[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

# Studies on the Thiazoles Obtained by Direct Thiocyanogenation[1]

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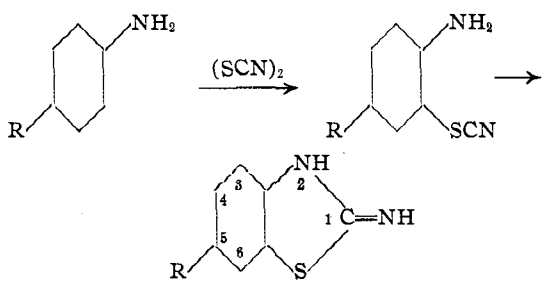
Considerable interest has been shown recently in the direct thiocyanogenation of aromatic amines. In the procedure[2] followed by most investigators the amine (1 mole) and ammonium thiocyanate (2 moles) were dissolved in glacial acetic acid and bromine or a chloramide was slowly added. The liberated thiocyanogen substituted in the position para to the amino group or, if that were occupied, in the ortho position. Such ortho thiocyanogenated products were of special interest to us because they automatically rearrange to substituted iminobenzthiazoles similar to others which have been studied previously in this Laboratory.




Our experiments dealing with the extension of this type of reaction and a study of the thiazoles thus produced may be described under four headings as follows:

**(A) General Application of the Method.**—Previous investigators have shown (1) that in the reaction indicated above the group R may be of almost any character (alkyl, halogen, carboxyl, nitro, etc.) but (2) that the reaction fails entirely if the amino group is acetylated or converted to a urethan. Both of these observations have been verified in our experiments. In addition we have found (1) that monoalkylated amines (ethyl-*p*-toluidine, benzyl-*p*-toluidine, etc.) undergo thiocyanogenation smoothly with rearrangement to the alkylated benzthiazoles, (2) that the reaction may also be applied to many disubstituted aminobenzenes such as 3-nitro-4-methylaminobenzene, 2,4-dimethylaminobenzene, 2-bromo-4-methylaminobenzene, and 2-methyl-4-nitroaminobenzene but (3) that the process fails in the case of 2-chloro-4-nitroaminobenzene and 2-nitro-4-methylaminobenzene where "steric hindrance" forces are quite large.

**(B) Alkylation.**—The imino-benzthiazoles undergo alkylation at position 2 upon boiling with alkyl halides for six to eight hours giving products identical with those obtained by direct thiocyanogenation of mono-N-alkylanilines.

**(C) Condensation with Loss of Ammonia.**—Fusion of the iminobenzthiazoles with aniline (or other primary aromatic amines) resulted in evolution of ammonia and production of 1-arylimino-benzothiazoles.

**(D) Formation of Thiazoles from Aryl Thioureas.**—Disubstituted thioureas of the type RNHCSNHR′ react with bromine in chloroform solution giving 1-aryliminobenzthiazoles which in many cases are identical with those obtained by condensation with loss of ammonia as mentioned in the preceding paragraph.

## Experimental

A typical procedure for the preparation of one of those iminobenzthiazoles by direct thiocyanogenation is described as follows.

2,4-Dimethylaminobenzene (12.1 g., 0.1 mole) and 16.2 g. (0.2 mole) of sodium thiocyanate were dissolved in 150 cc. of glacial acetic acid, cooled in ice and stirred mechanically while a solution of 16 g. of bromine in 25 cc. of acetic acid was slowly added drop by drop. External cooling was applied throughout the process to keep the temperature below 10° and the stirring was continued for thirty minutes after all of the bromine had been added. The precipitate of 1-imino-3,5-dimethylbenzthiazole hydrobromide[3] was removed by filtration at the pump, dissolved in warm water and the base precipitated with alkali. For purification it was recrystallized from alcohol or ligroin, yield 13 g. The melting points and analyses of this and other benzthiazoles not recorded in the literature which have been prepared by this method are shown in Table I.

(1) Presented at the San Francisco Meeting of the Society, August, 1935.

(2) Dyson, Hunter and Morris, *J. Chem. Soc.*, **130**, 1186 (1927); Kaufmann, *Arch. Pharm.*, **266**, 197 (1928); Likhosherstov and Petrov, *J. Gen. Chem.* (U. S. S. R.), **3**, 183 (1933); Kaufmann and Kuchler, *Ber.*, **67**, 944 (1934).

(3) In some instances the precipitate is a thiocyanate or a mixture of thiocyanate and hydrobromide.

TABLE I

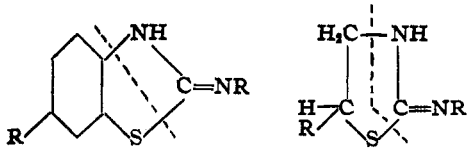
| No. | Benzthiazole | Source | M. p., °C. | %, N Calcd. | %, N Found | |
|---|---|---|---|---|---|---|
| I | 1-Imino-5-nitro | *p*-Nitraniline | 252 | 21.54 | 21.20 | 21.35 |
| II | 1-Imino-4-nitro-5-methyl | 3-Nitro-4-methylaniline | 257 | 20.10 | 19.95 | |
| III | 1-Imino-3,5-dimethyl | 2,4-Dimethylaniline | 140 | 15.93 | 15.74 | 15.81 |
| IV | 1-Imino-3-bromo-5-methyl | 2-Bromo-4-methylaniline | 211 | 11.52 | 11.50 | 11.44 |
| V | 1-Imino-3-methyl-5-nitro | 2-Methyl-4-nitroaniline | 280 | 20.10 | 20.04 | |
| VI | 1-Imino-2-ethyl-5-methyl | Ethyl-*p*-toluidine | 106 | 14.58 | 14.53 | 14.60 |
| VII | 1-Imino-2-benzyl-5-methyl | Benzyl-*p*-toluidine | 80 | 11.02 | 11.24 | 11.14 |
| VIII | 1-Imino-2,5-dimethyl | Methyl-*p*-toluidine | 51 | 15.73 | 15.70 | 15.81 |

### Alkylation of the Benzthiazoles

For these experiments 1-imino-5-methylbenzthiazole was used since it is easily obtained in quantity by thiocyanogenation of *p*-toluidine. 1-Imino-5-methylbenzthiazole (16.4 g., 0.1 mole) when boiled with 10 cc. of ethyl iodide and 50 cc. of ethyl alcohol on the water-bath for ten hours gave 17 g. of the slightly soluble hydriodic acid salt of 1-imino-2-ethyl-5-methylbenzthiazole. Solution of this salt in hot water and addition of alkali gave the free base, m. p. 106°. The location of the ethyl radical at position 2 was established by the fact that a mixture of this substance and compound VI, Table I, showed no depression of the melting point. Analysis of the hydriodic acid salt gave I, 39.50, 39.40. Calculated for $C_{10}H_{13}NSI$: I, 39.68.

Methylation of the 1-imino-5-methylbenzthiazole by the above method using either methyl iodide or methyl sulfate likewise gave a 2-methyl derivative identical with compound VIII. Its hydriodic acid salt is quite insoluble in cold water and analysis showed 41.35% I. Calculated for $C_9H_{11}NSI$: I, 41.53.

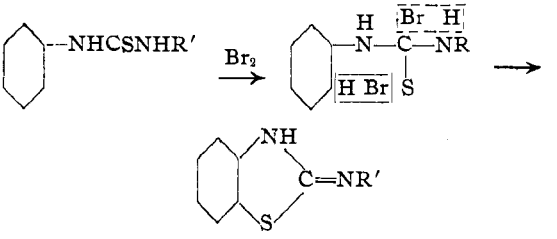
Benzylation of the 1-imino-5-methylbenzthiazole by eight hours of boiling with benzyl chloride in ethyl alcoholic solution gave the 2-benzyl derivative identical with compound VII. In none of the alkylations did the alkyl group unite with the nitrogen atom at position 1. Such benzthiazoles (with substituents at position 1) were made by another method shown in a following section. If the hydrogen at either position 1 or position 2 has been replaced by one radical, no further alkylation occurs even upon long heating. Thus 1-*o*-chlorophenylimino-5-methylbenzthiazole (XV) was not ethylated by ethyl iodide either by boiling for several days or by heating in a sealed tube at 150° for six hours. Other compounds in this series behaved similarly. In each case the original benzthiazole (XV) was recovered unchanged. Such difficulty of alkylation is analogous to the behavior of the 2-arylimino-5-alkylthiazolines as observed by Dains and Eberly.[4]



**Condensations with Loss of Ammonia.**—Fusion of 1-imino-5-methylbenzthiazole (8.2 g., 0.05 mole) with 8 g. (excess of 0.05 mole) of aniline[5] at 220° for thirty minutes resulted in the evolution of ammonia and the production of 11 g. of 1-phenylimino-5-methylbenzthiazole[6] which after crystallization from alcohol melted at 167°. Such condensations are typical of these substances and the following compounds which were prepared by this method and which are not listed in the literature are here reported.

Reduction of 1-*p*-nitrophenylimino-5-methylbenzthiazole (XIII) with tin and hydrochloric acid gave the amino compound $CH_3C_6H_3(N{=}C(S)-NHC_6H_4NH_2)$ which was purified by crystallization from ligroin; m. p. 147°; N, 16.47. Found: N, 16.40, 16.25. It was more conveniently prepared by boiling its acetyl derivative (XIV) with 15% hydrochloric acid for one hour and precipitation of the base with alkali. This compound has a close relation in structure to primuline and its diazotized solution was found to be substantive to cotton cloth and couples on the fiber with phenol or naphthol to give colors of almost the same shade as with primuline.

**Formation of Benzthiazoles from Substituted Thioureas and Bromine.**—Hugerschoff[7] has shown that thiocarbanilide reacts with bromine in chloroform solution to give the hydrobromide salt of 1-phenyliininobenzthiazole.



This process has heretofore been used only to prepare thiazoles from symmetrical thioureas. We have used unsymmetrical thioureas in order to obtain a check on the constitution of the benzthiazoles shown in Table II. Our observations show that in the conversion of a thiourea of the type RNHCSNHR′ to the substituted benzthiazoles the more positive of the two groups (R and R′) takes the

(4) Dains and Eberly, not yet published.

(5) If monomethylaniline is substituted for aniline no reaction occurs.

(6) On heating alone to 270° for thirty minutes, 1-imino-5-methylbenzthiazole evolves 1 mole of ammonia from 2 moles of the benzthiazole giving 5-$CH_3C_6H_3$(N=C(S)-NH-C(=N)-$C_6H_3CH_3$-5′); m. p. 278°; N, 13.50. Found: N, 13.30, 13.36. This compound is very slightly soluble in the usual solvents and is often a by-product in the formation of the substances shown in Table II.

(7) Hugerschoff, *Ber.*, **36**, 3121 (1903).

TABLE II

| No. | Benzthiazole | Source | M. p., °C. | % N Calcd. | % N Found | |
|---|---|---|---|---|---|---|
| IX | 1-Phenylimino-5-methyl | 5-Me-benzthiazole + aniline | 167 | 11.66 | 11.55 | |
| X | 1-Phenylimino-5-bromo | 5-Br-benzthiazole + aniline | 188 | 9.18 | 9.10 | 9.24 |
| XI[a] | 1-*p*-Anisylimino-5-methyl | 5-Methylbenzthiazole + *p*-anisidine | 160 | 10.36 | 10.41 | 10.54 |
| XII[a] | 1-*p*-Tolylimino-5-methoxy | 5-Methoxybenzthiazole + *p*-toluidine | 160 | 10.36 | 10.30 | 10.68 |
| XIII | 1-*p*-Nitrophenylimino-5-methyl | 5-Methylbenzthiazole + *p*-nitraniline | 272 | 14.63 | 14.50 | |
| XIV | 1-*p*-Acetaminophenylimino-5-methyl | 5-Methylbenzthiazole + *p*-aminoacetanilide | 220 | 14.12 | 13.92 | 14.02 |
| XV | 1-*p*-Chlorophenylimino-5-methyl | 5-Methylbenzthiazole + *p*-chloroanilin | 197 | 10.20 | 10.10 | 9.98 |

[a] A mixed melting point shows that XI and XII are not identical.

TABLE III

| No. | Thiazole | Source | M. p., °C. | Nitrogen, % Calcd. | Found | |
|---|---|---|---|---|---|---|
| XVI[a] | 5-$CH_3C_6H_3$—N=CNH$C_2H_5$ (S) | *p*-$CH_3C_6H_4NHCSNHC_2H_5$ | 133 | 14.58 | 14.38 | 14.49 |
| XVII[b] | 5-$CH_3C_6H_3$—N=CN$(C_2H_5)_2$ (S) | *p*-$CH_3C_6H_4NHCS(C_2H_5)_2$ | Oil | | | |
| XVIII | $C_6H_4$—N=CNH$C_6H_4$Br-*p* (S) | $C_6H_5NHCSNHC_6H_4$Br-*p* | 210 | 9.12 | 8.98 | 9.04 |
| XIX | 5-$BrC_6H_3$—N=CNH$C_6H_4$Br-*p* (S) | *p*-$BrC_6H_4NHCSNHC_6H_4$Br-*p* | 256 | 7.25 | 7.41 | 7.21 |
| XX[c] | 5-$CH_3C_6H_3$—N=CNH$C_6H_4$Cl-*p* (S) | *p*-$CH_3C_6H_4NHCSNHC_6H_4$Cl-*p* | | | | |
| XXI[d] | 5-$CH_3C_6H_3$—N=CNH$C_6H_4NHCOCH_3$-*p* (S) | *p*-$CH_3C_6H_4NHCSNHC_6H_4NHCOCH_3$-*p* | | | | |
| XXII | 5-$CH_3C_6H_3$—N=CNH$CH_2C_6H_5$ (S) | *p*-$CH_3C_6H_4NHCSNHCH_2C_6H_5$ | 159 | 11.02 | 11.17 | 11.10 |

[a] Isomeric but not identical with VI. [b] Picrate, m. p. 174°. Platinum salt ($C_{24}H_{34}N_4S_2PtCl_6$); Pt, 22.92. Found: Pt, 22.72. [c] Identical with XV by mixed melting point test. [d] Identical with XIV. Preparation of this compound from the *p*-tolyl-*p*-acetaminophenylthiourea is the most convenient method.

position 1[8] and the more negative forms the ring closure with the sulfur atom. The results of several experiments are shown in Table III.

## Summary

New methods for the preparation of the benzthiazoles and their derivatives have been developed and the properties of these compounds have been studied. In several cases substituted benzthiazoles have been obtained both by the direct thiocyanogenation of aromatic amino compounds and also by the action of bromine upon disubstituted thioureas. The behavior of these substances upon alkylation is also reported.

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(8) See table by Kharasch and Flenner, THIS JOURNAL, **54**, 678 (1932). If the two groups (R and R′) are close together in the table, such as phenyl and *p*-tolyl, a mixture of both possible isomeric benzthiazoles results which is practically impossible of separation.

It was also found in this Laboratory that disubstituted thioureas react with ethylene dibromide giving thiazoles in accordance with the same principle as above; *viz.*, the ring closure forming with the more electronegative group. Dains *et al.*, *ibid.*, **47**, 1987 (1925).