

Cyclizations of Isothiocyanates to 2-Aminobenzothiazoles (I)

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In 1887 Hofmann (2) first reported the cyclizations of 2-aminothiophenol (II) to 2-amino- or 2-mercaptobenzothiazoles. Since then the preparation of the rubber vulcanization accelerator, 2-mercaptobenzothiazole, has been studied extensively by many workers, but the synthesis of 2-substituted aminobenzothiazoles from the aminothiols and isothiocyanates has attracted much less attention. Hofmann noted only the formation of 2-anilinobenzothiazole (Ia) from the reaction of II and phenyl isothiocyanate. When this reaction was repeated in benzene, we obtained after chromatography, 2-aminophenyl disulfide, sulfur, and 1,3-diphenylthiourea as well as Ia. The disulfide may be an artifact formed by air oxidation of II during the work-up.

During this investigation, we read the paper of Anthoni, Larsen and Nielsen (3) and were most interested in their finding that when the reaction of II and phenyl isothio-

cyanate is run in ethanol, a dithiocarbamate (IIIa) is formed which can be converted to I by heating. We tried this reaction in other solvents such as acetone, chloroform and dioxane, but obtained the same products as with benzene. These reactions were run at room temperature, so no heating is needed to obtain Ia. Probably in hydroxylic solvents, a rapid exothermic reaction occurs to give IIIa, the kinetic product, while in other solvents, a difference in the solution complex prevents this reaction and the thermodynamic product, the thiourea, forms and rapidly cyclizes to Ia.

When II was allowed to react with benzyl isothiocyanate in benzene, the analogous compounds were obtained as in the phenyl case. When methanol was used as the solvent a dithiocarbamate, IIIb, was produced and heating this compound gave 2-benzylaminobenzothiazole, (Ib), 1,3-dibenzylthiourea and 2-mercaptobenzothiazole (IV).

CHART I

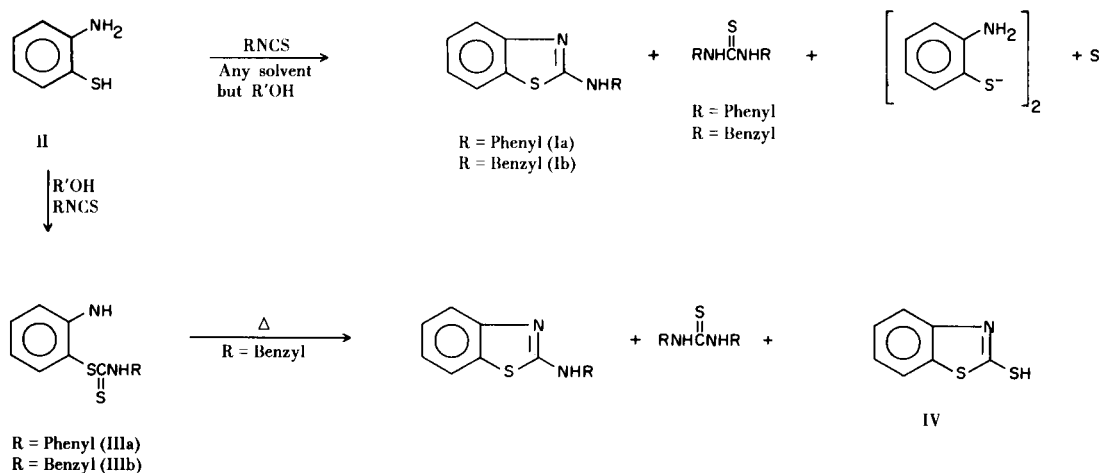
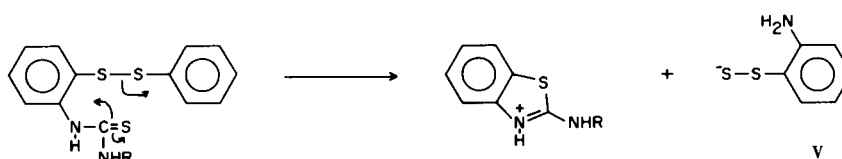


CHART II



Mixing I with methyl isothiocyanate in benzene gave products which appeared from thin layer chromatography to be IV and 2-methylaminobenzothiazole. The Danish workers (3) reported that 2-aminophenyl *N*-methylthiocarbamate is stable to heat, but cyclizes to give IV in acid. These results as well as those in the benzyl case provide additional evidence that the dithiocarbamate is not an intermediate in the reaction in non-hydroxylic solvents.

The most interesting reaction to us was the previously unreported one between 2-aminophenyl disulfide and isothiocyanates to yield 2-aminobenzothiazoles, thioureas and sulfur. This facile reaction requires no heating and gives the same results when run in either 2-propanol or benzene. Obviously the initial reaction is on the amino groups followed by further rapid reactions as no intermediates can be found.

A mechanism is suggested by the paper of Caldwell, Milligan and Swan (4) who found the thiosulfate derivative of 2-aminothiophenol to be converted to 2-anilinobenzothiazole quantitatively by phenyl isothiocyanate. Their mechanism can be modified to suggest the concerted rearrangement of an intermediate monothiourea as shown in Chart II. In the benzyl and methyl cases, additional isothiocyanate can react with the heterocyclic products to give a benzothiazole-substituted thiourea. The thioureas were isolated in these two cases, but not with the less nucleophilic phenylamino compound. Further reactions of the hypothetical disulfide V would lead to hydrogen sulfide, whose odor was detected, and sulfur which was isolated. Reaction of hydrogen sulfide with isothiocyanates to give *N,N'*-disubstituted thioureas has been reported by Proskauer and Sell (5). The stoichiometry of the reaction of phenyl isothiocyanate and 2-aminophenyl disulfide is consistent with this hypothesis. At a 2:1 mole ratio, only a little diphenyl thiourea is formed and some disulfide is recovered. As the ratio is increased to 3 and 4:1 the yields of both I and the thiourea increase. In the 4:1 reaction the recoveries of I, the thiourea, and sulfur are close to those predicted by this mechanism.

In one reaction using benzyl isothiocyanate and 2-aminophenyl disulfide, the corresponding trisulfide was isolated and identified by comparison with material synthesized from the disulfide and sulfur. The trisulfide can also be used as starting material, giving an increased yield of sulfur.

EXPERIMENTAL (6)

2-Anilinobenzothiazole (Ia).

Phenylisothiocyanate, 2.7 g. (0.02 mole) was mixed with 2.5 g. (0.02 mole) of 2-aminothiophenol (II) and 25 ml. of benzene and heated on a steam bath for 3 hours. Then the solvent was evaporated under nitrogen. The crystalline residue was triturated with methanol and the mixture was filtered to yield 3.1 g. of 2-anilinobenzothiazole (I), m.p. 159-161°, lit. m.p. 159° (8). The filtrate

was evaporated, then dissolved in benzene and chromatographed on 150 g. of CC-7 adsorbant (7). Elution with benzene gave about 0.3 g. of 2-aminophenyl disulfide and 0.5 g. of additional Ia. Elution with 2% ethyl acetate-benzene gave 0.7 g. of 1,3-diphenylthiourea, m.p. 150-151°.

The reaction was repeated using 2.5 g. of 2-aminophenyl disulfide instead of II. The initial product was recrystallized from methanol to yield 2.6 g. of Ia, m.p. 157-159°. Chromatography of the filtrate on CC-7, 170 g., gave 0.3 g. of additional Ia, 0.5 g. of a mixture of sulfur and disulfide and 0.3 g. of 1,3-diphenylthiourea, m.p. 152-153°.

2-Aminophenyl-*N*-benzylthiocarbamate.

Benzylisothiocyanate, 3.0 g. (0.02 mole) was mixed with 10 ml. of methanol and 2.5 g. (0.02 mole) of II. The temperature rose considerably. After some of the solvent had evaporated, a little water was added and on rubbing, crystals formed. They were recrystallized from methylene chloride-ether to give a total of 4.3 g. of 2-aminophenyl-*N*-benzylthiocarbamate. The melting point of the second crop was 104-106°, used for analysis. The first crop melted at 101-104°.

Anal. Calcd. for C₁₄H₁₄N₂S₂: C, 61.28; H, 5.14. Found: C, 61.39; H, 5.30.

Cyclization of 2-aminophenyl-*N*-benzylthiocarbamate.

2-Aminophenyl-*N*-benzylthiocarbamate, 3.0 g., was heated on a steam bath for 4 hours. The resulting yellow oil solidified and was dissolved in benzene and chromatographed on 250 g. of CC-7. Elution of the column with 2% ethyl acetate-benzene and identification of the resulting fractions gave 2-benzylaminobenzothiazole, about 0.8 g., m.p. of first fraction, 161.5-164°, lit. m.p. 160-161° (9); 1,3-dibenzylthiourea, about 0.7 g., m.p. of first fraction, 148-149.5°; and 2-mercaptobenzothiazole, about 0.7 g., m.p. of first fraction 172-182° lit. m.p. 179° (2). The materials were identified by m.p. and comparison of thin-layer chromatograms with authentic materials.

2-Aminophenyl Trisulfide.

2-Aminothiophenol (II), 97 g. (0.8 mole) and 50 g. (1.6 mole) of sulfur were mixed with 0.5 l. of carbon tetrachloride and heated on a steam bath until the odor of hydrogen sulfide could not be detected. The solution was evaporated to 0.2 l., filtered through Super-cel and diluted with benzene. A solid formed slowly on cooling, 83.6 g., m.p. 101-104°. The IR (chloroform) was the same as a sample isolated from the reaction of benzylisothiocyanate and 2-aminophenyl disulfide.

Anal. Calcd. for C₁₂H₁₂N₂S₃: C, 51.4; H, 4.31; S, 34.30. Found: C, 51.21; H, 4.55; S, 35.54.

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