[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

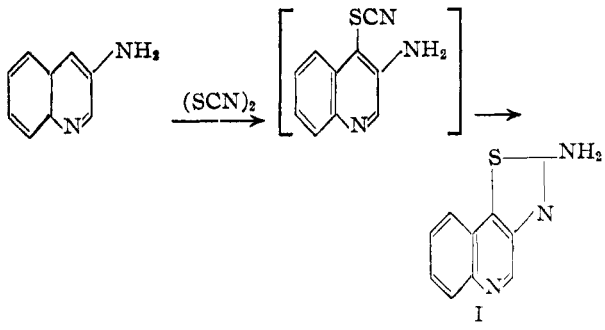
The Reaction of Thiocyanogen with Nitrogen Heterocycles; Pyridines, Pyrmidines and Quinolines[1]

BY ALLISON MAGGIOLO[2]

Investigation of the reaction of thiocyanogen with a variety of nitrogen heterocyclic compounds showed that thiocyanation can readily occur if there is a sufficient number of strong "electron donating" groups present in the heterocyclic compound. Cyclization of those which were *o*-aminothiocyano compounds enables new or heretofore otherwise difficulty accessible condensed thiazolo nitrogen ring systems to be realized.

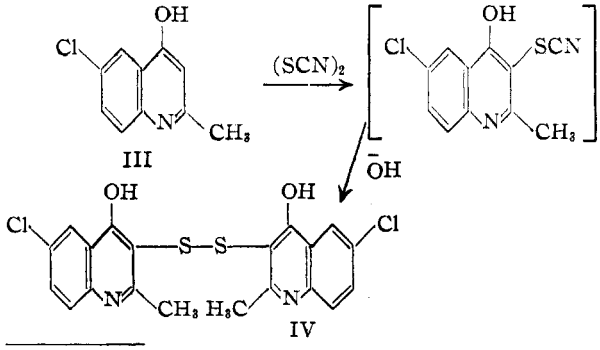
In contrast to the many examples in the literature of thiocyanation of aromatic phenols and amines in the benzene and naphthalene series only a very few unrelated heterocyclic substances[3,4,5] and just recently some pyrimidines[6] have been successfully thiocyanated.

A systematic investigation, as conducted in our laboratories, has revealed that thiocyanation takes place readily with a variety of amino and hydroxy pyridines, pyrimidines and quinolines. In the quinoline series a single such substituent in the heterocyclic ring is generally sufficient to induce the reaction. However, in the pyridine and pyrimidine[6] series disubstitution of the heterocycles by hydroxyl or amino groups is a prerequisite to successful thiocyanation; the monosubstituted compounds uniformly failed to react.



I

In the quinoline group, quinoline and 2- or 4-methylquinoline failed to react with thiocyano-



IV

(1) Presented before the American Chemical Society, April, 1951, at Boston. This work was supported by a grant from The Charles F. Kettering Foundation to The Wellcome Research Laboratories.

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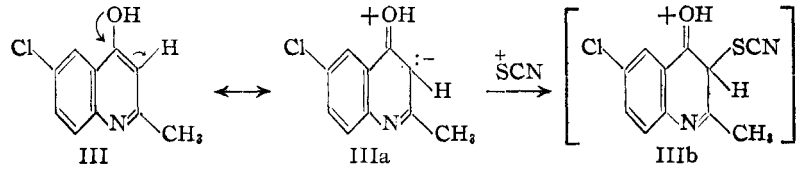
(3) H. P. Kaufmann and E. Weber, *Arch. Pharm.*, **267**, 192 (1929).

(4) H. P. Kaufmann and J. Liepe, *Ber.*, **56**, 2514 (1923).

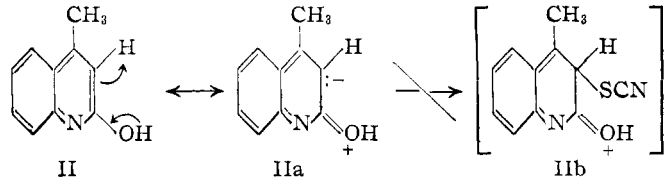
(5) P. Pratesi, *Atti Accad. Lincei*, **16**, 443 (1932).

(6) A. Maggiolo and G. H. Hitchings, THIS JOURNAL, **73**, 4226 (1951).

gen while 3-aminoquinoline was readily thiocyanated to give 2-aminothiazolo[4,5-d]quinoline



III IIIa IIIb



II IIa IIb

(I) which was identical with I as prepared by Bachman's[7] original five step synthesis. However, while 2-hydroxy-4-methylquinoline (II) failed to thiocyanate, 6-chloro-4-hydroxy-2-methylquinoline (III) yielded a thiocyano derivative which was transformed and isolated as bis-(6-chloro-4-hydroxy-2-methylquinolyl-3)-1-disulfide (IV). Treatment of thiocyano derivatives with alkali results in the cleavage of the thiocyano groups[3,6] with formation of the disulfide.

Though no structural proof was presented, Kaufmann's statement[3] that 2-hydroxyquinoline thiocyanates in the 4-position appears to be, for the present, substantiated; since blocking the 4-position with a methyl group as in 2-hydroxy-4-methylquinoline prevents thiocyanation from occurring.

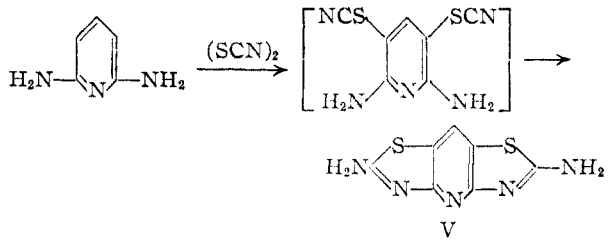
The ease of thiocyanation of (III) and the lack of reactivity of the isomeric (II) in this respect is a point of some interest. This phenomenon may be related to the lower energy level of the transition state IIIb (corresponding to the resonance variant IIIa or III) in comparison to the transition state IIb (corresponding to II↔IIa). Since IIIa and IIIb possess Kekule resonance in one ring they should have lower energy contents than the ortho-quinoid forms IIa and IIb. Waters[8] presents a somewhat similar explanation to account for the ready substitution at the 3-position in indole.

In the pyridine series, pyridine, 2- and 3-amino-3- or 4-methylpyridines failed to be thiocyanated, but 2,6-diaminopyridine yielded 1,7-dithia-2,6-diamino-3,4,5-triaza-*s*-indacene (V).

Likewise in the pyrimidine group replacement of one of the amino or hydroxy groups by alkylmercapto, alkyl or halogen substituents in the disubstituted amino or hydroxy pyrimidines resulted

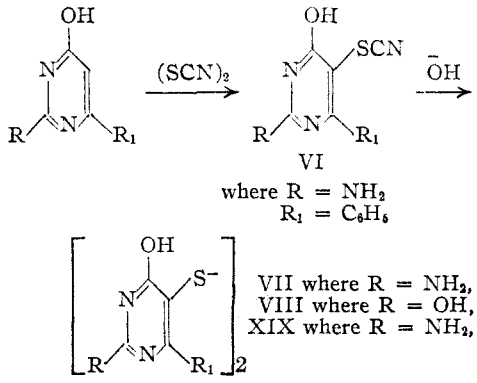
(7) G. B. Bachman, *et al.*, *ibid.*, **69**, 365 (1947).

(8) W. A. Waters, *J. Chem. Soc.*, 727 (1948).



V

in sufficient deactivation to render these compounds inert to thiocyanogen. Thus, 2-amino-4-chloro-6-methylpyrimidine, 2-amino-4,6-dimethylpyrimidine and 2-ethylmercapto-4-amino-6-methylpyrimidine did not thiocyanate. However, 2-amino-4-hydroxy-6-methyl, 2,4-dihydroxy-6-methyl and 2-amino-4-hydroxy-6-phenylpyrimidines readily thiocyanated. The products were isolated as their respective disulfides VII, VIII and XIX. The above 6-phenylpyrimidine has already been reported[6] as its 5-thiocyano intermediate VI as well as the disulfide XIX.



VI

where R = NH_2
R_1 = C_6H_5

VII where R = NH_2, R_1 = CH_3
VIII where R = OH, R_1 = CH_3
XIX where R = NH_2, R_1 = C_6H_5

Acknowledgments.—The author is indebted to S. W. Blackman, N. Martinez, Jr., and J. Tillmanns for microanalysis.

Experimental

All thiocyanations were conducted in a darkened room until the reaction was considered at an end. Reaction solvents were varied for the usual reasons of solubility, working up of product, etc. The solvents used were acetic acid, ethyl acetate, methyl alcohol or mixtures of them.

2-Aminothiazolo[4,5-d]quinoline (I).—To 14.4 g. (0.1 mole) of 3-aminoquinoline dissolved in a solution of 95 ml. of glacial acetic acid and 10 ml. of methyl alcohol was added a solution of 40 g. (0.41 mole) potassium thiocyanate in 100 ml. of glacial acetic acid. The flask was immersed in an ice-bath and a solution of 6 ml. (0.12 mole) of bromine in 100 ml. of glacial acetic acid was added dropwise over a period of one-half hour and then heated to 100° when 25 ml. of water was added with the lights now turned on. The hot solution was filtered by suction from the insoluble orange polymer. To the filtrate, cooled in an ice-bath was carefully added concentrated ammonia until the solution was alkaline. The almost white crystalline solid was allowed to stand several hours at 5°. Yield was 9.0 g. (45%). The crystalline solid slowly decomposed above 300°. 2-Aminothiazolo[4,5-d]quinoline prepared by Bachmann's synthesis[7] was identical with (I) in all respects (mixed m.p. determination and ultraviolet absorption spectra).

Anal. Calcd. for $C_{10}H_7N_3S$: N, 20.8; S, 15.9. Found: N, 20.8, 20.9; S, 16.0.

Bis-(6-chloro-4-hydroxy-2-methylquinolyl-3)-disulfide (IV).—A warm solution of 9.7 g. (0.05 mole) of 6-chloro-4-hydroxy-2-methylquinoline and 12.5 g. (0.15 mole) of sodium thiocyanate in 200 ml. of glacial acetic acid and 20 ml. of ethyl acetate was cooled to 5°. While stirring a solution of 2.6 ml. (0.07 mole) of bromine in 100 ml. of glacial acetic acid was added over a period of 20 minutes. The ice-bath was removed and stirring was contined for one hour. The solution was heated to boiling and 30 ml. of hot water was added. After 15 minutes the hot solution was filtered from polymer, cooled and made alkaline with ammonia. The gray solid which deposited was filtered off, and taken up in 5% sodium hydroxide. After standing for 3 hours the solution, upon acidification with 5% acetic acid yielded a precipitate which was dried overnight at 100°. Yield was 8.9 g. (81%), m.p. < 300°.

Anal. Calcd. for $(C_{10}H_7ONClS—)_2$: N, 6.2; S, 14.2. Found: N, 6.3; S, 13.9.

1,7-Dithia-2,6-diamino-3,4,5-triaza-s-indacene (V).—To a solution of 10.9 g. (0.1 mole) of 2,6-diaminopyridine and 40 g. (0.41 mole) of potassium thiocyanate in 200 ml. of glacial acetic acid and 10 ml. of methanol, cooled in an ice-bath, was added with mechanical stirring 9 ml. (0.18 mole) of bromine in 100 ml. of glacial acetic acid over a period of one-half hour. After the ice-bath was removed, the solution was stirred for an additional 40 minutes and then heated to 70° when 50 ml. of hot water was added. The contents were allowed to stand at 100° for 15 minutes and then filtered hot. The cooled filtrate was made decidedly basic with the careful addition of concentrated ammonia. The yellow crystalline precipitate was allowed to stand overnight at 5° and filtered off; dried at 60°, yield 15.0 g. (62%), m.p. 143–146°. Sample for analysis was crystallized from acetone–Skelly B mixture, m.p. 152–153°.

Anal. Calcd. for $C_7H_5N_5S_2$: N, 31.4; C, 26.9; H, 2.5; S, 28.7. Found: N, 31.1; C, 27.4; H, 2.9; S, 28.5.

Bis-(2-amino-4-hydroxy-6-methylpyrimidyl-5)-disulfide (VII).—To a solution of 12.5 g. (0.1 mole) of 2-amino-4-hydroxy-6-methylpyrimidine, 13.9 g. (0.16 mole) of sodium acetate and 33 g. (0.25 mole) of sodium thiocyanate in 100 ml. of glacial acetic acid and 10 ml. of ethyl acetate, cooled in an ice-bath, was gradually added with mechanical stirring 6 ml. (0.12 mole) of bromine in 50 ml. of glacial acetic acid. The contents were stirred for an additional hour at room temperature and heated to 100° when 20 ml. of water was added. After 15 minutes the hot solution was filtered, cooled, and made alkaline with ammonia. The gray-white solid which deposited was filtered off, taken up in 5% sodium hydroxide, reprecipitated with 5% acetic acid and dried overnight at 100°. Yield was 14.0 g. (90%), m.p. > 300°.

Anal. Calcd. for $(C_5H_6ON_3S—)$: N, 26.8; S, 20.5. Found: N, 26.5; S, 20.4.

Bis-(2,4-dihydroxy-6-methylpyrimidyl-5)-disulfide (VIII).—A solution of 6.3 g. (0.05 mole) of 2,4-dihydroxy-6-methylpyrimidine and 12.5 g. (0.15 mole) of sodium thiocyanate in 300 ml. of methanol, saturated with sodium bromide, was cooled to 5°. While stirring a solution of 2.6 ml. (0.07 mole) of bromine in 50 ml. of methanol, saturated with sodium bromide, was added over a period of 20 minutes. The ice-bath was removed and stirring was continued for one hour. The solution was diluted with 20 ml. of water and heated to boiling; no trace of any polymer was evident. The solution was made basic with ammonia and let stand for several hours. After concentration to one-third its volume, the solution, made to *p*H 6 with glacial acetic acid, deposited pale yellow crystals upon cooling and scratching. The yield was 4.0 g. (51%), m.p. 334° (dec.) after recrystallization from aqueous ethanol.

Anal. Calcd. for $(C_5H_5O_2N_2S—)_2$: N, 8.9; S, 20.4. Found: N, 8.8; S, 20.0.

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