SYNTHESIS OF PYRIDYL AND QUINOLYL SUBSTITUTED 2-AMINOTHIAZOLES

A Thesis

by

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GENERAL INTRODUCTION

In the first stage of the present investigation, the 2-amino-4-(x-pyridyl)-thiazole and 2-amino-4-(y-quinolyl)-thiazoles were synthesized. Various methods were investigated. The best method, giving the highest yields and the purest product, was found to be that in which the appropriate acetylpyridine and acetylquinoline hydrobromides were condensed with thiourea in polar solvents.

The nitration of 2-amino-4-(4'pyridyl)-thiazole, under mild conditions afforded 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine which subsequently failed to rearrange to give the 5-nitro derivative. Attempts to introduce a nitro group in the 5- position of the thiazole ring failed when either the 2-amino-4-(4'-pyridyl)-thiazole or 2-acetylamino-4-(4'-pyridyl)-thiazole were treated with fuming nitric acid under more drastic conditions.

Further, work was carried out on the synthesis of 2-amino-4-(x-pyridyl)-5-(y-pyridyl)-thiazoles. To obtain the required carbonyl compounds, the appropriate esters were condensed with 2-picoline and 4-picoline via their carbanions. In all cases, except for 2-amino-4,5-di-(2'-

pyridyl)-thiazole, the corresponding carbonyl reactant (a pyridyl pyridylmethyl ketone) was brominated and then treated, without prior isolation, with thiourea. The 2-amino-4,5-di-(2'-pyridyl)-thiazole was prepared by heating 2-pyridyl 2-pyridylmethyl ketone with two molar equivalents of thiourea in the presence of iodine.

The ring closure method established for the preparation of 2-N-(alkyl or aryl)-amino-thiazole was extended to the synthesis of 2-N-(3'-pyridyl)-amino-thiazoles and 2-N-(3'-quinolyl)-amino-thiazoles. At first, a method was developed for the unreported N-(3-pyridyl)-thiourea and N-(3-quinolyl)-thiourea. By condensing 3-aminopyridine and 3-aminoquinoline with benzoyl isothiocyanate, the 1-benzoyl-3-(3'-pyridyl)-2-thiourea and 1-benzoyl-3-(3'-quinolyl)-2-thiourea were obtained. Upon hydrolysis with sodium hydroxide, these benzoyl derivatives afforded N-(3-pyridyl)-thiourea and N-(3-quinolyl)-thiourea. The N-(3-pyridyl)-thiourea and N-(3-quinolyl)-thiourea were treated with various α- halo ketones (or their hydrobromides) in polar solvents at moderate temperatures. The procedures used were very simple and the yields were high.

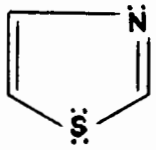
In the final stage, the infrared spectra of most of the compounds prepared during this investigation, were examined.

The infrared spectra of 2-N-(3'-pyridyl)-aminothiazoles and 2-N-(3'-quinolyl)-aminothiazoles revealed that these compounds have a resonance hybrid structure involving mainly the imino and the ionic forms having a positive charge on the thiazole ring nitrogen and a negative charge on the exocyclic nitrogen. The infrared spectrum of the nitration product of 2-amino-4-(4'-pyridyl)-thiazole was correlated with the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine structure. Examination of the infrared spectra of 2-pyridyl 2-pyridylmethyl-, 4-pyridyl 2-pyridylmethyl-, 2-pyridyl 4-pyridyl-, and 4-pyridyl 4-pyridylmethylketone indicated that these compounds have a resonance hybrid structure receiving contributions from dipolar and α,β - unsaturated ketone forms.

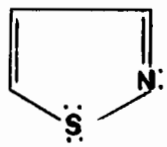
HISTORICAL INTRODUCTION

1. General

There are two kinds of five membered rings containing sulfur and nitrogen. In the thiazole ring (I), the sulfur and nitrogen are separated by one and two carbons, whereas in the isothiazole ring (II), the two heteroatoms are directly linked.



I



II

Because of their biological and industrial importance, the thiazoles have been extensively investigated and a great number of their derivatives are known.

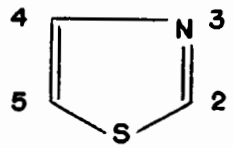
The isothiazoles have been investigated to a very limited extent.

2. Nomenclature

The naming of thiazoles and the numbering of the thiazole ring system follows the rules on nomenclature used in Chemical Abstracts and the Ring Index by Patterson (1) for the heterocyclic rings. According to these rules the heteroatoms are denoted by the use of prefixes oxa-, thia-, aza-, etc., and if more than one kind of atom occurs in the ring the prefixes are combined in the order which gives

preference to the atom of the highest group in the periodic table and of lowest atomic number in that group (i.e., O,S, Se, Te, N, P, As, Sb, Si, etc.). To the proper combination is attached a syllable denoting the size of the ring (- ol - for five -, in for six membered rings, etc.) and finally the ending. The ending denotes the degree of unsaturation as well as the absence or presence of nitrogen. For the thiazole ring we have: thi (a)- az (a)- ol - e. Here the ending e denotes the completely unsaturated thiazole ring. The ending ine and idine are used to denote the dihydrothiazole and tetrahydrothiazole rings, respectively.

The ring atoms are numbered in such a manner that when starting with the sulfur atom as no. 1, the nitrogen will have the lowest number (III).

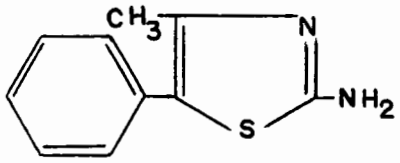


III

In the old chemical literature, the carbon atoms of the thiazole ring were designated by Greek letters. Two such systems were in use. According to one system (2,43,70) the 4- position was denoted by α and the 5- position by β. In another system the reverse notation was used (1,58), that

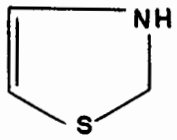
is the 4- position was denoted by β and the 5- position by α . In both systems μ was used to designate the 2-position. These notations are not used in the modern chemical literature.

Substituents in a thiazole derivative are named by alphabetic priority as in 2-amino-4-methyl-5-phenylthiazole (IV).

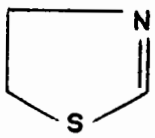


IV

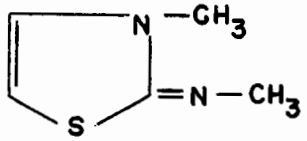
The 2,3-dihydrothiazole (V) and 4,5-dihydrothiazole (VI) are designated as 4-thiazoline and 2-thiazoline, respectively. The more complex 4-thiazoline (VII) is named as 2-methylimino-3-methyl-4-thiazoline.



V



VI



VII

In some of the French Chemical literature, the numbering of the ring thiazole starts with the nitrogen atom as no. 1 and proceeds to the sulfur as no. 3 (15,71). The French numbering is, however, inconsistent with the numbering of heterocyclic rings and is not widely used.

3. Structure of thiazole

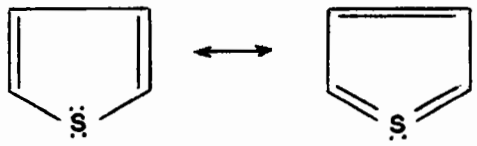
The classical structure (I) of thiazole possessing two double bonds in the 2,3- and 4,5- positions, failed to adequately explain its aromatic nature and chemical behaviour. Extension of the concept of oscillating bonds (3) and later of resonance of conjugated bond systems (as in the Kekule structure of benzene and of pyridine) to thiazole and other five-membered rings containing sulfur met with difficulty. According to the classical concepts of structure (3), the unsymmetrical nature of the thiazole ring did not allow alternate positions of double bonds.

The marked similarities, between the properties of thiazoles and their pyridine analogs, and the parallel similarities between the benzene and thiophene series (3, 10,40,41) lead to the conclusion that substitution of a sulfur atom for a vinylene group ($-CH=CH-$) results in compounds with similar properties (3). This enabled Erlenmeyer (6) to extend the concept of isosterism as developed by Langmuir (4) and Grimm (5) for inorganic compounds, to organic substances, particularly to thiazoles and thiophenes (6,7,8). According to this theory, the vinylene group, $-\overset{\cdot\cdot}{\underset{H}{C}}=\overset{\cdot\cdot}{\underset{H}{C}}-$, of an aromatic ring system and a sulfur atom, $-\overset{\cdot\cdot}{\underset{\cdot\cdot}{S}}-$, of the thiazole or thiophene molecule

are isosteric by virtue of each group having the same number of binding electrons, that is the group —CH=CH— is considered a "pseudo sulfur atom". But this concept of isosterism alone failed to rationalize all the chemical similarities and differences between the thiazole and pyridine series and proved inadequate when extended to the oxygen and nitrogen isosters, furan, oxazole, isoxazole, pyrrole (9).

At present, the concept of mesomerism and resonance (9,14) are successfully applied to account for the aromatic character of thiazole and other five-membered sulfur containing compounds.

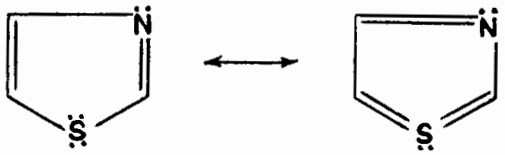
Electron diffraction studies, dipole moment measurements and resonance energy data, led Pauling and Schoemaker (11) to suggest that the thiophene molecule receives a 10% contribution from electronic structures in which the sulfur atom has ten electrons in its outer shell (IX).



VIII IX

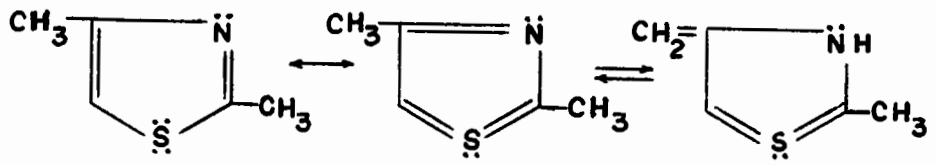
Thus the classical structure VIII and the structure IX having an expanded outer shell of the sulfur atom are among the resonance forms of thiophene. Based on the fact that the hydrogen atoms of a methyl group in either the

2- or 4- position of the thiazole ring undergo exchange with deuterium, Erlenmeyer, Weber and Wiesmer (12,13) proposed analogous resonating structures for thiazole (X,XI). In fact, they found that the sodium salt of 4-methylthiazole-5-carboxylic acid in deuterium oxide exchanged the three hydrogen atoms of the methyl group for deuterium.

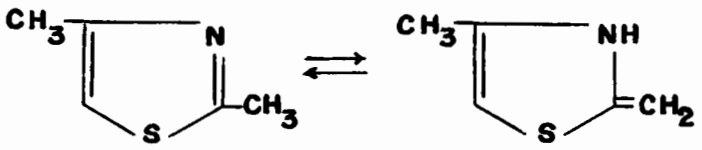


X XI

Moreover, they found that 2,4-dimethylthiazole-5-carboxylic acid exchanged the hydrogen atoms of both methyl groups for deuterium. This observation was interpreted by Erlenmeyer and coworkers as evidence for the resonance structure XI. Such a structure would support tautomerism involving the 4-methyl group (XIII $\rightleftharpoons$ XIV); the classical structure permits only the 2-methyl group to tautomerize (XV $\rightleftharpoons$ XVI).



XII XIII XIV

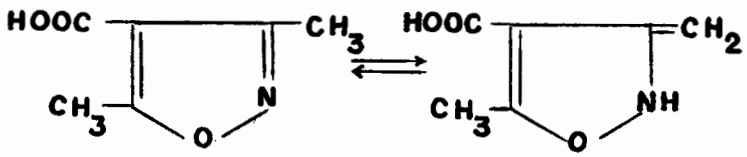


XV XVI

In the pyridine series, where the equivalence of the 2- and 6- position through resonance of the conjugated bond system is accepted (XVII ⟷ XVIII), similar deuterium exchanges were shown to take place (13).

XVII XVIII

Moreover, in the 2,3-dimethylisoxazole-4-carboxylic acid (XIX), where resonance structures involving the expansion of the outer shell of the oxygen atom are not possible, only the 3-methyl group enters into the deuterium exchange. (because of the tautomeric equilibrium: XIX XX)

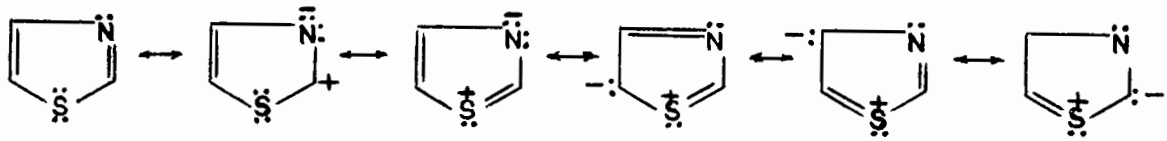


XIX XX

However, the chemical behaviour of many 2- and 4-substituted thiazoles suggests the unsymmetrical nature of the $-\overset{2}{C}-\overset{3}{N}-\overset{4}{C}$ groups in contrast to the symmetrical $-\overset{6}{C}-\overset{1}{N}-\overset{2}{C}-$ unit in the pyridine ring. With the exception of the deuterium exchange a methyl group in the 4- position is unreactive towards reagents that react readily with a similar group in the 2- position. In the pyridine series, alkyl groups attached to the 2- (or 6) and 4- positions are reactive. An alkyl group in the 5- position of the thiazole ring is inert, and consequently such a derivative resembles 3- (or 5)- alkylpyridine. Quaternization of the nitrogen of the thiazole ring enhances still further the reactivity of a 2- methyl group but does not confer reactivity upon a methyl group in the 4- position. The considerable differences in properties of amino, hydroxyl and carboxyl groups in the 2- and 4- positions are further proof that the group $-\overset{2}{C}-\overset{3}{N}-\overset{4}{C}-$ of the thiazole ring is not a symmetrical unit.

Chemical evidence (14) and quantum mechanical calculations (15) point out that the thiazole molecule has no classical double and single bonds but it is a resonance

hybrid (16) analogous to many other aromatic systems. Ochiai and Nagasawa (14) have studied the behaviour of thiazole and derivatives toward nucleophilic reagents and have suggested the following resonance structures for the unsubstituted molecule:

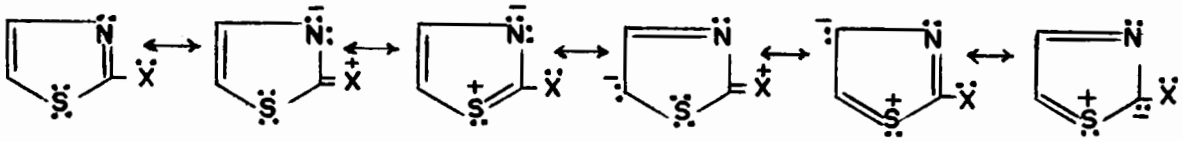


XXI XXII XXIII XXIV XXV XXVI

The important resonating forms would be XXI, XXII and XXIII; structures such as XXIV, XXV and XXVI make a very small contribution. Most of the chemical reactions of thiazole can be explained by considering these predominant forms (XXI, XXII and XXIII) without recourse to resonance involving the expanded shell of the sulfur atom (XI) which makes a small but significant contribution (61). Accordingly, the resonating structure XXII offers an adequate explanation, of the reactivity of this position in nucleophilic reactions, e.g. direct amination of thiazole by sodium amide (14), reactivity of halogens in the 2- position towards nucleophilic reagents such as sodium salts of amines (17), hydroxide anion (18), etc., reactivity of the 2-methyl group in Claisen Condensations under basic conditions and aldol type reactions (78). The activation of groups that occupy this

position is similar to that of the well-known activated groups in α - and γ - positions of pyridine and quinoline (78) and of groups adjacent to carbonyl functions (78). The reactivity of the 5- position of the thiazole ring in electrophilic reactions (14,37,79,80) is accounted for by the resonance structure XXIV.

In the case where the thiazole ring contains a group capable of +M effect such as $-\ddot{O}-H$, $-\ddot{O}-R$, $-\ddot{N}H_2$, that is a group possessing an unshared pair of electrons, the resonance form XXX corresponding to XXIV in the parent thiazole molecule is among the predominant resonance structures (XXVII,XXVIII,XXIX,XXX) (14).



XXVII XXVIII XXIX XXX XXXI XXXII

The 5-position is highly activated in such a system. In fact, it has been proved experimentally that in these compounds electrophilic substitution in the 5-position occurs under very mild conditions: e.g., 2-hydroxy-4-methylthiazole readily undergoes nitration

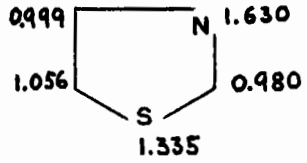
with a mixture of concentrated sulfuric and nitric acid at 0° or at room temperature (14), whereas 4-methylthiazole requires heating at 160° with 20% oleum and potassium nitrate to give 4-methyl-5-nitrothiazole (35).

Pullmann and Metzger (15), in 1948, have reported the molecular diagram of thiazole, benzothiazole and of their methyl derivatives. Their calculations were carried out in accordance with the procedure developed by Wheland and Pauling (72) for the quantum mechanical treatment of molecular structures. Only the molecular diagrams of thiazole and the three methylthiazole derivatives will be discussed here.

In general, molecular diagrams are used to summarize the significant numerical magnitudes for conjugated molecules. The parameters which are given in these diagrams are bond orders, net charges on each atom (in units of one electron) and free valences. These numerical values can be obtained by applying either the molecular or the valence-bond method to the molecule under consideration (72,75). Charges on atoms enable us to estimate the most likely place of attack by charged groups (electrophiles or nucleophiles) and, in

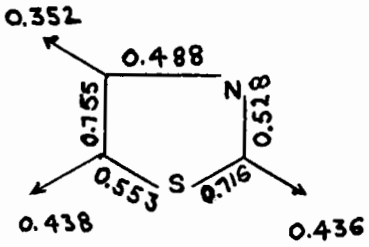
general, to determine the π- electron dipole moment and to see how they change as a result of substitution or further conjugation. Bond orders are written along the bonds. In general, they refer to the nature of the chemical bond, that is whether it has multiple or single bond character; thus they enable us to infer about the bond length (76,77) and to recognize the degree of bond fixation. By definition (m.o. or v.b.- method), the bond orders of the carbon- carbon bonds in ethane, ethylene and acetylene are 1,2 and 3, while their mobil bond order is 0,1 and 2, respectively. The bond order of a resonating molecule is fractional. For benzene, the molecular orbital method gives a bond order of 1.667 and thus a mobile bond order of 0.667 (77). This means that the bond length is intermediate between those of a normal single and double bond as a result of resonance of the double bond system. The free valency concept is the quantum mechanical version of Thiele's theory of partial valency or Werner's residual affinity. It determines to some extent the behaviour of the molecule in free radical reactions; the forces which start off these reactions being largely due to the residual affinities of the approaching atoms in the two reacting

groups. Free valence is represented by an arrow diverging from the nucleus and with the numerical value at its head (XXXIV).



XXXIII

Charge Distribution



XXXIV

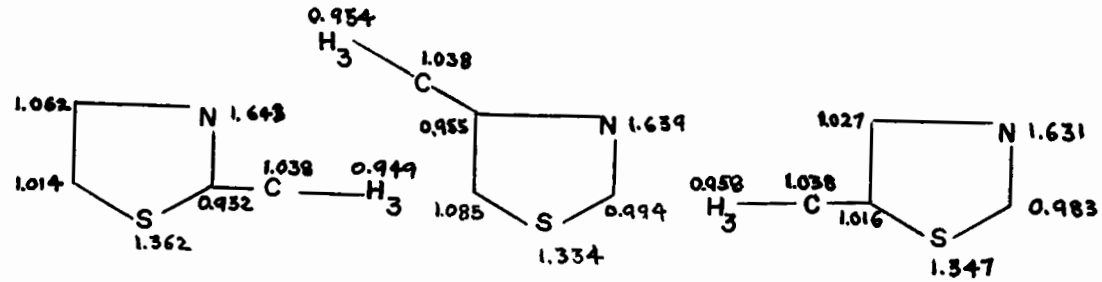
Bond orders and free valences

The defficiency of charge (or the presence of a positive charge) on carbon atom no. 2 of XXXIII explains the reactivity of thiazole towards nucleophilic reagents. The slight electric charge on carbon atom no. 5 accounts for the reactivity of this position in electrophilic reactions, e.g. sulfonation occurring in quite good yield (65%) at 250° with 28% oleum and mercuric sulfate (22). The electric charge on carbon no. 4 is practically equal to unity and therefore, as expected, this position is inert. The values for the mobile bond orders (0.716, 0.528, 0.488, 0.755, 0.553) indicate that the bonds in the thiazole molecule are intermediate between single and double bonds which is in agreement with the resonance hybrid structure postulated by Ochiai and Nagasawa (14).

Thiazole in the gaseous phase at 250-400°, in presence of pumice stone reacts with bromine to yield the 2-bromo derivative (23). This agrees well with the high free valence number (0.436) allotted to this position in XXXIV.

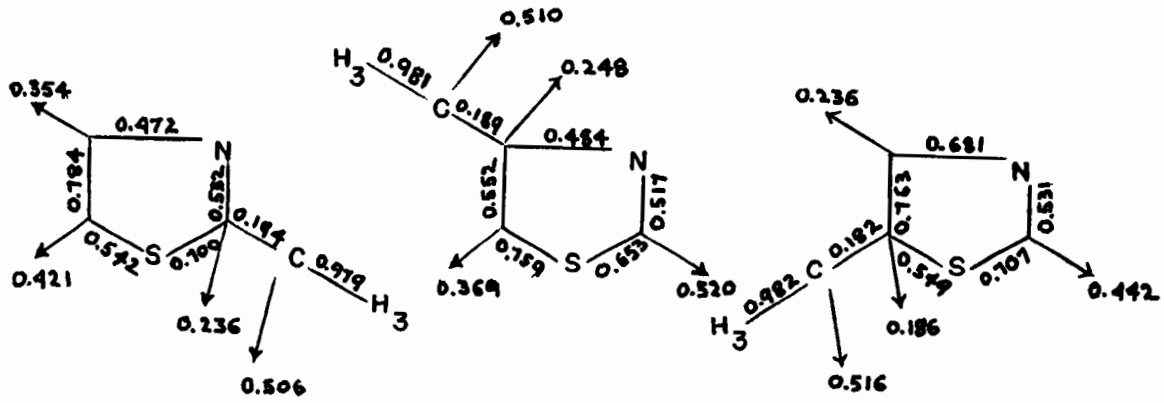
The study of the diagrams of 2-, 4- and 5-methylthiazoles (XXXV, XXXVI, XXXVII, XXXVIII, XXXIX, XL) permits an adequate explanation of the differences in reactivities of the methyl group and afford some information with regard to the electronic interactions between the ring system and substituents. The degree of conjugation of the methyl groups with the thiazole nucleus can be estimated from the following quantities: (a) magnitute of charges on the H_3 group (pseudo atom), (b) bond order or double bond character of the $C_{ar.} - C_{aliph.}$ linkage and (c) bond order of the linkage $C \equiv H_3$ (pseudo bond). The deficiency of charge on the H_3 group with regard to unity gives an indication of the electron transfer towards the ring. If no conjugation occurs, the linkage $C_{ar.} - C_{aliph.}$ will be a simple bond and consequently its mobile order will be zero. Thus the value of this mobile bond order represents the

degree of conjugation of the methyl group with the thiazole nucleus. The weakening of the bond $C \equiv H_3$ arising from hyperconjugation results in a decrease of its bond order with regard to unity.



XXXV XXXVI XXXVII

Charge distribution



XXXVIII XXXIX XL

Distribution of bond orders and free valences.

A close analysis of these data for the three molecules under consideration shows that the degree of conjugation of the methyl groups with the thiazole nucleus increases in the order 5-methyl 4-methyl 2-methyl. A comparison of the corresponding charges on the H_3, the mobile bond order of the $C_{ar.} - C_{aliph.}$ linkage and the bond order of the $C{\equiv}H_3$ group will substantiate this. The bond orders for the $C{\equiv}H_3$ group in the three compounds are decreasing in the order 5-methyl, 4-methyl and 2-methyl and thus the weakening of the pseudo bond $C{\equiv}H_3$, and the extent of hyperconjugation follows the same order. The mobile bond orders of the $C_{ar.} - C_{aliph.}$ and the positive charges on the H_3 group, both of which change as the degree of conjugation, are increasing from 5-methyl to 2-methyl. Since the reactivity of the methyl group depends on the degree of conjugation with the nucleus, it follows that 5-methylthiazole should be the least reactive and the 2-methylthiazole very reactive. One instance is known when the 4-methyl group shows greater reactivity than the 2-methyl, i.e., the condensation of 2,4-dimethylthiazole with formaldehyde in a sealed tube as 160° (74). But this

reaction is an addition to the carbon atom of the methyl group in the 4- position of the thiazole nucleus, followed by a rearrangement concerning exclusively this particular atom. It may be assumed to be a molecular or a free radical reaction and in this case its occurrence could be explained by the higher free valence number (0.510) allotted to the carbon atom of the methyl group in the 4- position as compared to that of the carbon atom of the methyl group in the 2- position (0.506). The reaction of an aromatic aldehyde such as benzaldehyde with 2-methylthiazole is favoured by the simultaneous occurrence of an appreciable positive charge on the H_3 group and a large negative charge on the oxygen atom of the carbonyl group due to resonance with the benzene ring. At the same time the reaction is promoted by the weakening of the C-H linkage of the methyl group as well as weakening of the C-O bond of the aldehyde.

Most of the chemical properties of 2-, 4- and 5-methylthiazole are in good agreement with the conclusions drawn from these diagrams (15).

Further, Pullmann and Metzger (73) concluded that the simultaneous presence of two adjacent methyl groups, as

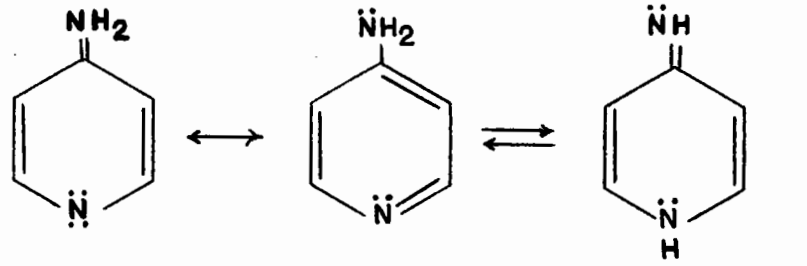
in 4,5-dimethylthiazole, has the effect of diminishing the extent of conjugation of each group (as compared to the conjugation which each group would have if present alone in the ring) because of the simultaneous charge transfers towards the ring. Thus the hydrogens of the methyl groups in the 4,5-dimethylthiazoles should be less reactive than these of the corresponding monosubstituted methyl derivatives. These assumptions were verified experimentally by Erne and Erlenmeyer (81).

4. Tautomerism

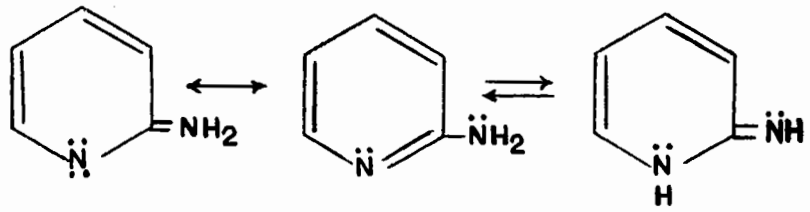
Tautomerism is said to occur when the reactions of an individual substance require the assignment of two or more distinct structures which differ markedly in the relative position of at least one atomic nucleus.

2-Aminothiazole possesses properties which are characteristic of aromatic amines (diazotation, coupling with diaronium salts, etc.). However, 2-aminothiazoles, like many other cyclic amidines or vinylogs of amidines, such as 2- and 4-aminopyridine, 2- and 4-aminoquinolines, exhibit properties which suggest a tautomeric nature, that is, they may exist either as amino derivatives (XLII,XLV,XLVIII)

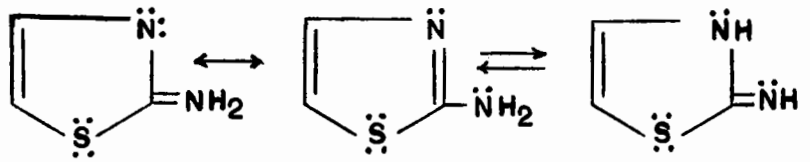
or as dihydro-imino-compounds (XLIII,XLVI,XLIX). In fact, derivatives of the imino- forms are known but the parent substances of this composition were never isolated. Tschitschibabin (24,36), used the concept of imino- form to explain the difference in chemical behaviour between potentially tautomeric amines and those which are not capable of such tautomerism, e.g., 3-aminopyridine. Since then it has been customary to assign the imino- structure to any N- heterocylic amine whose reactions did not correspond to those expected from an aromatic amine.



XLI XLII XLIII



XLIV XLV XLVI



XLVII XLVIII XLIX

The problem of tautomerism of these amines was extensively investigated and remained controversial for a long time. Two groups of investigators arrived at opposite conclusions. In 1948, Steck and Ewing (25), from the study of ultraviolet absorption spectra of ammopyridines, aminoquinolines and aminoisoquinolines assigned an imino structure to the 2- and 4-amino isomers. A year later, Anderson and Seeger (26) who also studied the ultraviolet absorption spectra of these compounds found no evidence for the presence of the imino-forms in solutions of 2- and 4-aminopyridine.

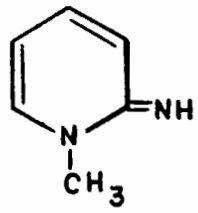
Most of the evidence presented in favour of the imino form is based on the isolation of the reaction products. However, since the tautomeric form are in equilibrium, a tautomer which is present in only a minute amount may still be responsible for a particular reaction and this, of course, invalidates the above evidence. According to Angyal and coworkers (27,28) the study of the physical properties of tautomers in equilibrium is the best evidence for their presence. These workers, from the study of infrared spectra (28), dipole moments, dissociation constants and considerations of resonance energy indicated that these

N-heteroaromatic amines including 2-aminothiazole existed in the amino form. They examined the infrared spectra (28) in the 3300 cm^{-1} and 1650 cm^{-1} regions of chloroform solutions of a series of amino derivatives of pyridine, quinoline, thiazole and pyrimidine, in which tautomerism might occur, and compared them with the spectra of related compounds of known structure or in which tautomerism is not possible. In the high frequency region, the close resemblance of the spectra of 2- and 4- aminopyridine 3453 cm^{-1}, 3404 cm^{-1}, (3330 cm^{-1}), 3190 cm^{-1} and 3492 cm^{-1}, 3405 cm^{-1}, 3216 cm^{-1}, respectively , -naphthylamine (3453 cm^{-1}, 3378 cm^{-1}, 3240 cm^{-1}) and 3-aminopyridine 3454 cm^{-1}, 3375 cm^{-1}, (3340 cm^{-1}), 3200 cm^{-1} strongly suggested that these substances exist in the amino rather than the imino- form. The spectrum of 1,2-dihydro-2-imino-1-methylpyridine (L) in which the imine-form is stabilized, has only one peak (3325 cm^{-1}) in this region and this strengthens the above conclusion.

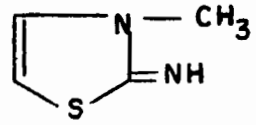
With 2-aminothiazole and 2-aminopyrimidine the same multiple absorption bands (3480 cm^{-1}, 3392 cm^{-1}, 3306 cm^{-1} and 3488 cm^{-1}, 3410 cm^{-1}, 3319 cm^{-1}, 3188 cm^{-1},

respectively) occur. In the same region, the spectrum of 2-imino-3-methyl-4-thiazoline (LI) shows only a single band (3335 cm^{-1}) characteristic of the imino group. This is additional evidence in favour of the amino structure of 2-aminothiazole.

The conclusions reached from the study of the infrared absorption spectra in the high frequency range is supported well by results obtained in the 1650-1400 cm^{-1} region.



L



LI

The amino-forms have an aromatic structure and are thus stabilized by resonance energy. The imino- forms have a quinonoid structure in which some of the aromatic stabilization has been lost. Consequently, the amino-forms would be expected to be the most stable form in all N-heteroaromatic amines (unless there is interference by substituents having a strong influence on the electron densities).

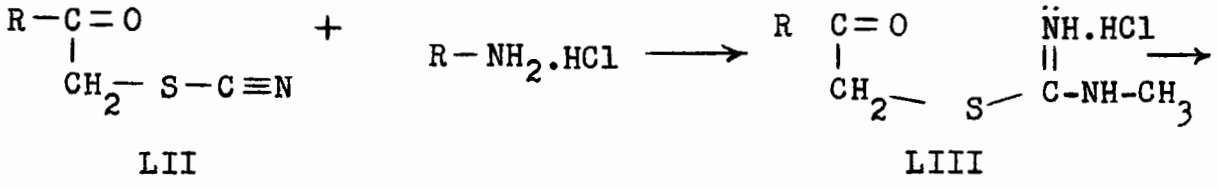
At first, this conclusion appears to be in contradiction with the fact that the analogous hydxoxy derivatives of these series have been shown to have the keto structure (29,30,31). The two classes, however, are not analogous. It has been shown by calculation (33) from Pauling's bond energy values that in the amide-imidol tautomeric system, $-NH-\underset{\underset{O}{\|}}{C}- \rightleftarrows -N=\underset{\underset{OH}{|}}{C}-$, the former tautomer is the most stable to the extent of about 10 Kcal./ mole. The loss in resonance energy by the tautomerisation of hydroxypyridines to pyridones may be compensated by the gain in bond energy. It is obvious that in the N-heteroaromatic amines, where the tautomeric system is that of an amidine, $NH-C=N- \rightleftarrows -N=C-NH-$, no change in bond energy takes place and thus there is nothing to compensate for the loss of resonance energy which would result from tautomerisation (XLII $\rightleftarrows$ XLIII, XLV $\rightleftarrows$ XLVI, XLVIII $\rightleftarrows$ XLIX).

At present, the amino structure of N-heteroaromatic amines is well established. Most of the reactions favouring the imino- form can be explained by resonance, e.g., methylation of the ring nitrogen occurs because of resonance structures such as XLI, XLIV, XLVII, which enhance the reactivity of this center towards electrophilic reagents.

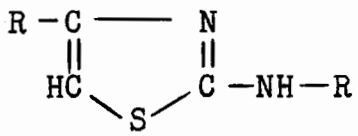
5. Preparation of 2-aminothiazoles by the ring closure methods.

There are three types of syntheses for 2-aminothiazoles: (a) direct amination of the thiazole ring (14); (b) replacement of a substituent such as a halogen by an amino group (17,37); (c) ring closure. The direct amination has very little preparative value. The second procedure is mainly used for the preparation of the N- substituted amino derivatives and serves as an independant method for checking the structure of compounds obtained by ring closure methods. The ring closure method constitutes the most important route to 2-aminothiazoles. In this method the following two reactions are used:

(1) Reaction of ∝ - thiocyanato ketones with amine hydrochlorides (19,38) or ammonium chloride (39):



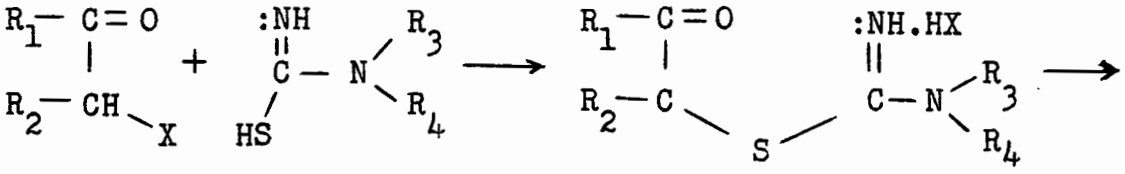
LII LIII



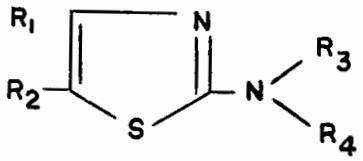
LIV

According to Hantzsch (38) the first step in this reaction is the addition of the amine or ammonia to the thiocyanate to give a straight-chain S- derivative of isothiourea. He succeeded in isolating S- acetonyl N-methylisothiourea in good yield (80%) by reacting methylamine at 0° in ethereal solution with acetonyl thiocyanate. This intermediate cyclized slowly on standing at room temperature and very readily on heating with dilute hydrochloric acid to produce 2-N-methylamino-thiazole (38).

(2) Reaction of an α - halocarbonyl compound with thiourea (43) or substituted thiourea (39).



LIV a LV LVI



LVII

This reaction was used in the synthesis of most of the compounds reported in the experimental part. This method was introduced originally by Hantzsch, Trauman and Arapides (40,41,42,43) for the preparation of thiazoles in general. The carbonyl reactant can be α - haloketones or α -haloaldehydes. To prepare thiazoles a thioamide is used instead of a thiourea.

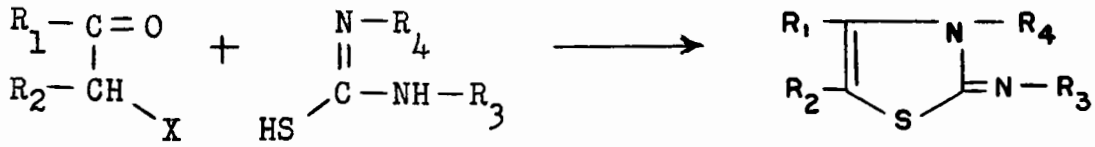
In the reaction of an α -halocarbonyl compound, $R_1-\underset{\underset{O}{\|}}{C}-\underset{\underset{R_2}{|}}{CH}-X$, with a thioamide, it has been assumed that the first step is elimination of hydrogen halide and formation of an open chain intermediate (44), $R-\underset{\underset{O}{\|}}{C}-\underset{\underset{R_2}{|}}{CH}-S-\underset{\underset{R_3}{|}}{C}=NH.HX$, which is a derivative of the imino-thiol form of the thioamide. This acyclic intermediate has a transitory existence in most of the reactions. In some reactions, if carried out at low temperature, this intermediate is relatively stable and thus could be isolated (44). The intermediate can be cyclized in most cases, but under more drastic conditions (heat, $ZnCl_2$, or concentrated hyrochloric acid) than those employed in the one-step synthesis of thiazoles. (44,45).

In the reaction of thiourea with α - halocarbonyl compounds, the ring closure is very facile. Thus an intermediate of the type, $R-\underset{\underset{O}{\|}}{C}-CH_2-S-\underset{\underset{NH}{\|}}{C}-NH_2$, could not be isolated. However, such compounds have been prepared by other methods and have been shown to cyclize (38). The reaction mechanism of thiourea with α - halocarbonyl compounds has not as yet been investigated.

Instead of the α - halocarbonyl compounds their derivatives can be used if these are able to generate the reactant under the reaction conditions. Trauman, in 1888, prepared 2-aminothiazole itself by refluxing α,β- dichloroethyl ethyl ether, $ClCH_2$-CHCl-O-CH_2-CH_3, with thiourea in aqueous solution (43). However, the reaction does not take place in the absence of water (43). The α,β- dichloroethyl ethyl ether gives chloroacetaldehyde in the reaction mixture. Other precursors of α - halocarbonyl compounds which have been successfully used to prepare 2-aminothiazole were bromo- and chloroacetal (46), brominated paraldehyde (47), bis- (α,β - dichloro- or dibromo-ethyl) ether (48) and α,β- dichloroethyl acetate (49,50,51).

The method using the condensation reaction of thiourea with α - halocarbonyl compounds is very versatile and widely used. By choosing the appropriate α - halocarbonyl compound the substituents of the 4- and 5- positions (R_1 and R_2 in LVII) can be varied to include functional groups as well as alkyl or aryl groups (53).

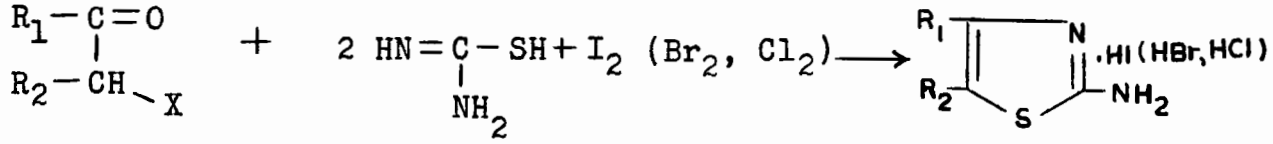
Mono- and di- substituted thioureas react with α - halocarbonyl compounds to yield 2-N- mono- and disubstituted 2-aminothiazoles and many of these derivatives are known (43,53,54). However, the symmetrically disubstituted thioureas (LIX) cannot form a true thiazole nucleus, but they do react with α - halo ketones or aldehydes to yield 2-iminothiazoles (LX) (43,62,63).



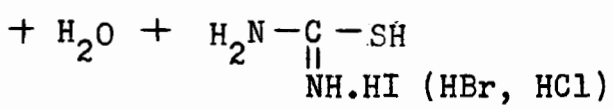
LVIII LIX LX

The synthesis of 2-aminothiazoles from thiourea by a modification that avoids α - halo ketones has been developed (55). In 1949, Dodson and King (55) treated a

mixture of one molecule of ketone having a methyl or a methylene group adjacent to the carbonyl function and two moles of thiourea with one mole of halogen and obtained mono- and disubstituted 2-aminothiazoles in accordance with the following scheme:



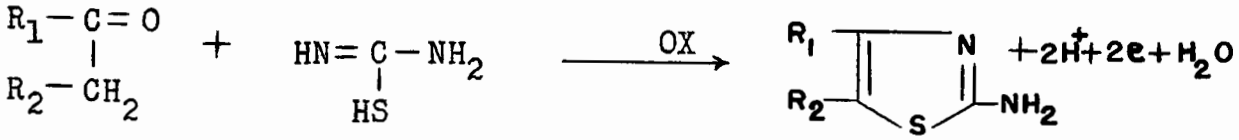
LXI LXII LXIII



LXIV

To establish the generality of this reaction, they condensed various ketones, namely acetone, ethyl acetoacetate, acetophenone, propiophenone, m- nitroacetophenone with thiourea using each of the common halogens (Cl_2, Br_2, I_2) and heating. Yields varied considerably depending on the halogen used. In a subsequent paper (56), these workers showed that other halogenated reagents such as sulfuryl chloride, thionyl chloride and chlorosulfonic acid can also be used to prepare 2-aminothiazoles in high

yields (60-88%). Furthermore, by using non-halogenated oxidizing agents, namely, sulfur trioxide, sulfuric acid, nitric acid and sulfur, they proved that the α - halocarbonyl compound is not a necessary intermediate in this reaction. They suggested that any reagent which would accept two electrons per molecule of 2-aminothiazole formed should be capable of effecting the reaction. Thus the formation of 2-aminothiazole from thiourea and a ketone can be represented by the following scheme:

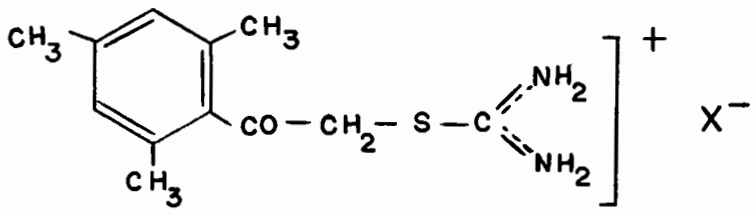


LXV LXVI LXVII

However, when non-halogenated oxidizing agents were used an appreciable amount of sulfur was formed and in each case the yield of 2-aminothiazole derivative was low (11-43%). In these cases it is assumed that two competing reactions take place: (1) the reaction of the ketone with thiourea and the oxidizing agent to form the 2-aminothiazole derivative and (2) the direct oxidation of thiourea to form sulfur. The mutual destruction of thiourea and the oxidizing agents would account for the lower yields obtained. King and Ryden (57)

suggested that formamidine disulfide, $H_2N-\underset{\underset{NH}{\|}}{C}-S-S-\underset{\underset{NH}{\|}}{C}-NH_2$, which is an oxidation product of thiourea, may be an intermediate in the reaction. They proved that this compound on heating with a ketone produces the corresponding 2-aminothiazole in variable yields (0-62%). The best yields of 2-aminothiazoles were obtained when the most reactive ketones were used, e.g., ethyl acetoacetate, under the best conditions, gave a 62% yield of thiazole, whereas acetophenone gave only 48%. An attempt to convert propiophenone into 2-amino-4-phenyl-5-methylthiazole by means of this reaction failed. Further investigation by King and Hlavacek (60), definitely established this method as a general preparative procedure for 2-aminothiazoles from ketones and thiourea. They prepared a variety of 2-aminothiazoles using iodine as an oxidizing agent. King and Hlavacek (60) also found that this method is not applicable to the preparation of 2-aminothiazole from certain ketones such as o-nitroacetophenone, 2-methylcyclohexanone, cyclopentanone and acetomesitylene. In the reaction of thiourea with acetomesitylene the isothiouronium salt (LXVIII)

was formed. This compound did not cyclize to yield the corresponding 2-aminothiazole. This is in agreement with the chemical behaviour of acetomesitylene which does not react as a normal ketone (64).



LXVIII

In 1955, Erlenmeyer, Herzfeld and Prij (65) successfully extended this method to the preparation of 2-aminothiazoles unsubstituted in the 4-position from aldehydes and thiourea. The best condensing agent was found to be sulfuryl chloride; using this, the yield of 2-aminothiazole derivative was 35%. Lower yields were obtained with bromine and iodine (24-26%). Non-halogenated oxidizing agents such as HNO_3 were also used but the yields were exceedingly low (3%). The preparation of 2-aminothiazoles by this method is in some cases more convenient than by the Hantzsch type synthesis because it avoids the α - halo aldehydes which are often unstable and unpleasant to handle.

Wiley, England and Behr, in Organic Reactions (58) gives a survey of the methods of thiazole syntheses. The reaction of thiourea and thioamides with α - halocarbonyl compounds is discussed. Prijs published, in 1952, a complete compilation (59) of the thiazole compounds and a monograph of thiazoles and benzothiazoles by Land and Sprague (61) is also available.

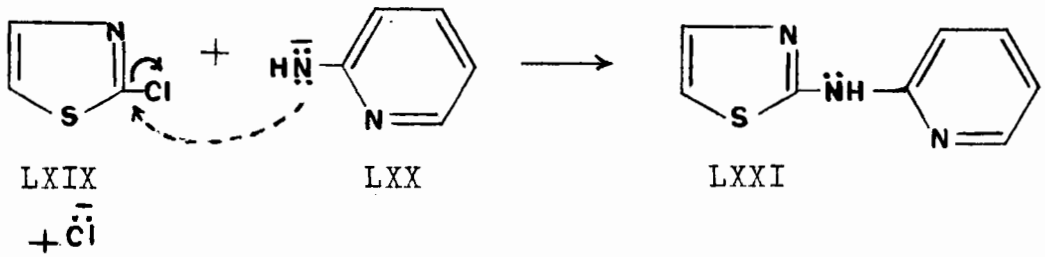
6. Pyridyl and quinolyl substituted thiazoles.

Although a great variety of thiazoles have been prepared only a few pyridyl and quinolyl substituted thiazoles are known.

In 1945, Karrer and Shukri (66) prepared the hydrochlorides of 4-methyl-2-(2'-pyridyl)-thiazole and of 4-methyl-2-(3'-pyridyl)-thiazole by reacting chloroacetone with pyridine-2- and pyridine-3-thiocarboxamide in ethanol under reflux for 8-10 hrs. Upon treatment of the aqueous solutions of these salts with sodium hydroxide the free bases were obtained. Knott and Breckenridge (67), synthesized under essentially the same conditions 4-(2'-pyridyl)-thiazole hydrochloride by reacting 2-bromoacetylpyridine with thioformamide. The yield of 4-(2'-pyridyl)-thiazole was low, 18.5%.

This investigation was well under way, when Magidson (68) synthesized the first 2-aminothiazole having a pyridyl substituent. He prepared 2-amino-4-(4'-pyridyl)-thiazole by refluxing with aqueous hydrochloric acid the 5-carbethoxy derivative. The 2-amino-5-carbethoxy-4-(4'-pyridyl)-thiazole was synthesized by treating isonicotinoylacetic ester with bromine in aqueous solution in the presence of hydrochloric acid and then adding thiourea.

Detweiler and Amschutz (17) reported the synthesis of 2-N-(2'-pyridyl)-ammothiazole which can also be called 2-N-(2'-thiazolyl)-aminopyridine. He treated 2-chlorothiazole with the sodium salt of 2-aminopyridine in anhydrous benzene, the reaction proceeding according to the following scheme:



LXIX LXX LXXI

$+\ddot{Cl}^{-}$

The product obtained was of low grade and needed extensive purification.

No thiazoles possessing quinolyl substituents are described in the literature. In 1951, a number of quinoline derivatives with the 2-aminothiazolyl group in the 4- position were prepared by Ganapathi and Shah (69) in connection with the synthesis of some antimalarials. The quinoline ring was substituted with various groups such as halogens, methyl, methoxy, etc. To prepare these compounds the 2-aminothiazole was treated with the appropriate 4-chloroquinoline derivative in the presence of phenol at 160-170°. 2-Aminothiazole, for instance, reacted with 4,7-dichloroquinoline to yield 4-(2-thiazolylamino)-7-chloroquinoline hydrochloride. The free base was obtained by treating the aqueous solution of the hydrochloride with diluted sodium hydroxide.

7. Infrared spectra of pyridines, quinolines and thiazoles.

In general, the amount of available information concerning the infrared spectra of the heterocyclic compounds is considerably less than their importance justifies. The similarity of the infrared spectra of pyridine and benzene has been recognized by many workers (82,83,84,91). The ring vibrations

of pyridine (84,85) and quinoline (85) parallel those of benzene and can readily be identified (84). On the other hand, the hydrogen vibrations do not compare to those of benzene and can only be tentatively assigned (84). However, the out-of-plane hydrogen deformation vibrations are analogous to those of benzene derivatives possessing an additional substituent (85,86). An account of the experimental work done on the infrared spectra of pyridines and quinolines up to 1958 has been published by Bellamy (85). The correlations which have been put forward will be summarized here. One should not overlook the fact that the assignments of absorption bands are based on a review of the spectroscopic properties of a limited number of compounds. The absorption bands from 3070 to 650 cm^{-1} can be grouped in frequency ranges and can be discussed in parallel with those of benzene.

a. Aromatic C-H stretching vibrations. Under high resolution (96), pyridine and picolines (84,85) show C-H stretching absorptions in the range 3070-3020 cm^{-1}. In general, the position and number of bands are very similar to those of benzene analogs. According to Marion, Ramsay and Jones (92), anabasine (in liquid phase) shows a band due to aromatic C-H

bond stretching of the pyridine nucleus which is absent from the spectrum of piperidine. An interesting feature of this region is the occurrence of bands in the 2830-2790 cm^{-1} range (85). These bands are not found in benzene derivatives and may be indicative of heterocyclic structures.

b. The stretching vibrations of C=C and C=N bonds. In general, two bands occur between 1600-1400 cm^{-1}. As in benzene, these bands are believed to be associated with interactions (85) between C=C and C=N bonds. Usually, the first of these bands occurs near 1600 cm^{-1} and the second near 1500 cm^{-1} (85). The 1600 cm^{-1} band may show a double maximum (85,91), the second maximum being at lower frequency. Pyridine itself absorbs at 1600 cm^{-1} (91), 1580 cm^{-1} (85,91) and 1486 cm^{-1} (91). Cook and Church (91) found that for monosubstituted pyridines, the average separation of the two maxima near 1600 cm^{-1} can be used to differentiate the 2- and 3-monoalkylpyridines from 4-monoalkylpyridines. For 2- and 3-monoalkylpyridines the average separation is 20 cm^{-1}, whereas for 4-monoalkylpyridines this value is about 40 cm^{-1}.

The pattern of absorption bands of quinoline is essentially the same as that of pyridine with one or more additional bands (85).

c. Ring vibrations and hydrogen deformations (1250-650 cm^{-1}). In the frequency range 1250-1000 cm^{-1}, pyridines and derivatives (85,91) show two strong bands, one between 1250 cm^{-1} and 1220 cm^{-1} and another between 1100 cm^{-1} and 1000 cm^{-1}. Cook and Church (91), during their investigation, attributed the peaks in the range 1220-1250 cm^{-1} to bending vibrations of hydrogen atoms on the pyridine nucleus. They also found additional bands at 1145-1152 cm^{-1} for 2-monoalkylpyridines which probably arise from the same source. The quinolines do not seem to show strong absorptions in this frequency range.

In the region 900-650 cm^{-1}, heteroaromatic compounds, like benzene derivatives (87), exhibit a strong band. This band is associated with in phase out-of-plane hydrogen bending vibrations. The frequency at which this band occurs is determined by the number of adjacent free hydrogen atoms. Pyridine with five free hydrogen atoms behaves similarly to mono-substituted benzene, whereas 2-methylpyridine resembles

ortho disubstituted benzene. Cook and Church (91) reported that this band occurs in the range 750-743 cm^{-1} for 2-monoalkylpyridines, 810-789 cm^{-1} for 3-monoalkylpyridines and 822-785 cm^{-1} for 4-monoalkylpyridines. In all the spectra of pyridines examined (91) a band near 710 cm^{-1} was continuously present, which, however, does not appear in the spectra of quinolines (85).

The (in phase) out-of-plane hydrogen deformation (band) correlation is valid also for quinolines if each ring is considered separately (85). For example, 2,6- and 2,7-dimethylquinolines, which have two adjacent free hydrogens in each ring, absorb very strongly at 831 cm^{-1} and 835 cm^{-1}, respectively, similar to para disubstituted aromatics. 8-Hydroxyquinoline exhibits a strong absorption band at 780 cm^{-1}, which is characteristic of meta substituted aromatics (85). This agrees well with the presence of three adjacent free hydrogens in each ring as in meta substituted benzenes.

Recently, Gardner, Hands, Jones and Katrinsky (88,89,90) studied the infrared absorption of a variety of 2-, 3- and 4- substituted pyridines in chloroform solution. The effect of various substituents on the position and

intensities of absorption were thoroughly discussed for each absorption region of the three classes of substituted pyridines.

Estep, Karr and Papa (95) have analysed the spectra of about twenty different quinolines in the frequency range 900-650 cm^{-1}. By comparing the frequencies of these quinolines with those of pyridines, benzene derivatives and naphthalenes, they found that, when compounds of the same hydrogen structure are compared, the frequency increase in going from benzenes to naphthalenes is about the same as the frequency increase in going from pyridines to quinolines. Moreover, they observed that napthalenoid rings and quinolinic carbocyclic rings with the same hydrogen structure show bands at about the same frequency.

Thiazoles show an infrared absorption pattern very similar to that of heteroaromatics and aromatics. Randall, Fowler, Fuson and Dangle (98) have reported the infrared spectra, in the 1600-1500 cm^{-1} region, of 2-aminothiazole (XLVIII) and 2-amino-4-(p-biphenyl)-thiazole as well as that of 2-mercapto-4-phenylthiazole and 2-mercapto-4,5-dimethylthiazole. They found two strong absorption peaks

for each of these compounds, occuring in the range 1634-1570 cm^{-1} and 1538-1493 cm^{-1}, respectively. These bands correspond to the aromatic ring stretching vibrations and are considered to be typical of the thiazole structure (85,98). Thiazole itself was found to absorb at 1626 cm^{-1} and 1515 cm^{-1} (98). Bogomolow, Sheinker and Postowskii(99) examined the infrared spectra of some N-acetyl derivatives of 2-amino-alkylthiazoles and the infrared spectrum of the sulfonic acid of 2-amino-4-methylthiazole.

Taurins, Fenyes and Jones (100) studied the infrared spectra of thiazole and its methyl derivatives in the liquid state and made a thorough interpretation of the absorption bands. Absorption peaks in the region 3110-3050 cm^{-1} were assigned to aromatic C-H stretching vibrations. Here again, bands occurring in the 1690-1480 cm^{-1} range were assigned to skeletal vibration of the thiazole ring. Several bands were found in the 900-640 region and very probably some of these could be associated with out-of-plane vibrations of the aromatic C-H bonds of the thiazole nucleus. However, no correlation could be made between the number of free hydrogens present in the ring and the number of bands.

Angyal and Werner (29) examined the infrared spectra of 2-aminothiazole (XLVIII) and 2-imino-3-methyl-4-thiazoline (LI) in the 3300 cm^{-1} and 1660 cm^{-1} regions in connection with studies of tautomerism of cyclic amidines (pg. 21).

Taurins (101) has studied the spectrum of 2-nitrimino-(3H)-thiazolium betaine. The spectrum did not show any absorption bands in the region 3400-3200 cm^{-1} which would arise if the N-H group were present either in the nitramino or nitrimino structures. Instead, this compound showed a wide band between 3140 cm^{-1} and 2270 cm^{-1}, which is in agreement with a betaine-like structure.

In 1958, Harris (106) analysed the infrared spectra of several 2-aminothiazoles and 2-nitrimino-(3H)-thiazolium betaines. The spectra of 2-aminothiazole carboxylic acids were correlated with the zwitterion structures of these compounds. The nitrimino-(3H)-thiazolium betaines showed a broad, structureless band between 3180 cm^{-1} and 2250 cm^{-1} which the author assigned to the quaternary ammonium cation ($\geqslant\overset{+}{N}H$). They exhibited no absorption band in the 3500-3200 cm^{-1} region, thus excluding the classical isonitramine and nitrimine structures.

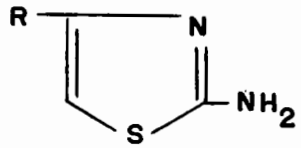
DISCUSSION

1. Synthesis of 2-amino-4-(x-pyridyl)thiazoles and 2-amino-4-(y-quinolyl)thiazoles.

In the first phase of this investigation, the synthesis of 2-aminothiazoles substituted by pyridyl and quinolyl groups in the 4-position was undertaken.

The synthesis of these compounds involved the following stages: (a) preparation of the acetylpyridines and acetylquinolines; (b) halogenation of the acetylpyridines and acetylquinolines; (c) condensation of the haloacetyl-pyridines and haloacetylquinolines with thiourea. An alternate method, in which the carbonyl reactant was treated with thiourea in the presence of a halogen, was also used.

These compounds are prepared for the first time by the methods described below and, with the exception of 2-amino-4-(4'-pyridyl)-thiazole, have not been reported in the literature. They are represented by the general formula LXXII and are listed in Table I.



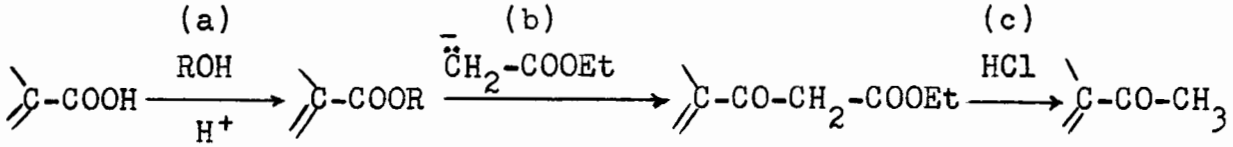
LXXII

TABLE I

Compound	R	m.p., °C.
2-Amino-4-(2'-pyridyl)-thiazole (LXXIII)	2-pyridyl	175.6-176°
2-Amino-4-(3'-pyridyl)-thiazole (LXXIV)	3-pyridyl	204-204.6°
2-Amino-4-(4'-pyridyl)-thiazole (LXXV)	4-pyridyl	269.8-271.5°
2-Amino-4-(2'-quinolyl)-thiazole (LXXVI)	2-quinolyl	218.5-219°
2-Amino-4-(4'-quinolyl)-thiazole (LXXVII)	4-quinolyl	268-269°

a. Preparation of acetylpyridines and acetylquinolines.

To prepare 2-, 3-, and 4-acetylpyridines from the corresponding pyridinecarboxylic acids the following synthetic path was chosen: (a) esterification of the pyridinecarboxylic acids; (b) Claisen condensation of the esters of pyridinecarboxylic acids with ethyl acetate using sodium ethoxide as a catalyst; (c) hydrolysis of the β-ketoesters and decarboxylation of the resulting keto-acids.



The method of Camps (108) was used to prepare ethyl picolinate (ethyl pyridine-2-carboxylate). To avoid formation of emulsion during the ether extraction, the carbonate and

the portion of ester which precipitated were filtered off and exhaustively washed with water and ether. The reported yield was 90%. The best yield obtained in the present study was 62%. The methyl nicotinate (methyl pyridine-3-carboxylate) was prepared according to the method of Levine and Sneed (107) by refluxing nicotinic acid with a molar equivalent of absolute methyl alcohol in the presence of sulfuric acid; the yield was slightly higher than reported (72.5% as compared to 69.8%).

To prepare ethyl isonicotinate (ethyl pyridine-4-carboxylate) the method of Camps (108) was modified by introducing the azeotropic distillation of a ternary mixture and by changing the refluxing time. The ternary mixture, consisting of 57.6% of carbon tetrachloride, 23% of ethanol and 19.4% (by volume) boils at 61.8°. At first isonicotinic acid was refluxed with absolute ethanol in the presence of concentrated sulfuric acid for one hour. Carbon tetrachloride was added and the solution was heated slowly so that a definite amount of the azeotropic mixture distilled over a period of two hours. The yield (82.5%) was comparable to that reported by Camps (90%). The two layers of the distillate could be separated and the carbon tetrachloride could be recovered by distillation. The esters of pyridinecarboxylic acids were converted into the corresponding acetylpyridines by the method

of Kolloff and Hunter (110) which was slightly modified. It was found that, when the method of Kolloff and Hunter was used for the preparation of 2-acetylpyridine, the condensation of ethyl picolinate with ethyl acetate was very vigorous and exothermic. The violent course of the reaction resulted in extensive degradation (tar formation) of the products and consequently the yields were lower. Kolloff and Hunter reported the yields of 4-acetylpyridine, 3-acetylpyridine and 2-acetylpyridine as 79.5%, 81% and 51% respectively.

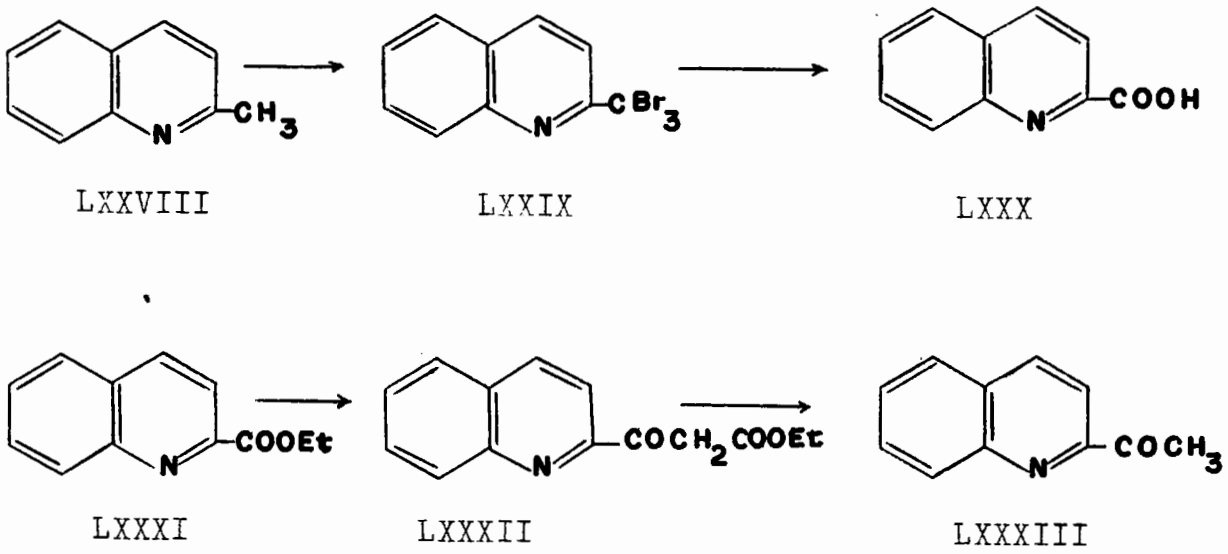
The method of Kolloff and Hunter entails the refluxing of the β - keto ester with hydrochloric acid for only two and a half hours. When the refluxing was increased to four and a half hours, the yields of 2-, 3-, and 4-acetylpyridine obtained in this laboratory were 60%, 80.2% and 75-77% respectively. Ethyl picolinate and ethyl isonicctinate were used for the preparation of 2- and 4-acetylpyridine. In the preparation of the isomeric 2-acetylpyridine, ethyl picolinate was used.

When the condensation of ethyl picolinate was conducted under milder conditions, by diluting the reaction mixture with dry toluene, a higher yield was obtained (81.4%); the reaction was less vigorous and very little or no tarring took place. 4-Acetylpyridine was also prepared from methyl

isonicotinate under conditions similar to those applied when ethyl isonicotinate was used. It has been found that methyl isonicotinate gives a higher yield of 4-acetylpyridine (88.9%) than ethyl isonicotinate (76.7%).

2- and 4-Acetylquinolines were prepared by two partially different synthetic routes. Campbell, Helbing and Kerwin's method (113) was used to convert quinaldine (LXXVIII) to quinaldic acid (LXXX). Quinaldine was first brominated in acetic acid in the presence of sodium acetate and the resulting α-tribromoquinaldine (LXXIX) was hydrolysed to quinaldic acid in dilute sulfuric acid under reflux. The yields in the bromination of quinaldine and in the hydrolysis step were 94% and 95% respectively. They compare very favourably with the reported yields of 84% and 90-98%. The ethyl quinaldate (LXXXI) was prepared in 83.3%, by refluxing quinaldic acid with absolute ethanol in the presence of concentrated sulfuric acid, as described by Ainley and King (117). The method of Campbell and Kerwin (112) was used to condense ethyl quinaldate with ethyl acetate in the presence of sodium ethoxide and subsequently to convert the β-keto

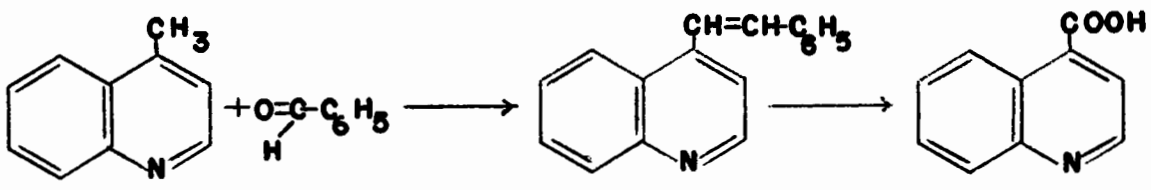
ester formed into 2-acetylquinoline (LXXXIII) by refluxing with dilute sulfuric acid. The yield of 2-acetylquinoline from ethyl quinaldate was 86%.



LXXVIII LXXIX LXXX

LXXXI LXXXII LXXXIII

A different route was used to convert lepidine (4-methylquinoline) to cinchoninic acid (117). Lepidine (LXXXIV) was condensed with benzaldehyde in the presence of anhydrous zinc chloride. Oxidation of 4-styrylquinoline (LXXXV) with potassium permanganate in 50% aqueous pyridine at 0° gave cinchoninic acid (LXXXVI) in 79% yield.



LXXXIV LXXXV LXXXVI

To prepare the 4-acetylquinoline, the cinchoninic acid was esterified by the same method as quinaldic acid (117) and condensed with ethyl acetate by the method of Campbell and Kerwin (112). Finally, the 4-acetylquinoline was isolated as the acetate by treating the oily free base with acetic acid.

b. Preparation of haloacetylpyridine hydrohalides and bromoacetylquinoline hydrobromides.

3-Bromoacetylpyridine hydrobromide was prepared using a modification of Brücken, Dornow and Machens' method (111) by adding bromine dropwise to a hot solution (70-75°) of 3-acetylpyridine in concentrated hydrobromic acid and stirring at 75° for three hours. The yield was 97%.

This method was applied, for the first time, to the preparation of 2- and 4-bromoacetylpyridine hydrobromide. At first, yields were low and products impure. The best yields were obtained when the bromination was carried out between 65-70° and when the reaction mixture was left for 24 hours during which period the perbromide which initially formed, changed to the bromo derivative. Under these conditions, the

yields of 2-bromoacetylpyridine hydrobromide and 4-bromoacetylpyridine hydrobromide were 88-90% and 80-82.6% respectively.

Originally, it was intended to isolate the free bases of the bromo derivative of the acetylpyridines. The 2-bromoacetylpyridine free base was prepared by Breckenridge and Knott (67) but in very low yield and in a very impure state by treating the hydrobromide salt with sodium bicarbonate. The 4-bromoacetylpyridine and its hydrobromide have not yet been described in the literature. The bromoacetylpyridine free base was very unstable and consequently could not be prepared in a satisfactory manner. In fact, upon addition of bases (dilute sodium hydroxide, dilute ammonium hydroxide or sodium bicarbonate) extensive decomposition occurred. The resulting mixture required long purification and the isolated free base decomposed upon standing. Since the hydrobromide, as it will be explained later, could be used more advantageously in the subsequent condensation with thiourea any further investigation involving the isolation of the bromoacetylpyridine free bases in the pure state was discontinued.

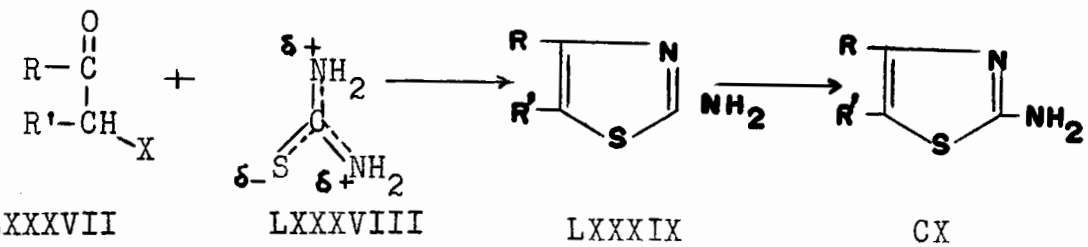
To prepare 3-chloroacetylpyridine hydrochloride, Brücken, Dornow and Machens (111) bubbled dry chloride in a solution of 3-acetylpyridine in anhydrous chloroform. This method was successfully used here and resulted in 83.3% yield of 3-chloroacetylpyridine hydrochloride, but failed when applied to the chlorination of 4-acetylpyridine hydrochloride.

2-Bromoacetylquinoline hydrobromide was prepared in 80.7% yield, by the procedure of Campbell, Helbing and Kerwin by adding bromine dissolved in 40% hydrobromic acid to a solution of the ketone in the same acid maintained at 65-68°. The same method was applied for the first time to the preparation of 4-bromoacetylquinoline hydrobromide from its acetate and the yield of product was 90.8%.

c. Condensation of the α-haloacetylpyridines with thiourea.

To prepare 2-aminothiazoles substituted in the 4-position by a pyridyl group, the appropriate α-haloacetyl-pyridine hydrohalides were condensed with thiourea according to the general equation (a, R' H).

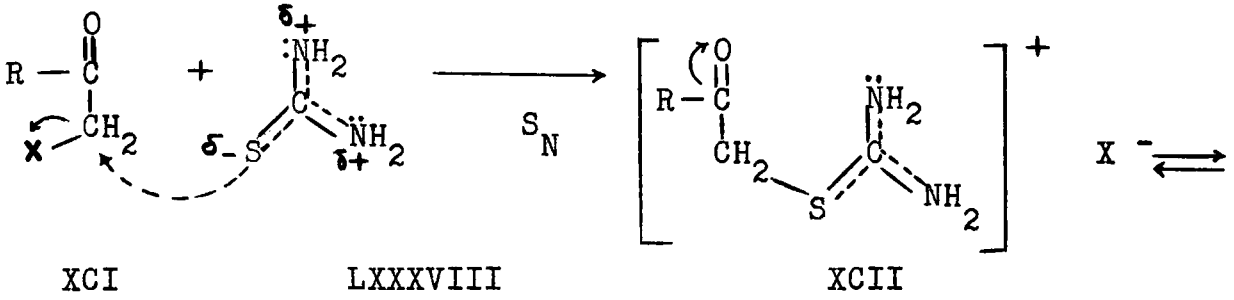
(a)



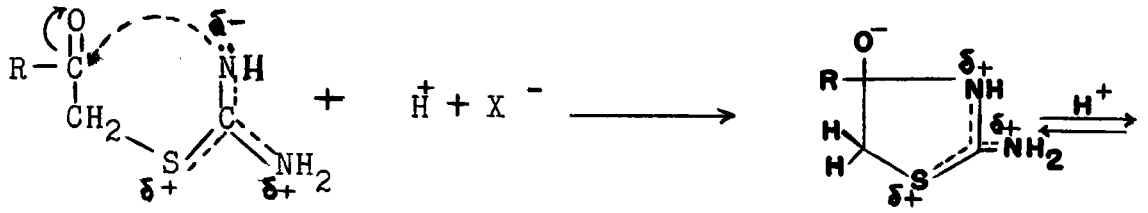
LXXXVII LXXXVIII LXXXIX CX

1. Reaction mechanism.

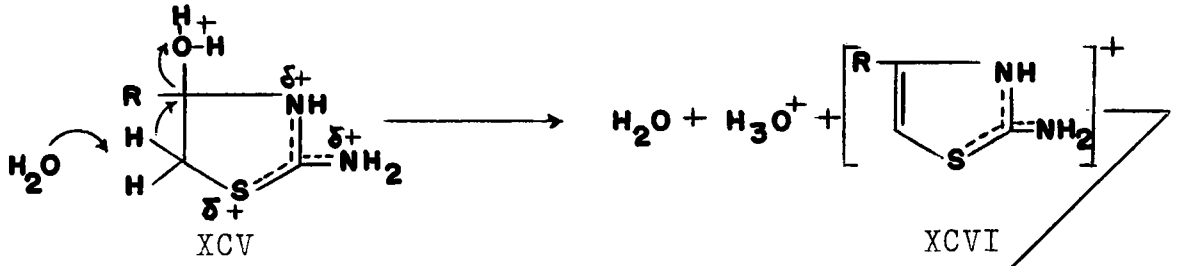
In the condensation of thiourea with α-halocarbonyl compounds, it is assumed that the first step is the formation of a straight chain intermediate (LVI). Since the reaction is very fast this intermediate cannot be isolated. In solution the mechanism of the reaction may occur according to the following scheme:



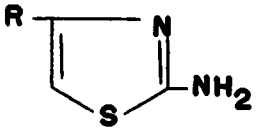
XCI LXXXVIII XCII



XCIII XCIV

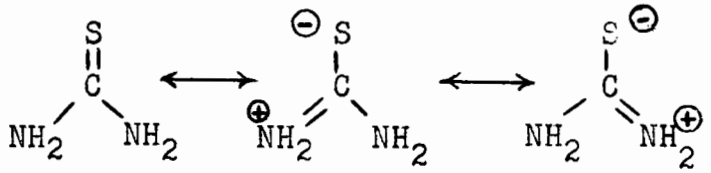


XCV XCVI



LXXVII

X-ray diffraction analysis (122), infrared spectra studies (123,124,125) and dipole moment measurements (126) established that the structure of thiourea can be represented as a resonance hybrid of three contributing forms (XCVII, XCVIII,XCIX); the contribution of the ionic resonance (XCVIII, XCIX) is twenty to thirty percent (126).



XCVII XCVIII XCIX

The structure of thiourea can also be represented by means of the mesomeric notation as in LXXXVIII. In the first step, the thiourea acts as a nucleophilic reagent and displaces the halogen atom of the α-halo carbonyl compound to form the acyclic intermediate XCII which is a thiuronium salt derivative. In the second phase, the cyclization is initiated by a nucleophilic attack of the negatively charged nitrogen atom of the amidine portion of the free thioamidine base (XCIII) which is in equilibrium with its hydrohalide salt. At this point, the cyclic intermediate loses one

molecule of water according to the general acid-base catalysis mechanism (XCV ⟶ XCVI) to give the more stable conjugated system (XCVI).

When the group R in XCI is a heterocyclic ring, the cyclization step of the above reaction should occur with great ease, because of the -Is effect of the latter. The -Is effect renders the carbon atom of the carbonyl group more reactive in the cyclization stage by decreasing its electron density and hence its electrophilic character.

2. Preparation of 2-amino-4-(x-pyridyl)-thiazoles.

To prepare 2-amino-4-(2'-pyridyl)-thiazole, an aqueous solution of 2-bromoacetylpyridine hydrobromide (about 0.8 mole/l.) was treated with an equivalent amount of thiourea at room temperature and the resulting hydrobromide salt was decomposed with dilute ammonium hydroxide. The yield of 2-amino-4-(2'-pyridyl)-thiazole was 90.8%, which was satisfactory since the product needed very little purification. However, only 45.2% yield of a very impure product was obtained when the reaction was carried by refluxing for five hours a methanolic

solution of 2-bromoacetylpyridine hydrobromide with thiourea. The low yield and the poor quality of the product was due to the extensive decomposition of the 2-bromoacetylpyridine hydrobromide under the combined influence of the heat generated locally by the exothermic reaction and that supplied by the heating.

Another method, consisting in heating for six hours at 80-90°, one molar equivalent of 2-acetylpyridine with two molar equivalents of thiourea and one equivalent of iodine gave 42.9% of crude product. The last method was not practical for the preparation of 2-amino-4-(2'-pyridyl)-thiazole because it yielded a substantial amount of by-products and the isolated crude compound needed extensive purification.

2-Amino-4-(3'-pyridyl)-thiazole (LXXIV) and 2-amino-4-(4'-pyridyl)-thiazole (LXXV) were prepared in a way similar to 2-amino-4-(2'-pyridyl)-thiazole (LXXIII) by treating the corresponding bromoacetylpyridine hydrochloride dissolved in water with an aqueous solution of thiourea and freeing the base with dilute ammonium hydroxide. When this method was applied, the yields were about 90%. Other methods were also used but the yields were much lower and the products very impure.

Table 2 includes the yields of 2-amino-4-(x-pyridyl)-thiazoles obtained by the various methods. When the 4-acetylpyridine was condensed with thiourea in the presence of bromine in a way analogous to the one where iodine was used, 64.7% of 2-amino-4-(4'-pyridyl)-thiazole was obtained. The reaction was quite vigorous and the product was very impure.

This method could not be applied to the preparation of 2-amino-4-(2'-pyridyl)-thiazole (LXXIII). In this case, when the bromine was added to the mixture of 2-acetylpyridine and thiourea a very violent reaction occurred (slight explosion) resulting in tarring of the materials.

In another experiment, the 2-amino-4-(4'-pyridyl)-thiazole was obtained in 58.0% yield by brominating the 4-acetylpyridine in 40% hydrobromic acid and adding an aqueous solution of thiourea.

TABLE 2

Yields of 2-amino-4-(pyridyl)-thiazoles obtained by various methods.

Compound	Method (1)	(2)	(3)	(4)	(5)
2-Amino-4-(2'-pyridyl)thiazole	90.8	-	-	42.9%	-
2-Amino-4-(3'-pyridyl)thiazole	90.6	84.0%	-	41.0%	-
2-Amino-4-(4'-pyridyl)thiazole	90.5	-	58.0%	-	64.7%

(1) Condensation of thiourea with bromacetylpyridine hydrobromides in aqueous solution.

(2) Condensation of thiourea with chloroacetylpyridine hydrochloride in aqueous solution.

(3) Condensation of bromoacetylpyridine hydrobromides (prepared in situ) with thiourea in aqueous solution.

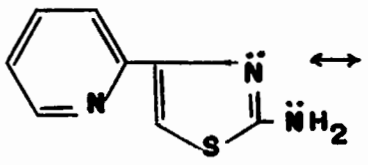
(4) Condensation of acetylpyridines with thiourea in the presence of iodine.

(5) Condensation of acetylpyridine with thiourea in the presence of bromine.

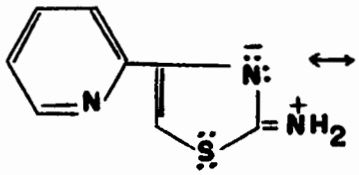
In conclusion, it can be said that the simplest and the most convenient method for the preparation of 2-amino-4-(x-pyridyl)-thiazole is that in which a bromoacetylpyridine hydrobromide is treated with thiourea in aqueous solution at room temperature. When the concentration of the solution is low (0.8 mole/l.) and if the reaction solution is neutralized carefully with dilute ammonium hydroxide to free the corresponding 2-amino-4-(x-pyridyl)-thiazole, the yields are high and the products are quite pure.

2-Amino-4-(4'-pyridyl)-thiazole (LXXV) was acetylated in high yield (84%) under mild conditions by treating an acetic acid solution with an excess of acetic anhydride at room temperature.

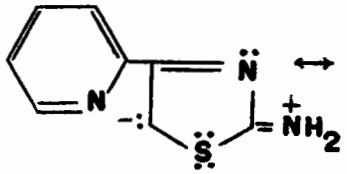
2-Amino-4-(2'-pyridyl)-thiazole (LXXIII) could be conceived as a resonance hybrid of structures involving the 2-aminothiazole ring, structures involving the pyridyl ring, the 4,5- double bond and the sulfur atom, and also resonance forms of the pyridyl ring alone.



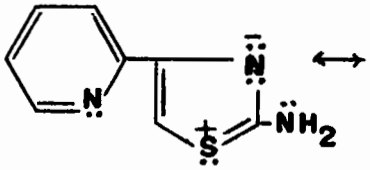
LXXIII



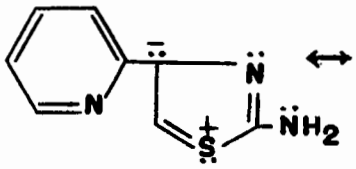
C



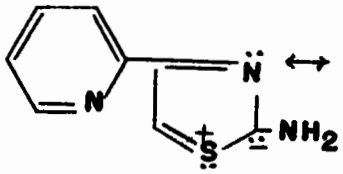
CI



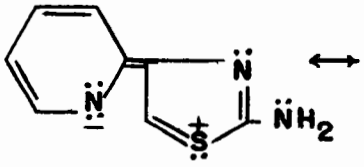
CII



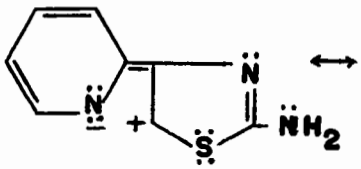
CIII



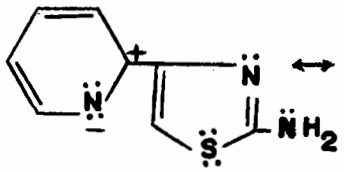
CIV



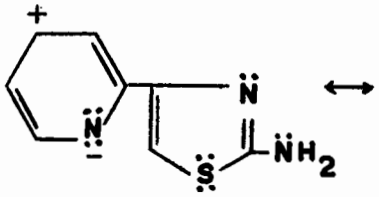
CV



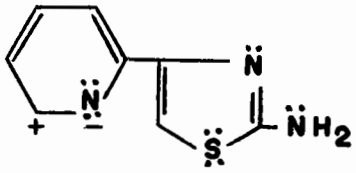
CVI



CVII



CVIII



CIX

As in 2-aminothiazole, the structures such as CIII and CIV, make very small contributions to the resonance hybrid of the 2-amino-4-(2'-pyridyl)-thiazole. Structures LXXIII, C, CI and CII are predominant. The conjugation between the pyridyl ring attached to the 4- position, the double bond and the sulfur atom of the thiazole create structures such as CV and CVI which may make small but significant contribution. Similar structures are suggested for 2-amino-4-(4'-pyridyl)-thiazole. In the case of 2-amino-4-(3'-pyridyl)-thiazole (LXXIV) no conjugation is possible between the pyridine ring and the thiazole ring. Consequently structures similar to CV and CVI are not possible.

d. Preparation of 2-amino-4-(y-quinolyl)-thiazoles.

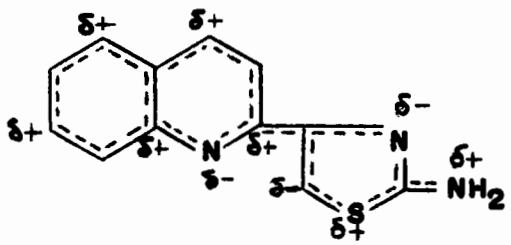
The best yields of 2-amino-4-(y-quinolyl)-thiazoles (LXXVI, LXXVII) were obtained when polar solvents were used and when temperatures were maintained as low as possible, as in the case of the preparation of 2-amino-4-(x-pyridyl)-thiazoles. Since the bromoacetylquinoline hydrobromides were not very soluble, the reactions were carried out at 60-65°. The concentration of the reaction solutions were thus much lower than for 2-amino-4-(x-pyridyl)-thiazoles.

The solution of 2-bromoacetylquinoline hydrobromide in a mixture of water, ethanol and concentrated hydrobromic acid was treated with thiourea. The 2-amino-4-(2'-quinolyl)-thiazole base (LXXVI) was freed with dilute ammonium hydroxide as usual. In a similar way an aqueous solution of 4-bromo-acetylpyridine hydrobromide afforded 2-amino-4-(4'-quinolyl)-thiazole (LXXVII). The yields of 2-amino-4-(2'-quinolyl)-thiazole and 2-amino-4-(4'-quinolyl)-thiazole were 91% and 90.5% respectively.

These two compounds were obtained in lower yields, when thiourea was added to the bromoacetylquinoline hydrobromide solution in 40% hydrobromic acid without prior isolation of the bromo derivatives.

In this case, the yields of 2-amino-4-(2'-quinolyl)-thiazole and 2-amino-4-(4'-quinolyl)-thiazole were of the order of 66%.

Resonance structures similar to those of 2-amino-4-(2'-pyridyl)-thiazole can be written for 2-amino-4-(2- and 4-quinolyl)-thiazoles. According to the mesomeric theory, the molecule of 2-amino-4-(2'-quinolyl)-thiazole (LXXVI) can be represented as in CX.



CX

The molecule possesses bonds which are intermediate between single and double bonds.

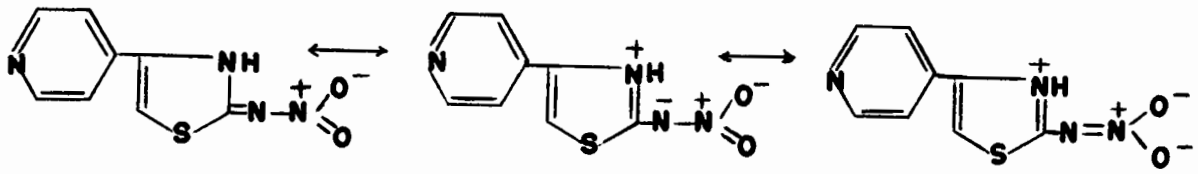
Similar structure can be postulated for 2-amino-4-(4'-quinolyl)-thiazole. The 2-amino-4-(2'-quinolyl)-thiazole is slightly colored (yellow) which is indicative of important contribution of dipolar structures.

e. Nitration of 2-amino-4-(4'-pyridyl)-thiazole.

To establish the structure of 2-aminothiazole substituted in the 4- position by 2- and 4-pyridyl groups, the behaviour of one of these compounds in electrophilic aromatic substitutions was investigated. The nitration of 2-amino-4-(4'-pyridyl)-thiazole (LXXV) was undertaken for this purpose. The reaction was carried out by carefully adding one equivalent of fuming nitric acid (in concentrated sulfuric acid) to 2-amino-4-(4'-pyridyl)-thiazole dissolved in sulfuric acid maintained at -5 and -3°. After stirring for thirty minutes, the solution was poured onto crushed ice and

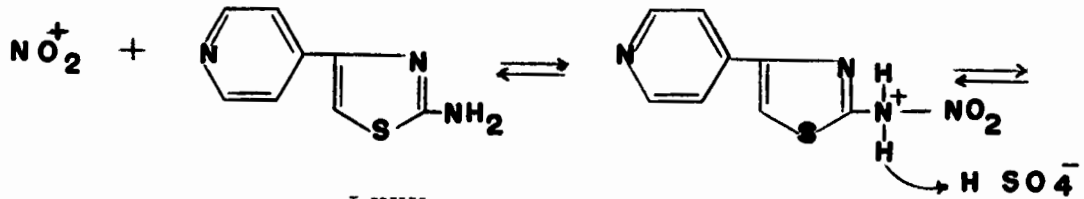
the yellow precipitate was crystallized from 60% pyridine. The product melted at 249-250° (dec.); the yield was 73%.

It has been established (105,106) that in the nitration of 2-aminothiazoles the first place of attack is the amino group and that the primary reaction product is a nitrimine. At present, the 2-nitriminothiazoles can easily be recognized by their characteristic infrared absorption spectra in the region 3150 to 2250 cm^{-1} (100,105) and the absence of the N-H stretching vibration bands between 3500-3200 cm^{-1}. The spectrum of the nitration product obtained in the present experiment showed no characteristic N-H stretching band in the 3400-3200 cm^{-1} range, but had, instead, a very broad structurless band between 3130 and 2140 cm^{-1} which was due to $\rightleftharpoons\overset{+}{N}H$ and aromatic C-H stretching vibration. This spectroscopic evidence indicates that the compound under investigation is a nitrimine and as such has a betaine structure, 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine (CXII). The compound may be considered to be a resonance hybrid of several structures (CXI,CXII,CXIII, etc.). The ionic structures CXII and CXIII make a major contribution to the ground state of the molecule.

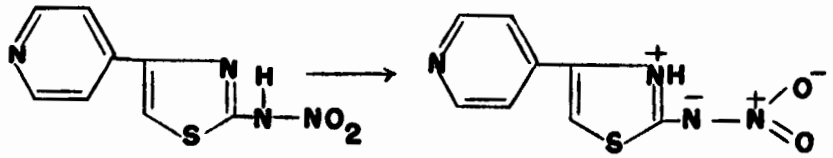


CXI CXII CXIII

The probable reaction mechanism for the formation of the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine can be formulated as follows:

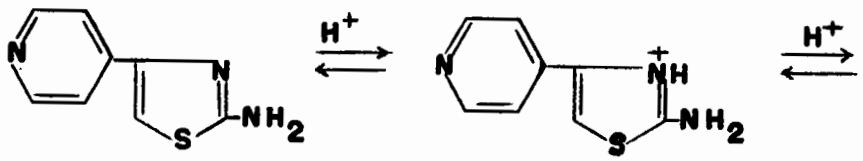


LXXV CXIV

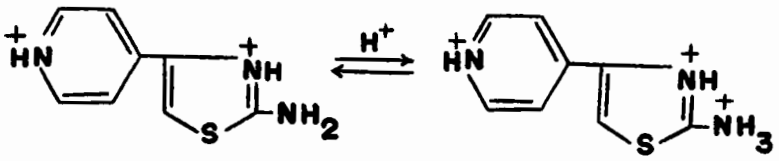


CXV CXII

In strong acid the following equilibrium is established:



LXXV CXVI



CXVII CXVIII

Structures CXVI, LXXV and CXVII are involved in the nitration by the NO_2 group. The nitronium cation attacks the unshared electrons of the primary amino group and the positive charge on the nitrammonium ion is removed by the uptake of a proton by the bisulfate base, HSO_4^-, probably, in a single step. This is followed by the migration of a proton to the ring nitrogen leaving a negative charge on the nitrimino group.

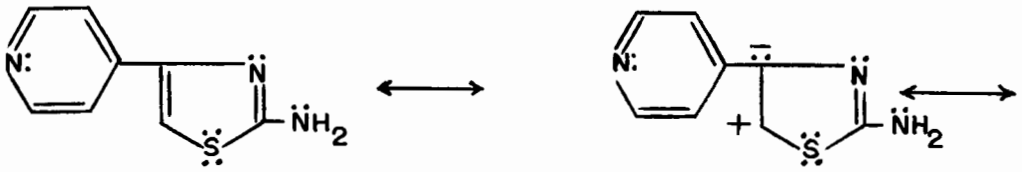
To investigate qualitatively the reactivity of the carbon atom in the 5- position of the 2-amino-4-(4'-pyridyl)-thiazole (LXXV) three kinds of experiments can be considered: (a) direct nitration of the 2-amino-4-(4'-pyridyl)-thiazole, (b) rearrangement of the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine and (c) nitration of the N-acetylamino-4-(4'pyridyl)-thiazole.

The direct nitration of 2-amino-4-(4'-pyridyl)-thiazole at about 30-35° resulted again in the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine. In the attempted rearrangement of the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine (CXII) to 2-amino-4-(4'-pyridyl)-5-nitrothiazole, a solution of the substance in concentrated sulfuric acid was stirred at room temperature for three hours. After pouring on crushed ice, 40% of the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine was recovered. No 5- nitro derivative was isolated. When the experiment was carried out at higher temperature (80-90°) again starting material was recovered in low yield (10-15%), along with tarry degradation products.

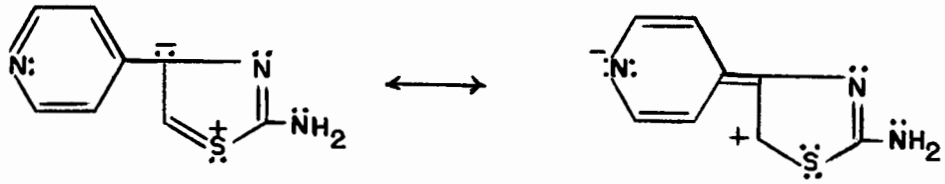
The nitration of the 5- position was then attempted by treating a solution of the N-acetylamino-4-(4'-pyridyl)-thiazole in concentrated sulfuric acid by one equivalent of fuming nitric acid and heating for half an hour on a water bath at 70-80°. The solution was poured onto crushed ice and neutralized with ammonium hydroxide. Only tarry degradation products were obtained.

The failure of 2-amino-4-(4'-pyridyl)-thiazole and 2-acetylamino-4-(4'-pyridyl)-thiazole to yield 5- nitro derivatives indicates that the 5- position of the thiazole

is deactivated in nitration reactions when a pyridyl substituent is attached to the 4- position. In such a molecular system, steric hindrance could not prevent the attacking nitronium cation to approach the 5- position of the thiazole. Therefore, resonance forms such as CXIX, CXX, CXXI may account for this deactivation.



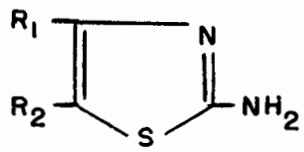
LXXV CXIX



CXX CXXI

2. Synthesis of 2-amino-4-(x-pyridyl)-5-(y-pyridyl)-thiazoles (CXXIII,CXXIV,CXXV,CXXVI).

In the second phase of this investigation, the synthesis of disubstituted 2-aminothiazoles possessing pyridyl rings in the 4 and 5- positions was achieved. These compounds, represented by the general formula CXXII, are shown in Table 3.



CXXII

TABLE 3

Compound	R_1	R_2	m.p.
2-Amino-4,5-di-(2'-pyridyl)-thiazole (CXXIII)	2-pyridyl	2-pyridyl	246-246.5°
2-Amino-4-(4'-pyridyl)-5-(2'-pyridyl)thiazole (CXXIV)	4-pyridyl	2-pyridyl	277-278°
2-Amino-4,5-di-(4'-pyridyl)-thiazole (CXXV)	4-pyridyl	4-pyridyl	292-293°
2-Amino-4-(2'-pyridyl)-5-(4'-pyridyl)thiazole (CXXVI)	2-pyridyl	4-pyridyl	216.5-217°

The synthesis of these compounds involved:

(a) preparation of the pyridyl pyridylmethyl ketones, and

(b) bromination of the ketones followed by the condensation of the resulting bromo derivatives with thiourea.

a. Preparation of pyridyl pyridylmethyl ketones.

There are nine possible derivatives, represented by the general formula CXXVII, possessing pyridyl substituents.

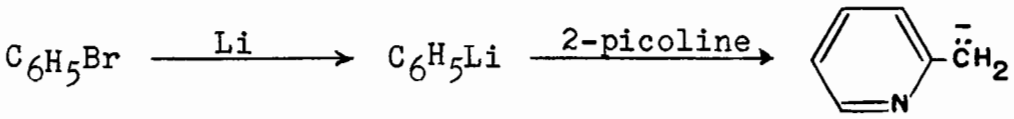
$$R_1 - CH_2 - CO - R_2$$

CXXVII

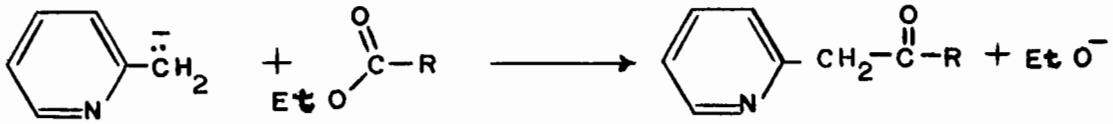
Four such compounds, required for the synthesis of the disubstituted 2-aminothiazoles (Table 3) were prepared, namely, 2-pyridyl 2-pyridylmethyl ketone or α - desoxypyridoin (CXXVII, $R_1 = R_2 =$ 2-pyridyl), 4-pyridyl 2-pyridylmethyl ketone (CXXVII, $R_1 =$ 2-pyridyl, $R_2 =$ 4-pyridyl), 4-pyridyl 4-pyridylmethyl ketone (CXXVII, $R_1 = R_2 =$ 4-pyridyl) and 2-pyridyl 4-pyridylmethyl ketone (CXXVII, $R_1 =$ 4-pyridyl, $R_2 =$ 2-pyridyl). The last compound, i.e., 2-pyridyl 4-pyridylmethyl ketone has not been described in the literature and consequently is reported here for the first time.

Generally, these compounds were prepared by acylating 2- and 4- picolines via their carbanions (as their metal derivatives) by means of 2- and 4- pyridinecarboxylates, according to the following schemes (1,2):

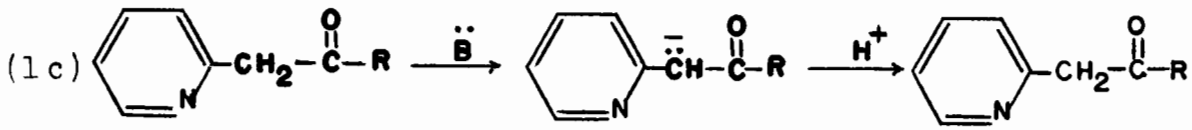
(1 a)

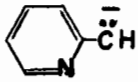


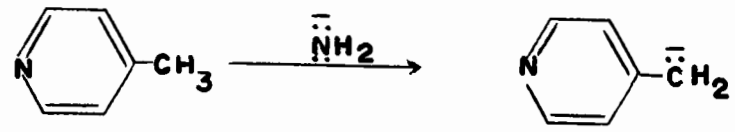
(1 b)

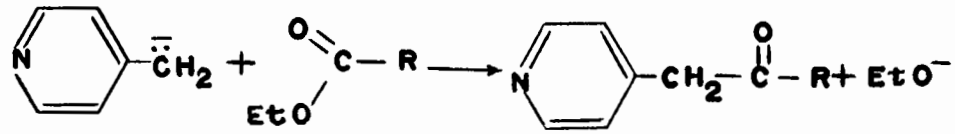


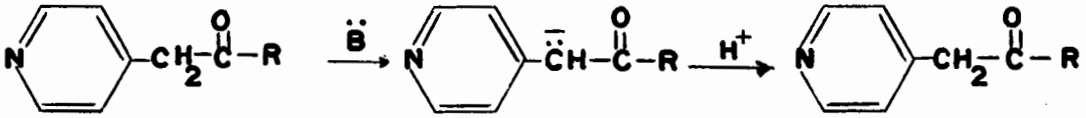
(1 c)

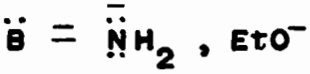


$\ddot{B} = \bar{O}Et$,  ; R = 2-PYRIDYL, 4-PYRIDYL

(2 a) 

(2 b) 

(2 c) 



The method of Barkely, Goldberg and Levine (115) was used for the synthesis of 2-pyridyl 2-pyridylmethyl ketone and 4-pyridyl 2-pyridylmethyl ketone. Accordingly, 2-picoline was acylated by treating an ethereal solution of two molar equivalents of picolyllithium (prepared as shown in scheme 1a) with one molar equivalent of the appropriate methyl pyridinecarboxylates. The methyl esters were added slowly to the stirred solution and then the mixture was refluxed for thirty minutes. The reaction mixture was processed further as described in the experimental part.

The yields of 2-pyridyl 2-pyridylmethyl ketone and 4-pyridyl 2-pyridylmethyl ketone were 64% and 68.5%

respectively. Only 46% of 2-pyridyl 2-pyridylmethyl ketone was obtained when ethyl picolinate was used as acylating agent. Probably the stronger +Is effect of the ethyl group as compared to the methyl group of the ester is responsible for the decrease in reactivity and for the lower yield.

Kloppenburg and Wibaut (127) who acylated 2-picoline obtained some phenyl-di-(2-picolyl)-carbinol from 2-picolyllithium and benzoyl chloride. These workers and Gilman and Towle (128) have isolated methyl-di-(2-picolyl)-carbinol (128) as well as methyl 2-picolyl ketone by the reaction of 2-picolyllithium with acetyl chloride. Barkely, Goldberg and Levine (115) and the author did not isolate any carbinol during the acylation of 2-picoline. The unreported 2-pyridyl 4-pyridylmethyl ketone was obtained in 49.5% yield by acylating 4-picoline with methyl picolinate using sodium amide as condensing agent. The reaction was carried out in liquid ammonia at -45 to -50°. Ethyl picolinate was also used to acylate the 4-picoline, but resulted in a low yield (22.7%). When phenyllithium was used as a condensing agent, addition of the latter across the bond -N=C- took place and 2-phenyl -4- methylpyridine was isolated along with other

non-identified compounds.

An attempted condensation of 4-picoline with methyl picolinate using methyllithium as a catalyst resulted in a complex mixture and no reaction product could be isolated. The method of Levine and Osuch (119) was used with slight modifications for the synthesis of 4-pyridyl 4-pyridylmethyl ketone. The 4-picoline was condensed in the presence of 2 molar equivalents of sodium amide with methyl isonicotinate in liquid ammonia at -35 to -30° and the reaction was quenched after one hour with ammonium chloride. The yield of 4-pyridyl 4-pyridylmethyl ketone was 50%.

b. Condensation of the bromo derivatives of pyridyl pyridylmethyl ketones with thiourea.

The halo derivatives of the pyridyl pyridylmethyl ketones required to prepare the 2-amino-4-(x-pyridyl)-5-(y-pyridyl)-thiazoles have not been described in the literature. Consequently, an attempt was made, at first, to develop a method for the preparation of 4-pyridyl 2-pyridylbromomethyl ketone. Bromination of this ketone in non polar solvents resulted in a gummy material which when filtered off and washed decomposed with evolution of bromine (probably

decomposition of perbromide). The bromination of 4-pyridyl 2-pyridylmethyl ketone in concentrated hydrobromic acid (48.5%) was also tried. Bromine, dissolved in concentrated hydrobromic acid was added carefully to the solution of the ketone maintained at 60-65°. Since the hydrobromide of the starting material as well as the hydrobromide of the bromo derivative formed are very soluble in the reaction medium, the desired product could not be isolated in the pure state. In one experiment, the reaction mixture was distilled under reduced pressure. The residue, a yellow precipitate, was thoroughly washed with acetone. After drying in vacuum a light yellow, powdery material was obtained, which melted at 148-151°. (dec.). The substance could not be crystallized. The calculate amount of bromine for the 4-pyridyl 2-pyridylbromomethyl ketone dihydrobromide was 54.44%. The analysis of a sample of the above substance gave only 51.10% Br which is between the above value of 54.44% and 44.40% calculated for 4-pyridyl 2-pyridylbromomethyl ketone monohydrobromide or 4-pyridyl 2-pyridylmethyl ketone dihydrobromide. This substance was probably a mixture of 4-pyridyl 2-pyridylmethyl

ketone dihydrobromide, the mono- and dihydrobromide of 4-pyridyl 2-bromomethylpyridyl ketone. This assumption was supported by the fact that upon condensation with thiourea, it afforded 2-amino-4-(4'-pyridyl)-5-(2"-pyridyl)-thiazole in low yield (35%).

Bromination of 4-pyridyl 2-pyridylmethyl ketone in anhydrous acetic acid and yielded gummy material from which the desired reaction product could not be isolated.

Since it was found that the 2-aminothiazoles could be prepared without prior isolation of the required α-bromo carbonyl compounds, further investigation of the bromination of the pyridyl pyridylmethyl ketones was discontinued.

Consequently, to prepare 2-amino-4-(4'-pyridyl)-5-(2"-pyridyl)-thiazole (CXXIV) the 4-pyridyl 2-pyridylmethyl ketone was brominated in 10% hydrobromic acid at 55-60° and after stirring for two hours the solution was treated with one molar equivalent of thiourea. Upon treatment of the solution with dilute ammonium hydroxide, the yield of the crude product was 72%.

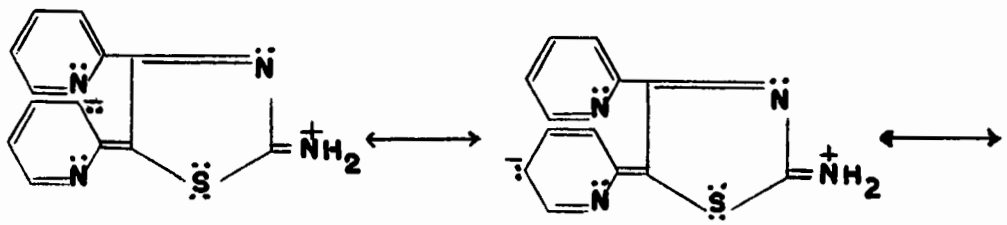
When one molar equivalent of ketone was treated with two molar equivalents of thiourea in presence of one molar equivalent of iodine, by heating at 80-90°, the yield was 55.5%.

The 2-amino-4,5-di-(2'-pyridyl)-thiazole (CXXIII) could not be prepared from the brominated 2-pyridyl 2-pyridylmethyl ketone. Thus the 2-pyridyl 2-pyridylmethyl ketone was treated with the theoretical amount of bromine at 80-90° in 48% or 10% hydrobromic acid and to the resulting solution thiourea dissolved in water was added. Upon treatment with ammonium hydroxide, no 2-amino-4,5-di-(2'-pyridyl)-thiazole was isolated. Instead, some unidentified oily degradation product was obtained. When the bromination reaction was done at 40°, a yellow material was isolated. This product was identified as starting material, 2-pyridyl 2-pyridylmethyl ketone, by means of mixed melting point determination and comparison of spectra. The amount of starting material obtained was 69%. Since, 2-pyridyl 2-pyridylmethyl ketone was recovered in high yield it meant that it was not brominated.

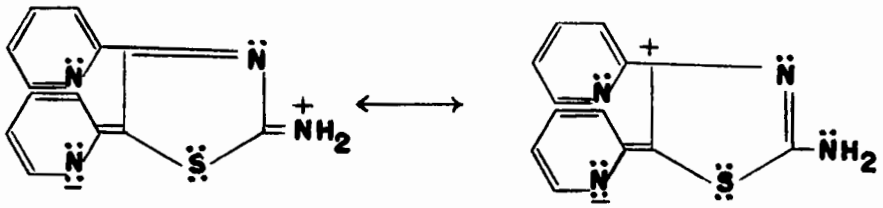
The 2-amino-4,5-di-(2'-pyridyl)-thiazole was prepared by heating 2-pyridyl 2-pyridylmethyl ketone with thiourea in presence of iodine at 80-90° for 8-10 hours. The reaction mixture was made slightly basic with dilute ammonium hydroxide. The yield of 2-amino-4,5-di-(2'-pyridyl)-thiazole (CXXIII) was 52.1%.

Finally, the 2 isomeric compounds, 2-amino-4-(2'-pyridyl)-5-(4"-pyridyl)-thiazole (CXXVI) and 2-amino-4,5-di-(4'-pyridyl)-thiazole (CXXV) were obtained from the corresponding pyridyl pyridylmethyl ketone in a way similar to 2-amino-4-(4'-pyridyl)-5-(2'-pyridyl)-thiazole. The yields were 60% and 73%.

All four 2-amino-4-(x-pyridyl)-5-(y-pyridyl)-thiazoles described above formed yellow crystals from ethanol. On the contrary, the 2-aminothiazoles monosubstituted by 2- and 4-pyridyl groups in the 4- position of the thiazole ring are colorless. Hence the colour appears when a second pyridyl (2- or 4-pyridyl) group is introduced in the 5- position of the 2-amino-4-(x-pyridyl)-thiazoles. The colour of these compounds may be attributed to significant contributions of ionic forms to the resonance hybrid structure of the molecule. Thus in addition to the resonance forms analogous to those postulated for 2-amino-4-(2'-pyridyl)-thiazole, the 2-amino-4,5-di-(2'-pyridyl)-thiazole, for example, receives significant contribution from structures such as CXXVIII,CXXIX,CXXX,CXXXI.



CXXVIII CXXIX



CXXX CXXXI

Among these dipolar structures, the structures CXXX should be the most important.

Similar structures may be postulated for the other three isomeric 2-amino-4,5-di-(pyridyl)-thiazoles.

3. Synthesis of 2-N-(3'-pyridyl)aminothiazoles (CXLI,CXLII, CXLIII,CXLIV) and 2-N-(3'-quinolyl)-aminothiazoles (CXLV, CXLVI,CXLVII).

The object of this work was to extend the ring closure method used for the preparation of 2-N- (aryl or alkyl)-aminothiazoles to the preparation of 2-N-(3'-pyridyl)-aminothiazoles and 2-N-(3'-quinolyl)-aminothiazoles.

2-N-Arylaminothiazoles (129) and 2-N-alkylaminothiazoles (31) are usually prepared by condensing the appropriate α - halo ketones or α- halo aldehydes with N-aryl or N-alkyl substituted thiourea according to the scheme shown on pg. 25.

The ring closure method had not been applied as yet for the preparation of 2-aminothiazoles possessing a pyridyl or quinolyl substituent attached to the nitrogen atom of the amino group.

The synthesis of the 2-N-(3'-pyridyl)-aminothiazoles and 2-N-(3'-quinolyl) aminothiazoles involved two stages: (a) development of a method for the preparation of the required N-(3'-pyridyl)-thiourea and N-(3'-quinolyl)-thiourea; (b) condensation of the thioureas with the various α - halo ketones.

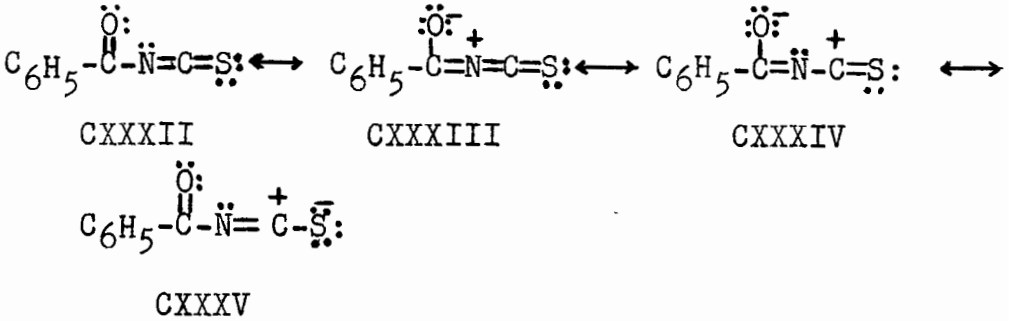
a. Preparation of N-(3'-pyridyl)-thiourea and N-(3'-quinolyl)-thiourea.

Benzoyl isothiocyanate (CXXXII) was prepared according to Organic Syntheses (102) by adding benzoyl chloride to a stirred suspension of ammonium thiocyanate in anhydrous acetone and refluxing. The suspension of benzoyl isothiocyanate was treated with a solution of 3-aminopyridine

in anhydrous acetone. The yellow precipitate of 1-benzoyl-3-(3'-pyridyl)-2-thiourea (CXXXVIII) was isolated by pouring the reaction mixture into water and filtering. The yield of crude 1-benzoyl-3-(3'-pyridyl)-2-thiourea was 90%. After crystallization the product melted at 165°.

The reaction of benzoyl isothiocyanate with 3-aminopyridine is very vigorous and rapid. For this reason the solution of the amine is added at such a rate that the acetone refluxes gently.

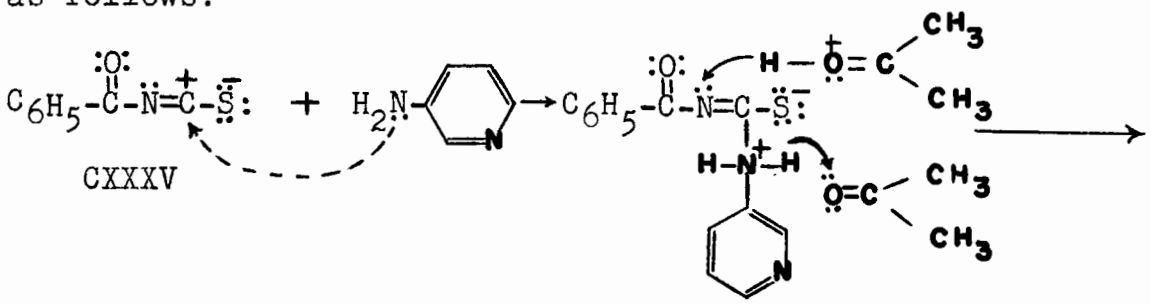
In benzoyl isothiocyanate, resonance structures such as CXXXIII and CXXXIV create an electron deficiency on the carbon atom of the isothiocyanate portion of the molecule. Further, the electron deficiency is increased by the -Is effect of the C_6H_5-CO group. Consequently, the reactivity of benzoyl isothiocyanate towards nucleophilic reagents should be considerably greater than in the isothiocyanic acid.



CXXXII CXXXIII CXXXIV

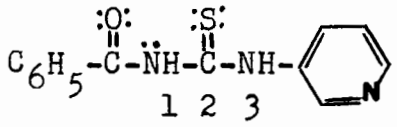
CXXXV

By assuming that the resonance form CXXXV is important in this reaction, the mechanism can be depicted as follows:



CXXXV

CXXXVII



CXXXVIII

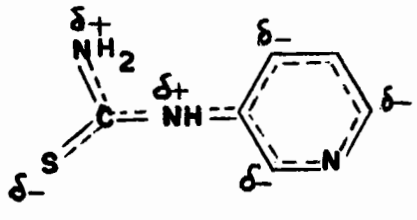
The reaction is initiated by a nucleophilic attack of the unshared electron pair of the amine. The proton of the positively charged amino group migrates to the nitrogen atom of the isothiocyanate portion of the molecule. Then the unshared pair of electrons of the sulfur atom shift to form the C=S bond. Simultaneously the π-electrons of the C=N bond shift towards the nitrogen forming the single C-N bond. This mechanism accounts for the vigorous and rapid reaction.

To obtain the N-(3'-pyridyl)-thiourea, the benzoyl derivative (CXXXVIII) was refluxed with aqueous 2.5N sodium

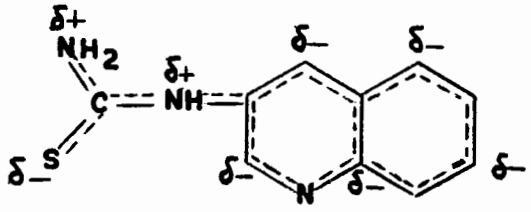
hydroxide. The yield of the colorless crystalline product was 75%.

1-Benzoyl-3-(3'-quinolyl)-2-thiourea was prepared in a way similar to 1-benzoyl-3-(3'-pyridyl)-2-thiourea. In this case, after the addition of the 3-aminoquinoline solution was completed, the reaction mixture had to be added immediately to cold water. When the reaction mixture was allowed to stand longer than one minute, it became a hard solid mass and the product was difficult to purify. The yields of 1-benzoyl-3-(3'-quinolyl)-2-thiourea were 90-93%.

The hydrolysis of the benzoyl derivative was best affected by refluxing with 3N sodium hydroxide solution for fifteen minutes. In this manner, the yield of N-(3'-quinolyl)-thiourea was 78.2%. By analogy with thiourea the structures of N-(3'-pyridyl)-thiourea and of N-(3'-quinolyl)-thiourea, using the mesomeric notation, can be represented by the formulae CXXXIX and CXL.



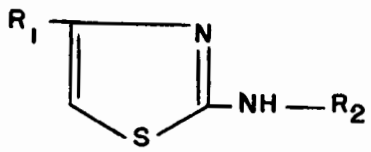
CXXXIX



CXL

b. Condensation of N-(3'-pyridyl)-thiourea and N-(3'-quinolyl)-thiourea with α - halo ketones.

To establish the cylization method as a general procedure for the preparation of 2-N-(3'-pyridyl)amino- and 2-N-(3'-quinolyl)amino-thiazoles, N-(3'-pyridyl)-thiourea and N-(3'-quinolyl)-thiourea were condensed with various ketones. The resulting compounds, represented by the general formula CXLI are listed in Table 4.



CXLI

The methods which were used to prepare the 2-N-(aryl- or alkyl-)-aminothiazoles gave very impure product in low yields. For instance, 2-N-methylamino-4-methyl-thiazole (129) was prepared by heating chloroacetone with N-methylthiourea, mixing the reaction product with sodium hydroxide and extracting the free base with ether. The product was obtained in 15% yield and could not be readily purified.

The procedure developed here for the preparation of the 2-N-(3'-pyridyl)aminothiazoles and 2-N-(3'-quinolyl)-thiazoles is simple, and gives high yields (72-94%) of products which are easily purified. Since the mechanism of the condensation (pg. 52) of the thioureas with the α - halo ketones was assumed to be ionic, the reaction was carried out in polar solvents. For convenience and also to avoid decomposition of some of the halo ketones, the solutions of these were added to the dissolved thioureas.

2-N-(3'-Pyridyl) amino-4-methylthiazole (CXLI) and 2-N-(3'-pyridyl)-amino-4-phenylthiazole (CXLII) were obtained by treating at 60-65° the N-(3'-pyridyl)-thiourea dissolved in aqueous methanol with a methanolic solution of bromoacetone and bromoacetophenone respectively. The 2-N-(3'-pyridyl)-amino-4-phenylthiazole hydrobromide was very insoluble and precipitated as it formed. Thus a heavy slurry resulted. The hydrobromides of both compounds were decomposed as usual by treating them in water or aqueous methanol solution with dilute ammonium hydroxide. The products obtained were of good grade. The yield of 2-N-(3'-pyridyl)-amino-4-phenylthiazole was higher than that of

2-N-(3'-pyridyl)-amino-4-methylthiazole (76.8%).

The bromoacetone required for the synthesis of 2-N-(3'-pyridyl)-amino-4-methylthiazole (CXLI) was prepared in 48% yield according to Organic Syntheses (118) by brominating aqueous acetone using acetic acid as a catalyst. Because of partial decomposition on standing, the bromoacetone was distilled in vacuum before being used.

Generally, 2-N-(3'-pyridyl)-amino-4-(3"-pyridyl)-thiazole (CXLIII) and 2-N-(3'-pyridyl)-amino-4-(4"-pyridyl)-thiazole (CXLIV) were prepared in a manner similar to the above. In this case, the hydrobromides of the appropriate bromoacetylpyridines were used in aqueous solution. The reactions were vigorous and yields were high (see Table 4).

N-(3'-Quinolyl)-thiourea was treated, under essentially the same conditions as N-(3'-pyridyl)-thiourea, with bromoacetone, bromoacetophenone or 4-bromoacetylpyridine hydrobromide to produce 2-N-(3'-quinolyl)amino-4-methylthiazole (CXLV), 2-N-(3'quinolyl)amino-4-phenylthiazole (CXLVI) and 2-N-(3'-quinolyl)amino-4-(4"-pyridyl)-thiazole (CXLVII) respectively. In all cases, except 2-N-(3'-quinolyl)-amino-4-(4"-pyridyl)-thiazole, the yields were high. A single

crystallization from aqueous ethanol or aqueous methanol gave analytical grade material.

Since the N-(3'-quinolyl)-thiourea was insoluble in the ordinary polar solvents at room temperature, the reaction was carried out at 60-65°. Under these conditions, the 4-bromoacetylpyridine hydrobromide reacted vigorously incurring some decomposition. This explains the lower yield of product obtained in the preparation of 2-N-(3'-quinolyl)-amino-4-(4"-pyridyl)-thiazole (CLXVII).

The structure of these compounds will be discussed in the section on infrared spectra.

TABLE 4

Compound	R_1	R_2	m.p.	yield %
2-N-(3'-pyridyl)amino-4-methylthiazole (CXLI)	methyl	3-pyridyl	203-204°	76.8%
2-N-(3'-pyridyl)amino-4-phenylthiazole (CXLII)	phenyl	3-pyridyl	199-199.5°	86.9
2-N-(3'-pyridyl)amino-4-(3"-pyridyl)thiazole (CXLIII)	3-pyridyl	3-pyridyl	203.5-204°	82.6
2-N-(3'-pyridyl)amino-4-(4"-pyridyl)thiazole (CXLIV)	4-pyridyl	3-pyridyl	228.5-229°	94.2
2-N-(3'-quinolyl)amino-4-methylthiazole (CXLV)	methyl	3-quinolyl	199.5-200°	90.2
2-N-(3'-quinolyl)amino-4-phenylthiazole (CXLVI)	phenyl	3-quinolyl	216.5-217°	83.3
2-N-(3'-quinolyl)amino-4-(4"-pyridyl)thiazole (CXLVII)	4-pyridyl	3-quinolyl	255-255.5°	72.3

4. Infrared Spectra.

I. Spectra of C- and N-substituted 2-aminothiazoles.

The infrared spectra of 16 2-aminothiazoles were recorded and the frequencies of the maximum absorption bands are listed in Tables 5-8.

Since all the compounds synthesized in the present investigation were insoluble in non-polar solvent, the spectra were taken in the solid state using the KBr technique.

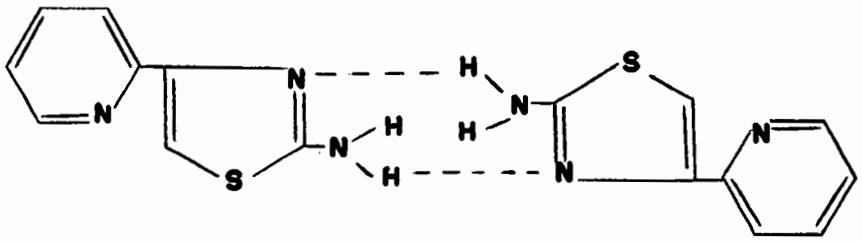
The C- and N-substituted 2-aminothiazoles synthesized in the present investigation are very complex and thus no attempt will be made to discuss all the absorption bands associated with their infrared spectra.

a. Infrared spectra of 2-amino-4(x-pyridyl)- and 2-amino-4(y-quinolyl)-thiazoles.

In general, all the 2-aminothiazoles with an unsubstituted primary amino group showed at least two bands between 3460-3120 cm^{-1}. The higher frequency band is attributed to the asymmetrical N-H stretching vibration, while the second band arises from the symmetric stretching of the primary amino group. The third band occurring at lower frequency may arise

from hydrogen bonding. Occasionally, in the spectra of some of these compounds, there was a weak band between 3060-3020 cm^{-1} which may be caused by aromatic C-H stretching vibrations.

In most cases, the frequencies of the asymmetrical and symmetrical N-H stretching motions were lower than normal. This may be attributed to intermolecular hydrogen bonding. The absorption band resulting from the symmetrical N-H stretching is broad which may be considered as another indication of hydrogen bonding (85). For instance, 2-amino-4-(2'-pyridyl)-thiazole has bands at 3330 cm^{-1} (m) and 3120 cm^{-1} (m) and the second band is broad. Thus the molecules of this compound may be involved in hydrogen bonding as shown in CXLVIII.



CXLVIII

b. <u>Infrared spectra of 2-N-(3'-pyridyl)-aminothiazoles and 2-N-(3'-quinolyl)-aminothiazoles</u>.

The spectra of 2-N-(3'-pyridyl)-aminothiazoles

(CXLI - CXLIV) and 2-N-(3'-quinolyl)-aminothiazoles (CXLV - CXLVII) show one weak band between 3280 cm^{-1} and 3240 cm^{-1}. This band may be assigned to the N-H stretching vibration. Normally, the non-associated secondary amines show a single band in the 3500-3400 cm^{-1} range. In aromatic amines the N-H stretching band occurs at higher frequencies than aliphatic amines. But when hydrogen bonding occurs the frequency of the N-H band is lowered and sometimes may be accompanied by a second band at a lower frequency (85). Heacock and Marion (104) quote a range of 3380-3205 cm^{-1} for a series of secondary amines which were associated by hydrogen bonding.

In addition to this band, the spectra of the 2-N-(3'-pyridyl)-aminothiazoles and 2-N-(3'-quinolyl)-aminothiazoles show a broad band of medium intensity between 3130 and 1960 cm^{-1}.

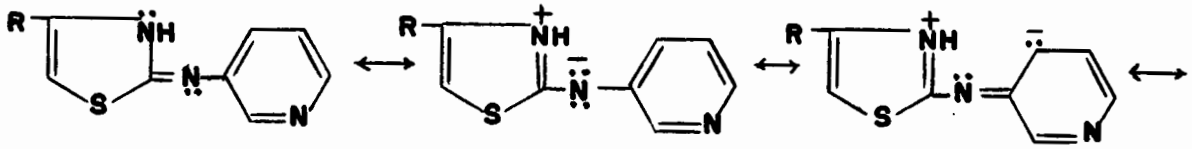
These bands have a maximum which is at 2920-2880 cm^{-1} for 2-N-(3'-pyridyl)-amino-4-(3"-pyridyl)-thiazole, 2-N-(3'-pyridyl)-amino-4-(4"-pyridyl)-thiazole and 2-N-(3'-quinolyl)-4-(4"-pyridyl)-thiazole, at 2940 cm^{-1} for 2-N-(3'-quinolyl)-amino-4-methylthiazole and at 2730 cm^{-1} for 2-N-(3'-pyridyl)-

4-methylthiazole. For 2-N-(3'-pyridyl)-amino-4-phenylthiazole this maximum is at 3030 cm^{-1} and for 2-N-(3'-quinolyl)-amino-4-phenylthiazole at 3040 cm^{-1}. All these bands have other small absorption maxima and shoulders.

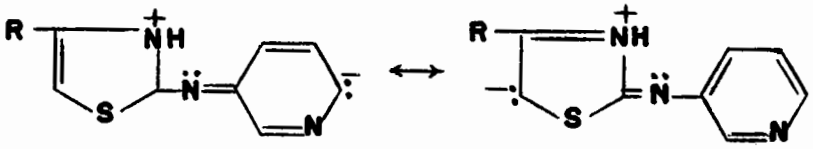
Similar broad bands were reported for compounds which have a positively charged nitrogen and were attributed to the N-H stretching vibrations in the ionic structures: $R\overset{+}{N}H_3$, $R_2\overset{+}{N}H_2$, and $R_3\overset{+}{N}H$. The polar character makes it difficult to study their infrared in solutions and thus the available information concerns only the solid state. The α- amino acids, which have a dipolar structure (Zwitterion) do not show any absorption bands in the region 3500-3300 cm^{-1}. Instead, they show a broad and structurless band between 3030 and 2546 cm^{-1} (120) which is attributed to aromatic C-H and to $-\overset{+}{N}H_3$ stretching vibrations. Hydrochlorides of secondary bases show a complex series of absorptions between 2800 cm^{-1} and 2000 cm^{-1} (104).

To account for the absorption pattern between 3130 cm^{-1} and 1960 cm^{-1} shown by the 2-N-(3'-pyridyl)-amino- and 2-N-(3'-quinolyl)-aminothiazoles the suggestion can be made that these compounds have an imino structure (CXLIX) which would

receive important contributions from dipolar resonance forms. To illustrate this, we shall consider the case of 2-N-(3'-pyridyl)-amino-thiazoles (CXLIX, R = methyl, phenyl, 3-pyridyl, 4-pyridyl):



CXLIX CL CLI

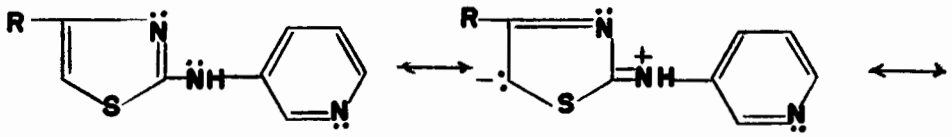


CLII CLIII

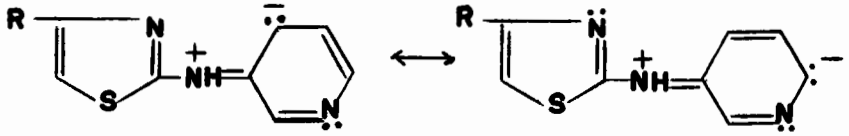
The main resonance structures are CXLIX and CL. The ionic resonance structures such as CLI, CLII and CLIII are expected to contribute less to the actual ground state of the molecule. The classical structure (CLIV) could not account for the strong to medium absorption between 3140-2000 cm^{-1}. The 2-N-(3'-pyridyl)-amino- and 2-N-(3'-quinolyl)-aminothiazole can be compared to 2-nitraminothiazoles, the NH group possessing a substituent capable of -Is effect and -M effect. The proton is very labile and would migrate to the more basic thiazole ring nitrogen.

The classical structure (CLIV), has less stabilization,

since it lacks important ionic resonance structures such as CL. All the dipolar resonance structures (CLV,CLVI,CLVII) which can be written for the classical structure are less stable.



CLIV CLV



CLVI CLVII

2-N-(3'-Pyridyl)-aminothiazoles and 2-N-(3'-quinolyl)-aminothiazoles mentioned above are colored, they are insoluble in non polar solvents, very slightly soluble in polar solvent and have relatively high melting points.

c. Infrared spectrum of 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine.

The spectrum of the nitration product of 2-amino-4-(4'-pyridyl)-thiazole, in the region 3130-2140 cm^{-1} was briefly discussed in connection with its structure (pg.62). Because of the absence of N-H stretching vibrations between

3500-3200 cm^{-1}, it was proved that the $-NO_2$ was substituted on the amino group. Further, it was suggested that because of the appearance of a broad structurless band between 3130-2140 cm^{-1}, the compound has a dipolar structure similar to that established for 2-nitrimino-(3H)-thiazolium betaine (101) and 2-nitrimino-(3H)-thiazolium carboxylic acids betaines (106).

Thus the compound under consideration has the structure of 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine (CXII).

A strong band occurring at 1520 cm^{-1} in the spectrum of 2-nitrimo-4-(4'-pyridyl)-(3H)-thiazolium betaine and which is absent in the spectrum of the parent compound, may be assigned to the asymmetrical stretching of the nitro group. A band at 1302 cm^{-1}, which is strong and is not present in 2-amino-4-(4'-pyridyl)-thiazole may arise from the symmetrical vibration of NO_2 group.

II. Spectra of pyridyl pyridylmethyl ketones.

The infrared spectra of four isomeric pyridyl pyridylmethyl ketones were recorded in the 4000-650 cm^{-1} range in the solid state and in carbon tetrachloride solution.

The absorption bands of the compounds in the solid state are listed in Table 9.

The spectrum of 2-pyridyl 4-pyridylmethyl ketone in solution shows a band of medium intensity at 3065 cm^{-1} and a small shoulder at 3030 cm^{-1}. Similarly, the isomeric 4-pyridyl 4-pyridylmethyl ketone, exhibits a band at 3030 cm^{-1} and a shoulder at 3065 cm^{-1}.

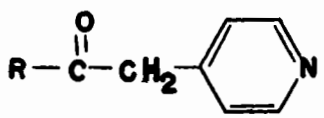
The bands may be attributed to aromatic C-H or to shifted N-H stretching vibration. In the solid state, only the spectrum of 2-pyridyl 4-pyridylmethyl ketone shows a weak band at 3030 cm^{-1}.

Usually, the bands caused by N-H stretching vibrations occur between 3500-3200 cm^{-1} (85). Randal, Fowler, Fuson and Dangl (98) have quoted an overall range of 3500-3050 cm^{-1} for the N-H vibration, but most of the spectra, on which this conclusion was based, were determined on solid material and thus intermolecular association might have occurred.

The spectra of 2-pyridyl 2-pyridylmethyl ketone and 4-pyridyl 2-pyridylmethyl ketone in carbon tetrachloride solution

showed a medium peak at 3075 cm^{-1} (shoulder at 3030 cm^{-1}) and 3030 cm^{-1} (shoulder at 3075 cm^{-1}) respectively. These absorption bands are similar to those of the other two isomeric ketones mentioned above and thus may arise from the same source. In addition, there are wide bands of weak to medium intensity at 2960-2200 cm^{-1} for 2-pyridyl 2-pyridylmethyl ketone and 2900-2200 cm^{-1} for 4-pyridyl 2-pyridylmethyl ketone. The spectra of the solid state show similar bands, but weaker and not as well defined. These bands may be assigned to the stretching vibrations of the N-H group which is present in the structures suggested subsequently.

In the carbonyl stretching range, the spectra of the solid 2-pyridyl 4-pyridyl ketone and 4-pyridyl 4-pyridylmethyl ketone showed very strong absorption band at 1693 cm^{-1} and 1688 cm^{-1}, respectively. In solution, the band occurred at 1698 cm^{-1} in the spectrum of the first compound, while the spectrum of the second compound showed a band with two peaks at 1702 and 1692 cm^{-1}. The classical structure of these two compounds (CLVIII, R=2- and 4-pyridyl) has a carbonyl group attached directly to an electron attracting group (2- or 4-pyridyl) and to a methylene unit, $-CH_2-$.



CLVIII

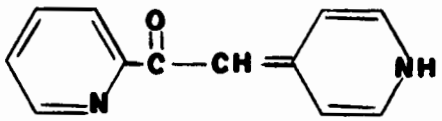
In saturated open chain ketones or dialkyl ketones, $R\text{-}CH_2\text{-}CO\text{-}CH\text{-}R'$ (which is the simplest case of undisturbed carbonyl stretching vibration), the carbonyl stretching vibration band occurs at 1725-1705 cm^{-1} (87). The carbonyl group, C=O is a resonance hybrid of structures such as, C=O and $\overset{+}{C}\text{-}O^-$ and consequently the carbon-oxygen bond has a certain amount of a single bond character. The carbonyl stretching frequency depends upon the double bond character of the carbon-oxygen bond.

Depending on whether the -CO- is directly attached to groups exhibiting +M or +Is effect, or to groups capable of -M or -Is effect, the double bond character will be decreased or increased. When the double bond character of the -CO- is decreased the stretching vibration band is shifted towards lower frequencies, while the opposite occurs if the double bond character is increased. Generally, when a group such as a halogen is directly attached to the -CO- function as in acid halides where the mesomeric effect (+M) is clearly negligeable (87) compared with the inductive affect (-Is), the frequency shift from the usual position in dialkyl ketones (1715 cm^{-1}) is 95 cm^{-1}, e.g., the acyl halides, R-CO-Cl,

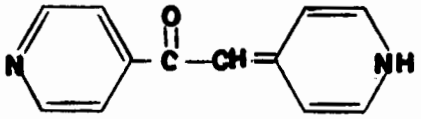
absorb at 1810 cm^{-1}. If the halogen is situated on the α- carbon atom the effect is still appreciable (approx. 20 cm^{-1}). In alkyl amides where the mesomeric effect (+M) predominates over the inductive effect (-Is), the double bond character of the -CO- is decreased and the absorption frequency is lower, for example butyramide absorbs at 1681 cm^{-1} (87).

In the present case, the carbonyl group is directly attached to the pyridyl ring (CLVIII, R=2-pyridyl or 4-pyridyl) which will exert an inductive effect (-Is) but mesomerism cannot occur. Moreover, on the α- carbon atom there is substituted another pyridine ring (4-pyridyl) which can also exhibit -Is effect but to a lower degree (because of the intervenieining carbon). If the classical structure were true, this would mean that, because of the inductive effect (-Is) exerted from both sides, the carbonyl group would have a higher double bond character than in the dialkyl ketones and consequently should absorb at higher frequency (higher than 1715 cm^{-1}). On the other hand,the two pyridyl pyridylmethyl ketones, are colored (bright yellow), indicating a conjugated system. For this reason, the structures CLIX and CLX are

suggested for 2-pyridyl 4-pyridylmethyl ketone and 4-pyridyl 4-pyridylmethyl ketone respectively, resonance, obviously, being possible.

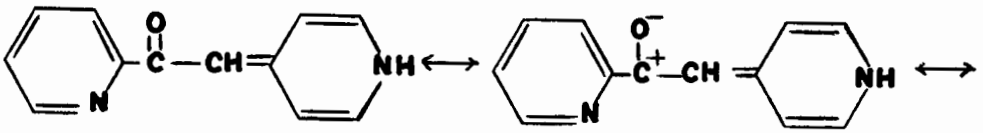


CLIX

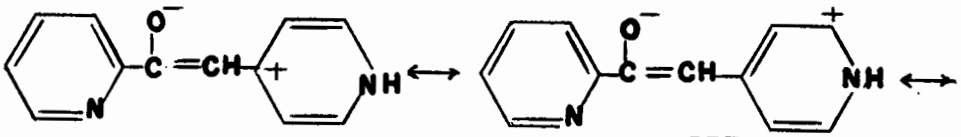


CLX

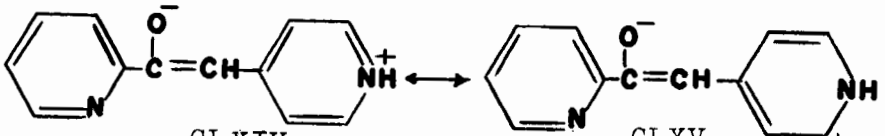
2-Pyridyl 4-pyridylmethyl ketone would then be a resonance hybrid of the following structures:



CLIX CLXI



CLXII CLXIII



CLXIV CLXV

Structure CLIX would make the largest contribution to the ground state of the molecule.

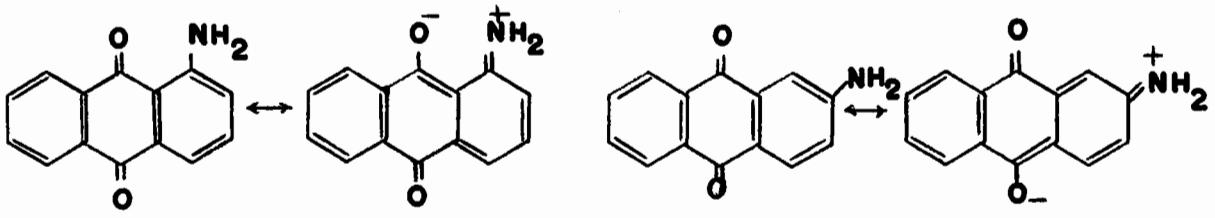
The infrared spectra in the solid state of 2-pyridyl 2-pyridylmethyl ketone and 4-pyridyl 2-pyridylmethyl ketone do not show any carbonyl stretching vibration band near 1700 cm^{-1}. Instead, there are strong bands at 1630 cm^{-1} and at 1620 cm^{-1} for 2-pyridyl 2-pyridylmethyl ketone and for 4-pyridyl 2-pyridylmethyl ketone, respectively. In solution, the same strong bands occur at 1635 and 1625 cm^{-1} respectively. In addition, the solution of 2-pyridyl 2-pyridylmethyl ketone shows a weak band at 1702 cm^{-1} (absent in the solid material) which cannot be attributed to the carbonyl stretching vibration.

The strong band present in the spectra of each of the two compounds may be caused either by carbonyl stretching or by N-H deformation. It may equally well arise from skeletul ring vibration (ring stretching vibrations). Since the spectra in solution or solid state are very similar in this region, the discussion will be referred to only one of them, namely the spectrum in the solid. Whether this band arises from carbonyl stretching or not is difficult to establish. However, if this is so, then, there is a considerable shift from the average frequency value of the other two isomeric

ketones described above. Moreover, for the same reasons as in the case of 2-pyridyl 4-pyridylmethyl- and 4-pyridyl 4-pyridylmethyl ketone, the spectra of the compounds under consideration, should show the carbonyl stretching band at a frequency much higher than that of dialkyl ketones (1715 cm^{-1}).

The fact that this band occurs at a lower frequency (65-70 cm^{-1}) as compared with the frequencies of the corresponding band in the two pyridyl 4-pyridyl ketones may be caused by two factors: higher conjugation and hydrogen bonding.

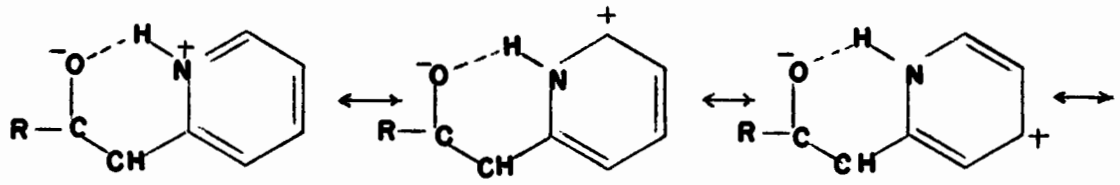
Flett (103) has found, for instance, that in amino-anthraquinones the lowering of the carbonyl stretching band results mainly from resonance and that hydrogen bonding plays only a small role. He found that 2--amino-anthraquinones (CLXIX) show nearly as much carbonyl stretching band shift as the 1-amino-anthraquinone (CLXVII). Since in 2-amino-anthraquinone , no hydrogen bonding is possible, he concluded that resonance structures of the type CLXVIII and CLXX may be responsible for the shift in the carbonyl stretching band.



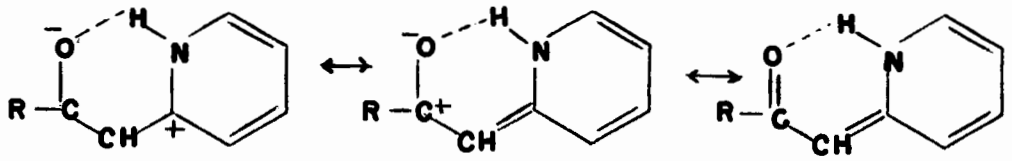
CLXVII CLXVIII CLXIX CLXX

The greater shift in the carbonyl stretching frequency of the pyridyl 2-pyridylmethyl ketones in comparison to that of the corresponding band in the isomeric pyridyl 4-pyridylmethyl ketones, would indicate that the carbon-oxygen bond acquired a greater single bond character and consequently that ionic resonance structures make a larger contribution to the ground state of the molecules.

The molecule is thus a resonance hybrid of structures such as CLXXI,CLXXII,CLXXIII,CLXXIV,CLXXV,CLXXVI, intramolecular hydrogen bonding being involved.



CLXXI CLXXII CLXXIII



CLXXIV CLXXV CLXXVI

TABLE 5

Infrared Absorption Maxima

of

2-Amino-4-(2'-pyridyl)-thiazole

2-Amino-4-(3'-pyridyl)-thiazole

2-Amino-4-(4'-pyridyl)-thiazole

2-Amino-4-(2'-quinolyl)-thiazole

TABLE 5

Regions	Compound			
	2-Amino-4-(2'-pyridyl)-thiazole	2-Amino-4-(3'-pyridyl)-thiazole	2-Amino-4-(4'-pyridyl)-thiazole	2-Amino-4-(2'-quinolyl)-thiazole
N-H stretching	3330 m.sh. 3300 m.br. 3120 m.br.	3300 (m.) 3130 (m.) -	3270 (m) 3095 (m)br. -	3460 (w.)shp. 3255 (v.w.)br. 3120 (v.w.)br.
Aromatic C-H stretching				
N-H bending	1628 (s.)	1632 s.	1658 v.s.	1608 s.
Ring vibrations	1590 s. 1570 m.sh. 1537 s. 1472 m. 1458 w.sh. 1423 s. 1400 w.sh.	1587 v.w. 1577 m. 1537 v.s. 1476 w. 1407 s.	1601 s. 1552 v.s. 1487 w. 1420 s.	1596 s. 1562 w. 1535 m. 1490 v.w. 1424 m.
C-N stretching	1345 s.	1346 s.	1351 s.	1353 m.
Ring skeletal vibrations, C-H in plane bending N-H wagging	1275 m. 1245 w. 1207 m. 1148 w. 1127 w. 1092 w. 1058 s. 1037 m.	1211 w. 1191 w. 1122 m. 1082 v.w. 1052 m. 1035 w. 1028 w. 1018 m.	1222 w. 1208 w. 1132 w. 1093 v.w. 1066 m. 1049 s. 1004 s.	1308 m. 1218 m. 1205 m.sh. 1140 w. 1043 -
Aromatic C-H out of plane bending, N-H twisting	995 s. 913 w. 842 m. 795 s. 755 s. 715 m. 682 m. 666 m.	937 v.w. 906 m. 849 m. 810 m. 697 s.br. 672 v.w.	918 v.w. 847 w.sh. 838 v.s. 740 m. 712 m. 696 w. 670 w.sh.	958 919 878 w. 848 v.s. 805 m. 762 v.s. 722 m. 692 m.

TABLE 6

Infrared Absorption Maxima

of

2-Amino-4-(4'-quinolyl)-thiazole

2-Amino-4-(2'-pyridyl)-5-(4"-pyridyl)-thiazole

2-Amino-4,5-di-(2'-pyridyl)-thiazole

2-Amino-4-(4'-pyridyl)-5-(2"-pyridyl)-thiazole

TABLE 6

Region	Compound: 2-Amino-4-(4'-quinolyl) thiazole	2-Amino-4-(2'-pyridyl)-5-(4"-pyridyl)thiazole	2-Amino-4, 5-di-(2'-pyridyl)-thiazole	2-Amino-4-(4'-pyridyl)-5-(2"-pyridyl)-thiazole
N-H stretching	3220(m.sh.) 3060(m.)br. -	3330(w.)br. 3202(m.)sh. 3160(m.)br.	3400(w.sh.) 3320(w.)br. 3130(w.)br.	3230(m.)br. 3050(s.)br. -
Aromatic C-H stretching	3060(m.)br.	3060(m.)br.	-	3050(s.)br. 2980(.sh.)
N-H bending	1658 s.	1657 (m.)	1627(m.)	1650(s.)
Ring vibrations	1588 s. 1538 s. 1502 m. 1460 w. 1420 w. 1382 w.	1590 s. 1545 w. 1530 m. 1471 w. 1425 w. 1416 m.	1590 s. 1563 w. 1550 m. 1518 m. 1473 m. 1460 m. 1431 m.	
C-N stretching	1340 m.	1332 m.	1348 m.	1336 s.
Ring skeletal vibration, arom. C-H in plane bending N-H wagging	1290 w.br. 1213 v.w. 1138 w.br. 1103 m. 1060 w. 1008 m.	1317 m. 1256 w. 1248 w. 1216 w. 1148 v.w. 1085 m. 1004 m. 998 m.	1268 w. 1238 v.w. 1175 w. 1148 w. 1082 w. 1000 w.sh.	1269 1212 1163 w. 1152 m. 1105 m. 1082 w. 1062 m. 997 m.
Arom. C-H out of plane bending N-H twisting	872 m. 861 m. 842 m. 812 v.w. 790 w. 778 s. 772 s. 766 v.s. 721 w. 702 m. 645 m.	977 w. 903 v.w. 877 w. 826 m. 822 m. 797 m. 756 v.w. 742 w. 700 m. 681 m.	977 w. 962 w. 883 w. 802 m. 775 m. 758 w. 742 w. 735 w. 692 w. 686 w. 680 w.	975 m. 880 w. 875 w. 832 v.s. 770 v.s. 738 s. 695 m. 682 w. 655 m.

TABLE 7

Infrared Absorption Maxima

of

2-Amino-4,5-di-(4'-pyridyl)-thiazole

2-N-(3'-Pyridyl)amino-4-phenylthiazole

2-N-(3'-Pyridyl)amino-4-(3"-pyridyl)-thiazole

2-N-(3'-Pyridyl)amino-4-(4"-pyridyl)-thiazole

2-N-(3'-Pyridyl)amino-4-methylthiazole

TABLE 7

Region	Compound: 2-Amino-4, 5-di-(4'-pyridyl)-thiazole	2-N-(3'-Pyridyl) amino-4-phenyl-thiazole	2-N-(3'-Pyridyl) amino-4-(3"-pyridyl)-thiazole	2-N-(3'-Pyridyl)-amino-4-(4"-pyridyl)-thiazole	2-N-(3'-Pyridyl)-amino-4-methyl-thiazole
N-H stretching	3270 m.br. 3100 m.br.	3260 w.	3260 vvw.	3250 w.	3280 v.w.
C-H stretching		3060 m. 3010 m.	2920 m.	3020 m.	3100 v.w. 3090 v.w.
NH stretching and combination bands		2900 m.sh. 2530 v.w. 2340 v.w. 1960 v.w.	2780 m. 2710 m.sh. 2320 w.	2960 s.br. 2880 s.sh. 2780 s.sh. 2310 w.sh.	2960 m. 2820 s.sh. 2740 s.br. 2330 m.sh. 1860 v.w.
N-H bending (scissoring)	1643	1618 v.s.	1620 s.	1618 s.sh.	1636 s.
Ring vibrations and CH_3 bending	1602 s. 1530 s. 1500 v.w. 1468 w. 1413 m.	1581 m. 1557 vs sh 1534 vs br 1480 v.s. 1442 m. 1412 m.	1584 m. 1560 v.s. 1528 v.s. 1483 s. 1420 m.	1600 v.s. 1550 vs.sh. 1546 vs.sh. 1537 v.s. 1514 s.sh. 1480 s. 1422 s.	1590 1562 1525 1484 1473 1425 1374
C-N stretching	1343 m.	1340 m. 1327 s.	1298 s.	1322 w.	1324 w.
Ring skeletal vibrations, aromatic C-H in plane bending N-H bending (wagging)	1262 w. 1217 w. 1160 v.w. 1101 w. 1086 v.w. 1065 v.w. 1000 s.	1297 v.s. 1238 s. 1189 s. 1172 m.sh 1155 w.sh 1120 w. 1101 w. 1070 m. 1053 s. 1041 w. 1023 w.	1238 m. 1190 m. 1167 w. 1120 w. 1110 w. 1090 w. 1058 m. 1043 m. 1017 m.	1295 s. 1285 s. 1237 w. 1213 w. 1190 m. 1122 w. 1098 v.w. 1060 m. 1020 w. 1000 m.	1294 s. 1287 v.s. 1239 m. 1193 m. 1174 w. 1127 s. 1119 m. 1101 w. 1042 w. 1020 w. 1000 w.

TABLE 7 (Continued)

Region	Compound: 2-Amino-4, 5-di-(4'-pyridyl)-thiazole	2-N-(3'-Pyridyl) amino-4-phenyl-thiazole	2-N-(3'-Pyridyl) amino-4-(3"-pyridyl)-thiazole	2-N-(3'-Pyridyl)-amino-4-(4"-pyridyl)-thiazole	2-N-(3'-Pyridyl)-amino-4-methyl-thiazole
Arom. C-H out of plane bending N-H twisting	982 m.sh. 890 v.w. 875 v.w. 841 m. 826 s. 758 w. 726 w. 685 m. 658 w.br.	972 v.w. 910 w. 891 w. 852 m. 811 w.sh. 797 v.s. 768 s. 697 v.s. 660 m. 630 m.	965 v.w. 943 v.w. 925 v.w. 915 v.w. 900 w. 848 m. 793 s. 717 s. 694 s.	965 v.w. 950 v.w. 918 w. 892 v.w. 855 w. 825 m. 800 m. 790 m. 742 w. 695 m. 660 m.	925 w. 905 v.w. 850 s. 825 v.w. 792 s. 693 v.s. 637 m.

TABLE 8

Infrared Absorption Maxima

of

2-N-(3'-Quinolyl)amino-4-phenylthiazole

2-N-(3'-Quinolyl)amino-4-(4"-pyridyl)-thiazole

2-N-(3'-Quinolyl)amino-4-methylthiazole

2-Nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine

TABLE 8

Region	Compound: 2-N-(3'-Quinolyl)-amino-4-phenylthiazole	2-N-(3'-Quinolyl)-amino-4-(4"-pyridyl)-thiazole	2-N-(3'-Quinolyl)-amino-4-methyl-thiazole	2-Nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine
N-H stretching	3265 w.	3250 v.w.br.	3260 v.w.br.	
C-H stretching	3120 w. 3030 m.	3100 v.w.sh. 3030 m.sh.	3100 v.w.sh 2980 m.br.	3090 m. 3010 m.
NH stretching and combination bands	2980 m.sh. 2950 m.sh. 2830 m.sh. 2320 w. 1953 v.w.	2900 m.br. 2820 m.sh. 2320 v.w.	2850 m.sh.	2330 m. br. 2060 w. 1975 v.w.
N-H bending	1629 w.sh.	1626 m.sh.	1618 v.s.	1630 s.
Ring vibration, CH_3 bending, nitrimino asym. stretching	1595 v.s. 1567 v.s. 1535 v.s. 1525 v.s.sh. 1492 m. 1477 m.sh. 1469 m. 1443 m. 1423 w. 1386 m. 1372 m.	1598 v.s. 1570 m. 1550 m. 1542 m. 1512 w.sh. 1441 v.w. 1468 w. 1415 w. 1387 w. 1372 w.	1562 w.sh. 1522 s.br. 1487 m. 1442 v.w. 1422 m. 1372 m.	1604 m.sh. 1540 s. 1462 v.w. 1395 s. 1364 s.sh.
C-N stretching	1345 m.	1342 w.	1322 m.	1345 v. 1332 v.w. 1305 s.
Ring skeletal vibration, aromatic C-H	1278 m. 1242 s. 1198 w. 1175 w.sh. 1148 v.w. 1135 w. 1125 v.w. 1069 m. 1058 m. 1021 w. 1015 w.	1296 w. 1273 w. 1221 m. 1212 m.sh. 1152 v.w. 1135 v.w. 1120 v.w. 1070 w.sh. 1012 v.w. 1000 m.	1285 m.sh. 1260 v.w. 1242 m. 1225 w. 1187 w. 1165 v.w. 1140 w. 1127 v.w. 1118 w. 1113 w. 1016 v.w. 1002 v.w.	1285 s.sh. 1262 m.sh. 1240 s.sh. 1212 s. 1192 s. 1064 m. 1012 m.

TABLE 8 (Continued)

	2-N-(3'-Quinolyl)-amino-4-phenylthiazole	2-N-(3'-Quinolyl)-amino-4-(4"-pyridyl)-thiazole	2-N-(3'-Quinolyl)-amino-4-methyl-thiazole	2-Nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine
Aromatic C-H out of plane bending	986 m. 945 w. 922 v.w. 912 v.w. 887 s. 850 m. 808 w. 774 m. 765 m. 748 s. 712 s. 702 s. 656 m.	983 w. 950 v.w. 916 v.w. 882 m. 862 v.w.br. 850 w. 829 m. 774 w. 751 w.sh. 743 m.sh. 716 v.w. 688 v.w. 661 w.sh. 655 m.	970 v.w. 945 v.w. 902 w. 892 m. 888 m. 847 m. 800 w. 775 m. 741 s. 715 w. 692 v.w.	902 m. 857 w. 827 m. 772 m.sh. 744 s. 672 v.w.sh. 662 m.

TABLE 9

Infrared Absorption Maxima

of

2-Pyridyl 2-pyridylmethyl ketone

4-Pyridyl 2-pyridylmethyl ketone

2-Pyridyl 4-pyridylmethyl ketone

4-Pyridyl 4-pyridylmethyl ketone

TABLE 9

Region	Compound: 2-Pyridyl 2-pyridylmethyl ketone	4-Pyridyl 2-pyridylmethyl ketone	2-Pyridyl 4-pyridylmethyl ketone	4-Pyridyl 4-pyridylmethyl ketone
N-H and aromatic C-H stretching and combination bands	3050 w. 3030 w. 2920 m.sh. 2770 m.sh. 2680 m.sh. 2340 w.sh. 1740 v.w.br.	3020 v.w. 2310 w.	3060 w. 3030 w. 2300 v.w. 1940 v.w.br.	3020 v.w. 2860 v.w. 2310 v.w.
C O stretching N-H bending	1630 s.	1625 s.	1692 v.s. 1652 m.sh.	1689 v.s.
Ring vibration N-H bending	1595 s. 1580 s.sh. 1565 s.sh. 1548 s. 1470 s.br. 1425 m. 1370 s.	1593 s. 1545 m. 1489 w.sh. 1468 m. 1452 m. 1410 m. 1372 m. 1315 v.w.	1602 s. 1582 s.sh. 1557 m.sh. 1497 m. 1465 w. 1440 m. 1415 s. 1396 m. 1337 v.s. 1327 v.s.sh.	1600 s. 1590 m. 1550 s. 1500 s. 1415 s. 1353 s. 1322 s.
C-N stretching	1292 s.	1284 m.	1290 m.	1243 w.sh.
Ring skeletal vibrations, aromatic C-H in plane bending	1245 m.sh. 1188 w.br. 1143 s. 1100 m.sh. 1090 m. 1062 s. 1042 m.sh. 1000 w.sh. 990 s.	1273 m. 1250 w.sh. 1150 m. 1098 v.w. 1066 s. 1040 w.sh. 988 w.	1266 m. 1225 s. 1200 w. 1150 m. 1090 v.w. 1068 1044 m. 1002 v.s. 992 v.s.	1220 v.s. 1210 m. 1192 v.s. 1080 v.w.sh. 1070 w. 1063 w. 1002 v.s. 985 m.sh.
Aromatic C-H out of plane bending	900 m. 878 s.sh. 870 s. 827 s. 782 v.s. 732 v.s. 690 w. 650 v.w. 638 w.	895 w. 882 m. 870 m. 830 m. 802 v.s. 735 s. 675 w.	917 v.w. 900 v.w. 897 v.w.sh. 870 w.sh. 867 m. 814 v.s. 776 v.s. 768 v.s.sh. 732 m. 651 s.	927 m.sh. 851 m. 812 s.sh. 805 v.s. 790 s. 729 v.w. 725 v.w. 670 s. 657 m.

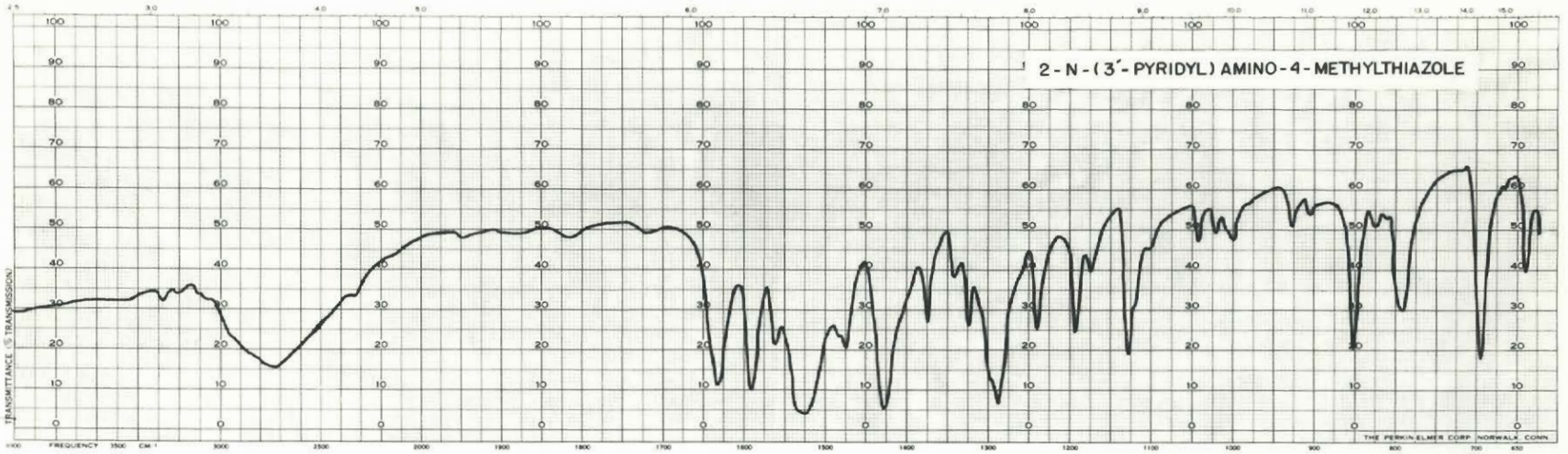
FIG. 1

Infrared Absorption Spectra

of

2-N-(3'-Pyridyl)amino-4-methylthiazole

2-N-(3'-Pyridyl)amino-4-phenylthiazole


2-N-(3'-PYRIDYL) AMINO-4-METHYLTHIAZOLE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM-1
THE PERKIN-ELMER CORP. NORWALK, CONN.

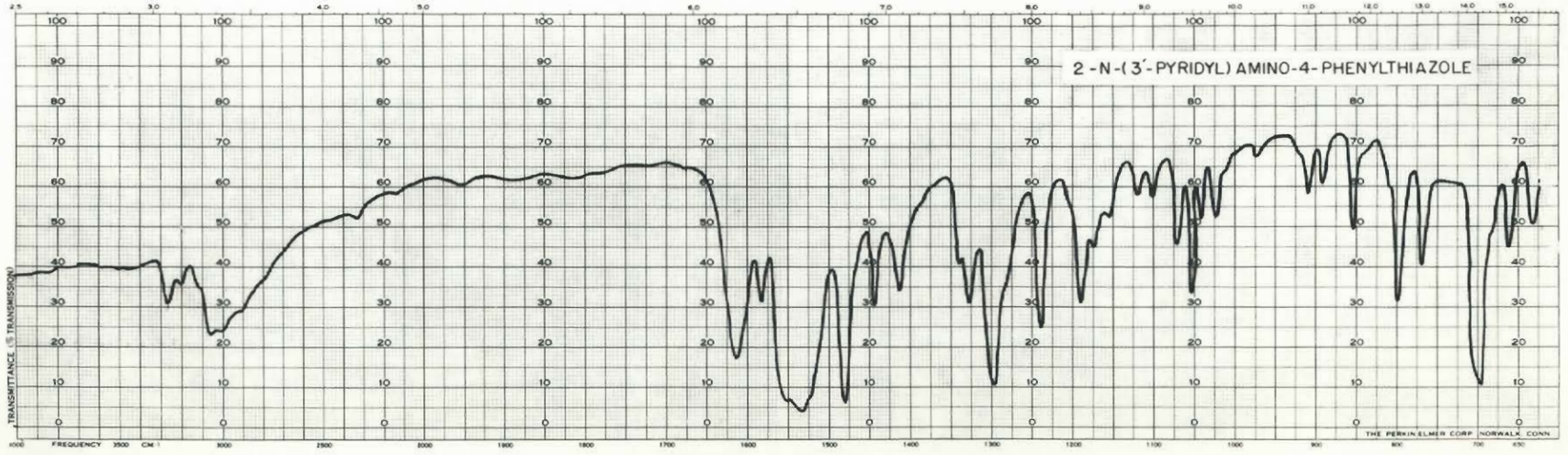

2-N-(3'-PYRIDYL) AMINO-4-PHENYLTHIAZOLE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM-1
THE PERKIN-ELMER CORP. NORWALK, CONN.

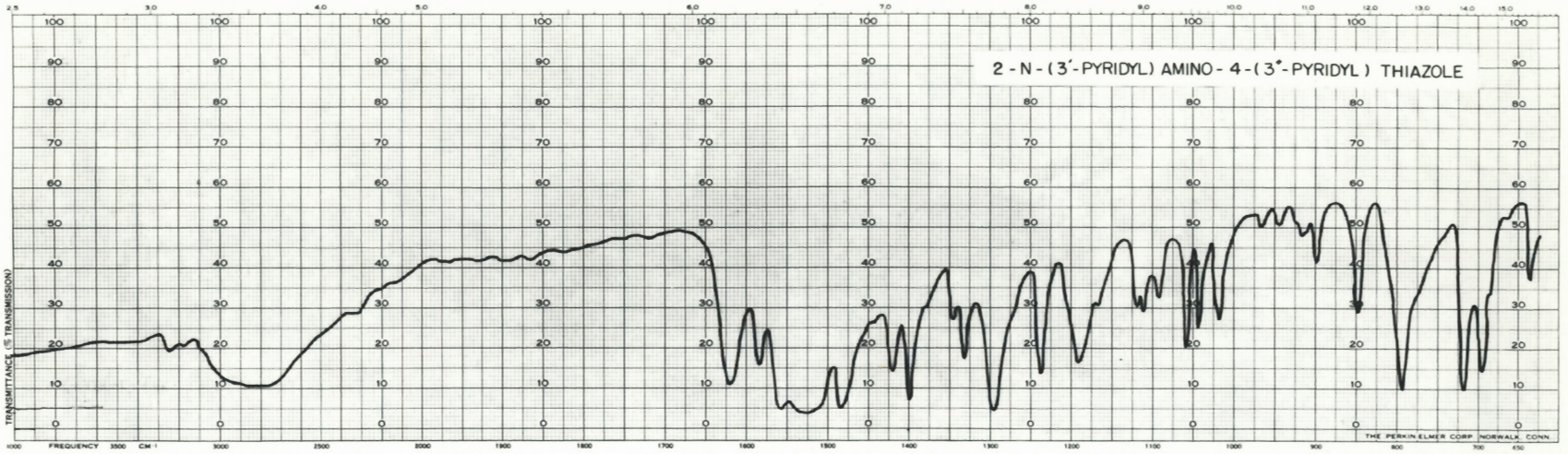
FIG. 2

Infrared Absorption Spectra

of

2-N-(3'-Pyridyl)amino-4-(3"-pyridyl)-thiazole

2-N-(3'-Pyridyl)amino-4-(4"-pyridyl)-thiazole


2 - N - (3'-PYRIDYL) AMINO - 4 - (3'-PYRIDYL) THIAZOLE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM-1
THE PERKIN-ELMER CORP NORWALK, CONN.

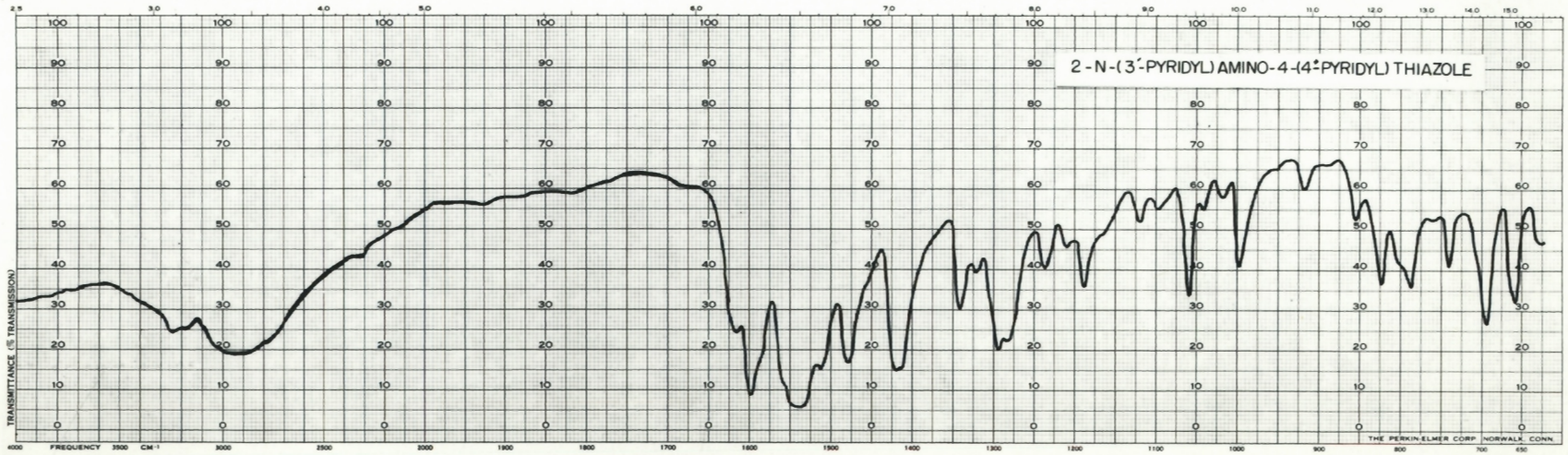

2 - N - (3'-PYRIDYL) AMINO - 4 - (4'-PYRIDYL) THIAZOLE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM-1
THE PERKIN-ELMER CORP NORWALK, CONN.

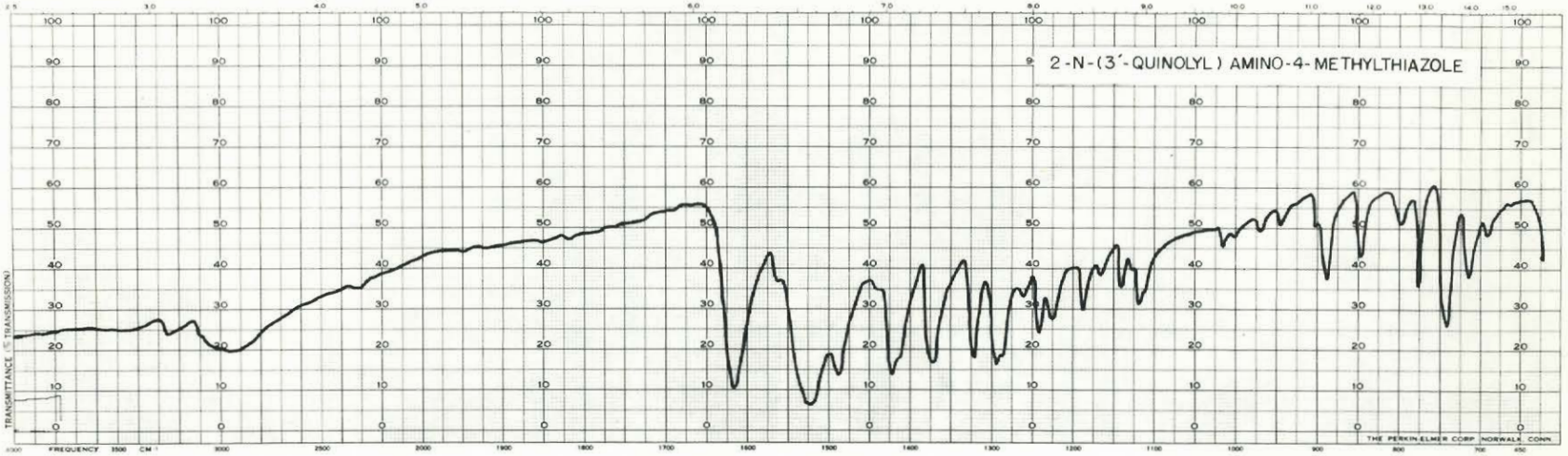
FIG. 3

Infrared Absorption Spectra

of

2-N-(3'-Quinolyl)amino-4-methylthiazole

2-N-(3'-Quinolyl)amino-4-phenylthiazole


2-N-(3'-QUINOLYL) AMINO-4-METHYLTHIAZOLE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM-1
THE PERKIN-ELMER CORP. NORWALK, CONN.

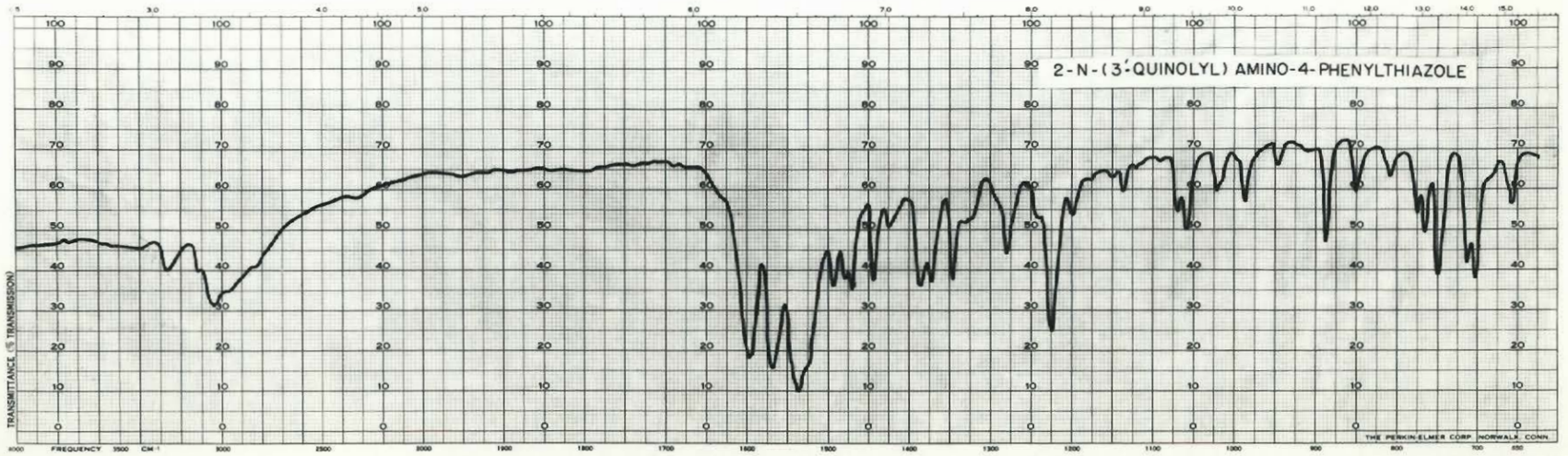

2-N-(3'-QUINOLYL) AMINO-4-PHENYLTHIAZOLE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM-1
THE PERKIN-ELMER CORP. NORWALK, CONN.

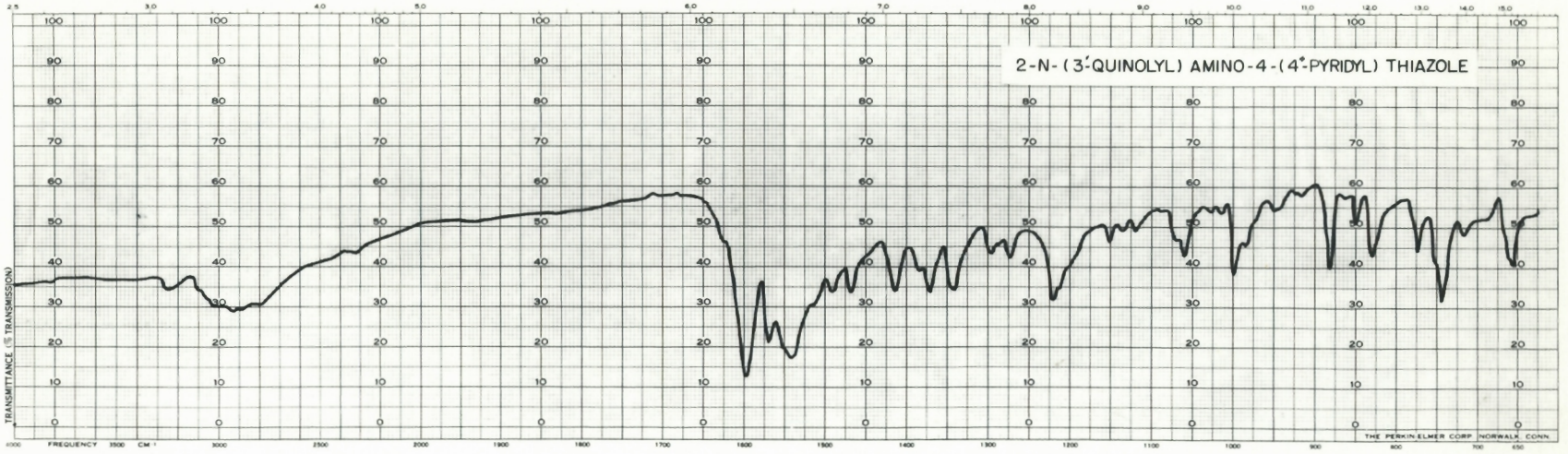
FIG. 4

Infrared Absorption Spectra

of

2-N-(3'-Quinolyl)amino-4-(4"-pyridyl)-thiazole

2-Nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine


2-N-(3'-QUINOLYL) AMINO-4-(4'-PYRIDYL) THIAZOLE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM⁻¹
THE PERKIN-ELMER CORP NORWALK, CONN.

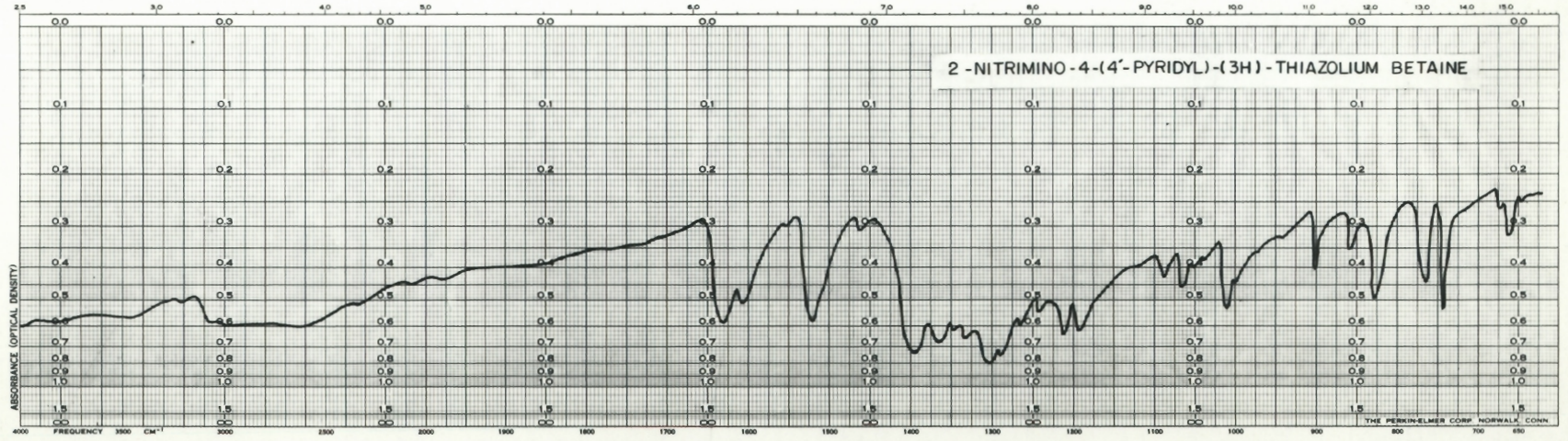

2-NITRIMINO-4-(4'-PYRIDYL)-(3H)-THIAZOLIUM BETAINE
ABSORBANCE (OPTICAL DENSITY)
FREQUENCY 3500 CM⁻¹
THE PERKIN-ELMER CORP NORWALK, CONN.

FIG. 5

Infrared Absorption Spectra

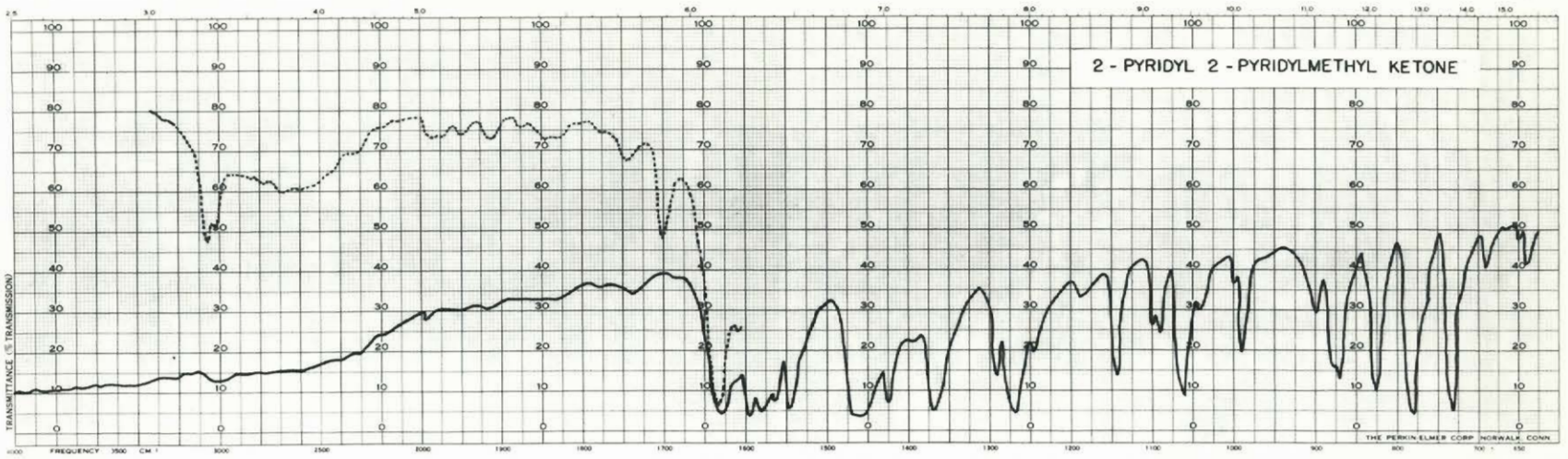
of

2-Pyridyl 2-pyridylmethyl ketone

4-Pyridyl 2-pyridylmethyl ketone

____ solid

---- solution


2 - PYRIDYL 2 - PYRIDYLMETHYL KETONE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM⁻¹
THE PERKIN-ELMER CORP NORWALK, CONN.

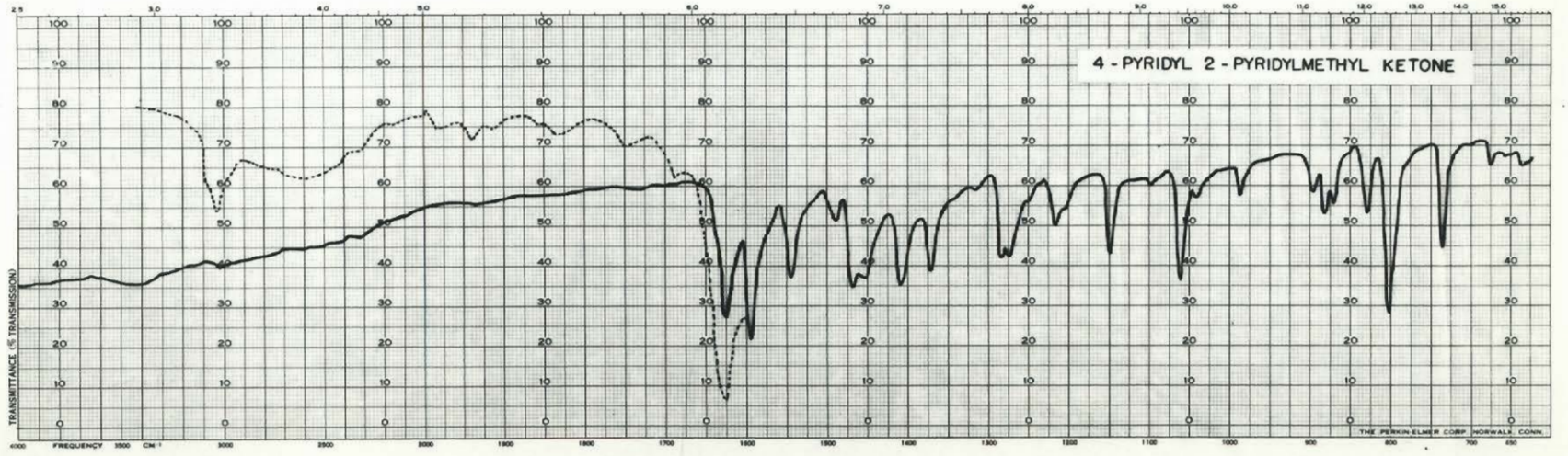

4 - PYRIDYL 2 - PYRIDYLMETHYL KETONE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY 3500 CM⁻¹
THE PERKIN-ELMER CORP NORWALK, CONN.

FIG. 6

Infrared Absorption Spectra

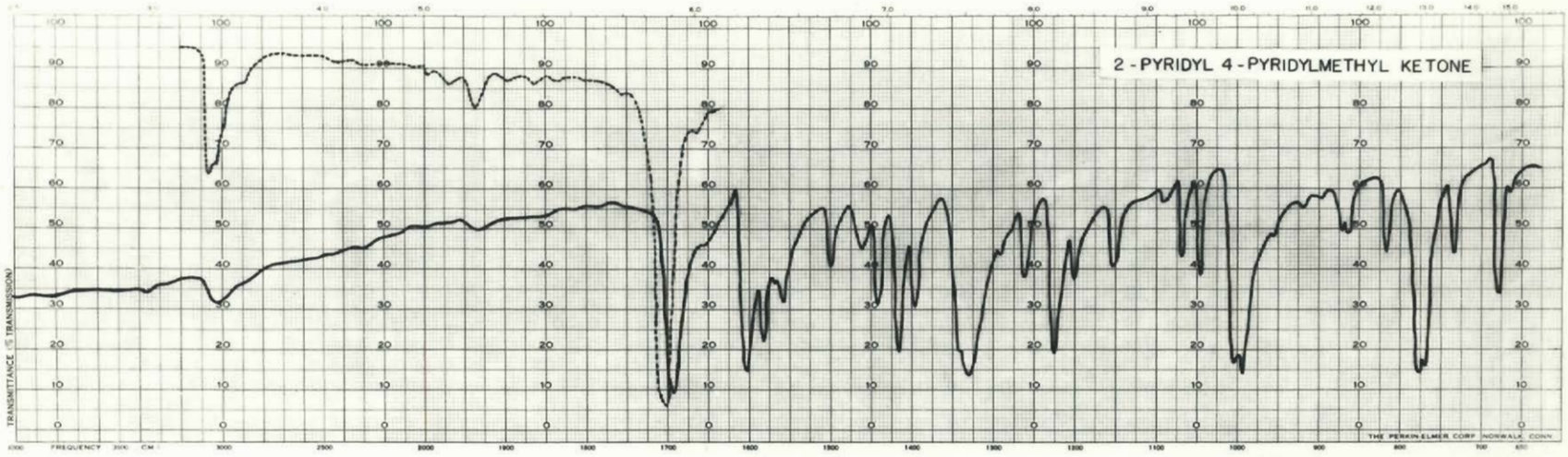
of

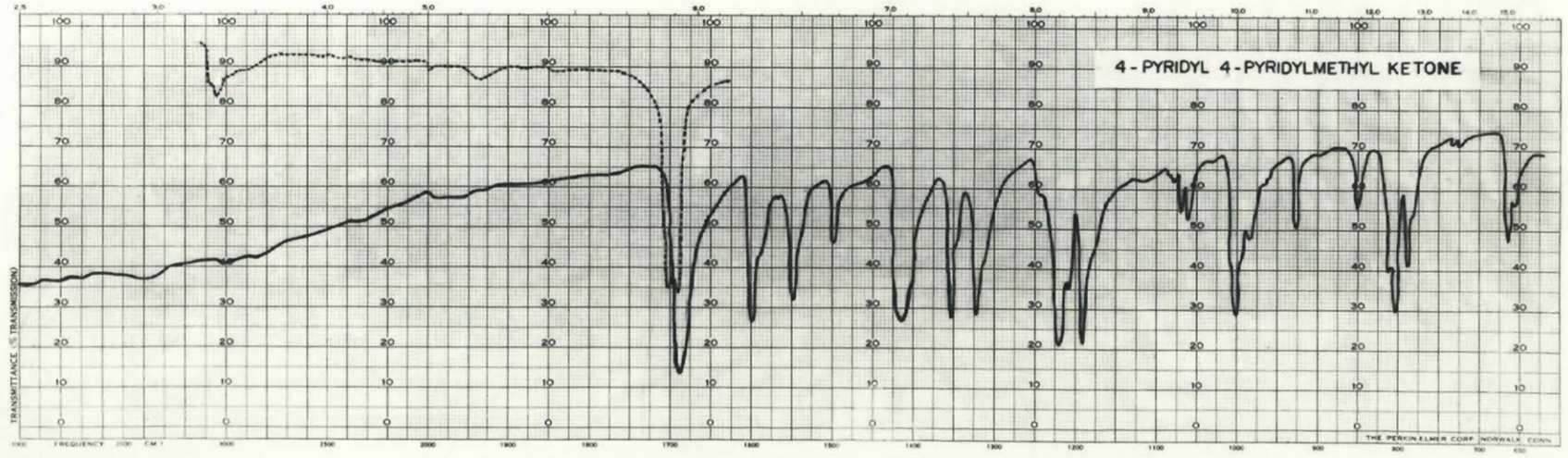
2-Pyridyl 4-pyridylmethyl ketone

4-Pyridyl 4-pyridylmethyl ketone

____ solid

---- solution


2 - PYRIDYL 4 - PYRIDYLMETHYL KETONE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY (CM⁻¹)
THE PERKIN-ELMER CORP. NORWALK, CONN.


4 - PYRIDYL 4 - PYRIDYLMETHYL KETONE
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY (CM⁻¹)
THE PERKIN-ELMER CORP. NORWALK, CONN.

EXPERIMENTAL

All melting points below 250° were determined in an ordinary melting point apparatus using silicone oil bath. Melting points above 250° were taken in a melting point block constructed according to Fieser's specifications (121). The reported melting points were corrected by using the set of melting point standards supplied by Bayer Company, Leverkussen, Germany.

Infrared Spectra.

The infrared spectra were recorded by means of a Perkin-Elmer model 21 double beam spectrophotometer equipped with a sodium chloride prism.

In recording the spectra in the solid state the potassium bromide pellet technique was used. The potassium bromide (400 mg.) was mixed with 1-2 mg. of the substance in a ground glass stoppered tube in the presence of 3 steel balls and then shaken for 3 minutes in a Perkin-Elmer vibrator. The pellets were formed by applying a pressure of 20,000 lbs./sq.in. for three minutes.

The setting of the instrument during the recording were as follows: resolution, 927; response, 1; gain, 5.5; speed, 5-6; suppression, 0. The scale used was: 100 cm^{-1}/1 cm. in the absorption range 4000-2000 cm^{-1} and 100 cm^{-1}/4 cm. in the range of 2000-650 cm^{-1}.

The absorption maxima of the bands listed in Tables 5,6,7,8,9 are characterized by the following abreviation: v.w. (very weak); w. (weak); m. (medium); s. (strong); v.s. (very strong); br. (broad); sh. (shoulder).

ESTERIFICATION OF PYRIDINE CARBOXYLIC ACIDS

1. Preparation of methyl picolinate (107).

In a 250 ml. three-necked round-bottom flask, equipped with ground glass joints, a reflux condenser provided with a drying tube, and a moisture tight mechanical stirrer, 30.75 g. of picolinic acid (0.25 mole) was placed. To the rapidly stirred acid, 36.5 ml. (0.5 mole) of thionyl chloride was added dropwise over an hour period. The flask content first turned green and finally dark purple. After one hour stirring under reflux, the mixture was allowed to stand overnight. Then, to the vigorously stirred mixture, 20.3 ml. (0.5 mole) of absolute methyl alcohol was added. This was followed by the slow addition of 150 ml. of a methanolic solution containing 35.5 g. (0.5625 moles) of commercial sodium methoxide. Refluxing and stirring was continued for another 30 minutes. The mixture was transferred to a large beaker, diluted to about 500 ml. with ether and filtered through a Büchner funnel. The precipitate of sodium chloride was washed with several 100 ml. portions of ether. The

combined filtrate and washings were dried over Drierite. After removal of the solvent by distillation, the residue was fractionated in vacuum to give methyl picolinate, b.p. 94-96° (5 mm.). Yield: 26.0 g. (75.8%).

2. Preparation of ethyl picolinate.

The method of Camps (108) was slightly modified.

Ethyl alcohol (80.0 g.) was mixed with 80 g. of concentrated sulfuric acid with cooling. Forty grams of picolinic acid (0.325 mole) was added and the mixture was refluxed for 3 hrs. The solution was then cooled to room temperature and poured onto 350 g. of finely crushed ice. The resulting mixture was made alkaline with solid sodium carbonate and then filtered. The filtrate was extracted with four portions of 100 ml. of ether. The ether extract was dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled under vacuum. The product was a colorless liquid, b.p. 241-242° (760 mm.). Yield: 32.3 g. (61.8%).

3. Preparation of methyl nicotinate (107).

In a 500 ml. flask was placed 20.0 g. (0.163 mole) of

nicotinic acid and 50 ml. of absolute methanol. From the dropping funnel, 25 ml. (0.446 mole) of concentrated sulfuric acid was added dropwise over an hour period. The solution was refluxed for two hours, cooled to room temperature, poured onto 200 g. of ice and made alkaline by slow addition of 54 g. (0.51 mole) of solid sodium carbonate. The mixture was filtered and the filtrate extracted with five portions of 100 ml. of ether. After drying of the combined ether extracts, the solvent was removed and the residue distilled in vacuum to give 16.2 g. (72.5%) of methyl nicotinate, b.p. 205-206° (760 mm.).

4. Preparation of ethyl isonicotinate (108).

Camps method was modified by introducing an azeotropic distillation of a ternary mixture (water - carbon tetrachloride - ethanol) boiling at 62°.

In a 500 ml. one neck flask, 80 g. of ethyl alcohol was mixed with 80 g. of concentrated sulfuric acid with cooling. Forty grams (0.325) of isonicotinic acid was added and the mixture was carefully heated until the solid dissolved. The solution was refluxed for one hour and allowed to cool. Carbon tetrachloride (150 ml.)

was added. After discontinuing the cooling water, the reflux condenser was connected at the top through a bent tube carrying a water trap to a Friedlich type condenser protected from moisture. The solution was then heated slowly so that during two hours 180 ml. of liquid distilled, (the trap being discontinuously emptied through a stopcock). The cooled reaction mixture was made alkaline with sodium carbonate and filtered. The filtrate was extracted with four portions of 100 ml. of ether. The ether extract was dried over anhydrous magnesium sulfate. After removal of the solvent the residue was distilled under vacuum. The product boiled at 216-217° (760 mm.). Yield: 40.5 g. (82.5%).

CLAISEN CONDENSATION OF PYRIDINE CABOXYLATES WITH ETHYL ACETATE

5. Preparation of alcohol free anhydrous sodium ethoxide (109).

Freshly cut sodium (8.80 g., 0.382 mole) was covered with 260 g. of xylene (previously purified with sodium). The mixture was heated until sodium melted.

The heating was turned off and the flask content was vigorously stirred while the mixture was cooling to room temperature. Sodium solidified as a finely divided powder. Xylene was decanted and 260 g. of ether was added. Absolute alcohol (17.6 g., 0.382 mole) diluted with 45 ml. of ether was added dropwise with stirring. After the vigorous initial reaction subsided, nearly all the sodium has reacted. The mixture was then refluxed with continuous stirring until all the sodium has completely disappeared. The ether was then distilled off and the last traces were removed under reduced pressure. The sodium ethoxide thus obtained was used in the subsequent preparation.

6. Preparation of 2-acetylpyridine (110).

To 26.0 g. (0.382 mole) of anhydrous sodium ethoxide was added with stirring a mixture of 37.7 g. (0.025 mole) of ethyl picolinate and 47.7 g. (0.47 mole) of ethyl acetate. The mixture became very warm, after the addition of the esters, and assumed a reddish brown color. The mixture was then stirred for one more hour. At the end of this period,

the reaction mixture was refluxed for 10 hrs. and left overnight. The solid mass which formed upon standing was dissolved in 250 ml. of water and unreacted esters were removed by extraction with four portions of 50 ml. of ether. The dissolved ether was removed from the aqueous solution by warming and the cooled solution was neutralized with concentrated hydrochloric acid (about 20 ml.). The dark oil which appeared was directly dissolved by the addition of 80 ml. of concentrated hydrochloric acid. Evolution of carbon dioxide began spontaneously and the hydrolysis was completed by vigorously refluxing the clear solution for two and one half hours. The cold acid solution was made alkaline with potassium carbonate and extracted with five portions of 120 ml. of ether. The combined ether extract was dried over anhydrous potassium carbonate. Ether was removed on a steam bath and the residual oil distilled under vacuum. A colorless oily liquid was obtained, b.p. 188-189° (760 mm.) Yield: 18.0 g. (59.8%).

By a modified procedure, 37.7 g. (0.25 mole) of ethyl picolinate was condensed with 47.7 g. (0.47 mole)

of ethyl acetate in the presence of 60 ml. of dry toluene. The refluxing period required for the hydrolysis of the -keto-ester intermediate and decarboxylation of the resulting -keto-acid, was increased from two and a half to four hours. Yield: 24.5 g. (81.4%), b.p. 188-189° (760 mm.).

7. Preparation of 3-acetylpyridine (110).

A mixture of 68.5 g. (0.5 mole) of methyl nicotinate and 71.6 g. (0.75 mole) of ethyl acetate was added to 39 g. (0.573 mole) of anhydrous sodium ethoxide. After one hour stirring, the mixture was refluxed for six hours and left overnight. The solid mass was dissolved in about 400 ml. of water and the unreacted esters were removed by extraction with three portions of 60 ml. of ether. After removal of the dissolved ether by warming, the cooled solution was neutralized with concentrated hydrochloric acid (30 ml.). The dark oil which appeared was dissolved by the addition of a further 125 ml. of concentrated hydrochloric acid. The solution was refluxed for 4 hrs. The cooled acid solution was then made alkaline with solid potassium carbonate and extracted with five

portions of 100 ml. of ether. The combined ether extract was dried over "Drierite". After removal of the solvent, the residue was distilled in vacuum to yield 48.6 g. (80.2%) of a colorless liquid. The product had a characteristic odor and boiled at 217-218° (760 mm.).

8. Preparation of 4-acetylpyridine (110).

In a 1 l. three-necked flask 26.0 g. (0.382 mole) of alcohol free anhydrous sodium ethoxide was prepared as described in exp. 5. Then a mixture of 75.5 g. (0.5 mole) of ethyl isonicotinate and 71.6 g. (0.705 mole) of ethyl acetate was added carefully while stirring. The stirring was continued for one hour and the mixture was then refluxed for 6 hrs. and left overnight. To dissolve the solid mass about 450 ml. of water was added and unreacted esters were removed by extraction with three portions of 60 ml. of ether. After removal of the dissolved ether by warming on a steam bath, the cooled solution was neutralized with concentrated hydrochloric acid (30 ml.). The dark oil which appeared was dissolved by the addition of a further amount of hydrochloric acid (125 ml.). After 4 hrs.

refluxing, the cooled solution was made alkaline by solid potassium carbonate and extracted with five portions of 100 ml. of ether. After drying the ether extract over anhydrous magnesium sulfate, the solvent was removed, and the residue was distilled in vacuum. The colorless liquid weighed 46.5 g. (76.7%) and boiled at 213-214° (760 mm.). Methyl isonicotinate (37.7 g., 0.25 mole) was condensed with ethyl acetate under the same condition as in exp. 8. Yield: 26.7 g. (88.9%), b.p. 213-214°.

BROMINATION OF ACETYLPYRIDINES

9. Bromination of 2-acetylpyridine.

The method developed by Dornow et al. (111) for the preparation of 3-bromoacetylpyridine was modified and applied to the preparation of 2-bromoacetylpyridine.

In a 100 ml. flask, 12.1 gms. (0.1 mole) of 2-acetylpyridine was dissolved in 20 ml. of concentrated hydrochloric acid (48.5%). To the solution maintained at 65-70°, was added dropwise, with vigorous stirring, 16.0 g. (0.1 mole) of bromine dissolved in 4 ml. of concentrated hydrobromic acid. An abundant, almost colorless precipitate formed. The mixture was stirred

for 2 hrs. at about 70° and then allowed to stand overnight. The crystalline mass was filtered off on a Büchner funnel, sucked dry and washed with five portions of 6 ml. of a mixture(1:1) of petroleum ether (60-75°) and methanol. After drying in vacuum the precipitate weighed 21.2 g. (75.5%) m.p. 226-228°(dec.). By concentrating the M.L., 4.0 g. of precipitate was recovered, m.p. 223-226° (dec.). Therefore, total yield 25.2 (89.7%).

10. Bromination of 3-acetylpyridine (111).

Sixteen grams of bromine diluted with 5 ml. of concentrated hydrobromic acid was added at 70-75° to 12.1 g. (0.1 mole) of 3-acetylpyridine dissolved in 25 ml. of concentrated hydrobromic acid (48.5%). The reaction mixture was stirred at 75°C for 3 hrs. and then allowed to stand for two days. The crystalline mass was filtered off on a Büchner funnel, sucked dry and washed with four portions of 5 ml. of a mixture (1:1) of methanol and petroleum ether (60-75°). The precipitate was dried under vacuum at 65°C. It weighed 27.1 g. (96.4%) and melted at 195-197°.

11. Bromination of 4-acetylpyridine.

In a 100 ml. flask 18.2 g. (0.15 mole) of 4-acetylpyridine was dissolved in 25 ml. of concentrated hydrobromic acid (48.6%). To this solution maintained at about 70°, was added dropwise with vigorous stirring, 24.0 g. (0.15 mole) of bromine dissolved in 4 ml. of concentrated hydrobromic acid. A crystalline precipitate started to form. The mixture was stirred for 3 hrs. at 70°C and then allowed to stand overnight. The crystalline hydrobromide was filtered off, sucked dry and washed with four portions of 5 ml. of a mixture (1:1) of methanol and petroleum ether (60-75°). After drying under vacuum the product weighed 23.2 g. (82.6%). After crystallization from dilute hydrobromic acid (20%), it melted at 209-210°(dec.). Anal. Calc'd. for $C_7H_7NOBr_2$: Br, 56.91 Found: Br, 57.49.

CHLORINATION OF ACETYLPYRIDINES

12. Chlorination of 3-acetylpyridine (111).

Six grams (0.05 mole) of 3-acetylpyridine was dissolved in 40 ml. of chloroform. Dry chlorine was bubbled during one half to an hour and the mixture was stirred for an additional hour. The crystalline precipitate

was filtered and washed with four portions of ethanol. The 3- acetylpyridine hydrochloride was then dried at 65° in vacuum and weighed. Yield 8.5 (88.3%). It melted at 190-193°. After crystallization from ethanol it melted at 195-196°.

13. Attempted chlorination of 4-acetylpyridine (111).

The above method was applied for the first time to the preparation of 4-bromoacetylpyridine hydrobromide.

Ten grams of 3-acetylpyridine was dissolved in 60 ml. of dry chloroform contained in a 100 ml. flask. Dry chlorine was allowed to bubble for 30 minutes. The reaction resulted in a complex mixture of a gummy nature and no 4-chloroacetylpyridine hydrochloride could be isolated.

14. Preparation of 2-amino-4-(2'-pyridyl)-thiazole.

1. Condensation of 2-bromoacetylpyridine hydrochloride with thiourea.

(a.) A mixture of 5.62 g. (0.02 mole) of 2-bromoacetylpyridine and 1.52 g. (0.02) of thiourea and 50 ml. of ethanol was refluxed for 5 hrs. During the

refluxing period a slight odor of H_2S was noticed. The reaction was allowed to stand for 24 hrs. After removal of the solvent, the precipitate was sucked dry, washed with three portions of 5 ml. of ethanol and dried in vacuum. The hydrochloride of 2-amino-4-(2'-pyridyl) thiazole weighed 2.8 g. (54.3%).

The precipitate was then dissolved in water and made alkaline with solid sodium hydroxide. The brown precipitate was filtered off, washed with water and cold ethanol. After drying in vacuum the precipitate weighed 1.60 g. (45.2%) and melted at 170.2-176°. The product was crystallized from methanol and it melted at 175.5-176°.

(b.) In a 50 ml. three-necked flask, 4.2 g. (0.015 mole) of 2-bromoacetylpyridine hydrobromide was dissolved in 18 ml. of water. A solution of 1.18 g. (0.0155) of thiourea in 4.5 ml. of water was added during 5 minutes with stirring. Temperature went up from 28° to 50° and the solution became slightly yellow. After a few minutes an almost colorless precipitate started to form. The stirring was continued for one hour at 38-40°. The batch was allowed to stand overnight.

The crystalline precipitate was filtered off, washed with four portions of 2 ml. of water and dried overnight in vacuum. The hydrochloride of 2-amino-4-(2'-pyridyl) thiazole weighed 3.0 g. (77.5%). The precipitate was then dissolved in 50 ml. of water and the solution was made slightly alkaline by adding carefully a 7% ammonium hydroxide aqueous solution with stirring. The colorless precipitate was then filtered off, washed with 5 portions of 5 ml. of water and dried over P_2O_5 in vacuum. The product weighed 1.87 g. (70.6%). The filtrate from the reaction mixture was made alkaline by 7% ammonium hydroxide and the precipitate collected weighed, after drying, 0.54 g. (19.3%). Overall yield: 2.41 g. (90.8%). The compound was recrystallized from ethanol and melted at 175.6-176°. Anal. Calc'd. for $C_8H_7N_3S$: C, 54.20; H, 3.98; N, 23.72; S, 18.08%. Found: C, 54.29; H, 4.03; N, 23.74; S, 18.05%. The dipicrate melted at 186-187° (dec.). Anal. Calc'd. for $C_{20}H_{13}N_9O_{14}S$: N, 19.85; Found: N, 20.00%.

2. Condensation of 2-acetylpyridine with thiourea in presence of iodine.

A mixture of 2.42 g. (0.02 mole) of 2-acetyl-pyridine, 3.04 g. (0.04 mole) of thiourea, 2.54 g. (0.02

mole) of iodine was heated for 6 hrs. at 80-90° in a 50.0 ml. flask. The solid mixture was shaken periodically. At the end of the heating period, the reaction mixture was treated with water and boiled for half an hour and filtered. After cooling, the filtrate was made alkaline with 7% ammonium hydroxide. The brown precipitate was filtered off and washed with three portions of 5 ml. of water and after drying it weighed 1.52 g. (42.9%). The recrystallized product melted at 176-177.° Mixed melting point technique indicated that this substance was identical to 2-amino-4-(2'-pyridyl)-thiazole.

15. Preparation of 2-amino-4-(3'-pyridyl)-thiazole.

(a) Condensation of 3-bromoacetylpyridine hydrobromide with thiourea.

3-Bromoacetylpyridine hydrobromide (5.62 g., 0.02 mole) was dissolved in 27 ml. of water with slight warming. The solution was cooled to room temperature (25°) and a solution of 1.52 g. (0.02 mole) of thiourea in 6 ml. of water was slowly added with stirring. An exothermic reaction took place and the solution became slightly yellow. The stirring was continued for one hour at 35-40°. The

flask content was transferred to a 250 ml. beaker. The volume was adjusted to 100 ml. with water and the reaction mixture was heated gently to dissolve the precipitate. The solution was allowed to cool to room temperature and made alkaline with 10% ammonium hydroxide. The almost colorless precipitate was collected on a Büchner funnel, sucked dry and washed with four portions of 5 ml. of water. After drying in vacuum over P_2O_5 it weighed 3.21 g. (90.6%). After recrystallization from ethanol, it melted at 204-204.6°. Anal. Calc'd. for $C_8H_7N_3S$: C, 54.20; H, 3.98; N, 23.72; S, 18.08%. Found: C, 54.25; H, 3.94; N, 23.70; S, 18.20%.

In a 100 ml. three-neck flask 3.86 g. (0.02 mole) of 3-chloroacetylpyridine hydrochloride was dissolved in 27 ml. of water. A solution of 1.52 g. (0.02 mole) of thiourea dissolved in 6 ml. of water was carefully added with stirring during 5 minutes. The solution became slightly yellow and the temperature rose to 50°. The solution was stirred for one hour at 35-40°. The reaction mixture was then transferred to a 250 ml. beaker and the volume was made up to about 100 ml. The solution was made slightly alkaline with 10% ammonium hydroxide. The colorless precipitate was filtered off, washed with four portions of

5 ml. of water and dried in vacuum over P_2O_5. It weighed 2.97 (84.0%). After recrystallization from ethanol it melted at 204-205°.

(b) Condensation of 3-acetylpyridine with thiourea in presence of iodine.

A mixture of 2.42 g. of (0.02 mole) of acetylpyridine, 3.04 g. (0.04 mole) of thiourea, 2.54 g. (0.02 mole) of iodine was heated for 6 hrs. at 80-90° in a 20 ml. flask. At the end of this period the reaction mixture was treated with water, boiled for half an hour and filtered. The cooled solution was made slightly alkaline with 10% ammonium hydroxide. The brown precipitate was filtered off and washed with four portions of water. After drying the precipitate weighed 1.45 g. (41.0%). The crude product melted at 196-199°. After crystallization from ethanol, it melted at 204-205.2°.

16. Preparation of 2-amino-4-(4'-pyridyl)-thiazole.

(a) Condensation of 4-bromoacetylpyridine with thiourea.

In a 100 ml. flask, 11.2 g. (0.04 mole) of 4-bromoacetylpyridine hydrochloride was dissolved in 54 ml.

of water with gentle heating (45°). The solution was allowed to cool to room temperature and 3.04 g. (0.04 mole) of thiourea dissolved in 12 ml. was carefully added. A sudden temperature rise was noticed (50°). The solution became slightly yellow. The solution was stirred for one hour at 35-40°. At the end of this period, an almost colorless precipitate formed. The reaction mixture was transferred to a 400 ml. beaker and about 150 ml. of water was added. To dissolve the precipitate the solution was gently warmed (50°). The cooled solution was made slightly alkaline with 10% ammonium hydroxide. The almost colorless precipitate was collected on a Büchner funnel and washed with four portions of 5 ml. of water. After drying in vacuum the precipitate weighed 6.41 (90.5%). It melted at 269.8-271.5°. Anal. Calc'd for $C_8H_7N_3S$: C, 54.20; H, 3.98; N, 23.72%. Found: C, 54.87; H, 4.13; N, 23.62%. The dipicrate melted at 246-246.5°. Anal. Calc'd for $C_{20}H_{13}N_9O_{14}S$: N, 19.85%. Found: N, 19.78%.

(b) Condensation of 4-acetylpyridine with thiourea in presence of bromine.

To a mixture of 6.05 g. (0.05 mole) of 4-acetylpyridine and 7.6 g. (0.10 mole) of thiourea, 8.0 g.

(0.05) of bromine was added dropwise over a period of 10 minutes. The resulting slurry was stirred for a half an hour and heated overnight on a steam bath. Then the reaction mixture was treated with water and heated until most of the solid material has gone into solution. The insoluble material was filtered off and discarded (a considerable amount of sulfur was identified). The cold filtrate was made alkaline with 10% ammonium hydroxide, the brown precipitate was filtered off and washed with 12 ml. of water. After drying in vacuum, the product weighed 5.73 g. (64.7%) and melted at 262-265°. After recrystallization from ethanol the compound melted at 270-271.6°. The mixed melting point techinque showed it to be identical with the compound prepared by the previous method.

In a 100 ml. flask, 6.05 g. (0.05 mole) of 4-acetylpyridine was dissolved in 25 ml. of concentrated hydrobromic acid (48.5%). Eight grams of bromine diluted with 3 ml. of concentrated hydrobromic acid was added dropwise at about 70°. The reaction mixture was then stirred for 3 hrs. and allowed to cool. To the reaction mixture was added 28 ml. of water.

From the dropping funnel 3.80 g. (0.05 mole) of thiourea was carefully added (temperature rose to 45°) while vigorously stirring. The solution was stirred for 1 hr. at 35-40°. The reaction mixture was then transferred to a 400 ml. beaker and the volume was made up to 250 ml. with water. The solution was made slightly alkaline with 10% ammonium hydroxide. The precipitate was filtered off and washed with four portions of 12 ml. of water. After drying in vacuum, the product weighed 5.13 g. (58.0%). After recrystallization from ethanol the compound melted at 270.3-271.2°. The comparison of the spectra with those of the substances prepared by the other procedures indicated that they were identical.

(c) Preparation of 2-N-acetylamino-4-(4'-pyridyl)-thiazole.

2-Amino-4-(4'-pyridyl) thiazole (1.77 g., 0.01 mole) was dissolved in 15 ml. of glacial acetic acid and 3 ml. of acetic anhydride. After standing for half an hour crystals started to separate. The mixture was allowed to stand overnight. Water (50 ml.) was added and the precipitate was filtered off, washed with five portions of 5 ml. of water and dried. The product weighed 1.85 g. (84.5%) and melted

at 342-343°. Anal. Calc'd. for $C_{10}H_9N_3OS$: C, 54.79; H, 4.14; N, 19.17; S, 14.62%. Found: C, 54.25; H, 3.96; N, 18.98; S, 13.94%.

17. Preparation of quinoline carboxylic acids.

(a) Bromination of quinaldine (113).

In a 2 l. flask, were placed 71.6 g. (0.5 mole) of quinaldine, 250 g. (3.05 mole) of anhydrous sodium acetate and 625 ml. of glacial acetic acid. To this solution maintained at 70-75°, a solution of 240 g. of bromine in 20 ml. of glacial acetic acid was added during twenty-five minutes with stirring. The mixture was then heated at 90-95° for one hour and allowed to stand overnight. The colorless solid was collected on a Büchner funnel and washed with three portions of 25 ml. of glacial acetic acid and four portions of 30 ml. of water. After drying in vacuum for 60 hrs., the product weighed 178.6 g. (94.0%). It melted at 128-129.6°.

(b) Preparation of quinaldic acid (Hydrolysis of α-tribromoquinaldine) (113).

One hundred and twenty-five grams (0.33 mole) of

α - tribromoquinaldine was dissolved in 1100 ml. of dilute sulfuric acid (1 volume of acid to 10 volumes of water) and the solution was stirred at 115-125° for 12 hrs. The cooled solution was adjusted to a pH of 3-4 with ammonium hydroxide, and extracted with six to eight 300 ml. portions of chloroform. After removal of the solvent 54.1 g. (94.7%) of quinaldic acid was obtained. It melted at 153.9-155.9°.

(c) Condensation of lepidine with benzaldehyde (117).

A mixture of 85.9 g. (0.6 mole) of lepidine, 345 ml. of benzaldehyde and 24 g. of anhydrous zinc chloride was refluxed for 5 hrs. To the cooled solution, was added 900 ml. of 2N hydrochloric acid and 700 ml. of benzene. The mixture was then warmed up on a steam bath and the precipitated styrylquinoline hydrochloride was collected and washed with benzene. The hydrochloride was decomposed with 50% sodium hydroxide solution and the base was extracted with ether. On removal of the ether the residue crystallized and for purification was washed with low boiling petroleum ether. The dried product weighed 89.6 g. (64.5%) and melted at 87-89°.

(d) Preparation of cinchoninic acid (117).

4-Styrylquinoline (69.3 g., 0.3 mole) was dissolved in 1500 ml. of 50% aqueous pyridine. Finely powdered potassium permanganate (126 g.) was added with stirring over a period of 20 minutes. Stirring was continued for a further 2 hours, the temperature being allowed to rise to normal (room temperature). Manganese oxide was separated, suspended in water and heated on the water bath and then the suspension filtered to recover the remainder of the oxidation products. The filtrate and the original concentrate were combined, concentrated to a small volume and neutralized to Congo paper. The precipitated acids were collected on a Büchner funnel, washed with water, dried and then shaken with cold ether to remove benzoic acid. The residue was dried. It weighed 41.0 g. (79.0%) and melted at 255-258.5°. After crystallization from water it melted at 257-258°.

18. Esterification of Quinoline Carboxylic Acids.

(a) Preparation of ethyl quinaldate (ethyl quinaldinate) (117).

Absolute ethyl alcohol (375 ml.) was mixed carefully with 36 g. of concentrated sulfuric acid with

cooling. Quinaldic acid (45 g., 0.26 mole) was added and the solution was refluxed for 5 hrs. The greatest part of ethanol was then distilled off and the residual liquid poured onto 300 g. of crushed ice. The liquid was made alkaline with concentrated ammonium hydroxide and then extracted with five portions of 110 ml. of ether. After removal of ether, the residue was distilled in vacuum, b.p. 154-155° at 0.3 mm. The colorless oily liquid obtained weighed 43.5 g. (83.3%).

(b) Preparation of ethyl cinchoninate (117).

Absolute ethyl alcohol (174 ml.) was mixed with 27.6 g. of concentrated sulfuric acid with cooling. Cinchoninic acid (34.6 g., 0.2 mole) was added and the resulting solution was refluxed for 5 hrs. At the end of this period, the greatest part of ethanol was distilled off and the residual liquid poured onto 340 g. of crushed ice. The liquid was made alkaline with concentrated ammonium hydroxide and then extracted with five portions of 125 ml. of ether. After removal of the solvent, the residue was distilled in vacuum, b.p. 174-175° at 14 mm. The colorless liquid weighed 31.3 g. (77.8%).

19. Claisen Condensation of Quinoline Carboxylic Acid Ethyl Esters with Ethyl Acetate.

(a) Preparation of 2-acetylquinoline (112).

In a 250 ml. three-necked flask, sodium ethoxide was prepared, in 42 ml. of dry toluene from 3.4 g. (0.148 gram atom) of powdered sodium (109) and 6.8 g. (0.148 mole) of absolute ethanol. A mixture of 20.1 g. (0.1 mole) of ethyl quinaldate and 13.1 g. (0.148 mole) of dry ethyl acetate was added during ten minutes and the flask content was stirred at 115° for 6 hrs. The cooled solution was poured into 400 ml. of ice water and then 90 ml. of 30 percent sulfuric acid was carefully added. The aqueous layer was then refluxed with stirring for 8 hrs. After cooling, the solution was made alkaline with sodium hydroxide and distilled to give 14.6 g. (85.5%) of 2-acetylquinoline. The product melted at 44-45°.

(b) Preparation of 4-acetylquinoline acetate.

In a 250 ml. flask, sodium ethoxide was prepared, in 63 ml. of dry toluene, from 5.1 g. (0.222 gram atom) of powdered sodium (109) and 10.2 g. (0.222 mole) of absolute

ethanol. From the dropping funnel, a mixture of 30.3 g. (0.15 mole) of ethyl cinchoninate and 19.6 g. (0.222 mole) of ethyl acetate was added during 10 minutes and the flask content was stirred at 115° for 6 hrs. The solution was allowed to cool to room temperature and then poured into 600 ml. of ice-water. A solution of 30% (w./v.) of sulfuric acid was added and the aqueous layer was refluxed with stirring for 8 hrs. After cooling the solution was made alkaline with sodium hydroxide and extracted with four portions of 100 ml. of ether. The ether extract was dried over Drierite and the solvent removed by distillation. To the liquid residue, glacial acetic acid was added and the crystalline material formed was collected on a Büchner funnel and washed with glacial acetic acid and petroleum ether (65-75°). After drying the acetate of 4-acetylpyridine weighed 27.4 g. (79%). The product melted at 74-75°.

20. Bromination of acetylquinolines.

(a) Preparation of 2-bromoacetylquinoline hydrobromide (113).

2-Acetylquinoline (8.96 g., 0.05 mole) was dissolved

in 25 ml. of 40% hydrobromic acid contained in a 100 ml. flask. Eight grams (0.05 mole) of bromine dissolved in 10 ml. of 40% hydrobromic acid was added with stirring at 65-68° for ten minutes. The mixture was kept at 65° for one hour, and the flask was then chilled in an ice bath until no more precipitate formed. The precipitate was collected on a Büchner funnel, washed with 10 ml. of acetone and three portions of 10 ml. of ether. After drying in vacuum, the precipitate weighed 13.7 g. (80.7%) and melted at 212-215.7°. (dec.).

(b) Preparation of 4-bromoacetylquinoline hydrobromide (113).

In a 100 ml. flask, were placed 23.1 g. (0.1 mole) of 4-acetylquinoline acetate and 50 ml. of 40% hydrobromic acid. A solution of 16.0 g. (0.1 mole) of bromine in 20 ml. of 40% hydrobromic acid was added at 65-68° in the course of ten minutes. The mixture was kept at 65° with stirring for one hour, and the flask was then thoroughly chilled in an ice bath until no more precipitate formed. The precipitate was filtered off and washed with 15 ml. of acetone and four portions of 10 ml. of ether. The dried product weighed 30.0 g. (90.8%), m.p. 224-225.6°.

21. Preparation of 2-amino-4-(2'-quinolyl)thiazole.

Condensation of 2-bromoacetylquinoline hydrobromide with thiourea.

2-Bromoacetylquinoline hydrobromide (6.62 g., 0.02 mole) was added to a mixture of 15 ml. of water, 30 ml. of ethanol and 2 ml. of hydrobromic acid. The mixture was warmed with stirring until all the solid dissolved. To the stirred solution maintained at 60-65°, 1.52 g. (0.02 mole) of thiourea, dissolved in 10 ml. of water, was added through the dropping funnel. Stirring was continued at 50-55° for 1 hour and the reaction mixture was allowed to stand overnight. The crystalline precipitate was filtered off, washed with four portions of 6 ml. of acetone and dried in the air.

To free the base the precipitate was dissolved in 200 ml. of hot water and the solution treated with charcoal. The filtrate was made alkaline with 10% ammonium hydroxide and the tan precipitate was washed with three portions of 10 ml. of water. After drying in vacuum at 65° for 48 hrs., the product weighed 5.98 g. (91.1%) and melted at 216-217.8°. The compound was

crystallized twice from 50% ethanol and melted at 218.5-219°.

Anal. Calc'd. for $C_{12}H_9N_3S$: C, 63.43; H, 3.99; N, 18.49; S, 14.11%. Found: C, 63.37; H, 3.96; N, 18.50; S, 14.13%.

In a 100 ml. flask, 6.85 g. (0.04 mole) of 2-acetylquinoline was dissolved in 20 ml. of 40% hydrobromic acid. Through the dropping funnel was added, at 65-68° with stirring, a solution of 6.40 g. (0.04 mole) of bromine in 8 ml. of 40% hydrobromic acid. After the addition was finished (ten minutes), the mixture was kept at 65°, with stirring for one hour. The reaction mixture was transferred to a 250 ml. flask. A mixture of 80 ml. of ethanol and 60 ml. of water was added and heating at 65° was continued until all the solid dissolved. A solution of 3.04 g. (0.04 mole) of thiourea in 20 ml. of water was added in the course of 10 minutes. Stirring was continued at 55-60° for 1 hour and the reaction mixture was allowed to stand overnight. The crystalline precipitate was filtered off, washed with four portions of 12 ml. of acetone and dried in the air. The precipitate was then dissolved in 400 ml. of hot water and the solution made

alkaline with 10% ammonium hydroxide. After filtration and washing with five portions of 20 ml. of water, the precipitate was dried in vacuum and it weighed 6.07 g. (67.0%). It melted at 215-218°. After three recrystallizations from 50% ethanol, it melted at 218-219°. Mixed with 2-amino-4-(2'-quinolyl) thiazole, it did not show any melting point depression. The infrared spectra of both compounds were identical.

22. Preparation of 2-amino-4-(4'quinolyl)-thiazole.

4-Bromoacetylquinoline hydrobromide (3.31g., 0.01 mole) was added to 35 ml. of water. The mixture was heated at 60° until all the solid dissolved. To the stirred solution, maintained at 60°, 0.76 g. (0.01 mole) of thiourea dissolved in 5 ml. of water was added in the course of ten minutes. The reaction mixture was stirred for one hour without heating. The yellow-orange precipitate was collected on a Büchner funnel, washed with three portions of 5 ml. of cold ethanol and then dissolved in 200 ml. of dilute hydrobromic acid (10%) with gentle heating. The solution was treated with charcoal, heated for 15 minutes, and filtered. The almost

colorless solution was made basic with 10% ammonium hydroxide (slow addition). The very fine precipitate was filtered off, washed with five portions of 10 ml. of water and dried in vacuum. It weighed 1.98 g. (87.4%) and melted at 258-260°. After three crystallizations from methanol the product melted at 268-269°.
Anal. Calc'd. for $C_{12}H_9N_3S$: C, 63.43; H, 3.99; N, 18.49; S, 14.11%. Found: C, 63.61; H, 4.02; N, 18.49; S, 13.80%.

In a 250 ml. flask, 9.24 g. (0.04 mole) of 4-acetylquinoline acetate was dissolved in 45 ml. of 40% hydrogen bromide. A solution of 6.4 g. (0.04 mole) of bromine in 8 ml. of 40% hydrobromic acid was added while temperature was kept at 65-68°. The stirring at 65° was continued for one hour. To dissolve the precipitate, 100 ml. of water was added. To the stirred solution kept at 60°, 3.04 g. (0.04 mole) of thiourea dissolved in 5 ml. of water was added in the course of ten minutes and the reaction mixture was stirred for one hour without heating. The yellow-orange precipitate was filtered off and washed with three portions of 5 ml. of cold ethanol and then

dissolved in 800 ml. of dilute (10%) hydrobromic acid with gentle heating. The resulting solution was heated at 65° with Nuchar, filtered, and made alkaline with 10% ammonium hydroxide. The crystalline precipitate was filtered off, and washed with three portions of 30 ml. of water. After drying, the product weighed 6.10 g. (66.1%) and melted at 259-263°. The crude product was crystallized three times from methanol. It melted at 268-269°. Its infrared spectrum was identical with that of 2-amino-4-(4'-quinolyl) thiazole prepared in the previous experiment.

23. Preparation of 2-pyridyl 2-pyridylmethyl ketone (α - Desoxypyridoin).

(a) Acylation of 2-picoline with ethyl picolinate.

Phenyllithium was prepared according to the procedure given in Organic Syntheses (114). For the preparation of picolyllithium and 2-pyridyl 2-pyridylmethyl ketone the slightly modified method of Barkley, Goldberg and Levine (115) was used.

While a current of dry nitrogen was passed through the apparatus, 400 ml. of dry ether and 6.9 g. (1 gram atom)

of lithium (in small pieces) were placed in a 1 l. three-necked, round-bottom flask fitted with a reflux condenser provided with a drying tube filled with Drierite, a pressure equalizing dropping funnel and a sealed mechanical stirrer. The stirrer was started and 10 ml. of a solution of 79 g. (0.5 mole) of dry bromobenzene in 100 ml. of dry ether was added from the dropping funnel. The mixture was warmed slightly to start the reaction. The remainder of the bromobenzene solution was added at such a rate that the ether refluxed gently. The stirring was continued until the last traces of lithium reacted (6 hrs.). Forty-six grams (0.5 mole) of purified 2 - picoline was added to the rapidly stirred solution in the course of fifteen minutes. The mixture became first greenish and then assumed a reddish brown color. The stirring was continued for one and a half hours at room temperature.

A solution of 37.8 g. (0.25 mole) of ethyl picolinate in 30 ml. of dry ether was added over a twenty-five minute period so that the ether refluxed rapidly. After the ester was added, the reaction mixture was refluxed

for forty minutes longer. Then 100 ml. of water was added slowly and the mixture poured onto 200 ml. of 6N hydrochloric acid and 600 g. of ice. The ether phase was extracted with three portions of 25 ml. of 6N hydrochloric acid and the combined aqueous solution was treated with 20% sodium hydroxide until it remained slightly acid.

Then sodium bicarbonate was added until the mixture was slightly basic. The basic mixture was extracted with five portions of 200 ml. of ether. The combined ether extract was dried over Drierite, the solvent was distilled off and the residue was then fractionated in vacuum, b.p. 148-152° (1.5 mm.). The product weighed 22.9 g. (46.3%). After crystallization from petroleum ether (65-75°), it melted at 86-87°.

(b) When methyl picolinate (6.86 g., 0.05 mole) was used as the acylating agent, 6.34 g. (64.0%) of 2-pyridyl 2-pyridylmethyl ketone (α - desoxypyridoin) was obtained. After crystallization the product melted at 85.5-86.5°.

24. Preparation of 4-pyridyl 2-pyridylmethyl ketone (114,115).

The picolyllithium was prepared according to the procedure used for the synthesis of 2-pyridyl 2-pyridylmethyl ketone.

To a solution of picolyllithium prepared from 6.9 g. (1 gram atom) of lithium, 79 g. (0.5 mole) of bromobenzene and 46.0 g. (0.5 mole) of 2 - picoline (purified), contained in a 1 l. three-necked flask, 34.3 g. (0.25 mole) of methyl isonicotinate in 30 ml. of ether was added during twenty-five minutes, while a current of dry nitrogen passed through the apparatus. After the ester was added, the reaction mixture was refluxed for forty-five minutes longer. At the end of this period, 100 ml. of water was added and the mixture poured onto 200 ml. of 6N hydrochloric acid and 600 ml. of ice. The ether layer was separated and extracted with four portions of 20 ml. of 6N hydrochloric acid. The combined aqueous solution was treated with 20% sodium hydroxide until it remained slightly acidic. The mixture was made slightly basic with solid sodium bicarbonate. The abundant yellow precipitate was then filtered off and washed

with four portions of 15 ml. of H_2O and two portions of 5 ml. of ethanol. The precipitate was dried in vacuum. It weighed 28.2 g. (56.9%) and melted at 113-115°. After crystallization from petroleum ether it melted at 114.4-115°.

The basic filtrate was extracted with four portions of 150 ml. of ether and the ether extract dried over Drierite. After removal of ether, the product crystallized. It was filtered off, washed with three portions of 5 ml. of water and dried in vacuum. It weighed 5.75 g. (11.6%) and melted at 112-114°. After crystallization from petroleum ether (65-75°), the product melted at 114.5-115°. No depression of melting point was observed when samples of the two materials were mixed. The total yield of 4-pyridyl 2-pyridylmethyl ketone was 33.95 g. (68.5%).

25. Preparation of 2-pyridyl 4-pyridylmethyl ketone.

(a) Preparation of sodamide (116).

In a 250 ml. three-necked flask equipped with a sealed mechanical stirrer, a removable glass plug, and a dry ice condenser, was placed 150 ml. of anhydrous liquid ammonia. To the rapidly stirred liquid ammonia was added

in small portions 4.6 g. (0.2 gram atom) of sodium and a small crystal of ferric nitrate (to catalyse the conversion of sodium to sodamide). After the conversion of sodium to sodamide was complete (about fifty minutes after the sodium addition was finished) as indicated by the change of the blue solution to a dark grey suspension, the glass plug was replaced by a dropping funnel. The sodamide was now ready to be used for the metalation of 4-methylpyridine.

(b) Acylation of 4-picoline with methyl picolinate.

To the stirred suspension of sodamide in liquid ammonia, prepared in the previous experiment, 18.6 g. (0.2 mole) of undiluted pure 4-picoline was added in the course of fifteen minutes and the mixture was stirred for an additional twenty minutes. Methyl picolinate (13.73 g., 0.1 mole) dissolved in 20 ml. of anhydrous ether was added over a period of 30 minutes and stirring was continued for one more hour. The dry ice condenser was replaced by a water cooled reflux condenser.

To quench the reaction, 11.0 g. (0.205 mole) of solid ammonia chloride was carefully added. The liquid ammonia was replaced by the addition of 130 ml. of anhydrous ether and to remove the remainder of ammonia the mixture was warmed gently on a water bath until the ether started to reflux. Then the mixture was cooled, poured onto 200 g. of ice, made strongly acidic with concentrated hydrochloride acid, and washed with three portions of 25 ml. of ether. The acid solution was then made basic by the addition of sodium carbonate and extracted with five portions of 60 ml. of ether. The combined ether extract was dried over Drierite and the solvent and the 4-picoline were distilled off. The residue was allowed to stand overnight and the yellow crystalline solid was collected on a Büchner funnel and washed with four portions of petroleum ether (65-75°). The product weighed 9.8 g. (49.5%) and melted at 82.4-84°. After crystallization from petroleum ether the product melted at 86-87°.

Anal. Calc'd. for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.09; N, 14.14%.

Found: C, 72.86; H, 5.24; N, 14.17%.

(c) Acylation of 4-picoline with ethyl picolinate.

When ethyl picolinate (30.2 g., 0.2 mole) was used to acylate 4-picoline by the method described in the previous experiment, 9.0 g. (22.7%) of 2-pyridyl 4-pyridylmethyl ketone was obtained. After crystallization from petroleum ether (65-75°) it melted at 85-86°. The mixed melting point determination showed that it was identical with the compound prepared from methyl picolinate and 4-picoline.

26. Preparation of 4-pyridyl 4-pyridylmethyl ketone (119).

To the suspension of sodamide in liquid ammonia prepared from 4.6 g. of sodium, 18.6 (0.2 mole) of undiluted pure 4-picoline was added with stirring in the course of fifteen minutes. The mixture was stirred for an additional half hour. Methyl isonicotinate (13.73 g., 0.1 mole) dissolved in 15 ml. of anhydrous ether was added during thirty minutes and stirring was continued for one more hour. The dry ice condenser was replaced by a water cooled reflux condenser and solid ammonium chloride (11.0 g., 0.205 mole) was added to quench the reaction. The liquid ammonia was replaced by adding 150 ml. of anhydrous ether and

carefully warming the solution on a water-bath until the ether started to reflux. The mixture was cooled, poured onto 200 g. of crushed ice, made strongly acidic with concentrated hydrochloric acid, and washed with three portions of 25 ml. of ether. The acid solution was then made basic by the addition of solid sodium carbonate and extracted with five portions of 60 ml. of ether. The ether extract was dried over Drierite and the solvent and 4-picoline were distilled off. The bright yellow solid residue was collected on a Büchner funnel and washed with four portions of petroleum ether (65-75°). The product weighed 9.9 g. (50%) and melted at 114-116°. After one crystallization from petroleum ether (65-75°), the product melted at 116-116.5°.

In another acylation reaction, carried out under the same conditions, 13.73 g. (0.1 mole) of methyl isonicotinate gave 10.2 g. (51.5%) of 4-pyridyl 4-pyridyl methyl ketone. The crude product melted at 113-115°.

When, 15.1 g. (0.1 mole) of ethyl isonicotinate was used as acylating agent, the yield was 7.1 g. (35.7%).

27. Attempted preparation of 2-amino-4,5-di(2'-pyridyl)-thiazole.

(a) 2-Pyridyl 2-pyridylmethyl ketone (9.90 g., 0.05 g.) was dissolved in 45 ml. of concentrated hydrobromic acid in a 100 ml. flask. To the vigorously stirred solution kept at 40-45°, 8.00 g. (0.05 mole) of bromine dissolved in 10 ml. of concentrated hydrobromic acid was added in the course of ten minutes. The solution was stirred for 2 hrs. at 40°C. and then 3.81 g. (0.05 mole) of thiourea dissolved in 15 ml. of water was added. Stirring was continued for four more hours at 50-55°. The cooled solution was then made basic with 20 percent sodium hydroxide. The yellow precipitate was filtered off, washed with four 15 ml. portions of water and dried in vacuum. The product weighed 6.85 g. and melted at 84-86.5°. After crystallization from petroleum ether (b.p. 65-75°), it melted at 86-86.5°. Mixed melting point determination and similar spectra proved it to be the starting material, 2-pyridyl 2-pyridylmethyl ketone. The amount of starting material recovered was 69.3%.

(b) In another experiment, 7.92 g. (0.04 mole) of 2-pyridyl 2-pyridylmethyl ketone was treated with bromine, followed by thiourea, at 90-95°. Upon addition of 20 percent ammonium hydroxide, a brown oil separated. The solution was extracted with ether and after removal of the solvent a very impure starting material melting at 78-85 was obtained. A great amount of brown, gummy substance was also obtained.

28. Preparation of 2-amino-4,5-di-(2'-pyridyl)-thiazole by the condensation of 2-pyridyl 2-pyridylmethyl ketone with thiourea in presence of iodine.

A mixture of 1.98 g. (0.01 mole) of 2-pyridyl 2-pyridylmethyl ketone, 1.52 g. (0.02 mole) of thiourea and 1.27 g. (0.01 mole) of iodine was heated for 10 hrs. at 85-95° on a water bath in a tightly stoppered 50 ml. one neck ground glass flask. At the end of the heating period, the solid reaction mixture was boiled for 20 minutes with 50 ml. of water. The mixture was filtered and the filtrate made alkaline with sodium hydroxide. The filtrate containing some dark, gummy material was discarded. The solid substance collected on the Büchner funnel was dissolved in 50 ml. of

20 percent hydrochloric acid. The solution was then made alkaline with 10 percent ammonium hydroxide. The abundant precipitate which formed was filtered off, washed with four portions of 5 ml. of water and dried. It weighed 1.32 g. (52.1%) and melted at 240-244°. After two crystallizations from 95 percent ethanol, the bright yellow crystals (needles) melted at 246-246.5°.

Anal. Calc'd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.04; S, 12.61%. Found: C, 61.42; H, 4.01; N, 22.09; S, 12.66%.

29. Preparation of 2-amino-4-(4'-pyridyl)-5-(2"-pyridyl)-thiazole.

(a) In a 100 ml. flask, 3.96 g. (0.02 mole) of 4-pyridyl 2-pyridylmethyl ketone was dissolved in 35 ml. of 10 percent hydrobromic acid. To the rapidly stirred solution, 3.2 g. (0.02 mole) of bromine dissolved in 10 ml. of 20 percent hydrobromic acid was added in the course of 10 minutes. The mixture was stirred for 2 hours at 55-60°. At the end of this period, a solution of 1.52 g. (0.02 mole) of thiourea dissolved in 20 ml. of water was added during five minutes and stirring was continued for 2 hours. The solution was then made alkaline with 10 percent aqueous ammonium

hydroxide. The bright yellow precipitate was filtered off, washed with four portions of 10 ml. of water and dried. It weighed 3.65 g. (71.8%) and melted at 271-273.5°. After crystallization from 95 percent ethanol the product melted at 277-278°.

Anal. Calc'd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.04; S, 12.61%. Found: C, 61.48; H, 4.02; N, 22.17; S, 12.69%.

(b) A mixture of 1.98 g. (0.01 mole) of 4-pyridyl 2-pyridylmethyl ketone, 1.27 g. (0.01 mole) of iodine and 1.52 g. (0.02 mole) of thiourea was placed in a 50 ml. tightly stoppered flask. The container was heated for 10 hours at 85-95° on a water bath. At the end of this period, the solid mixture was boiled for 20 minutes with 50 ml. of water. The solid was filtered off and dissolved in 50 ml. of 20 percent hydrochloric acid and the resulting solution made alkaline with 10 percent ammonium hydroxide. The abundant precipitate which formed was filtered off, washed with four portions of 5 ml. of cold water and dried in vacuum. It weighed 1.41 g. (55.5%) and melted at 268-273°.

30. Preparation of 2-amino-4-(2'-pyridyl)-5-(4"-pyridyl)-thiazole.

2-Pyridyl 4-pyridylmethyl ketone (3.96 g., 0.02 mole) was dissolved by heating in 25 ml. of concentrated hydrobromic acid contained in a 100 ml. flask. To the rapidly stirred solution maintained at 68-70°, 3.2 g. (0.02 mole) of bromine dissolved in 20 ml. of concentrated hydrobromic acid was added in the course of five minutes. Stirring was continued for two more hours at 75-80°. Thiourea (1.52 g., 0.02 mole) dissolved in 20 ml. of water was added during five minutes to the vigorously stirred solution kept at 60-65°. The solution was stirred for two hours at this temperature. After cooling, the yellow solution was made alkaline with 10 percent ammonium hydroxide and the precipitate formed was filtered off and washed with four portions of 5 ml. of water. The dried product weighed 3.05 g. (60.0%) and melted at 211-214°. After crystallization from 95% ethanol, the product melted at 216.5-217°.
Anal. Calc'd. for $C_{13}H_{10}N_4S.H_2O$: C, 57.33; H, 4.44; N, 20.58; S, 11.77%. Found: C, 57.94; H, 4.44; N, 20.63; S, 12.04%.

31. Preparation of 2-amino-4,5-di-(4'-pyridyl)-thiazole.

In a 100 ml. flask, 3.96 g. (0.02 mole) of 4-pyridyl 4-pyridylmethyl ketone was dissolved by heating in 25 ml. of concentrated hydrobromic acid (48.5%). To the rapidly stirred solution kept at 68-70°, 3.20 g. (0.02 mole) of bromine dissolved in 20 ml. of concentrated hydrobromic acid was added over a 10 minute period. The solution was then stirred for two more hours at 75-80°. Thiourea (1.52 g., 0.02 mole) dissolved in 20 ml. of water was added during five minutes to the vigorously stirred solution kept at 60-65°. The stirring at this temperature was continued for 2 hrs. The cold yellow solution was made alkaline with 10 percent ammonium hydroxide, the precipitate was filtered off, and washed with four portions of 5 ml. of water. The dried product weighed 3.7 g. (72.6%) and melted at 288-291°. After two crystallizations from 95 percent ethanol, it melted at 292-293°.

Anal. Calc'd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.04; S, 12.61%. Found: C, 62.02; H, 3.88; N, 21.95; S, 13.16%.

32. Preparation of N-(3'-pyridyl)-thiourea.

(a) Preparation of 1-benzoyl-3-(3'-pyridyl)-2-thiourea.

Ammonium thiocyanate (6.68 g., 0.088 mole) and 45 ml. of dry acetone was placed in a 100 ml. flask. Through the dropping funnel was added slowly, with vigorous stirring, 11.28 g. (0.08 mole) of benzoyl chloride. The mixture was refluxed for fifteen minutes and then a solution of 7.52 g. (0.08 mole) of 3-aminopyridine in 25 ml. of dry acetone was added at such a rate that the solution refluxes gently (5 minutes).

The reaction mixture was poured into 700 ml. of water, and the resulting bright yellow precipitate was filtered off, washed with eight portions of 10 ml. of water, and dried in vacuum. The product weighed 18.52 g. (90.2%) and melted at 160-163°. After crystallization from water, it melted at 165-165.5°.

Anal. Calc'd. for $C_{13}H_{11}N_3OS$: C, 60.69; H, 4.31; N, 16.33%.
Found: C, 60.33; H, 4.54; N, 16.28%.

In another preparation, 3.76 g. (0.04 mole) of 3-aminopyridine was treated under essentially the same conditions,

and it yielded 9.03 g. (87.7%) of a dried product melting at 161-164°. The product was crystallized from water. It melted at 165-165.4°.

(b) Hydrolysis of 1-benzoyl-3-(3'-pyridyl)-2-thiourea.

To 12.87 g. (0.05 mole) of 1-benzoyl-3-(3'-pyridyl)-2-thiourea, 70 ml. of 2.5N sodium hydroxide solution was added. The mixture was refluxed for 15 minutes. After cooling, the resulting solution was filtered to remove small amounts of impurities. The solution was then transferred to a 25 ml. beaker, and while stirring, acidified with concentrated hydrochloric acid, made slightly basic with ammonium hydroxide and left overnight. The colorless precipitate was filtered off, washed with three portions of 5 ml. of cold water and dried in vacuum. It weighed 5.71 g. (74.6%) and melted at 152-154°. The product was crystallized from water. The colorless crystals melted at 153.5-154°.
Anal. Calc'd. for $C_6H_7N_3S$: C, 47.03; H, 4.61; N, 27.43; S. 20.92%. Found: C, 47.20; H, 4.56; N, 27.31; S, 21.11%.

When, 7.72 g. (0.03 mole) of the benzoyl derivative of N-(3'-pyridyl)-thiourea was hydrolized by refluxing with 2.5N sodium hydroxide aqueous solution for only ten

minutes, 2.96 g. (64.4%) of substance melting at 152-154° was obtained.

33. Preparation of N-(3'-quinolyl)-thiourea.

(a) Preparation of 1-benzoyl-3-(3'-quinolyl)-2-thiourea.

In a 100 ml. flask, was placed 4.18 g. (0.055 mole) of ammonium thiocyanate and 35 ml. of anhydrous acetone. Benzoyl chloride (7.00 g., 0.05 mole) was added, with stirring, during five minutes. The mixture was then refluxed for fifteen minutes. At the end of this period, a solution of 7.20 g. (0.05 mole) of 3-aminoquinoline was added, while stirring, at such a rate that the acetone refluxes gently (5 minutes). Immediately, the reaction mixture was poured into 600 ml. of water, and the yellow precipitate was collected on a Büchner funnel, washed with eight portions of 10 ml. of water. After drying, the precipitate weighed 14.20 g. (92.6%) and melted at 158.6-161°. One crystallization from water and ethanol yielded light yellow crystals melting at 163.5-164°.
Anal. Calc'd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.68; S, 10. 43%. Found: C, 66.47; H, 4.24; N, 13.77; S, 10.58%.

(b) Hydrolysis of 1-benzoyl-3-(3'-quinolyl)-2-thiourea.

In a 100 ml. flask, 15.3 g. (0.05 mole) of 1-benzoyl-3-(3'-quinolyl)-2-thiourea and 70 ml. of 3N sodium hydroxide solution were placed. The mixture was refluxed for 15 minutes and the resulting solution was transferred to a 250 ml. beaker. The stirred solution was made acid with concentrated hydrochloric acid and then slightly basic by adding concentrated ammonium hydroxide. The precipitate was filtered off, washed with three portions of 5 ml. of water and dried. The product weighed 7.94 (78.2%) and melted at 163-165.5°. The substance was recrystallized from water and melted at 169-169.5°. Anal. Calc'd. for $C_{10}H_9N_3S$: C, 59.10; H, 4.46; N, 20.68; S, 15.78%. Found: C, 58.76; H, 4.33; N, 20.35; S, 15.52%.

34. Preparation of 2-N-(3'-pyridyl)amino-4-methylthiazole.

(a) Preparation of bromoacetone.

The bromoacetone was prepared according to procedure described in Organic Syntheses (118).

In a 500 ml. flask, was placed 160 ml. of water, 50 ml. of purified acetone and 37 ml. of glacial acetic acid.

The stirring was started and temperature inside the flask was kept at 65° by heating with a water bath. Bromine (117.4 g., 0.73 mole) was carefully added, through the separatory funnel, with stirring. The addition required one and a half hours. After the solution became colorless (fifteen minutes after the addition of bromine was complete), 80 ml. of cold water was added. The solution was cooled to 10, made neutral to Congo Red with solid anhydrous sodium carbonate and the oil which separated was collected. After drying over 8.0 g. of anhydrous calcium chloride, the oil was fractionated and the fraction distilling at 38-48° under 13 mm. was collected. The yield was 45 g. (48.3%).

(b) Condensation of bromoacetone with N-(3'-pyridyl)-thiourea.

N-(3'-pyridyl)-thiourea (6.12 g., 0.04 mole) was dissolved in 40 ml. of 80 percent methanol at 60°, in a 100 ml. flask. Through the dropping funnel 5.48 g. (0.04 mole) of bromoacetone dissolved in 3 ml. of methanol was added with vigorous stirring in the course of five minutes. The stirring was continued for 3 hrs. while the temperature was kept at 65°. The solution was then concentrated to

evaporate the greatest part of methanol and 450 ml. of water was added. Ammonium hydroxide (10 percent) was added until the solution became slightly alkaline. The slightly greenish precipitate was filtered off, washed with five 10 ml. portions of water and dried in vacuum. The crude product weighed 5.98 g. (78.2%) and melted at 197-199.5°. No more precipitate was formed upon further addition of ammonia to the basic filtrate.

The product was crystallized from 60 percent ethanol. It melted at 203-204°.

Anal. Calc'd. for $C_9H_9N_3S$: C, 56.53; H, 4.74; N, 21.99; S, 16.76%. Found: C, 56.60; H, 4.73; N, 21.88; S, 16.59%.

35. Preparation of 2-N-(3'-pyridyl)amino-4-phenylthiazole.

N-(3'-pyridyl)-thiourea (7.65 g., 0.05 mole) was dissolved in 50 ml. of 60 percent methanol by heating, in a 100 ml. flask. To the vigorously stirred solution kept at 60°, 9.95 g. (0.05 mole) of bromoacetophenone dissolved in 18 ml. of methanol was added over a period of 10 minutes. A very heavy, bright yellow, crystalline precipitate formed immediately. The slurry was stirred for

3 hrs. at 65° and then was allowed to cool. The flask content became a solid mass which did not dissolve in either water or dilute hydrochloric acid. The solid was therefore suspended in 400 ml. of water and the suspension was stirred for ten minutes at 50-55°. The precipitate was collected on a Büchner funnel and washed with water and then dissolved with heating in 300 ml. of 60 percent methanol. The solution was made alkaline with 20 percent ammonium hydroxide. The precipitate was filtered off, washed with five portions of 10 ml. of water and dried. The product weighed 11.0 g. (86.9%) and melted at 194-196°. After crystallization from 70 percent ethanol, the product melted at 199-199.5°.

Anal. Calc'd. for $C_{14}H_{11}N_3S$: C, 66.53; H, 4.37; N, 16.59; S, 12.65%. Found: C, 66.42; H, 4.45; N, 16.64; S, 12.79%.

36. Preparation of 2-N-(3'-pyridyl)amino-4-(3"-pyridyl)thiazole.

In a 100 ml. flask, 6.12 g. (0.04 mole) of N-(3'-pyridyl)-thiourea was dissolved by heating in 40 ml. of 50 percent ethanol. To the stirred solution kept at 65°, 11.2 g. (0.04 mole) of 3-bromoacetylpyridine hydrobromide

dissolved in 15 ml. of water was added. The stirring was continued for one hour and the reaction mixture was allowed to stand overnight. The solution was then transferred to a 600 ml. beaker, diluted with 350 ml. of water and made slightly basic with 10 percent ammonium hydroxide. The precipitate was collected on a Büchner funnel, washed with six portions of 10 ml. of water and dried. It weighed 8.4 g. (82.6%) and melted at 198-203°. The substance was crystallized from 60 percent methanol, m.p. 203.5-204°. Anal. Calc'd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.04; S, 12.61%. Found: C, 61.54; H, 3.93; N, 22.13; S, 12.54%.

37. Preparation of 2-N-(3'-pyridyl)amino-4-(4"-pyridyl)thiazole.

N-(3'-pyridyl)-thiourea (6.12 g., 0.04 mole) was dissolved by heating in 40 ml. of 50 percent ethanol in a 100 ml. flask. To the vigorously stirred solution kept at 40-45° was added 11.2 g. (0.04 mole) of 4-bromoacetylpyridine hydrobromide dissolved in 20 ml. of water. After the addition was complete (10 minutes), the solution was stirred for one more hour at 50° and allowed to stand overnight. The precipitate formed was filtered off and washed with five

portions of 5 ml. of cold water and then dissolved in 350 ml. of water. The resulting solution was made slightly alkaline with 10 percent sodium hydroxide and the red orange precipitate was filtered off, washed with five portions of 10 ml. of cold water and dried. It weighed 6.08 g. (59.8%) and melted at 225-227.5°. Crystallization from 60 percent methanol yielded pink crystals (needles) melting at 228.5-229°.

Anal. Calc'd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.04; S, 12.61%. Found: C, 61.54; H, 4.04; N, 21.95; S, 12.73%.

When treated with 10% ammonium hydroxide, the mother liquors gave a further 3.50 g. of product bringing the total yield to 94.2%.

38. Preparation of 2-N-(3'-quinolyl)-amino-4-methylthiazole.

To a solution of 2.03 g. (0.01 mole) of N-(3'-quinolyl)-thiourea in 40 ml. of 60 percent methanol kept at 60° and contained in a 100 ml. flask, was added with stirring 1.37 g. (0.01 mole) of bromoacetone dissolved in 6 ml. of methanol. The stirring was continued for 3 hrs. at 80-85°. The solution was allowed to stand overnight and

the precipitate which formed was separated and washed with water. Then, the precipitate was dissolved by heating in 200 ml. of water and 150 ml. of methanol. The cooled solution was made alkaline with concentrated ammonia and the green precipitate was filtered off, washed with five portions of water and dried. The product weighed 2.02 g. (83.8%) and melted at 187-189.5°. The mother liquor, after treatment with 10 percent ammonium hydroxide, yielded 0.15 g. of dried material melting at 185-189°. The total yield was thus 2.17 g. (90.2%). After, crystallization from 50 percent ethanol, the green crystals melted at 199.5-200°.

Anal. Calc'd. for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.42; S, 13.28%. Found: C, 64.55; H, 4.53; N, 17.38; S, 13.11%.

39. Preparation of 2-N-(3'-quinolyl)amino-4-phenylthiazole.

In a 100 ml. flask, 2.03 g. (0.01 mole) of N-(3'-quinolyl)-thiourea was dissolved in 50 ml. of 60 percent methanol with heating (65°). From the dropping funnel, a solution of 1.99 g. (0.01 mole) of bromoacetophenone in 10 ml. of methanol was added, with stirring, in the course of five

minutes. Stirring was continued for 2 hrs. at 75-80°. At the end of this period, the reaction mixture was cooled and the precipitate filtered off and washed with five portions of 10 ml. of water. The needle-like crystals were insoluble in all the solvents used including hydrochloric acid. The crystalline precipitate was suspended in 300 ml. of water and the aqueous suspension was made alkaline with 20 percent ammonium hydroxide. The yellow precipitate became colorless upon addition of base. After washing with five portions of 10 ml. of water, the precipitate was dried. It weighed 2.40 g. (79.3%) and melted at 215-216.5°. After crystallization from 60 percent ethanol, it melted at 216.5-217°. The mother liquors, upon treatment with 20 percent ammonium hydroxide gave 0.12 g. of dried material melting at 214.5-216.5°. Thus, the total yield was 2.52 g. (83.3%).

Anal. Calc'd. for $C_{18}H_{13}N_3S$: C, 71.27; H, 4.32; N, 13.85; S, 10.57%. Found: C, 71.15; H, 4.50; N, 13.78; S, 10.58%.

40. Preparation of 2-N-(3'-quinolyl)amino-4-(4"-pyridyl)thiazole.

N-(3'-quinolyl)-thiourea (2.03 g., 0.01 mole) was dissolved by heating in 50 ml. of 60 percent methanol. To the rapidly stirred solution kept at 60-65°, 2.81 g. (0.01 mole) of 4-bromoacetylpyridine hydrobromide dissolved in 10 ml. of water was added during five minutes and stirring was continued for two more hours. The flask content was then transferred to a 400 ml. beaker and 200 ml. of water was added. The solution was filtered to remove colloidal particles and the filtrate was made alkaline with 10 percent ammonium hydroxide. The tan precipitate formed was collected on a Büchner funnel, washed with four portions of 5 ml. of water and dried at 114° in vacuum to constant weight. The dried product weighed 2.20 g. (73.2%) and melted at 249-253°. The substance was crystallized from 40 percent ethanol. It melted at 255-255.5°. Anal. Calc'd. for $C_{17}H_{12}N_4S.\ H_2O$: C, 63.33; H, 4.38; N, 17.38%. Found: C, 63.96; H, 4.52; N, 17.58%.

41. Nitration of 2-amino-4-(4'-pyridyl)thiazole.

2-Amino-4-(4'-pyridyl)thiazole (7.08 g., 0.04 mole) was added in portions to 30 ml. of concentrated sulfuric acid (d = 1.84), while vigorously stirring and cooling (-3 to -5°).

Fuming nitric acid (3.08 g., 0.044 mole) was dissolved in cold sulfuric acid (-30°). After the mixture warmed up, it was thoroughly mixed and added dropwise to the vigorously stirred solution kept at -3 to 0° during fifty minutes. The solution was stirred at 0° for thirty minutes and poured onto 70 g. of ice. The yellow precipitate was filtered off and washed with several portions of 10 ml. of water and three portions of 5 ml. of ethanol. The product was dried over P_2O_5 in vacuum. It weighed 6.45 g. (73.2%) and melted at 238-242°. After crystallization from 60% aqueous pyridine, the yellow crystals (prisms) melted at 249.0-250° (dec.). Anal. Calc'd. for $C_8H_6N_4O_2S$: C, 43.23; H, 2.73; N, 25.32; S, 14.39%. Found: C, 43.26; H, 2.78; N, 25.41; S, 14.48%.

42. Attempted rearrangement of 2-nitramino-4-(4'-pyridyl)-thiazole.

2-Nitramino-4-(4'-pyridyl)-thiazole (2.95 g., 0.013 mole) was dissolved in 15 ml. of concentrated sulfuric acid (d 1.84) cooled at -10°. The solution was allowed to warm up to room temperature and then it was stirred for 3 hrs. Then, the solution was poured onto 30 g. of chipped

ice. The yellow precipitate which formed was filtered off and washed with several portions of 5 ml. of methanol. The dried material weighed 1.18 g. (40.0%) and melted at 238-242°. After crystallization from 60% aqueous pyridine, it melted at 249-250° (dec.). Mixed melting point determination showed it to be identical with the starting material.

43. Attempted nitration of the 2-acetylamino-4-(4'-pyridyl)-thiazole.

The slightly modified method of Ganapathi and Venkataraman was used (80).

2-Acetyl-4-(4'-pyridyl)-thiazole (2.19 g., 0.01 mole) was dissolved in 5 ml. of concentrated sulfuric acid (d 1.84) cooled at 2 to 5°. Fuming nitric acid (0.70 g., 0.01 mole) was added to the stirred solution. The solution was then heated for thirty minutes on a water bath at 70-80° and allowed to cool. After pouring onto 50 g. of crushed ice, some tarry material formed. The black material was filtered off and the dark colored filtrate was neutralized by dilute ammonium hydroxide. The tarry material which formed upon neutralization was filtered off and washed, but no reaction product could be isolated.

SUMMARY AND CONTRIBUTION TO KNOWLEDGE

1. The synthesis of 2-amino-4-(x-pyridyl)-thiazoles and 2-amino-4-(x-quinolyl)-thiazoles was achieved. This synthesis involved three stages:

(a) preparation of the acetylpyridines and acetylquinolines from the corresponding acids via their esters in a Claisen condensation with ethyl acetate in the presence of sodium ethoxide;

(b) halogenation of the acetylpyridines and acetylquinolines. The method for the preparation of 3-bromopyridine in concentrated hydrobromic acid was reinvestigated and then applied for the first time to the preparation of 2- and 4-bromoacetylpyridine hydrobromides. The established method for the preparation of 2-bromoacetylquinoline was adapted to the preparation of 4-bromoacetylquinoline from 4-acetylquinoline acetate;

(c) Condensation of thiourea with bromoacetylpyridine hydrobromides and bromoacetylquinoline hydrobromides.

It was found that 2-amino-4-(x-pyridyl)-thiazoles and 2-amino-4-(y-quinolyl)-thiazoles could be prepared from the hydrobromide salts of the corresponding bromoacetyl-

pyridine and bromoacetylquinolines. When the x-bromoacetylpyridine hydrobromides were treated with thiourea in aqueous solution, at room temperature, the 2-amino-4-(x-pyridyl)-thiazoles were obtained in very high yields. However, owing to the low solubility of the bromoacetyl-quinolines, a mixture of water and ethanol was used and temperatures of 60-65° had to be applied to prepare the 2-amino-4-(y-quinolyl)-thiazoles.

2. The method for the preparation of ethyl isonicotinate was improved to obtain higher yields, by introducing the azeotropic distillation of a ternary mixture.

3. The method for the preparation of 2-acetylpyridine from the corresponding ester was improved. To moderate the vigorous reaction, the mixture of the alkyl picolinate and ethyl acetate was added to a suspension of sodium ethoxide in anhydrous toluene. The refluxing period for the hydrolysis and decarboxylation step was lengthened to obtain a better yield.

4. A reasonable mechanism was suggested for the condensation of thiourea with bromoacetylpyridines and bromoacetylquinolines. Thiourea in a nucleophilic attack displaces the bromine atom

of the α - bromo ketone as its anion to produce a thiuronium salt derivative. The free base which is in equilibrium with its salt, cyclizes, and dehydration of the partly saturated intermediate yields the corresponding 2-aminothiazole.

5. The condensation of the acetylpyridines with thiourea in presence of a halogen (Br_2, I_2), gave low yields and impure products.

6. The 2-amino-4-(4'-pyridyl)-thiazole and 2-amino-4-(x-quinolyl)-thiazoles could also be obtained by condensing the unisolated bromo derivative of the corresponding acetylpyridine or acetylquinolines in the presence of hydrobromic acid with thiourea.

7. Resonance structures were suggested for 2-amino-4-(x-pyridyl)-thiazoles. It was shown by nitration studies of the 2-amino-4-(4'-pyridyl)-thiazole that resonance structures involving the conjugated system formed by the 4-pyridyl ring, the 4,5 carbon-carbon double bond and the sulfur atom make significant contributions to the ground state of the molecule.

8. The nitration of 2-amino-4-(4'-pyridyl)-thiazole yielded a 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine.

a. The 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine did not rearrange under the ordinary conditions, e.i., prolonged standing of a solution of the compound in sulfuric acid at room temperature. Under more drastic conditions, the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine decomposed.

9. A mechanism for the formation of 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine was suggested.

10. The 2-amino-4-(4'-pyridyl)-thiazole and 2-N-acetylamino-4-(4'-pyridyl)-thiazole did not nitrate to yield the 5-nitro derivative. This indicates that the electron density in the 5- position is lowered by resonance forms involving the 4-pyridyl nucleus, the 4,5 carbon-carbon double bond and the sulfur. The -Is effect of the 4-pyridyl group may also contribute to deactivate this position towards electrophilic reagents.

11. Suitable synthetic routes were found for the preparation

of 2-amino-4-(x-pyridyl)-5-(y-pyridyl)-thiazoles.

These methods involved:

a. Preparation of the required pyridyl pyridylmethyl ketone by the acylation of 2-picoline and 4-picoline using the pyridinecarboxylates as acylating agents.

b. Condensation of thiourea with the brominated pyridyl pyridylmethyl ketone at 60-65°. The 2-amino-4-(x-pyridyl)--5-(y-pyridyl)-thiazoles, except 2-amino-4,5-di-(2'-pyridyl)-thiazole, were obtained in satisfactory yields by treating the unisolated bromo derivative of the appropriate pyridyl pyridylmethyl ketone with thiourea.

12. A method was developed for the synthesis of the unreported 2-pyridyl 4-pyridylmethyl ketone from 4-picoline and alkyl picolinate in the presence of sodium amide in liquid ammonia.

13. A method was developed for the preparation of 2-amino-4, 5-di-(2'-pyridyl)-thiazole. The 2-pyridyl 2-pyridylmethyl ketone was heated at 85-95° with thiourea in the presence of thiourea.

14. The ring closure method long established for the

preparation of 2-N-(alkyl or aryl)-aminothiazoles was successfully extended to the synthesis of 2-N-(3'-pyridyl)-aminothiazoles and 2-N-(3'-quinolyl)-aminothiazoles. To obtain these compounds, N-(3'-pyridyl)-thiourea and N-(3'-quinolyl)-thiourea were treated with the appropriate α - halo ketones or their salt derivatives (e.g., 4-bromoacetylpyridine hydrobromide). The reaction was carried out in polar solvents, usually at 60-65°.

15. The reaction of benzoyl isothiocyanate with 3-aminopyridine and 3-aminoquinoline was used for the first time for the preparation of 1-benzoyl-3-(3'-pyridyl)-2-thiourea and 1-benzoyl-3-(3'-quinolyl)-2-thiourea. Alkaline hydrolysis of the two benzoyl derivatives afforded N-(3-pyridyl)-thiourea and N-(3-quinolyl)-thiourea.

16. A mechanism was suggested for the reaction of benzoyl isothiocyanate with 3-aminopyridine. This mechanism could be valid also for the reaction of benzoyl isothiocyanate with 3-aminoquinoline or any other primary or secondary amines.

17. During this investigation, the following new compounds were prepared and characterized:

2-Amino-4-(2'-pyridyl)-thiazole
2-Amino-4-(3'-pyridyl)-thiazole
2-Amino-4-(2'-quinolyl)-thiazole
2-Amino-4-(4'-quinolyl)-thiazole
2-Amino-4-(2'-pyridyl)-thiazole dipicrate
2-Amino-4-(4'-pyridyl)-thiazole dipicrate
2-N-acetylamino-4-(4'-pyridyl)-thiazole
2-Nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine

4-Bromoacetylpyridine hydrobromide.

2-Amino-4,5-di-(2'-pyridyl)aminothiazole
2-Amino-4-(4'-pyridyl)-5-(2'-pyridyl)-thiazole
2-Amino-4-(2'-pyridyl)-5-(4'-pyridyl)-thiazole
2-Amino-4,5-di-(4'-pyridyl)-thiazole

2-Pyridyl 4-Pyridylmethyl ketone

2-N-(3'-pyridyl)-amino-4-methylthiazole
2-N-(3'-pyridyl)-amino-4-phenylthiazole
2-N-(3'-pyridyl)-amino-4-(3"-pyridyl)-thiazole
2-N-(3'-pyridyl)-amino-4-(4"-pyridyl)-thiazole

2-N-(3'-quinolyl)-amino-4-methylthiazole
2-N-(3'-quinolyl)-amino-4-phenylthiazole
2-N-(3'-quinolyl)-amino-4-(4"-pyridyl)-thiazole

1-benzoyl-3-(3'-pyridyl)-2-thiourea
1-benzoyl-3-(3'-quinolyl)-2-thiourea
N-(3'-pyridyl)-thiourea
N-(3'-quinolyl)-thiourea

18. The infrared absorption spectra of the compounds listed in Tables 5,6,7,8 and 9 have been recorded for the first time.

19. The infrared spectra of 2-N-(3'-pyridyl)-aminothiazoles and 2-N-(3'-quinolyl)-aminothiazoles were correlated with the structure of these compounds. The spectra of these compounds show only a weak band between 3280 and 3240 cm^{-1}. This band was assigned to N-H stretching vibration. In addition, there was a wide band of medium to strong intensity between 3130 and 1960 cm^{-1}. It was attributed to N-H stretching. Based on this evidence, it was suggested, that these compounds are resonance hybrids of structures involving the imino form and the dipolar form having a plus charge on the thiazole ring nitrogen and a negative charge on the exocyclic nitrogen. The ground state would also receive small contributions from other ionic resonance structures.

20. The infrared spectrum of the nitration product of 2-amino-4-(4'-pyridyl)-thiazole was correlated with the 2-nitrimino-4-(4'-pyridyl)-(3H)-thiazolium betaine structure. The N-H stretching band between 3500 and 3200 cm^{-1} was absent. The wide band occurring between 3130 and 2140 cm^{-1} was assigned to the $\geq\overset{+}{N}$-H stretching.

21. Examination of the infrared spectra of 2-pyridyl 2-pyridylmethyl-, 4-pyridyl 2-pyridylmethyl-, 2-pyridyl 4-pyridylmethyl-, and 4-pyridyl 4-pyridylmethyl ketone indicated that these compounds may not have the classical structure (CXXVII, R_1 = 2-pyridyl or 4-pyridyl, R_2 = 2-pyridyl or 4-pyridyl). It was suggested that these compounds have a resonance hybrid structure receiving contributions from dipolar and α ,β - unsaturated ketone forms. In the two pyridyl 2-pyridylmethyl ketones, the contribution of the ionic forms to the ground state of the molecule is greater than that of the isomeric pyridyl 4-pyridylmethyl ketones.

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