3-Amino-2,1-benzoisothiazole. Synthesis of Some Chloro and Trifluoromethyl Derivatives

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The syntheses of the 7-chloro-, 4,7-dichloro-, 5- and 7-trifluoromethyl, 5-chloro-6-trifluoromethyl- and 5-chloro-7-trifluoromethyl- derivatives of 3-amino-2,1-benzoisothiazole are described. Preparative details are included for a number of the precursors to the benzoisothiazole derivative which have not previously been described. Visible spectra of some azo dyes prepared from the title compounds with a selected coupler are discussed with reference to the substituent effects.

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Derivatives of 3-amino-2,1-benzoisothiazole have found use in the dye, pharmaceutical and agricultural industries. The synthesis of the four possible monochloro- and nitro-derivatives has been reviewed (3,4) and azo dyes based on the derivatives are claimed in several patents (5). In this paper the syntheses of some novel 3-amino-2,1-benzoisothiazoles are reported. Azo dyes prepared from these amines are disclosed in the patent literature (6).

The usual synthesis of 3-amino-2,1-benzoisothiazoles by addition of hydrogen sulphide to the appropriate anthranilonitrile followed by oxidation and cyclisation of the resulting thioamide with hydrogen peroxide was reported by Meyer, *et al.* in 1965 (7). These final stages of the synthesis normally proceed smoothly and in good yield and hence a discussion of routes to the title compounds should include a description of the preparation of the anthranilonitrile compounds and their precursors, many of which have not been described previously.

A convenient route (Figure 1), particularly for 7-substituted 3-amino-2,1-benzoisothiazoles, was from the corresponding ortho-substituted aniline by conversion to the isonitrosoacetanilide followed by cyclisation to the isatin. At this stage two alternative routes are available. Reaction with hydroxylamine yields the isatin-β-oxime (8,9), which on heating dehydrates to give the anthranilonitrile (10). Alternatively treatment of the substituted isatin with hydrazoic acid gives the anthranilamide (11,12) which can either be dehydrated to the anthranilonitrile or converted into the thioanthranilamide (3,4,13,14). The latter route has been used in the synthesis of 3-amino-5,7-dichloro-2,1-benzoisothiazole recently (15). Other routes include nucleophilic displacement of a bromine atom in an ortho-bromoaniline with cuprous cyanide (16,17) reduction of an ortho-cyanoazo compound or amination of an *ortho*-halogenobenzonitrile (18).

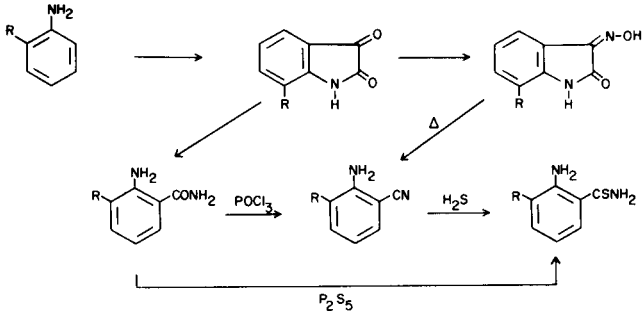
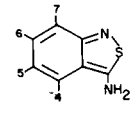


Figure 1. Some routes to substituted anthranilonitrile and thioanthranilonitrile.

The 3-amino-2,1-benzoisothiazoles prepared are listed in Table 1. Attempts to prepare 3-amino-5-trifluoromethyl-2,1-benzoisothiazole in good yield failed owing to the tendency of 5-trifluoromethylthioanthranilamide to lose the elements of hydrogen sulphide on treatment with an oxidising agent. The required product was therefore separated from the anthranilonitrile by column chromatography.

Table 1

3-Amino-2,1-benzoisothiazoles



3-Amino-2,1-benzoisothiazole	M.p. °C	References to Route Taken
7-Chloro-	199	8,9,10
7-Trifluoromethyl-	188	8,9,10
5-Trifluoromethyl-	209	18
4,7-Dichloro-	220-224	11,12,13,14
5-Chloro-7-trifluoromethyl-	220	11,12,13,14
5-Chloro-6-trifluoromethyl-	152-154	16,17

Spectra of Azo Dyes Derived from 3-Amino-2,1-benzoisothiazole.

The visible spectra of azo dyes derived from the title compounds and appropriate alkylaniline couplers should indicate bathochromic shifts in accord with the Hammett Constants (σ) of the substituents at the various sites (19).

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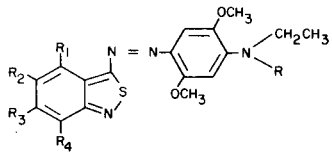
Earlier work (3) indicated very little variation in λ max for a series of dyes in which a chlorine atom is substituted in the four available sites of the benzo-ring. The strongest electron withdrawing effect and greatest extension of the conjugated system, however, was observed in the dye with a 7-chloro-substituent, interpreted from the largest bathochromic shift of the visible band.

A comparison of the effect of a trifluoromethyl group with that of a chlorine atom however does not give the result anticipated from the Hammett Constants [measured as para-substituents on a benzene ring (20)]. The higher positive value of the trifluoromethyl group would be expected to result in more pronounced bathochromic shifts of the visible absorption bands. However, this is not always the case.

Table 2

Visible Spectra of Some Benzoisothiazole Dyes



Dye	R	R_1	R_2	R_3	R_4	λ max (nm, acetone)
a	H	H	H	H	Cℓ	580
b	H	H	H	H	CF_3	580
c	H	Cℓ	H	H	Cℓ	604
d	H	H	Cℓ	H	CF_3	600
e	H	H	Cℓ	CF_3	H	595
f	Et	H	Cℓ	H	H	592
g	Et	H	CF_3	H	H	600

With the 5-substituted dyes compared (Table 2, dyes f and g) the introduction of a trifluoromethyl group results in a larger bathochromic shift but this is not so with the 7-substituted compounds (Table 2; dyes a and b). This effect is presumably associated with the increased influence of the mesomeric effect of the halogen and steric influences of the "peri" nitrogen atom on the large trifluoromethyl group.

The effect of introducing two groups is of course additive as illustrated by the 4,7-dichloro compound (Table 2, dye c), the 4-chlorine atom resulting in a further shift of 24 nm. This is larger than the introduction of a 5-chlorine atom (20 nm; Table 2; dyes b and d) and in agreement with figures due to Wippel (3). It is not clear why the 4-chlorine atom is more effective than the 5-substituent and indeed the opposite case would be expected.

EXPERIMENTAL

Visible spectra were measured on a Unicam SP800 instrument in "spectral grade" acetone solution.

2-Amino-5-chloro-4-trifluoromethylbenzonitrile.

Pyridine (36 g.) was added slowly to cuprous cyanide (33 g.) with stirring and heated slowly to 125° to remove the slight excess of pyridine. At 110°, 5-amino-4-bromo-2-chlorobenzotrifluoride (40 g.) was added and the temperature was raised to 170-180°. After stirring for 2 hours the mass was cooled to 90° and added to a saturated solution of sodium cyanide (78 g.) in water (90 ml.). Extraction with benzene, removal of the organic solvent and crystallisation of the residue from 100-120° petroleum ether gave 2-amino-5-chloro-4-trifluoromethylbenzonitrile (13.1 g.), m.p. 112-113°.

Anal. Calcd. for $C_8H_4C\ell F_3N_2$: C, 43.6; H, 1.8; N, 12.7; Cℓ, 16.1. Found: C, 44.0; H, 1.4; N, 12.2; Cℓ, 16.4.

2-Amino-3,6-dichlorothiobenzamide.

4,7-Dichloroindole-2,3-dione (41 g.) was dissolved in concentrated sulphuric acid (100 ml.) and stirred at 0-5°. Sodium azide (13.2 g.) was added slowly below 5° and the reaction mixture was allowed to stand overnight (carry out this reaction in a good fume hood as some hydrazoic acid gas may be evolved). The reaction mixture was poured slowly into ice-water (2000 ml.) and neutralised with sodium hydroxide solution. The precipitate was collected, well washed with petroleum ether, and dried to give 2-amino-3,6-dichlorobenzamide (24.3 g.), m.p. 132-134°.

Anal. Calcd. for $C_7H_6C\ell_2N_2O$: Cℓ, 34.6. Found: Cℓ, 34.9.

2-Amino-3,6-dichlorobenzamide (20.5 g.) was dissolved in toluene (500 ml.) and, at reflux temperature, phosphorus pentasulphide (4 g.) was added. Reflux was continued for 4 hours and the mixture filtered hot. The filtrate was concentrated to half volume and allowed to cool. The resultant precipitate was collected and dried to give 2-amino-3,6-dichlorothiobenzamide (6.1 g.), m.p. 141-142°.

Anal. Calcd. for $C_7H_6C\ell_2N_2S$: C, 38.0; H, 2.7; N, 12.7; S, 14.5. Found: C, 38.2; H, 2.7; N, 12.2; S, 14.4.

7-Chloroindole-2,3-dione 3-Oxime.

7-Dichloroindole-2,3-dione from 2-chloroaniline (63.5 g.) (8) was dissolved in 20% v/v ethanol/water (500 g.). Hydroxylamine hydrochloride (50 g.) was added and the solution was heated under reflux for 30 minutes. The cooled solution was filtered to give 7-chloroindole-2,3-dione 3-oxime (43 g.), m.p. 300°.

Anal. Calcd. for $C_8H_5C\ell N_2O_2$: C, 48.9; H, 2.6; N, 14.3; Cℓ, 18.1. Found: C, 48.7; H, 2.6; N, 13.8; Cℓ, 18.4.

2-Amino-3-trifluoromethylbenzonitrile.

7-Trifluoromethylisatin β-oxime (82 g.) from 2-trifluoromethylaniline (8,9) was decomposed by careful melting. The residue was extracted with hot acetone and passed through a florisil column eluting with 5% acetone in 60-80° petroleum ether. Evaporation of the appropriate fractions and crystallisation from aqueous ethanol gave 2-amino-3-trifluoromethylbenzonitrile (11.5 g.), m.p. 72°.

Anal. Calcd. for $C_8H_5F_3N_2$: C, 51.7; H, 2.7; N, 15.1. Found: C, 52.0; H, 2.9; N, 14.9.

5-Chloro-7-trifluoromethylindole-2,3-dione (21).

7-Trifluoromethylindole-2,3-dione (54 g.) was dissolved in carbon tetrachloride (500 ml.) and *N*-chlorosuccinimide (39 g.) added. The mixture was heated under reflux with stirring for six hours. On completion of the reaction the solvent was removed and the residue extracted with hot water to remove succinimide. The remaining residue was crystallised from chloroform to give 5-chloro-7-trifluoromethylindole-2,3-dione (30.9 g.), m.p. 208-210°.

Anal. Calcd. for $C_9H_3C\ell F_3NO_2$: C, 43.3; H, 1.2; N, 5.6; Cℓ, 14.2. Found: C, 43.4; H, 1.0; N, 5.9; Cℓ, 14.4.

2-Amino-5-chloro-3-trifluoromethylbenzamide.

Treatment of 5-chloro-7-trifluoromethylindole-2,3-dione (32 g.), as described above, with sodium azide in sulphuric acid gave 2-amino-5-chloro-3-trifluoromethylbenzamide (25 g.), m.p. 148°.

Anal. Calcd. for $C_8H_6C\ell F_3N_2O$: C, 40.3; H, 2.5; N, 11.7; Cℓ, 14.8. Found: C, 40.4; H, 2.2; N, 11.7; Cℓ, 14.6.

2-Amino-5-chloro-3-trifluoromethylbenzonitrile.

2-Amino-5-chloro-3-trifluoromethylbenzamide (25 g.) was dissolved in phosphorus oxychloride (90 g.) and heated at 90-100° for two hours. The mixture was poured into ice-water (700 ml.) and the residue crystallised from ethanol to give 2-amino-5-chloro-3-trifluoromethylbenzonitrile (21 g.), m.p. 76-80°.

Anal. Calcd. for $C_8H_4C\ell F_3N_2$: C, 42.6; H, 1.8; N, 12.7; Cℓ, 16.1. Found: C, 42.5; H, 1.8; N, 12.3; Cℓ, 16.0.

3-Amino-7-trifluoromethyl-2,1-benzoisothiazole.

Treatment of 2-amino-3-trifluoromethylbenzonitrile with hydrogen sulphide gas in ethanol followed by oxidation of the thioanthranilamide with hydrogen peroxide in pyridine according to the literature method (7) gave 3-amino-7-trifluoromethyl-2,1-benzoisothiazole, m.p. 188°.

Anal. Calcd. for $C_8H_5F_3N_2S$: N, 12.8; S, 14.7. Found: N, 12.9; S, 14.2.

3-Amino-5-trifluoromethyl-2,1-benzoisothiazole.

Treatment of the corresponding anthranilonitrile as described (7) and separation by column chromatography gave 3-amino-5-trifluoromethyl-2,1-benzoisothiazole, m.p. 209°.

Anal. Calcd. for $C_8H_5F_3N_2S$: C, 44.0; H, 2.3; N, 12.8; S, 14.7. Found: C, 44.3; H, 2.5; N, 13.2; S, 15.0.

3-Amino-4,7-dichloro-2,1-benzothiazole.

Treatment of the corresponding anthranilonitrile as described (7) gave 3-amino-4,7-dichloro-2,1-benzoisothiazole, m.p. 220-224°.

Anal. Calcd. for $C_7H_4C\ell_2N_2S$: C, 38.4; H, 1.8; N, 12.8; S, 14.6. Found: C, 38.4; H, 1.7; N, 12.7; S, 14.4.

3-Amino-5-chloro-7-trifluoromethyl-2,1-benzoisothiazole.

Similarly, treatment of 2-amino-5-chloro-3-trifluoromethyl benzonitrile as described (7) gave 3-amino-5-chloro-7-trifluoromethyl-2,1-benzoisothiazole, m.p. 220°.

Anal. Calcd. for $C_7H_4C\ell F_3N_2S$: C, 38.0; H, 1.6; Cℓ, 14.1; N, 11.1; S, 12.7. Found: C, 38.2; H, 1.8; Cℓ, 14.0; N, 11.2; S, 12.6.

3-Amino-5-chloro-6-trifluoromethyl-2,1-benzoisothiazole.

Treatment of 2-amino-5-chloro-4-trifluoromethylbenzonitrile as described (7) gave 3-amino-5-chloro-6-trifluoromethylbenzoisothiazole, m.p. 152-154°.

Anal. Calcd. for $C_7H_4C\ell F_3N_2S$: C, 38.0; H, 1.6; Cℓ, 14.1; S, 12.7. Found: C, 38.1; H, 1.6; Cℓ, 14.1; S, 12.7.

3-Amino-7-chloro-2,1-benzoisothiazole.

Treatment of 2-amino-3-chlorobenzonitrile as previously described (7) gave 3-amino-7-chloro-2,1-benzoisothiazole, m.p. 199°, as previously, though not fully, described (3).

Anal. Calcd. for $C_7H_5C\ell N_2S$: C, 45.5; H, 2.7; N, 15.2; Cℓ, 19.2. Found: C, 45.2; H, 3.0; N, 14.9; Cℓ, 19.1.

Preparation of the Dyes.

The dyes were prepared by well-documented methods (5), the diazotisation of the amines being carried out in mixed acetic: propionic acid with nitrosyl sulphuric acid. The couplings were carried out in the same solvent and the dyes crystallised from ethanol or acetone.

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