[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

THIOCARBONYLS. V. N-METHYL-4-THIOQUINOLONE DERIVATIVES

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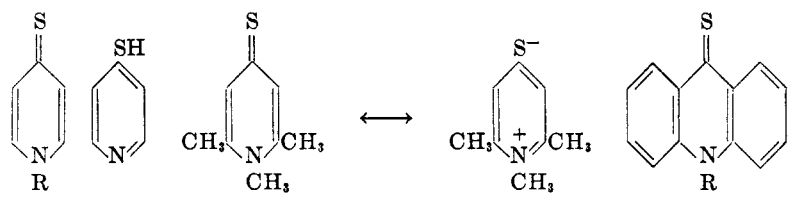
Received November 14, 1949

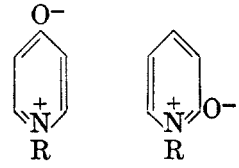
Efforts to synthesize nitrogen heterocyclic thiones usually lead to the formation of mercaptans unless the nitrogen atom is substituted. King and Ware (1) treated 4-pyridone with phosphorus pentasulfide and obtained a yellow, water-soluble, high-melting, salt-like substance which they regarded as 4-thiopyridone (I, R = H). I reacted with methyl iodide to yield 4-methylmercaptopyridine hydriodide. The properties of I indicate that it exists entirely as 4-mercaptopyridine (Ia). Gleu and Schaarschmidt (2) found similarly that thioacridones gave exclusively the S-alkyl derivatives upon alkylation and concluded that they exist principally in the thiol form. Surrey (3) points out that although 4-amino- and 4-hydroxy-quinoline form 1-quinolineacetic acids with chloroacetic acid, 4-mercaptoquinoline yields 4-quinolylmercaptoacetic acid under the same conditions. This reaction indicates a greater degree of aromatic resonance in 4-mercaptoquinoline than in 4-hydroxyquinoline. Renfrew (4) suggests that the darker color and greater degree of solubility in organic solvents exhibited by 4-mercaptoquinolines indicate a greater shift toward the thione form than is found in the 2-mercaptoquinolines.

Several N-substituted nitrogen heterocyclic thiones have been synthesized, however. Kendall (5) prepared N-methyl-4-thiopyridone (I, R=CH_3) from 4-methylmercaptopyridine by heating the quaternary methyl tosylate in pyridine. Michaelis and Holken (6) synthesized N-methyl-4-thiolutidone (II) by treating 4-chlorolutidine methiodide with two equivalents of potassium bisulfide. Gleu and Schaarschmidt (2) obtained almost quantitative yields of N-substituted thioacridones (III, R=CH_3, C_2H_5, C_6H_5) when the appropriate N-substituted-9-chloroacridinium dichlorophosphate was treated with sodium bisulfide or sodium thiosulfate in water solution.



[1] From a thesis submitted by Richard E. Cline to the Graduate School of Indiana University in partial fulfillment of the requirements for the degree, Master of Arts in Chemistry. For the fourth paper in this series, see *J. Org. Chem.*, **12**, 807 (1947).

It is probable that even the N-substituted thiones exist primarily in the aromatic ionic form. Bergstrom (7) points out that the ultraviolet absorption spectra of N-alkylpyridones indicate that the aromatic ring is still present, and suggests that these compounds are best illustrated by formulas such as IV and V.

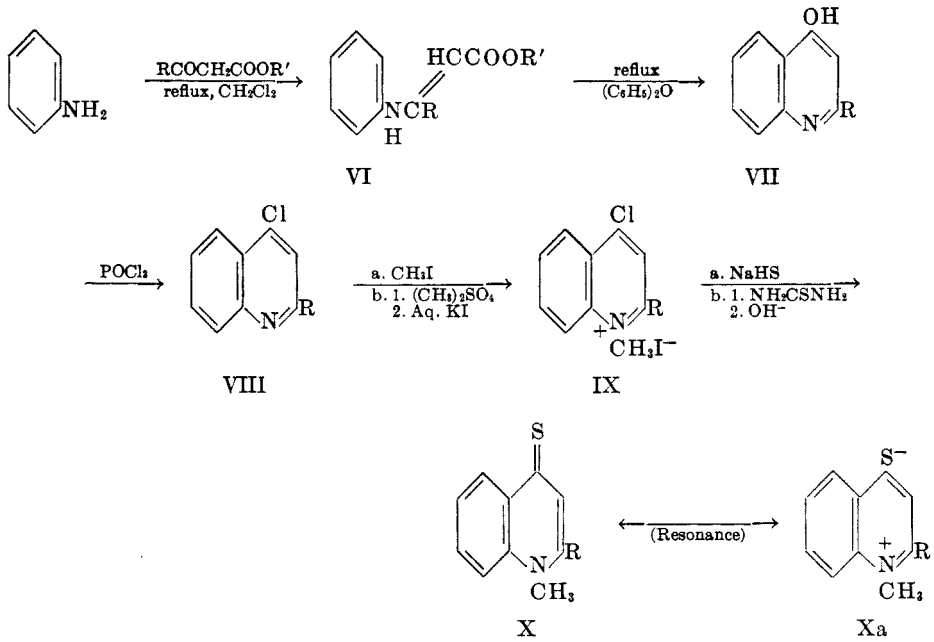


IV V

In view of the decreased tendency of sulfur to form double bonds, and the greater acidity of mercaptans, one would expect even more of the ionic aromatic structure in thiopyridones than in pyridones. Michaelis and Holken (6) suggest that N-methyl-4-thiolutidone exists in a salt form (IIa), since it reacts with methyl iodide to produce 4-methylmercaptolutidine methiodide, rather than N,N-dimethyl-4-thiolutidone iodide.

Although both 4-thiopyridones and thioacridones have been prepared, no N-alkyl-4-thioquinolones have been reported in the literature. Recent interest in sulfur-containing quinolines (3, 4, 8) and our concern with thiocarbonyl derivatives (9) led us to prepare N-methyl-4-thioquinolone (X, R=H), N-methyl-4-thioquinaldone (X, R=CH_3), N-methyl-2-phenyl-4-thioquinolone (X, R=C_6H_5), and N-methyl-2-carbethoxy-4-thioquinolone (X, R = $COOC_2H_5$). Methods of synthesizing N-heterocyclic thiones have been reviewed (9). It was apparent that the most promising methods of synthesizing the 4-thioquinolone derivatives involved treating a 4-haloquinolinium salt with a sulfurizing agent such as bisulfide, thiosulfate, or thiourea.

The 4-chloroquinolines involved in the preparation of the 4-thioquinolones were obtained through well-known methods of synthesis. 4-Chloroquinaldine was produced in an over-all yield of 65% through the Conrad-Limpach procedure (10) for the preparation of 4-hydroxyquinaldine, and was then treated with phosphoryl trichloride. Both 4-chloroquinoline and 2-carbethoxy-4-chloroquinoline were obtained from 2-carbethoxy-4-hydroxyquinoline; the latter substance was prepared through the Lisk and Stacy (11) method of condensing aniline and oxalacetic ester and ring closure of the ethyl β-anilino-β-carbethoxyacrylate in boiling phenyl ether. 2-Carbethoxy-4-hydroxyquinoline was saponified and the 4-hydroxyquinaldic acid decarboxylated in boiling phenyl ether to give a 57% over-all yield of 4-hydroxyquinoline. The condensation of aniline and ethyl benzoylacetate in boiling chloroform and ring-closure of the ethyl β-anilino-β-phenylacrylate in boiling phenyl ether gave 2-phenyl-4-hydroxyquinoline which was converted to 2-phenyl-4-chloroquinoline in an over-all yield of 48%.



The character of the group in the 2-position has a definite influence, both on the synthesis and the properties of the thiones. The groups used in this study were either electron-attracting or electron-releasing, the order of electron-attraction being:

$$COOC_2H_5 > C_6H_5 > H > CH_3$$

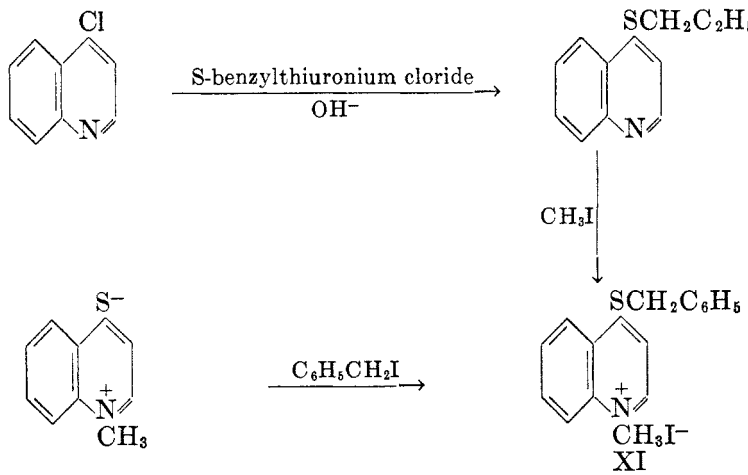
This gradation in influence is apparent in the formation of the quinolinium salts. Thus 4-chloroquinaldine methiodide and 4-chloroquinoline methiodide were obtained in nearly quantitative yield by allowing the respective quinoline derivatives to react with methyl iodide for several days at room temperature. The 2-phenyl- and 2-carbethoxy-4-chloroquinolines did not react under these conditions. 2-Phenyl-4-chloroquinoline methiodide was prepared by heating 2-phenyl-4-chloroquinoline with methyl sulfate and treating the impure methosulfate salt with aqueous potassium iodide. All attempts to isolate a pure quinolinium salt of 2-carbethoxy-4-chloroquinoline failed.

The thiones were readily prepared by treating the 4-chloroquinolinium salts in alcohol solution with either sodium or potassium bisulfide, or thiourea. In the first experiments potassium hydrosulfide was prepared by passing hydrogen sulfide into an alcoholic solution of potassium ethoxide, but later it was found that a commercial grade of solid sodium hydrosulfide gave equally satisfactory results.

The reaction with sodium hydrosulfide was found to give the best and most consistent results, except with 2-carbethoxy-4-chloroquinoline. In this case

apparently the alkaline reagent hydrolyzed the ester linkage, and no product was isolated. When the quinolinium salt (either methiodide or methosulfate) was treated with thiourea in alcohol, a precipitate was obtained, which is probably a thiuronium salt. The thiuronium salt obtained from 2-carbethoxy-4-chloroquinolinemethosulfate hydrolyzed at once when added to water, to form the thioquinolone, but the thiuronium salts from 4-chloroquinoline methiodide and 4-chloroquinaldine methiodide required dilute alkali for hydrolysis.

The properties of the 4-thioquinolones bear out the observation that even in the N-alkylheterocyclic thiones the aromatic resonance form (Xa) is a major contribution to the structure. The influence of this contribution is decreased, however, by electron-attracting groups in the 2-position. Thus the melting points decrease as R varies in electron-releasing character from $CH_3 > H > C_6H_5 > COOC_2H_5$, indicating a decrease of the ionic form of the compound (Xa). The colors change from bright yellow through yellow, orange, and red-orange in the same way, indicating a greater contribution of the chromophoric thione structure (X). All of the thioquinolones form white hydrochlorides when benzene solutions are treated with dry hydrogen chloride. However, only the N-methyl-4-thioquinaldone hydrochloride could be filtered out. The other white hydrochlorides evolved hydrogen chloride and reverted to the yellow free bases in air. The solubility of the free bases in dilute hydrochloric acid decreased as R varied from methyl to carbethoxyl, N-methyl-2-carbethoxy-4-thioquinolone being completely insoluble. The product formed when benzyl iodide was allowed to react with N-methyl-4-thioquinolone was 4-benzylmercaptoquinoline methiodide (XI). This was demonstrated by synthesizing XI in an unequivocal manner from 4-chloroquinoline through 4-benzylmercaptoquinoline, as shown.



XI

The ultraviolet absorption curves (Fig. 1) of the four compounds, taken in methanol on a Model DU Beckman specrophotometer, show a definite, though small, shift toward the visible range as the substituent varies from methyl to

carbethoxyl. This would be the expected effect. The important maxima and minima are tabulated in Table I.

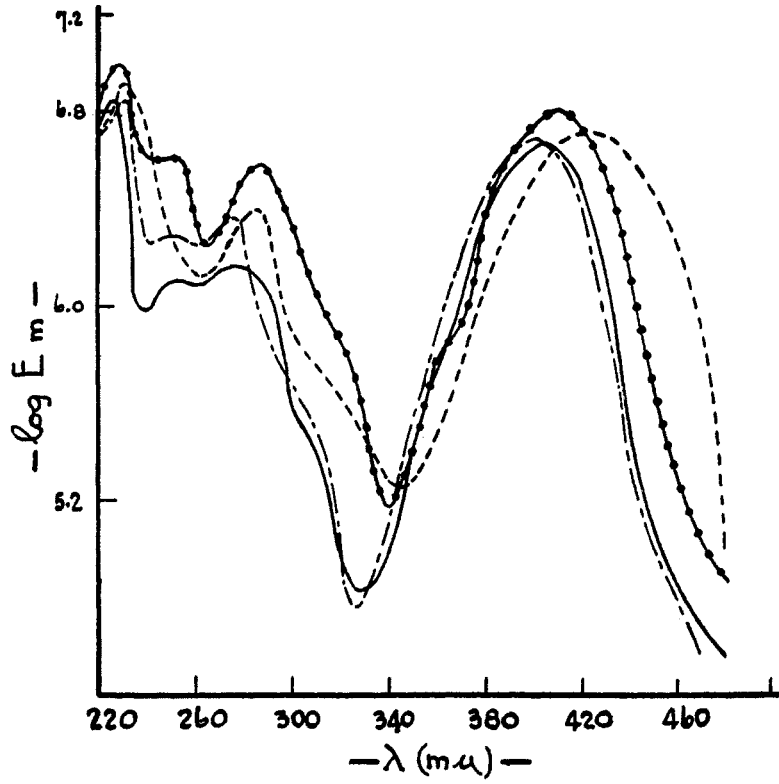


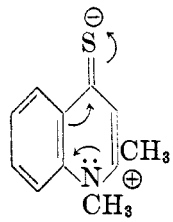
FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (in methanol solution) of 2-substituted-N-methyl-4-thioquinolones (X). — - — - R = methyl; ——— R = hydrogen; —·—·— R = phenyl; -------- R = carbethoxyl.

TABLE I

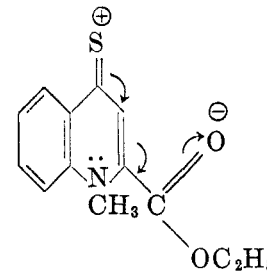
ABSORPTION MAXIMA AND MINIMA OF 2-SUBSTITUTED-N-METHYL-4-THIOQUINOLONES IN MILLIMICRONS

2-SUBSTITUENT	1ST MAXIMUM	MINIMUM	2ND MAXIMUM
Methyl	275	326	401
Hydrogen	275	330	404
Phenyl	286	340	410
Carbethoxyl	286	346	424

The inductive effect of electron-attracting and electron-releasing groups may be pictured as in XII and XIII.



XII



XIII

It can be readily seen that structure XII augments the aromatic resonance contribution, increases ionic character, and provides a center of reactivity on the sulfur atom, whereas structure XIII counteracts the aromatic resonance, and would tend to decrease the negative ionic charge of the sulfur atom. These are the effects observed.

EXPERIMENTAL

4-Chloroquinaldine methiodide (IX, R = CH_3). In an ice-cooled flask 10 g. (0.056 mole) of 4-chloroquinaldine (12) was mixed with 6.2 ml. (8.4 g., 0.066 mole) of dimethyl sulfate. A white precipitate formed at once, but the mixture was heated for a few minutes on a steam-bath to insure completeness of the reaction. Then 20 g. (0.12 mole) of potassium iodide dissolved in 26 ml. of water was added, and a brownish-yellow solid precipitated. After recrystallization from glacial acetic acid, bright yellow needles m.p. 223–224°, and weighing 13.5 g. (0.042 mole, 75%) were obtained. Alekseeva (13) found m.p. 222–223°. The same product was obtained if 4-chloroquinaldine was allowed to stand in excess methyl iodide for 24 hours.

N-Methyl-4-thioquinaldone (X, R = CH_3). A mixture of 4 g. (0.012 mole) of IX (R = CH_3), and 3 g. (0.038 mole) of sodium hydrosulfide[2] in 400 ml. of absolute ethanol was refluxed for 12 hours. Upon cooling, reddish-yellow needles were deposited. These were washed with water, and recrystallized from ethanol, giving 1.96 g. (0.010 mole, 83%) of yellow needles m.p. 224–225° with decomposition. A mixed melting point with IX (R = CH_3) was depressed.

Anal. Calc'd for $C_{11}H_{11}NS$: N, 7.4; S, 16.93.

Found: N, 7.7; S, 17.51.

A solution of X (R = CH_3) in benzene was treated with dry hydrogen chloride until no further precipitation occurred. The white crystalline product, 4-mercaptoquinaldine methochloride, melted at 203–205°.

Anal. Calc'd for $C_{11}H_{12}ClNS$: Cl, 16.35; N, 6.20.

Found: Cl, 16.62; N, 6.05.

4-Chloroquinoline methiodide (IX, R = H). This compound was prepared by adding 47 g. (0.29 mole) of 4-chloroquinoline (14) in 5-ml. portions at 24-hour intervals to 80 ml. of methyl iodide. The methyl iodide solution was cooled before each addition, and then allowed to stand at room temperature. The excess methyl iodide was then removed by evaporation, and the product washed with ether; 79.7 g. (0.26 mole, 90%) of yellow crystals, m.p. 208–210° with decomposition, was obtained. Hamer (14) reported a 62% yield of product melting at 208° by a similar procedure.

N-methyl-4-thioquinolone (X, R = H). A mixture of 4 g. (0.051 mole) of commercial so-

[2] Kindly supplied by the Hooker Electrochemical Company. It contained 28% water of crystallization.

dium hydrosulfide and 5 g. (0.0162 mole) of IX (R = H) in 200 ml. of ethanol was refluxed for 6 hours. Upon cooling, yellow needles of N-methyl-4-thioquinolone were deposited. These were washed with water, yielding 2.75 g. (0.0157 mole, 97%); m.p. 209–210°. A mixed melting point with IX (R = H) was 180–185°.

Anal. Calc'd for $C_{10}H_9NS$: N, 8.0; S, 18.28.

Found: N, 8.01; S, 18.88.

The same compound was obtained when 5 g. (0.016 mole) of IX (R = H) was refluxed in 200 ml. of ethanol with 3 g. (0.04 mole) of thiourea for 5 minutes, and the dark red precipitate (thiuronium salt) filtered, dissolved in 200 ml. of water, and treated with 20 ml. of 10% NaOH. The orange precipitate was recrystallized from ethanol as yellow needles, 1.43 g. (81%); m.p. 208–209°. A mixed melting point with the compound prepared from sodium hydrosulfide was 208–209°.

4-Benzylmercaptoquinoline methiodide (XI). A small amount of X (R = H) was added to excess benzyl iodide and allowed to stand for several days. The yellow precipitate was recrystallized from methanol; m.p. 210–212° with decomposition. This compound gave a positive halogen test with aqueous silver nitrate, and a mixed melting range with N-methyl-4-thioquinolone of 168–210°.

Anal. Calc'd for $C_{17}H_{16}INS$: N, 3.56. Found: N, 3.44.

The same product was obtained when 4-benzylmercaptoquinoline was treated with methyl iodide for several days. 4-Benzylmercaptoquinoline was synthesized from 4-chloroquinoline by the method of Baker, Dodson, and Riegel (8). Refluxing 1.1 g. (0.0067 mole) of 4-chloroquinoline with 1.1 g. (0.0055 mole) of S-benzylthiuronium chloride and 1 g. of KOH in 10 ml. of ethanol for 1½ hours gave, after washing with water and recrystallizing, 1.3 g. (0.0052 mole, 77%) of white crystals of *4-benzylmercaptoquinoline*, m.p. 135–136°.

Anal. Calc'd for $C_{16}H_{13}NS$: S, 12.80. Found: S, 12.54.

N-Methyl-2-phenyl-4-thioquinolone (X, R = C_6H_5). Crude 2-phenyl-4-chloroquinoline methiodide was prepared by heating 3.3 g. of 2-phenyl-4-chloroquinoline (15) and 2 ml. of dimethyl sulfate for four hours at 100–120°. When cooled, the transparent glassy solid was boiled with 6 g. of potassium iodide in 9 ml. of water for several hours, and the oily layer allowed to crystallize. A mixture of 2 g. of the yellow needles so obtained, 3 g. of commercial sodium hydrosulfide, and 225 ml. of absolute alcohol was refluxed for 12 hours. The N-Methyl-2-phenyl-4-thioquinolone crystallized from the cooled reaction mixture, and after washing with water, was recrystallized from methanol in yellow-orange needles, m.p. 175–176°; weight 0.74 g. (0.0028 mole, 56%).

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.6; S, 12.74.

Found: N, 5.4; S, 12.96.

The same product was obtained in 30% yield when the crude 4-chloro-2-phenylquinoline methosulfate was treated with alcoholic potassium bisulfide.

2-Carbethoxy-4-chloroquinoline (VIII, R = $CO_2C_2H_5$). Four grams (0.018 mole) of 2-carbethoxy-4-hydroxyquinoline (16) was mixed with 8.4 g. (0.055 mole) of phosphoryl trichloride and allowed to stand at room temperature until the reaction ceased. Before pouring the reaction mixture into ice-water, the gummy material was dissolved by the addition of 10 ml. of absolute ethanol. After neutralization, the solid was recrystallized from dilute acetone as white needles. The yield of 2-carbethoxy-4-chloroquinoline was 3.2 g. (74%), m.p. 85–86°.

Anal. Calc'd for $C_{12}H_{10}ClNO_2$: N, 5.94. Found: N, 6.03.

N-Methyl-2-carbethoxy-4-thioquinolone (X, R = $COOC_2H_5$). Since a crystalline methiodide could not be isolated, the crude methosulfate was reacted directly with thiourea. A mixture of 3 ml. (0.03 mole) of dimethyl sufate and 2.7 g. (0.0096 mole) of 2-carbethoxy-4-chloroquinoline was heated at 110–120° for 15 minutes. The dark brown oil was added to 50 ml. of ethanol containing a large excess of thiourea. After refluxing about ten minutes, it was poured into 200 ml. of water and the crystals recrystallized from ethanol as red-orange needles, weighing 0.9 g. (0.0036 mole, 37%); m.p. 140–141°.

Anal. Calc'd for $C_{13}H_{13}NO_2S$: N, 5.67; S, 12.95.

Found: N, 5.84; S, 12.59.

SUMMARY

N-methyl-4-thioquinolone, and its analogs containing the methyl, phenyl, and carbethoxyl groups in the 2-position have been synthesized.

The properties of these compounds are those of the ionic aromatic structure, but electron-attracting groups in the 2-position decrease this resonance contribution. An electronic interpretation is discussed.

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