzo[1,2-c:3,4-c':5,6-c'']trisisothiazole (4). Compound 4 is a stable, colorless



crystalline solid, m.p. 267.5-268°, sparingly soluble in chloroform and acetone but insoluble in benzene. The pmr spectrum shows only a sharp singlet at  $\delta$  9.50, typical of all 2,1-benzisothiazoles unsubstituted in the heterocyclic ring (4). The simple infrared spectrum also indicates a high degree of symmetry, and the molecular ion at  $m/e$  249 is the base peak of the mass spectrum. The fragmentation pattern is typical of 2,1-benzisothiazoles in that the significant peaks in the high mass range appear to be due to loss of hydrogen cyanide, sulfur, or carbon monosulfide.

Compound 1, 2, 3, and 4 resemble 8 in their pmr spectra; the heterocyclic ring proton resonates between  $\delta$  8.80 and 9.50, compared with  $\delta$  9.06 for 2,1-benzisothiazole (8). The carbocyclic ring protons in 1, 2 and 3 resonate as singlets at 7.25, 7.40 and 7.65 ppm, respectively, typical aromatic protons and similar to the range 7.09-7.78 ppm observed in 2,1-benzisothiazole (8). In 2 these carbocyclic protons, though non-equivalent, produce a singlet; a similar effect was noticed in an analogous thiadiazolo-benzisothiazole (see following paper). In 2,1-benzisothiazole the heterocyclic proton (C-3) is coupled ( $J \sim 1$  Hz) with the proton at C-4; no such coupling was observed in the bisisothiazoles 2 and 3.

In this series of isothiazoles there appears to be no real difference in chemical or physical properties between the bicyclic compound 8 which is, in any case, much less reactive than the benzothiophene (7), and the tricyclic compounds 1, 2, 3 or tetracyclic compound 4. Although we do not, at present, have direct evidence we believe that the 6-membered ring in 4 is fully aromatic; we consider that the tetravalent sulfur form 22 makes a significant contribution to the overall structure of 4. This question is currently being investigated.



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## EXPERIMENTAL

## General.

Melting points (uncorrected) were determined in open capillary tubes in a Büchi apparatus. Analyses were performed by the Australian Micro-analytical Service, Melbourne. Infrared spectra were recorded on a Perkin-Elmer 257 instrument. Pmr spectra were obtained on a Varian T-60 or a Perkin-Elmer R32 spectrometer, with internal TMS as reference. Mass spectra (75 eV) were obtained on a JEOL D-100 double focussing spectrometer.

## General Procedures.

## A. Nitration.

The compound (0.1 mole) was added portionwise to sulfuric acid (45 ml., d. 1.84) chilled in an ice-salt bath. A mixture of nitric acid (9 ml., d. 1.42) and sulfuric acid (12 ml., d. 1.84) was then added dropwise at such a rate that the reaction temperature was kept below 5°. On complete addition, the mixture was stirred for a further 30 minutes at room temperature. It was then poured onto ice (500 g.) and the yellow nitro compound filtered off.

## B. Reduction.

The nitro compound (0.075 mole), iron filings (15 g.) and dilute acetic acid (200 ml., 2%) were vigorously stirred and heated on a steam bath for 1 hour. After cooling, the mixture was filtered and both filtrate and the iron residue extracted several times with ether (4  $\times$  200 ml.). The combined extracts were dried and evaporated and the residue recrystallized.

## C. Cyclisation.

Singerman's method (3) using *N*-sulfinylmethanesulfonamide was employed.

## 6-Methyl-2,1-benzisothiazole (12).

Cyclisation of 2,5-dimethylaniline by Singerman's method (3) afforded 6-methyl-2,1-benzisothiazole (12) as a yellow oil, b.p. 68-70° (0.1 mm); pmr (deuteriochloroform):  $\delta$  2.2, s, 3H, CH<sub>3</sub>; 6.6-7.4, q, 2H, J = 9 Hz, aromatic; 7.5 s, 1H, aromatic; 8.7, s, 1H, heterocyclic.

## 6-Methyl-7-nitro-2,1-benzisothiazole (13).

Nitration of 12 by general procedure A afforded the nitro compound 13 in 88% yield as pale yellow needles (ethanol), m.p. 164-165°, pmr (deuteriochloroform):  $\delta$  2.6, s; 7.1-8.0, q, J = 9 Hz, 2H; 9.5, s, 1H; ms: (relative intensity) 196 (9), 195 (14), 194 (100, M<sup>+</sup>), 177 (73), 149 (26), 148 (43), 122 (36), 121 (50), 109 (36), 104 (43), 77 (43), 51 (26), 45 (69).

Anal. Calcd. for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>S: C, 49.48; H, 3.12; N, 14.43; S, 16.5. Found: C, 49.27; H, 3.14; N, 14.25, S, 16.6.

## 7-Amino-6-methyl-2,1-benzisothiazole (14).

Reduction of 13 by general procedure B gave the amino compound 14 in 62% yield as yellow needles (acetone and light petroleum), m.p. 113.5-115°; pmr (DMSO-d<sub>6</sub>):  $\delta$  2.0, s, 5.0-5.3, s; 6.6-6.9, q, J = 7 Hz; 9.1, s; ir: 3430, 3320 cm<sup>-1</sup> (NH<sub>2</sub>); ms:  $m/e$  (relative intensity): 166 (7), 165 (18), 164 (98, M<sup>+</sup>), 163 (100), 136 (16), 109 (8), 82 (9), 65 (9), 51 (8), 45 (12), 39 (11).

Anal. Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>S: C, 58.50; H, 4.92; N, 17.06; S, 19.5. Found: C, 58.31; H, 4.81; N, 16.98; S, 19.4.

## Benzo[2,1-c:3,4-c']bisisothiazole (1).

Cyclisation of the amino methyl compound 14 by the general procedure C afforded the benzobisisothiazole (1) in 28% yield as long col-

orless needles (carbon tetrachloride), m.p. 116-117°; pmr (deuteriochloroform):  $\delta$  7.25, s, 2H; 8.9, s, 2H; ir (potassium bromide): 3085, 2945, 1390, 1350, 1175, 1065, 880, 845, 785, 670  $\text{cm}^{-1}$ ; ms: m/e (relative intensity) 194 (10), 193 (13), 192 (100, M<sup>+</sup>), 165 (10), 160 (3), 148 (8), 121 (5), 96 (14, M<sup>+</sup>), 70 (4), 69 (10), 45 (20).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>S<sub>2</sub>: C, 49.97; H, 2.10; N, 14.57; S, 33.4. Found: C, 49.85; H, 2.22; N, 14.76; S, 33.1.

#### 5-Methyl-4-nitro-2,1-benzisothiazole.

Nitration of 5-methyl-2,1-benzisothiazole (3) by general procedure A afforded the nitro compound in 80% yield as yellow needles (ethanol), m.p. 107-108°; pmr (deuteriochloroform):  $\delta$  2.7, s; 7.3-8.9, q, J = 8 Hz; 9.4, s; ms: m/e (relative intensity) 196 (7), 195 (11), 194 (86, M<sup>+</sup>), 177 (91), 149 (100), 148 (45), 122 (45), 121 (31), 109 (14), 104 (62), 77 (62), 51 (43), 45 (88), 39 (36).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>S: C, 49.48; H, 3.12; N, 14.43; S, 16.5. Found: C, 49.60; H, 3.27; N, 14.28; S, 16.6.

#### 4-Amino-5-methyl-2,1-benzisothiazole.

Reduction of 5-methyl-4-nitro-2,1-benzisothiazole by general procedure B afforded the corresponding 4-amino compound in 45% yield as yellow needles (acetone and light petroleum), m.p. 174-175°; pmr (DMSO-d<sub>6</sub>):  $\delta$  2.1, s; 4.6-6.0, s; 6.7-7.2, q, J = 9 Hz, 9.7, s; ir (mull): 3410, 3310  $\text{cm}^{-1}$  (NH<sub>2</sub>); ms: (relative intensity): 166 (7), 165 (16), 164 (100, M<sup>+</sup>), 163 (97), 148 (8), 136 (26), 109 (8), 82 (9), 52 (16), 45 (15).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>S: C, 58.50; H, 4.92; N, 17.06; S, 19.5. Found: C, 58.33; H, 4.91; N, 16.54; S, 20.0.

#### Benzo[1,2-c:3,4-c']bisothiazole (2).

Cyclisation of 4-amino-5-methyl-2,1-benzisothiazole by general procedure C afforded 2 in 20% yield as colorless needles (carbon tetrachloride), m.p. 76.5-78°; pmr (deuteriochloroform):  $\delta$  7.4, s, 2H; 8.8, s, 1H; 9.5, s, 1H; ir (potassium bromide): 2960, 1720, 1410, 1360, 1160, 1070, 855, 810, 750  $\text{cm}^{-1}$ ; ms: m/e (relative intensity): 195 (2), 194 (11), 193 (13), 192 (100, M<sup>+</sup>), 191 (6), 165 (7), 160 (2), 148 (21), 121 (8), 96 (8), 83 (7), 82 (8), 69 (11), 57 (9), 45 (25).

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>S<sub>2</sub>: C, 49.97; H, 2.10; N, 14.57; S, 33.4. Found: C, 49.90; H, 2.12; N, 14.12; S, 33.3.

#### Benzo[1,2-c:4,3-c']bisothiazole (3).

Cyclisation of 1,4-diamino-2,3-dimethylbenzene (7) by general procedure C using twice the quantity of *N*-sulfinylmethanesulfonamide afforded the bisothiazole (3) in 41% yield as fine colorless needles (carbon tetrachloride), m.p. 124-125°; pmr (deuteriochloroform):  $\delta$  7.65, s; 9.20, s; ir (potassium bromide): 2970, 1400, 1360, 1170, 1070, 860, 820, 770  $\text{cm}^{-1}$ ; ms: m/e (relative intensity): 195 (2), 194 (16), 193 (19), 192 (100, M<sup>+</sup>), 191 (6), 165 (13), 160 (3), 148 (19), 121 (6), 96 (10, M<sup>+</sup>), 70 (16), 69 (32), 45 (29).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>S<sub>2</sub>: C, 49.97; H, 2.10; N, 14.57; S, 33.4. Found: C, 49.88; H, 2.13; N, 14.40; S, 33.1.

#### 5,7-Dimethyl-2,1-benzisothiazole (18).

Cyclisation of 2,4,6-trimethylaniline by general procedure C afforded 5,7-dimethyl-2,1-benzisothiazole (18) in 48% yield as a yellow oil, b.p. 94-98° (0.5 mm), lit. (8) b.p. 60° (0.01 mm).

#### 5,7-Dimethyl-4-nitro-2,1-benzisothiazole (19).

Nitration of 18 by general procedure A gave the nitro derivative (19) in 90% yield as yellow needles (ethanol), m.p. 133-133.5°, pmr (deuteriochloroform):  $\delta$  2.7, s; 2.8, s; 7.1, s; 9.5, s; ms: m/e (relative intensity) 210 (5), 209 (12), 208 (84, M<sup>+</sup>), 191 (100), 163 (89), 136 (35), 91 (49), 51 (37), 45 (65), 39 (57).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>S: C, 51.90; H, 3.88; N, 13.46; S, 15.4. Found: C, 51.81; H, 3.92; N, 13.68; S, 15.5.

#### 4-Amino-5,7-dimethyl-2,1-benzisothiazole.

Reduction of 19 by general procedure B afforded the corresponding amino compound in 71% yield as yellow needles (light petroleum), m.p.

144-145°; pmr (DMSO-d<sub>6</sub>):  $\delta$  1.45, s; 1.77, s; 4.5-4.9, s, NH<sub>2</sub>; 6.17, s; 8.97, s; ms: m/e (relative intensity) 180 (6), 179 (16), 178 (100, M<sup>+</sup>), 177 (66), 163 (48), 150 (10), 136 (6), 89 (10), 65 (8), 51 (13), 45 (13).

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>S: C, 60.63; H, 5.67; N, 15.72; S, 18.0. Found: C, 60.49; H, 5.59; N, 15.40; S, 17.7.

#### 8-Methylbenzo[1,2-c:3,4-c']bisothiazole (20).

Cyclization of 4-amino-5,7-dimethyl-2,1-benzisothiazole by general procedure C gave the bisothiazole (20) in 59% yield as colorless needles (light petroleum), m.p. 131-131.5°; pmr (deuteriochloroform):  $\delta$  2.5, d, J = 1.3 Hz, 3H, CH<sub>3</sub>; 7.2-7.3 q, J = 1.3 Hz, 1H, aromatic; 8.7, s, 1H, heterocyclic; 9.55, s, 1H, heterocyclic; ir (potassium bromide): 3130, 3055, 1545, 1460, 1425, 1390, 1375, 1345, 1210, 1050, 880, 825, 765  $\text{cm}^{-1}$ ; ms: m/e (relative intensity) 208 (11), 207 (17), 206 (100, M<sup>+</sup>), 205 (44), 178 (6), 173 (5), 161 (11), 103 (5), 89.5 (3), 69 (15), 45 (39).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>S<sub>2</sub>: C, 52.40; H, 2.94; N, 13.58; S, 31.1. Found: C, 52.64; H, 3.16; N, 13.72; S, 30.9.

#### 8-Methyl-7-nitrobenzo[1,2-c:3,4-c']bisothiazole.

Nitration of 20 by general procedure A afforded only unreacted starting material, so more vigorous conditions were employed. Nitric acid (2.5 ml., d. 1.42) was added dropwise to a chilled solution of 20 (1.0 g.) in oleum (5 ml. 15% SO<sub>3</sub>). The mixture was heated on a steam-bath for 20 minutes then poured onto ice (200 g.). Recrystallization of the product from acetone afforded the nitro derivative as fine yellow needles (1.11 g., 91%), m.p. 216-217°; pmr (DMSO-d<sub>6</sub>):  $\delta$  2.7, s; 9.65, s; 10.25, s; ms: (relative intensity) 253 (6), 252 (9), 251 (52, M<sup>+</sup>), 234 (34), 221 (5), 206 (100), 193 (13), 179 (16), 161 (33), 134 (16), 69 (24), 45 (59).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: C, 43.01; H, 2.01; N, 16.72; S, 25.5. Found: C, 42.75; H, 2.10; N, 16.39; S, 25.2.

#### 7-Amino-8-methylbenzo[1,2-c:3,4-c']bisothiazole (21).

(i) Reduction of the 7-nitro compound (above) by general procedure B afforded the 7-amino compound 21 in 24% yield as yellow needles (acetone and light petroleum), m.p. 207.5-208°; pmr (DMSO-d<sub>6</sub>):  $\delta$  2.25, s; 5.7-6.0, s, 2H, NH<sub>2</sub>; 9.6, s, 1H, heterocyclic; 9.7, s, 1H, heterocyclic; ms: m/e (relative intensity): 223 (9), 222 (17), 221 (71, M<sup>+</sup>), 220 (46), 205 (5), 193 (14), 166 (5), 151 (9), 135 (11), 122 (7), 110.5 (7, M<sup>+</sup>), 93 (13), 84 (26), 83 (27), 69 (21), 57 (37), 52 (84), 45 (100), 32 (34).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>S<sub>2</sub>: C, 48.84; H, 3.19; N, 18.99; S, 29.0. Found: C, 49.16; H, 3.52; N, 18.17; S, 28.1.

(ii) A much better yield was obtained by using Komin and Carmack's reduction procedure (1). The 7-nitro compound (1.00 g., 0.0040 mole) in water (20 ml.) was stirred overnight to produce a fine suspension. The mixture was heated to boiling and sodium dithionite monohydrate (2.50 g., 0.0130 mole) added in one portion. Heating was continued a further 5 minutes, the solution was cooled, and the solid filtered off, dried, and recrystallized from a mixture of acetone and light petroleum, affording the amino compound (21) as yellow needles (0.828 g., 94%), identical with that obtained in (i) above.

#### Benzo[1,2-c:3,4-c':5,6-c'']trisothiazole (4).

Cyclization of 21 by general procedure C gave the trisothiazole (4) in 42% yield as fine colorless needles (acetone), m.p. 267.5-268°; pmr (deuteriochloroform):  $\delta$  9.50, s, heterocyclic; ir (potassium bromide): 3130, 1550, 1370, 1170, 860, 810, 760  $\text{cm}^{-1}$ ; ms: m/e (relative intensity) 253 (1), 252 (3), 251 (16), 250 (21), 249 (100, M<sup>+</sup>), 248 (2), 222 (4), 217 (2), 205 (19), 178 (5), 124.5 (7, M<sup>+</sup>), 115 (7), 83 (12), 70 (6), 57 (7), 45 (32), 32 (5).

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>3</sub>S<sub>3</sub>: C, 43.35; H, 1.22; N, 16.86; S, 38.5. Found: C, 43.24; H, 1.29; N, 16.78; S, 37.9.

## REFERENCES AND NOTES

- (1) A. P. Komin and M. Carmack, *J. Heterocyclic Chem.*, **12**, 829 (1975).
- (2) H. Hart and M. Sasaoka, *J. Am. Chem. Soc.*, **100**, 4326 (1978).

- (3) G. M. Singerman, *J. Heterocyclic Chem.*, **12**, 877 (1975).
- (4) M. Davis and A. W. White, *J. Org. Chem.*, **34**, 2985 (1969).
- (5) M. Davis and A. W. White, *J. Chem. Soc. (C)*, 2189 (1969).
- (6) B. Danylec and M. Davis, following paper in *J. Heterocyclic Chem.*
- (7) This diamine was prepared from 2,3-dimethylaniline (Aldrich) by acetylation, nitration, deacetylation and hydrogenation; it was obtained as yellow crystals, m.p. 115-116°. E. Noetling, A. Braun and G. Thesmar, *Ber.*, **34**, 2252 (1901) quote a m.p. of 116°.
- (8) U. Klingebiel and D. Bentmann, *Z. Naturforsch.*, **34b**, 123 (1979) report the preparation of 5,7-dimethyl-2,1-benzisothiazole but describe it as 5,7-dimethylbenzo[c]-1 $\lambda^4$ ,2-thiazole.