

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

**Researches on Thiazoles. XXIII. The Synthesis of Certain Benzothiazoles Structurally Related to Quinoline Antimalarials**

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Of the numerous synthetic organic compounds tested as possible antimalarials, Plasmoquine and Atebrine generally have been regarded as among the most useful. The former of these is a 6-methoxy-8-( $\delta$ -diethylamino- $\alpha$ -methyl-butyl) aminoquinoline (XXVI), the latter a 2-chloro-7-methoxy-5-( $\delta$ -diethylamino- $\alpha$ -methyl-butyl)-aminoacridine (XXVII).

At the time our research was initiated, no work had been reported, at least so far as we could discover, on the synthesis of benzothiazoles structurally related to Plasmoquine, for the purpose of investigating them as possible antimalarials. It was not until the latter part of March, 1938, when most of our work had been completed, that we learned that Knunyantz and Benevolenskaya<sup>1</sup> had been conducting studies also in this field and had found that 6-methoxy-4-( $\gamma$ -diethylaminopropyl)-aminobenzothiazole and its 2-methyl derivative were devoid of antimalarial effect. It seems unlikely, therefore, that the 6-methoxy-4-(and 7) ( $\beta$ -diethylaminoethyl)-aminobenzothiazoles, described in the following pages, will exhibit any antimalarial properties.

The methods used by us in these syntheses were quite different from those employed by Knunyantz and Benevolenskaya. The latter prepared their benzothiazoles from thiamides by the familiar Jacobson<sup>2</sup> reaction, whereas we utilized the Herz process<sup>3</sup> as applied to *p*-substituted aromatic amines with a free *o*-position. The various steps in our syntheses are shown on the Flow Sheets.

**Experimental****Series A**

**2-Amino-5-methoxyphenylmercaptan (III).**—The Herz reaction product (II) was prepared as described by Ast and Bogert,<sup>4</sup> except that it was found possible to reduce by 40% the proportion of sulfur monochloride to *p*-anisidine hydrochloride without loss of yield. As reported by them, it formed a reddish brown microcrystalline solid, melting with decomposition at 168° (corr.), when crystallized from a mixture of ligroin and chloroform.

(1) Knunyantz and Benevolenskaya, *J. Gen. Chem. (U. S. S. R.)*, **7**, 2471 (1937); *C. A.*, **32**, 2119 (1938).

(2) Jacobson, *Ber.*, **19**, 1067 (1886).

(3) Herz, German Patents 360,690, 364,822, 367,346, 367,493 (1914); *Friedlaender*, **14**, 908, 918–923.

(4) Ast and Bogert, *Rec. trav. chim.*, **54**, 917–930 (1935).

From the crude Herz reaction product, a clear colorless aqueous solution of the sodium salt of the 2-amino-5-methoxyphenylmercaptan was obtained by the Ast and Bogert<sup>4</sup> technique (except that sodium hydroxide was used instead of the bicarbonate), which was likewise followed in the preparation of the corresponding zinc salt (IV).

**Hydrochloride.**—A cold concentrated aqueous solution of the above sodium salt was neutralized carefully with dilute acetic acid. There resulted a yellow precipitate or suspension. The mixture was extracted with ether, the ether extract dried with anhydrous magnesium sulfate and treated with a current of dry hydrogen chloride. The precipitated hydrochloride was collected, dried, and crystallized from a mixture of absolute ethanol and dry benzene. It formed small yellow needles, m. p. in sealed tube, 210–211° (corr.), with decomposition and previous darkening; yield of crude product, 41%, calculated to the initial *p*-anisidine hydrochloride. It was soluble in water, in excess of aqueous caustic alkali, or in alcohol, but not in benzene.

*Anal.* Calcd. for  $C_7H_{10}ClNOS$ : C, 43.8; H, 5.3; N, 7.3. Found: C, 43.6; H, 4.9; N, 7.6.

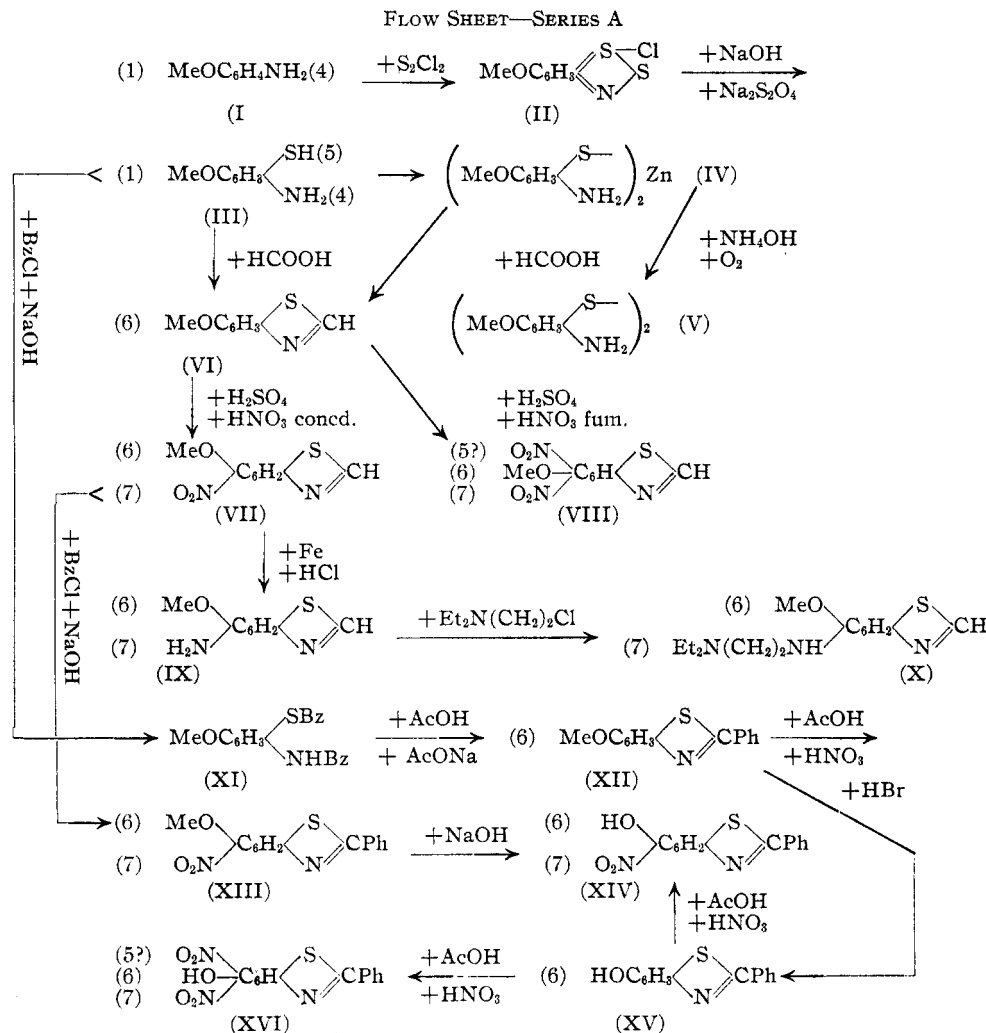
**2,2'-Diamino-5,5'-dimethoxydiphenyl Disulfide (V).**—A suspension of 3 g. of the zinc salt of the mercaptan (IV) in 100 cc. of concentrated ammonium hydroxide solution was treated for four hours with a vigorous current of air. A red precipitate replaced the suspended salt. The solid material was removed, extracted with alcohol, the alcoholic extract decolorized with Norite, concentrated, treated with three times its volume of water, and allowed to stand. Long yellow needles separated, which were crystallized repeatedly from 25% ethanol, and then melted at 73–73.5° (corr.). The product was insoluble in water or aqueous caustic alkali, but dissolved in the usual organic solvents.

*Anal.* Calcd. for  $C_{14}H_{16}O_2N_2S_2$ : C, 54.5; H, 5.2. Found: C, 54.5; H, 4.9.

**6-Methoxybenzothiazole (VI).**—A mixture of 15.4 g. of the zinc mercaptide (IV), sufficient glacial acetic acid to dissolve it (about a liter), an excess of anhydrous formic acid, and some metallic zinc, was refluxed for four hours. The bulk of the acid was then distilled off, the residue made alkaline with sodium hydroxide and distilled with steam, giving an 82% yield (11.1 g.) of the crude thiazole. Crystallized from petroleum ether, it was obtained in glistening colorless plates, m. p. 72.5–73° (corr.); freely soluble in carbon bisulfide, alcohol, ether, or benzene, moderately soluble in petroleum ether or hot water, and practically insoluble in cold water.

*Anal.* Calcd. for  $C_8H_7ONS$ : C, 58.1; H, 4.3; N, 8.5. Found: C, 58.1; H, 4.1; N, 8.3.

This compound was prepared also from the aminomercaptan hydrochloride (III) and anhydrous formic acid, in the presence of zinc. The yield was 46%. The method



was less satisfactory, because the isolation of the pure aminomercaptan hydrochloride was rather troublesome.

**6-Methoxy-7-nitrobenzothiazole (VII).**—A solution of 1.5 g. of 6-methoxybenzothiazole in 6 cc. of concentrated sulfuric acid was treated gradually with 6 cc. of concentrated nitric acid, the solution being maintained at room temperature for five minutes and then poured upon ice. The precipitated nitro derivative was collected, washed with water, and crystallized from alcohol. The product formed pale yellow plates, m. p. 202–203.5° (corr.); yield, 1.5 g. or 78%. In subsequent runs, the yields were nearly that calculated.

*Anal.* Calcd. for  $C_8H_6O_3N_2S$ : C, 45.7; H, 2.9; N, 13.3. Found: C, 45.6; H, 3.1; N, 13.1.

The same product was obtained by treating a solution of the thiazole in concentrated phosphoric acid with a slight excess of fuming nitric acid; but for all of our subsequent work the first method of preparation was preferred.

**6-Methoxy-5(?),7-dinitro-benzothiazole (VIII).**—To a solution of 1 g. of the thiazole (VII) in 6 cc. of concentrated sulfuric acid, there was added dropwise 4 cc. of fuming nitric acid, the mixture being kept for five minutes at 45°

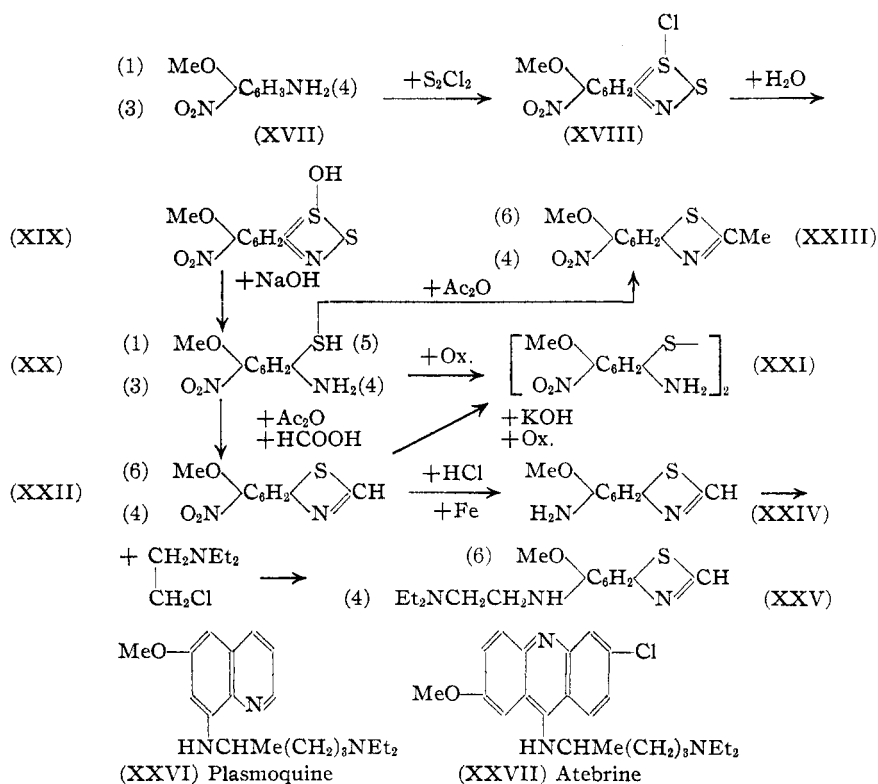
and then poured upon ice. The yellow precipitate, when crystallized from alcohol, formed very long needles, of an exceedingly pale yellowish tinge, m. p. 161–162.5° (corr.).

*Anal.* Calcd. for  $C_8H_4O_3N_4S$ : C, 37.6; H, 2.0. Found: C, 37.9; H, 2.0.

Since, in what follows, evidence is submitted that the first nitro group is attached to C<sup>7</sup>, it seems probable that the second one is on C<sup>5</sup>.

**6-Methoxy-7-aminobenzothiazole (IX).**—A suspension of the corresponding nitro derivative in hot dilute hydrochloric acid was reduced by successive additions of iron powder, and the mixture refluxed until the reaction was complete. The cold mixture was made strongly alkaline with sodium carbonate and filtered hot. As the filtrate cooled, a tan precipitate of the amine separated which was filtered out. The filtrate from this was added to the iron oxide residue and the whole extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and dry hydrogen chloride passed in, to precipitate the amine hydrochloride. This precipitate was dried, dissolved in water and the aqueous solution made slightly

FLOW SHEET—SERIES B



alkaline with sodium carbonate. The free amine so recovered was added to that obtained from the first alkaline filtrate from the iron oxide, and the whole was purified by solution in dilute acid and reprecipitation by alkali; yield 62%. Purified by repeated crystallization from hot water, it formed tan plates, m. p. 130.5–131.5° (corr.).

Another portion was sublimed *in vacuo*, and the white sublimate crystallized from "Skellysolve D." Nearly white plates were thus secured, m. p. 130–131° (corr.), with previous softening.

*Anal.* Calcd. for  $C_8H_8ON_2S$ : C, 53.3; H, 4.5; N, 15.6.  
Found: C, 53.2; H, 4.6; N, 16.0.

**HCl Salt.**—Nearly colorless transparent flakes (from alcohol), melting with decomposition and previous darkening at 223–224° (corr.) (sealed tube).

*Anal.* Calcd. for  $C_8H_8ON_2S \cdot HCl$ : 0.0992 g. requires 1.055 cc. of 0.434 *N* NaOH. Found: 1.068 cc.

**6 - Methoxy - 7 - ( $\beta$  - diethylaminoethyl) - aminobenzo-thiazole (X).—**A mixture of 5 g. of the above amine (IX), 6 g. of  $\beta$ -diethylaminoethyl chloride hydrochloride, and 15 cc. of absolute ethanol was heated at 110° for fifty-six hours under a short air condenser carrying a calcium chloride guard tube, to permit the distillation of the alcohol without ingress of moisture. The reaction product was dissolved in hot water, the reddish-brown solution cooled and a large excess of potassium carbonate added. The solution separated into two layers. The upper viscous dark brown oily one was taken up in ether, the ether solution dried over potassium carbonate, filtered, and the ether boiled off. The residue was distilled at a pressure

of about 0.0001 mm. and gave, in addition to some unchanged initial material, a light yellow viscous oily fraction at 140–145°, which darkened rapidly on exposure to the air, and was the compound sought (X);  $n_D^{25}$  1.5792.

*Anal.* Calcd. for  $C_{14}H_{21}ON_3S$ : C, 60.2; H, 7.6. Found: C, 60.0; H, 7.7.

**2 - Benzoylamino - 5 - methoxybenzoylphenylmercaptan (XI)** was prepared from the sodium mercaptide (III) and benzoyl chloride, as described by Ast and Bogert<sup>4</sup> and a similar product obtained (m. p. 162-163°, corr.).

**2-Phenyl-6-methoxy-benzothiazole (XII)**, obtained from the foregoing dibenzoyl derivative by the action of acetic anhydride and fused sodium acetate, as described by Ast and Bogert,<sup>4</sup> formed fine long colorless needles, m. p. 114–114.5° (corr.), as reported by them.

**2-Phenyl-6-methoxy-7-nitrobenzothiazole (XIII).**—To a mixture of 2.4 g. of the above thiazole (XII) with 10 cc. of glacial acetic acid, there was added 2 g. of nitric acid (sp. gr., 1.4) in 4 cc. of glacial acetic acid. There resulted a red solution, which was warmed for a short time at 60°, then cooled and poured into water. The yellow precipitate which formed was collected, washed with water and dried; yield 2.5 g., or 82%. Recrystallized from glacial acetic acid, it formed small yellow needles, m. p. 210–211°.

*Anal.* Calcd. for  $C_{14}H_{10}O_3N_2S$ : C, 58.7; H, 3.5. Found: C, 58.6; H, 3.7.

To a hot solution of 2 g. of 6-methoxy-7-nitrobenzothiazole in 5 cc. of benzoyl chloride,<sup>5</sup> an excess of 10% sodium hydroxide solution was added slowly and carefully, and

(5) Cf. Reissert, *Ber.*, **38**, 3432 (1905).

the heating continued for a short time longer. The solution was filtered hot and the gummy precipitate thus removed was crystallized repeatedly from glacial acetic acid first and then from ethanol. The purified product formed small yellow needles, m. p. 210–211° (corr.).

*Anal.* Calcd. for  $C_{14}H_{10}O_3N_2S$ : C, 58.7; H, 3.5. Found: C, 59.0; H, 3.6.

The product from this second method was apparently identical with that obtained by the direct nitration of the phenylmethoxythiazole (XII) as described above. A mixture of the two melted at 210–211° (corr.).

**2-Phenyl-6-hydroxybenzothiazole (XV).**—A mixture of 3 g. of 2-phenyl-6-methoxybenzothiazole with 40 cc. of 48% hydrobromic acid was refluxed for six hours, cooled, and made alkaline with dilute sodium hydroxide. A dirty white precipitate separated at first, but soon redissolved, giving a solution with a strong green fluorescence. This solution, after decolorization with Norite, was acidified with excess of dilute acetic acid. A whitish gummy solid precipitated and soon became crystalline. Recrystallized from dilute ethanol, it formed white needles which melted, with previous softening, at 227–227.5° (corr.); yield, nearly that calculated.

Fries and Buchler<sup>6</sup> prepared this compound in much the same way, except that they used glacial acetic acid saturated with hydrogen bromide and heated the mixture for eighteen hours at 100° in sealed tubes. They reported the m. p. of their product as 227°.

**2-Phenyl-6-hydroxy-7-nitrobenzothiazole (XIV).**—1.01 g. of the above crude hydroxythiazole was nitrated as described by Fries and Buchler.<sup>6</sup> The long orange needles so obtained melted at 170–171° (corr.).

In another experiment, 1 g. of 2-phenyl-6-methoxy-7-nitrobenzothiazole was refluxed for seven hours with an excess of 10% sodium hydroxide solution. The mixture, consisting of a red solution containing a red precipitate, was filtered hot. The red precipitate was extracted by boiling with dry benzene, which recovered a large amount of unchanged initial thiazole. The small quantity of red solid undissolved by the benzene was taken up in hot alcohol, the alcohol solution acidified with hydrochloric acid, decolorized with Norite, and precipitated by careful dilution of the hot solution. Orange needles separated which, when recrystallized from dilute alcohol, melted at 171° (corr.). A mixture of this product with that obtained by the method described in the first paragraph, melted at 170.5–171° (corr.).

*Anal.* Calcd. for  $C_{13}H_8O_3N_2S$ : C, 57.3; H, 3.0. Found: C, 57.5; H, 3.0.

**2-Phenyl-6-hydroxy-5(?)7-dinitrobenzothiazole (XVI).**—A solution of 0.4 g. of 2-phenyl-6-hydroxybenzothiazole in 5 cc. of glacial acetic acid was treated with a solution of 1 cc. of nitric acid (sp. gr., 1.4) in 2 cc. of glacial acetic acid. The red mixture was warmed gently for a short time, then poured into water, the precipitate collected, washed with water, dried, and crystallized from glacial acetic acid. Long fine deep yellow needles were thus obtained, m. p. 194.5–196° (corr.).

*Anal.* Calcd. for  $C_{13}H_7O_5N_4S$ : C, 49.2; H, 2.2. Found: C, 49.4; H, 2.4.

(6) Fries and Buchler, *Ann.*, **454**, 240 (1927).

## Series B

**2-Amino-3-nitro-5-methoxyphenylmercaptan (XX).**—The Herz reaction as applied to *p*-anisidine proved very unsatisfactory with *m*-nitro-*p*-anisidine, because of the sensitivity to moisture of the hydrochloride of the latter, and other complications. Recourse was had, therefore, to a modification of the Herz process described in a later German Patent, no. 367,346.<sup>8</sup>

A suspension of 150 g. of *m*-nitro-*p*-anisidine (XVII) in 900 cc. of glacial acetic acid, at 20°, was treated with 440 cc. (750 g.) of previously cooled sulfur monochloride. After being stirred for some time at room temperature, it was heated slowly to 75–80° and maintained at that point until the evolution of hydrogen chloride ceased (about five hours). After a brief additional heating at 90°, the mixture was cooled to room temperature, the orange-yellow precipitate collected, washed with dry benzene, and dried in the air; yield 170 g.

Some of this crude product, purified by crystallization from a mixture of benzene and glacial acetic acid, yielded a yellowish orange microcrystalline solid (XVIII), 1-chloro-4-nitro-6-methoxyisobenz-1,2,3-dithiazole, which melted with decomposition at 220° (corr.), with previous darkening. However, if heated suddenly at any temperature above 190°, melting and decomposition ensued almost immediately. The compound was soluble in water, alcohol, or glacial acetic acid, but insoluble in benzene. Its aqueous solution, however, soon underwent hydrolysis on standing, with separation of a voluminous flocculent precipitate, which crystallized from absolute ethanol in long yellow needles of the corresponding *hydroxyl derivative* (XIX), which decomposed at 162.5° (corr.) with preliminary darkening; yield, 68%, based on the initial nitroanisidine.

*Anal.* Calcd. for  $C_7H_6O_4N_2S_2$ : C, 34.1; H, 2.5. Found: C, 34.3; H, 2.6.

This product easily was converted by caustic alkali into the sodium amino mercaptide (XX), as described for the 2-amino-5-methoxyphenylmercaptide, except that the solution so obtained was blood-red instead of colorless.

The zinc salt, prepared from the aqueous solution of the sodium mercaptide and zinc sulfate, by the Ast and Bogert<sup>4</sup> technique, was obtained in small red needles (from a mixture of ethanol and benzene), freely soluble in ethanol or glacial acetic acid, only slightly soluble in chloroform, and practically insoluble in water or benzene; yield, 40%, calculated to the *m*-nitro-*p*-anisidine.

**2,2' - Diamino - 3,3' - dinitro - 5,5' - dimethoxydiphenyl Disulfide (XXI).**—The aqueous alkaline solution of the sodium mercaptide (XX) was acidified with hydrochloric acid. A red flocculent precipitate separated, which was removed, washed with water, and crystallized from ethanol. Beautiful bright red needles were thus obtained, m. p. 171° (corr.).

*Anal.* Calcd. for  $C_{14}H_{14}O_6N_4S_2$ : C, 42.2; H, 3.5; mol. wt., 396. Found: C, 42.2; H, 3.7; mol. wt. (Rast), 392.

In the above reaction, the free mercaptan, which separated first, rapidly oxidized in the air to the disulfide. The presence of the mercaptan in the freshly precipitated material was demonstrated easily by its solubility in dilute alkali.

**4-Nitro-6-methoxy-benzothiazole (XXII).**—All attempts to obtain this thiazole by the action of anhydrous formic acid upon either the freshly precipitated mercaptan (XX), or its zinc salt, proved futile.

To a solution of the sodium mercaptide (XX) obtained by hydrolysis of 100 g. of the Herz reaction product, there was added all at once 140 cc. of crude formic-acetic anhydride, prepared as described by Béhal.<sup>7</sup> The whole was shaken vigorously, and then allowed to stand for five to ten minutes with occasional shaking. A yellow solid precipitated. This was collected, washed with water, and crystallized from dilute ethanol, giving long glistening yellow flat needles, m. p. 150–152°; yield 23.5 g.; or 21%, calculated to the nitroanisidine. Knunyantz and Benevolenskaya,<sup>1</sup> who prepared this compound in another way, gave its m. p. as 151°.

*Anal.* Calcd. for  $C_8H_6O_3N_2S$ : C, 45.7; H, 2.9; N, 13.3. Found: C, 45.7; H, 2.8; N, 13.2.

**2-Methyl-4-nitro-6-methoxybenzothiazole (XXIII).**—A few cc. of the aqueous alkaline solution of the sodium mercaptide (XX) was treated with sufficient acetic anhydride to redissolve the precipitate which first appeared. The solution was warmed and allowed to stand as long as crystals continued to separate. These small yellow needles were removed, washed with water and recrystallized from dilute ethanol. The first recrystallization yielded large intense yellow glistening plates, but all subsequent recrystallizations gave long yellow needles, m. p. 147° (corr.). Knunyantz and Benevolenskaya<sup>1</sup> prepared this compound by a different method and found its m. p. as 149–150°.

*Anal.* Calcd. for  $C_9H_8O_3N_2S$ : C, 48.2; H, 3.5; N, 12.5. Found: C, 48.1; H, 3.5; N, 12.4.

**4-Amino-6-methoxybenzothiazole (XXIV).**—A suspension of 60 g. of the corresponding nitro derivative (XXII) in dilute hydrochloric acid (50 cc. of concentrated acid to 500 cc. of water) was reduced by the gradual addition of 60 g. of iron powder. After refluxing the mixture for two and one-half hours, it was extracted with benzene and the filtered extract distilled. After the removal of the benzene, the residue was crystallized from absolute ethanol, after decolorization by Norite. The crystals obtained varied in form with the rate of cooling, the concentration, and probably other factors, being lightly tinted transparent plates, thick spikes, or long needles in rectangular clusters. The m. p. remained constant at 145.5–146° (corr.), even after the carefully purified material had been sublimed in a vacuum. Knunyantz and Benevolenskaya,<sup>1</sup> who reduced the nitro derivative by stannous chloride and crystallized their product from dilute alcohol, obtained long needles, m. p. 151°.

(7) Béhal, *Ann. chim.*, [7] 20, 417 (1900).

*Anal.* Calcd. for  $C_8H_8ON_2S$ : C, 53.3; H, 4.5; N, 15.5. Found: C, 53.3; H, 4.6; N, 15.3.

**Hydrochloride.**—Long colorless needles, from concentrated hydrochloric acid, melting with decomposition, in a sealed tube, at 207–209° (corr.) (literature,<sup>1</sup> m. p. 206–208°).

*Anal.* Calcd. for  $C_8H_8ON_2S \cdot HCl$ : 0.1 g. requires 1.061 cc. of 0.434 N NaOH; found, 1.069 cc.

**4-( $\beta$ -Diethylaminoethyl)-amino-6-methoxybenzothiazole (XXV)** was prepared from the foregoing amine and  $\beta$ -diethylaminoethyl chloride hydrochloride in essentially the same way as the 7-( $\beta$ -diethylaminoethyl) isomer (X) was obtained from the corresponding amine, except that no ethanol was used in the mixture. Distillation of the crude product, at a pressure of 5–6 mm., in an atmosphere of nitrogen, yielded two fractions. One, b. p. 188–215°, consisted mainly of unchanged initial amine; and the other, b. p. 215–217°, was a yellow viscous oil, which darkened rather less rapidly on standing than its isomer (X);  $n_D^{20}$  1.5978.

*Anal.* Calcd. for  $C_{14}H_{21}ON_3S$ : C, 60.2; H, 7.6. Found: C, 60.2; H, 7.3.

**Acknowledgments.**—Our grateful thanks are due to E. I. du Pont de Nemours & Co., Inc., of Wilmington, Delaware, and to the National Aniline and Chemical Co., Inc., of New York, for a generous supply of *p*-anisidine and of *m*-nitro-*p*-anisidine, for use in these investigations.

We are indebted also to Mr. Saul Gottlieb, of these Laboratories, who carried out the analyses recorded in this paper.

### Summary

1. 6-Methoxy-4(and 7)-( $\beta$ -diethylaminoethyl)-aminobenzothiazoles have been synthesized from *p*-anisidine in the one case, and from 3-nitro-4-aminoanisole in the other.

2. It was planned to study these compounds as possible antimalarials, but work recently published in Russia, on some closely related benzothiazoles, makes it seem unlikely that they will prove of any value in that direction.

3. From *m*-nitro-*p*-anisidine, 4-amino-6-methoxybenzothiazole is easily prepared.

4. Nitration of 6-methoxy, or of 2-phenyl-6-methoxybenzothiazole, substitutes the H in position 7.

NEW YORK, N. Y.

RECEIVED MAY 13, 1939