[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

SYNTHESIS AND REACTIONS OF CERTAIN BENZOTHIAZOLES[1, 2]

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The observation that 2-methoxy-8-(3-diethylaminopropylamino)quinoline (I) exerts a definite effect on the development and course of poliomyelitis (1) in monkeys prompted an investigation of analogous compounds. I, despite its definite effect on the disease, was too toxic to be of practical use (1). Replacement of the diethylamino group of I by a primary amino group (2) provided a substance of greatly decreased toxicity (3) but devoid of effect on poliomyelitis (1). It therefore seemed of interest to investigate the action of the S-isoster of I, namely 2-methoxy-4-(3-diethylaminopropylamino)benzothiazole (II). A report describing the results of an exploration of one synthetic approach to II has already appeared (4). In the present paper we wish to report our further experience on the attempted synthesis of II. Although preparation of II has not been achieved, certain observations on the synthesis and reactions of benzothiazoles have been made which may be of interest.

The logical approach to II involves alkylation of 2-methoxy-4-aminobenzothiazole (III) by 3-diethylaminopropyl chloride. III thus becomes the key intermediate in the synthesis of the candidate drug and efforts have been directed towards its preparation or towards the preparation of 2-methoxy-4-nitrobenzothiazole (IV).

o-Nitrophenyl isothiocyanate (V) was prepared in good yield from *o*-nitroaniline and thiophosgene by a modification of the general procedure of Dyson and George (5, 6). Reaction of V with alcoholic ammonia gave *o*-nitrophenylthiourea (VI) (5, 7, 8) although the yield was disappointingly low. Oxidative ring closure of VI with bromine (7) gave 2-amino-4-nitrobenzothiazole (VII) in good yield. However all attempts to convert VII to 2-chloro-4-nitrobenzothiazole (VIII) failed. The complete resistance of VII to diazotization was unexpected although there are reports of failure to diazotize 2-aminobenzothiazoles (9). On the other hand several reports of the successful diazotization of these compounds are at hand (10).

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[2] The work here reported forms part of a dissertation submitted by Franklin W. Short, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University.

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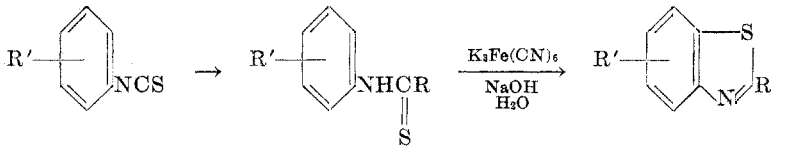
Attention was then turned to the possibility of obtaining IV by the general method (11):

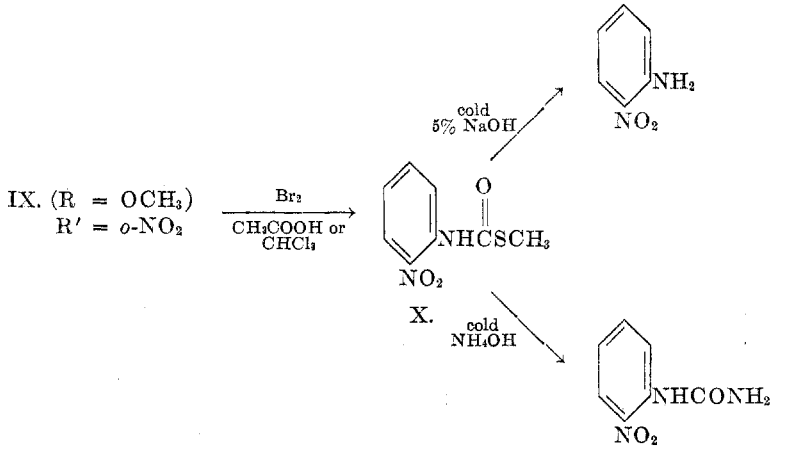


IX. IV. R = OCH_3, R′ = 4-NO_2

It has been reported that this synthesis proceeds in good yield when R is methyl and R′ is *p*-methoxy, *p*-methyl, or *p*-chloro, whereas when these substituents are in the *ortho* position of IX or a nitro group is in the *para* position of IX the yields of benzothiazoles are poor (12). Jacobson and Klein (13) report that *p*-nitrophenylthionurethan (IX, R = OC_2H_5, R′ = *p*-NO_2) gave *p*-nitrophenylurethan with cold alkaline ferricyanide.

Oxidation of IX (R = OCH_3, R′ = *o*-NO_2) gave only *o*-nitroaniline and unreacted starting material. Thus the above generalization may be extended to include the effect of a cationoid *ortho* nitro group which completely inhibits ring closure.

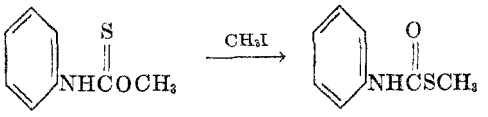
The effect of bromine on compounds of the type of IX in which R is a group other than amino has not been investigated as thoroughly. In certain cases bromine in acetic acid oxidizes these to benzothiazoles in good yield (14). When IX (R = OCH_3, R′ = *o*-NO_2) was treated with bromine in acetic acid or chloroform at room temperature an exothermic reaction ensued and an isomeric product to which the structure of the rearranged substance, methyl *o*-nitrophenylthiolcarbamate (X), is assigned was formed. This proposal is supported



by conversion of X to *o*-nitroaniline by cold 5% aqueous sodium hydroxide and to *o*-nitrophenylurea by cold concentrated ammonium hydroxide. Will (15) noted

that the related methyl phenylthiolcarbamate undergoes the same reactions to give aniline and phenylurea.

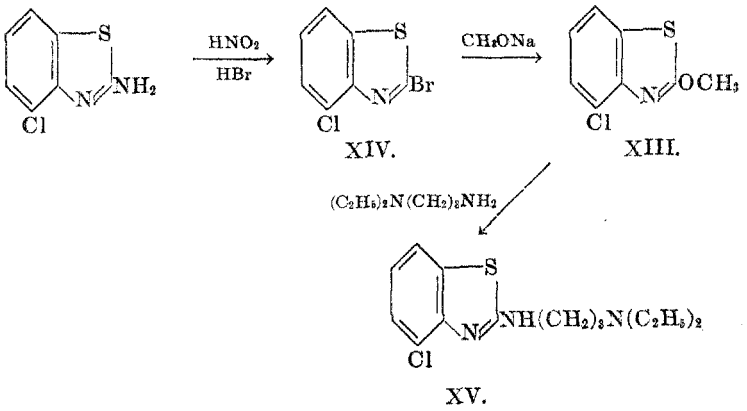
An analogy for this rearrangement is found in the reported (16) conversion of methyl phenylthioncarbamate (XI) to XII by the action of methyl iodide at room temperature. Several thioncarbamic, thioncarbanilic, and thioncarbazinic



XI. XII.

esters have been observed to undergo this rearrangement when heated with alkylhalides. However, the present case apparently represents the first bromine-induced rearrangement of this type. Likewise, similar rearrangements have been induced thermally (17).

In view of the report that the chlorine in 8-chloroquinoline is activated towards nucleophilic reagents especially in the presence of copper (18), the reaction of 2-methoxy-4-chlorobenzothiazole (XIII) with 3-diethylaminopropylamine[5] was investigated although it was realized that the methoxyl group of XIII might also undergo aminolysis. 2-Amino-4-chlorobenzothiazole (19) was converted in good yield to 2-bromo-4-chlorobenzothiazole (XIV) by Craig's procedure for the preparation of 2-bromopyridine (20). The yield by this procedure is far better than those previously reported by diazotization of the weakly basic



XIV. XIII.

XV.

2-aminobenzothiazoles. Reaction of XIV with sodium methoxide gave XIII which was heated with 3-diethylaminopropylamine alone and in the presence of anhydrous cupric chloride or anhydrous sodium acetate. Only with sodium acetate at 180–200° was there obtained a very low yield of a substance the analytical data for which indicated the structure XV.

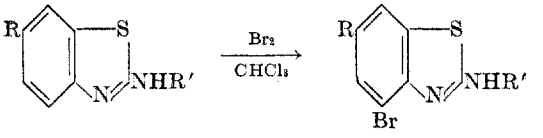
All of the methods explored for the preparation of III failed because of the

[5] For a review of the methods for replacement of aromatic halogens with amines see Bennett and Zahler, *Chem. Revs.*, **49**, 281 (1951).

presence of the deactivating 4-nitro group. An alternative scheme involves introduction of the nitro group into the 4-position after the necessary functional group (methoxyl or a group readily convertible to methoxyl) had been placed at the 2-position.

The literature on electrophilic substitution reactions of benzothiazole and its *Bz*-substituted derivatives is fairly confused. Pullman and Metzger (21) have calculated the electron distribution about benzothiazole and 2-methylbenzothiazole by the molecular orbital method. From their calculations electrophilic substitution should occur predominantly at the 4- and/or 6-positions. Experimentally it has been observed that halogenation, nitration, and sulfonation of benzothiazoles unsubstituted in the benzene ring give the 6-substituted derivatives either exclusively or very nearly so (22–29). Nishizawa and co-workers (25) report that nitration of benzothiazole at 0° gave, in addition to 6-nitrobenzothiazole, a small amount of the 7-nitro isomer (m.p. 138°). Petitcolas, *et al.* (24) also obtained an isomer, m.p. 135°, which they believed to be 4-nitrobenzothiazole.

Hunter and co-workers (30) observed that certain benzothiazoles already substituted in the 6-position (XVI) gave the 4-bromo derivative on bromination in chloroform.



XVI

R = Br, Cl, CH_3
R′ = H, CH_3

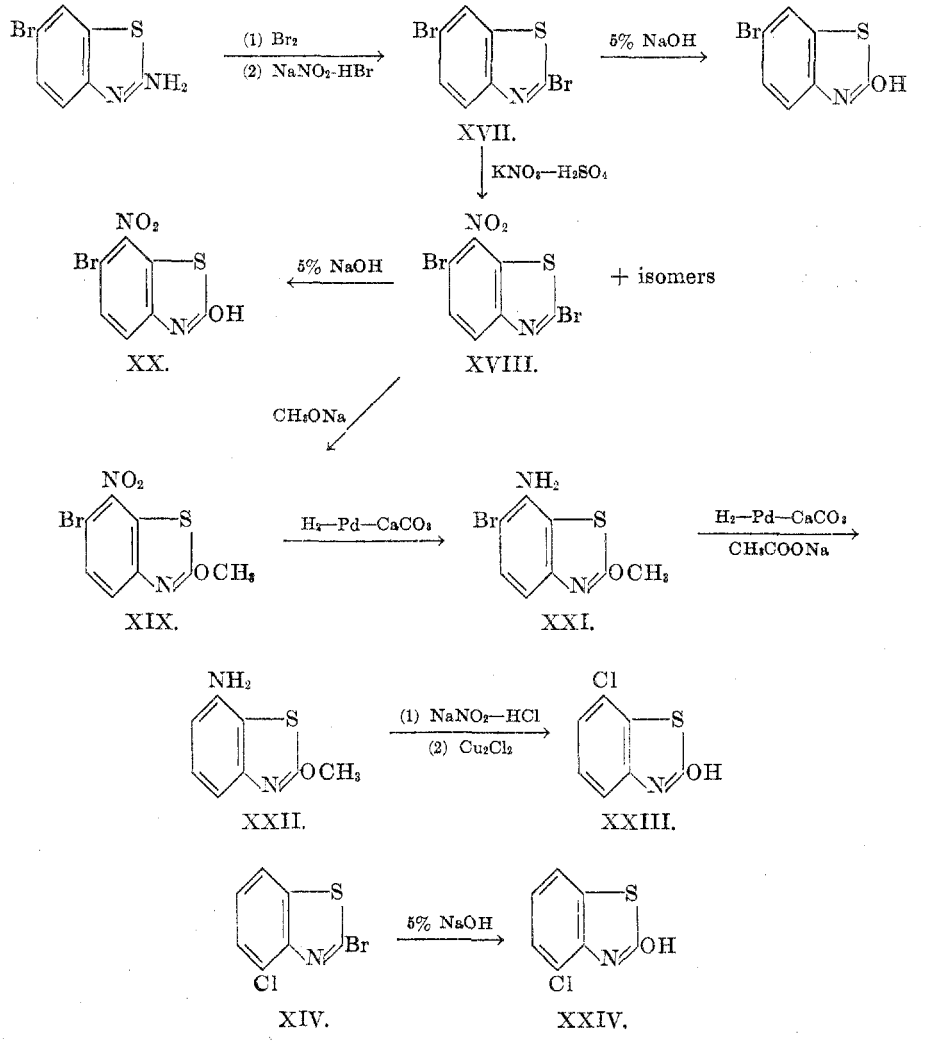
A different orientation has been noted with 6-aminobenzothiazole. Boggust and Cocker (26) found that this substance on bromination in chloroform gave the 7-bromo derivative whereas in the presence of sodium acetate an isomer which they believed to be the 5-bromo derivative was produced. When the bromination was done in acetic acid a mixture of the two isomers was obtained.

Similarly, bromination of 2-hydroxy-6-methylbenzothiazole gave a product which was shown to be either the 5- or 7-bromo derivative (31). Fries and Buckler (32) observed that 6-hydroxy-2-phenylbenzothiazole gave the 7-chloro derivative on chlorination, but that bromination led to the 5-bromo derivative. Nitration of the same substance gave a mixture of the 5- and 7-nitro derivatives with the latter predominating. Fox and Bogert (33) on the other hand isolated only the 7-nitro compound from the same reaction and also from the products of nitration of 6-methoxy- and 6-methoxy-2-phenyl-benzothiazole. Sulfonation of 2-amino-6-methylbenzothiazole gave the 5-sulfonic acid, whereas sulfonation of 2,6-dimethyl- and 6-methyl-2-phenyl-benzothiazole gave the 7-sulfonic acid (34).

We have found no report of the nitration of a benzothiazole carrying a weakly

ortho, para-directing bromine or chlorine at the 6-position as the only substituent in the benzene ring. In view of the orientation noted by Hunter, *et al.* (22, 30) in the bromination of 6-bromobenzothiazoles (further substitution at the 4-position) it seemed reasonable to expect that nitration of such a substance would lead to a 4-nitro derivative from which the bromine can subsequently be removed.

Accordingly the reactions outlined below were investigated:



Nitration of 2,6-dibromobenzothiazole (XVII) with potassium nitrate and sulfuric acid (28) gave a mixture of the three possible isomers in quantitative yield. By recrystallization from alcohol 71% of a mono-nitro compound, m.p. 142–143°, which is assigned the structure of 2,6-dibromo-7-nitrobenzothiazole

(XVIII) for reasons given below, was obtained. On concentration of the mother liquors from XVIII a mixture of the other two isomers was obtained. Extraction with boiling methanol gave a methanol-soluble substance, m.p. 125–126°, and a methanol-insoluble substance, m.p. 176–178°.

The major product (XVIII) was converted to 6-bromo-2-methoxy-7-nitrobenzothiazole (XIX) by sodium methoxide in pyridine-methanol. A considerable amount of 6-bromo-2-hydroxy-7-nitrobenzothiazole (XX) was also formed presumably as a result of an incomplete exclusion of moisture. XX also resulted from the action of 5% sodium hydroxide on XVIII.

Considerable difficulty was encountered in the reduction of XIX to 7-amino-2-methoxybenzothiazole (XXII). When the reduction was carried out in methanol or ethanol over palladium on calcium carbonate (35) at room temperature and 3–4 atmospheres of hydrogen only 7-amino-6-bromo-2-methoxybenzothiazole (XXI) was obtained. However when the reduction was carried out in the presence of sodium acetate as a hydrogen ion acceptor, XXII was obtained.

TABLE I

MELTING POINTS OF THE BENZOTHIAZOLES

BENZOTHIAZOLE	M.P., °C.
5-Amino-2-methoxy (36)	171–172
7-Amino-2-methoxy	73–75
5-Chloro-2-hydroxy (37)	230–231
7-Chloro-2-hydroxy	203–205

The amino group in XXII was converted to chlorine by the Sandmeyer reaction during which the methoxyl group was also cleaved to give 7-chloro-2-hydroxybenzothiazole (XXIII), m.p. 203–205°.

An authentic sample of 4-chloro-2-hydroxybenzothiazole (XXIV) was prepared by reaction of the previously described 2-bromo-4-chlorobenzothiazole (XIV) with 5% sodium hydroxide solution. This melted at 202–203°. However a mixture melting point of XXIV and XXIII was 163–167°. Therefore the major product of the nitration of XVII was not the desired 6-bromo-4-nitrobenzothiazole, but rather either the 5- or 7-nitro derivative.

A rigorous proof of the structure of XVIII is complicated by the fact that unambiguous methods have not been devised for the ready synthesis of 7-substituted benzothiazoles and by the difficulty of degrading XVIII or the benzothiazoles derived from it to derivatives which may be readily synthesized for comparison. However, 5-amino-2-methoxy- (36) and 5-chloro-2-hydroxy-benzothiazole (37) have been described. It should be pointed out that the structure assigned to 5-amino-2-methoxybenzothiazole is open to question. The methyl group was introduced by methylation of the 2-hydroxy derivative with dimethyl sulfate in alkaline solution. Experience (31, 38) indicates that under these conditions the N-methyl derivative is to be expected. However the structures of the 5- and 7-chloro-2-hydroxybenzothiazoles appear to rest on firm ground. On the

basis of the differences of melting points for these substances and those observed for XXII and XXIII as shown in Table I we have assigned to our benzothiazoles the 7-substituted structures.

EXPERIMENTAL[6, 7]

o-Nitrophenyl isothiocyanate (V). This was prepared by a modification of the general method of Dyson (5, 6). A solution of 25 g. (0.18 mole) of *o*-nitroaniline in 500 ml. of hot 20% hydrochloric acid was placed in a three-necked flask equipped with a stirrer, reflux condenser, and thermometer (hood). After cooling the mixture to 50°, 10 ml. (15 g., 0.13 mole) of thiophosgene (Rapter Laboratories, Argo, Ill.) was added in one portion. Stirring was started and the temperature of the mixture was maintained at 45–50° for 4 hours during which period a yellow solid precipitated. The mixture was stirred at room temperature for an additional 18 hours. Recrystallization of the crude product by solution in 200 ml. of hot acetone and dilution with 50 ml. of water gave 20.1 g. (86%) of product as yellow needles, m.p. 75–76°.

Condensation of *o*-nitroaniline with thiophosgene in chloroform according to Erlenmeyer and Ueberwasser (7b) gave low yields of extremely impure product.

o-Nitrophenylthiourea (VI). After considerable experimentation the following modification of published methods (5, 7) gave the most consistent results. To a solution of 45.5 g. (0.25 mole) of V in 450 ml. of warm 95% ethanol which had been cooled slowly to 36° was added 225 ml. of conc'd ammonium hydroxide in one portion with stirring. After standing at room temperature with occasional shaking for one hour, the dark red solution was diluted to 2 l. and refrigerated for 3 days. The thiourea, m.p. 136–137°, crystallized as fine yellow needles or glistening platelets. The yield was 26.6 g. (53.5%).

An attempt to prepare VI from impure V prepared by the method of Erlenmeyer and Ueberwasser (7b) resulted only in the formation of *o*-nitrophenylcyanamide, m.p. 152–153°, [reported 152° (39)] which was identified by hydrolysis to *o*-nitrophenylurea, m.p. 183–184° [reported 183–184° (39)].

2-Amino-4-nitrobenzothiazole (VII), m.p. 248°, was obtained in 98% yield by oxidative ring closure of VI by bromine in chloroform (7).

Methyl o-nitrophenylthioncarbamate (IX, R = OCH_3, R′ = *o*-NO_2). A solution of 2 g. (0.01 mole) of *o*-nitrophenyl isothiocyanate in 10 ml. of dry methanol was heated under reflux for 17 hrs. (13, 16, 31). On cooling 0.7 g. of yellow crystals separated and dilution of the mother liquor gave an additional 1.5 g. The total yield was 93%. On recrystallization from methanol, the substance formed yellow rods, m.p. 67–68°.

Anal. Calc'd for $C_8H_8N_2O_3S$: C, 45.3; H, 3.8; N, 13.2; S, 15.1.
Found: C, 45.3; H, 3.9; N, 13.1; S, 15.3.

When the reaction time was decreased to 6 hours the yield dropped to 72%. When 1 g. of the isothiocyanate was allowed to stand in a solution of 1 g. of potassium hydroxide in 10 ml. of methanol for 65 hours (40) the yield was 63.5%.

Methyl o-nitrophenylthiolcarbamate (X). A solution of 1.52 g. (0.0095 mole) of bromine in 5 ml. of glacial acetic acid was added dropwise with cooling to a solution of 2.0 g. (0.0094 mole) of methyl *o*-nitrophenylthioncarbamate in 10 ml. of glacial acetic acid during which period a thick finely crystalline precipitate separated. An additional 10 ml. of acetic acid was added. After 4 hours the precipitate was collected and washed with a few ml. of methanol yielding 1.50 g. (75%) of X, m.p. 152–153° (dec.). Recrystallization from benzene gave light yellow platelets, m.p. 153.5–154° (dec.).

Anal. Found: C, 45.0; H, 3.7; N, 13.3; S, 15.4.

When the above reaction was run in acetic acid without addition of bromine only starting material was recovered.

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

[7] Microanalyses by Schwarzkopf Microanalytical Laboratories, Middle Village, L. I., N. Y.; Dr. A. Elek, Los Angeles, Cal.; or Micro-tech Laboratories, Skokie, Ill.

When the reaction was run in dry chloroform with bromine for 18 hours a lower yield of less easily purified X was obtained.

X is soluble in cold 5% aqueous sodium hydroxide solution. On acidification of this orange solution a mercaptan-like odor was apparent and 2-nitroaniline, m.p. and mixture m.p., 69–71° after recrystallization from water, separated.

When X was treated with cold conc'd ammonium hydroxide it was converted to *o*-nitrophenylurea, m.p. and mixture m.p. 183–185° after recrystallization from water containing a little ethanol. Acidification of the ammoniacal filtrate gave a mercaptan-like odor.

o-Chlorophenylthiourea. The present procedure is similar to but considerably simpler than that previously reported (41). A hot solution of 44.6 g. (0.35 mole) of freshly distilled *o*-chloroaniline in 32.5 ml. (0.38 mole) of conc'd hydrochloric acid and 175 ml. of water was added to a solution of 56.0 g. (0.735 mole) of ammonium thiocyanate in 1200 ml. of water in a flask equipped with a sealed stirrer and reflux condenser. The mixture was stirred and heated under reflux for 6 hours. After cooling for 18 hours during which period the solid product precipitated, the aqueous slurry was decanted from a heavy oil, and 18.0 g. (27.6%) of the thiourea, m.p. 142–143°, was collected. Recrystallization from benzene gave glistening white plates, m.p. 143.5–144.5°. Reported m.p. 144–146° (41) and 145° (19).

An alternate procedure, a modification of that of Dalgleish and Mann (42) was also used. To a solution of 319 g. (2.5 moles) of *o*-chloroaniline in 1750 ml. of chlorobenzene (600 ml. of which was saturated from a previous run) 135 g. (1.3 moles) of conc'd sulfuric acid was added dropwise with stirring over 5 min. After addition of 225 g. (2.78 moles) of sodium thiocyanate the mixture was heated under reflux at 100° for 5 hours and then allowed to stand at room temperature for 18 hours. The solvent was poured off and the solid residue was washed with ether by decantation and dried. The crude product was stirred with 625 ml. of water for 30 min., collected, and dried, giving 239 g. (51.3%) of material, m.p. 140–142°. The yield from smaller runs in which the reaction time was only 3 hours and fresh solvent was used was only 40%.

2-Bromo-4-chlorobenzothiazole (XIV). (20). 2-Amino-4-chlorobenzothiazole, m.p. 208–209° [reported 203° (19a)], was prepared in 72.3% yield (7, 19b). To 125 ml. (1.1 moles) of 48% hydrobromic acid chilled to 10°, 46.2 g. (0.25 mole) of 2-amino-4-chlorobenzothiazole was added slowly with stirring. After cooling the mixture to 0° to −5°, 39 ml. (0.76 mole) of bromine was added dropwise followed by a solution of 45.5 g. (0.625 mole) of sodium nitrite in 65 ml. of water. The temperature rose to 5° toward the end of the addition of the nitrite. The dark viscous mixture was stirred in the cooling bath for 2 hours and then was made alkaline by dropwise addition of a solution of 94 g. (2.35 moles) of sodium hydroxide in 94 ml. of water during which time the temperature was maintained below 20°. After 20 min. the dark solid was collected, washed with water, air-dried, and extracted with several portions of boiling 95% ethanol. After treatment with decolorizing carbon, the cooled extracts yielded 44.9 g. (72.3%) of XIV as yellow needles, m.p. 107–108°.

Anal. Calc'd for $C_7H_3BrClNS$: C, 33.8; H, 1.2; Br, 32.1; Cl, 14.3; N, 5.6; S, 12.9.
Found: C, 34.0; H, 1.4; Br, 31.9; Cl, 14.3; N, 5.8; S, 12.7.

When the reaction was allowed to run only 30 min. before addition of sodium hydroxide, the yield of XIV, m.p. 105–106° was only 47.5%.

4-Chloro-2-methoxybenzothiazole (XIII). 2-Bromo-4-chlorobenzothiazole (4.98 g., 0.02 mole) was added to a solution of sodium methoxide prepared from 0.46 g. (0.02 mole) of sodium and 8 ml. of absolute methanol. After boiling under reflux for 2 hours, the mixture was poured into 50 ml. of water. The granular precipitate was washed with water and dried to yield 3.8 g. (95%) of XIII, m.p. 56–58°. After recrystallization from methanol with carbon the substance formed hard white plates, m.p. 57–59°.

Anal. Calc'd for C_8H_6ClNOS: C, 48.1; H, 3.0; Cl, 17.8; N, 7.0; S, 16.1.
Found: C, 48.4; H, 3.3; Cl, 17.7; N, 7.1; S, 16.0.

4-Chloro-2-(3-diethylaminopropylamino)benzothiazole (XV). A mixture of 5.0 g. (0.025 mole) of XIII, 3.25 g. (0.025 mole) of 3-diethylaminopropylamine, and 4.1 g. (0.05 mole) of anhydrous sodium acetate was heated under reflux in an oil bath at 180–200° (bath tem-

perature) for 11 hours. The cooled semi-solid mass was treated with 100 ml. of water and extracted with 3 portions of ether. The combined ether extracts were washed with water until the washings were nearly neutral and were dried over potassium carbonate. The oily residue after removal of the ether, (1.4 g.), was taken up in ethyl acetate and filtered from a small amount of insoluble material. A solution of oxalic acid in ethyl acetate was added to the filtrate until precipitation was complete. After addition of ethanol to dissolve the oily salt, the filtered solution was taken to dryness. Trituration of the residue with ethyl acetate gave 0.3 g. of a light tan powder which formed platelets, m.p. 173–175° (dec.), after two recrystallizations from ethanol-ethyl acetate.

Anal. Calc'd for $C_{16}H_{22}ClN_3O_4S$: C, 49.5; H, 5.7; Cl, 9.1; O, 16.5; $(COOH)_2$, 23.21.
Found: C, 50.0; H, 5.7; Cl, 8.7; O, 13.1; $(COOH)_2$, 19.5.

Although the product was not analytically pure, the analytical data indicated that reaction had occurred at position 2 rather than at position 4.

2,6-Dibromobenzothiazole (XVII). This was prepared from 2-amino-6-bromobenzothiazole [prepared by thiocyanation of *p*-bromoaniline in acetic acid (43, 44)] by the procedure used for the preparation of 2-bromo-4-chlorobenzothiazole. The yield of crude material, m.p. 109–114° was 78.5%. Two recrystallizations from ethanol gave fine white needles, m.p. 119–121°.

Anal. Calc'd for $C_7H_3Br_2NS$: C, 28.7; H, 1.0; Br, 54.5.
Found: C, 28.9; H, 1.0; Br, 54.4.

In this preparation the hydrobromic acid must be colorless. In one experiment in which this precaution was not observed, no XVII was obtained. Rather, an orange substance, m.p. 264°, was isolated. 2-Amino-4,6-dibromobenzothiazole is reported as melting at 261° (22). The substance was not investigated further.

6-Bromo-2-hydroxybenzothiazole. 2,6-Dibromobenzothiazole (10.0 g., 0.034 mole) was boiled under reflux for 2.5 hours with 250 ml. of 5% sodium hydroxide solution. The cooled filtered solution was acidified with 10% nitric acid and a precipitate of 3.3 g. (46%) of crude product, m.p. 223–227°, separated. Recrystallization from benzene gave fine needles, m.p. 226–228°. The reported m.p. for 6-bromo-2-hydroxybenzothiazole prepared by bromination of 2-hydroxybenzothiazole is 226° (44).

Nitration of 2,6-dibromobenzothiazole. 2,6-Dibromo-7-nitrobenzothiazole (XVIII). To 20 ml. of conc'd sulfuric acid, 7.85 g. (0.0268 mole) of 2,6-dibromobenzothiazole was slowly added with stirring at 15–20°. Finely ground potassium nitrate (3.0 g.) (28) was then added to the mixture over 30 min. during which time the temperature was kept below 40° by intermittent cooling. The mixture was stirred at room temperature for 1.5 hours, poured into 200 ml. of ice and water, and diluted to 500 ml. The crude product (9.0 g., m.p. 123–127°) was washed with water until the filtrate was neutral to Congo Red and dried. Slow crystallization from 95% ethanol gave 6.4 g. (71%) of XVIII as yellow needles, m.p. 141–143°. Several further recrystallizations gave an analytical sample, m.p. 142–143°.

Anal. Calc'd for $C_7H_2Br_2N_2O_2S$: C, 24.9; H, 0.6; Br, 47.3; N, 8.3.
Found: C, 24.9; H, 0.7; N, 8.3.

Concentration of the alcoholic mother liquor from the first recrystallization of XVIII to 70 ml. gave 2.1 g. of a mixture, m.p. 123–140°. Recrystallization of this from methanol with removal of a small amount of insoluble material gave an isomeric mononitro compound as light orange needles, m.p. 125–126° in very low yield.

Anal. Found: C, 25.1; H, 0.8; Br, 47.4; N, 8.4.

Repeated recrystallization of the above methanol-insoluble material from ethanol gave a third isomer as orange plates, m.p. 176–178°.

Anal. Found: C, 24.9; H, 0.7; Br, 47.5; N, 8.5.

Since the major product (XVIII, m.p. 142–143°) apparently is the 7-nitro derivative, the two minor products are 2,6-dibromo-4-nitro- and 2,6-dibromo-5-nitro-benzothiazole.

6-Bromo-2-methoxy-7-nitrobenzothiazole (XIX) *and 6-bromo-2-hydroxy-7-nitrobenzothiazole* (XX). Because of the insolubility of XVIII in methanol the procedure used for the preparation of XIII was not applicable. The following method (45) was successful. To a

solution of 7.10 g. (0.309 mole) of sodium in 1 l. of dry methanol was added 100 ml. of pyridine (freshly distilled from barium oxide) and 104.5 g. (0.309 mole) of XVIII. After heating to boiling under reflux an additional 250 ml. of pyridine was added. After boiling for 2 hours the cooled, dark red solution was poured into 3.5 l. of water and diluted to 6.5 l. The brown flocculent precipitate was collected, washed with water, dried, and extracted in portions with a total of about 2 l. of boiling methanol. After treating the extract with decolorizing carbon, concentration and refrigeration gave 30.5 g. (34.2%) of XIX as tiny golden needles, m.p. 123–125°. Two further recrystallizations from methanol gave fine yellow needles, m.p. 128–128.5°.

Anal. Calc'd for $C_8H_5BrN_2O_3S$: C, 33.2; H, 1.7; Br, 27.6; N, 9.7.
Found: C, 33.5; H, 1.6; Br, 27.4; N, 9.6.

An acidic product was isolated by acidification of the aqueous mother liquor from a smaller run in which the pyridine had not been freshly dried. Recrystallization of this from ethanol gave XX as golden needles, m.p. 283° (dec.).

Anal. Calc'd for $C_7H_3BrN_2O_3S$: C, 30.6; H, 1.1; Br, 29.0; N, 10.2.
Found: C, 30.7; H, 1.3; Br, 29.1; N, 10.3.

For comparison XX was prepared by hydrolysis of XVIII with 5% sodium hydroxide solution as described for the preparation of 6-bromo-2-hydroxybenzothiazole. The m.p. and mixture m.p. was 280° (dec.).

7-Amino-6-bromo-2-methoxybenzothiazole (XXI). A solution of 2.0 g. (0.0069 mole) of 6-bromo-2-methoxy-7-nitrobenzothiazole in 100 ml. of 95% ethanol was shaken at 40 p.s.i.g. hydrogen pressure with 2 g. of palladium on calcium carbonate (35) for 22 hours. The filtered solution on evaporation to dryness under reduced pressure gave 1.8 g. (100%) of XXI as a light yellow solid, m.p. 103° (dec.). Attempted recrystallization from methanol or ethanol gave a black tar but the substance separated from hexane (decolorizing carbon) as fine white needles, m.p. 125–127°.

Anal. Calc'd for $C_8H_7BrN_2OS$: C, 37.1; H, 2.7; Br, 30.8; N, 10.8.
Found: C, 37.4; H, 2.9; Br, 30.6; N, 10.7.

7-Amino-2-methoxybenzothiazole (XXII). A solution of 2.0 g. (0.0069 mole) of XIX in 100 ml. of methanol containing 2.0 g. (0.024 mole) of anhydrous sodium acetate (46) was shaken as above with 2.0 g. of palladium on calcium carbonate. After 4.5 hours an additional 2.0 g. of catalyst was added. After 72 hours the filtered, colorless solution was concentrated nearly to dryness under reduced pressure and diluted with water. The white solid was collected giving 0.75 g. (60%) of crude XXII. Recrystallization from petroleum ether (30–60°) gave white rods, m.p. 73–75°.

Anal. Calc'd for $C_8H_8N_2OS$: C, 53.3; H, 4.5; N, 15.5.
Found: C, 53.7; H, 4.5; N, 15.4.

Reductions in which only an equimolar amount of sodium acetate was present and no fresh catalyst was added after the initial rapid reduction of the nitro group gave mixtures of XXI and XXII. These mixtures could be separated by recrystallization from aqueous ethanol in which XXI is the less soluble.

7-Chloro-2-hydroxybenzothiazole (XXIII). To a suspension of 0.5 g. (0.0028 mole) of 7-amino-2-methoxybenzothiazole in 6 ml. of conc'd hydrochloric acid and 3 ml. of water cooled to below 0° was added dropwise with stirring a solution of 0.21 g. (0.0029 mole) of sodium nitrite in 1 ml. of water. After a few minutes the clear orange diazonium salt solution was poured slowly into a cold solution of 0.5 g. (0.005 mole) of cuprous chloride in 5 ml. of conc'd hydrochloric acid. After warming the mixture to 40° until gas evolution ceased and cooling, the yellow solid (0.40 g., 78%) was collected. The crude product was dissolved in 20 ml. of cold 5% sodium hydroxide solution, and the solution was filtered and acidified with 10% nitric acid. The precipitate was recrystallized twice from benzene (carbon) to give pure XXIII, m.p. 203–205°.

Anal. Calc'd for C_7H_4ClNOS: C, 45.3; H, 2.2; Cl, 19.1; N, 7.5.
Found: C, 45.2; H, 2.1; Cl, 19.4; N, 7.4.

4-Chloro-2-hydroxybenzothiazole (XXIV). 2-Bromo-4-chlorobenzothiazole (0.30 g., 0.0012

mole) was boiled under reflux with 15 ml. of 5% sodium hydroxide solution for 1.5 hours. The product was isolated as described above for 6-bromo-2-hydroxybenzothiazole. Recrystallization of the crude substance (0.17 g., 77%), m.p. 200–201°, from benzene gave fine white needles, m.p. 202–203°. The reported m.p. for XXIV prepared by another method (47) is 204–205°.

Anal. Found: C, 45.7; H, 2.44; Cl, 18.9; N, 7.3.

A mixture of XXIII and XXIV melted at 163–167°.

SUMMARY

1. 2-Amino-4-nitrobenzothiazole has been found to be extremely resistant to diazotization.

2. Methyl *o*-nitrophenylthioncarbamate has been prepared and found to rearrange to methyl *o*-nitrophenylthiolcarbamate in the presence of bromine in acetic acid or chloroform.

3. Weakly basic 2-aminobenzothiazoles have been converted to 2-bromobenzothiazoles by Craig's diazotization procedure.

4. 4-Chloro-2-methoxybenzothiazole reacts with 3-diethylaminopropylamine by displacement of the methoxyl group rather than of the chlorine.

5. Nitration of 2,6-dibromobenzothiazole gives as the major product a mononitro derivative which is assigned the structure of 2,6-dibromo-7-nitrobenzothiazole along with small amounts of the 4- and 5-nitro isomers.

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