5-Thiocyano-8-quinolinol

BY QUINTUS FERNANDO, J. F. EMERY AND J. P. PHILLIPS

The product of thiocyanation of 8-quinolinol was shown to be 5-thiocyano-8-quinolinol. The absorption spectrum, acid-base properties and reaction with alkali of this compound were examined. The solubilities of its metal chelate compounds agreed with qualitative predictions based on the properties of other substituted 8-quinolinols. Thiocyanic acid salts of some substituted 8-quinolinols were prepared.

Although the reaction of 8-quinolinol with thiocyanogen has been reported[1] to yield 4-thiocyano-8-quinolinol, the pseudohalogen properties of thiocyanogen would instead be expected to cause substitution para to the phenolic hydroxyl group giving 5-thiocyano-8-quinolinol. This expectation was substantiated by obtaining the same compound from the Sandmeyer reaction of diazotized 5-amino-8-quinolinol with cuprous thiocyanate. Further evidence was supplied by oxidizing the thiocyano compound with nitric acid to quinolinic acid; if the thiocyano group were in the 4-position, this product would not be obtained.

The absorption spectrum of 5-thiocyano-8-quinolinol in 0.1 N hydrochloric acid was very much like that of 8-quinolinol[2]; absorption maxima were found at 254, 319 and 358 mμ with molecular extinctions of 41000, 2400 and 3000, respectively. The variation in light absorption with pH of solutions of 5-thiocyano-8-quinolinol showed the existence of a hydrochloride, free base and sodium salt; approximate values of pK_a and pK_b computed graphically from these data (Fig. 1) were 8.2 and 10.6, respectively, indicating that this compound is more acidic and less basic than 8-quinolinol.[3] In strongly alkaline solutions (pH 11–12) a further change in spectrum was noted, probably representing hydrolysis of the thiocyano group. On standing in alkali changes in absorption with time occurred, and after several hours there was precipitation of a compound presumed to be the disulfide.

To confirm the interpretation of the effects of alkali a comparison was made with the light absorption of p-thiocyanodimethylaniline solutions when subjected to the same pH variations. From the acidic and neutral solution measurements (Fig. 1) a pK_b value of 10.7 for p-thiocyanodimethylaniline was obtained, this being apparently the first such measurement on this compound. In slightly basic solutions no further changes in absorption occurred because the compound contains no phenolic group; in stronger alkali (pH 11) there was precipitation of the disulfide, so that no measurements could be made.

Bis-(8-hydroxy-5-quinolyl) disulfide was then prepared by boiling 5-thiocyano-8-quinolinol with alcoholic potassium hydroxide in the presence of air. It was also obtained as one of the products of the Sandmeyer reaction of diazotized 5-amino-8-quinolinol with cuprous thiocyanate, a result in accord with the behavior of some other aromatic amines.[4]
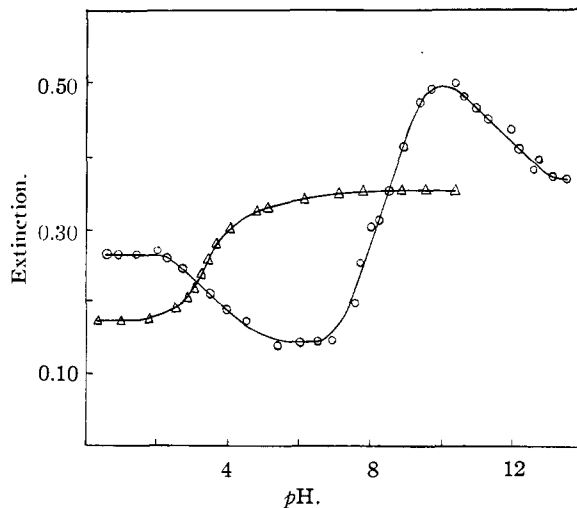
(1) P. Kaufmann and E. Weber, Arch. Pharm., **267**, 192 (1929).

(2) J. P. Phillips, W. H. Huber, J. W. Chung and L. L. Merritt, THIS JOURNAL, **73**, 630 (1951).

(3) J. P. Phillips and L. L. Merritt, ibid., **70**, 410 (1948).

(4) F. Challenger and A. D. Collins, J. Chem. Soc., **125**, 1379 (1924).

Fig. 1.—Variation of extinction as a function of pH: ⊙, 5-thiocyano-8-quinolinol at 280 mμ; △, p-thiocyanodimethylaniline at 250 mμ.

In some preliminary thiocyanation experiments the addition of 8-quinolinol to acetic acid containing potassium or ammonium thiocyanate was found to yield a crystalline precipitate within a minute or two. Analysis indicated that the precipitate was the thiocyanic acid salt of 8-quinolinol. The compound is a true salt, dissolving in water, giving a red color with ferric ion and possessing a different crystal habit from 5-thiocyano-8-quinolinol. A series of thiocyanic acid salts of some substituted 8-quinolinols were prepared readily by the same method (Table I) and seem to be practically ideal characterization derivatives.

TABLE I

THIOCYANIC ACID SALTS OF SUBSTITUTED 8-QUINOLINOLS

Substituent	Yield, %	M.p., °C.	Sulfur, % Calcd.	Sulfur, % Found
None	76	147	15.7	15.7, 15.6[a]
2-Methyl	85	158	14.7	14.4, 14.7[a]
3-Methyl	58	166	14.7	14.6, 14.9[a]
4-Methyl	77	203	14.7	14.5
2,3-Dimethyl	82	219	13.8	13.6
2-Phenyl	..	162	11.4	11.0
2-Styryl	97	196	10.4	10.1
2-Methyl-5,7-dibromo	71	159	8.5	8.4

[a] Analyzed by Parr bomb method as well as by the Volhard method.

The fact that 5-thiocyano-8-quinolinol is more acidic than 8-quinolinol should mean that its chelate compounds are quantitatively insoluble in more acidic solutions than are the chelate compounds of

8-quinolinol.[5,6] To test this hypothesis the chelate compounds with zinc, cupric, magnesium, ferric and aluminum ions were prepared. With the exception of the magnesium salt these compounds were all sufficiently soluble in chloroform to obtain their absorption spectra (Fig. 2). The water solubilities at various pH values were measured by the spectrophotometric method previously described.[6]
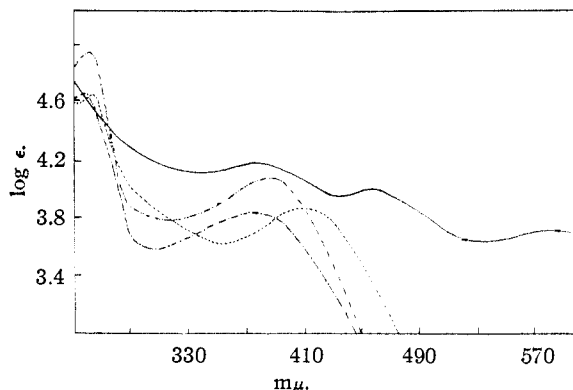

Fig. 2.—Absorption spectra of 5-thiocyano-8-quinolinol chelate compounds in chloroform: —, ferric; – –, cupric; –·, zinc, –··, aluminum.

The results (Table II) may not be considered as having the highest utility for comparative purposes because the ionic strengths of the solutions varied; nevertheless, it is clear that these chelate compounds are quantitatively insoluble at pH values low enough for the corresponding oxinates not to be completely precipitated.[7] All the chelate compounds were found to dissolve completely if the solutions were made sufficiently acid, and, with the zinc and aluminum compounds, measurements were made to high enough pH values to find that they would probably also dissolve in alkali. This tendency of solubility to a minimum in neutral solution has been claimed to be characteristic of chelated metal complexes generally.[8]

TABLE II

SOLUBILITY OF CHELATE COMPOUNDS OF 5-THIOCYANO-8-QUINOLINOL

Aluminum		Ferric		Cupric		Zinc	
	Molarity		Molarity		Molarity		Molarity
pH	× 10⁶	pH	× 10⁶	pH	× 10⁶	pH	× 10⁶
2.4	12.8	1.6	9.6	1.7	32.0	2.8	19.2
2.7	8.5	2.0	6.7	2.0	24.1	3.0	13.7
3.5	2.8	2.6	4.3	2.3	20.0	3.9	6.4
4.5	1.7	3.0	2.1	3.1	6.2	4.6	3.5
10.5	11.0	4.1	0.9	3.9	5.3	11.0	4.8

Experimental

5-Thiocyano-8-quinolinol.—Thiocyanogen (0.01 mole), prepared by the addition of bromine to lead thiocyanate suspended in carbon tetrachloride,[9] was added to 1.45 g. (0.01 mole) of 8-quinolinol dissolved in the minimum volume of carbon tetrachloride. The solution was allowed to stand overnight and then was filtered to remove polymerized material. The carbon tetrachloride solution was concentrated to about 25 ml. and cooled. Yellow needles (0.4 g., 20%) separated, which after two recrystallizations from isopropyl alcohol melted at 147°. The compound gave no color with ferric ion in acid solution. Calcd. for $C_{10}H_6N_2OS$: N, 13.86; S, 15.86. Found: N, 13.82; S, 15.72.

Good results were also obtained if the thiocyanogen was generated by adding bromine to dry potassium thiocyanate suspended in carbon tetrachloride. Attempts to thiocyanate by generating thiocyanogen with bromine in the 8-quinolinol solution gave an impure product with a low melting point.

Quinolinic Acid.—Oxidation of 5-thiocyano-8-quinolinol with nitric acid was performed by Sucharda's method.[10] The product was quinolinic acid as indicated by crystal habit, m.p. 190° with decomposition, and undepressed mixed m.p. with authentic sample. The copper salt was also prepared.

Preparation of Disulfide.—Refluxing 5-thiocyano-8-quinolinol in 20% alcoholic potassium hydroxide for four hours gave, after cooling and neutralizing with dilute acetic acid, a yellow precipitate of bis-(8-hydroxy-5-quinolyl) disulfide which was recrystallized from ethanol; m.p. 215°, yield 20%. Calcd. for $C_{18}H_{12}N_2O_2S_2$: S, 18.2. Found: S, 18.3. Absorption maxima in 0.1 N hydrochloric acid: 254, 385 mμ.

Sandmeyer Reaction.—5-Amino-8-quinolinol sulfate (10 g.) was diazotized with sodium nitrite and sulfuric acid and 12 g. of potassium thiocyanate and 15 g. of cuprous thiocyanate added. The solution was allowed to stand until evolution of nitrogen ceased (3 hr.); the reaction was completed by warming for 30 minutes on a water-bath. If the precipitate after filtration was extracted with chloroform, a. yellow solid (0.2 g.) was obtained on concentrating the solution. This substance had a m.p. and mixed m.p. with 5-thiocyano-8-quinolinol of 141°. If the precipitate was extracted with hot alcohol instead of chloroform, the product (0.5 g.) was identical with the bis-(8-hydroxy-5-quinolyl) disulfide described above, m.p. 215°.

Chelate Compounds of 5-Thiocyano-8-quinolinol.—To an acid solution containing 0.003 mole of cupric, zinc, magnesium, ferric or aluminum ion was added a 5% excess of 5-thiocyano-8-quinolinol. The pH was raised by adding dilute ammonia slowly and with stirring until precipitation was judged to be complete. After standing for two hours the precipitates were filtered, washed with about 4 liters of water each and finally dried at room temperature over magnesium perchlorate. Analysis for water by heating weighed samples at 105° to constant weight indicated 2, 2, 3, 2 and 4 molecules of water for the copper, magnesium, zinc, aluminum and ferric salts, respectively, although it is not necessarily true that these values represent water of hydration. By ignition to the metal oxides the analyses for metal content were obtained. Calcd. for $Cu(C_{10}H_6N_2OS)_2 \cdot 2H_2O$: Cu, 12.7; found, 12.6; for $Mg(C_{10}H_6N_2OS)_2 \cdot 2H_2O$: Mg, 5.26; found, 5.25; for $Zn(C_{10}H_6N_2OS)_2 \cdot 3H_2O$: Zn, 12.5; found, 12.4; for $Al(C_{10}H_6N_2OS)_3 \cdot 2H_2O$: Al, 4.05; found, 4.11; for $Fe(C_{10}H_6N_2OS)_3 \cdot 4H_2O$: Fe, 7.65; found, 7.50.

Thiocyanic Acid Salts.—Salts of the 8-quinolinols listed in Table I were prepared by the following general procedure: To 0.5 g. of the 8-quinolinol dissolved in the minimum amount of glacial acetic acid (usually about 5 ml.) was added an equal volume of a saturated solution of potassium thiocyanate in acetic acid. In less than five minutes a precipitate formed. After filtration the salt was recrystallized from acetic acid.

Spectrophotometric Measurements.—All spectra were determined with a Beckman DU spectrophotometer using 1.00-cm. silica cells.

The variation of extinction at 280, 330 and 350 mμ of 0.002% solutions of 5-thiocyano-8-quinolinol with pH was measured. About thirty solutions ranging in pH from 1 to 13 were employed. A similar study of p-thiocyanodimethylaniline was performed at 240 and 250 mμ using a 0.005% solution. Details of the method have been reported before.[3] The solubilities of the metal chelate compounds measured at 30 ± 0.1° were obtained by spectrophotometric determination of the amount dissolved in a saturated solution by the method detailed previously.[6]

(5) J. P. Phillips and L. L. Merritt, THIS JOURNAL, 71, 3984 (1949).

(6) J. P. Phillips and H. P. Price, ibid., 73, 4414 (1951).

(7) F. J. Welcher, "Organic Analytical Reagents," Vol. I, D. Van Nostrand Co., Inc., New York, N. Y., 1947, p. 266.

(8) H. F. Walton, "Principles and Methods of Chemical Analysis," Prentice-Hall, Inc., New York, N. Y., 1952, p. 101.

(9) J. L. Wood, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 255.

(10) E. Sucharda, Ber., 58, 1728 (1925).

# Syntheses in the Thiochromanone Field[1]

BY D. S. TARBELL, H. P. HIRSCHLER AND T. J. HALL

The synthesis of 5-phenyl-8-methoxythiochromanone by the hydrogen fluoride cyclization of β-carboxyethyl 4-methoxy-3-xenyl sulfide is described. The latter has been prepared by the addition of the appropriate thiophenol to methyl acrylate, or, more conveniently, by the action of diazotized 3-amino-4-methoxybiphenyl on β-mercaptopropionic acid in an acetate buffer. Study of the cleavage of the thiochromanone ring to form a vinyl ketone group, either in the above compound or in 5,6-benzothiochromanone and the corresponding sulfone, indicates that it is not a synthetically useful reaction.

The experiments described in this paper were undertaken to explore a possible route for the synthesis of N-acetylcolchinol methyl ether (I), an important degradation product of colchicine.[2] Previously, attempts to prepare the ketone II as a precursor of I by cyclization of the biphenyl-propionic acid III had failed, because the bromine atom in III, put in as a blocking group, migrated during the Friedel–Crafts cyclization, and a 5-ring ketone resulted,[3] instead of the desired 7-ring ketone II.

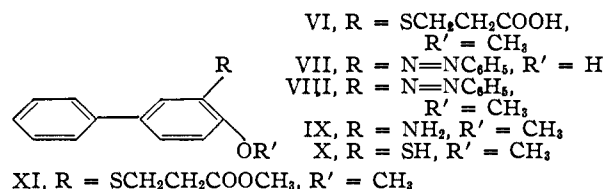I, R = H, R′ = NHCOCH₃
II, R = R′ = =O

III
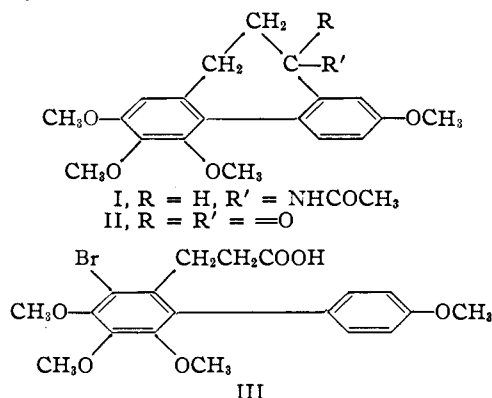
The object of the present work was to prepare a biphenyl with a three carbon chain containing a carbonyl group (potential or actual), and another functional group which would allow cyclization in the reverse direction from that attempted in III. For this purpose, the vinyl xenyl ketone IV, or the β-hydroxy- or β-haloethyl ketone derived from it, appeared suitable for study. It seemed that IV could be prepared by a basic cleavage[4] of the thiochromanone ring in V, followed by methylation. The –SCH₃ group in IV would be valuable as a blocking group to prevent cyclization to an in-

danone, and it could be easily removed later in the synthesis by Raney nickel desulfuration.[5] Although the thiochromanone V was synthesized, it was not possible to convert it to the vinyl ketone IV, and hence the over-all synthesis was unsuccessful

IV, R = H, R′ = OCH₃, R″ = SCH₃   V, R = OCH₃
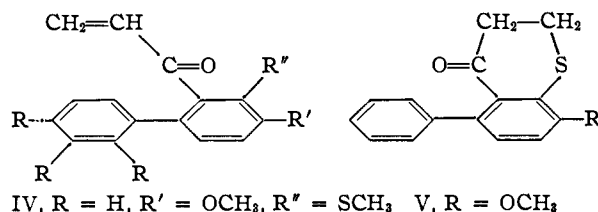
The thiochromanone V was obtained by cyclization of the mercaptopropionic acid derivative VI with anhydrous hydrogen fluoride[6]; the mercaptopropionic acid was prepared as follows. 3-Phenyl-

VI, R = SCH₂CH₂COOH, R′ = CH₃
VII, R = N=NC₆H₅, R′ = H
VIII, R = N=NC₆H₅, R′ = CH₃
IX, R = NH₂, R′ = CH₃
X, R = SH, R′ = CH₃
XI, R = SCH₂CH₂COOCH₃, R′ = CH₃

azo-4-hydroxybiphenyl (VII) was methylated with an excess of alkali and methyl sulfate to form the methoxy compound VIII, and the azo group was reductively cleaved with hydrogen and platinum, yielding 3-amino-4-methoxybiphenyl (IX). The latter was also prepared by catalytic reduction of 3-nitro-4-methoxybiphenyl,[7] but the synthesis through the phenylazo compound was much more satisfactory. The amino group was converted to the thiophenol X through the xanthate procedure, and the thiophenol added smoothly to methyl acrylate in the presence of piperidine, giving the mercaptopropionic ester XI. This ester could not

(1) Aided by a grant from the National Institutes of Health.

(2) While this work was in progress, the synthesis of dl-I was reported by H. Rapoport, A. R. Williams and M. E. Cisney, THIS JOURNAL, **72**, 3324 (1950); **73**, 1414 (1951), while the l-form of I, obtainable by degradation of colchicine, was synthesized by J. W. Cook, et al., Chem. and Ind., 650 (1950); J. Chem. Soc., 1397 (1951).

(3) H. R. Frank, P. E. Fanta and D. S. Tarbell, THIS JOURNAL, **70**, 2314 (1948); H. T. Huang, D. S. Tarbell and H. R. V. Arnstein, ibid., **70**, 4181 (1948); N. Barton, J. W. Cook and J. D. Loudon, J. Chem. Soc., 1079 (1949).

(4) Cf. (a) D. S. Tarbell and D. P. Harnish, Chem. Revs., **49**, 6, 24 (1951); (b) B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(5) The projected synthesis is somewhat similar to the method for the formation of indanones by cyclization of Mannich bases of aryl alkyl ketones described by J. H. Burckhalter and R. C. Fuson, ibid., **70**, 4184 (1948).

(6) Numerous other methods of cyclization, including stannic chloride or aluminum chloride and the acid chloride, the inverse Friedel–Crafts procedure (W. S. Johnson and H. W. Glenn, ibid., **71**, 1092 (1949)), polyphosphoric acid (H. R. Snyder and F. X. Werber, ibid., **72**, 2962, 2965 (1950)), fluosulfonic acid (W. Baker, et al., J. Chem. Soc., 1376 (1951)), and others, were unsuccessful.

(7) F. Bell and J. Kenyon, ibid., 3047 (1926).