The Preparation and Characterization of 2-Amino-5,6-dichloro and 2-Amino-6,7-dichlorobenzothiazole

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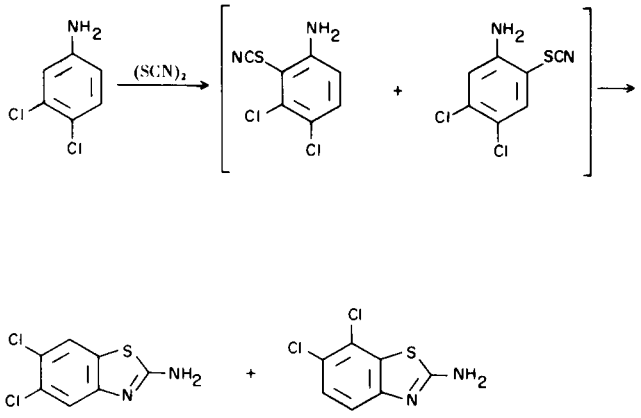
During the course of research work on the synthesis of novel heterocyclic systems, it became necessary to prepare a sample of 2-amino-5,6-dichlorobenzothiazole. Following the published procedure exactly (1), a quantity was prepared; however, a routine nmr spectrum of the product showed that it was actually a mixture of the 5,6- and 6,7-dichloro isomers in approximately equal amounts. The synthesis, separation, identification and characterization of these two isomers are now reported.

The general method for the preparation of 2-aminobenzothiazoles involves the reaction of a suitably substituted aniline with thiocyanogen [$(SCN)_2$] and the subsequent cyclization of the intermediate by heat or acid. The thiocyanogen is normally generated *in situ* by the action of bromine on an inorganic thiocyanate in a non-aqueous solvent. With 3,4-dichloroaniline, both *ortho* positions are open, allowing the formation of both of the observed products as shown in Scheme I.

SCHEME I



The isomers in the crude product were separated by utilizing the differential solubilities of the respective hydrochloride salts in water as described in the experimental section. Although the isomers were present in the crude reaction mixture in approximately equal amounts, as seen by nmr, only a 10% yield of the 5,6-dichloro and a 21% yield of the 6,7-dichloro isomer were actually isolated in pure form.

The British patent (1) describes the reaction product as being only 2-amino-5,6-dichlorobenzothiazole (melting at 185-190°) which is obtained in a 60% yield. When pure, the 5,6-dichloro isomer has an onset melting point of 210.3° and the 6,7-dichloro isomer has an onset melting point of 222.5° as determined by a differential thermal analyzer. The approximately 50:50 mixture of the two isomers has an onset melting point of 178.0°.

The identity of the materials was confirmed by elemental analysis, the purity of the isomers by gas chromatographic analysis and the structure assignments by nmr spectroscopy. The nmr spectra of the individual isomers and the original reaction mixture are shown in Figure 1. Gas chromatographic separation data are included in the experimental section.

An examination of the nmr spectra (Figure 1) shows the 4 and 7 protons of the 5,6-dichloro isomer as two singlets centered at 7.55 and 8.0 ppm. The 4 and 5 protons of the 6,7-dichloro isomer appear as a pair of doublets centered at 7.25 and 7.45 ppm. These doublets are in an AB pattern with an apparent coupling constant of 8.5 cps.

EXPERIMENTAL

The nmr spectra were recorded on a Varian A60A Spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Melting points were determined mechanically using a custom-made differential thermal analyzer and visually in open capillaries using a Mel-Temp melting point apparatus and are corrected.

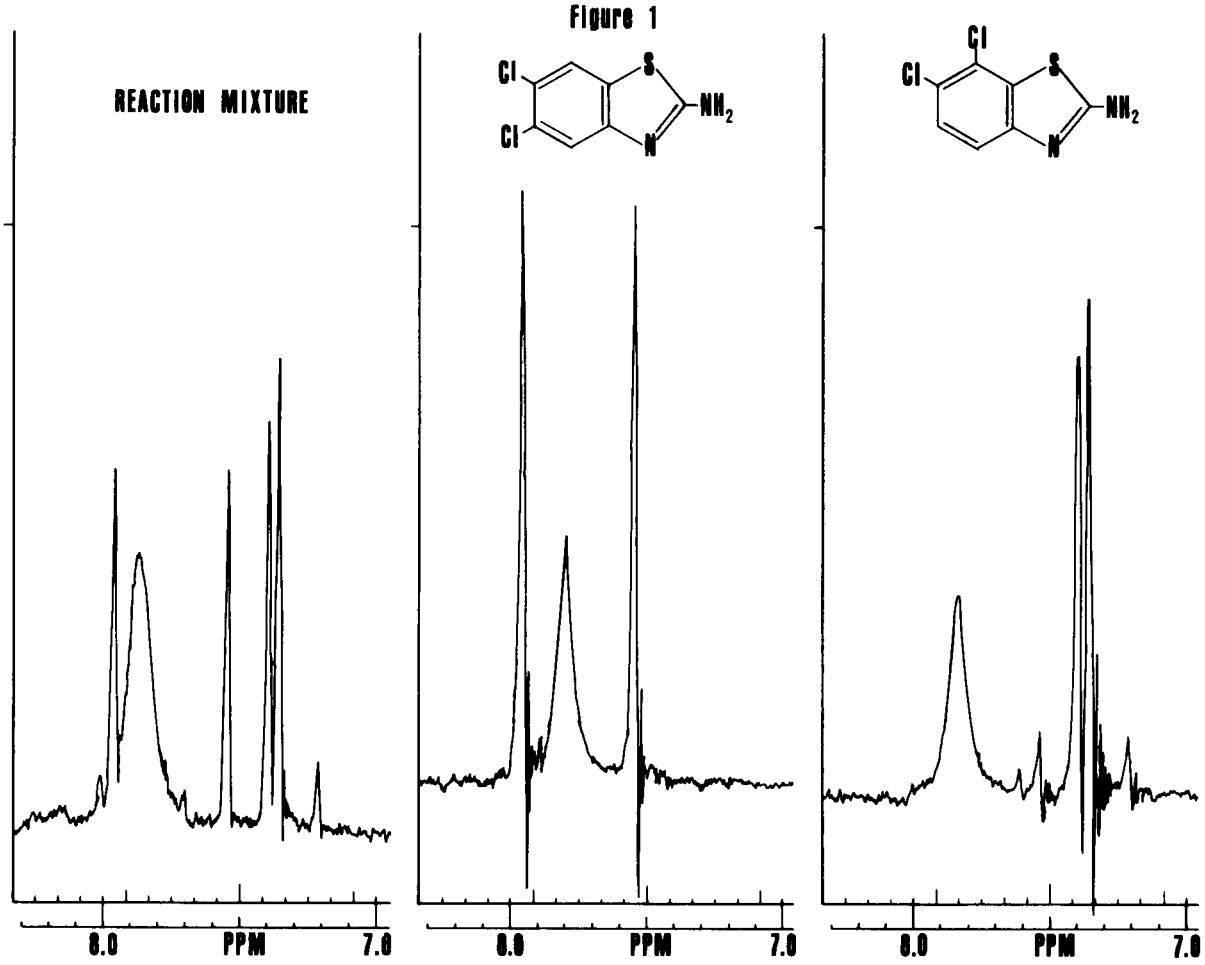
Gas Chromatographic Data.

Gas chromatography was performed on a Perkin-Elmer Model 900 using a 3 ft x 1/8 in column of 5% OV-17 on AW-DMCS treated chromosorb W. The pertinent temperatures are as follows: Column - 255°; Injector - 300°; Detector - 300°. The helium flow rate was 42 ml. per minute and the samples gave retention times of 2 minutes 24 seconds for the 6,7-dichloro and 2 minutes 50 seconds for the 5,6-dichloro isomer.

2-Amino-5,6-dichlorobenzothiazole.

A mixture of potassium thiocyanate (388 g., 4.0 moles) and 3,4-dichloroaniline (162 g., 1.0 mole) was dissolved in 96% acetic

Figure 1



acid (1 l.). To this mixture was added dropwise a solution of bromine (160 g., 1.0 mole) in acetic acid (500 ml.), and the temperature was maintained below 35° throughout the addition. After the addition was complete, the reaction mixture was stirred at room temperature for 16 hours.

The reaction mixture was poured into water and neutralized with dilute aqueous ammonia. The precipitated product was removed by filtration and air dried. The dry solid was dissolved in ether (2 l.) and saturated with dry hydrogen chloride gas.

The hydrochloride salt was removed by filtration, the ether filtrate discarded and the salt stirred in water (1.5 l.) for about 10 minutes. The suspension was then filtered and the aqueous filtrate retained for further use. The filtered solid after drying weighed 87 g.

The solid (87 g.) after suspension in water, was made basic with ammonium hydroxide, filtered and dried. This material was dissolved in ether (1.5 l.) and saturated with hydrogen chloride as before. The precipitated hydrochloride salt was stirred in water (1 l.) a second time and after filtering, both the solid and aqueous filtrate were retained. This cycle was repeated three times and the aqueous supernatant solutions from the first two cycles were combined. This aqueous solution was made basic with ammonium hydroxide to give 49 g. of white powder. This material was placed in methanol (300 ml.) and boiled, filtered and allowed to crystallize. The crystalline product weighed 21 g. (10%) and assayed better than 95% pure by gas chromatography.

Recrystallization a second time from methanol (Darco) provided an analytical sample as white crystals which melted at 211-212° in an open capillary. The structure was confirmed by nmr spectroscopy as 2-amino-5,6-dichlorobenzothiazole.

Anal. Calcd. for $C_7H_4Cl_2N_2S$: C, 38.37; H, 1.84; N, 12.78. Found: C, 38.38; H, 1.79; N, 12.84.

2-Amino-6,7-dichlorobenzothiazole.

After three cycles the solid remaining from the water treatment after the separation of the 5,6-dichloro isomer was neutralized with aqueous ammonium hydroxide. Filtration gave 45 g. (21%) of material which assayed better than 95% pure by gas chromatography. Nmr confirmed the structure as 2-amino-6,7-dichlorobenzothiazole. An analytical sample was prepared by recrystallization from ethyl acetate-petroleum ether and gave white crystals which melted at 225-227° in an open capillary.

Anal. Calcd. for $C_7H_4Cl_2N_2S$: C, 38.37; H, 1.84; N, 12.78. Found: C, 38.67; H, 2.06; N, 12.55.

Acknowledgments.

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REFERENCES

(1) British Patent No. 873,602; *Chem. Abstr.*, 56, 2454a (1962).