[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

SOME OBSERVATIONS ON REPORTED SYNTHESES OF BENZOTHIAZOLE DERIVATIVES[1]

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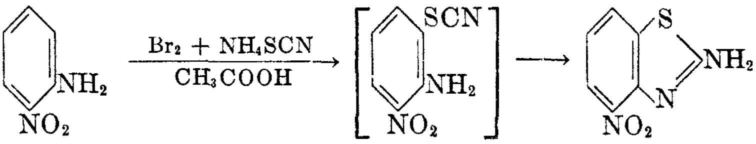
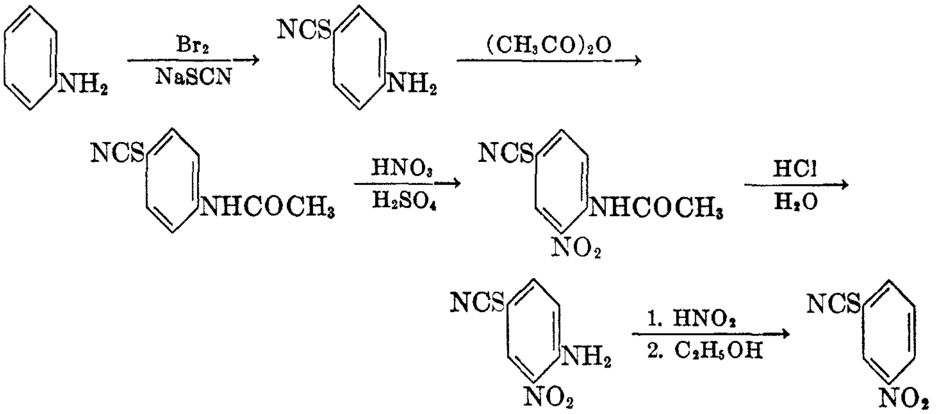
Received January 21, 1952

In connection with the synthesis of certain derivatives of benzothiazole, we have recently required 2-amino-4-nitrobenzothiazole (I). Two methods for the synthesis of I are reported. The first involves oxidative ring closure of *o*-nitrophenylthiourea with bromine (1, 2). The over-all yield from *o*-nitroaniline is 35–40%. The second, and at first sight more attractive, method has been reported by Blomquist and Diuguid (3). This involves thiocyanation of *o*-nitroaniline and presumably proceeds through an unstable intermediate, 2-amino-3 nitrophenyl thiocyanate (II). A yield of 70% of I is reported.



II I

The melting point of I reported by Blomquist and Diuguid (3) is 110–112° whereas the older literature reports 254° (1) and 232° (2). This discrepancy together with the fact that thiocyanation of aromatic amines is known to occur predominantly in the *para* position unless this position is blocked (4) led us to suspect that the substance reported by Blomquist and Diuguid was actually 4-amino-3-nitrophenyl thiocyanate (III) rather than I.



III

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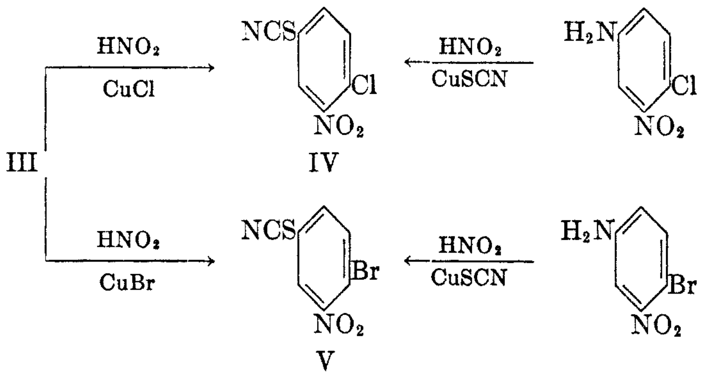
[1] We wish to acknowledge a grant from the National Foundation for Infantile Paralysis through the Childrens Hospital, University of Cincinnati Medical School, Cincinnati, Ohio, under which this work was done.

Further, Blomquist and Diuguid (3) prepared an N-acetyl derivative, m.p. 138–139°, of their product which was reported as 2-acetamido-4-nitrobenzothiazole. They also reported 2-chloro-4-nitrobenzothiazole, m.p. 59.5–61.5° as arising from the Sandmeyer reaction on their product. Erlenmeyer and Ueberwasser (1) report 2-chloro-4-nitrobenzothiazole as melting at 169–170°.

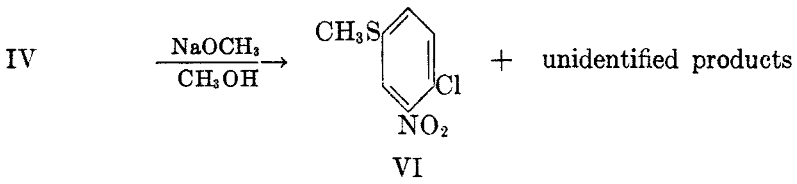
Challenger and Peters (5) have prepared III and its N-acetyl derivative by the reactions shown on preceding page.

The structure of III was proved by conversion to *m*-nitrophenyl thiocyanate. Further, IV and V were prepared by two routes as follows.



We have repeated the thiocyanation procedure of Blomquist and Diuguid (3) and obtained an orange product in 60.5% yield. This was converted to a chloro derivative in 43% yield and to a bromo derivative by the procedure of Craig (6), in 24% yield.

The action of sodium methoxide on the chloro compound was investigated and a mixture of products was obtained. From this a substance giving analytical figures for 4-chloro-3-nitrothioanisole (VI) was isolated.



If the chloro compound were 2-chloro-4-nitrobenzothiazole, it would be expected to react smoothly with sodium methoxide to give the 2-methoxy derivative (7, 8). If, however, the chloro compound is a phenyl thiocyanate it would be expected to give a mixture of thiophenols, sulfides, and disulfides (9).

Table I lists the melting points of the various substances prepared in the present work together with those reported by Challenger and Peters (5) and Blomquist and Diuguid (3). We therefore conclude that the compounds in question are indeed derivatives of phenyl thiocyanate.

Since thiocyanation of *o*-nitroaniline did not give the desired 2-amino-4-nitrobenzothiazole, the preparation of 2-amino-4-benzamidobenzothiazole (VII) from

N-benzoyl-*o*-phenylenediamine was attempted. Blomquist and Diuguid (3) report the formation of VII when N-benzoyl-*o*-phenylenediamine sulfate is treated with sodium thiocyanate in chlorobenzene followed by ring closure of the intermediate thiourea with sulfuryl chloride. This previously unreported benzothiazole was characterized by m.p. 291–293°, and by nitrogen analyses (Calc'd, 15.56; Found, 14.82, 15.03).

We have repeated this reaction and obtained a good yield of a sulfur-free compound, m.p. 295–297°, which was identified as 2-phenylbenzimidazole.

Blomquist and Diuguid (3) further describe the conversion of the substance described by them as 2-amino-4-benzamidobenzothiazole to 2-chloro-4-benzamidobenzothiazole by the Sandmeyer reaction. The latter substance is described as melting at 304°, and no analysis was given. According to our experience, this material is in all probability the hydrochloride of 2-phenylbenzimidazole which has been reported as melting at 303° (10) and at 343° (11).

TABLE I

MELTING POINTS OF THE PHENYL THIOCYANATES

PHENYL THIOCYANATE	M.P., °C.		
	Present work	Challenger and Peters (5)	Blomquist and Diuguid (3)
4-Amino-3-nitro	114–115	113	110–112[a]
4-Acetamido-3-nitro		138–139	138–139
4-Chloro-3-nitro	57.5–59	63	59.5–61.5
4-Bromo-3-nitro	85–85.5	83	

[a] Blomquist and Diuguid (3) also report m.p. 130° for material purified through the acetyl derivative.

2-Phenylbenzimidazole was subjected to the conditions of the Sandmeyer reaction as described by Blomquist and Diuguid (3). A 97.5% yield of the imidazole hydrochloride, m.p. 330–332°, was obtained. This gave 2-phenylbenzimidazole on treatment with ammonium hydroxide.

It was further reported (3) that the supposedly 2-chloro-4-benzamidobenzothiazole was converted in 83% yield to 4-benzamidobenzothiazole by the action of phosphorus and hydriodic acid. The m.p. of 4-benzamidobenzothiazole was given as 287° and the product was further characterized by a nitrogen analysis (Calc'd for $C_{14}H_{10}N_2OS$: N, 11.02. Found: N, 11.08, 11.07). We have repeated this experiment with the hydrochloride of 2-phenylbenzimidazole and have shown that the product is actually 2-phenylbenzimidazole.

EXPERIMENTAL[2, 3]

4-Amino-3-nitrophenyl thiocyanate (III). The procedure was that of Blomquist and Diuguid for the reported preparation of 2-amino-4-nitrobenzothiazole with some minor modi-

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[2] All melting points are corrected for stem exposure.

[3] Microanalyses by Schwarzkopf Microanalytical Laboratories, Middle Village, L. I., N. Y., and by Dr. A. Elek, Los Angeles 16, Calif.

fications. After allowing a mixture of 69 g. of *o*-nitroaniline, 92 g. of ammonium thiocyanate, and 460 g. of 95% acetic acid (to which had been added over two hours 92 g. of bromine in 140 ml. of glacial acetic acid) to stand for 16 hours, the mixture was heated to 85°, diluted with 900 ml. of hot water, and filtered hot from 23 g. of brown solid, m.p. above 250°. This was not investigated further. The orange filtrate deposited an orange solid on cooling. The filtrate from this was made alkaline with saturated sodium carbonate solution (4 l.). Very little solid separated, so the original orange solid was re-slurried in the alkaline filtrate, filtered, washed with water, and dried, giving 84 g. of crude product. One recrystallization from 400 ml. of 95% ethanol gave 59 g. (60.5%) of orange crystals, m.p. 109–112°. An analytical sample was recrystallized three times from aqueous ethanol giving orange-yellow plates, m.p. 114–115°. Reported m.p., 113° (5).

Anal. Calc'd for $C_7H_5N_3O_2S$: C, 43.1; H, 2.6; N, 21.5; S, 16.4.
Found: C, 43.0, 42.9; H, 2.6, 2.7; N, 21.7; S, 16.3, 16.5.

4-Chloro-3-nitrophenyl thiocyanate. The procedure of Blomquist and Diuguid (3) was followed. After the reaction mixture had stood for 1½ days, it was steam-distilled. From an experiment using 49 g. of 4-amino-3-nitrophenyl thiocyanate, 49 l. of steam-distillate yielded 25 g. of crude yellow product. Crystallization of the crude product from methanol with decolorizing carbon gave 22.9 g. (42.7%) of yellow needles, m.p. 57.5–59°. We were unable to raise the m.p. to 63° as reported (5).

Anal. Calc'd for $C_7H_3ClN_2O_2S$: C, 39.2; H, 1.4; Cl, 16.5; N, 13.1.
Found: C, 39.1; H, 1.3; Cl, 16.4; N, 12.9.

Reaction of 4-chloro-3-nitrophenyl thiocyanate with sodium methoxide, 4-chloro-3-nitrothioanisole (VI). To a solution of sodium methoxide prepared from 40 ml. of absolute methanol and 2.4 g. of sodium was added with cooling 21.5 g. of 4-chloro-3-nitrophenyl thiocyanate. The mixture was refluxed for 3 hours, poured into 200 ml. of cold water, and the yellow precipitate was collected. The crude product (19 g.) appeared to be a mixture and softened around 60° and was not completely melted at 270°. Its aqueous suspension was neutral to litmus as was the aqueous suspension of the residue after ignition, indicating the absence of sodium salts. The substance was only partially soluble in hot methanol, ethanol, acetone, ethyl acetate, chloroform, benzene, and ligroin. One-half of the product was extracted with 150 ml. of hot methanol. The insoluble yellow solid (3 g.) melted at 200–225° with softening at 150°. The cooled methanol extract deposited 2 g. of a yellow solid, m.p. 70–72° after one recrystallization from methanol. This was completely soluble in acetone and acetone-ligroin. It gave a positive test for halogen. Analytical data corresponded to those for 4-chloro-3-nitrothioanisole.

Anal. Calc'd for $C_7H_6ClNO_2S$: C, 41.3; H, 3.0; N, 6.9; S, 15.7.
Found: C, 41.5, 41.4; H, 2.9, 2.8; N, 6.8; S, 15.8.

The other products formed were not investigated further.

4-Bromo-3-nitrophenyl thiocyanate. To a mixture of 25 ml. of 48% hydrobromic acid and 10 g. of 4-amino-3-nitrophenyl thiocyanate cooled in an ice-salt bath to −9° was added with good stirring over a period of 20 min., 8.0 g. of bromine. The temperature rose to −5° during the addition. A solution of 8.8 g. of sodium nitrite in 13 ml. of water was then added dropwise to the viscous orange mixture over 45 min. during which the temperature was kept below 0°. After stirring the mixture for one hour in the cooling bath, 19 g. of sodium hydroxide in 19 ml. of water was added dropwise over 30 min., during which the temperature was kept below 20°. The neutralization was very exothermic and oxides of nitrogen and bromine were evolved. After slowly allowing the mixture to come to room temperature, the aqueous alkaline solution was decanted from a red, spongy solid and the latter was washed several times with water by decantation. The solid was treated with 50 ml. of methanol whereupon gas evolution occurred and the solid turned to a dark oil; the mixture was cooled to control the reaction. When the reaction subsided, the mixture was heated slowly to boiling to dissolve the oil, filtered, and the filtrate was treated with decolorizing carbon. From the chilled filtrate 3.2 g. (42%) of a dark orange powdery solid, m.p. 77–82°, was obtained. A sample for analysis was recrystallized once from benzene, and twice from benzene-hexane giving small tan needles, m.p. 85–85.5°. Reported m.p. 83° (5).

Anal. Calc'd for $C_7H_3BrN_2O_2S$: C, 32.5; H, 1.2; Br, 30.8; N, 10.8.
Found: C, 32.6, 32.5; H, 1.2, 1.2; Br, 30.9; N, 10.8.

2-Phenylbenzimidazole. The method was that of Blomquist and Diuguid (3) which in turn was that outlined in Organic Syntheses (12) for the conversion of *p*-toluidine into 2-amino-6-methylbenzothiazole. The only variations introduced were in the working up of the reaction mixture. The reaction mixture from a run using 85 g. of N-benzoyl-*o*-phenylenediamine (13) in 400 ml. of chlorobenzene was cooled and the supernatant liquid was decanted from the solid. The dried solid was boiled with 400 ml. of water, filtered hot, and the filter cake was washed with water and dried, leaving 106 g. of material. A slurry of this material, after grinding, in 400 ml. of water was treated with 50 ml. of conc'd ammonium hydroxide. The insoluble material was collected, washed with water, and dried leaving 81 g. (quantitative yield) of crude 2-phenylbenzimidazole. Recrystallization of a small portion once from aqueous ethanol gave light yellow needles, m.p. 286–288°. Three further recrystallizations gave shining white plates, m.p. and mixture m.p. with a known sample 295–297°.

Anal. Calc'd for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4.
Found: C, 80.3; H, 4.9; N, 14.2.

This substance did not produce a dye when its suspension in dilute hydrochloric acid was treated with sodium nitrite and then added to an alkaline solution of β-naphthol. This indicates the absence of a primary amino group.

Behavior of 2-phenylbenzimidazole in the sandmeyer reaction. Following the procedure of Blomquist and Diuguid (3), 5.0 g. of 2-phenylbenzimidazole in 18 ml. of conc'd hydrochloric acid at 0° was treated dropwise with 2.3 g. of sodium nitrite in 5 ml. of water. The resulting thick suspension was added to 2.5 g. of cuprous chloride in 20 ml. of conc'd hydrochloric acid cooled in an ice-bath. After warming to room temperature, the mixture was diluted with an equal volume of water and the separated solid was collected and washed with 5% hydrochloric acid, giving 5.8 g. (97%) of 2-phenylbenzimidazole hydrochloride, m.p. 330–332°. Reported m.p. 303° (10) and 343° (11). Treatment of the aqueous suspension of the hydrochloride with ammonium hydroxide and recrystallization of the product from dilute ethanol gave 2-phenylbenzimidazole, m.p. and mixture m.p. with a known sample 294–296°.

Reaction of 2-phenylbenzimidazole hydrochloride with phosphorus and hydriodic acid. Following the procedure of Blomquist and Diuguid (3) which is reported as leading to 4-benzamidobenzothiazole, a mixture of 3.2 g. of the above hydrochloride, 1 g. of potassium iodide, 3 g. of red phosphorus, 35 ml. of 85% orthophosphoric acid, and 5 ml. of water was heated under reflux for 6 hours. The cooled mixture was diluted and neutralized with 300 ml. of 10% sodium hydroxide with external cooling. The red solid was filtered off, washed with a solution of 2 g. of sodium bisulfite in 50 ml. of water, then with water, and extracted with two 25-ml. portions of alcohol. The filtered alcoholic extracts gave 1.4 g. (52%) of 2-phenylbenzimidazole, m.p. and mixture m.p. with a known sample, 295–296°.

SUMMARY

1. The reaction of *o*-nitroaniline with ammonium thiocyanate and bromine has been shown to give 4-amino-3-nitrophenyl thiocyanate rather than 2-amino-4-nitrobenzothiazole.

2. The reaction of N-benzoyl-*o*-phenylenediamine with sodium thiocyanate and sulfuryl chloride has been shown to give 2-phenylbenzimidazole rather than 2-amino-4-benzamidobenzothiazole.

New York 27, N. Y.

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