Anal. Calcd. for $C_{11}H_9ON$: C, 77.21; H, 5.31; N, 8.18. Found: C, 77.43; H, 5.05; N, 8.17.

C^{14}-Labeled Quinoline-3-carboxylic Acid.—Oxidation with potassium hypochlorite was used to obtain the activity of the methyl group of the above ketone. The hypochlorite solution was prepared by adding a warm solution of 0.30 g. of potassium carbonate and 0.105 g. of potassium hydroxide in 1.4 ml. of water to 0.427 g. of commercial HTH partially dissolved in 1.7 ml. of water. The calcium carbonate was filtered and to the magnetically stirred filtrate was added 200 mg. (1.17 mmoles) of 3-acetylquinoline. In 15 minutes the reaction was complete and the mixture was heated to 70° with a nitrogen sweep. The evolved chloroform was collected in a cold-trap at −70°.

The excess hypochlorite was destroyed with 20% sodium bisulfite (until a negative test with starch–iodide paper was obtained) and the solution acidified with glacial acetic acid. The precipitate of quinoline-3-carboxylic acid was centrifuged, washed and recrystallized from glacial acetic acid. A white, micro-crystalline product was obtained, m.p. 272–275°, yield 160 mg. (79%).

The acid was converted into its amide by grinding 125 mg. (0.723 mmole) of it with 150 mg. of phosphorus pentachloride in a glass-stoppered vial. The mixture was heated on a steam-bath for one hour. The acid chloride was then added in portions to 5 ml. of concentrated ammonium hydroxide at 0° and allowed to stand for one hour. The crude amide was recrystallized from water to give slender, white needles, m.p. 197.5–198.5°, yield 70 mg. (57%).

Anal. Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.69; N, 16.27. Found: C, 69.47; H, 4.63; N, 16.49.

C^{14}-Labeled 3-Aminoquinoline.—Quinoline-3-carboxamide (70 mg., 0.407 mmole) was added in one portion to a magnetically stirred solution consisting of 65 mg. of bromine (0.021 ml., 0.41 mmole), potassium hydroxide (0.3 g., 5.36 mmoles) and 6 ml. of water. The solution was stirred for 10 minutes by which time almost all of the amide had dissolved. The reaction mixture was then heated to 70° for 15 minutes, acidified with glacial acetic acid and the evolved carbon dioxide collected.

The aqueous solution containing the amine salt was made basic with sodium hydroxide and extracted with methylene chloride. The solvent was evaporated and the residue recrystallized from toluene, m.p. 81–82°, yield 43.4 mg. (74%).

3-Acetylaminoquinoline.—Since the amine was observed to decompose slowly in air, the acetyl derivative was used for activity determinations. 3-Aminoquinoline (0.301 g., 2.09 mmoles) was allowed to reflux for five minutes with 0.3 ml. of acetic anhydride, to which a catalytic amount of sodium acetate had been added, and the mixture was hydrolyzed with 50 ml. of water. The viscous black reaction mixture was instantly converted upon hydrolysis to a white micro-crystalline solid, which was recrystallized twice from water (charcoal), m.p. 166.2–167°, yield 0.292 g. (75%).

Anal. Calcd. for $C_{11}H_{10}ON_2$: C, 70.94; H, 5.42; N, 15.05. Found: C, 70.90; H, 5.51; N, 15.07.

Radioactivity Determinations.—All C^{14}-compounds were oxidized under reduced pressure with the oxidation mixture of Van Slyke and Folch,[12] the carbon dioxide collected in sodium hydroxide solution and precipitated in the usual fashion. The activity was determined with thin uniform layers of barium carbonate, using a thin mica-windowed Geiger–Mueller tube.[13] To correct for the dilution of the activity of a specific carbon in the compound, the observed activity obtained when the compound was combusted is always multiplied by the total number of carbon atoms in the molecule.

(12) D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 309 (1940).

(13) W. G. Dauben, J. C. Reid and P. E. Yankwich, *Anal. Chem.*, **19**, 828 (1947).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF TENNESSEE]

Syntheses of Some 2-Thiocyanoimidazoles[1]

BY ROGER E. KOEPPE AND JOHN L. WOOD

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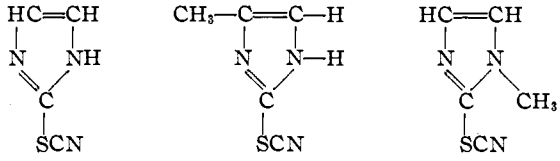
Several 2-thiocyanoimidazoles have been prepared from the corresponding mercaptoimidazoles and cyanogen bromide. Best results were obtained when the reactants were mixed in the solid state. No evidence was found for thiocyanation of imidazoles by treatment with thiocyanogen.

Thiocyano derivatives of imidazoles were desired for biological studies of this Laboratory. Such compounds have not been reported.

Since direct thiocyanation of imidazoles did not prove successful, cyanation of mercaptoimidazoles was resorted to.

Abramovitch[2] has prepared aliphatic thiocyanates by interaction of mercaptans and cyanogen halides in the presence of alkali and suitable solvents. Using a modification of this method, 2-thiocyanoimidazole (I) has been obtained in good yield from 2-mercaptoimidazole and cyanogen bromide. Efforts to convert 4(5)-methyl-2-mercaptoimidazole and 1-methyl-2-mercaptoimidazole to the corresponding thiocyano compounds II and III by this procedure met with limited success. Although the desired products were likely produced, pure crystalline compounds were not isolated from the reaction mixtures.

Elimination of the use of alkali and solvents resulted in a procedure for synthesizing 2-thiocyanoimidazoles in pure crystalline form and satisfactory yield. The method involved the thorough mixing of solid cyanogen bromide and the mercaptoimidazole with subsequent gentle heating. The hydrobromide of the desired thiocyano compound was produced, from which the free base was readily isolated. In this manner 2-thiocyano-4(5)-methyl-2-thiocyano- and 1-methyl-2-thiocyanoimidazole have been prepared. In preliminary studies it was found that benzyl mercaptan was converted to benzyl thiocyanate by direct interaction of cyanogen bromide.



I II III

The thiocyanoimidazoles are relatively unstable. On standing at room temperature the colorless crystals gradually turn yellow. However, 2-thiocyanoimidazole, when suspended in chloroform, is stable at room temperature for several months.

(1) These studies were supported by the Atomic Energy Commission under Contract AT-(40-1)-283, Title VII.

(2) B. Abramovitch, U. S. Patent 2,486,090, Oct. 25, 1949; *C. A.*, **44**, 2018 (1950).

TABLE I
PAPER CHROMATOGRAPHY OF MERCAPTO- AND THIOCYANOIMIDAZOLES[a]

	Imidazole	R_f
1	2-Mercapto-	0.61
2	2-Thiocyano-	.86
3	1-Methyl-2-mercapto-	.70[b]
4	1-Methyl-2-thiocyano-	.82[b]
5	4(5)-Methyl-2-mercapto-	.72
6	4(5)-Methyl-2-thiocyano-	.87
7	$ZnCl_2$ complex of 4(5)-methyl-2-mercapto-	.72

[a] Butanol–95% ethanol–water, 80:20:20. [b] Red spots in contrast to yellow-orange obtained with other imidazoles.

Thiocyanoimidazoles are readily soluble in ethanol, and 1-methyl-2-thiocyanoimidazole is also relatively soluble in water and ether. In contrast to the N-substituted compound, 2-thiocyano- and 4(5)-methyl-2-thiocyanoimidazole are rather insoluble in water and ether.

Treatment with diazotized sulfanilic acid[3] gave colors similar to those produced by the corresponding mercaptoimidazoles. This reaction was convenient for detecting the compounds on paper chromatograms (Table I). Thiocyanoimidazoles, in contrast to mercaptoimidazoles, did not give a deep orange color when added to methanolic gold chloride.[4] This result confirms the conclusion that substitution had occurred at the sulfur atom.

On testing with Grote reagent,[5] the thiocyanoimidazoles were found to give green colors similar to those produced by analogous mercaptoimidazoles. However, color development was noticeably slower in the case of the thiocyanoimidazoles.

Treatment with zinc and acid resulted in the immediate production of cyanide, a reaction typical of thiocyano compounds. Hydrogen cyanide was removed by aeration, trapped in dilute alkali and identified as Prussian blue. Presumably, the other products formed were the corresponding mercapto compounds. This was definitely established in the case of 4(5)-methyl-2-thiocyanoimidazole from which 4(5)-methyl-2-mercaptoimidazole was isolated. Cyanide was also detected when 2-thiocyanoimidazole was treated with stannous chloride in the presence of acid.

Alkali decomposed 2-thiocyanoimidazole and 1-methyl-2-thiocyanoimidazole with the formation of cyanide. Cyanide was not formed when 4(5)-methyl-2-thiocyanoimidazole was treated with alkali. However, 4(5)-methyl-2-thiocyanoimidazole decomposes or rearranges in the presence of alkali to a product which no longer yields cyanide with zinc and acid.

2-Thiocyanoimidazoles absorb rather strongly in the low ultraviolet. The spectra resemble those of the mercaptoimidazoles, with a 10 to 15 mμ shift in the maximum of the broad band to the range of 235–248 mμ.

Since the imidazole ring is rather readily iodinated and brominated, thiocyanation of this moiety with the pseudohalogen, thiocyanogen, seemed plausible. Many of the methods described[6] for the synthesis of thiocyano compounds from thiocyanogen, or its precursors, have been applied to imidazole. In no instance was a thiocyanoimidazole isolated. Attempts to combine thiocyanogen with histamine dihydrochloride, histidine, histidine methyl ester and α-N-acetylhistidine also have been uniformly unsuccessful. Treatment of imidazole and histamine dihydrochloride in pyridine with a nitromethane solution of thiocyanogen resulted in 56 and 39% yields of the respective sulfates.

Preliminary studies have shown thiocyanoimidazoles to have anti-thyroid activity.

Experimental[7]

The 2-mercaptoimidazole and 4(5)-methyl-2-mercaptoimidazole used were prepared according to the method of Lawson and Bullerwell.[8]

We are indebted to Dr. Reuben Jones of Eli Lilly Co. for samples of 2-mercaptoimidazole and 1-methyl-2-mercaptoimidazole used in preliminary work.

2-Thiocyanoimidazole. Method A.—To a solution of 5 g. (0.05 mole) of 2-mercaptoimidazole in 450 ml. of dry dioxane was added 3.2 g. (0.08 mole) of powdered sodium hydroxide. The stirred suspension was cooled (8–10°) and 7.5 g. (0.07 mole) of cyanogen bromide in 90 ml. of dioxane was added dropwise over a 1.5-hr. period. The mixture was heated to 65° on a water-bath and stirred for 0.5 hr. while cooling. After standing for several days, the suspension was brought to 60°, filtered, the filtrate concentrated *in vacuo* to 45 ml., and 4 volumes of petroleum ether (35–60°) added. The solution was cooled in the refrigerator. Yellow, slightly gummy precipitate was recovered by filtration and recrystallized from chloroform. Shiny, yellow crystals of 2-thiocyanoimidazoles were obtained in 36% (2.24 g.) yield, m.p. 116–117° (dec.).

Anal. Calcd. for $C_4H_3N_3S$: S, 25.6. Found: S, 25.9.

Method B.—Cyanogen bromide (3.8 g., 0.036 mole) and 2-mercaptoimidazole (1 g., 0.01 mole) were thoroughly mixed in a test-tube, the heat of reaction causing the material to become partially molten. The tube was then placed in a 45–55° water-bath for 0.5–1 hr. When the reaction mixture had become dry and powdery, it was dissolved in 10 ml. of water. This slightly colored solution was treated with activated charcoal, filtered, neutralized with 10% sodium carbonate (immediate precipitation) and placed in the cold overnight. The crude product was then filtered from solution and recrystallized twice from chloroform. Shiny white crystals, microscopic or long needle-like plates, of 2-thiocyanoimidazole were obtained, yield 0.3 g. (24%), m.p. 119–120° (dec.).

Anal. Calcd. for $C_4H_3N_3S$: S, 25.6; C, 38.4; H, 2.42; N, 33.6. Found: S, 25.9; C, 38.3; H, 2.58; N, 32.5.[9]

2-Thiocyanoimidazole Hydrochloride.—An ethanolic solution of 2-thiocyanoimidazole was saturated with hydrogen chloride, a white precipitate of the hydrochloride forming; m.p. 195–196° (dec.).

Anal. Calcd. for $C_4H_3N_3S \cdot HCl$: H^+, 0.62. Found: H^+, 0.59.

4(5)-Methyl-2-thiocyanoimidazole.—Cyanogen bromide (3.1 g., 0.029 mole), and 4(5)-methyl-2-mercaptoimidazole, (1 g. 0.009 mole), were thoroughly mixed in a test-tube, the heat of reaction melting part of the material. As in method B above, the tube was heated (45–55°) for 0.5–1 hr. and the powdery reaction product dissolved in 10 ml. of water. After treatment with charcoal, the filtered solution was neutralized with 10% sodium carbonate (immediate precipitation), and placed in the cold overnight. This crude product was crystallized from warm chloroform with petroleum ether (60–75°) and then recrystallized from a small volume of chloroform. Nearly white, microscopic plates of 4(5)-methyl-2-thiocyanoimidazole were obtained, yield 0.72 g. (59%), m.p. 118.5–119° (dec.).

Anal. Calcd. for $C_5H_5N_3S$: S, 23.0; C, 43.1; H, 3.59; N, 30.2. Found: S, 23.3; C, 42.7; H, 3.55; N, 29.0.

(3) K. K. Koessler and M. T. Hanke, *J. Biol. Chem.*, **39**, 497 (1919).
(4) I. E. Balaban and H. King, *J. Chem. Soc.*, 1858 (1927).
(5) I. W. Grote, *J. Biol. Chem.*, **93**, 25 (1931).
(6) J. L. Wood in Adams' "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 240.
(7) All melting points are corrected.
(8) R. A. F. Bullerwell and A. Lawson, *J. Chem. Soc.*, 3030 (1951).
(9) The low nitrogen values of these compounds are not surprising in view of the difficulties inherent with analysis of thiocyano derivatives.

Degradation of 4(5)-Methyl-2-thiocyanoimidazole.—About 0.7 g. of 4(5)-methyl-2-thiocyanoimidazole was dissolved in 5 ml. of 4% hydrochloric acid and the solution treated with zinc. After standing overnight, a precipitate had formed which was slightly gray due to undissolved zinc. It was extracted with 95% ethanol, the extract being concentrated to a small volume and treated with water to yield a white product, the zinc chloride complex of 4(5)-methyl-2-mercaptoimidazole, m.p. 223° (dec.). This material gave an immediate orange color with methanolic gold chloride[4] and produced no depression of melting point when mixed with an authentic sample prepared as below.

When solid zinc chloride was added to a suspension of 4-methyl-2-mercaptoimidazole in 4% hydrochloric acid, solution occurred, followed almost immediately by precipitation. The white product, after washing with ethyl acetate and chloroform melted at 221° dec. This material also gave a deep orange color with methanolic gold chloride.

1-Methyl-2-thiocyanoimidazole.—Cyanogen bromide (1.2 g., 0.011 mole) and 1-methyl-2-mercaptoimidazole (0.4 g., 0.0035 mole) were thoroughly mixed, heated at 50–65° for 0.5–1 hr., and then allowed to stand for several hours. The resulting powder was dissolved in 4 ml. of water, the solution was neutralized with 10% sodium carbonate (no precipitation) and then continuously extracted with ether for 14 hr. Concentration of this ether extract yielded a slightly yellowish oil which solidified on cooling. This semi-solid material, 1-methyl-2-thiocyanoimidazole, contaminated with 1-methyl-2-mercaptoimidazole, was repeatedly extracted with warm petroleum ether (35–60°). Concentration of the petroleum ether extracts to dryness *in vacuo* resulted in white microscopic plates of pure 1-methyl-2-thiocyanoimidazole, yield 210 mg. (43%), m.p. 64–65°. The product yielded no gold chloride test for mercaptoimidazole. Paper chromatographs showed one spot only.

Anal. Calcd. for $C_5H_5N_3$: S, 23.0; C, 43.1; H, 3.59; N, 30.2. Found: S, 22.8; C, 42.9; H, 3.81; N, 29.6.

Imidazole Sulfate.—To a solution of 1 g. (0.015 mole) of imidazole in 8 ml. of dry pyridine was added 1.7 g. (0.015 mole) of thiocyanogen in 25 ml. of nitromethane. Thiocyanogen was prepared from lead thiocyanate and bromine.[5] The solution was mixed by stirring, and after 0.5 hr. the addition of thiocyanogen was repeated. After standing overnight the solution was brought to a boil and 1 volume of acetone was added. The suspension was then cooled and filtered and the somewhat gummy precipitate was washed with acetone. It was recrystallized from boiling ethanol, using charcoal to decolorize the solution, giving a white, crystalline product, imidazole sulfate, m.p. 84–85°, yield 0.97 g. (56%). In aqueous solution this compound gave an immediate white precipitate with barium chloride or benzidine hydrochloride.

Anal. Calcd. for $2C_3H_4N_2 \cdot H_2SO_4$: S, 13.67. Found: S, 13.64.

The same compound was prepared by addition of sulfuric acid to an ethanolic imidazole solution, m.p. 84–85°.

Histamine Sulfate.—To 100 ml. of dry pyridine was added 1 g. (0.0054 mole) of histamine dihydrochloride, most of which was dissolved. This suspension was treated with 1.8 g. (0.016 mole) of thiocyanogen in 30 ml. of nitromethane. The solution, which rapidly turned reddish, was stirred for complete mixing and allowed to stand overnight. A precipitate formed; the suspension was brought to a boil, a small amount of nitromethane added and the mixture was cooled. The precipitate was removed by filtration, washed with acetone and recrystallized three times from ethanol–water, using charcoal for decolorization. White needles of histamine sulfate were obtained, m.p. 254° (dec. 254–255°), yield 0.45 g. (39%). In aqueous solution this compound gave an immediate precipitate with barium chloride or benzidine hydrochloride.

Anal. Calcd. for $C_5H_9N_3 \cdot H_2SO_4$: S, 15.33. Found: S, 15.31.

The same compound was prepared by addition of pyridine and sulfuric acid to an ethanol–water solution of histamine dihydrochloride, m.p. 252° dec.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

A New Method of Preparing Substituted Thiophenols

BY A. H. HERZ[1] AND D. S. TARBELL

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Attempts to carry out Friedel–Crafts acylations of diphenyl disulfide or formaldehyde diphenyl mercaptal were unsuccessful; however, it was shown that the readily formed addition product of a thiophenol and 3-nitrobenzalacetophenone is amenable to electrophilic substitution, and that this substituted addition product may be nearly quantitatively converted to the correspondingly substituted thiophenol. It was demonstrated by the preparation of acetylated, brominated and nitrated thiophenols that this scheme constitutes a general method for the preparation of electrophilically substituted thiophenols.

Thiophenols and their esters, in marked contrast to phenols, have been found to give ordinary electrophilic substitution reactions only in exceptional cases. Attempts to nitrate or to brominate thiophenols give first the disulfides,[2] which may undergo some nuclear substitution; the nuclear acylation of thiophenol, either directly,[3] or *via* the Fries reaction on the ester,[4] has been unsuccessful. There seem to be almost no examples of electrophilic substitution in thiophenol esters.[5]

This resistance of thiophenols and their esters to electrophilic substitution makes it usually necessary to prepare substituted thiophenols by introducing the substituents before the thiol group.[6]

This problem of nuclear substitution in thiophenols arose in connection with our previous work.[4] It might be expected that diphenyl disulfide would undergo general electrophilic substitution satisfactorily, since it brominates well[2a,7]; Friedel–Crafts acetylation, however, does not occur with aluminum chloride and acetyl chloride[3]; with aluminum bromide and acetyl chloride, we have

(1) Eastman Kodak Fellow, 1952–1953.

(2) (a) E. Bourgeois and A. Abraham, *Rec. trav. chim.*, **30**, 422 (1911); (b) T. Van Hove, *Bull. soc. chim. Belg.*, **36**, 548 (1927); **37**, 88 (1928).

(3) G. B. Bachman and C. L. Carlson, THIS JOURNAL, **73**, 2857 (1951); the only case we have noted in which direct nuclear acylation is successful is 3-methoxythiophenol (German Patent 202,632; *Chem. Zentr.*, **79**, II, 1659 (1908), and ref. 4 below).

(4) D. S. Tarbell and A. H. Herz, THIS JOURNAL, **75**, 1668 (1953).

(5) *Cf.* E. Gehauer-Fülnegg and F. Meissner, *Monatsh.*, **50**, 59 (1928), for the chlorsulfonation of phenyl thiolacetate: chlorination of phenyl thiolbenzoate does not give simple nuclear substitution (R. Schiller and R. Otto, *Ber.*, **9**, 1634 (1876)).

(6) R. Connor, in Gilman's "Organic Chemistry," Second Edition, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 844 ff.

(7) T. Zincke and W. Frohneberg, *Ber.*, **43**, 837 (1910); the dibromodiphenyl disulfide is readily reduced to the *p*-bromothiophenol.