[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

BENZOTHIAZOLES. II. NUCLEAR CHLORINATION IN THE HERZ PROCESS[1]

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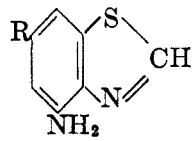
An investigation of the pharmacological properties of certain benzothiazole derivatives required, as intermediates for syntheses, a number of 4-aminobenzothiazoles variously substituted in the 6-position (I).

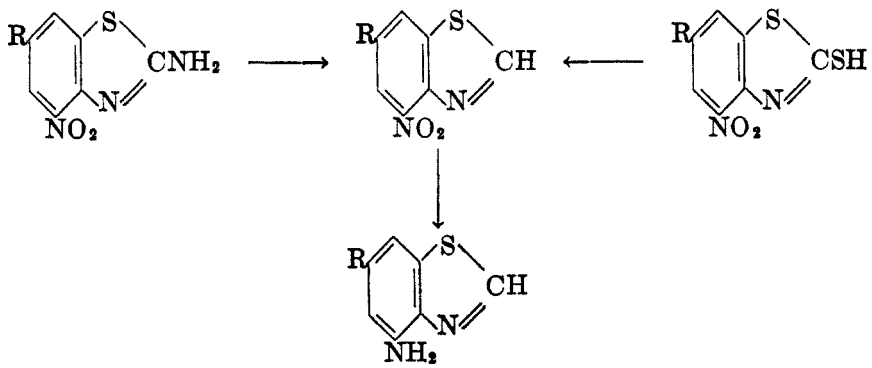


R = H, CH_3, Cl, CH_3O, CN

I

Benzothiazoles of this type (I) must be prepared indirectly through application of various cyclization procedures to *ortho*-substituted anilines and related compounds, as substitution methods cannot be used for the direct introduction of a group into the 4-position of the benzothiazole nucleus.

The more generally useful benzothiazole syntheses lead to 2-substituted derivatives such as 2-amino- and 2-mercapto-benzothiazoles. Accordingly, some attention was given to the replacement by hydrogen of substituents occupying the 2-position, with the object of achieving a convenient procedure for synthesizing 6-substituted-4-aminobenzothiazoles.



This proposed route to benzothiazoles of type I proved to be of limited value, for it was observed that (a) either the cyclization of a particular benzene derivative to the 2-amino- or 2-mercapto-benzothiazole went poorly or not at all, or

[1] This paper is an abstract of part of the doctoral dissertation of Lincoln I. Diuguid submitted to the Graduate Faculty of Cornell University in June, 1945.

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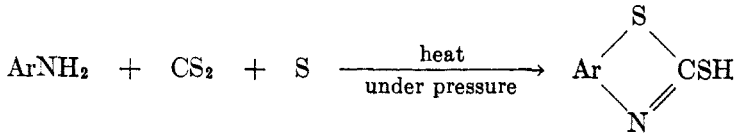
(b) subsequent replacement of the 2-amino or 2-mercapto group by hydrogen was difficult.

Although several 2-mercaptobenzothiazoles were obtained conveniently through the Sebrell and Boord synthesis (1) from primary aromatic amines, it

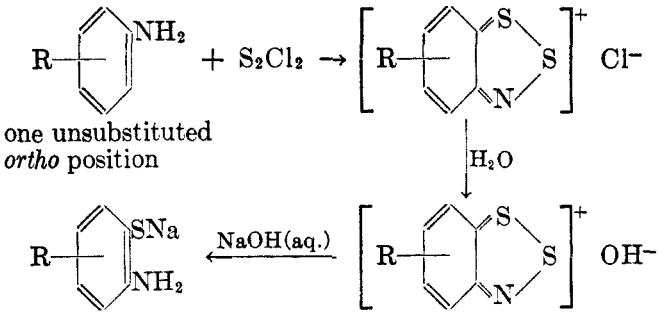


was observed that with certain aniline derviatives, *e.g.* 3-nitro-4-aminotoluene and 3-nitro-4-aminoanisole, the method failed when preparations were attempted on a scale larger than 0.1 mole. The replacement of the 2-mercapto group by hydrogen using iron and acetic acid succeeded with 2-mercapto-6-methylbenzothiazole, but failed with 2-mercapto-4-nitro-6-methyl- and 2-mercapto-4-nitro-6-methoxy-benzothiazoles.

The route to 6-substituted-4-aminobenzothiazoles through the corresponding 2-amino derivatives proved to be even less satisfactory. Both the procedure described in "Organic Syntheses" (2) and the method of Kaufmann (3) proved to be rather limited in scope. Thus, while the Kaufmann procedure gave good yields of 2-amino-4-nitro- and 2-amino-4-nitro-6-methyl-benzothiazole, it failed when applied to the cyclization of 3-nitro-4-aminobenzonitrile. Further, replacement of the 2-amino group by hydrogen could not be effected smoothly. Diazotization of the 2-amino derivatives and replacement of the diazonium salt group with hydrogen, using a number of reagents, did not work well. Only with 2-amino-4-benzamidobenzothiazole was there success in effecting a smooth conversion to 4-benzamidobenzothiazole by reduction of 2-chloro-4-benzamidobenzothiazole with red phosphorus and hydrogen iodide.

Because of the difficulties encountered with the 2-amino- and 2-mercapto-benzothiazole derivatives, attention was given to the Herz process which had been used successfully by Bogert (4) in the synthesis of 4-amino-6-methoxybenzothiazole.

The oroginal Herz process for the synthesis of *o*-aminothiophenols (5) involves the interaction of primary aromatic amines, their salts, or N-acetyl derivatives with sulfur monochloride either in the presence or absence of an unreactive diluent such as benzene, nitrobenzene, acetic acid, etc.



In a normal reaction the resulting chlorides formulated above are readily hydrolyzed to insoluble bases which on treatment with aqueous alkali afford *o*-aminothiophenols.

In the original patents Herz indicated that there was a strong tendency for nuclear chlorination to occur during the first step of the synthesis, particularly in the position *para* to the amino group. Further, this tendency is so marked that replacement by chlorine may even occur when the *para* position is occupied by $-NO_2$, $-CO_2H$, or $-SO_2$-groups.

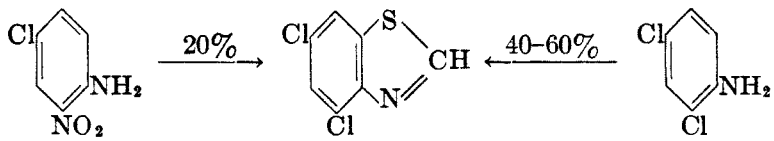
Subsequently, certain of these observations have been confirmed by other investigators in applying the Herz process to the synthesis of benzothiazoles. Thus, König (6) observed nuclear chlorination in the preparation of certain 2-methylbenzothiazoles. The Herz products derived from aniline and *o*-toluidine gave respectively 2-methyl-6-chloro- and 2,4-dimethyl-6-chloro-benzothiazole upon alkaline hydrolysis and treatment with acetic anhydride. Also with *p*-anisidine he observed the formation of a small amount of a chlorinated benzothiazole as an accessory product in the synthesis of 2-methyl-6-methoxybenzothiazole. It was suggested that this benzothiazole probably contained chlorine in the 5-position, although the positions 4 and 7 were not excluded.

Similarly Hixson and Cauwenberg (7) found that the Herz condensation product derived from *o*-amino-*p*-cymene contained chlorine in the position *para* to the amino group, as the same product was obtained on treatment of 2-amino-5-chloro-*p*-cymene with sulfur monochloride.

Finally, Ast and Bogert (8) noted that the condensation of *m*-nitrobenzoyl chloride with the *o*-aminothiophenol obtained by applying the Herz reaction to *p*-anisidine hydrochloride gave, in addition to the expected 2-(*m*-nitrophenyl)-6-methoxybenzothiazole, a small amount of a chlorinated benzothiazole of undetermined structure.

An investigation in our laboratory of the Herz process for benzothiazole syntheses has disclosed further abnormalities in the reaction. In these studies Bogert's excellent procedure for the conversion of 3-nitro-4-aminoanisole to 4-nitro-6-methoxybenzothiazole (4) was selected as a suitable standard procedure for evaluating the behavior of various substituted anilines in the Herz process.

Under these conditions it was observed that the crude Herz product derived from 2-nitro-4-chloroaniline did not afford the expected 4-nitro-6-chlorobenzothiazole when hydrolyzed with alkali and condensed with acetic-formic anhydride. The product, obtained, in about 20% yield, proved to be 4,6-dichlorobenzothiazole (m.p. 141.5–142.5°), for it was identical with the benzothiazole obtained from the Herz product derived from 2,4-dichloroaniline (40–60% yields).



It was also observed that both *o*-nitroaniline and *o*-chloroaniline afforded only 4,6-dichlorobenzothiazole when their crude Herz condensation products were treated with acetic-formic anhydride.

Thus it appears that the original remarks of Herz concerning the tendency for nuclear chlorination to occur in treating aromatic primary amines with sulfur monochloride may be extended to include the position *ortho* to the amino group as well as the *para* position.

The application of the Herz process to 3-nitro-4-aminotoluene and 3-nitro-4-aminobenzonitrile in an attempt to prepare 4-nitro-6-methylbenzothiazole and 4 nitro-6-cyanobenzothiazole did not prove useful. These amines on treatment with sulfur monochloride gave products which could not be hydrolyzed by water and the solutions obtained on alkaline hydrolysis gave no benzothiazole derivatives when treated in the usual way with acetic-formic anhydride.

The 4,6-dichlorobenzothiazole obtained from the several aniline derivatives was used as a starting material for the preparation of 4,6-dichloro-7-(β-diethylaminoethyl)aminobenzothiazole. 4,6-Dichlorobenzothiazole was readily nitrated by 98% nitric acid in the presence of concentrated sulfuric acid to yield 7-nitro-4,6-dichlorobenzothiazole. Reduction of this nitrobenzothiazole with iron and hydrochloric acid afforded 7-amino-4,6-dichlorobenzothiazole (m.p. 164–165°) in good yield. Alkylation of the aminobenzothiazole using the hydrobromide of β-diethylaminoethyl bromide proceeded smoothly upon heating in anhydrous *n*-butyl alcohol.

EXPERIMENTAL[3]

Preparation of Substituted 2-Mercaptobenzothiazoles

2-Mercapto-6-methylbenzothiazole, m.p. 175.5–178.5°, was prepared as described by Sebrell and Boord (1).

2-Mercapto-4-nitro-6-methylbenzothiazole, prepared similarly, was obtained in 30–65% yield in 0.1-mole runs; m.p. 258–259.5° from alcohol.

Anal. Calc'd for $C_8H_6N_2O_2S_2$: N, 12.39. Found: N, 12.49, 12.46.

2-Mercapto-4-nitro-6-methoxybenzothiazole was also obtained by the Sebrell and Boord procedure. In a typical preparation, on a 0.1-mole scale, 54% of the 2-mercaptobenzothiazole was obtained: unmelted at 360° on the Maquenne block.

Anal. Calc'd for $C_8H_6N_2O_3S_2$: N, 11.57. Found: N, 11.43, 11.58.

Preparation of 2-mercapto-4-nitro-6-methyl- (and 6-methoxy)-benzothiazole on a scale larger than 0.1 mole failed, as extensive decomposition always occurred.

Preparation of Substituted 2-Aminobenzothiazoles

2-Amino-4-nitrobenzothiazole was obtained in a highly impure state and in low yield by the method described in Organic Syntheses (2). Preparation by the method of Kaufmann (3) proved to be much more satisfactory and is described. To a solution of 30 g. (0.22 mole) of *o*-nitroaniline in 200 g. of 95% acetic acid contained in a 1-liter flask was added 40 g. of ammonium thiocyanate. A mixture of 40 g. of bromine in 60 cc. of glacial acetic acid was then added dropwise with stirring over a period of 1.75 hours. The mixture was allowed to stand 12 hours after the addition was complete. The reaction mixture was

[3] All melting points recorded are uncorrected unless otherwise specified.

warmed on a water-bath, diluted with 400 cc. of hot water, and filtered. An excess of saturated sodium carbonate solution was added to the cooled orange colored filtrate, precipitating the crude 2-amino-4-nitrobenzothiazole as a yellow solid. After recrystallization from alcohol there was obtained 30 g. (70%) of the aminobenzothiazole, m.p. 110–112°. After purification through the acetyl derivative it melted at 130°. This compound has been reported by Dyson, Hunter, and Morris (9) as melting at 232°.

Anal. Calc'd for $C_7H_5N_3O_2S$: N, 21.54. Found: N, 21.17, 21.33.

N-Acetyl derivative, m.p. 138–139°

Anal. Calc'd for $C_9H_7N_3O_3S$: C, 45.57; H, 2.95; N, 17.72.
Found: C, 45.28, 45.56; H, 3.20, 3.05; N, 17.87, 18.90.

2-Amino-6-methyl-4-nitrobenzothiazole. This aminobenzothiazole was prepared by the Kaufmann method outlined above. From 40 g. of 3-nitro-4-aminotoluene there was obtained 30 g. of a crude product which was contaminated with considerable amounts of thiocyanogen polymer; m.p. 110–220°. Extensive purification by recrystallization and sublimation in a vacuum gave a product satisfactory for analysis, m.p. 256–261°d.

Anal. Calc'd for $C_8H_7N_3O_2S$: N, 20.09. Found: N, 19.81, 19.71.

3-Nitro-4-aminobenzonitrile failed to give 2-amino-6-cyano-4-nitrobenzothiazole when subjected to the Kaufmann procedure outlined above. Most of the starting material was recovered unchanged together with a small amount of resinous material.

2-Amino-4-benzamidobenzothiazole. Using the method of Organic Syntheses (2), 40 g. of the monobenzoyl derivative of *o*-phenylenediamine, prepared according to Witt (10), afforded 23 g. (47%) of the desired 2-amino-4-benzamidobenzothiazole, m.p. 291–293° (on the Maquenne block).

Anal. Calc'd for $C_{14}H_{11}N_3OS$: N, 15.56. Found: N, 14.82, 15.03.

Preparation of Substituted 2-Chlorobenzothiazoles

2-Chloro-4-nitrobenzothiazole. Diazotization of 2-amino-4-nitrobenzothiazole followed by replacement of the diazonium salt group with chlorine proved to be the most satisfactory method for preparing 2-chloro-4-nitrobenzothiazole. To a solution of 10 g. of 2-amino-4-nitrobenzothiazole in 35 cc. of concentrated hydrochloric acid cooled to 0° was added with stirring a cold solution of 4.6 g. of sodium nitrite in 10 cc. of water over a period of 10–15 minutes. The solution of the diazonium salt was added with stirring to a solution of 5 g. of cuprous chloride in 40 cc. of concentrated hydrochloric acid at 0°. After the mixture had come to room temperature, it was steam distilled. From 2 l. of distillate was obtained 1.5 g. of crude product, which after several recrystallizations from methanol gave 1 g. of 2-chloro-4-nitrobenzothiazole, m.p. 59.5–61.5°.

Anal. Calc'd for $C_7H_3ClN_2O_2S$: N, 13.08. Found: N, 12.83, 12.96.

The preparation of 2-chloro-4-nitrobenzothiazole by (a) the action of sulfur monochloride on 2-mercapto-4-nitrobenzothiazole (11) or (b) the interaction of *o*-nitrophenylisothiocyanate and phosphorus pentachloride (12) proved to be unsatisfactory. Only viscous, tarry products, which could not be distilled at reduced pressure, were obtained.

2-Chloro-4-benzamidobenzothiazole. This substance was obtained by the diazotization and replacement procedure described above. From 24 g. of 2-amino-4-benzamidobenzothiazole there was obtained 13.5 g. (52%) of the desired 2-chloro derivative, m.p. 304° on the Maquenne block.

2-Chloro-6-methylbenzothiazole. Diazotization of 2-amino-6-methylbenzothiazole (2) followed by treatment with cuprous chloride-hydrochloric acid afforded the desired 2-chloro derivative in 8% yield, m.p. 48–49°.

Conversion of 2-Substituted Benzothiazoles to Benzothiazoles Unsubstituted in the 2-Position

4-Benzamidobenzothiazole. A mixture of 6.5 g. of 2-chloro-4-benzamidobenzothiazole, 2 g. of potassium iodide, 6 g. of red phosphorus, 70 cc. of orthophosphoric acid (85%), and 10 cc. of water was heated under reflux for 6 hours. The cooled reaction mixture was made

alkaline with dilute sodium hydroxide, filtered, and the solid material washed with a little sodium bisulfite solution and with water. The crude product was then crystallized from alcohol, and yielded 4.4 g. (83%) of the desired 4-benzamidobenzothiazole, m.p. 287° on the Maquenne block.

Anal. Calc'd for $C_{14}H_{10}N_2OS$: N, 11.02. Found: N, 11.08, 11.07.

Since other 2-chlorobenzothiazoles were obtained with such great difficulty and in low yield through the Sandmeyer reaction on the 2-aminobenzothiazoles they were not studied in the reductive procedure given above.

Conversion of 2-amino-4-benzamidobenzothiazole to 4-benzamidobenzothiazole through the reduction of its diazonium salts by various standard procedures was not successful.

All attempts to hydrolyze 4-benzamidobenzothiazole with the object of obtaining 4-aminobenzothiazole failed. Treatment of the benzoyl derivative with boiling 25% sulfuric acid, 25% alcoholic potassium hydroxide, and 100% phosphoric acid were without effect.

6-Methylbenzothiazole. 2-Mercapto-6-methylbenzothiazole was used as a model compound for studying the replacement of the 2-mercapto group by hydrogen. A mixture of 10 g. of 2-mercapto-6-methylbenzothiazole, 100 cc. of 90% acetic acid, 25 cc. of ethyl alcohol, and 10 g. of iron powder was heated under reflux for 36 hours. During the period five 10-cc. portions of water were added at regular intervals. At the end of this time hydrogen sulfide evolution had ceased, and the reduction appeared to be complete. The cooled mixture was diluted with water to 500 cc. and extracted with benzene. The aqueous layer was neutralized with sodium carbonate and also extracted with benzene. The combined benzene extracts were dried and the benzene removed by distillation. The residue was then distilled under reduced pressure, and afforded 6.4 g. (82%) of pure 6-methylbenzothiazole, b.p. 118–120°/1.3 mm.; m.p. 15.5°; m.p. of picrate, 163.5°. These constants agree well with the values recorded in the literature for 6-methylbenzothiazole (13).

The reduction of 2-mercapto-4-nitro-6-methylbenzothiazole and 2-mercapto-4-nitro-6-methoxybenzothiazole by the method described above failed to give useful products. Other metal-acid combinations and low-pressure hydrogenation using a large excess of Raney nickel in Methyl Cellosolve and in dioxane also gave negative results.

Behavior of Some Substituted Anilines in the Herz Process

The procedure of Bogert and Fox (4) for the conversion of 3-nitro-4-aminoanisole to 4-nitro-6-methoxybenzothiazole was used as a standard procedure for evaluating the behavior of the aniline derivatives listed below in the Herz process.

2,4-Dichloroaniline gave an orange-red Herz condensation product which was converted smoothly into 4,6-dichlorobenzothiazole. From 32 g. of the aniline there was obtained 27 g. of crude product, m.p. 136–138°. Recrystallization from ethyl alcohol gave 21 g. (50%) of white needle-like crystals, m.p. 142–142.5°.

Anal. Calc'd for $C_7H_3Cl_2NS$: N, 6.86; Cl, 34.75.
Found: N, 6.73, 6.80; Cl, 34.64, 34.88.

o-Chloroaniline gave a crude Herz product which was not completely soluble in aqueous alkali. The filtered alkaline solution, when treated with acetic-formic anhydride, gave a crude benzothiazole which after recrystallization melted at 140–141°, 38% yield. A mixed melting point with the 4,6-dichlorobenzothiazole derived from 2,4-dichloroaniline showed no depression.

4-Chloro-2-nitroaniline gave a crude Herz product which was almost completely soluble in aqueous alkali. Treatment of the alkaline solution of the thiophenol with acetic-formic anhydride gave a light yellow precipitate which crystallized from alcohol in white needles, m.p. 141.5–142.5°, 20% yield. This substance showed no depression in melting point when mixed with 4,6-dichlorobenzothiazole.

o-Nitroaniline gave a crude Herz product which was resistant to alkaline hydrolysis, most of the material failing to go into solution. Treatment of the clear alkaline solution

with the mixed anhydride gave, after recrystallization from alcohol, 1 g. (2.7%) of 4,6-dichlorobenzothiazole.

3-Nitro-4-aminotoluene (152 g.) gave a crude Herz product which was for the most part unaffected by aqueous alkali. The precipitate (19 g.) obtained on treatment of the clear alkaline solution with the mixed anhydride did not behave like a simple benzothiazole derivative. It was insoluble in all the common organic solvents and was not altered by metal-acid reducing agents. It was not investigated further.

p-Chloroaniline (25 g.) afforded a crude Herz product which, when treated with aqueous alkali, gave a dark blue solution depositing an orange-yellow oil after the addition of acetic-formic anhydride. The oil solidified slowly, and was then crystallized from alcohol, m.p. 185–205°. After three more recrystallizations of the crude product (21 g.) from alcohol the substance melted sharply at 212–214°.

Analytical and molecular weight data indicated that 6-chlorobenzothiazole was not at hand.

Anal. Calc'd for C_7H_4ClNS: N, 8.26; Cl, 20.93; Mol. wt., 169.5.
Found: N, 8.01, 7.82; Cl, 18.17, 18.25; Mol. wt. (Micro Rast), 458.

The product was not investigated further.

3-Nitro-4-aminobenzonitrile gave a crude Herz product which was insoluble in aqueous alkali. Treatment of the alkaline filtrate with acetic-formic anhydride gave no water-insoluble product.

Benzothiazoles Derived from 4,6-Dichlorobenzothiazole

7-Nitro-4,6-dichlorobenzothiazole. To 15 g. of 4,6-dichlorobenzothiazole dissolved in 25 cc. of concentrated sulfuric acid was added dropwise 25 cc. of 98% nitric acid, maintaining the temperature of the reaction mixture at 50°. After all the nitric acid had been added, the mixture was heated at 70° for ten minutes, and then poured onto ice. The solid precipitate was filtered, washed, and recrystallized from ethyl alcohol. There was obtained 16.5 g. (85%) of 7-nitro-4,6-dichlorobenzothiazole as light yellow crystals, m.p. 154–155°.

Anal. Calc'd for $C_7H_2Cl_2N_2O_2S$: N, 11.25. Found: N, 11.34, 11.32.

4,6-Dichloro-7-aminobenzothiazole. Reduction of 16.5 g. of 7-nitro-4,6-dichlorobenzothiazole with iron and hydrochloric acid gave 12 g. (85%) of 4,6-dichloro-7-aminobenzothiazole, m.p. 164–165°.

Anal. Calc'd for $C_7H_4Cl_2N_2S$: Cl, 32.39. Found: Cl, 32.37.

4,6-Dichloro-7-(β-diethylaminoethyl)aminobenzothiazole. A mixture of 10 g. of 4,6-dichloro-7-aminobenzothiazole, 10 g. of β-diethylaminoethyl bromide hydrobromide and 20 cc. of dry *n*-butyl alcohol was heated under reflux at 130–140° for 40 hours. The mixture was then poured into 100 cc. of water, made alkaline with excess sodium carbonate, and extracted with ether. The ether extract was dried over potassium carbonate, filtered, and distilled. The alkylated aminobenzothiazole (5 g.) was obtained as an amber-colored viscous liquid, b.p. 205–215°/0.1 mm.

Anal. Calc'd for $C_{13}H_{17}Cl_2N_3S$: N, 13.22. Found: N, 13.29, 13.15.

SUMMARY

1. The synthesis of certain 4,6-disubstituted benzothiazoles by several routes has been investigated. Such syntheses through the corresponding 2-mercapto and 2-amino derivatives have not proved to be generally useful.

2. The behavior in the Herz process of a number of substituted anilines has been studied. *o*-Nitroaniline, *o*-chloroaniline, and 2-nitro-4-chloroaniline undergo nuclear chlorination by substitution or replacement in the *ortho* and/or *para*

positions. *p*-Chloroaniline, 3-nitro-4-aminotoluene, and 3-nitro-4-aminobenzonitrile afford complex products not hydrolyzable to simple thiophenols.

3. A few benzothiazoles derived from 4,6-dichlorobenzothiazole are described.

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