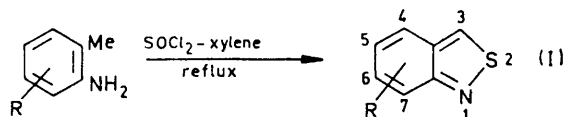


The Chemistry of 2,1-Benzisothiazoles. Part VII.¹ Reaction of α -Substituted *o*-Toluidines with Thionyl Chloride. A One-stage Synthesis of 2,1-Benzisothiazole-3-carboxylic Acid

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o-Benzylaniline (II; R = Ph) affords a quantitative yield of 3-phenyl-2,1-benzisothiazole (III; R = Ph) when heated with thionyl chloride, but *o*-toluidines functionally substituted at the methyl group (II; R = CN, OH, or Cl) give only *N*-sulphinyl derivatives or tars. *o*-Ethylaniline (II; R = Me) probably affords 3-methyl-2,1-benzisothiazole (III; R = Me) as an intermediate, but the latter is rapidly chlorinated at the methyl group, and after hydrolysis 2,1-benzisothiazole-3-carboxylic acid (III; R = CO₂H) is obtained in 30% yield. More highly substituted *o*-alkylanilines produce *N*-sulphinylamines, only traces of 2,1-benzisothiazoles being formed.

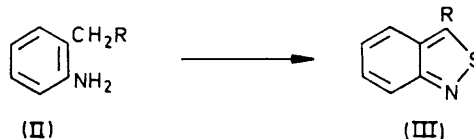
We have reported that the reactions of *o*-toluidine and ring-substituted *o*-toluidines with thionyl chloride in xylene at reflux temperature yield 2,1-benzisothiazoles (I).^{2,3} Similar treatment³ of *o*-ethylaniline (II; R =



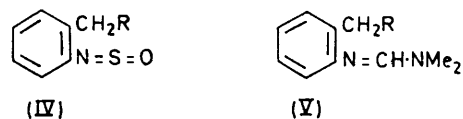
Me) afforded a compound, m.p. 103°, which we identified³ as 3-methyl-2,1-benzisothiazole (III; R = Me) on the basis of elemental analysis and analogy with the *o*-toluidine reactions. However we later found that the ¹H n.m.r. spectrum of this material indicated the presence of an ethyl group, and two years later Ashby and Suschitzky⁴ prepared authentic 3-methyl-2,1-benzisothiazole (III; R = Me), a solid of m.p. 55°, by pyrolysis of 2-azidothioacetophenone. We have now examined the reactions of several α -substituted *o*-toluidines with thionyl chloride.

o-Benzylaniline (II; R = Ph) and thionyl chloride gave a quantitative yield of 3-phenyl-2,1-benzisothiazole (III; R = Ph), identified by comparison with an authentic sample. Other α -substituted *o*-toluidines gave different results. *o*-Aminobenzyl alcohol (II; R = OH) yielded a tarry material, probably polymeric, and we could not detect 3-hydroxy- or (more likely) 3-chloro-2,1-benzisothiazole in the reaction mixture. *o*-Aminobenzyl chloride (II; R = Cl), as its hydrochloride, similarly failed to yield 3-chloro-2,1-benzisothiazole. *o*-Aminobenzyl cyanide (II; R = CN) also yielded no benzisothiazole, even under extreme reaction conditions; in this case the product was the sulphinyl-

amine (IV; R = CN) or, when the reaction was carried out in dimethylformamide, the amidine (V; R = CN).



Reinvestigation of the *o*-ethylaniline (II; R = Me) reaction showed that several products were formed. That of m.p. 103° appears to be 2-(2,1-benzisothiazol-3-yl)-7-ethylbenzothiazole (VI), on the basis of analytical



and spectroscopic evidence. Two other products were *N*-(*o*-ethylphenyl)-2,1-benzisothiazole-3-carboxamide (VII) and 2,1-benzisothiazole-3-carboxylic acid (III; R = CO₂H). This acid is a convenient starting compound for the synthesis of other 3-substituted 2,1-benzisothiazoles; by careful control of the reaction conditions it may readily be obtained in yields of about 30% from a one-stage reaction between *o*-ethylaniline and thionyl chloride. The preparation of the analogous 1,2-isomer requires a four-step procedure from benzene-thiol and oxalyl chloride.⁵

We have been unable to isolate 3-methyl-2,1-benzisothiazole from this reaction, although the ¹H n.m.r. spectrum of the crude product indicates the presence of a small quantity of the compound. However,

¹ Part VI, M. Davis, E. Homfeld, and K. S. L. Srivastava, *J.C.S. Perkin I*, 1973, 1863.

² M. Davis and A. W. White, *Chem. Comm.*, 1968, 1547.

³ M. Davis and A. W. White, *J. Org. Chem.*, 1969, **34**, 2985.

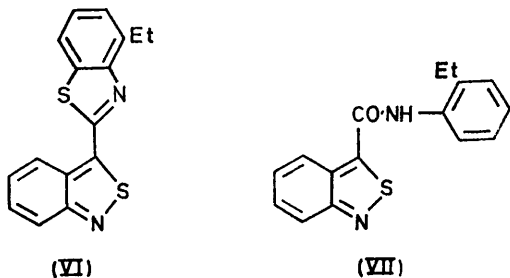
⁴ J. Ashby and H. Suschitzky, *Tetrahedron Letters*, 1971, 1315.

⁵ R. Stollé, W. Geisel, and W. Badstübner, *Ber.*, 1925, **58**, 2095.

3-methyl-2,1-benzisothiazole is itself rapidly α -chlorinated when heated with thionyl chloride, as reported for several other methyl-substituted heterocyclic compounds.⁶ It seems probable that 3-methyl-2,1-benzisothiazole is an intermediate in the reaction, but that its steady-state concentration is low owing to the subsequent rapid chlorination. It is also possible that chlorosulphenyl derivatives, as well as chloro-derivatives, are produced, as has been demonstrated in the similar preparation of benzo[*b*]thiophens from hydrocinnamic acids.⁷ The reaction of these derivatives with unchanged *o*-ethylaniline could account for the formation of compounds (VI) and (VII); the carboxylic acid (III; R = CO₂H) itself is presumably formed by hydrolysis of the trichloromethyl derivative (III; R = CCl₃) or a related species.

The formation of 2,1-benzisothiazole-3-carboxylic acid from *o*-ethylaniline is apparently a unique example of the multifunctional use of thionyl chloride in organic synthesis; the thionyl chloride is involved in three consecutive, distinct reactions: introduction of the sulphur atom, closure of the heterocyclic ring, and oxidation of the newly-positioned α -methyl group.

We have examined briefly the reactions of some other *o*-alkyl- and *oo'*-dialkyl-anilines with thionyl chloride. The reaction of 2,6-dimethylaniline (giving 7-methyl-



2,1-benzisothiazole) has already been reported;³ 2-ethyl-6-methylaniline afforded a trace of 7-ethyl-2,1-benzisothiazole, the main product being a sulphinylamine; 2,6-diethylaniline, *o*-isopropylaniline, and 2,6-di-isopropylaniline yielded the corresponding sulphinylamines only, with no evidence of heterocyclic ring formation.

EXPERIMENTAL

Analyses were performed by the Australian Micro-analytical Service, Melbourne. A Perkin-Elmer 257 spectrophotometer and Varian A-60D and T60 spectrometers were used for i.r. and ¹H n.m.r. measurements.

3-Phenyl-2,1-benzisothiazole (III; R = Ph).—*o*-Benzylaniline⁸ (3 g), xylene (mixture of isomers; 20 ml) and thionyl chloride (5 ml, 8.3 g) were heated together under reflux for 24 h. Extraction of the resulting solution with hydrochloric acid (10M; 3 × 20 ml), washing of the extracts with light petroleum (b.p. 40–60°; 3 × 20 ml)

⁶ J. R. Merchant, A. R. Bhat, and D. V. Rege, *Tetrahedron Letters*, 1972, 2061; earlier examples are given by R. Graf and F. Zette, *J. prakt. Chem.*, 1936, **147**, 188, and W. R. Boon, *J. Chem. Soc.*, 1945, 601.

⁷ A. J. Krubsack and T. Higa, *Tetrahedron Letters*, 1972, 4823.

⁸ F. Seidel, *Ber.*, 1928, **61**, 2276.

and dilution with water (150 ml) afforded an oil which was extracted and dried in the usual way. The product initially failed to crystallise,⁹ but seeding afforded needles (3.2 g, 93%), m.p. 56° (lit.,⁴ 56°) (from aqueous methanol) (Found: C, 73.8; H, 4.4; N, 6.8; S, 15.0. Calc. for C₁₈H₉NS: C, 73.9; H, 4.3; N, 6.6; S, 15.2%), ν_{\max} 1615, 1488, 1449, 1396, 1374, 1147, 877, 830, 772, 755, 695, 685, and 634 cm⁻¹, δ 7.1–8.0 (aromatic).

Attempted Preparations of 3-Hydroxy-, 3-Chloro-, and 3-Cyano-2,1-benzisothiazole.—Reactions similar to the foregoing were attempted with *o*-aminobenzyl alcohol (II; R = OH), *o*-aminobenzyl chloride hydrochloride¹⁰ (II; R = Cl; HCl salt), and *o*-aminobenzyl cyanide¹¹ (II; R = CN). The crude products were examined (t.l.c., i.r.) for the presence of the expected 3-substituted 2,1-benzisothiazoles¹² but in no case were these observed. The alcohol and the chloride yielded tarry (probably polymeric) substances; the cyanide afforded a quantitative yield of *o*-(sulphinylamino)benzyl cyanide (IV; R = CN), isolated by dilution of the reaction mixture with light petroleum (b.p. 60–80°); it formed *needles*, m.p. 70–71° (Found: C, 53.7; H, 3.3; N, 15.6. C₈H₆N₂OS requires C, 53.9; H, 3.4; N 15.7%), δ 3.80 (s, CH₂), 7.1–7.4 (3H), and 8.1–8.4 (1H). When the reaction between *o*-aminobenzyl cyanide and thionyl chloride was carried out in dimethylformamide (conditions which Naito *et al.*¹³ found satisfactory for the analogous preparation of cyanoisothiazoles) the product was *N*²-*o*-(cyanomethyl)phenyl-*N*¹*N*¹-dimethylformamidine (V), which formed *needles*, m.p. 38° [from light petroleum (b.p. 40–60°)] (Found: C, 70.3; H, 7.1; N, 22.3. C₁₁H₁₃N₃ requires C, 70.5; H, 7.0; N, 22.4%), ν_{\max} 2260 (CN) and 1645 cm⁻¹ (C=N), δ 3.01 (s, CH₃), 3.64 (s, CH₂), 6.7–7.5 (aromatic), and 7.52 (s, CH).

Reaction of *o*-Ethylaniline with Thionyl Chloride.—The following procedure seems to afford the best yield of the carboxylic acid (III; R = CO₂H). Thionyl chloride (22 ml, 36 g, 0.3 mol) was added dropwise to a stirred, cooled mixture of *o*-ethylaniline (12.1 g, 0.1 mol) and xylene (50 ml). The mixture was heated under reflux, the evolved gas (SO₂ and HCl) being passed through sodium hydroxide solution. After 12 h heating more thionyl chloride (22 ml) was added dropwise and heating was continued for a further 12 h. Water (200 ml) was added, followed by sodium hydroxide solution (2.5M; 400 ml) and the mixture was steam distilled (*ca.* 300 ml of distillate). The residual alkaline solution was stirred with charcoal (1 g), filtered, and acidified with acetic acid. Crystals of 2,1-benzisothiazole-3-carboxylic acid (III; R = CO₂H) separated (5.3 g, 30%), m.p. 212° (decomp.), identical with an authentic sample.¹²

Other products were isolated by extraction of the crude mixture prior to the addition of water. The brown liquid was shaken with hydrochloric acid (10M; 50 ml), left at room temperature for 1 h, and filtered through a coarse fritted filter to remove *o*-ethylaniline hydrochloride (produced by the action of the acid on *o*-ethyl-*N*-sulphinyl-

⁹ Other workers have experienced difficulty in obtaining this compound crystalline: O. Aki, Y. Nagakawa, and K. Sirakawa, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2372, report it as an oil.

¹⁰ S. Gabriel and T. Posner, *Ber.*, 1894, **27**, 3513.

¹¹ R. Pschorr and G. Hoppe, *Ber.*, 1910, **43**, 2547.

¹² R. K. Buckley, M. Davis, and K. S. L. Srivastava, *Austral. J. Chem.*, 1971, **24**, 2405.

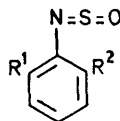
¹³ T. Naito, S. Nakagawa, J. Okumura, K. Takahashi, K. Masukuo, and Y. Narita, *Bull. Chem. Soc. Japan*, 1968, **41**, 965.

aniline). The acid layer in the filtrate was washed with light petroleum (b.p. 40–60°) and diluted with ice-water (200 ml), and the gummy precipitate was taken up in ether (100 ml). The ethereal solution was dried and evaporated, and the residue dissolved in warm methanol (15 ml). Brown crystals of 2-(2,1-benzisothiazol-3-yl)-7-ethylbenzothiazole (VI) slowly separated (0.5 g, 4%), m.p. 103° (Found: C, 64.5; H, 4.1; N, 9.2; S, 21.8%; *M*, 296. C₁₆H₁₂N₂S₂ requires C, 64.8; H, 4.1; N, 9.4; S, 21.6%; *M*, 296), δ 1.46 (t, *J* 8 Hz), 3.23 (q, *J* 8 Hz), and 7.2–8.5 (aromatic) (3:2:7). The i.r. spectrum in the range 650–1000 cm⁻¹ was similar to a sum of the spectra of 2,1-benzisothiazole and a 7-substituted benzothiazole: ν_{\max} at 965, 913, 890, 858, 842, 816, 797, 765, and

way as *o*-ethylaniline. Apart from 2-ethyl-6-methylaniline, which appeared to yield small quantities of 7-ethyl-2,1-benzisothiazole and 7-methyl-2,1-benzisothiazole-3-carboxylic acid, the amines afforded only the *N*-sulphinyl derivatives. These are quickly hydrolysed by aqueous work-up, but could be isolated as yellow oils by fractional distillation of the crude reaction mixture. Together with *o*-ethyl-*N*-sulphinylaniline, they are listed in the Table.

Reaction of 3-Methyl-2,1-benzisothiazole with Thionyl Chloride.—3-Methyl-2,1-benzisothiazole⁴ (0.5 g), toluene (5 ml), and thionyl chloride (3 ml, 5 g, 12 equiv.) were heated together under reflux for 4 h. The mixture was boiled with sodium hydroxide solution (2.5*M*; 50 ml) for 15 min, steam-distilled briefly to remove toluene,

o-Alkyl- and *oo'*-dialkyl-*N*-sulphinylanilines



| R ¹ | R ² | B.p. (°C at 0.1 mmHg) | Formula | Found (required) (%) | | | |
|-----------------|-----------------|-----------------------|-------------------------------------|----------------------|-----------|-----------|-------------|
| | | | | C | H | N | S |
| Et | H | 70–72 | C ₈ H ₉ NOS | 58.1 (57.5) | 5.5 (5.4) | 8.7 (8.4) | 18.9 (19.2) |
| Pr ⁱ | H | 74–77 | C ₉ H ₁₁ NOS | 59.3 (59.6) | 6.1 (6.1) | 8.0 (7.7) | 17.4 (17.7) |
| Et | Me | 78–80 | C ₉ H ₁₁ NOS | 59.4 (59.6) | 6.4 (6.1) | 7.4 (7.7) | 17.3 (17.7) |
| Et | Et | 80–82 | C ₁₀ H ₁₃ NOS | 61.3 (61.5) | 6.5 (6.7) | 7.0 (7.2) | 16.1 (16.4) |
| Pr ⁱ | Pr ⁱ | 82–85 | C ₁₂ H ₁₇ NOS | 64.6 (64.5) | 8.0 (7.7) | 6.0 (6.3) | 14.1 (14.4) |

745 cm⁻¹. The mass spectrum indicated the presence of a 2,1-benzisothiazolyl system (*m/e* 134); the basicity of the compound was also characteristic of a substituted 2,1-benzisothiazole.

The methanolic mother liquor was cooled to *ca.* –30°; crystals of *N*-(*o*-ethylphenyl)-2,1-benzisothiazole-3-carboxamide (VII) (1.5 g, 11%) separated. Recrystallisation (aqueous methanol) gave long needles, m.p. 121–122° (Found: C, 67.5; H, 4.9; N, 9.6; S, 11.6. C₁₆H₁₄N₂OS requires C, 68.1; H, 5.0; N, 9.9; S, 11.4%), ν_{\max} 3220 (NH) and 1635 cm⁻¹ (CO), identical with an authentic sample prepared from 2,1-benzisothiazole-3-carboxylic acid and *o*-ethylaniline.

Reactions of other o-Alkylanilines with Thionyl Chloride.—2-Ethyl-6-methylaniline, 2,6-diethylaniline, *o*-isopropylaniline, and 2,6-diisopropylaniline were treated in the same

treated with charcoal, filtered, and acidified. Crystals of 2,1-benzisothiazole-3-carboxylic acid (0.3 g, 50%) separated.

Reactions of 2,1-Benzisothiazole-3-carboxylic Acid.—The acid decarboxylates at its m.p., or more slowly above 150°, with quantitative formation of 2,1-benzisothiazole. It is readily esterified, *e.g.* by heating under reflux with methanol containing a few drops of sulphuric acid. The *methyl ester* formed needles, m.p. 53° (from aqueous methanol) (Found: C, 55.6; H, 3.7; N, 7.2. C₉H₇NO₂S requires C, 55.9; H, 3.6; N, 7.2%).

We thank the Ethyl Corporation for gifts of *o*-alkylanilines, and Professor H. Suschitzky for a gift of crystalline 3-phenyl-2,1-benzisothiazole.

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