STUDIES IN THE HETEROCYCLIC SERIES. IX. SYNTHESIS OF HETEROCYCLIC THIOLS

Charles O. Okafor[a]

[a] Department of Chemistry, University of Nigeria, Nsukka, Nigeria

PLEASE SCROLL DOWN FOR ARTICLE

STUDIES IN THE HETEROCYCLIC SERIES. IX.
SYNTHESIS OF HETEROCYCLIC THIOLS

by

Charles O. Okafor

*Department of Chemistry, University of Nigeria, Nsukka, Nigeria*

CONTENTS

I. INTRODUCTION

A survey of the chemical literature recently undertaken by us, has revealed that much greater attention is being given nowadays to organo-sulfur compounds. New products containing sulfur have emerged and many of them were isolated from petroleum,[1,2] coal,[3] plants,[4] animals[5] and soil microbes.[6] A great majority of them are, however, man-made and are obtained by intricate but often exciting synthetic procedures which give rise to new reactions, new chemistry and a great variety of potentially useful chemical compounds. These studies led to the synthesis of derivatives of phenothiazine (1)[7] the sulfur analog of phenoxazine, and to dithieno(2,3-b: 2′,3′-e)(1,4)thiazine (2)[8], cyclopental(1,2-b: 4,3-b′)-dithiophene (3)[9] and benzothienoacridine (4)[10] derivatives which are thiophene analogs of phenothiazine, fluorene and benz(c)acridine respectively.

Many of these compounds have found uses which are comparable, and in many cases, superior to their carbocyclic analogs. Their uses as dyestuffs, lubricants,
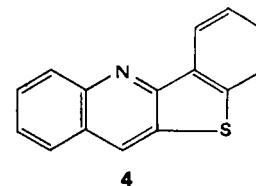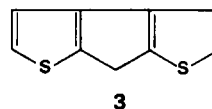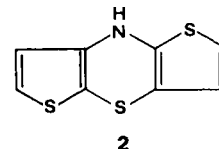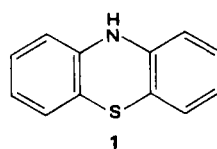
industrial antioxidants, vulcanization-accelerators, insecticides, herbicides, disinfectants, germicides and above all as drugs indicate the wide range of applications of these products.[11–14] The aliphatic mercaptans, which are characterized by their disagreeable odour, have now found some interesting applications based on this property. These mercaptans, particularly those obtained as by-products of petroleum refining, are

Charles O. Okafor

added to household gas as a warning against leaks or escaping gas, the effects of which could be disastrous. Furthermore, they are used in some industrial warning signals of various types.[15] Organo-sulfur compounds, in general, find the greatest applications in medicine where they are used as antitussive and antitumor agents, antihistamines, anthelmintics, antibacterial agents, antimalarials, local anaesthetics, antipsychotic agents, anticonvulsants, tranquilizers, antiemetics and sedatives to mention a few.[16,17] A study of the effect of replacement of benzene in carcinogenic benzenoid and benzoheteroaromatic systems with thiophene, benzothiophene, thiazole, thiopyran and other sulfur heterocycles has been recently undertaken by many workers notably Buu-Hoi and his team. A general reduction in carcinogenic activity was observed and in the thiophene analog of benz(c)acridine, a complete destruction of carcinogenic property was reported.[10] Replacement of benzene with thiophene can therefore be recommended for drugs with the undesirable and lethal carcinogenic activity.

In spite of these interesting advances, a lot of work remains undone in this direction as several aromatic systems are known for which the sulfur analogs remain unknown. The main obstacle in this regard is the scarcity of suitable stable sulfur precursors. Such sulfur compounds are somewhat more reactive than their oxygen analogs and are therefore more difficult to preserve. Mercaptans are readily oxidized to disulfides by mild oxidizing agents and are regenerated from the disulfides upon mild reduction. These oxidation–reduction reactions are claimed to be utilized in the respiration of living cells where

cysteine (5)-cystine (6) interconversion is probably involved.
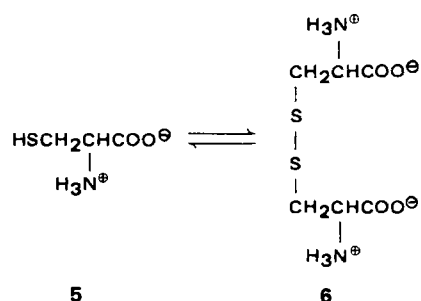
Although the sulfides are quite stable, they are more sensitive to oxidizing agents than ethers and are therefore readily converted to sulphoxides and sulfones. In contrast to ether peroxides, these sulfoxides and sulfones are quite stable. Some theories[18-21] have been put forward to explain these properties but no general agreement has been reached.

Many of the precursors in question are heterocyclic thiols, thiocyanates, sulfides, disulfides, thiocarbamates, and thioureas obtained essentially by methods which depend on the reactivity of the substrate. It is the purpose of this paper to highlight the various methods of introducing the mercapto group on to furan, thiophene, thiazole, pyridine, thianaphthene, quinoline, isoquinoline, pyridazine, pyrimidine, pyrazine, quinoxaline, purine, pteridine, and pyridazino(4,5-d)-pyridazine ring systems. It is hoped that this survey will provide a useful guide in choosing the right method of preparing the appropriate thiols required as precursors in the synthesis of novel organo-sulfur compounds particularly in the phenothiazine series.

II. ELECTROPHILIC SUBSTITUTIONS ON HETEROCYCLIC RING SYSTEMS

Owing to the presence of one or more heteroatoms in heterocyclic rings, an uneven distribution of π-electron density is expected. This results in certain positions acquiring more negative characters than the others. Electrophilic substitutions will therefore take place at the more negative centers while nucleophilic substitutions occur in the more positive ones. In pyridine and pyrimidine, the 2-, 4-, and 6-positions are most affected by the electron-withdrawing effect of the more electronegative ring nitrogens are thus positive in character. Nucleophilic substitutions will occur at these carbon centers. The 3- and 5- positions of pyridine and the 5-position of pyrimidine are more negative as they are relatively unaffected by the electronic effects of the annular nitrogen. Electrophilic substitutions will, therefore, take place at these

carbon centers. These substitution reactions may be facilitated, retarded, or modified, as the case may be, by the presence of certain groups in the ring. As examples of these effects pyridine and pyrimidine that have been utilized in the synthesis of the heterocyclic thiols.

A. Electrophilic Thiocyanation Followed by Hydrolysis

1. Kaufmann's Thiocyanation Reaction

One of the most successful methods of introducing sulfur into organic compounds is the application of Kaufmann's thiocyanation of aromatic amines. This reaction was extensively studied by Kaufmann after whom it was named in recognition of his outstanding

contributions towards its development. Kaufmann found that aromatic amines could be thiocyanated at the *para*-position with thiocyanogen (7) which is liberated *in situ* by the action of chlorine or bromine on inorganic thiocyanates at low temperatures.

$$Br_2 + 2KSCN \rightleftharpoons (SCN)_2 + 2KBr$$

<div align="center">7</div>
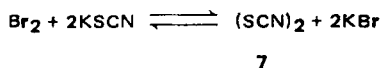
The reaction works best in an acid medium which hinders the hydrolysis of the thiocyanogen. Glacial acetic acid is the widely used solvent for this purpose. Satisfactory results were also obtained by the use of acetone, methyl, and ethyl acetates as solvents. The use of methanol is equally successful if it is first saturated with potassium bromide to protect the solvent from attack by the halogen. 4-Thiocyano-aniline was obtained in this manner from aniline.[22] If the *para*- position is blocked thiocyanation takes place at the *ortho*-carbon. In β-naphthylamine where the *p*-position is blocked, thiocyanation took place at the α-carbon leading to 1-thiocyano-2-naphthyl-amine.[23] With the appropriate thiocyanated product, cyclization could occur leading t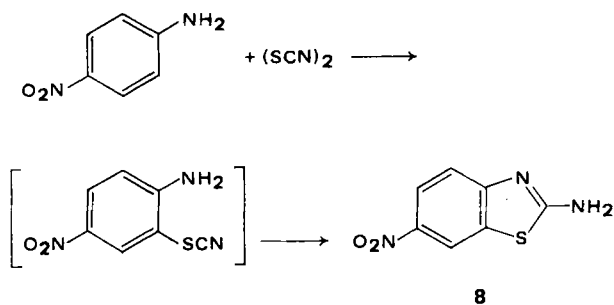o benzothiazoles. *p*-Nitroaniline, for example, reacts with ammonium thiocyanate and bromine in glacial acetic acid to yield 2-amino-5-nitrobenzothiazole (8).[24]


<div align="center">8</div>

These reactions are apparently well established in aromatic carbocyclic systems and have been applied to heterocyclic systems by several workers, notably Takahashi and his Japanese school.[25] Owing to the directive influence of the ring nitrogen in competition with the amino group, the position of attack by nascent thiocyanogen will depend on the dominating group. 3-Aminopyridines bearing electron-releasing groups at the 6-position were converted in this way to 2-aminothiazolo(5,4-*b*)pyridines 9[26-29] *via* the 2-thiocyano derivatives. The thiocyanation of 2,6-diaminopyridine was investigated by three groups of workers whose results led to contradictions on the structures, melting points and purity of the products. Yamamoto, Takahashi and Ueda[30, 31] obtained a

product which they formulated as 2,5-diamino-thiazolo(4,5-*b*)pyridine, 10.

<div align="center">9   10</div>
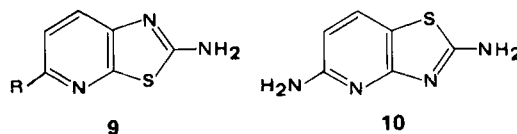
Bernstein[32] confirmed these results and obtained, in addition, 2,6-diaminobisthiazolo(4,5-*b*: 5',4'-*e*)-pyridine, 11, if two equivalents of the thiocyanating agent were used.

<div align="center">11</div>

<div align="center">12   13</div>
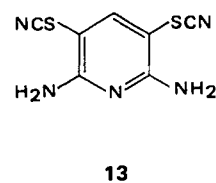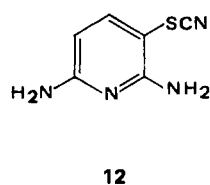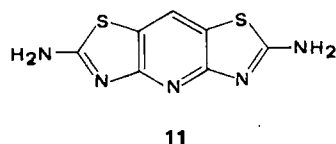
Maggiolo,[33] on the other hand, reported that the bisthiazolopyridine compound, 11, is the only product of the reaction. Baker and Hill[34] reinvestigated these reactions and proved that the product purported as 10 by Yamamoto, Takahashi, and Bernstein is, in fact, 2,6-diamino-3-thiocyanopyridine (12) melting at 141°-141.5°. The compound had a strong infrared absorption at 2160 cm^{-1} corresponding to the thiocyano group. Upon boiling in water for several hours, it isomerized to 2,5-diaminothiazolo-(4,5-*b*)pyridine (10) which lacked the SCN absorption. A second and less soluble product was also isolated and identified as 2,6-diamino-3,5-dithiocyanopyridine (13) (mp ~ 200°(dec)). Like compound 12, it is cyclized to the bisthiazolopyridine, 11, mp > 300°, by refluxing this time, in pentyl alcohol for six hours.

Owing to contradictory reports on the structures and melting points of these products,[35] a reinvestigation of these reactions with 3-aminopyridines was recently undertaken by us.[36] The thiocyanation of 3-amino-6-methoxy- and 3-amino-6-chloropyridines, 14, gave products which agree with structures 9 and 15 on the basis of their analysis, ultraviolet and infrared spectra. There was no SCN band in their infrared spectra (Figures I and II).
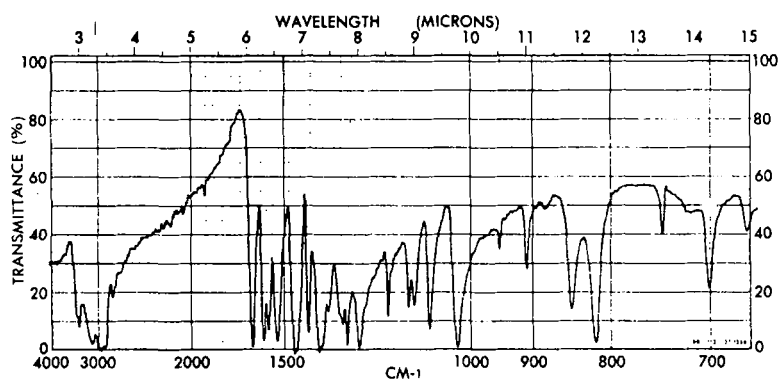
FIGURE I

Infrared spectrum of 2-amino-5-methoxythiazolo[5,4-*b*] pyridine, (9, R = OMe) in Nujol.
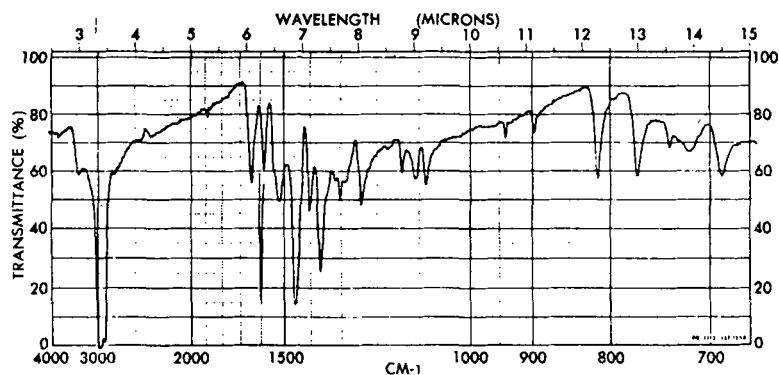
FIGURE II

Infrared spectrum of 2-amino-5-chlorothiazolo[5,4-*b*]-pyridine, (9, R = Cl) in Nujol.

15
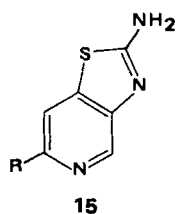
Their proton nmr spectra gave strongly coupled aromatic protons, J = 10 Hz if R = OMe and J = 8 Hz if R = Cl, showing that these protons are *cis* to each other (normal *cis* — J_{HH} ~ 4–12 Hz while *para* — J_{HH} ~ 0–3 Hz; Figures III and IV and hence the correct structures are 9 (R = OMe, Cl). Molecular orbital calculations of the π-electron densities in 3-amino-6-chloropyridine (16) by LCAO-MO method also favors an attack of the 2-position by the electrophilic thiocyanogen.

16

17
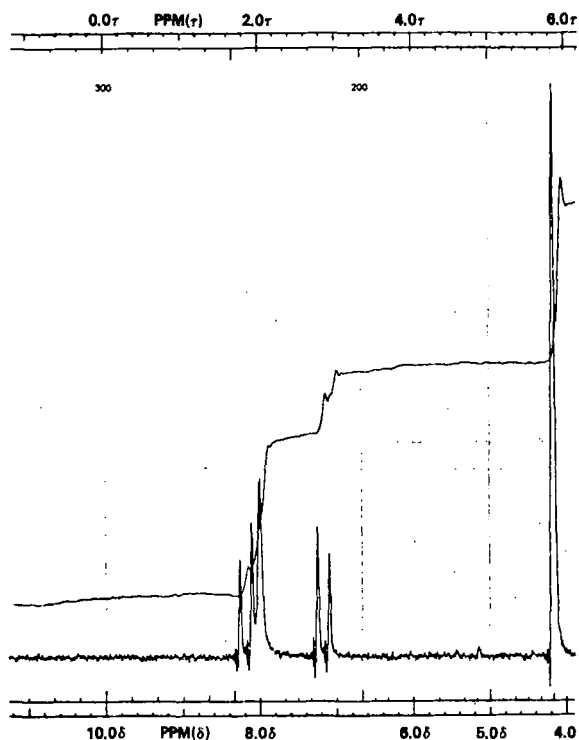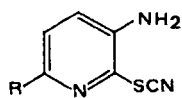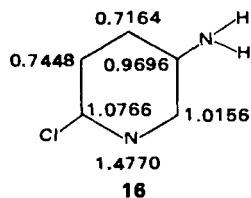
FIGURE III

Nmr spectrum of compound 9, R = OMe.
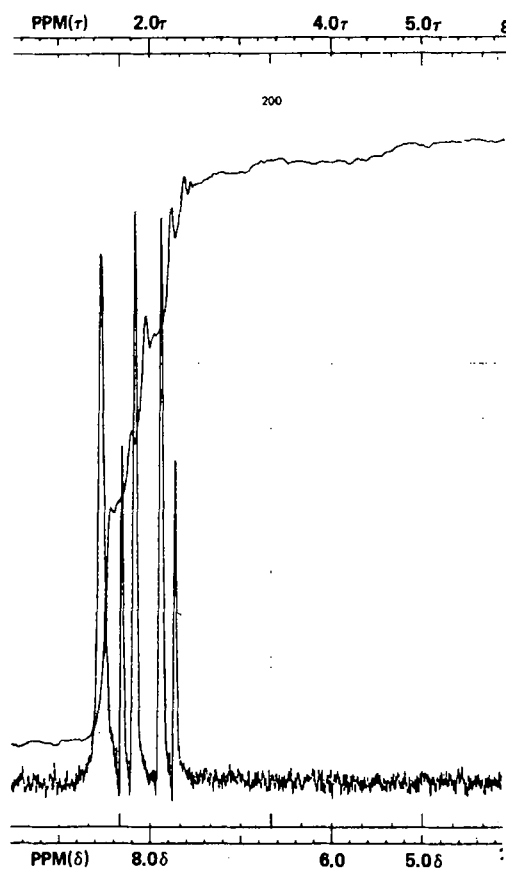
FIGURE IV

Nmr spectrum of compound 9, R = Cl.

These results show that in 3-aminopyridines sub-
stituted at the 6-position with electron releasing
groups, thiocyanation takes place preferentially at
the 2-position followed by cyclization of the inter-
mediates, 17, to the bicyclic products, 9.

The thiocyanation of 2-amino-6-picoline gave the
3-thiocyano derivative, 18, which cyclizes to 2-amino-
5-methylthiazolo(4,5-b)pyridine (19) on prolonged
heating. Compound 18 had a strong infrared absorp-

tion at 2145 cm^{-1} (Figure V) and the cis-J_{HH} for
the two aromatic protons in the nmr spectrum is
9 Hz (Figure VI).
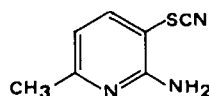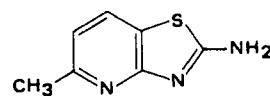
18   19

The thiocyanation of heterocyclic compounds is
not confined to pyridine systems. Quinoline,[33]
isoquinoline,[37-39] pyrimidine,[40-41] and thiazole[42,43]
were successfully thiocyanated with bromine and
inorganic thiocyanates in glacial acetic acid. Mag-
giolo[33] reported the conversion of 3-aminoquinoline,
20, to 2-aminothiazolo(4,5-d)quinoline (21) but no
physical or chemical evidence was obtained in favor
of the cyclized structure over the thiocyano deriva-
tive, 22 invoked as an intermediate.
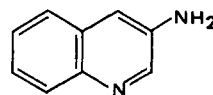
20
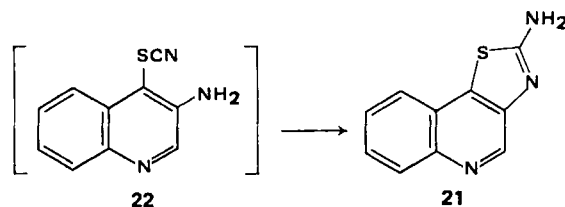
22   21

3-Aminoisoquinoline (23), on the other hand, gave
the 4-thiocyano derivative (24) in 65% yield. The
SCN band appeared at 2143 cm^{-1} in the infrared spec-
trum. In the nmr spectrum, the low field singlet at
1.29τ corresponds to the C-1 proton of the isoquino-
line ring. Cyclization was achieved by refluxing in
aqueous alcoholic HCl.[37]
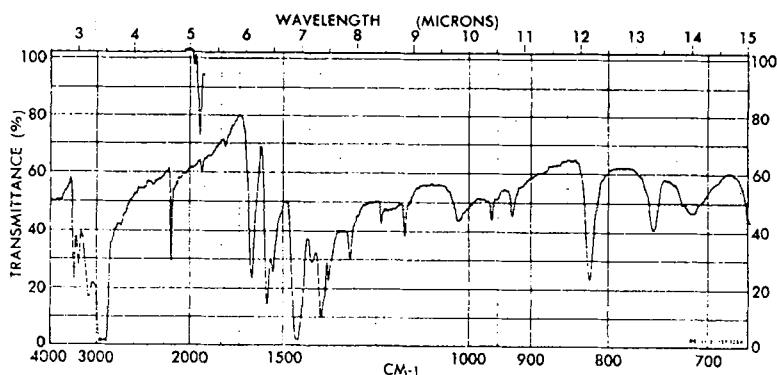
FIGURE V

Infrared spectrum of compound 18 in Nujol.
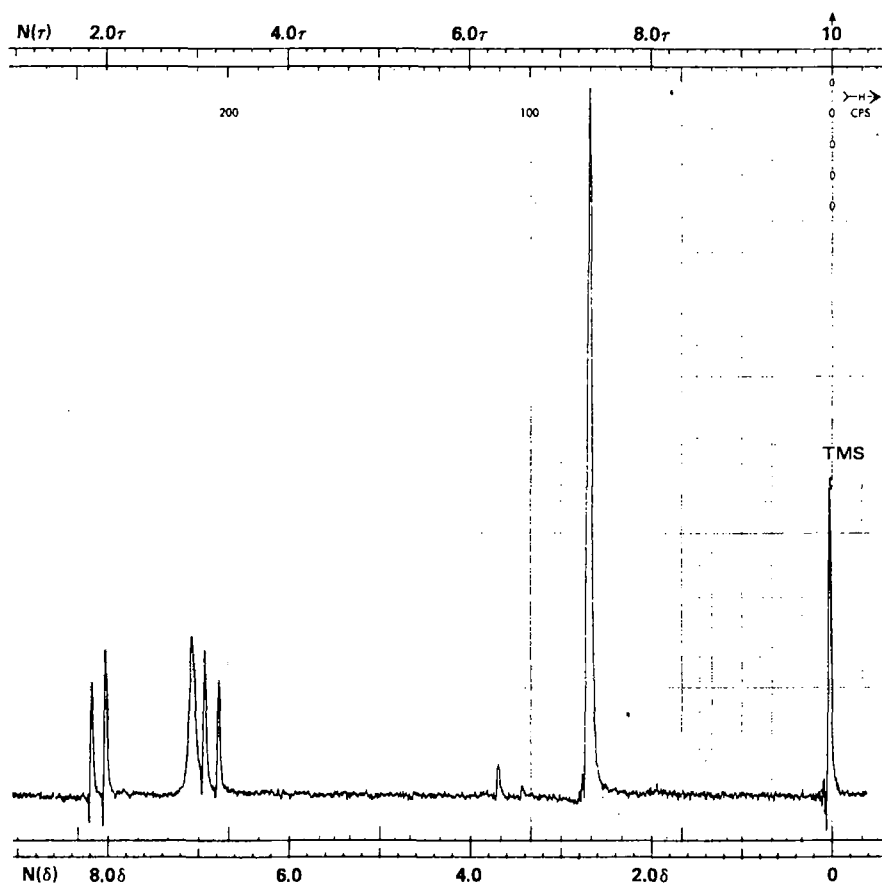
FIGURE VI

Nmr spectrum of compound 18.
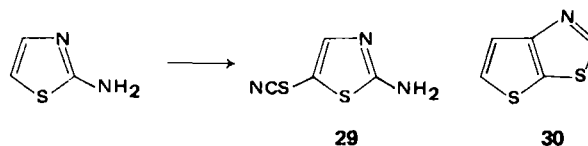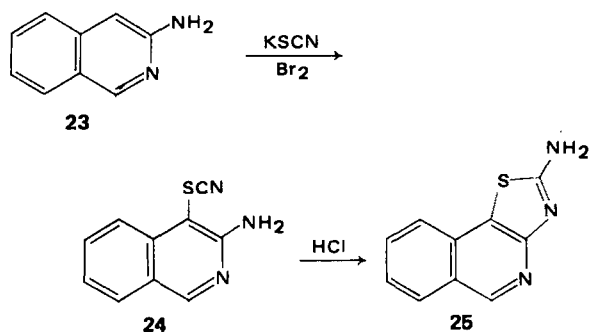
A similar reaction with 4-aminoisoquinoline (26) gave a mixture of 4-amino-3-thiocyanoisoquinoline (27) and 2-aminothiazolo(5,4-c)isoquinoline (28) in 33% and 21% yields respectively.

The infrared and nmr spectra of these products are in good agreement with the assigned structures.[38] The thiocyanation of 2,4-diamino-6-hydroxypyrimidine by the same method gave the expected 5-thiocyano derivative which had a sharp medium-to-strong peak at 2151 cm^{-1}.[41]

The thiocyanation of heterocyclic compounds is not confined to six-membered heterocycles. Bellavita

and Vantaggi[42,43] reported the thiocyanation of 2-aminothiazole with these reagents. The 5-thiocyano derivative (29), required as an intermediate in their synthesis of thieno(3,2-d)thiazole derivative (30) was obtained.

Soderback[44] successfully thiocyanated thiophene and pyrrole using bromine and excess inorganic thiocyanates in the presence of aluminium chloride and ethyl ether[45] as solvent. With thiophene, 2-thiocyanothiophene (31; X = S, R = H) was obtained.
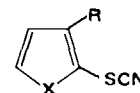
31: X = S, R = H
32: X = S, R = SCN
33: X = O, R = SCN

However, if the reaction is left to continue for 48 hr at 0° 2,3-dithiocyanothiophene (32; X = S, R = SCN) separated. Owing to the high reactivity of pyrrole compared to thiophene, the thiocyanation of pyrrole by the method used for monothiocyanation of thiophene gave 2,3-dithiocyanopyrrole (33; X = O, R = SCN) in a good yield.

2. Effect of Substitution on Thiocyanation with Nascent Thiocyanogen

The effect of substitution in 2- and 3-aminopyridines and 2-aminopyrimidines on these thiocyanation reactions was also studied. The presence of two electron-releasing groups was found to be a prerequisite for successful thiocyanation with "nascent" thiocyanogen. 2,6-Diaminopyridine[30-33] and 3-aminopyridines substituted at the 6-position with chlorine, methoxy, ethoxy, hydroxy, isopropoxy and butoxy groups were thiocyanated with ease.[30, 31] 2-Amino-4-methyl- and 2-amino 5-methylpyridines could not react with this reagent owing to the lower electron releasing effect of the methyl group.[33, 36] For the same reason, 2-amino-5-bromo- and 2-amino-5-iodopyridines failed to react.[30, 31] However, if a methyl group is substituted at the 6-position, thiocyanation of the 2-amino-6-methyl-pyridine was successful but in a lower yield.[36] Similar results were obtained in 2-amino-4-hydroxypyrimidines and in these cases, replacement of the hydroxyl group with chlorine or an alkyl group resulted in sufficient deactivation which rendered these compounds inert to thiocyanogen. Thus, 2-amino-4-hydroxypyrimidines substituted at the 6-position with methyl and phenyl groups (31) were readily thiocyanated while 2-amino-4-methylpyrimidines substituted with chlorine and a methyl group at the 6-position (32) could not react with this reagent.[33]

31: R = CH₃, Ph   32: R = Cl, CH₃

A stronger reagent is needed therefore for the thiocyanation of monosubstituted heterocyclic compounds. In this regard, Baker and Hill[34] used chlorothiocyanogen, a stronger thiocyanating agent than thiocyanogen, but instead of the expected product, a complex compound of unknown structure was obtained.
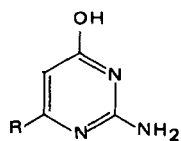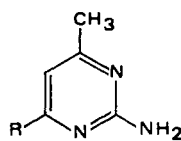
3. Base-Catalyzed Hydrolysis of Thiocyanopyridines and Thiazolopyridines

One of the most useful properties of these thiazolopyridines and thiocyano derivatives of heterocyclic compounds is the readiness with which they are converted to pyridine thiols. Takahashi and Yoshii[46] claimed that 2-amino-5-ethoxythiazolo(5,4-b)pyridine, (9, R = OEt) could be hydrolyzed by refluxing in 20% NaOH for one hour. The ease of cleavage of the thiazole ring is puzzling because of the anticipated aromatic stabilization of the thiazole ring. As an explanation, Baker and Hill[34] suggested that the reported hydrolysis could well be that of the non-rearranged structure 33. This, in fact, is the case with compound 12[34] which was incorrectly reported as the cyclized structure, 10.[30, 31]

33   34

35
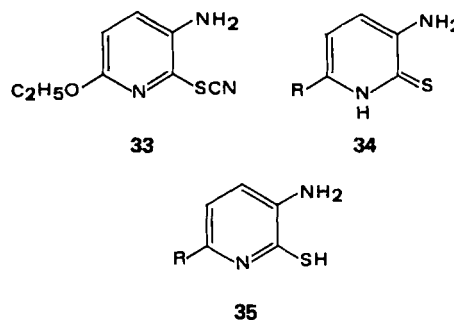
Since ortho-aminomercaptopyridines are useful precursors for our azaphenothiazine work, these base-catalysed reactions of thiazolopyridine and ortho-aminothiocyanopyridines were further investigated by us.[36] Base-catalyzed hydrolysis of 2-amino-thiazolo(5,4-b)pyridines (9) gave the corresponding 3-aminopyridine-2(IH)-thiones, 34, after acidification, and no evidence for the thiol (lactim) tautomers 35 was found in the nmr spectra.

Takahashi, Yoshii, and Maki[46, 47] had previously reported their inability to recrystallize compound 34 formed by hydrolysis of the thiazolo(5,4-b) pyridines using 10-20% sodium hydroxide solution. If barium hydroxide, however, is used purer products were obtained.[47] In a subsequent study, the impurities were identified as 2-mercapto-3-pyridylureas, 36, formed by incomplete hydrolysis of the thiazolopyridine.[48]

36
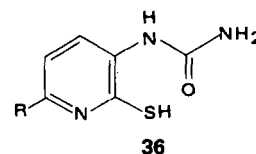
In our studies, we found that by refluxing these thiazolopyridines with 20% sodium hydroxide

solution for 3 hr, the corresponding 3-aminopyridine-2(IH)-thiones, 34, were obtained in excellent yields. These products are recrystallizable from methanol, and analytically pure products were obtained in this way.[36]

Base hydrolysis of 2-amino-3-thiocyano-6-picoline (18) gave the dipolar salt of 2-amino-3-mercapto-6-picoline, formulated as structure 37, on the basis of infrared and nmr evidence.[49]

37
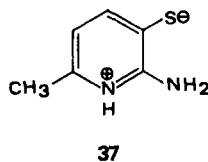
These ortho-aminomercaptopyridines were successfully converted to derivatives of 1,3,6-triaza- (38)[50] and 1,3,9-triazaphenothiazines (39)[49] by reacting with 4,5-dihalogenopyrimidines. The two rings are the only known isomers of triazaphenothiazine.

38

39
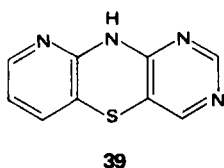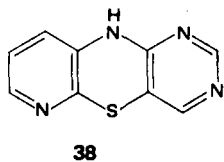
The cleavage of the thiazole ring in thiazolo(4,5-c)-quinoline[51] and thiazolo(4,5-d)pyrimidine[52] by acid and base catalysis respectively was also reported.

40   **41**

42   **43**
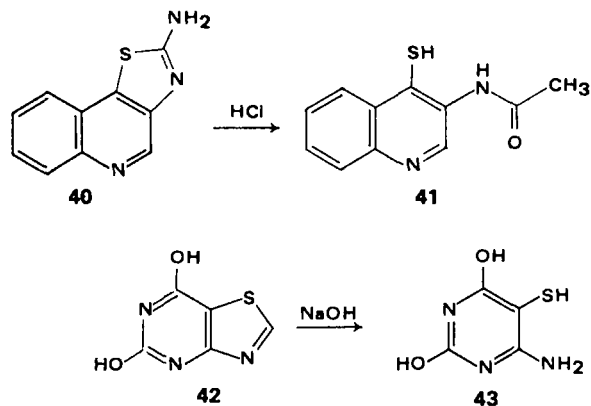
Bachman, Welton, Jenkins, and Christian[51] reported the hydrolysis of 2-methylthiazolo(4,5-c)quinoline (40) in dilute acids to yield 3-acetylamino-4-quinolinethiol (41). Using 10% sodium hydroxide solution,

Baker and Chatfield converted thiazolo(4,5-d)-pyrimidine-5,7-diol (42) to 4-amino-5-mercapto-pyrimidine-2,6-diol (43) in 86% yield.[52]

B. Sulfenylation and Hydrolysis of the Sulfide

Sulfur heterocyclic thiols have been successfully prepared by Friedel Crafts reaction of the heterocyclic compound with a reactive benzenesulfenyl chloride followed by base-catalyzed hydrolysis.

44   **45**

46
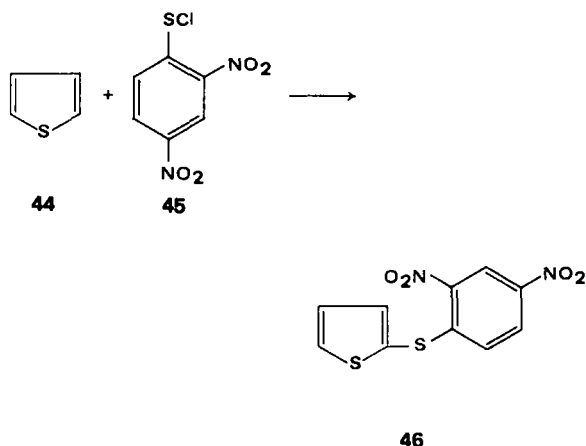
In the presence of stannic chloride catalyst, 2,4-dinitro-benzenesulfenyl chloride (45) reacts with thiophene and the mono- and di-alkyl derivatives in methylene chloride to give a variety of thienyl 2,4-dinitrophenyl sulfides, 46, in good yields.[53]

In Table I, the results obtained by alkyl substitution on thiophene and thianaphthene rings are presented. It can be seen that owing to the electrophilic nature of

TABLE I

Compound	R	Yield, %	Mp
44		89	119-120
47		63	120
48		65	105-106
49		92	115
50		73	176-177

these reactions, the presence of electron releasing groups at the 2-, 3- and 5-positions of thiophene facilitates the reaction leading to increased yields. As expected, the yield is highest in 2,5-dimethylthiophene. With 2-methylnaphthalene, the corresponding thianaphthyl 2,4-dinitrophenyl sulfide (50) was isolated in a good yield. Thianaphthene itself gave a mixture of 2- and 3- thianaphthyl 2,4-dinitrophenyl sulfides.

The use of other catalysts was also investigated. Anhydrous lithium aluminium hydride and anhydrous ferric chloride gave intractable tarry products while anhydrous stannic chloride was ineffective at temperatures below the boiling point of methylene chloride. With stannic chloride, the reaction works best at the reflux temperature of methylene chloride for a period of, at least 1½ hr.

The diaryl sulfide, 51, is cleaved by methanolic sodium hydroxide to yield the heterocyclic thiols, 52, and 2,4-dinitroanisole (53) with extensive disulfide, 54, formation, after acidification.
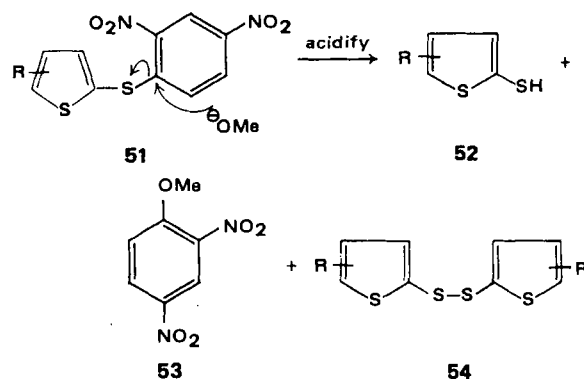
The yields of the thiophene thiols were increased to 48% by reducing the reflux time to 20 min while running the reaction in a nitrogen atmosphere to reduce decomposition and air oxidation of the mercaptide ion. Further increase in the yield of the heterocyclic thiols was obtained by isolating them as their mercuric chloride salts by reacting with mercuric acetate.[53]

III. NUCLEOPHILIC SUBSTITUTIONS ON HETEROCYCLIC RING SYSTEMS

The ease of nucleophilic substitution in nitrogen heterocyclic systems is the major difference between them and aromatic carbocyclic rings. As we pointed out earlier in this paper, the 2-, 4- and 6-positions in pyridine and pyrimidine are most susceptible to nucleophilic attack. The readiness with which these heterocyclic rings undergo nucleophilic substitution has been utilized in the synthesis of heterocyclic thiols.

A. Nucleophilic Thiocyanation Followed by Hydrolysis

Although Kaufmann's reaction provides a workable method for thiocyanating heterocyclic compounds, nucleophilic displacement of halogen with thiocyano group has been found useful. This reaction works well if the heterocyclic halide is substituted with an electron-withdrawing group. Takahashi and Ueda[54] converted 4-chloro-3-nitropyridine (55) to 3-nitro-4-thiocyano-pyridine (56) by reacting with potassium thiocyanate at room temperature.
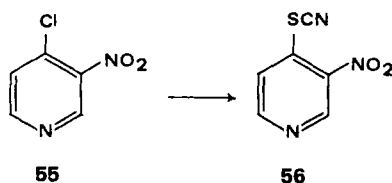
By treating 2-chloro-3-nitropyridine with potassium thiocyanate in the presence of copper powder, 3-nitro-2-thiocyanopyridine (57) was obtained. Reduction of the nitro group with stannous chloride and concentrated hydrochloric acid gave 2-aminothiazolo-(5,4-b)pyridine (58) in a good yield.[55] The same product was isolated if the nitrothiocyanopyridine (57) were treated with concentrated ammonia.[56]
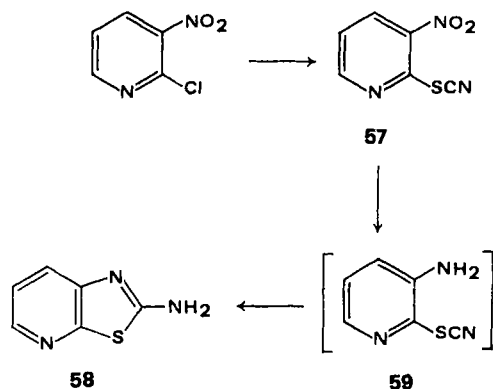
By refluxing the thiazolopyridine with 10% sodium hydroxide solution at 140° in the presence of arsenious oxide, 3-aminopyridine-2(1H)-thione (34, R = H) was obtained.

In the pyrimidine series, 2,4-dichloro-5-nitropyrimidine reacts with potassium thiocyanate to give 2-chloro-5-nitro-4-thiocyanopyrimidine.[57] These

thiocyanated heterocyclic systems can be converted to the corresponding thiols by refluxing with dilute sodium hydroxide followed by acidification.

B. Direct Introduction of SH Group with HS⊖ as the Nucleophile

Heterocyclic thiols are also prepared by nucleophilic displacement of halogen in heterocyclic halides with hydrosulfide ion.

60
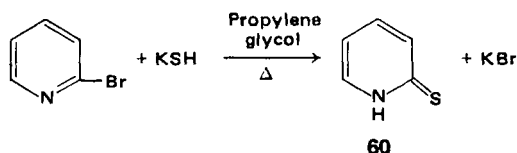
Pyridine-2(IH)-thione (**60**) was obtained in 85% yield by reacting 2-bromopyridine in propylene glycol[58] with potassium hydrosulfide (generated by saturating an aqueous solution potassium hydroxide with hydrogen sulfide) at 170°-175°. The reaction is facilitated by the presence of suitably substituted electron-withdrawing groups in the heterocyclic ring. By refluxing 2-chloro-3-nitropyridine (**61**) with methanolic potassium hydrosulfide, 3-nitropyridine-2(IH)-thione (**62**) and bis(3-nitro-2-pyridyl)disulfide (**63**)[59] were obtained.

61

62   **63**
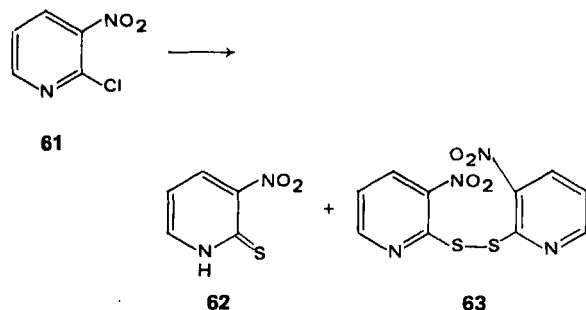
Also Kruger and Mann[60] obtained 3-nitropyridine-4(IH)-thione (**64**) in this way while Rodig[61] and his coworkers prepared, by an identical method, 3-aminopyridine-2(IH)-thione (**34**; R = H) required for their azaphenothiazine studies.[62] 3-Amino-2-chloropyridine, **65**, required for the preparation of compound 34, R = H, is obtained by Hofmann's rearrangement of nicotinamide (**66**) using chlorine and sodium hydroxide as the catalyst.[63] The rearrangement proceeded smoothly in small amounts and was accompanied by chlorination at the 2-position. A violent explosion was reported during the rearrangement of nicotinamide if large amounts of the reactants were used.[61] The explosion is probably due to a high build-up of perchlorate ions by interaction with

chlorine and sodium hydroxide. If bromine were used in place of chlorine in this reaction 3-aminopyridine, **67**, was obtained without 2-halogenation taking place.[64]

66

67   **65**
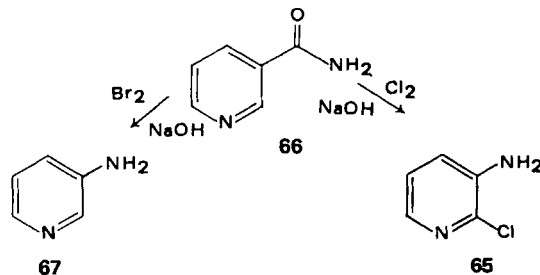
2-Chloro-5-methyl-3-nitropyridine, 2-amino-3,5-dibromopyrazine, 5-amino-3,6-dichloropyridazine and 2-amino-3-chloroquinoxaline were converted to 5-methyl-3-nitropyridine-2(IH)-thione (**68**)[65] 2-amino-5-bromo-3-mercaptopyrazine (**69**),[66,67] 5-amino-3-chloro-6-mercaptopyridazine (**70**)[68] and 2-amino-3-mercaptoquinoxaline (**71**)[69] respectively by refluxing with methanolic potassium hydrosulfide. In a similar way, 2,5-dimethylpyrazine-3-thiol (**72**) was prepared. This compound inhibits the growth of phythopathogenic fungi.[70] 2,5-Dimethyl-3-thiocyanopyrazine has a similar effect.[71]

68   **69**

70   **71**
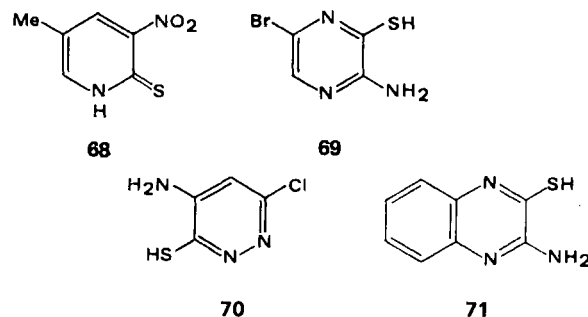
When 2-chloro-3,5-dinitropyridine (**72**) on the other hand, was treated with the same reagent, a vigorous reaction took place; the desired 3,5-dinitropyridine-2(IH)-thione could not be separated. The expected substitution of chlorine with mercapto group took place accompanied by reduction of the 5-nitro group.[72] The product, 5-amino-3-nitropyridine-2(IH)-thione (**73**; R = H) was characterized by the failure to convert the monoacetyl derivative (**74**, R = acetyl) to a thiazolopyridine showing that the amino and mercapto groups are not in *ortho*-position to each other.

73: R = H
74: R = Ac
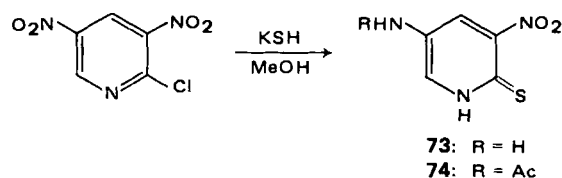
C. Organometallic Method

The introduction of mercapto group into hetero-cyclic rings has also been achieved by conversion of heterocyclic halides to the corresponding organo-metallic salts followed by the action of elemental sulfur and acidification. This method is most applic-able to thiophene heterocycles and was extensively studied by Gronowitz and his co-workers.

A series of 2-(75)[73] and 3-thiophenethiols (76)[74] were prepared by Gronowitz in good yields by halogen-metal interconversion between 2- and 3-bromothiophenes and n-butyl lithium at $-70°$ followed by the action of elemental sulfur and acidification.
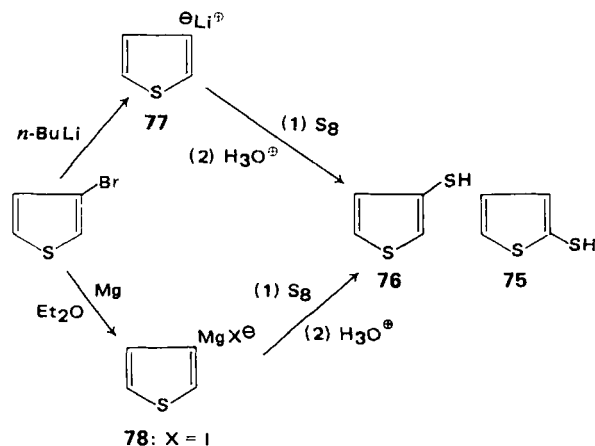
A lower yield of compound 76, however, was obtained by treating 3-thienyl-magnesium iodide (78; X = I) with sulfur followed by acid hydrolysis.[75] Challenger and Harrison reported the isolation of 2-ethyl-3-thiophenethiol, 79, by reduction of thieno(3,2-b)-thiophene, 80, with sodium and ethanol.[76]
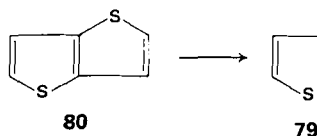
Other methods involving zinc dust–sulfuric acid[77] and lithium aluminum hydride[78,79] reductions of some 2- and 3-thiophenesulfonyl chlorides gave the corresponding 2- and 3-thiophenethiols.

D. Substitutions Proceeding Through Diazonium Intermediate—The Chugaev Reaction

Another method of practical importance for the conversion of aromatic amines to thiols, known as the Chugaev Reaction, was first described by Chugaev[80] after whom the reaction was named. It involves the conversion of alcohols to their xanthates, 81, by the reaction of their potassium salts with carbon disulfide.

The aromatic amine was then diazotized and reacted with the potassium alkyl xanthate, 81, thus obtained, to give the aralkyl xanthate 82.
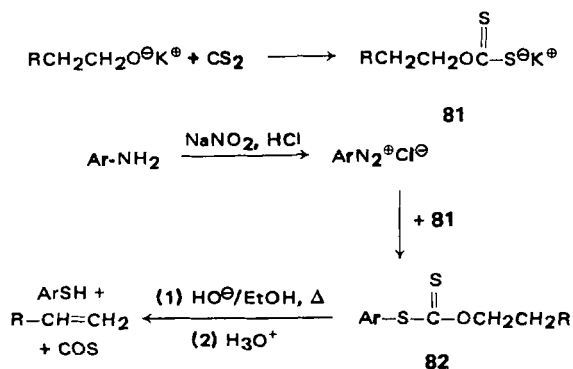
Base catalysed decomposition of this ester would give a high yield of the thiophenol as well as an olefin and carbon oxysulfide. The reaction is well estab-lished for converting aromatic carbocyclic amines to thiophenols[81-83] and has been extended to hetero-cyclic systems by Katz, Schroeder and Cohen.[84] Instead of the anticipated heterocyclic thiol, the disulfide, 83, was obtained in 77% yield.
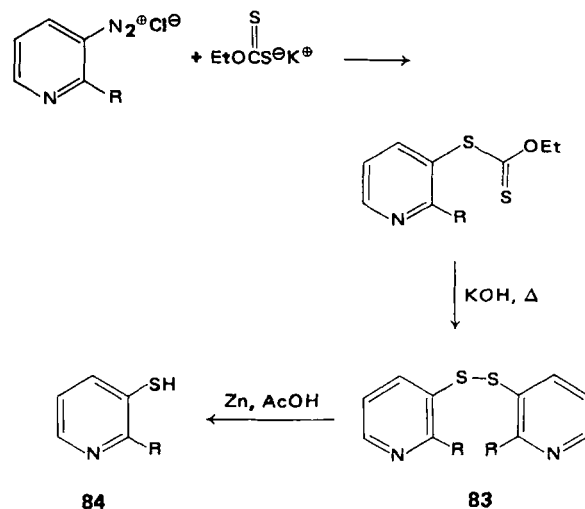
The desired mercaptopyridine, 84, can be obtained however by reducing the disulfide with hydrazine,[84] zinc and acetic acid[85] or lithium aluminium hydride.[78,79]

E. The Use of Thiourea as Nucleophile

A useful method of introducing the mercapto group into heterocyclic systems was provided by Surrey and Lindwall.[86] They reacted 2-chloro-5-nitropyridine with thiourea in absolute alcohol and obtained 85% yield of an addition product identified

as the isothiouronium salt, **85**. This product was
formed by nucleophilic displacement of the halogen
by the thiourea and it is quite stable and isolable.
However, when treated with sodium carbonate, it
decomposed to yield 5-nitropyridine-2(IH)-thione,
86, in 95% yield.

85

86
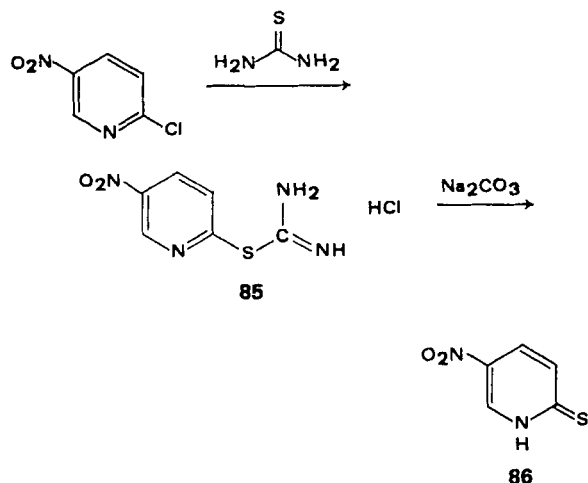
This reaction was successfully applied by Bradsher,
Lohr and Andrew to prepare some interesting
thiazolo(3,2-a)-pyridinium- (**87**)[87] and thiazolo-
(2,3-a)isoquinolinium salts (**88**)[88] and by Caldwell
and Kornfeld[89] to obtain some potential antiparasitic
pyridine sulfonamides.

87   **88**
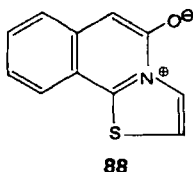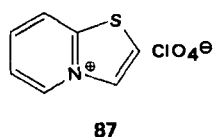
F. Intramolecular Schönberg Rearrangement and Hydrolysis

A very successful and widely applicable method of
synthesizing thiophenols, **89**, from phenols, **90**, was
discovered by Schönberg[90,91] and his co-workers in
1930. The Schönberg rearrangement involves the
pyrolytic conversion of O-aryl thiocarbonate to S-aryl
thiocarbonate. Hydrolysis of the S-aryl thiocarbonate
led to the desired aryl thiol. Improved yields were
obtained by converting the phenol to O-aryl dialkyl-
thiocarbamate, **91**, by the action of dialkylthio-
carbamyl chloride in DMF.[92] Pyrolysis of compound
91 led to its isomerization to S-aryl dialkylthio-
carbamate **92** in high yields. The S-aryl dialkylthio-
carbamate is easily hydrolyzed in 10% sodium
hydroxide and gave the corresponding thiophenol
89 in near quantitative yields.[93]

90   **91**

93   **89**   **92**
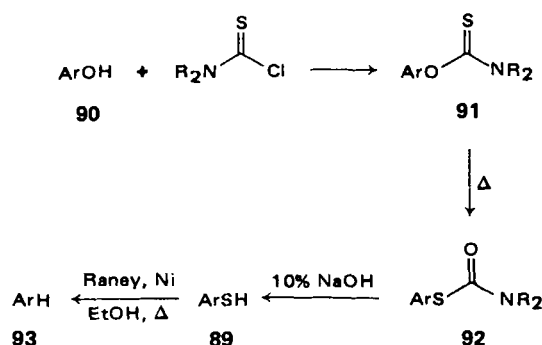
These reactions were recently investigated thoroughly
by Newman and Karnes[94] who also found them
applicable for the conversion of heterocyclic phenols
to the thiols. Hydrogenolysis of the thiophenols with
Raney nickel led to the replacement of the mercapto
group with hydrogen and thus affords a good method
of converting heterocyclic phenols to their parent
compounds, **93**. Blanz and his coworkers[95] used this
method recently to prepare 5-mercapto-2-picoline
required for their anticancer agents.

The mechanism of Schönberg rearrangement was
also studied by Newman and Karnes.[94] They observed
that the presence of electron-attracting groups in the
aryl portion lowers considerably the temperature
needed for the isomerization. The rearrangement of
boron trifluoride and hydrochloride salts of O-(2-
pyridyl)- and O-(4-pyridyl) dimethylthiocarbamates
proceeded smoothly at room temperature. Further-
more, it was observed that O-p-nitrophenyl dimethyl-
thiocarbamate (**94**) rearranges more readily than
O-p-nitrophenyl methyl-p-nitrophenylthiocarbamate
(**95**).

94

95
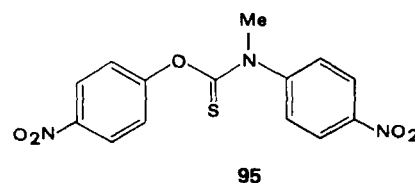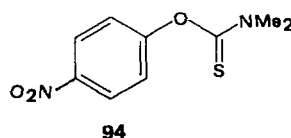
These observations support an ionic mechanism
involving a nucleophilic attack of the sulfur ion on
the ring carbon bonded to the oxygen followed by
scission of the Ar–O bond and formation of the
S-arylthiocarbamate, **96**.

Hydroxide ion attack on the carbonyl carbon of
the thiocarbamate would lead to hydrolysis and the
formation of the thiophenol.

97

96
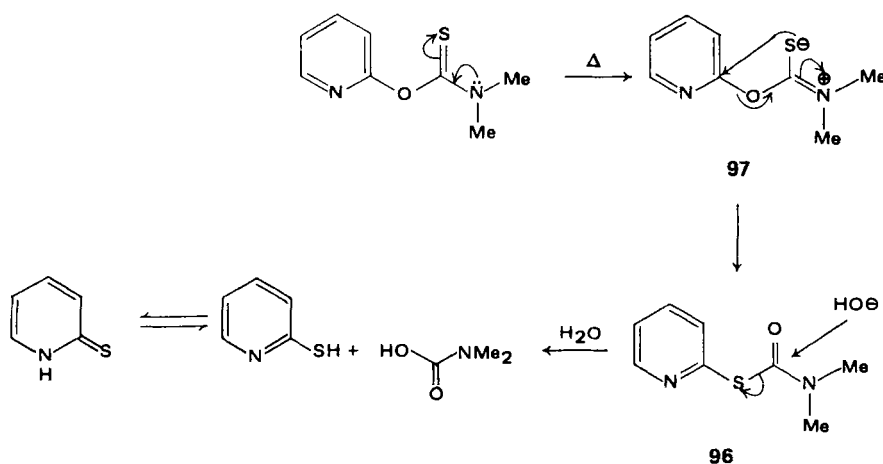
IV. CONDENSATION OF PHENOLS WITH P₂S₅

The replacement of oxygen by sulfur using P_2S_5 as the thiating agent has been widely applied to heterocyclic systems particularly the nitrogen heterocycles where the phenolic hydroxyl group attached to the ring is tautomeric with the cyclic amide structure. In the absence of a solvent, King and Ware[96] converted 4-pyridone to pyridine-4(IH)-thione in 86% yield by this method. The reaction was also successful in benzene[97] and toluene solvents.[98] These reactions are apparently limited to low melting pyridones which would be soluble in benzene or toluene or would react, without decomposition, in the absence of a solvent. Klingsberg and Papa[99] later found that pyridine is a more suitable solvent for this reaction owing to its high solvent power for the reactants, a suitable reflux temperature (100°) and its miscibility with water, providing a simple method of isolation. Thus, on heating a mixture of 3,5-diiodo-2(IH)-pyridone (98) with P_2S_5 in pyridine for 1½ hr, 89% yield of 3,5-diiodopyridine-2(IH)-thione (99) was obtained. In a similar way, 3,5-diiodopyridine-4(IH)-thione (100) was obtained in a quantitative yield from the 4-keto analog.

Pteridine-7-thiol (103) was prepared in 48% yield by Albert, Brown, and Wood[101] by the action of P_2S_5 on 7-hydroxypteridine in pyridine.

101   **102**   **103**
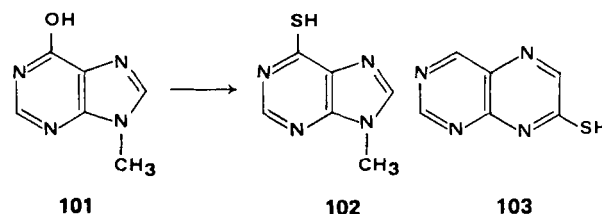
Similarly Castle and his co-workers obtained a better yield of 4-mercaptocinnoline (from 4-chlorocinnoline) compared to the yield obtained by reaction with thiourea.[102] More recently Dorman,[103] Singerman and Castle[104] converted pyridazino(4,5-d)pyridazine-1,4-thiol and 3-methyl-pyridazino(4,5-c)pyridazine-5,8-diol to the corresponding 1,4-dithiol, 104, and 5,8-dithione, 105, respectively by the action of phosphorus pentasulfide in refluxing pyridine.

104   **105**

98   **99**   **100**

The thiation of heterocyclic phenols is not confined to pyridine systems. Robins and Lin[100] converted some 6-hydroxypurines, 101, to the corresponding 6-mercaptopurines (102) in this way.

106   **107**

Hanh, Prijs, and Erlemeyer[105] also converted 5-amino-4,6-dihydroxypyrimidine to the 4,6-dithiol analog, 106, required as an intermediate in the synthesis of 7-mercaptothiazolo(5,4-d)pyrimidine (107), an anti-tumor growth inhibitor.[106] Falco and Hitchings[107] used the same reaction to convert some 4-amino- and 4-hydroxy-5-benzamidopyrimidines (108) to the corresponding thiazolo(5,4-d)pyrimidines (109).

108: X = OH, NH₂   **109**
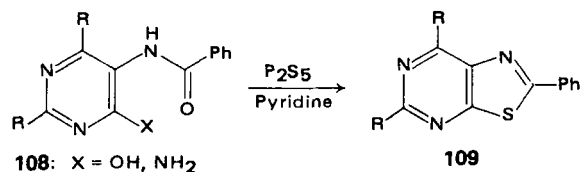
When Räth[108] treated 5-iodo-2-pyridone (110) with phosphorus pentasulfide at 185° pyridine-2(1H)-thione (60) was obtained. Contrary to expectation, the iodine was lost in the process, being replaced by hydrogen.

110   **111**

112: R = Cl   **114**
113: R = Br
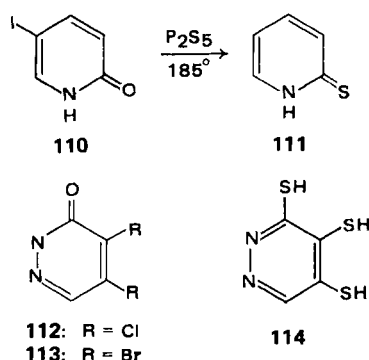
An equally interesting result was reported by Castle and his coworkers[109] who observed a novel nucleophilic displacement of halogen in pyridazine halides with phosphorus pentasulfide in refluxing pyridine solution. 4,5-Dichloro-3-pyridazone (112) and 4,5-dibromo-3-pyridazone (113) were converted, in this way, to pyridazine-3,4,5-trithiol (114) in 76% and 89% yields respectively. This reaction was further investigated by these authors[110-112] who also extended it to cinnoline ring systems.[113] The condensation of

4,5-dichloro-3-pyridazone (112) with sodium hydrosulfide in ethanol did not give the expected 3-pyridazone-4,5-dithiol, 115, but rather a dimer whose structure was established as compound 116 was obtained in 90% yield. The phenyl derivative 117 was isolated in 62% yield by a similar reaction with 4,5-dichloro-1-phenyl-6-pyridazone (III).
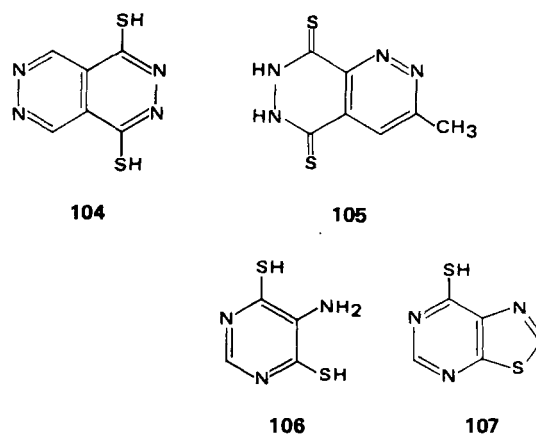

115   **116**

117
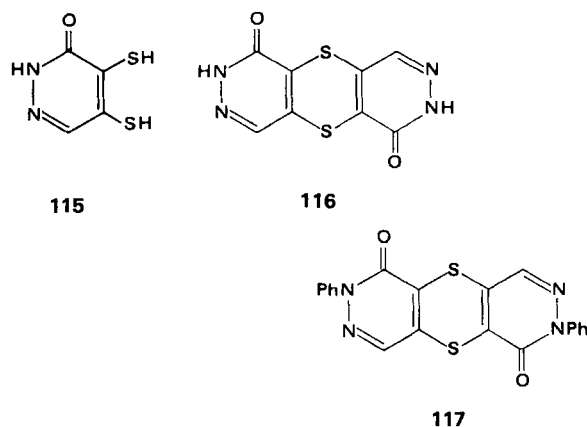
The dimer, 116, was subsequently converted to pyridazine-3,4,5-trithiol (114) in 88% yield by the action of phosphorus pentasulfide in pyridine.[112]

In an attempt to extend this thiation reaction to imidazopyridazine systems, 7-chloroimidazo(4,5-c)-pyridazine (118) was treated with phosphorus pentasulfide in pyridine.[114]

118   **120**   **119**
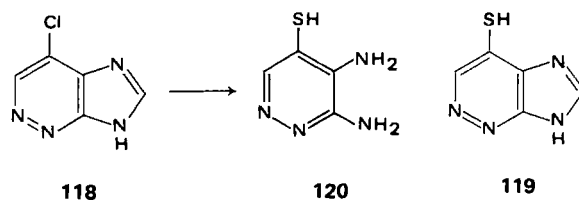
The expected imidazo(4,5-c)pyridazine-7-thiol (119) did not form, but rather, the halogen atom was replaced by a mercapto group while the imidazole ring was ruptured to give 3,5-diaminopyridazine-5-thiol (120) in only 17% yield.

REFERENCES

1. G. D. Gal'pern, *Int. J. Sulfur Chem., B*, 6, 115 (1971). Organosulfides of Petroleum.
2. H. J. Coleman, R. L. Hopkins, and C. J. Thompson, *Int. J. Sulfur Chem., B*, 6, 41 (1971). Highlights of Some 50 Man—Years of Petroleum Sulfur Studies by the Bureau of Mines.
3. P. Tooley, "Chemistry in Industry: Fuels, Explosives and Dyestuffs", John Murray Publishers Ltd., London, 1971, pp 1-160. Chemicals from Coal and Petroleum.
4. T. Wieland in "The Chemistry of Natural Products", Vol. 3, Special Lectures presented

at the Third International Symposium on The Chemistry of Natural Products, Kyoto, Japan, 12-18 April, 1964, Butterworths Publishers Inc., London, 1964, pp 145-157. Peptide of *Amanita phalloides*.

5. Z. M. Bacq, *Int. J. Sulfur Chem.*, *B*, 6, 93 (1971). Some Considerations on the Role of Sulfur in Living Organisms.

6. "New Drugs" Evaluated by the A.M.A. Council on Drugs, American Medical Association, Chicago, Illinois, U.S.A. 1965, Chapter 1, pp 1-48. Antibacterial Agents.

7. C. Bodea and I. Silberg in "Advances in Heterocyclic Chemistry", Vol. 9, A. R. Katritzky and A. J. Boulton, Eds., Academic Press Inc., New York, N.Y. 1968, pp 321-460. Recent Advances in the Chemistry of Phenothiazines.

8. C. J. Grol and J. S. Faber, *Rec. Trav. Chim. Pays-Bas*, 89, 68 (1970). Dithieno-1,4-thiazines. Part I.

9. H. Wynberg and A. Kraak, *J. Org. Chem.*, 29, 2455 (1964). The Synthesis of Thiophene Analogs of Fluorene.

10. N. P. Buu-Hoi, *Quart. Rept. Sulfur Chem.*, 5, 9 (1970). Biochemical Properties of Compounds derived from polycyclic Aromatic systems by Replacement of Benzene Rings by Equivalent Sulfur Heterocycles.

11. C. O. Okafor, *Int. J. Sulfur Chem.*, *B*, 6, 237 (1971). Studies in the Heterocyclic Series. III. The Chemistry of Azaphenothiazine Compounds.

12. C. O. Okafor, *Int. J. Sulfur Chem.*, *B*, 7, 121 (1972). Studies in the Heterocyclic Series. VI. The Chemistry and Applications of Isomeric Thiazolopyridines and Related Systems.

13. C. O. Okafor, *Int. J. Sulfur Chem.*, *B*, 7, 109 (1972). Studies in the Heterocyclic Series V. The Chemistry of Sulfur Analogs of Phenothiazine.

14. H. D. Hartough in "The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives", A. Weissberger, Consulting Ed., Interscience Publishers, Inc., New York, N.Y., 1952, Ch. 2, pp 29-45. Biological and Pharmacological Activity of Thiophene and Its Derivatives.

15. J. English, Jr., and H. G. Cassidy, "Principles of Organic Chemistry," 3rd Ed., McGraw-Hill Book Co., Inc., New York, N.Y., 1961, pp 324-337. Sulfur Compounds.

16. S. P. Massie, *Chem. Rev.*, 54, 791 (1954). The Chemistry of Phenothiazine.

17. "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N.Y., 1960, pp 89-1177.

18. C. Kissel, R. J. Holland, and M. C. Caserio, *J. Org. Chem.*, 37, 2720 (1972). Electron—Accepting Through—Conjugation Effects in Organosulfur Compounds.

19. H. D. Hartough in, "The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives," A. Weisseberger, Consulting Ed., Interscience Publishers, Inc., New York, N.Y. 1952, pp 143-144. Resonance in the Thiophene Nucleus.

20. M. P. Cava, *Int. J. Sulfur Chem.*, *C*, 7, 55 (1972). The Chemistry of Some Tetracovalent condensed Thiophenes.

21. G. Marino, *Int. J. Sulfur Chem.*, *C*, 7, 61 (1972). Quantitative Aspects of the Aromatic Reactivity of Thiophene and Related Compounds.

22. H. P. Kaufmann, *Chem. Ber*, 62B, 390 (1929). Further Communication on My Method of Thiocyanating Organic Compounds.

23. H. P. Kaufmann and M. Schubert, German Patent 493,025 (April 8, 1927). Organic Thiocyano Compounds.

24. H. P. Kaufmann and P. Schulz, *Arch. Pharm.*, 273, 31 (1935). Benzothiazolylureas.

25. T. Takahashi, Y. Yoshikawa, Y. Yamamoto, and T. Okada, *J. Pharm. Soc. Japan*, 66, 26 (1946). Pyridine Derivatives Containing Sulfur XVII. Synthesis of Pyridothiazoles and Pyrimidazoles.

26. Y. Yamamoto, *J. Pharm. Soc. Japan*, 71, 662 (1951). Pyridine Derivatives Containing Sulfur. XXXII. Synthesis of Pyridothiazoles.

27. Y. Yamamoto, *J. Pharm. Soc. Japan*, 71, 916 (1951). Pyridine Derivatives Containing Sulfur, XXXIII. Synthesis of Pyrido(3,2-d)-thiazoles and Cleavage of Thiazole Rings.

28. Y. Yamamoto, *J. Pharm. Soc. Japan*, 71, 920 (1951). Pyridine Derivatives Containing Sulfur. XXXIV. Synthesis of 2-Alkylmercapto-5-chloro (and Ethoxy) Pyrido(3,2-d)thiazole and Related Compounds.

29. Y. Yamamoto, *J. Pharm. Soc. Japan*, 71, 1436 (1951). Pyridine Derivatives Containing Sulfur. XXXV. Synthesis of 2'-Methylpyrido-2,3:5',4'-thiazoles (2-Methylpyrido(3,2-d)thiazoles) and Related Compounds.

30. Y. Yamamoto and T. Takahashi, *J. Pharm. Soc. Japan*, 71, 169 (1951). Pyridine Derivatives Containing Sulfur. XXXI. Synthesis of Pyrido-Thiazoles and Pyridooxazoles.

31. T. Takahashi and K. Ueda, *J. Pharm. Soc. Japan*, 73, 442 (1953). Sulfur-containing Pyridine Derivatives. XXXVIII. Pyrido-2,3:4',5'-thiazoles and Pyridyl Sulfones.

32. J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, *J. Amer. Chem. Soc.*, **69**, 1151 (1947). II. Derivatives of 2,6-Diaminopyridine.

33. A. Maggiolo, *J. Am. Chem. Soc.*, **73**, 5815 (1951). The Reaction of Thiocyanogen with Nitrogen Heterocycles; Pyridines, Pyrimidines and Quinolines.

34. J. A. Baker and S. A. Hill, *J. Chem., Soc.*, 3464 (1962). The Synthesis of Thiazolopyridines and Bisthiazolopyridines.

35. Maggiolo (Ref. 33) reported that the product is 2,6-diaminobisthiazolo(4,5-b: 5',4'-e)pyridine 11, mp 152-153, while Bernstein (Ref. 32) and his co-workers obtained two products claimed to be 2,5-diaminothiazolo(4,5-b)pyridine, 10, mp 138-139; and compound 11, mp > 300°. Yamamoto and Takahashi (Ref. 30) had reported a melting point of 137° for their compound 10 which now turns out to be 2,6-diamino-3-thiacyanopyridine, mp 141-141.5° from the work of Baker and Hill (Ref. 34).

36. C. O. Okafor, *J. Org. Chem.*, **38**, 4383 (1973). Studies in the Heterocyclic Series. VII. The Use of Kaufmann's Reaction as a Route to *o*-aminomercaptopyridines.

37. C. E. Hall and A. Taurins, *Can. J. Chem.*, **44**, 2465 (1966). Thiazoloisoquinolines. I. The Synthesis of Thiazolo(4,5-c)isoquinoline.

38. C. E. Hall and A. Taurins, *Can. J. Chem.*, **44**, 2473 (1966). Thiazoloisoquinolines, II. The Synthesis of Thiazolo(5,4-c)isoquinoline.

39. A. Taurins and R. Kang-Chuan Hsia, *Can. J. Chem.*, **49**, 4054 (1971). Thiazoloisoquinolines. IV. The Synthesis and Spectra of Thiazolo-(4,5-h)- and Thiazolo(5,4-f)isoquinolines. The Ultraviolet and Proton Magnetic Resonance Spectra of Some Substituted Isoquinolines.

40. A. Maggiolo and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 4226 (1951). Studies on Condensed Pyrimidine Systems. VI. Some 2-Aminothiazolo(4,5-d)pyrimidines.

41. J. A. Baker and P. V. Chatfield, *J. Chem. Soc.*, *C*, 603 (1969). Synthesis of Derivatives of Thiazolo(4,5-d)pyrimidine. Part I.

42. V. Bellavita, *Ann. Chim. Appl.*, **38**, 449 (1948). The Thiazoles: Thiocyanation and Nitration.

43. V. Bellavita and L. Vantaggi, *Ann. Chim.* (Rome), **46**, 275 (1956). The Thiazole Series. III. Sulfur Heterocyclic Derivatives of 2-Aminothiazole.

44. E. Soderback, *Acta. Chem. Scand.*, **8**, 1851 (1954). Catalytic Thiocyanation of Aromatic Nuclei.

45. E. Soderback, *Justus Liebigs Ann. Chem.*, **419**, 217 (1919). Free Thiocyanogen.

46. T. Takahashi and E. Yoshii, *Chem. Pharm. Bull.* (Tokyo), **2**, 382 (1954). Sulfur Containing Pyridine Derivatives. XLII. Synthesis of Pyrido-(2,3:2',3')-*p*-thiazine (1).

47. T. Takahashi and Y. Maki, *Chem. Pharm. Bull* (Tokyo), **3**, 92 (1955). Sulfur Containing Pyridine Derivatives. XLIII. Synthesis of Pyrido(2,3:2',3')-*p*-thiazines (2).

48. K. Ueda, *Chem. Pharm. Bull.* (Tokyo), **4**, 396 (1956). Sulfur Containing Pyridine Derivatives. L. Mechanism of Cleavage of Thiazole Ring of 2-Aminothiazolo(5,4-b)pyridines by Means of Aqueous Alkali.

49. (a). C. O. Okafor, M. L. Steenberg and J. P. Buckley, *J. Heterocyclic Chem.*, **12**, 813 (1975). A New Triazaphenothiazine Ring with Tranquilizing Activity.
    (b). C. O. Okafor, *J. Org. Chem.*, **40**, 2753 (1975). Studies in the Heterocyclic Series. X. 1,3,9-Triazaphenothiazine Ring System, a New Phenothiazine Ring.

50. C. O. Okafor, *J. Org. Chem.*, **38**, 4386 (1973). Studies in the Heterocyclic Series. VIII. The First Synthesis of a Triazaphenothiazine Ring.

51. G. B. Bachman, D. E. Welton, G. L. Jenkins, and J. E. Christian, *J. Am. Chem. Soc.*, **69**, 365 (1947). Quinoline Derivatives from 3-Nitro-4-hydroxyquinoline.

52. J. A. Baker and P. V. Chatfield, *J. Chem. Soc.*, C, 2478 (1970). Synthesis of Derivatives of Thiazolo(4,5-d)pyrimidine. Part II.

53. R. D. Schuetz and W. L. Fredericks, *J. Org. Chem.*, **27**, 1301 (1962). A new Synthesis of Thiophene- and Thianaphthenethiols.

54. T. Takahashi and K. Ueda, *Chem. Pharm. Bull.* (Tokyo), **2**, 34 (1954). Sulfur Containing Pyridine Derivatives. XXXIX. Behaviour of 3-Nitro-4-thiocyanopyridine and synthesis of 2'-Aminopyrido-3,4:4',5'-thiazole and Related Compounds.

55. T. Takahashi and H. Goto, *J. Pharm. Soc. Japan* **63**, 425 (1943). Pyridine Derivatives Containing Sulfur. VI. Derivatives of 2-Chloro-5-nitropyridine and 2-Chloro-3-nitropyridine.

56. T. Takahashi and Y. Yamamoto, *J. Pharm. Soc. Japan*, **72**, 1491 (1952). Pyridine Derivatives Containing Sulfur. XXXVIa. Pyrido-2,3:5',4'-thiazoles.

57. T. Takahashi, T. Naito, and S. Inoue, *Chem. Pharm. Bull.* (Tokyo), **6**, 334 (1958). Pyrimidine Derivatives. I. Synthesis of Thiazolo(5,4-d)-pyrimidines and Related Compounds.

58. J. R. Thirtle, *J. Am. Chem. Soc.*, **68**, 342 (1946), 2-Mercaptopyridine.

59. H. Saikachi, *J. Pharm. Soc. Japan.*, **64**, 201
(1944). Pyridine Derivatives Containing Sulfur.
VII. Synthesis of Pyridoxazoles and Pyrido-
thiazoles.

60. S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2755
(1955). Xanthones and Thioxanthones. Part VI.
The Preparation and Properties of 9-Thia-3-aza-
anthrone.

61. O. R. Rodig, R. E. Collier, and R. K. Schlatzer,
J. Org. Chem., **29**, 2652 (1964). Pyridine
Chemistry. I. The Smiles Rearrangement of the
3-Amino-2,2'-dipyridyl Sulfide System.

62. O. R. Rodig, R. E. Collier, and R. K. Schlatzer,
J. Med. Chem., **9**, 116 (1966). Pyridine Chem-
istry. II. Further studies on the Smiles Rearrange-
ment of the 3-Amino-2,2'-dipyridyl Sulfide
System. The Synthesis of Some 1,6-Diazapheno-
thiazines.

63. Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, 4516
(1954). Acylarylnitrosamines. Part VII. Reactions
of 3-Aminomethoxypyridines and 3-Amino-
1-methylpyridones. The Preparation of
2-Methoxy-3-phenyl-, 4-Methoxy-3-phenyl-,
and 2-Methoxy-5-phenylpyridine.

64. C. F. H. Allen and C. N. Wolf in "Org- Synth.",
Coll, Vol. 4, N. Rabjohn, Ed.-in-chief, J. Wiley
and Sons, Inc., New York, N.Y., 1963, pp 45-
47. 3-Aminopyridine.

65. S. J. Childress and R. L. McKee, *J. Am. Chem.
Soc.*, **73**, 3504 (1951). Pyrido(3,2-d)thiazoles.

66. B. Camerino and G. Palamidessi, *Gazz. Chim.
Ital.*, **90**, 1815 (1960). Pyrazine Derivatives. II.
Sulfonamidopyrazines.

67. G. Palamidessi and L. Benardi, *Gazz. Chim.
Ital.*, **91**, 1438 (1961). Pyrazine Derivatives. IV.
Pyrazine-N-oxides and their Reactions with
Phosphorus Oxychloride.

68. J. Kinugawa, M. Ochiai, and H. Yamamoto,
Yakugaku Zasshi, **80**, 1559 (1960). Fungicides.
III. Synthesis and Antifungal Activity of Some
Pyridazine Derivatives.

69. H. Saikachi and S. Tagami, *Chem. Pharm. Bull.*
(Tokyo), **9**, 941 (1961). Compounds Related
to Pyrazine. III. Synthesis of 2-Substituted
Thiazolo(b)quinoxaline.

70. J. Koromogawa and M. Ochiai (Takeda Chemical
Industries, Ltd.), Japanese Patent 9989 (1962).
2-Mercapto-3,6-dimethylpyrazine.

71 J. Koromogawa and M. Ochiai (Takeda Chemical
Industries, Ltd.), Japanese Patent 9990 (1962).
2-Thiocyano-3,6-dimethylpyrazine.

72. T. Takahashi and Y. Yamamoto, *J. Pharm. Soc.
Japan*, **70**, 187 (1950). Pyridine Derivatives
Containing Sulfur. XXX. Synthesis of 2-(Alkyl-

mercapto)pyridines, Pyridothiazoles and Related
Compounds.

73. S. Gronowitz, P. Moses, and A. Hornfeldt, *Arkiv.
Kemi.*, **17**, 237 (1961). Proton Magnetic Reson-
ance of Thiophenes. IX. Preparation of Sub-
stituted Thiophenethiols.

74. S. Gronowitz and R. Hakansson, *Arkiv. Kemi.*,
16, 309 (1960). 3-Substituted Thiophenes: New
Preparations of 3-Thiophenethiol, 3-Thiocyano-
thiophene and 3-Iodothiophene.

75. P. D. Caesar and P. D. Branton, *Ind. Eng. Chem.*,
44, 122 (1952). By-products of the Thiophene
Synthesis.

76. F. Challenger and J. B. Harrison, *J. Inst. Petro-
leum Technol.*, **21**, 135, 169 (1935). Sulfur
Compounds of Technical Interest. Isomeric
Thiophthenes.

77. W. H. Houff and R. D. Schuetz, *J. Am. Chem.
Soc.*, **75**, 6316 (1953). The Preparation and
Properties of a Few *omega*-(N,N-Dialkylamino)-
alkyl-2-thienyl Sulfide Hydrochlorides and
2-Thiophenethiol.

78. R. D. Schuetz and R. J. Fawcett, *Abst. American
Chemical Society Meeting*, San Francisco,
California, April 13-18, 1958, p 48.

79. R. J. Fawcett, *Doctoral Dissertation*, Michigan
State University, East Lansing, Michigan. *Diss.
Abstr.*, **20**, 3510 (1960). Synthesis of Sub-
stituted thiophenethiols and some ω-(N,N-
Dialkylaminoalkyl)thienyl Sulfide Hydro-
chloride Derivatives.

80. L. Chugaev, *Chem. Ber*, **32**, 3332 (1899). Ueber
eine neue Methode zur Darstellung ungesättigter
Kohlenwasserstoffe.

81. A. J. Saggiomo, P. N. Craig and M. Gordon,
J. Org. Chem., **23**, 1906 (1958). Synthesis of
2-Aza- and 8-Chloro-2-azaphenothiazine.

82. D. S. Tarbell and D. K. Fukushima in "Org.
Synth.," Coll. Vol. 3, E. C. Horning, Ed.-in-
Chief, J. Wiley and Sons, Inc., New York, N.Y.,
1955, pp 809-811. *m*-Thiocresol.

83. C. H. DePuy and R. W. King, *Chem. Rev.*, **60**,
431 (1960). Pyrolytic *cis*-Eliminations.

84. L. Katz, W. Schroeder, and M. Cohen, *J. Org.
Chem.*, **19**, 710 (1954). Hydrazine Derivatives.
II. Ortho-Mercaptopyridine Carbohydrazides.

85. A. O. Fritton and R. K. Smalley, "Practical
Heterocyclic Chemistry", Academic Press, Inc.,
London, 1968) pp 64-65. 2-Phenylbenzo-
thiazole.

86. A. R. Surrey and H. G. Lindwall, *J. Am. Chem.
Soc.*, **62**, 1697 (1940). The Reaction of 2-Chloro-
5-nitropyridine and Thiourea.

87. C. K. Bradsher and D. F. Lohr, Jr., *J. Hetero-cyclic Chem.*, **3**, 27 (1966). Thiazolo(3,2-a)-pyridinium Salts.

88. H. F. Andrew and C. K. Bradsher, *J. Hetero-cyclic Chem.*, **3**, 282 (1966). Derivatives of the Thiazolo(2,3-a)isoquinolinium System.

89. W. T. Caldwell and E. C. Kornfeld, *J. Am. Chem. Soc.*, **64**, 1695 (1942). Substituted 2-Sulfon-amido-5-aminopyridines.

90. A. Schönberg and L. von Vargha, *Chem. Ber*, **63B**, 178 (1930). Organic Sulfur Compounds. XVI. (Thermal) Rearrangement of thiono-carbonic esters into thiolcarbonic esters.

91. A. Schönberg, L. von Vargha, and W. Paul, *Justus Liebigs Ann. Chem.*, **483**, 107 (1930). Organic Sulfur Compounds. XVIII. Thermal Rearrangement of Thionocarbonic Esters into Thiolcarbonic Esters. 2. Formation of Disulfides from Phenols.

92. *N,N*-Dimethylthiocarbamyl chloride can be purchased from Aldrich Chemical Company, Milwaukee, Wisconsin 53233, U.S.A. The diethyl analog can be prepared as described by R. H. Goshorn, W. W. Levis, E. Jaul, and E. J. Ritter in "Org. Synth.", Coll. Vol. 4, N. Rabjohn, Ed-in-chief, J. Wiley and Sons, Inc., New York, N.Y., 1963, pp 307–310. Diethylthiocarbamyl Chloride.

93. H. R. Al-Kazimi, D. S. Tarbell, and D. Plant, *J. Am. Chem. Soc.*, **77**, 2479 (1955). A Study of the Schönberg Rearrangement of Diaryl Thioncarbonates to Diaryl Thiolcarbonates.

94. M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966). The Conversion of Phenols to Thiophenols *via* Dialkylthiocarbamates.

95. E. J. Blanz, Jr., F. A. French, J. R. Deamaral, and D. A. French, *J. Med. Chem.*, **13**, 1124 (1970). Carcinostatic Activity of Thiosemi-carbazones of Formyl Heteroaromatic Com-pounds. VII. 2-Formylpyridine Derivatives Bearing Additional Ring Substituents.

96. H. King and L. L. Ware, *J. Chem. Soc.*, 873 (1939). 4-Thiopyridone and Derived Substances.

97. F. Arndt and A. Kalischek, *Chem. Ber*, **63B**, 587 (1930). Constitution of the So-Called γ-Pyridones.

98. F. Arndt, *Chem. Ber*, **65B**, 92 (1932). N-γ′-Pyridyl-γ-pyridone.

99. E. Klingsberg and D. Papa, *J. Am. Chem. Soc.*, **73**, 4988 (1951). Thiation with P_2S_5 in Pyridine Solution.

100. R. K. Robins and H. H. Lin, *J. Am. Chem. Soc.*, **79**, 490 (1957). Potential Purine Antagonists. IV. Synthesis of Some 9-Methyl-6-substituted Purines.

101. A. Albert, D. J. Brown, and H. S. C. Wood, *J. Chem. Soc.*, 3832 (1954). Pteridine Studies. Part V. The Monosubstituted Pteridines.

102. R. N. Castle, H. Ward, N. White and K. Adachi, *J. Org. Chem.*, **25**, 570 (1960). Cinnoline Chemistry. V. 4-Mercaptocinnolines and Related Compounds.

103. L. C. Dorman, *J. Heterocyclic Chem.*, **4**, 491 (1967). 1,4-Disubstituted Pyridazino(4,5-d)-pyridazines.

104. G. M. Singerman and R. N. Castle, *J. Hetero-cyclic Chem.*, **4**, 393 (1967). Synthesis of Sub-stituted Pyridazino(4,5-c)pyridazines.

105. H. von Hahn, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 341 (1956). Thiazolo(5,4-d)-pyrimidines.

106. CIBA Ltd., British Patent 815,976 (July 8, 1959). Thiazolo(5,4-d)pyrimidines.

107. E. A. Falco and G. H. Hitchings, *J. Am. Chem. Soc.*, **72**, 3203 (1950). Studies on Condensed Pyrimidine Systems. IV. Some Thiazolo(5,4-d)-pyrimidines.

108. C. Räth, *Justis Liebigs Ann. Chem.*, **487**, 105 (1931). Derivatives of Pyridine. XII. Mercap-tans and Sulfonic Acids of Pyridine.

109. R. N. Castle and K. Kaji, *Tetrahedron Lett.*, 393 (1962). The Nucleophilic Displacement of Halogen in Pyridazines with P_2S_5.

110. T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.*, **1**, 42 (1964). Synthesis of Imidazo (4,5-c)-, s-triazolo(4,3-b)- and tetrazolo(1,5-b) pyridazines.

111. R. N. Castle, *U.S. Govt. Res. Rept.*, **37**, 7 (1962). Synthesis of Heterocyclic β-Mercaptoethyl Compounds as Potential Radiation Protection Agents.

112. R. N. Castle and K. Kaji, *Naturwissenschaften*, **51**, 38 (1964). Synthesis and Cleavage of Dipyridazo(4,5-b:4,5-e)-1,4-dithiin-1,6-dione.

113. R. N. Castle, R. R. Shoup, K. Adachi, and D. L. Aldous, *J. Heterocyclic Chem.*, **1**, 98 (1964). Cinnoline Chemistry. IX. 5-, 6-, 7- and 8-Halo- Substituted 4-Mercaptocinnolines and Related Compounds.

114. H. Murakami and R. N. Castle, *J. Heterocyclic Chem.*, **4**, 555 (1967). The Synthesis of Imidazo-(4,5-c)- and *v*-Triazolo(4,5-c)pyridazines.