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Richard Kang-Chuan Hsia

SYNTHESES AND SPECTRA OF THIAZOLOISOQUINOLINES

ABSTRACT

Thiazolo(5,4-f)isoquinoline, a new heterocyclic ring system has been synthesized from 6-aminoisoquinoline in four steps by reaction with potassium thiocyanate and bromine to give 6-amino-5-thiocyanoisoquinoline, cyclization with hydrochloric acid to produce 2-aminothiazolo(5,4-f)isoquinoline, Sandmeyer reaction to yield 2-chlorothiazolo(5,4-f)isoquinoline and reduction with hydriodic acid and red phosphorus to give thiazolo(5,4-f)isoquinoline. The synthesis of thiazolo(4,5-h)isoquinoline was achieved in a similar way. The attempted syntheses of thiazolo(5,4-h)- and thiazolo(4,5-f)-isoquinolines were unsuccessful, however some substituted thiazolo-(5,4-h)isoquinolines were obtained. The infrared, ultraviolet and nuclear magnetic resonance spectra of isoquinolines, thiazolo(4,5-h)- and thiazolo(5,4-f)isoquinolines and their derivatives were also studied.

SYNTHESES AND SPECTRA OF THIAZOLOISOQUINOLINES

A thesis

by

Richard Kang-Chuan Hsia

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Department of Chemistry,
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To Mama, Papa and Tina

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Compound or Structure	Roman Numeral
Thiazolo(4,5-c)isoquinoline	1
Thiazolo(5,4-c)isoquinoline	11
Thiazolo(4,5-f)isoquinoline	111
Thiazolo(5,4-f)isoquinoline	1V
Thiazolo(4,5-g)isoquinoline	V
Thiazolo(5,4-g)isoquinoline	V1
Thiazolo(4,5-h)isoquinoline	V11
Thiazolo(5,4-h)isoquinoline	V111
2-Chlorothiazolo(4,5-h)isoquinoline	1X
2-Aminothiazolo(4,5-h)isoquinoline	X
2-Hydroxythiazolo(4,5-h)isoquinoline	X1
2-Acetamidothiazolo(4,5-h)isoquinoline	X11
2-Chlorothiazolo(5,4-f)isoquinoline	X111
2-Aminothiazolo(5,4-f)isoquinoline	X1V
2-Hydroxythiazolo(5,4-f)isoquinoline	XV
2-Acetamidothiazolo(5,4-f)isoquinoline	XV1
2,5-Diaminothiazolo(5,4-h)isoquinoline	XV11
2,5-Diacetamidothiazolo(5,4-h)isoquinoline	XV111
2-Amino-4-chlorothiophenol	X1X
2-Benzoylamino-4-chlorothiophenol	XX
5-Chloro-2-phenylbenzothiazole	XX1
m-Nitrothioacetanilide	XX11
5-Nitro-2-phenylbenzothiazole	XX111

Compound or Structure	Roman Numeral
Diphenylthiourea	XX1V
2-Phenyl-aminobenzothiazole	XXV
2-Bromo-4-methylthioacetanilide	XXV1
6-Methyl-2-phenylbenzothiazole	XXV11
4-Methyl-2-thiocyanoaniline	XXV111
2-Amino-6-methylbenzothiazole	XX1X
Triethylammonium-5-isoquinolyldithiocarbamate	XXX
5-Isoquinolylisothiocyanate	XXX1
5-Isoquinolylthiourea	XXX11
m-Hydroxybenzaldehyde	XXX111
m-Hydroxybenzylidene-aminoacetal	XXX1V
7-Hydroxyisoquinoline	XXXV
7-Aminoisoquinoline	XXXV1
7-Amino-8-thiocyanoisoquinoline	XXXV11
Isoquinoline	XXXV111
5-Nitroisoquinoline	XXX1X
5-Aminoisoquinoline	XL
5-Amino-6-thiocyanoisoquinoline	XL1
5-Amino-8-thiocyanoisoquinoline	XL11
5-Amino-8-mercaptoisoquinoline	XL111
5-Bromoisoquinoline	XL1V
5-Bromo-8-nitroisoquinoline	XLV
8-Aminoisoquinoline	XLV1
8-Amino-7-thiocyanoisoquinoline	XLV11

Compound or Structure	Roman Numeral
8-Amino-5-thiocyanoisoquinoline	XLVIII
8-Amino-5-mercaptoisoquinoline	XLIX
5-Acetamidoisoquinoline	L
5-Acetamido-8-nitroisoquinoline	LI
5-Acetamido-8-aminoisoquinoline	LII
m-Methoxybenzaldehyde	LIII
m-Methoxy-ω-nitrostyrene	LIV
ω-3-Methoxyphenethylamine	LV
6-Methoxy-1,2,3,4-tetrahydroisoquinoline	LVI
6-Methoxyisoquinoline	LVII
6-Hydroxyisoquinoline	LVIII
6-Aminoisoquinoline	LIX
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GENERAL INTRODUCTION

This dissertation reports the syntheses of some thiazoloisoquinolines, a class of compounds resulting from fusion of the thiazole and the isoquinoline rings through two adjacent carbon atoms. Eight thiazoloisoquinolines are possible and of the eight isomers, only thiazolo(4,5-c)- and thiazolo(5,4-c)isoquinolines have already been investigated. These two isomers differ only in the orientation of the thiazole ring on the pyridine ring of the isoquinoline nucleus. Therefore it was of significance and interest to develop methods for the syntheses of the unknown thiazoloisoquinolines and their derivatives. The isomers chosen for this work were thiazolo(4,5-h)- and thiazolo(5,4-f)isoquinolines. In these structures, the thiazole ring is fused to the benzenoid ring of the isoquinoline nucleus. The study of the spectra of thiazolo(4,5-h)- and thiazolo(5,4-f)isoquinolines and their derivatives was also undertaken.

The spectra of the substituted isoquinolines used as intermediates in this work were unknown, therefore it was of great interest to record their infrared, ultraviolet and nuclear magnetic resonance spectra and to establish the main spectral characteristics of these compounds.

Some unexpected reactions were observed during the attempted

syntheses of thiazolo(5,4-h)- and thiazolo(4,5-f)isoquinolines, e.g. conversion of a thiocyano group to a thiol using merely hydrochloric acid and ethanol.

HISTORICAL INTRODUCTION

Of the eight possible thiazoloisoquinolines, only thiazolo(4,5-c)- and thiazolo(5,4-c)isoquinolines have already been investigated (2,3). No thiazolo(4,5-f)-, thiazolo(5,4-f)-, thiazolo(4,5-g)-, thiazolo(5,4-g)-, thiazolo(4,5-h)- and thiazolo(5,4-h)-isoquinolines have been previously synthesized. Several thiazolo-(2,3-a)isoquinolinium compounds have also been prepared by 1,3-dipolar addition of carbon disulfide to benzylisoquinolinium salts and also by the reaction of acid chlorideswith 1-isoquinolylthio-acetonitrile (38, 77).

NOMENCLATURE AND STRUCTURE

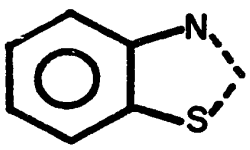
The thiazoloisoquinolines are named according to the nomenclature rules given in the Ring Index by Patterson et al. (1). The base component of thiazoloisoquinolines is isoquinoline, because it is the largest individual ring. Both angular and linear annelations are possible in the thiazoloisoquinoline series. The angular annelation provides six of the eight possible isomers which are analogous to the phenanthrene series, while the two isomers, thiazolo(4,5-g)- and thiazolo(5,4-g)isoquinolines, involve linear annelation analogous to the anthracene series. The four thiazoloisoquinolines which will be discussed presently (thiazolo(4,5-f)-, thiazolo(5,4-f)-, thiazolo(4,5-h)- and thiazolo(5,4-h)isoquinolines) are of the angular annelation type. The first two compounds form a pair differing only in the orientation of the thiazole ring on

the benzenoid ring of the isoquinoline nucleus. This applies similarly to the remaining two compounds. The structure and numbering of the eight possible thiazoloisoquinolines are listed on the following page.

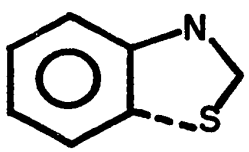
GENERAL CONSIDERATIONS OF THE SYNTHESES OF THIAZOLOISOQUINOLINES

Apart from thiazolo(4,5-c)- and thiazolo(5,4-c)isoquinolines, other compounds of this series may be prepared by either annelation of a thiazole ring onto an isoquinoline nucleus or building of a pyridine ring onto the benzene ring of the benzothiazole nucleus. The syntheses of thiazolo(4,5-c)- and thiazolo(5,4-c)isoquinolines involve only the formation of the thiazole ring, since the thiazole ring of both compounds is fused to the pyridine ring of the isoquinoline nucleus. However, the method involving the formation of the pyridine ring was not considered because it would require lengthy preparation of benzothiazole derivatives. The methods of synthesizing the thiazole ring have been grouped according to the type of ring closure. Three important types of ring closure are indicated below.

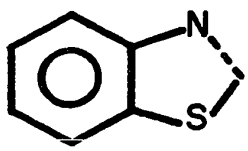
Type A

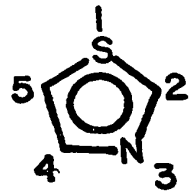


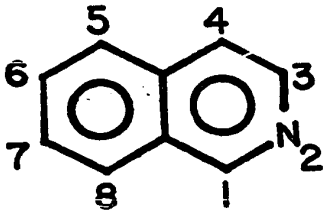
Type B

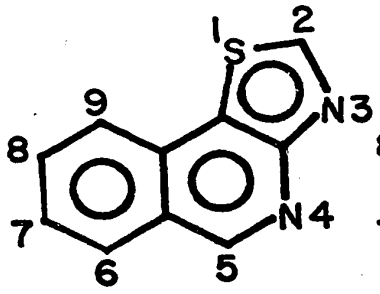


Type C

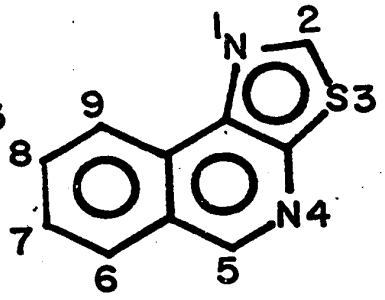




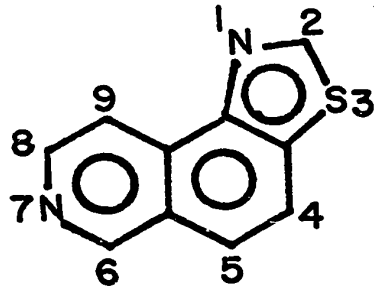




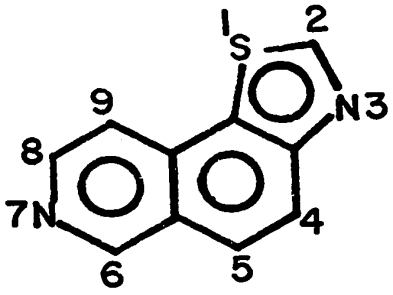
[4,5-c] I



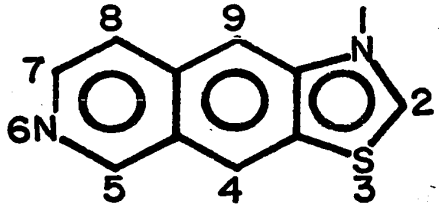
[5,4-c] II



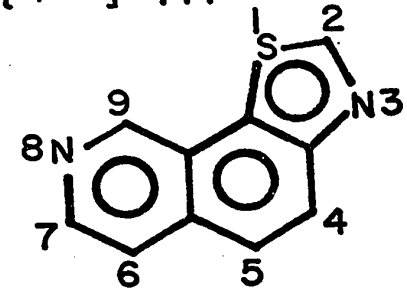
[4,5-f] III



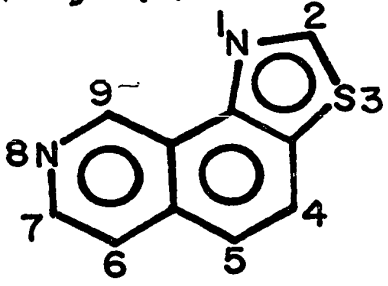
[5,4-f] IV



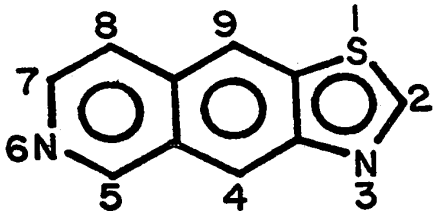
[4,5-g] V



[4,5-h] VII



[5,4-h] VIII

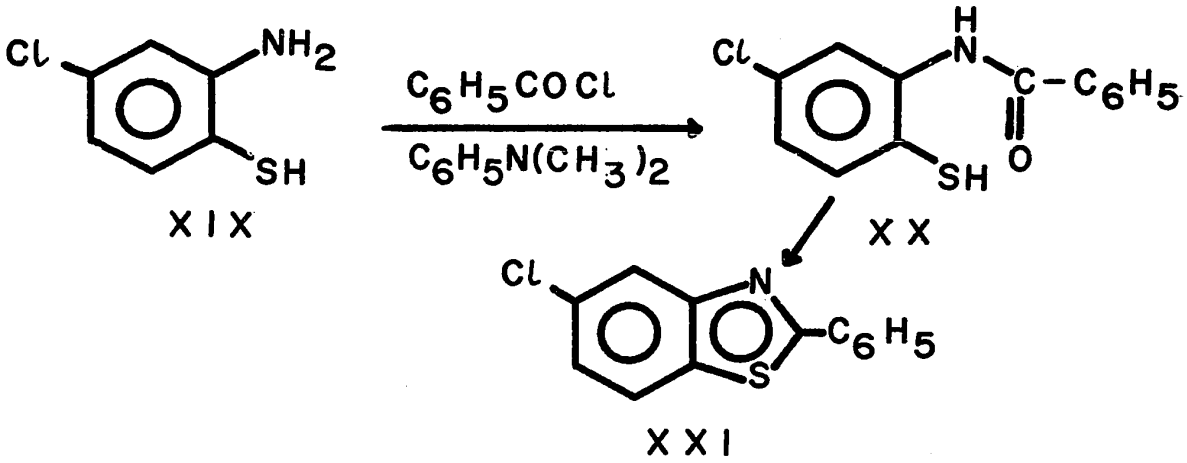


[5,4-g] VI

C H A R T I

The methods of these cyclizations are grouped into types A, B and C, respectively. They can be extended to the preparation of naphthothiazoles and thiazoloquinolines as well (9,12,67,68).

Type A synthesis involves reactions of o-aminoarylthiols with aldehydes and carboxylic acids or derivatives such as acid chlorides, or anhydrides.



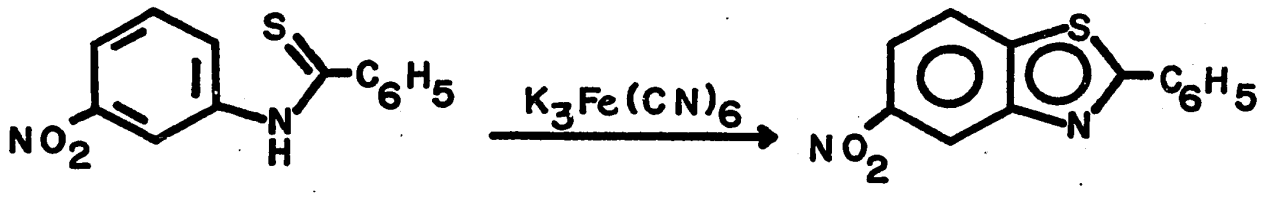
XIX XX XXI

An example of this synthesis is the conversion of 2-amino-4-chlorothiophenol (XIX) to 5-chloro-2-phenylbenzothiazole (XXI) by treatment with benzoyl chloride in dimethylaniline (7). 2-Benzoylamino-4-chlorothiophenol (XX), an intermediate, was prepared and shown to cyclize readily. Similarly, 2-methylthiazolo(4,5-c)pyridine was prepared from 3-amino-4-mercaptopyridine and acetic anhydride (90) and 5-chloro-2-methylbenzothiazole was prepared from 2-amino-4-chlorothiophenol (7). On the other hand, the reaction of 2-amino-4-chlorothiophenol with acetaldehyde in

pyridine gave 2-amino-5-chlorobenzothiazoline which was converted to 2-amino-5-chlorobenzothiazole upon recrystallization (8). The required p-aminoarylthiols can be obtained through the reduction of bis-nitrophenyldisulfide derivatives or by the action of sulfur monochloride on the hydrochlorides of arylamines (40, 41)

Type B synthesis involves cyclization of thioacylamido aromatic compounds. It can be divided into two classes depending upon the nature of the substituents required to bring about the cyclization.

1) Jacobson Synthesis

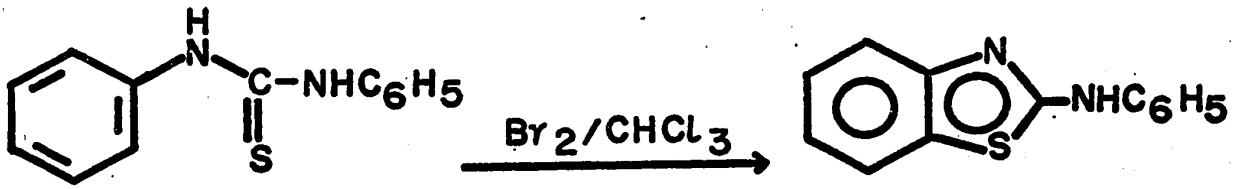


XXII — XXIII

The cyclization of m-nitrothiobenzanilide (XXII) to 5-nitro-2-phenylbenzothiazole (XXIII) is an example in this group. It was found by Jacobson (6) that thioanilides and thiourethanes yielded upon oxidation with potassium ferricyanide benzothiazoles and their 2-alkoxy derivatives. When the method was applied to the cyclization of thioacetanilide, it led to the formation of

2-methylbenzothiazole (6). Similarly, the cyclization of 2-acetamidopyridine with potassium ferricyanide gave 2-methylthiazolo(4,5-b)pyridine (88).

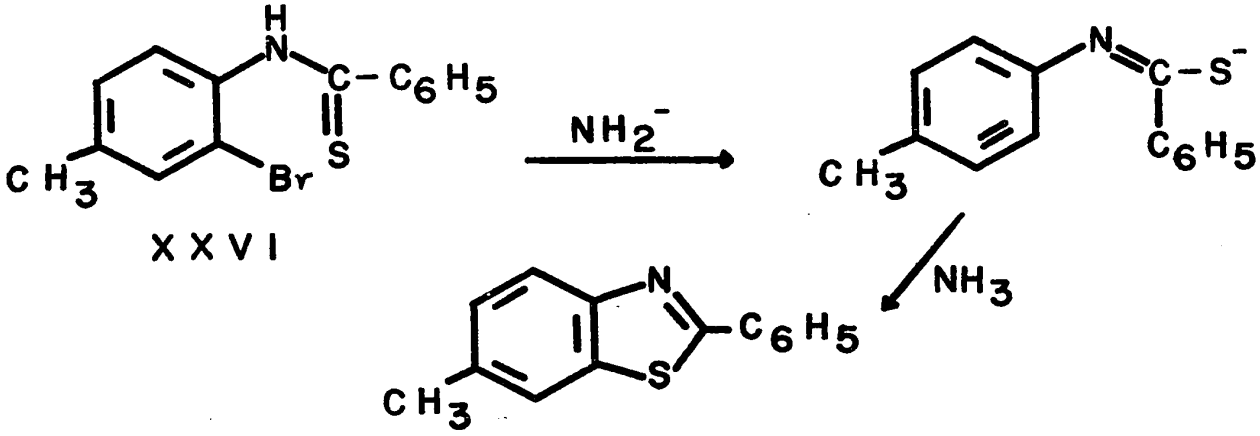
(2) Hugerschoff Synthesis



XXIV XXV

This method is restricted to the preparation of aminobenzothiazoles from arylthioureas. Hugerschoff (4), using diphenylthiourea (XXIV) and bromine, obtained 2-phenylaminobenzothiazole (XXV). Similarly, 2-nitrophenylthiourea yielded 2-amino-4-nitrobenzothiazole (10) and 2-aminonaphtho(1,2-d)-thiazole was obtained from 1-naphthylthiourea (43).

(3) Syntehsis Through Aryne Intermediate

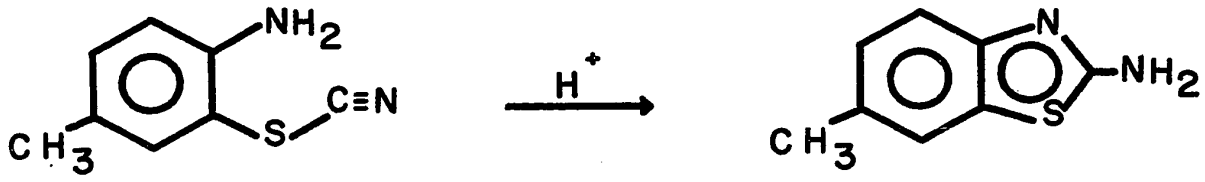


XXVI

XXVII

2-Phenylbenzothiazoles were also prepared from o-bromothioacetanilides by the action of potassium amide in ammonia (84, 85). Thus, 6-methyl-2-phenylbenzothiazole (XXVII) was obtained from 2-bromo-4-methylthiobenzanilide. This reaction involves the addition of a sulfur nucleophile to an aryne intermediate which is formed by treatment of a suitable aryl halide with strong base.

Type C synthesis involves the cyclization of o-thiocyano arylamines.



XXVIII

XXIX

The cyclization of 4-methyl-2-thiocyanoaniline (XXVIII) to 2-amino-6-methylbenzothiazole (XXIX) is a good example of this type (18). The required thiocyano arylamines are directly produced by treatment of p-substituted arylamines with thiocyanogen. Thiocyanogen can be formed by electrolysis of concentrated aqueous solution of alkali metal thiocyanates (39), oxidation of a thiocyanic acid by means of lead tetraacetate or lead oxide (82), or reaction of alkali thiocyanates with chlorine and bromine (22,58). Thiocyanogen forms a colorless crystalline solid on cooling and melts at -3° and -2°. It is hydrolyzed by water and is decomposed by alcohols. In most of its chemical properties, thiocyanogen displays marked resemblance to the halogens and may be assigned a place between bromine and iodine. The ortho-substituted thiocyano arylamines can usually be isolated, although direct cyclization is also possible. 2-Aminothiazolo(5,4-f)quinoline has been directly obtained by the reaction of 6-aminoquinoline with thiocyanogen (57). Hall and Taurins (2) have reported the thiocyanation of 3-aminoisoquinoline which gave 3-amino-4-thiocyanoisoquinoline. The cyclization of 3-amino-4-thiocyanoisoquinoline to 2-aminothiazolo(4,5-c)isoquinoline was then effected by treatment with hydrochloric acid.

Generally speaking, for the syntheses of thiazoloisoquinolines, the immediate precursors could be o-aminomercaptoisoquinolines, thioacylamidoisoquinolines, isoquinolylthioureas and o-aminothiocyanoisoquinolines, however, these have not been reported in the literature.

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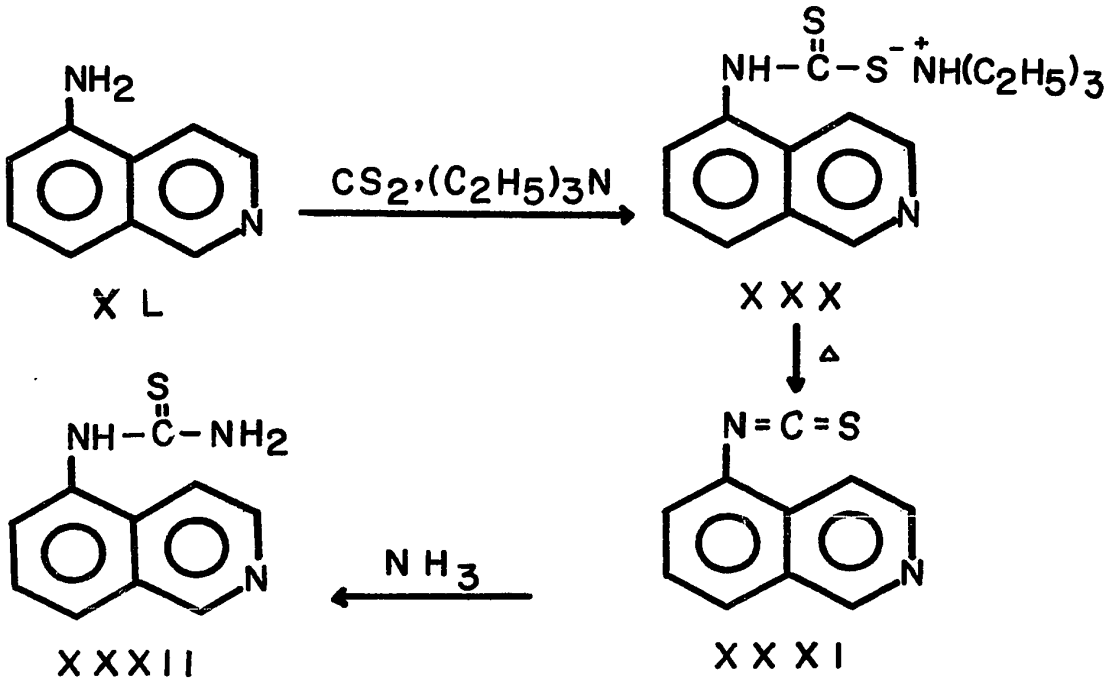
Generally speaking, for the syntheses of thiazoloisoquinolines, the immediate precursors could be o-aminomercaptoisoquinolines, thioacylamidoisoquinolines, isoquinolylthioureas and o-aminothiocyanoisoquinolines, however, these have not been reported in the literature.

In the A type synthesis, 7-amino-8-mercaptoisoquinoline can be prepared from 7-chloro-8-nitroisoquinoline (13) in a manner analogous to the preparation of o-aminothiophenol from o-chloronitrobenzene via a disulfide intermediate. The immediate precursor for the B type synthesis, 5-thioacetamidoisoquinoline and 5-isoquinolylthiourea can both be prepared form 5-aminoisoquinoline (XL). 5-Thioacetamidoisoquinoline can be prepared by the reaction of 5-acetamidoisoquinoline in benzene in the presence of phosphorus pentasulfide. The preparation of 5-isoquinolylthiourea (XXXII) involves the condensation of 5-aminoisoquinoline (XL), carbon disulphide and triethylamine at room temperature to give triethylammonium-5-isoquinolyldithiocarbamate (XXX). The latter compound when heated gives 5-isoquinolylisothiocyanate (XXXI). The reaction of 5-isoquinolylisothiocyanate (XXXI) with ammonia gives 5-isoquinolylthiourea (XXXII) (79).



In the C type synthesis, a convenient method of preparing o-aminothiocyanoisoquinolines can involve the treatment of amino-isoquinolines directly with thiocyanogen.

5-, 6-, 7-, and 8-Aminoisoquinolines were obtained from the corresponding hydroxyisoquinolines by the Bucherer reaction or by reduction of the corresponding nitro compounds (13,15,16,31).

DISCUSSION OF RESULTS

SYNTHESIS OF THIAZOLO(4,5-h)ISOQUINOLINE (V11)

The first intermediate required for the synthesis of thiazolo(4,5-h)isoquinoline (V11) was 7-amino-8-thiocyanoisoquinoline (XXXV11). Thiocyanation of 7-aminoisoquinoline (XXXV1) with thiocyanogen gave 7-amino-8-thiocyanoisoquinoline (XXXV11) which was converted to 2-aminothiazolo(4,5-h)isoquinoline (X) on cyclization. Diazotization of 2-aminothiazolo(4,5-h)isoquinoline (X) and subsequent reaction with cuprous chloride led to the formation of 2-chlorothiazolo(4,5-h)isoquinoline (1X). The reduction of 1X with red phosphorus and hydriodic acid gave thiazolo(4,5-h)isoquinoline (V11).

(1) Preparation of 7-Aminoisoquinoline (XXXV1)

The preparation of 7-aminoisoquinoline (XXXV1) is outlined in chart 2. m-Hydroxybenzaldehyde (XXX111) was condensed with aminoacetaldehyde diethylacetal giving m-hydroxybenzylidene aminoacetal (XXX1V), a Schiff base, and cyclization of the latter compound with 76% sulfuric acid gave 7-hydroxyisoquinoline (XXXV) (17). Reaction of XXXV with a solution of ammonium sulfite under Bucherer reaction conditions gave 7-aminoisoquinoline (XXXV1) (5).

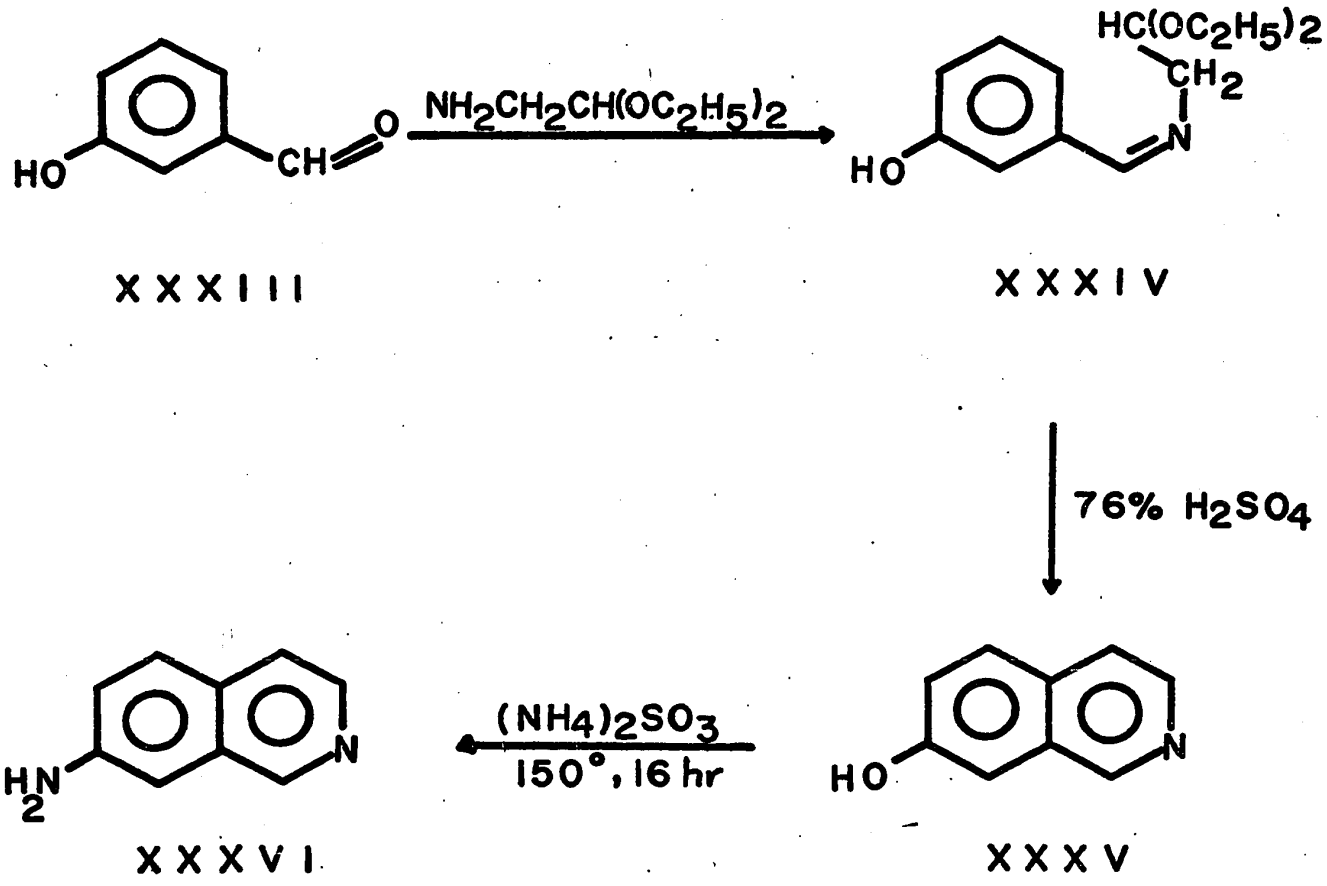


CHART 2

(2) Preparation of Thiazolo(4,5-h)isoquinoline (VII)

Thiocyanation of 7-aminoisoquinoline (XXXVI), with bromine and potassium thiocyanate in 95% glacial acetic acid solution gave a yellow precipitate. Attempts to purify this yellow compound were unsuccessful, the compound being insoluble in the common sol-

vents. However the crude substance was identified as a thiocyano derivative by its infrared spectrum which showed the thiocyano absorption at 2144 cm^{-1}. Also the absorption pattern of the primary amino group for 7-aminoisoquinoline (XXXVI) (three bands at 3415, 3290 and 3148 cm^{-1}) was changed to 3445, 3365 and 3228 cm^{-1}.

The nmr spectrum of the thiocyanation product in deuterioacetic acid showed two doublets centered at 8.45 and 8.02 δ which were assigned to H_3 and H_4 respectively. The poorly resolved quartet centered at 7.75 δ of an intensity equivalent to two protons was assigned to two protons (H_5 and H_6) and the singlet at 9.23 δ was assigned to H_1. In all probability, this suggested the presence of 7-amino-8-thiocyanoisoquinoline (XXXVII).

Treatment of the yellow crude substance with alcoholic hydrochloric acid (ethanol ; 4N hydrochloric acid 1:1) for three hours gave a yellow crystalline compound. It was found to be 2-aminothiazolo(4,5-h)isoquinoline (X). The absence of the thiocyano band in the infrared spectrum at 2144 cm^{-1} supported the assigned structure. A strong band at 833 cm^{-1} for out-of-plane C-H vibration showed the presence of two adjacent ring hydrogen atoms on the benzenoid ring. The nmr spectrum of 2-aminothiazolo(4,5-h)-isoquinoline (X) had a singlet at 9.63 δ for H_9 and two doublets centered at 7.96 and 8.20 δ were assigned to H_4 and H_5. In addition, two doublets with splitting centered at 8.70 and 8.52 δ were assigned

to H_7 and H_6 respectively. H_7 is expected at lower field than H_6 because of its proximity to the ring nitrogen atom N_8. While H_6 and H_7 were expected to show coupling with H_9 on the pyridine ring, H_4 and H_5 could not couple because of the large seperation of those protons from pyridine ring protons.

The cyclisation reaction of amino-thiocyanocompounds involves a nucleophilic attack of the amino nitrogen on the carbon atom of the thiocyano group. The ease of cyclization varies with the nucleophilic strength of the amino nitrogen in the thiocyanation product. When the thiocyanation of aromatic amino-compounds takes place in the position ortho to an amine group, the final product is often an amino-thiazole derivative which is formed immediately by a secondary reaction between the amino and the thiocyano groups. Thus, 2-amino-6-chlorobenzothiazole was directly formed by the reaction of p-chloroaniline with thiocyanogen (11). It was reasonable to assume that thiocyanation of 7-aminoisoquinoline (XXXVI) gave 7-amino-8-thiocyanoisoquinoline (XXXVII) and 2-aminothiazole-(4,5-h)isoquinoline (X). When the mixture was refluxed in alcoholic hydrochloric acid 7-amino-8-thiocyanoisoquinoline (XXXVII) was converted to 2-aminothiazolo(4,5-h)isoquinoline (X).

Diazotization of 2-aminothiazolo(4,5-h)isoquinoline (X) with sodium nitrite in 70% nitric acid and 85% ortho phosphoric acid mixture (1:4 ratio), followed by the treatment of the diazonium salt with cuprous chloride gave a 42% yield of 2-chlorothiazolo-

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(4,5-h)isoquinoline (1X). The infrared spectrum of the latter showed the absence of the primary amino bands in the region 3400-3100 cm^{-1} indicating that the primary amino group was replaced by the chlorine atom. The N-H deformation absorption at 1640 cm^{-1} was also missing. The nmr spectrum of this compound showed a singlet at lower field (8.94 δ) for H_9 and two doublets at 8.34 and 7.35 δ which were assigned to H_7 and H_6 ($J_{6,7}$=5.9 Hz). Two additional doublets centered at 7.77 and 7.43 δ were assigned to both H_4 and H_5 ($J_{4,5}$=8.9 Hz).

Reduction of 2-chlorothiazolo(4,5-h)isoquinoline (1X) with red phosphorus in hydriodic acid gave thiazolo(4,5-h)isoquinoline (V11) in 58% yield. Only slight change was observed in the infrared spectrum of thiazolo(4,5-h)isoquinoline (V11) except for the presence of a band of medium strength at 3090 cm^{-1}, which was assigned to C-H stretching vibration for the thiazole proton. The nmr spectrum of this compound (V11) showed two singlets at lower field (9.40 and 9.14 δ) for H_2 and H_9. The singlet at lower field with splitting was assigned to H_9 because of its coupling with protons H_6 and H_7. Two doublets centered at 8.62 and 7.78 δ were assigned to H_7 and H_6 and two doublets centered at 8.33 and 7.82 δ were assigned to H_4 and H_5. The complete synthesis of thiazolo(4,5-h)-isoquinoline (V11) is outlined in Charts 3,4 and 5.

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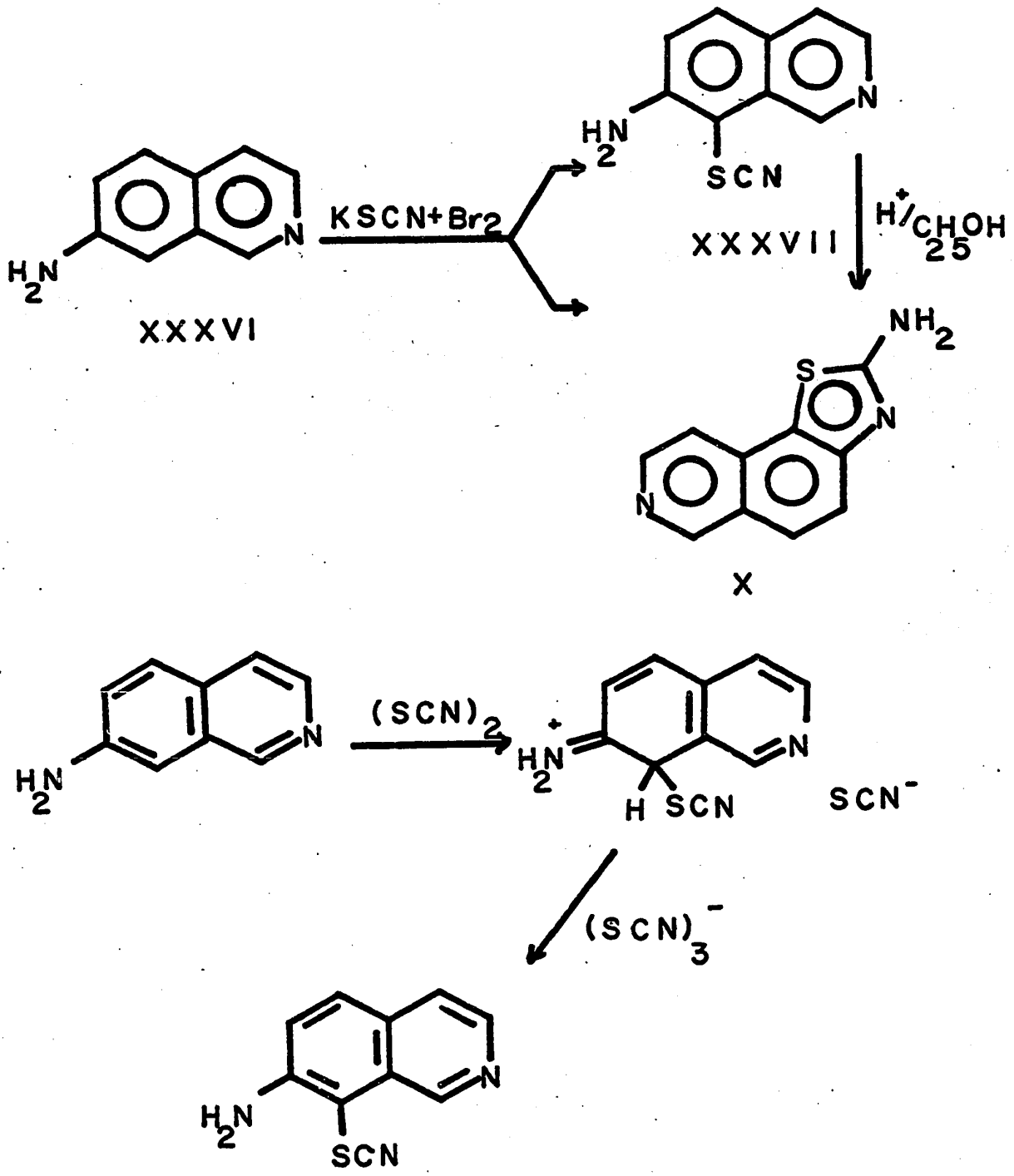


CHART 3

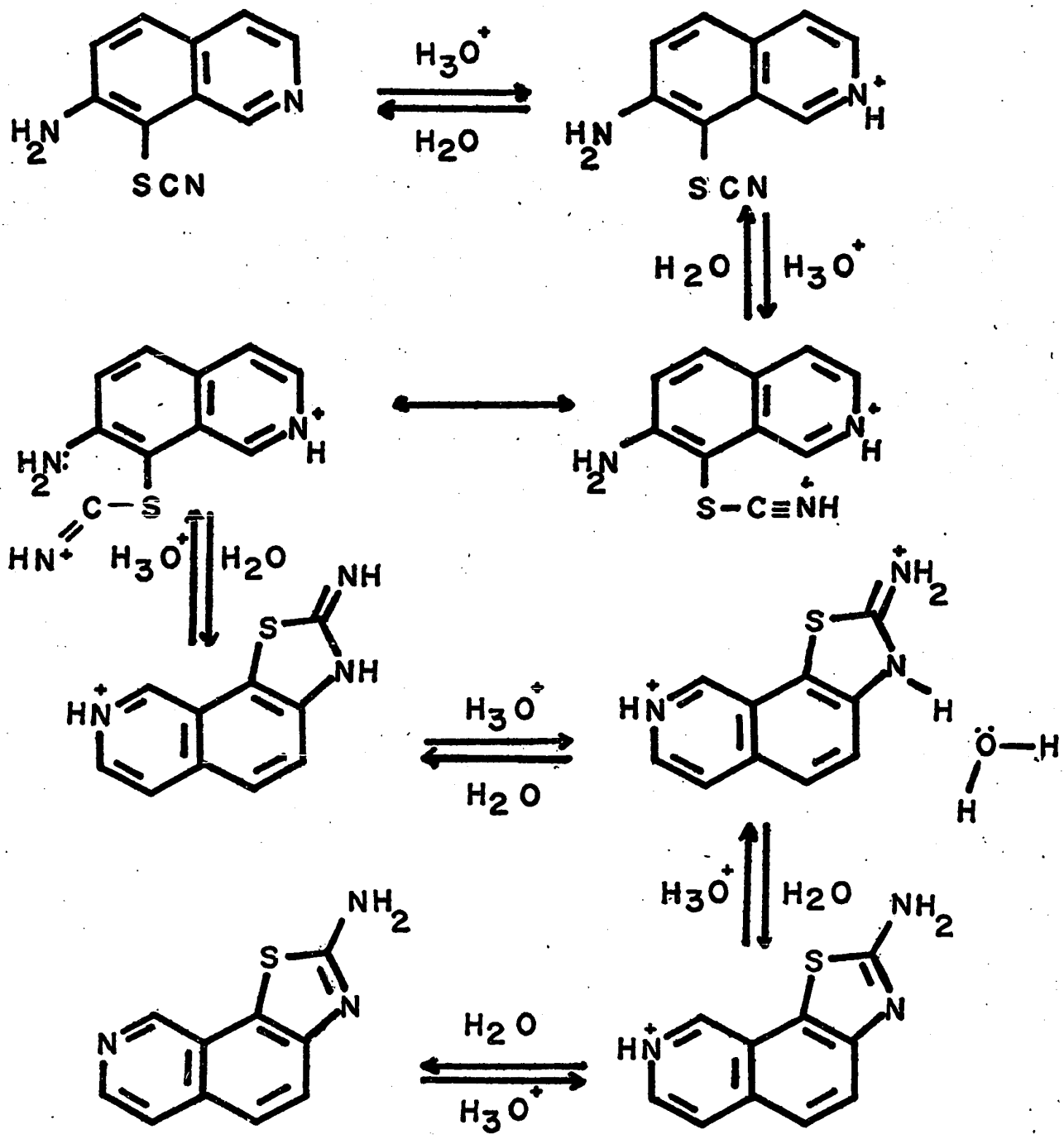
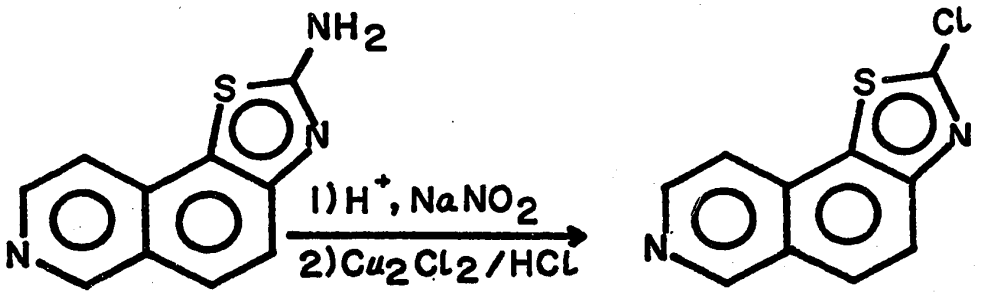
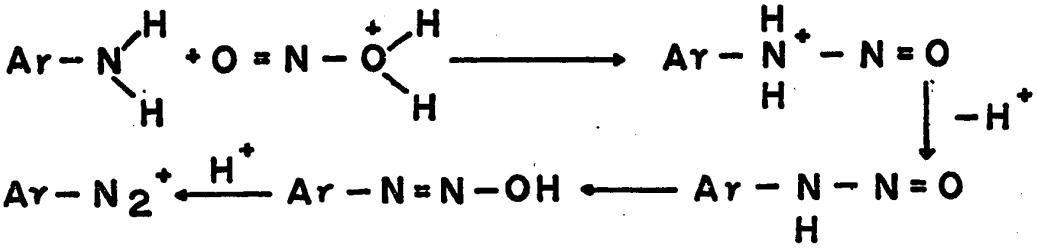
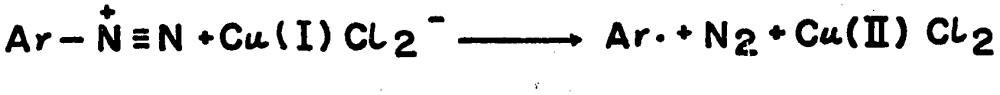


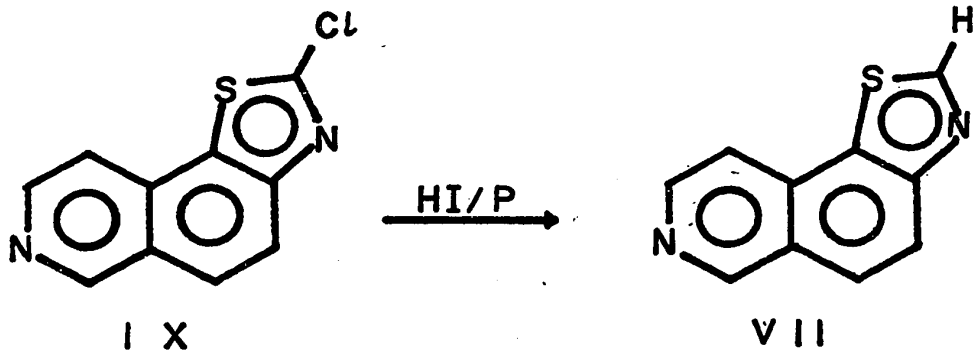
CHART 4



X IX







IX VII

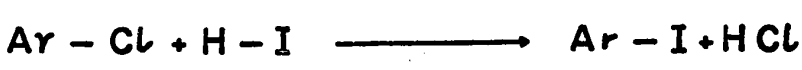


CHART 5

ATTEMPTED SYNTHESIS OF THIAZOLO(4,5-f)ISOQUINOLINE (111)

The synthesis of thiazolo(4,5-f)isoquinoline (111) required the preparation of the unknown 5-amino-6-thiocyanoisoquinoline (XL1) as an intermediate. However, the attempted preparation of this compound by thiocyanation of 5-aminoisoquinoline (XL) was unsuccessful. The attempted preparation of thiazolo(4,5-f)isoquinoline (111) is outlined in Chart 6.

5-Aminoisoquinoline (XL) was prepared by nitration of isoquinoline (XXXV111) in concentrated sulfuric acid with potassium nitrate (20), followed by reduction of 5-nitroisoquinoline (XXX1X) with hydrogen in the presence of 5% palladised charcoal (64).

Thiocyanation of 5-aminoisoquinoline (XL) with potassium thiocyanate and bromine in 95% glacial acetic acid solution gave a yellow crystalline compound. The infrared spectrum of this compound showed the presence of the thiocyano band at 2140 cm^{-1} and bands at 3440, 3345 and 3208 cm^{-1} for the primary amino group. This suggested the presence of 5-amino-x-thiocyanoisoquinoline. The nmr spectrum showed a singlet at 9.64 δ for H_1 and two doublets centered at 8.68 and 8.19 δ assigned to H_3 and H_4 with coupling constant $J_{3,4} = 5.8$ Hz. Two additional doublets centered at 6.99 and 7.87 δ could arise by coupling of H_7 and H_6 in 5-amino-8-thiocyanoisoquinoline (XL11), or by H_7 and H_8 in the case of 5-amino-6-thiocyanoisoquinoline (XLI). From this information alone, it was

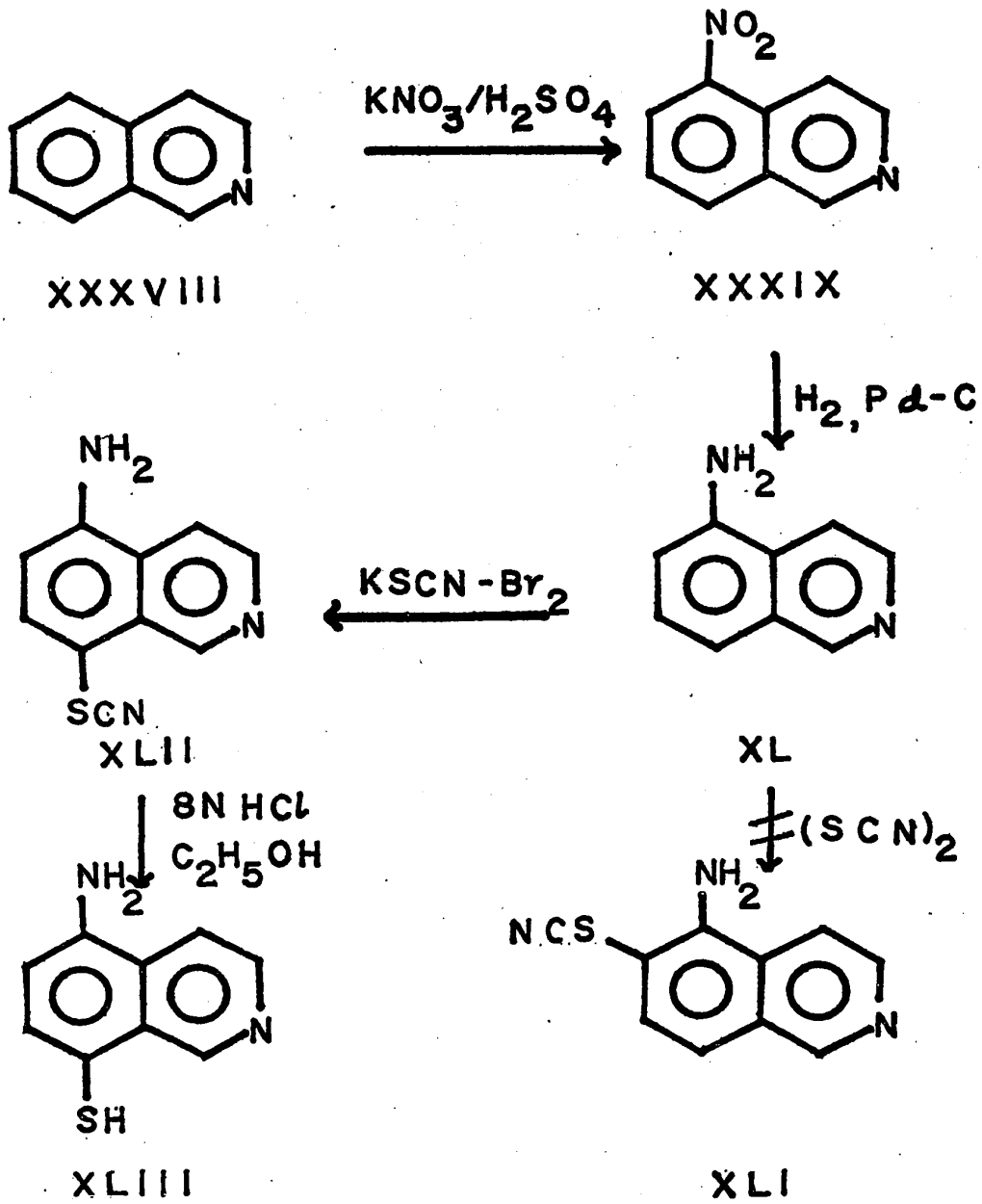

NO2
KNO3/H2SO4
N
XXXVIII
XXXIX
H2, Pd-C
NH2
KSCN-Br2
SCN
XLII
XL
8N HCl
C2H5OH
(SCN)2
NCS
SH
XLIII
XLI

CHART 6

impossible to decide whether the reaction product was 5-amino-6-thiocyanoisoquinoline (XLI) or 5-amino-8-thiocyanoisoquinoline (XLII).

The thiocyanation product of 5-aminoisoquinoline (XL) was refluxed in alcoholic hydrochloric acid (4N hydrochloric acid: ethanol 1:1) for three hours. But there was only a slight change, since most of the original compound was recovered. When the concentration of hydrochloric acid was increased from 4N to 8N while keeping the ratio of ethanol and acid at 1:1, a yellow precipitate was formed. The infrared spectrum of this compound showed that the band for the thiocyano group at 2140 cm^{-1} was absent. Also the absorption pattern for the amino group (three bands at 3440, 3345 and 3208 cm^{-1} in 5-amino-x-thiocyanoisoquinoline) was changed to two bands at 3319 and 3176 cm^{-1}. The nmr spectrum showed a pattern similar to that of 5-amino-x-thiocyanoisoquinoline. It exhibited four well defined doublets at 8.43, 8.02, 6.71 and 7.31 δ and a singlet at 9.33 δ .

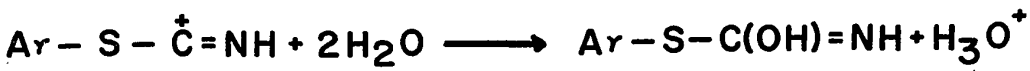
The elemental analysis of this compound gave the formula $C_9H_8N_2S$. It was therefore reasonable to assume that the thiocyano group was converted to the mercapto group on acid hydrolysis. The infrared spectrum however did not indicate any bands for the mercapto group which usually appears weakly in the region 2650-2550 cm^{-1}. Nevertheless, the presence of the mercapto group was supported by the fact that a yellow precipitate was formed when this compound was treated in ethanol solution with mercuric chloride.

If an amino group was present, no yellow precipitate should be formed (21).

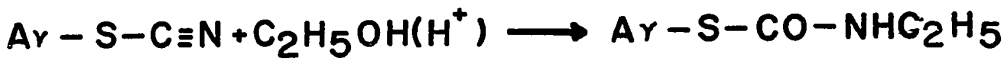
$$R-SH + HgCl_2 \longrightarrow R-S-HgCl + HCl$$

From the preceeding experiments, it can be concluded that thiocyanation of 5-aminoisoquinoline (XL) gives 5-amino-8-thiocyanoisoquinoline (XLII) instead of 5-amino-6-thiocyanoisoquinoline (XLI). Hence further work on the synthesis of 2-aminothiazolo(4,5-f)isoquinoline could not be done. It is perhaps not surprising that thiocyanation occurs para to an activating group since it has been found that thiocyanation of aniline gave only p-thiocyanoaniline (22). Similarly, thiocyanation of α-naphthylamine gave 4-thiocyano-1-naphthylamine in 80% yield (18).

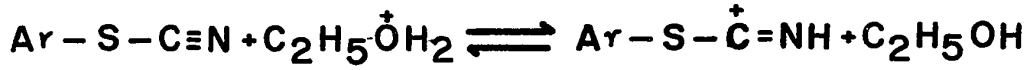
Conversion of the thiocyanates to thiols was usually achieved by reduction with zinc and hydrochloric acid (91). No cases of conversion of an thiocyano group into a thiol using merely hydrochloric acid and ethanol have been reported previously. Riemschneider et al. (24,25) found that the thiocyanates were converted to thiocarbamates by treatment with sulfuric acid at 0-5°. They showed the reaction proceeds as follows.

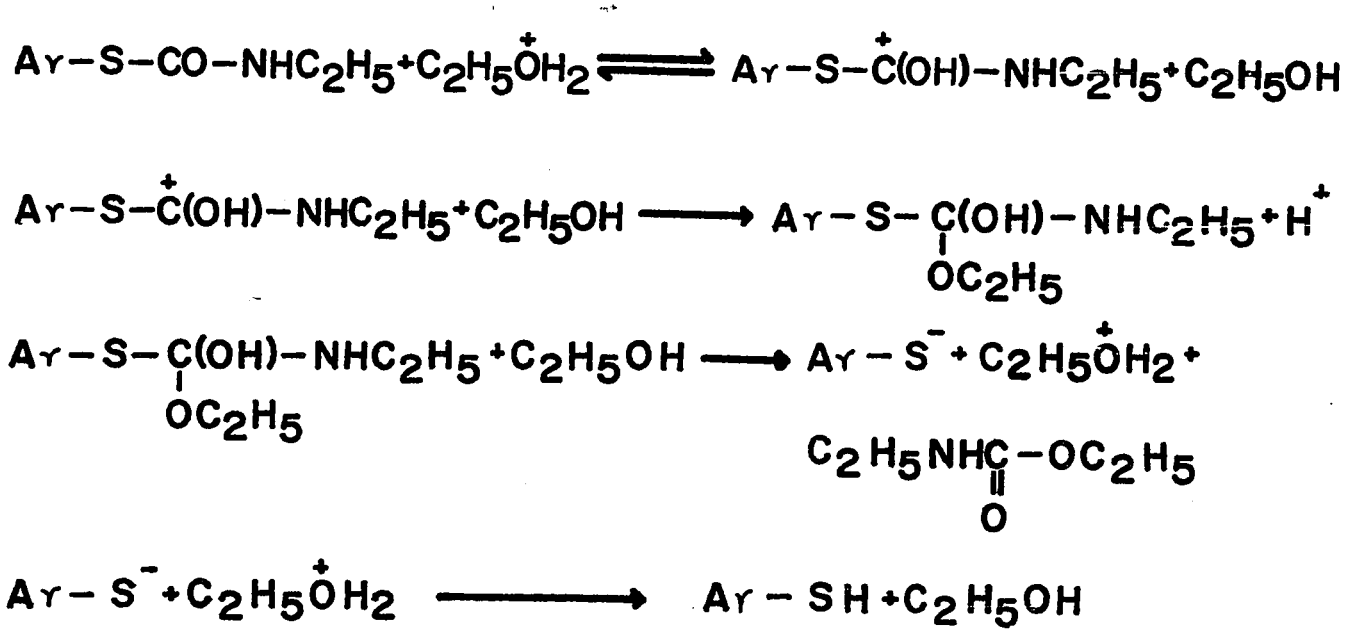


Similarly, with ethanol replacing [illegible] water:



The conversion of the thiocyanate into thiol probably is preceded by an arylthiocarbamate intermediate which is hydrolyzed to a thiol. For this reaction the following mechanism is proposed:





Since the introduction of the thiocyano group ortho to the amino group failed, the further study of this reaction was not carried out.

ATTEMPTED SYNTHESIS OF THIAZOLO(5,4-h)ISOQUINOLINE (VIII)

The route chosen for the synthesis of thiazolo(5,4-h)-isoquinoline (VIII) involved the preparation of 8-amino-7-thiocyanoisoquinoline (XLVII) as an intermediate. However, thiocyanation of 8-aminoisoquinoline (XLVI) did not yield 8-amino-7-thiocyanoisoquinoline (XLVII), but 8-amino-5-thiocyanoisoquinoline (XLVIII), as the only product. In order to prevent the thiocyano group from entering para to the amino group, the acetamido group was introduced in the 5-position, in the hope that 5-acetamido-8-amino-7-thiocyanoisoquinoline (LXI) would serve as an intermediate leading to the formation of thiazolo(5,4-h)isoquinoline (VIII). 5-Acetamido-8-aminoisoquinoline (LII) was prepared which gave 5-acetamido-8-amino-7-thiocyanoisoquinoline (LXI) on thiocyanation. 2,5-Diaminothiazolo(5,4-h)isoquinoline (XVII) was formed when LXI was refluxed in dilute hydrochloric acid and ethanol. Diazotization of 2,5-diaminothiazolo(5,4-h)isoquinoline (XVII) and subsequent reaction with cuprous chloride failed to give 2,5-dichlorothiazolo(5,4-)isoquinoline, consequently this sequence of reactions could not be continued (Chart 8).

The scheme for the attempted preparation of 8-amino-7-thiocyanoisoquinoline (XLVII) is given in the Chart 7. Diazotization of 5-aminoisoquinoline (XL) followed by the reaction of sodium bromide in 48% hydrobromic acid gave 5-bromoisoquinoline (XLIV) (19). Nitration of 5-bromoisoquinoline (XLIV) in concentrated sulfuric acid with potassium nitrate yielded 70% of 5-bromo-8-nitroisoquinoline

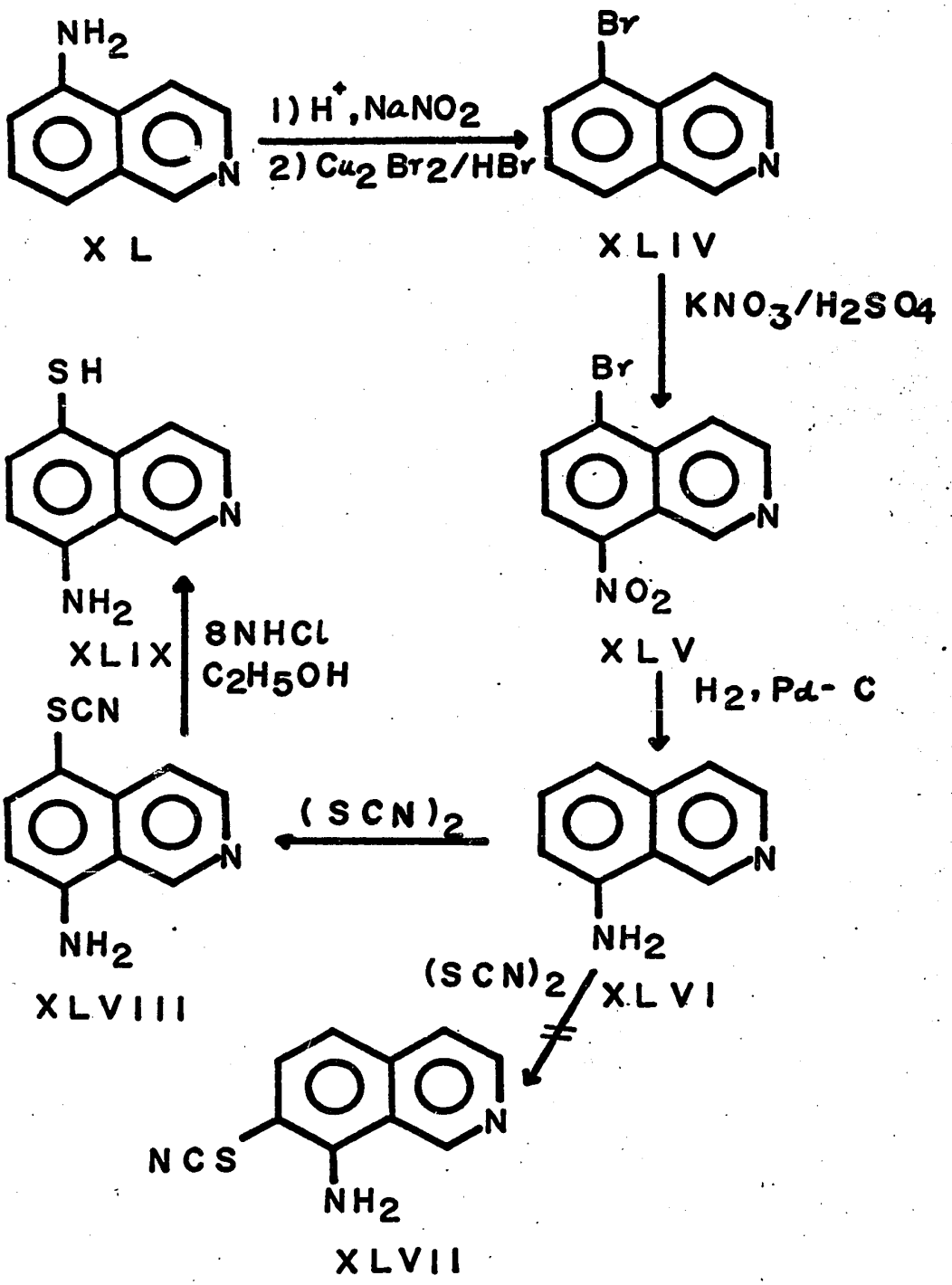

NH2
1) H+, NaNO2
2) Cu2 Br2/HBr
Br
N
XL
XLIV
KNO3/H2SO4
SH
Br
NO2
XLV
XLIX
8NHCl
C2H5OH
H2, Pd-C
SCN
(SCN)2
XLVIII
XLVI
(SCN)2
NCS
XLVII

CHART 7

(XLV) (19). Catalytic hydrogenation of 5-bromo-8-nitroisoquinoline (XLV) resulted in 8-aminoisoquinoline (XLVI) (26).

Thiocyanation of 8-aminoisoquinoline (XLVI) gave only 8-amino-5-thiocyanoisoquinoline (XLVIII) instead of 8-amino-7-thiocyanoisoquinoline (XLVII) which would have led to the formation of 2-aminothiazolo(5,4-h)isoquinoline. The assignment of the structure of 8-amino-5-thiocyanoisoquinoline (XLVIII) was based on the evidence given by the infrared and nmr spectra. The infrared spectrum showed the characteristic thiocyano band at 2142 cm^{-1} and the presence of the primary amino bands at 3436, 3349 and 3218 cm^{-1}. The nmr spectrum showed two doublets centered at 8.65 and 7.95 δ for H_3 and H_4 with a coupling constant $J_{3,4}$=5.8 Hz and a singlet at 9.64 δ for H_1. In addition, two doublets centered at 7.89 and 6.65 δ were also observed and assigned to H_7 and H_6 respectively. The coupling constant $J_{6,7}$ is 9.0 Hz. A further confirmation of the structure was obtained by the formation of the thiol when 8-amino-5-thiocyanoisoquinoline (XLVIII) was refluxed with hydrochloric acid and ethanol (8N hydrochloric acid: ethanol 1:1).

The attempted preparation of thiazolo(5,4-h)isoquinoline (VIII) was modified, as outlined in Chart 8. The 5-position in isoquinoline was blocked by an acetamido group and the amino group was introduced in 8- position. Acetylation of 5-

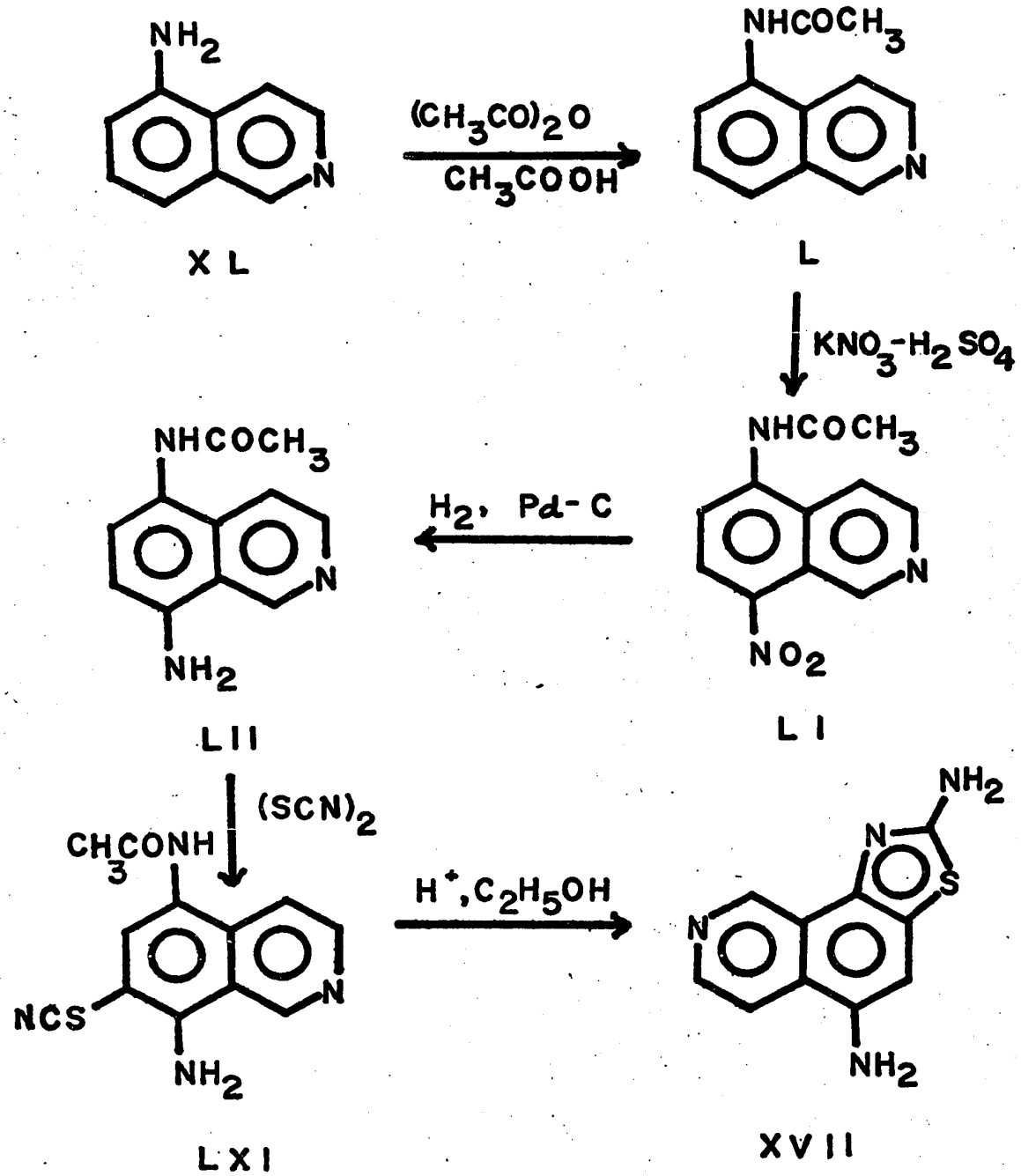

NH2
N
XL
(CH3CO)2O
CH3COOH
NHCOCH3
N
L
KNO3-H2SO4
NHCOCH3
N
NO2
LI
H2, Pd-C
NHCOCH3
N
NH2
LII
(SCN)2
CH3CONH
NCS
N
NH2
LXI
H+, C2H5OH
NH2
N
S
N
NH2
XVII

CHART 8

aminoisoquinoline (XL) gave 5-acetamidoisoquinoline (L) (14) which was nitrated with potassium nitrate in concentrated sulfuric acid to give 5-acetamido-8-nitroisoquinoline (L1) (29). Catalytic hydrogenation of 5-acetamido-8-nitroisoquinoline (L1) using 5% palladium charcoal produced 5-acetamido-8-aminoisoquinoline (L11) whose structure was proved by infrared and nmr spectra. The appearance of bands at 3403, 3290 and 3319 cm^{-1} showed the presence of the amino and acetamido groups. The band at 1530 cm^{-1} for the nitro group was absent. In the nmr spectrum of this compound two doublets centered at 8.60 and 7.62 δ were assigned to H_3 and H_4 respectively. Another two doublets centered at 7.45 and 6.73 δ were assigned to H_6 and H_7 respectively. In addition to these four doublets, the spectrum displayed a broad band centered at 6.09 δ for the amino group; the singlet at higher field (2.22 δ) was assigned to the methyl group of the acetamido group. The overlapping of the two singlets for H_1 and the amide proton of the acetamido group was centered at 9.49 δ .

Thiocyanation of 5-acetamido-8-aminoisoquinoline (L11) under standard conditions gave a yellow compound having extremely low solubility in most commonly used solvents. This prevented successful characterization of the product. However, its infrared spectrum showed the characteristic thiocyano band in the 2140 cm^{-1} region.

The yellow compound, being refluxed in hydrochloric acid and ethanol (4N hydrochloric acid; ethanol 1:1), gave

a yellowish-green crystalline substance which was identified as 2,5-diaminothiazolo(5,4-h)isoquinoline (XVII) by both infrared and nmr spectra. The infrared spectrum of this compound showed several broad bands in the region 3400-3100 cm^{-1}, but the thiocyano band was no longer present. The nmr spectrum of 2,5-diaminothiazolo(5,4-h)-isoquinoline (XVII) showed a singlet at lower field (9.67 δ) which was due to the isolated proton H_9, two doublets at 8.45 and 7.99 δ for H_7 and H_6 ($J_{6,7}$ = 6.1 Hz). The singlet at higher field (7.27 δ), being overlapped with a broad band centered at 7.33 δ for the amino group in the 5- position on the benzenoid ring, was assigned to H_4. Another broad band at 5.01 δ belonged to the amino group in the 2-position of the thiazole ring. After exchange with deuterium oxide, two broad bands were missing from this region, thus, confirming that the bands at 7.33 and 5.01 δ originated from the amino protons.

Diazotization of 2,5-diaminothiazolo(5,4-h)isoquinoline (XVII) followed by treatment with cuprous chloride failed to give 2,5-dichlorothiazolo(5,4-h)isoquinoline. The explanation for the failure originates from the fact that the yields of the Sandmeyer reaction are generally not high. Moreover, a double diazotization in the same molecule would encounter increased difficulty, especially since these two amino groups are located each on separate rings, benzenoid and thiazole respectively, which would in effect render them of different reactivity. Perhaps these obstacles are the cause of the failure in the reaction. Thiazolo(5,4-h)isoquinoline (VIII)

could not be obtained because of the unsuccessful preparation of 2,5-dichlorothiazolo(5,4-h)isoquinoline.

SYNTHESIS OF THIAZOLO(5,4-f)ISOQUINOLINE (1V)

The important intermediate in this synthesis was 6-amino-5-thiocyanoisoquinoline (LX) which was obtained by thiocyanation of 6-aminoisoquinoline (L1X). LX was cyclized to 2-aminothiazolo(5,4-f)isoquinoline (X1V). When the latter was diazotized and then treated with cuprous chloride, 2-chlorothiazolo-(5,4-f)isoquinoline (X111) was formed. Reduction of 2-chlorothiazolo(5,4-f)isoquinoline with hydriodic acid and red phosphorus gave thiazolo(5,4-f)isoquinoline (1V).

(1) Preparation of 6-Aminoisoquinoline (L1X)

6-Aminoisoquinoline (L1X) was prepared in a series of eight steps starting from m-hydroxybenzaldehyde (XXX111) as outlined in Chart 9. m-Hydroxybenzaldehyde (XXX111) was converted into m-methoxybenzaldehyde (L111) by alternate addition of dimethyl sulfate and aqueous sodium hydroxide (27). Osborn and Schofield (19) reported that m-methoxy-ω-nitrostyrene (L1V) was formed when m-methoxybenzaldehyde (L111) was refluxed with nitromethane and ammonium acetate in acetic acid. We found that the yield of m-methoxy-ω-nitrostyrene (L1V) was raised from 51% to 79% when the reaction of nitromethane with m-methoxybenzaldehyde (L111) was carried out in the presence of ethanolic alkali. Reduction of m-methoxy-ω-nitrostyrene (L1V) with lithium aluminum hydride (28) gave ω-3-methoxyphenethylamine (LV). Condensation of ω-3-methoxyphenethylamine (LV) with formaldehyde and then the cyclization of the azo-

methine in 20% hydrochloric acid led to the formation of 6-methoxy-1,2,3,4-tetrahydroisoquinoline (LVl) (30). Despite the report of Robinson (5) on the successful dehydrogenation of the tetrahydro compound with Raney Nickel in naphthalene, several attempts to repeat this procedure were unsuccessful. Osborn (19) also experienced similar difficulty. Dehydrogenation of 6-methoxy-1,2,3,4-tetrahydroisoquinoline (LVl) was carried out successfully with 10% palladium charcoal in decalin to obtain 6-methoxyisoquinoline (LVll), which on refluxing in 48% hydrobromic acid yielded 6-hydroxyisoquinoline (LVlll) (15). The preparation of 6-aminoisoquinoline (LlX) consisted of treating 6-hydroxyisoquinoline (LVlll) with a solution of ammonium sulfite (Bucherer reaction) (16,19).

(2) Preparation of Thiazolo(5,4-f)isoquinoline (lV)

Thiocyanation of 6-aminoisoquinoline (LlX) under standard conditions gave 6-amino-5-thiocyanoisoquinoline (LX). The infrared and nmr spectra confirmed the structure. The infrared spectrum of 6-amino-5-thiocyanoisoquinoline (LX) showed strong absorption at 2148 cm^{-1} for the thiocyano group and bands at 3382, 3316 and 3162 cm^{-1} for the primary amino group. In the nmr spectrum, the singlet at 9.23 δ was attributed to H_1 and two doublets centered at 8.53 and 8.26 δ to H_3 and H_4 ($J_{3,4}$=6.0 Hz). In addition, another two doublets at 7.47 and 8.16 δ were assigned to H_7 and H_8 ($J_{7,8}$=9.0 Hz). The lone singlet excluded the possibility that the thiocyano group could be in the 7- position, that is, 6-amino-7-thiocyanoisoquinoline

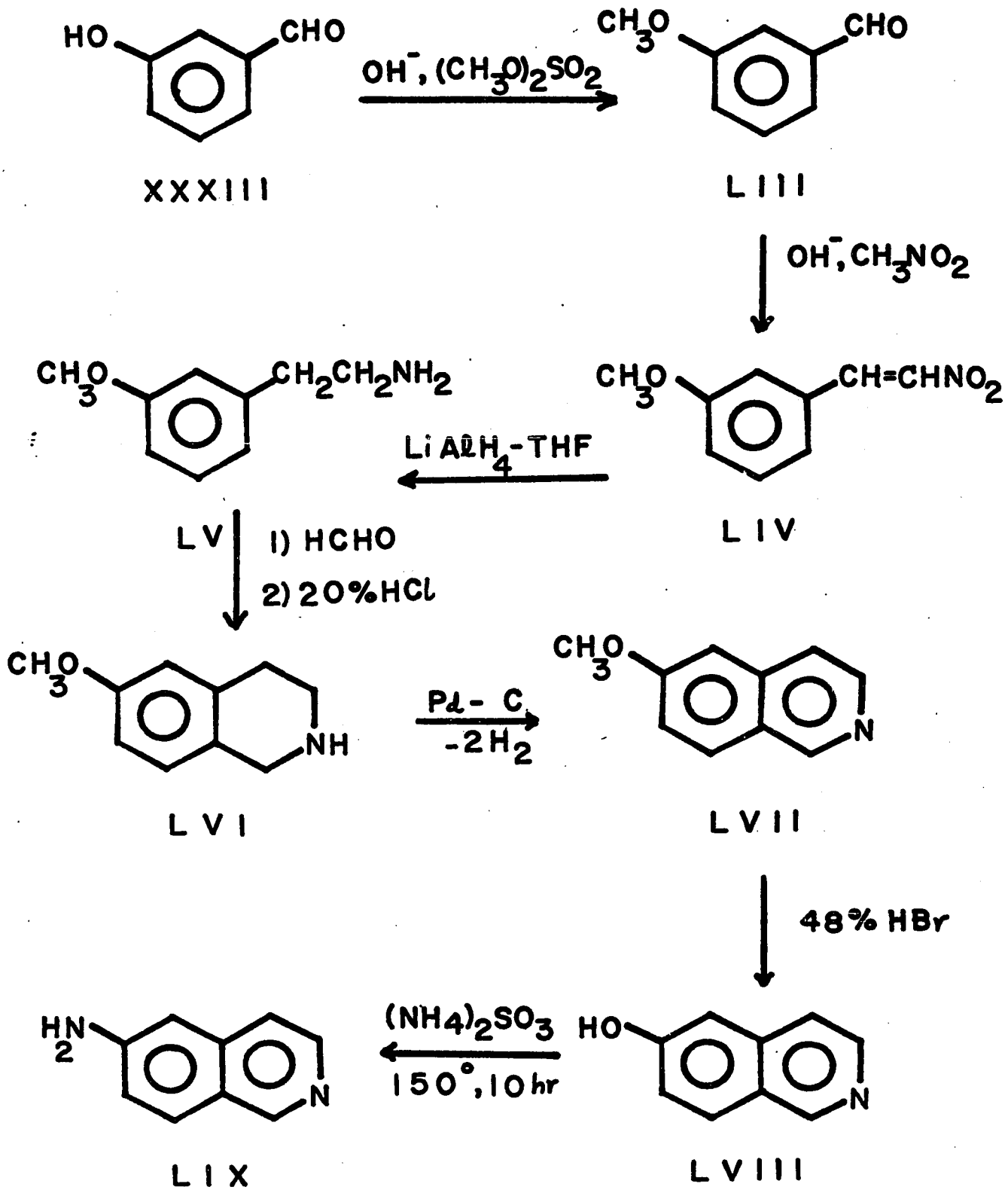
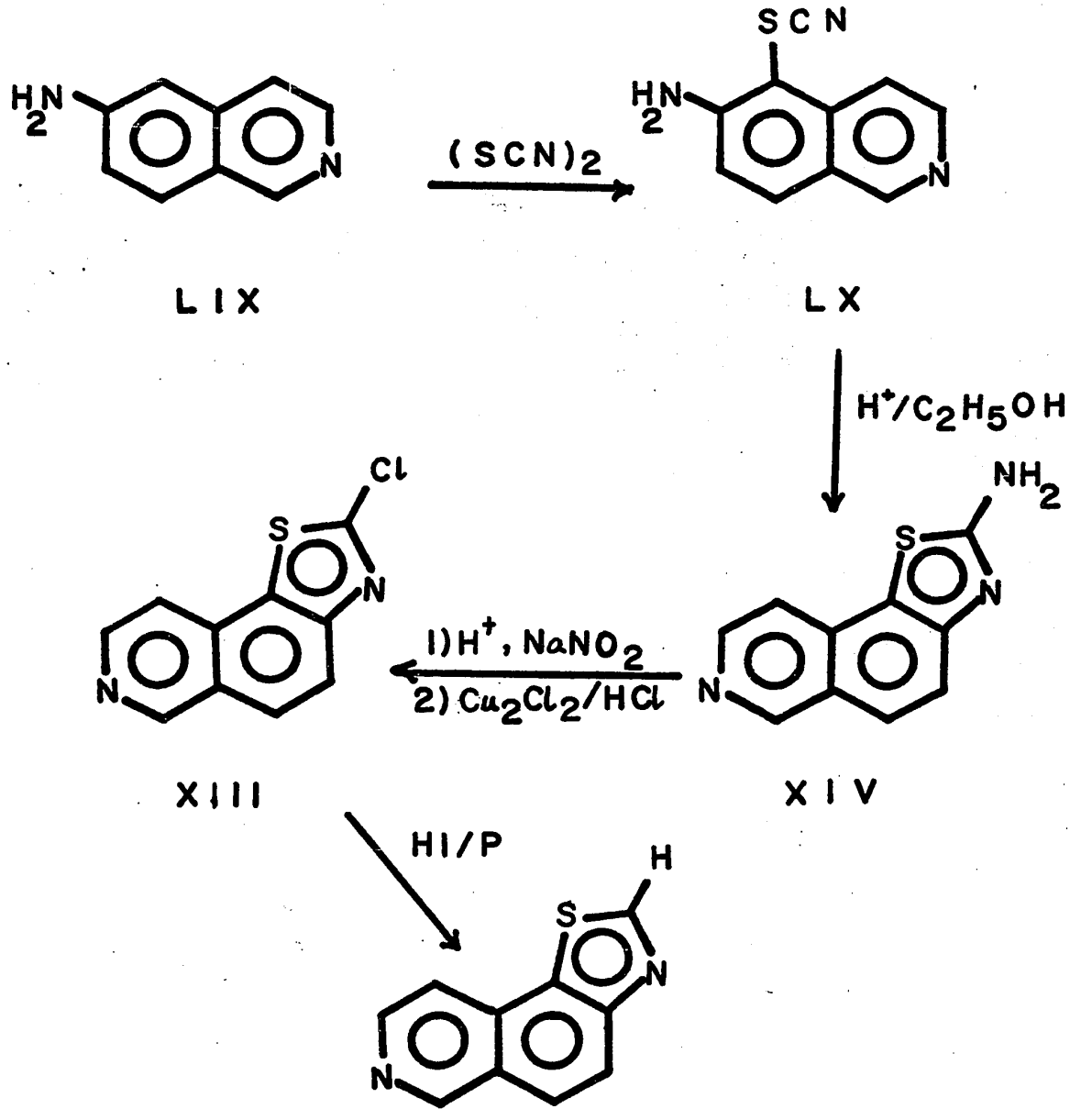

HO
CHO
OH⁻, (CH3O)2SO2
CH3O
CHO
XXXIII
LIII
OH⁻, CH3NO2
CH3O
CH2CH2NH2
CH3O
CH=CHNO2
LiAlH4-THF
LV
1) HCHO
2) 20% HCl
LIV
CH3O
NH
Pd - C
-2H2
CH3O
N
LVI
LVII
48% HBr
H2N
N
(NH4)2SO3
150°, 10 hr
HO
N
LIX
LVIII

CHART 9

would show three singlets in the nmr spectrum.

It is significant that 6-amino-5-thiocyanoisoquinoline (LX) was the only product in the thiocyanation of 6-aminoisoquinoline (LIX), whereas both 7-amino-8-thiocyanoisoquinoline (XXXVII) and 2-aminothiazolo(4,5-h)isoquinoline (X) were found in the thiocyanation of 7-aminoisoquinoline (XXXVI). As was mentioned before, the ease of cyclization depends upon the electron density on the amino nitrogen. The amino group in the 6-position is involved in resonance interaction with the ring nitrogen, in accordance with the spectroscopic studies of Short (19). The effect has also been used to explain the thiocyanation of 4-aminoisoquinoline leading to the formation of 4-amino-3-thiocyanoisoquinoline and 2-aminothiazolo(5,4-c)-isoquinoline, while in the 3-aminoisoquinoline case, only 3-amino-4-thiocyanoisoquinoline was found by the thiocyanation of 3-aminoisoquinoline.

The infrared spectrum of 2-aminothiazolo(4,5-f)isoquinoline (XIV) no longer showed the thiocyano absorption at 2148 cm^{-1} but there were two broad bands at 3305 and 3110 cm^{-1} for the primary amino group. The nmr spectrum showed a singlet at 9.30 δ for H_6 and two doublets centered at 8.53 and 7.66 δ were assigned to H_8 and H_9 respectively ($J_{8,9}$=5.9 Hz). Another two doublets centered at 8.03 and 7.74 δ for H_4 and H_5 ($J_{4,5}$=9.1 Hz) were found to overlap with a broad band centered at 7.66 δ with a re-



LIX LX XIII XIV IV

CHART IO

lative intensity equivalent to two protons due to the primary amino group protons.

2-Aminothiazolo(5,4-f)isoquinoline (XIV) was converted in 38% yield to 2-chlorothiazolo(5,4-f)isoquinoline (XIII) through the Sandmeyer reaction. The infrared spectrum of the latter compound did not show any bands in the region 3400-3100 cm^{-1}, indicating that the primary amino group had been replaced by the chlorine atom. The nmr spectrum showed two doublets centered at 8.65 and 7.73 δ for H_8 and H_9 respectively, and another two doublets at 7.74 and 8.12 δ for H_4 and H_5 ($J_{4,5}$= 6.0 Hz). The remaining singlet at higher field (9.30 δ) was assigned to the isolated proton (H_6).

Reduction of 2-chlorothiazolo(5,4-f)isoquinoline (XIII) with red phosphorus in hydriodic acid gave thiazolo(5,4-f)-isoquinoline (IV) in 55% yield. The nmr spectrum showed two singlets at lower field (9.38 and 9.19 δ) for H_6 and H_2 respectively. Two doublets at 8.65 and 7.82 δ were assigned to H_8 and H_9 ($J_{8,9}$=9.0 Hz) respectively and another two doublets at 8.12 and 7.74 δ were due to H_4 and H_5 ($J_{4,5}$=6.0 Hz). The complete synthesis of thiazolo(5,4-f)isoquinoline (IV) is outlined in Chart 10.

INFRARED SPECTRA OF ISOQUINOLINES, THIAZOLO(4,5-h)- AND THIAZOLO-(5,4-f)ISOQUINOLINES

The infrared spectra of isoquinolines, thiazolo(4,5-h)- and thiazolo(5,4-f)isoquinolines as well as their derivatives were studied in the region 4000-400 cm^{-1}. The main regions of the spectra are discussed and the principal bands are classified according to the types of vibration they represent.

The 3600-2900 cm^{-1} region

a) CH = stretching vibration :

Multiple weak bands occur in the region 3100-3000 cm^{-1} for aromatic C-H vibrations, both in the heterocyclic compounds and benzenoid hydrocarbons. In addition, many heterocyclic compounds also show relatively weaker absorptions in the region 3000-2900 cm^{-1}. Luther et al. (32) found that isoquinoline shows five bands in the region 3060-3010 cm^{-1} as well as bands at 2970 and 2940 cm^{-1}, due to C-H vibrations. Various substituted isoquinolines show one to four weaker bands in the region. For some amino-isoquinolines, the C-H stretching absorption is masked by that of N-H absorptions. However, bands at 3060 and 3040 cm^{-1} have been assigned to the C-H stretching vibrations in amino-thiocyanoisoquinolines.

The infrared spectrum of the unsubstituted thiazolo(4,5-h)isoquinoline has bands at 3092 (m), 3045 (w), 2980 (w) and 2930 (w) cm^{-1}. Various substituted thiazolo(4,5-h)isoquinolines

exhibit two to four relatively weak bands in this region. The unsubstituted thiazole(5,4-f)isoquinoline possesses bands at 3090 (m), 3038 (w), 2954 (w) et 2918 (w) cm^{-1}, while various substituted thiazole(5,4-f)isoquinolines also show two to four bands in this region.

In the spectra of isoquinolines and thiazoloisoquinolines, substituents affect these vibration absorptions, but no correlations have been made between the nature of the substituent and the position and the intensity of the C-H stretching vibrations.

b) N-H stretching vibration :

In aromatic and heterocyclic compounds, primary amines show two medium absorption bands in the region 3500-3200 cm^{-1} due to the asymmetric and symmetric stretching vibrations of the primary amine group. For the aminoisoquinolines, e.g. 5-aminoisoquinoline, there are two bands at 3410 and 3272 cm^{-1} due to the asymmetric and symmetric stretching vibrations, respectively. In some cases, a third medium band due to intermolecular hydrogen bonding appears in this region. In the amino-thiazoloisoquinolines, two broad bands for the primary amino group (asymmetric and symmetric vibrations) appeared at lower frequencies (in the region 3300-3100 cm^{-1}).

The 1700-1350 cm^{-1} region

a) C= C and C= N vibrations:

Characteristic aromatic ring stretching absorptions resulting from C= C and C= N skeletal vibrations appear in the region between 1650-1350 cm^{-1} in most heterocyclic compounds.

Isoquinoline shows eight bands in the region at 1628, 1590, 1560, 1502, 1462, 1436 and 1386 cm^{-1}. In addition to those bands, substituted isoquinolines with the groups -CONH-, $-NH_2$, and $-NO_2$ display seven to nine bands appearing in the range 1630-1600, 1590-1570, 1560-1540, 1510-1490, 1480-1440, 1420-1400 and 1380-1350 cm^{-1}. The intensity of the first two bands is greatly enhanced in isoquinolines substituted by a conjugated substituent such as the nitro group.

Bassignana (33) has found that benzothiazole has bands around 1630, 1530, 1450 and 1358 cm^{-1} in this region. These bands are due to C=N and C=C stretching vibrations. In the spectra of thiazolo(4,5-h)isoquinolines, there are seven to eight bands originating from C=N and C=C vibrations in this region and they occur usually at 1610-1590 (m), 1580-1540 (m), 1540-1510 (m), 1510-1490 (s), 1460-1440 (m), 1430-1410 (s), 1390-1370 (m) and 1360-1345 (m) cm^{-1}. Unsubstituted thiazolo(4,5-h)isoquinoline exhibits bands at 1604, 1578, 1528, 1495, 1452, 1437, 1409, 1383 and 1347 cm^{-1}. Similarly, thiazolo(5,4-f)isoquinoline shows eight to nine bands due to C=N and C=C vibrations in the range 1620-1590 (m), 1570-1550 (m), 1550-1520 (m), 1500-1485 (s), 1475-1445 (m), 1440-1410 (s), 1400-1380 (m) and 1360-1345 (s) cm^{-1}. Unsubstituted thiazolo(5,4-f)isoquinoline displays bands at 1615, 1602, 1565, 1486, 1460, 1428, 1390 and 1350 cm^{-1}.

(b) Other substituent absorptions between 1700-1300 cm^{-1}:

In this region, the primary amino group shows its deformation vibration in the range 1660-1620 cm^{-1} in both thiazoloisoqui-

nolines and isoquinolines. 5-Aminoisoquinoline and 2-aminothiazolo (4,5-h)isoquinoline show their deformation vibrations of the primary amino group at 1635 and 1650 cm^{-1} respectively. Aromatic and heterocyclic nitro compounds have bands at 1560-1515 and 1385-1345 cm^{-1} assigned to the absorption of the nitro group. The acetamido group in the isoquinolines shows its band at 1680 cm^{-1} due to the carbonyl absorption. This is in agreement with the fact that the carbonyl stretching vibration of the secondary amide group appears in the region 1680-1630 cm^{-1}.

The 1300-950 cm^{-1} region

Heterocyclic compounds show a series of characteristic bands in the 1250-1000 cm^{-1} region which may be assigned to in-plane C-H deformation and ring breathing mode. The position and the number of C-H in-plane deformation mode depend on the orientation and the number of the isolated ring hydrogen atoms (56).

Unsubstituted thiazole(4,5-h)isoquinoline has bands at 1300, 1290, 1252, 1217, 1200, 1162, 1040 and 962 cm^{-1}. Unsubstituted thiazole(5,4-f)isoquinoline shows bands at 1300, 1285, 1268, 1200, 1168, 1120, 1040, 1010 and 980 cm^{-1}. Substituents do not influence the position of these bands greatly in the spectra of thiazoloisoquinolines.

Isoquinoline was reported to have bands at 1278, 1257, 1219, 1139, 1120, 1036 and 1014 cm^{-1} (32). Substituted isoquinolines show similar patterns in this region, especially for those having the substituents at the same position.

The 900-650 cm^{-1} region

In the spectra of aromatic and heterocyclic compounds, strong bands due to the out-of-plane deformation vibration of ring hydrogens appear in this region. These bands are highly characteristic of the substitution type because their number and position depend upon the number of adjacent ring hydrogens. As the number of adjacent ring hydrogens is reduced, the absorption frequency of the out-of-plane C-H vibration usually shifts to higher frequencies. The absorption in the 770-730 cm^{-1} range was assigned to the out-of-plane bending vibration in mono-substituted aromatic compounds, while the C-H absorption of one isolated hydrogen atom appeared in the region 900-860 cm^{-1} (42).

Isoquinoline shows a very strong band at 741 cm^{-1} which may be associated with four adjacent ring hydrogen atoms (H_{5-8}). The band at 824 cm^{-1} which could originate from two adjacent hydrogen atoms (H_3, H_4) and the absorption at 858 cm^{-1}, could be due to the isolated ring hydrogen atom (H_1). For the isoquinolines substituted at 5- position, the strong bands are located in the 810-780 cm^{-1} region with a weaker band in the region 710-670 cm^{-1} and they are

assigned to three adjacent hydrogen atoms (H_6, H_7, H_8). Two bands in the region 840-810 and 890-860 cm^{-1} could originate from two (H_3, H_4) and one (H_1) ring hydrogen atoms respectively. Thus 5-nitroisoquinoline shows bands at 875, 836, 815, 795, 758, 731 and 674 cm^{-1}. The 6- and 7-hydroxy or amino-isoquinolines show at least three bands in the region. Two bands in the 840-810 cm^{-1} region are assigned to two ring hydrogen atoms on both pyridine and benzenoid rings, while a weaker band in the 900-860 cm^{-1} region is due to the isolated hydrogen atom. Thus 7-aminoisoquinoline shows bands at 830, 840 and 896 cm^{-1}. For the 5,8-disubstituted isoquinolines, the spectra are similar to those of isoquinolines mono-substituted at 6- position.

Thiazolo(4,5-h)- and thiazolo(5,4-f)isoquinolines and their derivatives show two to five bands in this region. The only prominent band the position of which remains constant throughout is the strong band in the range of 840-810 cm^{-1} which is due to the out-of-plane deformation for two adjacent hydrogen atoms on both benzenoid and pyridine rings. Most of the thiazoloisoquinolines show a medium band at 890-860 cm^{-1} resulting from the isolated hydrogen atom. While thiazolo(4,5-h)isoquinoline displays three bands at 860, 838 and 824 cm^{-1}, thiazolo(5,4-f)isoquinoline shows three bands at 859, 828 and 811 cm^{-1}.

The 650-400 cm^{-1} region

Several medium to strong bands appearing in this region are attributed to the ring deformation vibrations of aromatic compounds, both benzenoid and heterocyclic (59). The position of these bands appear to be associated with, and characteristic of, the type of substitution. In addition, the wavelength and inten-

sity of these bands serve, to a degree, to indicate the nature of the substituent on the ring.

The aromatic compound nearest to isoquinoline studied in this region is naphthalene. The absorption spectrum of naphthalene was reported to have bands at 620 and 475 cm^{-1}. Person et al. and Lippincott et al. (60, 61) assigned the band at 620 cm^{-1} to in-plane ring deformation and the band at 475 cm^{-1} to out-of-plane ring deformation.

Isoquinoline shows bands at 637, 520 and 506 cm^{-1} in this region. These bands could be analogous to those of naphthalene and the band at 637 cm^{-1} could be tentatively assigned to in-plane deformation and the bands at 520 and 506 cm^{-1} to out-of-plane deformation. Substituted isoquinolines also display three to seven bands in this region and bands constantly occur at 640-620, 550-525 and 515-490 cm^{-1}. In addition, a strong band between 570-535 cm^{-1} is observed in all 5- and 8- substituted isoquinolines which happen to be in the same region as the band arising by the out-of-plane deformation vibration in 1,2,3-trisubstituted benzenes. The frequency position of the out-of-plane ring deformation for mono-substituted benzenes appear to be dependent upon the nature of the substituent (62). However, no definite correlations could be made in the isoquinoline series.

The spectra of thiazolo(4,5-h)isoquinolines exhibit three

to six bands in this region. Two bands, the positions of which remains constant throughout, appear in the range 590-540 and 485-450 cm^{-1}. The former could be due to ring hydrogens (H_6, H_7, and H_9 in thiazolo(4,5-h)isoquinoline) similar to the out-of-plane ring deformation in 1,2,4-trisubstituted benzenes; while the latter may be associated with two protons on the benzenoid ring (H_4 and H_5) analogous to out-of-plane ring deformation vibrations for 1,2,3, 4-tetrasubstituted benzenes. In the spectra of thiazoloisoquinolines with strong electron-donating substituents such as the amino group, both bands appear at higher frequencies. Unsubstituted thiazolo(4,5-h)isoquinoline has bands at 571, 525, 505 and 473 cm^{-1}. The similarities in the pattern and position of the bands appear in the spectra of thiazolo(5,4-f)isoquinolines. Unsubstituted thiazolo(5,4-f)isoquinoline display bands at 571, 525, and 478 cm^{-1}.

Other characteristic absorptions :

The organic thiocyanates show their characteristic C≡N stretching frequency in the region 2175-2130 cm^{-1}. In the isoquinoline series, amino-thiocyanoisoquinolines always show their strong absorptions between 2150-2140 cm^{-1}.

The S-H stretching vibration generally appears as a weak band in the region 2650-2550 cm^{-1} (70). However in the amino-mercaptoisoquinolines, it is difficult to detect any band in this region.

Figure 1

Infrared Spectrum of Thiazolo(4,5-h)-isoquinoline (V11) in a KBr disc

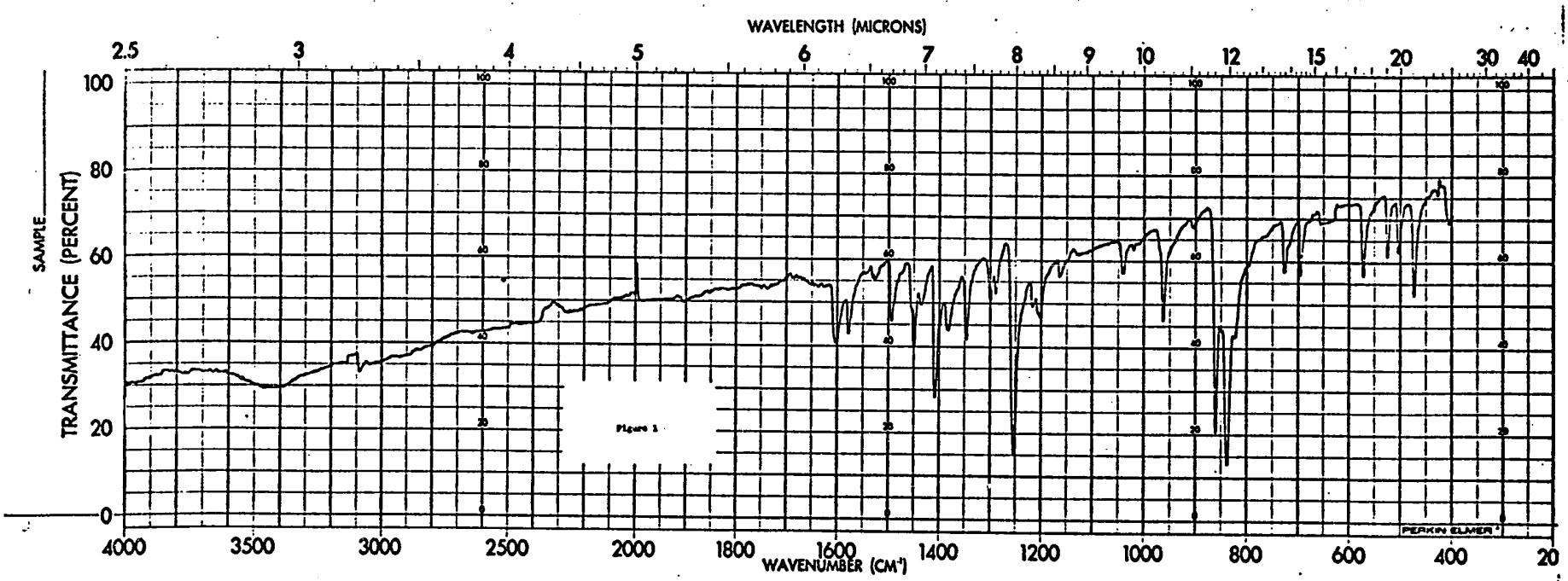
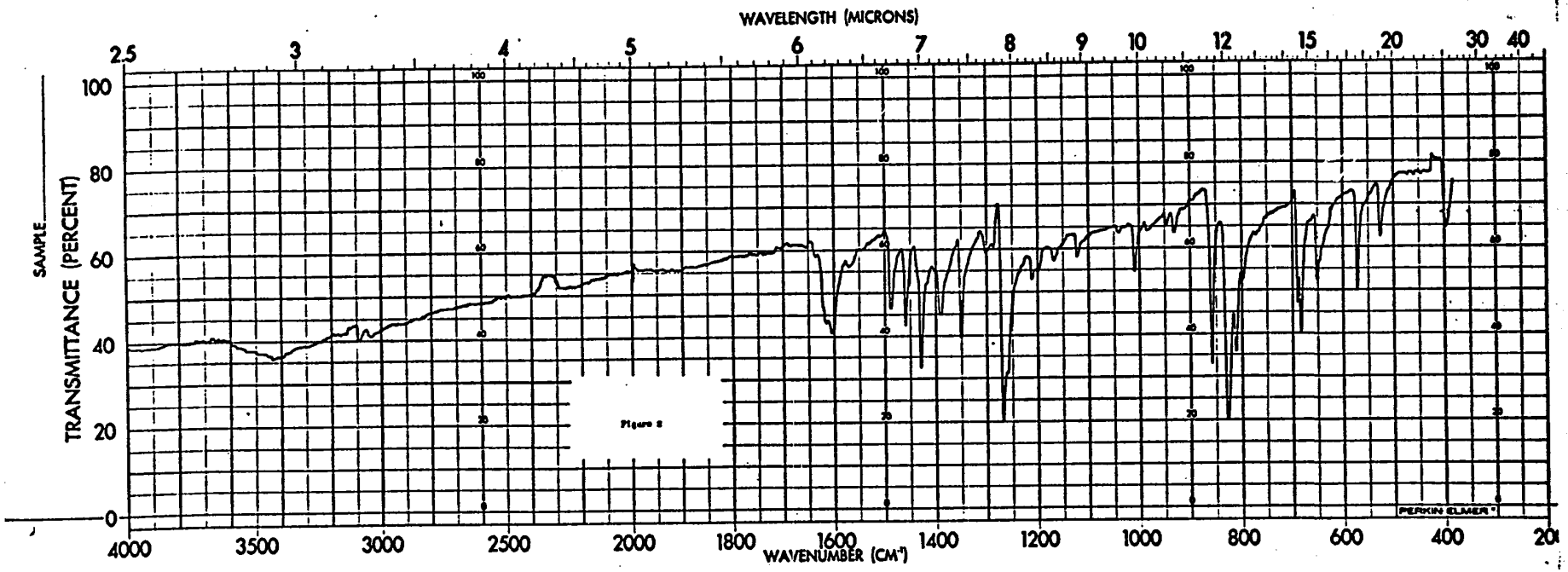

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
SAMPLE
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
20
WAVENUMBER (CM⁻¹)
PERKIN ELMER

Figure 2

Infrared Spectrum of Thiazolo(5,4-f)-isoquinoline (1V) in a KBr disc


WAVELENGTH (MICRONS)
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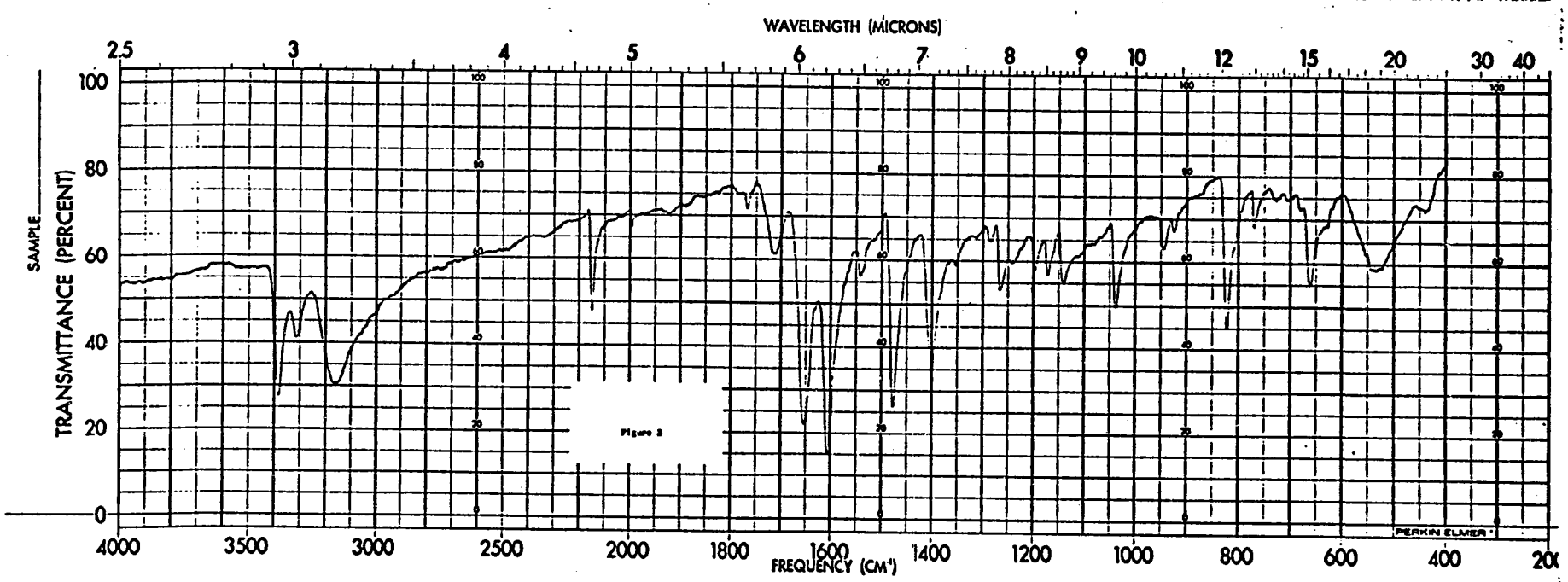
3
4
5
6
7
8
9
10
12
15
20
30
40
SAMPLE
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
WAVENUMBER (CM⁻¹)
PERKIN ELMER

Figure 3

Infrared Spectrum of 6-Amino-5-thiocyano-isoquinoline (LX) in a KBr disc


WAVELENGTH (MICRONS)
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9
10
12
15
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30
40
SAMPLE
TRANSMITTANCE (PERCENT)
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80
60
40
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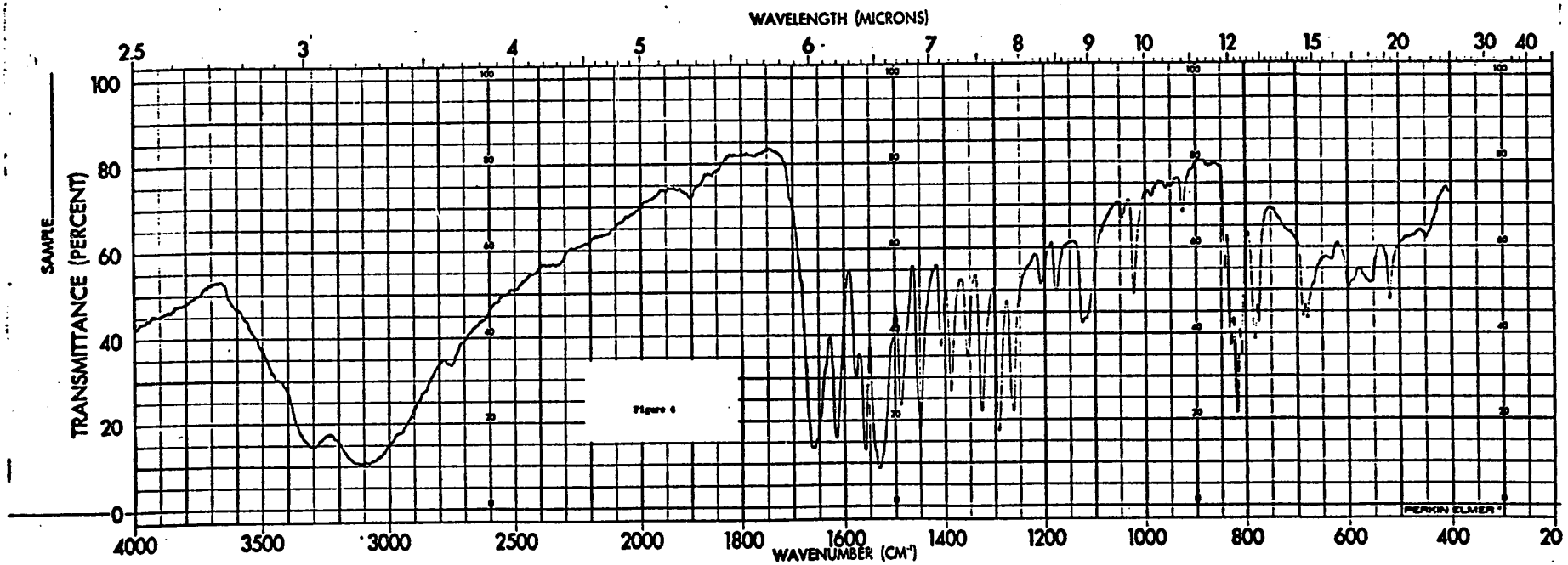
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM⁻¹)
PERKIN ELMER

Figure 4

Infrared Spectrum of 2-Aminothiazolo-(5,4-f)isoquinoline (X) in a KBr disc


WAVELENGTH (MICRONS)
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4
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6
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8
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10
12
15
20
30
40
SAMPLE
TRANSMITTANCE (PERCENT)
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80
60
40
20
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4000
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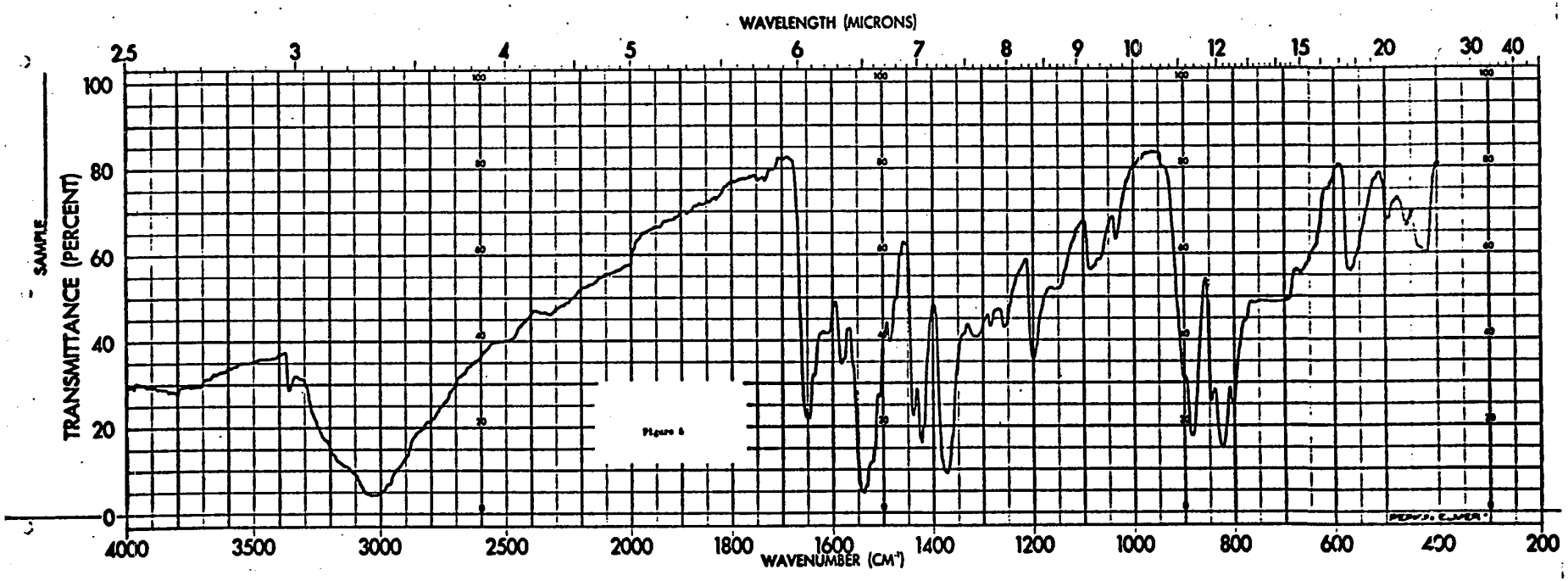
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
20
WAVENUMBER (CM⁻¹)
PERKIN ELMER

Figure 6

Figure 5

Infrared Spectrum of 2,5-Diaminothiazolo-(5,4-h)isoquinoline (XVll) in a KBr disc


WAVELENGTH (MICRONS)
2.5
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4
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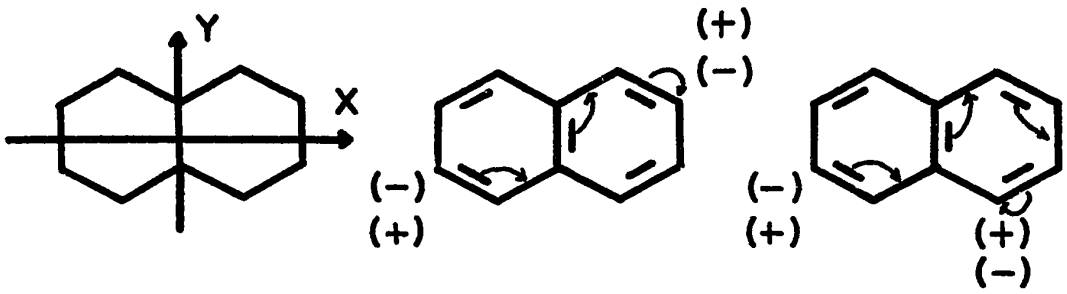
6
7
8
9
10
12
15
20
30
40
SAMPLE
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
WAVENUMBER (CM⁻¹)

ULTRAVIOLET SPECTRAL ABSORPTIONS OF ISOQUINOLINES, THIAZOLO(4,5-b)- AND THIAZOLO(5,4-f)ISOQUINOLINES

Aromatic hydrocarbons show three main types of absorption bands which are designated as α-, p- and β-bands by Clar (63). When a =CH group in aromatic hydrocarbon is replaced by = N, there is little change in the spectrum (37). The ultraviolet spectra of isoquinolines show the corresponding bands in the region 450-200 mμ . The α-bands ($\varepsilon_{max} \sim 10^2-10^3$, related to L_b bands in Platt's classification (53)) are weak and they occur at the longest wavelengths. In some cases, they show a complicated vibrational structure with fine splitting. The p-bands ($\varepsilon_{max} \sim 10^4$, related to L_a bands in Platt's classification) are of moderate intensity. The β-bands ($\varepsilon_{max} \sim 10^5$, related to B_a or B_b bands in Platt's classification) are of strong intensity and they appear at lowest wavelengths.

In the spectrum of isoquinoline, the observed red shift of the α-band is due to the presence of the nitrogen atom which creates an effect similar to the β-substitution in naphthalene (19). The α-and β-bands of naphthalene and other related compounds are assigned to longitudinally (x) polarized electronic transitions, while the p- bands are due to transversely (y) polarized electronic transition. A substituent at C-2 (or C-3) in naphthalene gives a greater polarization along the x- axis thus causing pronounced bathochromic displacement of the α - and β - bands.

On the other hand, a substituent at C-1 (or C-4), yields a greater polarization along the y- axis, rendering a large red shift of the p-band.



Osborn et al. (19) reported that 7-aminoisoquinoline, in which the substituent position is corresponding to C-3 in naphthalene, produces a considerable bathochromic shift in the α- and β- bands, but only a slight change in the p- band. It indicates that the bathochromic shift of the α- and β- bands is due to the electronic transition occuring along the x - axis. A halogen substituent, such as bromine in the 5- position, produces a greater red shift in the p- band than those of α- and β-bands, indicating that the p-band should be attributed to electronic transitions occurring along the y- axis. It may be concluded that the p- band is sensitive to the conjugative effect of the substituent rather than to the inductive effect in the isoquinoline series. This phenonmenon is also found in the ultraviolet spectra of naphthalenes and quinolines (34). An acetamido group at 5- position causes only slight changes in all the three main bands.

The ultraviolet spectra of di-substituted isoquinolines,

mainly at 5- and 8- positions, agree with the previous correlations. In the amino-thiocyanoisoquinolines, the amino group still exerts a great influence upon the spectra. The presence of the thiocyano group produces a large red shift in the α- band when placed in the 5- and 8- positions, but a slight change was found for the p- band. For example, 5-amino-8-thiocyanoisoquinoline (XL11) shows absorption bands at 214, 252 and 390 mμ relative to that of 5-aminoisoquinoline (XL) at 208, 244 and 335 mμ, further, and an increase in intensity is noticed with the α- band. The ultraviolet spectra of aminomercaptoisoquinolines resemble those of aminoisoquinolines.

A significant feature of the absorption spectra of thiazoloisoquinolines is that the three corresponding bands (α-, p- and β- bands) are similar to those of phenanthrenes. These bands are due to the $\pi - \pi^*$ transitions and are in agreement with the classification for the aromatic and six-membered heteroaromatic systems. It has been found that there is a little effect on the energy of the electronic transitions in aromatic compounds accompanying the replacement of a =CH group by -N= and replacement of a -CH=CH- group by -S- (35). The wavelength order of those bands is $\alpha > p > \beta$. The band positions are influenced by substitution effects.

The annelation effects also play an important role in these compounds. In general, linear and angular annelations of the aromatic hydrocarbons and their aza- analogs result in the batho-

chromic shift of the three absorption bands. Similarly, the benzoderivatives of the five membered heteroaromatic compounds show also a marked red shift of the entire spectra. The fusion of a thiazole ring to benzene, naphthalene or quinoline displaced all three bands of the parent compounds to longer wavelengths (9,44,54).

There is a remarkable difference between the spectra of angular and linear annelations (63). The p- bands shift strongly to longer wavelength with linear annelation, but angular annelation produces only small shifts. The β-bands move moderately to longer wavelengths with both angular and linear annelations, however the linear annelation has only one narrow β-band which is broader in the angular annelation and is split into two or more bands in many cases. The α-bands disappear under the p- bands in both types and then emerge between the p- and β-bands in the linear annelation in the polyaromatic hydrocarbons.

The fusion of the thiazole ring to isoquinoline shows a similar displacement towards longer wavelength. Thiazolo(4,5-h)-isoquinoline has its main absorption bands at 254, 288 and 355 mμ and shows a bathochromic displacement of all the three bands relative to those of the isoquinoline bands at 217, 266 and 317 mμ. Attempts were made to study the effects of the substituent in the 2-position in the thiazolo(4,5-h)isoquinoline with regard to the position of these bands. It was found that an electron-donating substituent such as the amino or acetamido group shows a larger bathochromic.

shift of the α- band than that of the p- band. Chloro-subtituent however, causes a small red shift of the p- band and little change was found in the α- and β- bands. This tends to suggest that the conjugation effect of the chloro-substituent predominates over the inductive effect.

The ultraviolet spectra of thiazolo(5,4-f)isoquinolines showed marked similarities to those of thiazolo(4,5-h)isoquinolines except that three absorption bands of the former occurred at longer wavelength than the corresponding bands of the latter.

TABLE [illegible] I

ULTRAVIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOG ε VALUES OF MONO-SUBSTITUTED ISOQUINOLINES IN ABSOLUTE ETHANOL

COMPOUND	α-band		p-band		β-band	
	mμ	logε	mμ	logε	mμ	logε
5-AMINO (XL)	335	3.64	244	4.04	208	4.26
5-ACETAMIDO (L)	320	3.86	268 290-294	4.27 3.90	220	4.62
5-BROMO (XL1V)	312 325	3.70 3.76	276 286	3.86 3.82	220	4.76
5-NITRO (XXX1X)	330	3.72	230-232	4.02	214	4.49
6-AMINO (L1X)	335-340	3.56	296-298 308	3.91 3.95	242	4.54
6-HYDROXY (LV111)	320	3.25	286	3.66	230	4.69
7-AMINO (XXXV1)	360	3.42	280	3.97	236 214	4.50 4.16
8-AMINO (XLV1)	360	3.93	242	4.39	212	4.63
7-HYDROXY (XXXV)	335-340	3.35	258-260 266-268	3.48 3.49	224	4.45

TABLE 11

ULTRAVIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOGε VALUES OF DI-SUBSTITUTED ISOQUINOLINES IN ABSOLUTE ETHANOL

COMPOUND	α-band mμ	logε	p- band mμ	logε	β- band mμ	logε
5-AMINO-8-THIOCYANO (XL11)	345 390	3.95 3.99	252	4.16	214	4.41
8-AMINO-5-THIOCYANO (XLV111)	330 370	3.74 388	252	4.11	214	4.41
6-AMINO-5-THIOCYANO (LX)	340	3.55	292 302	3.80 3.72	248 204	4.58 3.84
8-AMINO-5-MERCAPTO (XL1X)	335	3.98	244	4.40	214-216	4.41
5-AMINO-8-MERCAPTO (XL11)	340	3.82	254	4.06	214	4.31
5-BROMO-8-NITRO (XLV)	330	3.80	296	3.78	220	4.40
5-ACETAMIDO-8-NITRO (L1)	350	3.93	230	4.32	212	4.27
5-ACETAMIDO-8-AMINO (L11)	370	3.72	248	4.13	210	4.40

TABLE 111

ULTRAVIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOG ε VALUES OF THIAZOLO(4,5-h)ISOQUINOLINE AND ITS DERIVATIVES IN ABSOLUTE ETHANOL

COMPOUND	α-band mμ	log ε	p-band mμ	log ε	β-band mμ	log ε
UNSUBSTITUTED (V11)	318-320	3.55	278	3.71	227	4.24
			288	3.69	254	4.58
	335	3.55				
2-CHLORO (1X)	335	3.51	288-292	3.77	228	4.14
	320	3.47			254	4.50
2-AMINO (X)	360	3.71	296	4.28	206	4.38
			308	4.29	228	4.40
					266	4.83
2-ACETAMIDO (X11)	335	3.74	300	4.26	206	4.45
			312	4.22	238	4.40
					270	4.80
2-HYDROXY (X1)	350	3.65	274	4.26	216	4.40
					252	4.54

TABLE IV

ULTRAVIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOGε VALUES OF THIAZOLO(5,4-f)ISOQUINOLINE AND ITS DERIVATIVES IN ABSOLUTE ETHANOL

COMPOUND	α-band mμ	logε	p-band mμ	logε	β-band mμ	logε
UNSUBTITUTED (IV)	320 335	3.60 3.60	272-274 306	3.75 3.45	244	4.66
2-CHLORO (XIII)	320	3.55	278 306-308	3.76 3.44	250	4.59
2-AMINO (XIV)	a +		318	3.87	266 206	4.68 4.02
2-ACETAMIDO (XVI)	333 318	3.54 3.78	306 300	3.83 3.82	262 272 240 206	4.54 4.55 4.16 4.05
2-HYDROXY (XV)	317	4.02	272	4.17	252 220-221	4.73 4.24

+ a) No α-band was found in the region 200-450 mμ. The intense yellow color of the compound indicated that the α-band had shifter to the visible region.

Figure 6

Ultraviolet Spectrum of Thiazolo(4,5-h)-isoquinoline (VII) in absolute ethanol

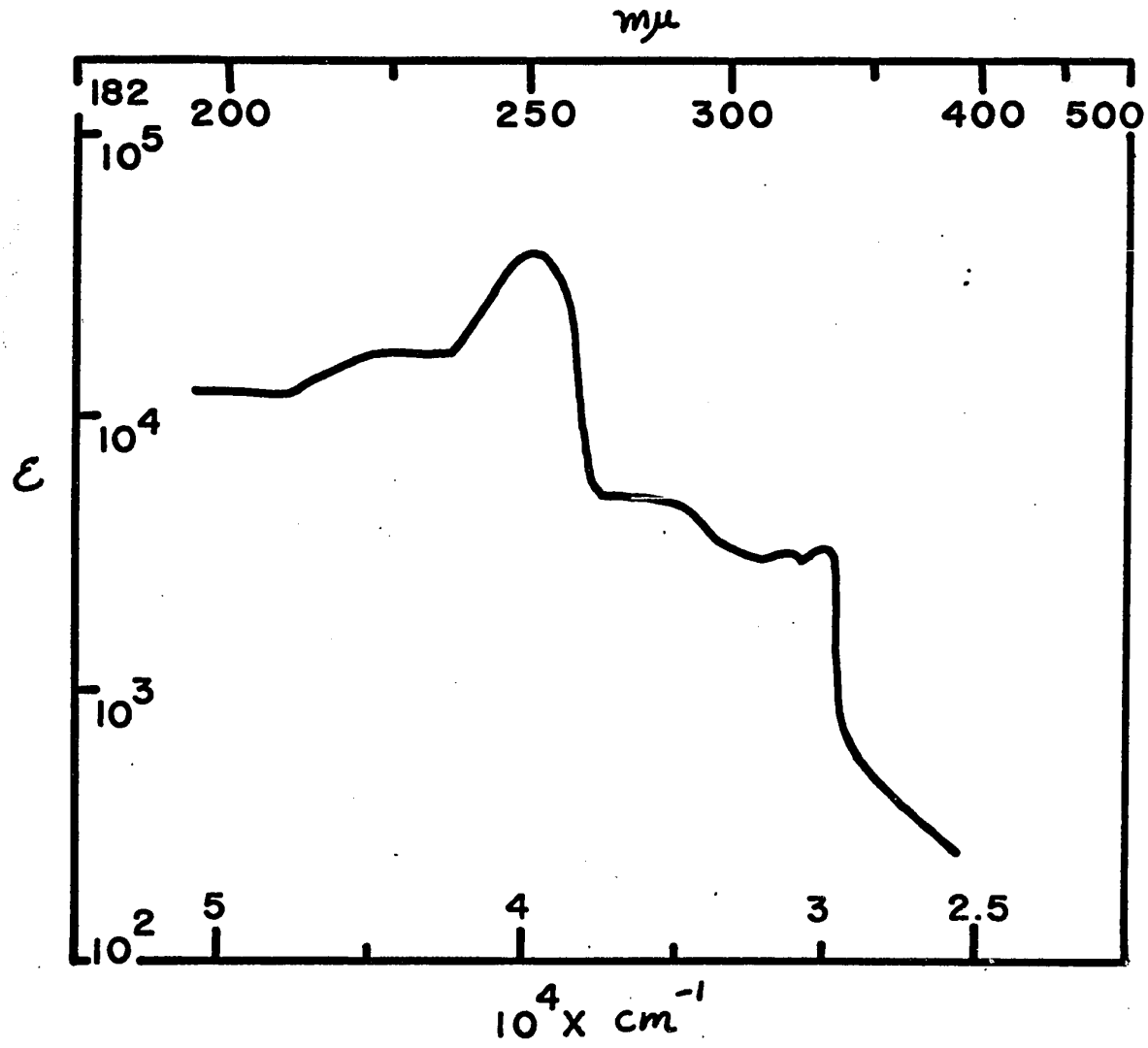


FIGURE 6

Figure 7

Ultraviolet Spectrum of Thiazolo(5,4-f)-isoquinoline (IV) in absolute ethanol

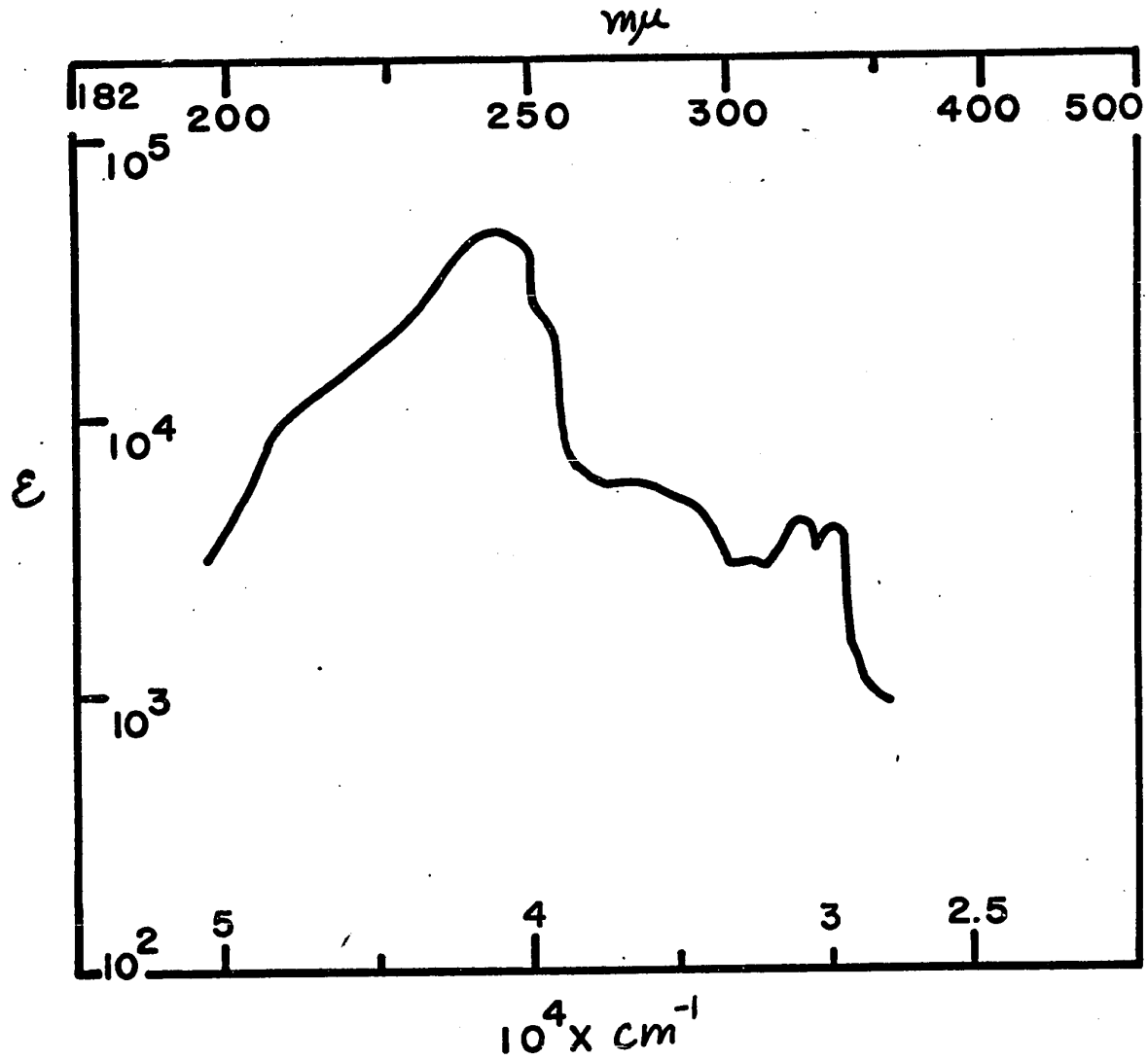


FIGURE 7

Figure 8

Ultraviolet Spectrum of 2,5-Diaminothiazolo-(5,4-h)isoquinoline (XVII) in absolute ethanol

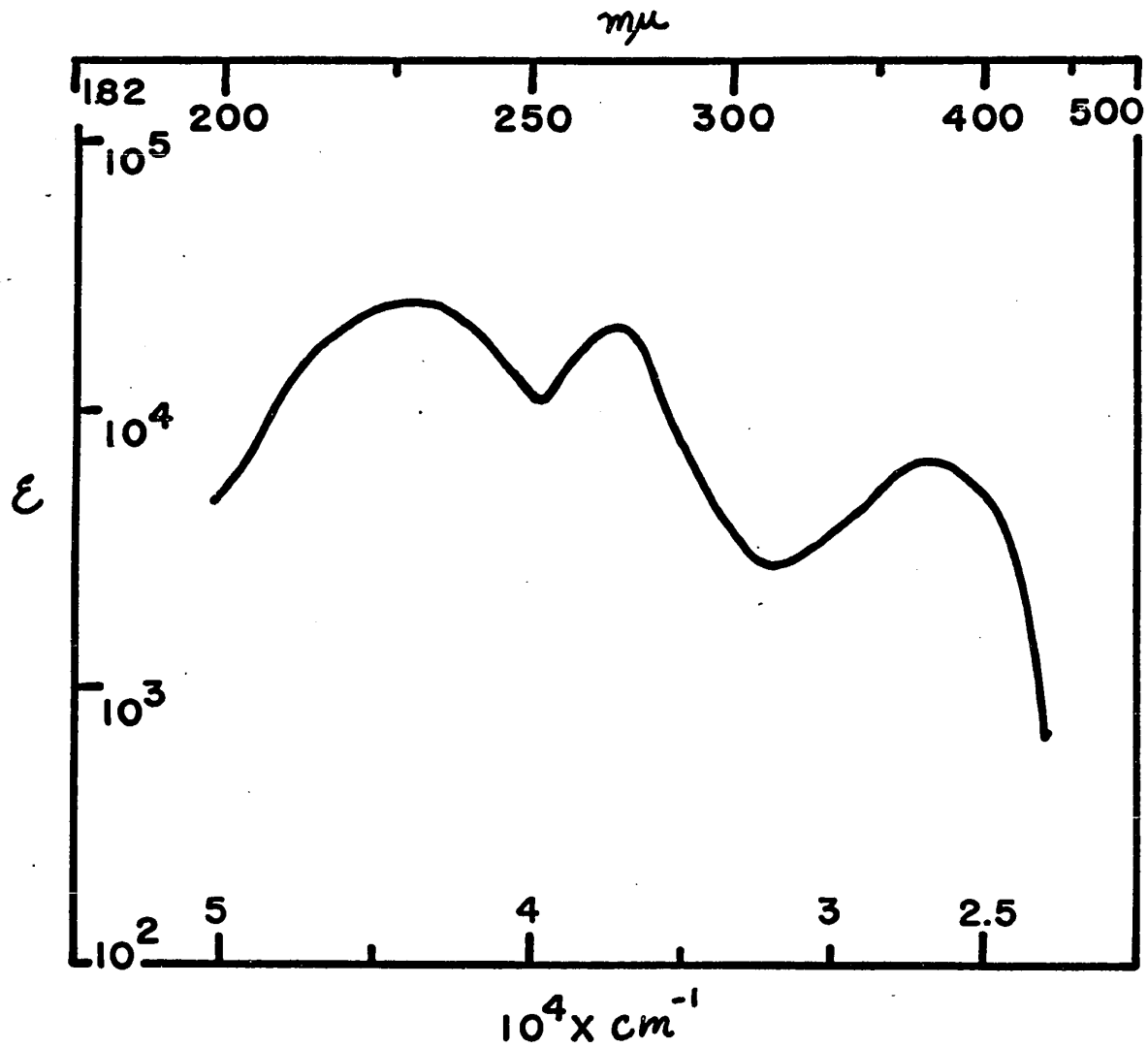


FIGURE 8

Figure 9

Ultraviolet Spectra of 6-Amino-5-thiocyano-isoquinoline (LX) and 2-Aminothiazolo(5,4-f)-isoquinoline (XVII) in absolute ethanol

Figure 9

Ultraviolet Spectra of 6-Amino-5-thiocyano-isoquinoline (LX) and 2-Aminothiazolo(5,4-f)-isoquinoline (XVll) in absolute ethanol

- - - - - - - - - - - XVll

_____ LX

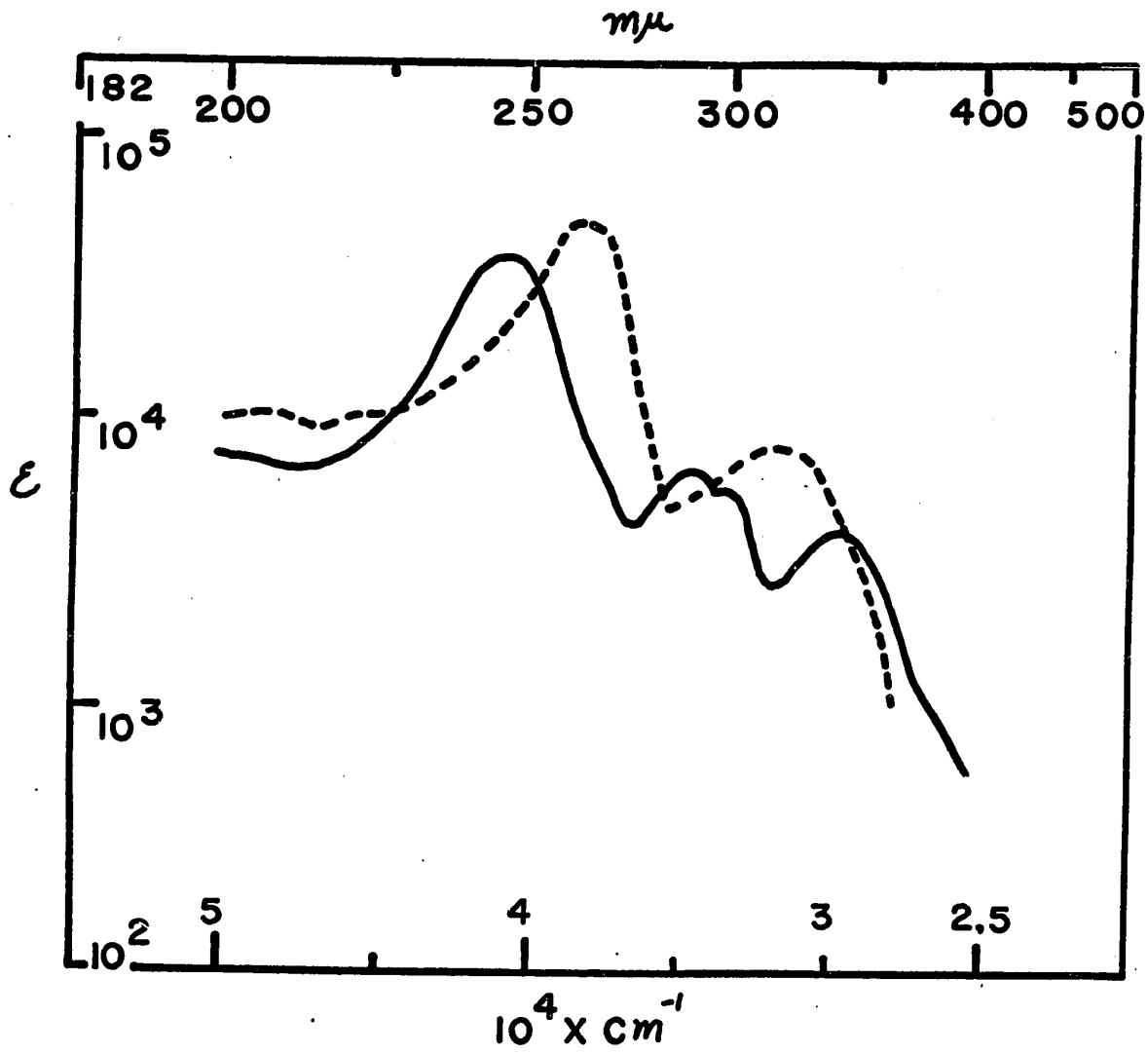


FIGURE 9

N. M. R. SPECTRA OF ISOQUINOLINES, THIAZOLO(4.5-h)- and THIAZOLO-(5,4-f)ISOQUINOLINES

(a) N. M. R. Spectra of Isoquinolines

A survey of the literature reveals that only a few nmr spectra of substituted isoquinolines have been recorded (47, 48, 49, 55). The spectrum of isoquinoline (46) shows a singlet at lower field (9.26 δ) assigned to H_1. H_3 produces a doublet centered at 8.52 δ, forming a part of an AB quartet from H_3 and H_4. The band from H_3 is expected at lower field because H_3 is in proximity to N atom. All the spectra of the substituted isoquinolines studied show the same pattern for H_1 and H_3 (appearing as singlet and doublet respectively), only the position of these bands is changed depending upon the nature of the substituent. The coupling constant $J_{3,4}$ in isoquinolines is approximately 6.0 Hz. In the spectrum of isoquinoline, four nonequivalent protons on the benzenoid ring give a complicated pattern in the region 7.95-7.20 δ . The bands for H_4 also fall in this region.

For the mono-substituted isoquinolines with the substituents on the benzenoid ring, three remaining benzenoid protons form an ABX or ABC system. The nmr spectrum of 6-aminoisoquinoline (LIX) shows a typical ABX pattern due to H_5, H_7 and H_8. Theoretically it can have twelve lines since each of the original four AB lines are split into doublets and the X line is split into a quartet. Also, there are two additional lines from combination transition, usually too weak to be observed (50).

In the spectrum of 6-aminoisoquinoline, the ABX pattern is simplified as J_{AX} is almost zero. The nature of splitting clearly shows that the quartet centered at 7.11 δ is due to H_7 ($J_{5,7}$=2.4 Hz and $J_{7,8}$=9.0 Hz). The A part of the ABX system (H_5) corresponds to the doublet centered at 6.83 δ ($J_{5,7}$=2.4 Hz). The assignment of the remaining bands for the protons H_4 and H_8 is made by noting that H_4 is a part of an AB (H_3 and H_4) system and H_8 is a part of an ABX system. Thus, the doublet centered at 7.79 δ is attributed to H_8 ($J_{7,8}$=9.0 Hz) and the doublet centered at 7.38 δ is due to H_4 ($J_{3,4}$=6.0 Hz) (51).

In the spectrum of 5-aminoisoquinoline (XL), three benzenoid protons form an ABC system. A triplet at higher field (6.48 δ) is assigned to the A part of the ABC system (H_6). The doublet centered at 7.37 δ with a relative intensity equivalent to two protons is due to H_7 and H_8. The analysis of the complicated ABC system is usually carried out by computer methods utilizing an iterative technique for calculation of the line positions and their intensities (50).

In the spectra of many mono-substituted isoquinolines, the doublets at higher field assigned to H_4 are superimposed on the multiplet of the aromatic protons on the benzenoid ring. These produce complex spectra which can only be partially analysed. Some inaccuracy will result in chemical shift determination when attempts are made to

assign a band to H_4 on the pyridine ring in partially resolved spectra. It is therefore not possible to assign bands to all protons of the benzenoid ring. Hence for the discussion of the substituent effects, only the range covered by the benzene ring protons will be shown. The resulting chemical shifts and spin-spin constants of the substituted isoquinolines are shown in Table 5 and 6.

As can be seen, the spectrum may appear at the lower (or the higher) field relative to the isoquinoline spectrum depending upon the nature of the substituent. A general correlation has been found that if an electron-withdrawing substituent such as the nitro group is present, the whole spectrum occurs at the lower field with respect to that of isoquinoline. On the other hand, compounds with an electron-donating substituent such as an amino group shifts to the higher field compared with isoquinoline. Halogen substituent such as bromine has little effect on the proton signals. It indicates that the inductive effect of the bromine is compensated by the effect of conjugation.

5-and 8- Disubstituted isoquinolines give simple spectra in which two benzenoid protons form a typical AB quartet. In amino-thiocyanoisoquinolines, the upfield shift of the band is observed. The presence of an electron withdrawing substituent (e. g., thiocyano group) in any of these compounds counteracts the up-field

shift of the amino group. Hence, the corresponding chemical shift of the observed bands is similar to that of isoquinoline.

A nitro substituent at 8- position on the benzenoid ring in di-substituted isoquinolines shifts the whole spectrum to the lower field. The isolated proton at 1- position experiences a considerable downfield displacement due to the de-shielding effect of the highly anisotropic nitro group. A similar effect of H_8 in 1-nitronaphthalene has been observed by Wells and Alcorn (52). The band of H_8 occurs at 8.36 δ , while H_5 occurs at 8.18 δ .

The whole spectrum of a di-substituted isoquinoline with an acetamido group on benzenoid ring is shifted to the lower field. The downfield shift may be rationalized as a result of the long range de-shielding effect by the amide carbonyl group. This phenomenon has also been observed in most of the acetamido derivatives of aromatic and heterocyclic compounds (45).

In the amino-mercaptoisoquinolines, 5-amino-8-mercapto-isoquinoline (XLIII) and 8-amino-5-mercaptoisoquinoline (XLIX), only a small change was observed in the corresponding chemical shift relative to the aminoisoquinolines. The isolated proton at 1- position in XLIX shows the downfield displacement comparable to that of XLIII. This may arise from the de-shielding effect of the aniso-tropic amino group. The difference of the shift in both compounds for

H_1 was found to be 0.3 p. p. m.. Comparable values (0.5 p. p. m.) for the difference of chemical shifts between 8-aminoisoquinoline and 6-amino- or 7-aminoisoquinoline were also obtained.

(b) N. M. R. Spectra of Thiazolo(4,5-h)- and Thiazolo(5,4-f)isoquinolines

Thiazolo(4,5-h)isoquinoline has six aromatic protons. In comparison to isoquinoline, the spectrum of the benzenoid ring of thiazolo(4,5-h)isoquinoline is simplified since two protons are replaced by the thiazole ring. The pattern of the spectrum of the pyridine ring of thiazolo(4,5-h)isoquinoline is similar to that of isoquinoline. In the spectrum of thiazolo(4,5-h)isoquinoline in deuteriochloroform, it shows that two doublets at 8.68 and 7.78 δ are assigned to H_7 and H_6 (corresponding to H_3 and H_4 in isoquinoline nucleus) respectively, and a singlet at lower field (9.40 δ) is assigned to H_9 (H_1 in the isoquinoline). The coupling constant $J_{6,7}$ is 5.8 Hz. A downfield displacement was observed for the bands of H_7 and H_9 as compared to the positions of the corresponding protons of isoquinoline.

In addition to the singlet at 9.40 δ assigned to H_9, another singlet at 9.14 δ is attributed to H_2. Such an assignment to H_9 is in agreement with the nmr spectra of most of the thiazolo-(4,5-h)isoquinolinesin which the singlet at lower field shows a fine structure due to coupling. In this instance, H_9 couples with both H_6 and H_7. The coupling of H_2 however is not favoured because of the large se-

paration of the proton in the thiazole ring and the protons of the benzene ring. The comparison of the nmr spectra of thiazolo(4,5-h)- and thiazolo(5,4-f)isoquinolines also supports this assignment. The chemical shift between H_2 and H_9 is 0.26 p. p. m. for thiazolo-(5,4-f)isoquinoline, while thiazolo(4,5-h)isoquinoline shows a shift of 0.35 p. p. m.. The difference in these chemical shift is probably due to the ring current effect causing H_9 of thiazolo(4,5-h)-isoquinoline to be shifted downfield by both the benzene and thiazole rings.

The two remaining aromatic protons in the thiazolo(4,5-h)-isoquinoline also exhibit a typical AB pattern of two doublets centered at 8.33 and 7.82 δ ($J_{4,5}$=9.0 Hz). The magnitude of the coupling constant is in accordance with the ortho coupling occurring between H_4 and H_5 observed in the nmr spectrum of 2,7-dimethylthiazolo(5,4-f)-quinoline (44). However, the assignment for both H_4 and H_5 is not possible in the present work.

The nmr spectrum of thiazolo(5,4-f)isoquinoline is analogous to that of thiazolo(4,5-h)isoquinoline. Two singlets at 9.38 and 9.10 δ are assigned to H_6 and H_2 respectively. The doublets assigned for H_8 and H_9 with a corresponding coupling constant $J_{8,9}$=5.8 Hz appear at 8.68 and 7.68 δ respectively. In addition, another two doublets centered at 8.12 and 7.74 δ are assigned to H_4 and H_5 ($J_{4,5}$=6.0 Hz). Similarly, it is not possible to differentiate between H_4 and H_5. The nmr spectra of the derivatives of thiazolo-

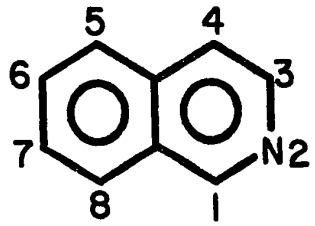
(4,5-h)- and thiazolo(5,4-f)isoquinolines, the coupling constants $J_{4,5}$ and $J_{6,7}$ ($J_{4,5}$ and $J_{8,9}$ in the thiazolo(5,4-f)isoquinoline series) remain essentially unchanged.

Attempts were made to study the substituent effect on the chemical shifts on the ring protons in both thiazolo(4,5-h)- and thiazolo(5,4-f)isoquinolines at the 2- position. Generally, an electron-donating substituent, such as the amino group in the thiazoloisoquinolines, shifts the spectrum to higher field with respect to thiazolo(4,5-h)isoquinoline itself. Due to the de-shielding effect by the amide carbonyl group, the spectra of acetamidothiazoloisoquinolines show a downfield shift of the proton bands. Halogen substituent, such as chlorine, shows little effect compared with the unsubstituted thiazoloisoquinolines.

It should be pointed out however, that solvent and temperature may exert some influence on chemical shift. Normally, little change in chemical shift will be expected for the spectra obtained at different temperatures and in different solvents, such as chloroform and dimethyl sulfoxide. The large solvent effects are caused by the formation of π-complexs with acetone, acetonitrile, pyridine and dimethylformamide (23).

TABLE V

NMR SPECTRA OF DI-SUBSTITUTED ISOQUINOLINES



COMPOUND	Chemical Shifts (δ) H_1	H_3	H_4	H_6	H_7	H_8	Other	J (Hz) $J_{3,4}$	$J_{6,7}$
5-ACETAMIDO-8-NITRO (L1) a	9.90	8.73	8.30	8.42 to8.48			3.25(CH_3)	6.1	
5-ACETAMIDO-8-AMINO (L11) a	9.30	8.39	7.61	7.44	6.72		3.10(CH_3) 6.08(NH_2)	6.0	8.7
5-BROMO-8-NITRO (XLV) a	9.53	8.60	7.88	8.0 to8.15				6.0	
5-AMINO-8-MERCAPTO (XL111) a	9.33	8.43	8.02	6.71	7.31		6.57(NH_2)	5.9	8.7
8-AMINO-5-MERCAPTO (XL1X) b	9.57	8.37	7.78	7.37	6.66				8.6
5-AMINO-8-THIOCYANO (XL11) a	9.64	8.66	8.19	6.97	7.87		6.88(NH_2)	5.8	8.7

TABLE V (cont.)

COMPOUND	Chemical Shifts (δ) H_1	H_3	H_4	H_6	H_7	H_8	Other	J (Hz) $J_{3,4}$	$J_{6,7}$
6-AMINO-5-THIOCYANO (LX) b	9.23	8.53	8.26		7.47	8.16		6.0	9.0
8-AMINO-5-THIOCYANO (XLVIII) a	9.64	8.65	7.95	7.89	6.65		7.10(NH_2)	6.0	9.0

(a) In DMSO-d_6 solution (b) In acetic acid-d_4 solution

TABLE VI

NMR SPECTRA OF MONO-SUBSTITUTED ISOQUINOLINES

COMPOUND	Chemical Shifts (δ) H_1	H_3	H_4	H_6	H_7	H_8	H_5	Other	J (Hz) $J_{3,4}$
UNSUBSTITUTED (XXXVIII) a	9.22	8.52	c	(7.23			-7.90)		6.0
5-AMINO (XL) a	9.18	8.47	7.57	(6.80		-7.46)		4.37(NH_2)	6.0
6-AMINO (LIX) b	8.94	8.24	c		(6.77		-7.90)	5.98(NH_2)	6.0
7-AMINO (XXXVI) b	9.00	8.20	c	d		(7.00	-7.80)	4.10(NH_2)	6.0
8-AMINO (XLVI) b	9.53	8.37	c	(6.67	-7.65)		d	6.05(NH_2)	6.0
5-NITRO (XXXIX) b	9.48	8.73	c	(7.70		-8.71)			6.0

TABLE VI (cont.)

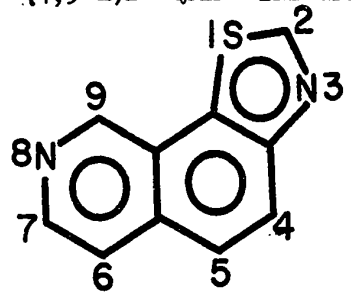
COMPOUND	Chemical Shifts (δ)								J (Hz)
	H_1	H_3	H_4	H_6	H_7	H_8	H_5	Other	$J_{3,4}$
5-ACETAMIDO (L) b	9.30	8.54	c	(7.45		-8.20)		2.22(CH_3)	6.0
5-BROMO (XLIV) a	9.24	8.66	c	(7.25		-8.10)			6.0
6-HYDROXY (LVIII) b	9.22	8.45	7.65		(7.30		-8.17)	9.18(OH)	6.0
7-HYDROXY (XXXV) b	9.16	8.35	c	d		(7.34-7.98)		7.75(OH)	5.9

(a) In $CDCl_3$ solution (b) In DMSO-d_6 solution (c) H_4 absorbs in the same region as H_6, H_7, H_8 (or H_5)

(d) H_5 or H_8 absorb in the same region as H_6 and H_7

TABLE VII

NMR SPECTRA OF THIAZOLO(4,5-h)ISOQUINOLINE AND ITS DERIVATIVES



COMPOUND	Chemical Shifts (δ)							J (Hz)	
	H_4	H_5	H_6	H_7	H_9	H_2	Other	$J_{4,5}$	$J_{6,7}$
UNSUBSTITUTED (VII) a	7.82 or8.33	8.33 or7.82	7.78	8.62	9.40	9.14		5.9	9.0
2-CHLORO (IX) a	7.84 or8.04	8.04 or7.84	7.59	8.67	9.32			5.9	9.0
2-AMINO (X) b	7.84	8.04	d	8.47	9.26		3.39(NH_2)	5.8	
2-ACETAMIDO (XII) b,c,	8.22 or8.43	8.43 or8.22	8.21	8.91	9.79		2.61(CH_3)	5.8	9.0
2-HYDROXY (XI) b	7.51 or8.24	8.24 or7.51	7.59	8.53	9.32			5.8	8.9

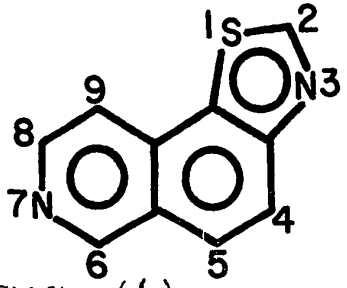
TABLE VII (cont.)

(a) In $CDCl_3$ solution (b) In DMSO-d_6 solution (c) At high temperature (160°)

(d) H_6 absorbs in the same region as H_4 and H_5

TABLE V111

NMR SPECTRA OF THIAZOLO(5,4-f)ISOQUINOLINE AND ITS DERIVATIVES



COMPOUND	Chemical Shifts (δ)							J (Hz)	
	H_4	H_5	H_6	H_8	H_9	H_2	Other	$J_{4,5}$	$J_{6,7}$
UNSUBSTITUTED (1V) a	7.74 or8.12	8.12 or7.74	9.38	8.65	7.82	9.19		6.0	9.0
2-CHLORO (X111) a	7.74 or8.12	8.12 7.74	9.30	8.65	7.73			6.0	8.7
2-AMINO (X1V) b	7.80	to8.15	9.30	8.53	7.66		d (NH_2)	5.9	
2-ACETAMIDO (XV1) b	8.20	to8.35	9.56	8.82	8.12		2.51(CH_3)	5.8	
2-HYDROXY (XV) b	7.58 or7.90	7.90 7.58	9.12	8.49	7.93			5.8	9.0

(a) In $CDCl_3$ solution (b) In DMSO-d_6 solution (c) At high temperature (160°)

(d) NH_2 absorbs in the same region as H_4 and H_5

Figure 10

NMR Spectrum of Thiazolo(4,5-h)isoquinoline

(VII) in $CDCl_3$

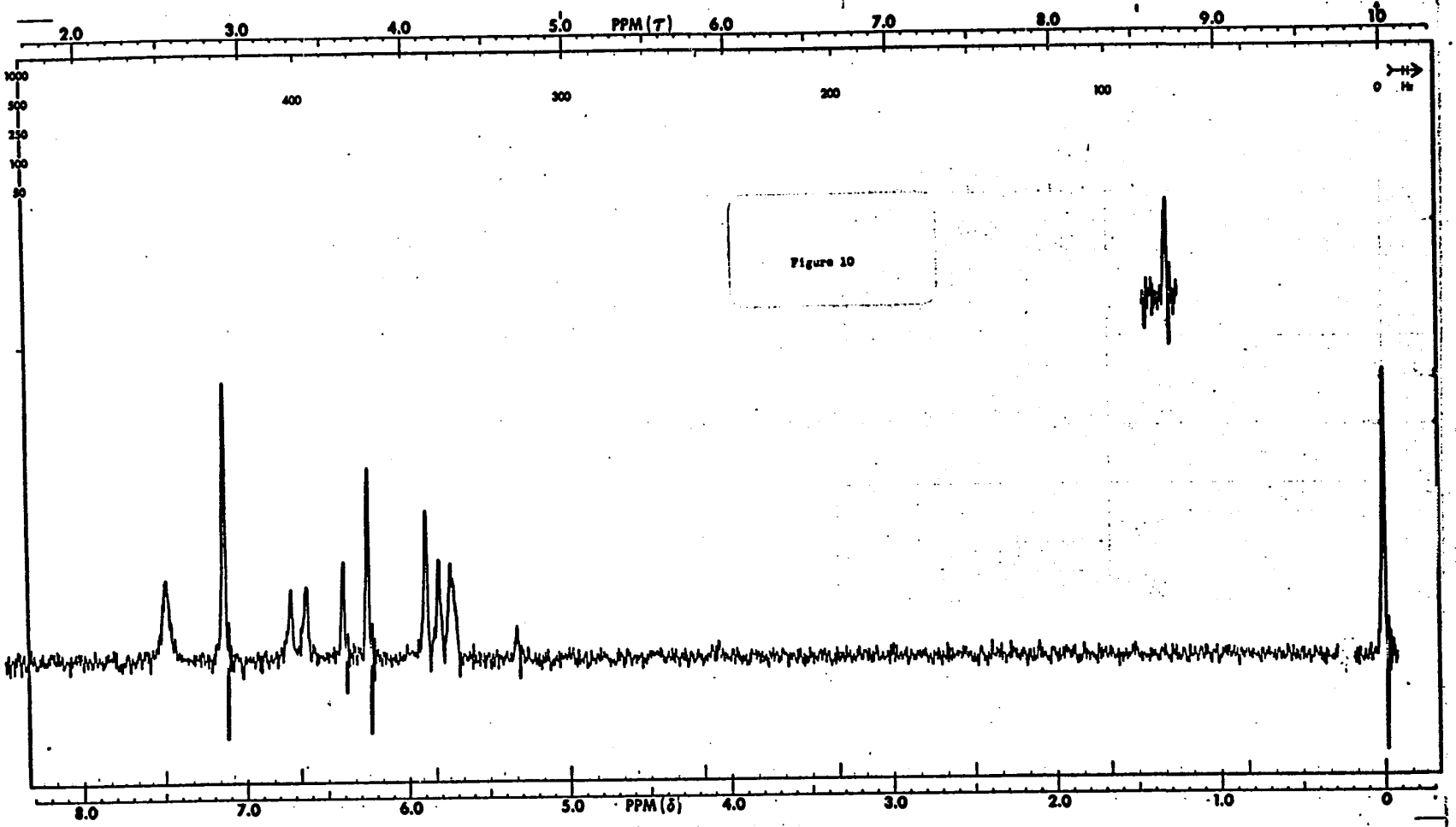


Figure 10

Sweep Offset 120 Hz.

Figure 11

NMR Spectrum of Thiazolo(5,4-f)isoquinoline

(1V) in $CDCl_3$

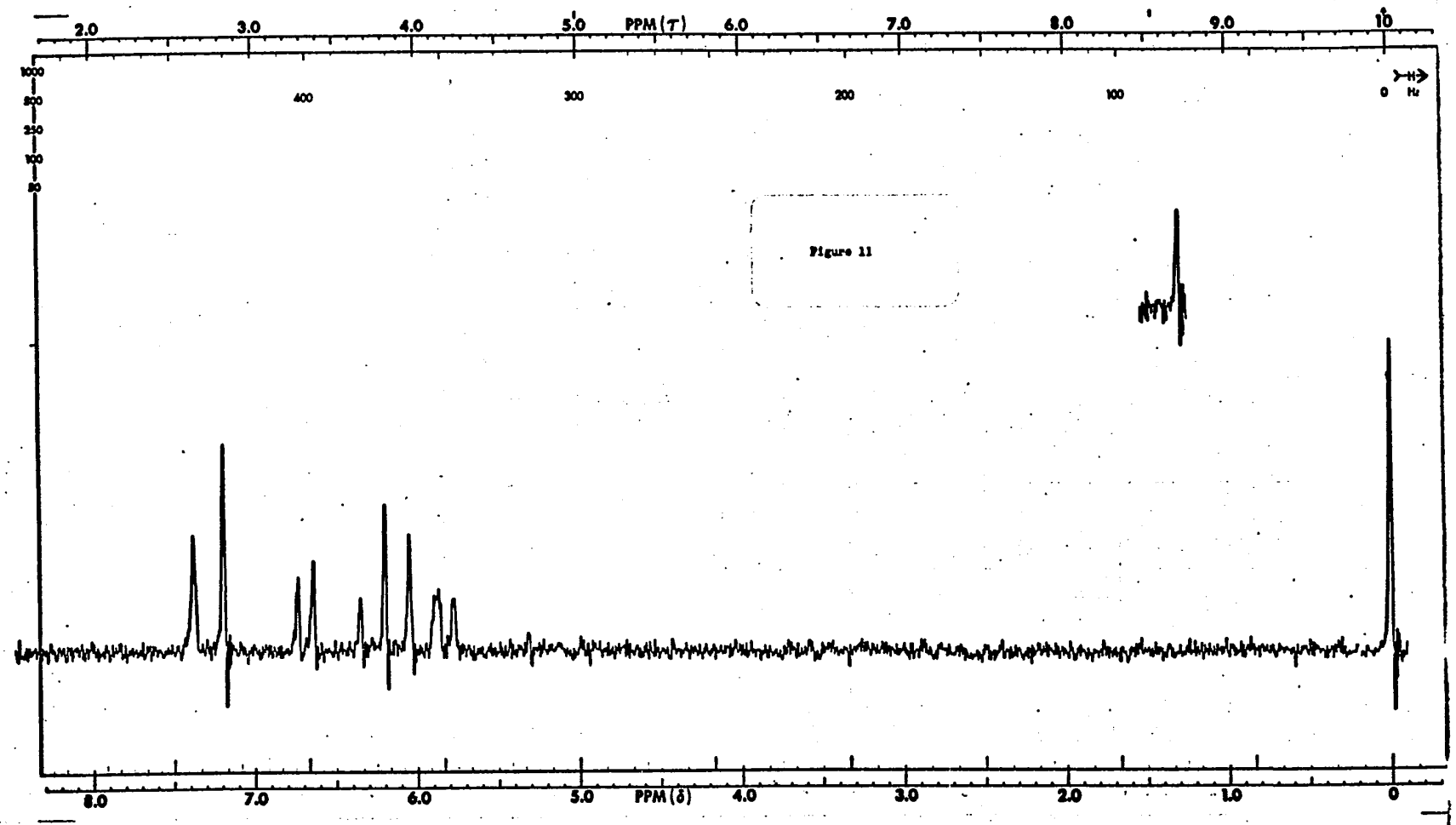


Figure 11

Sweep Offset 120 Hz.

Figure 12

NMR Spectrum of 6-Amino-5-thiocyano-isoquinoline (LX) in CD_3COOD

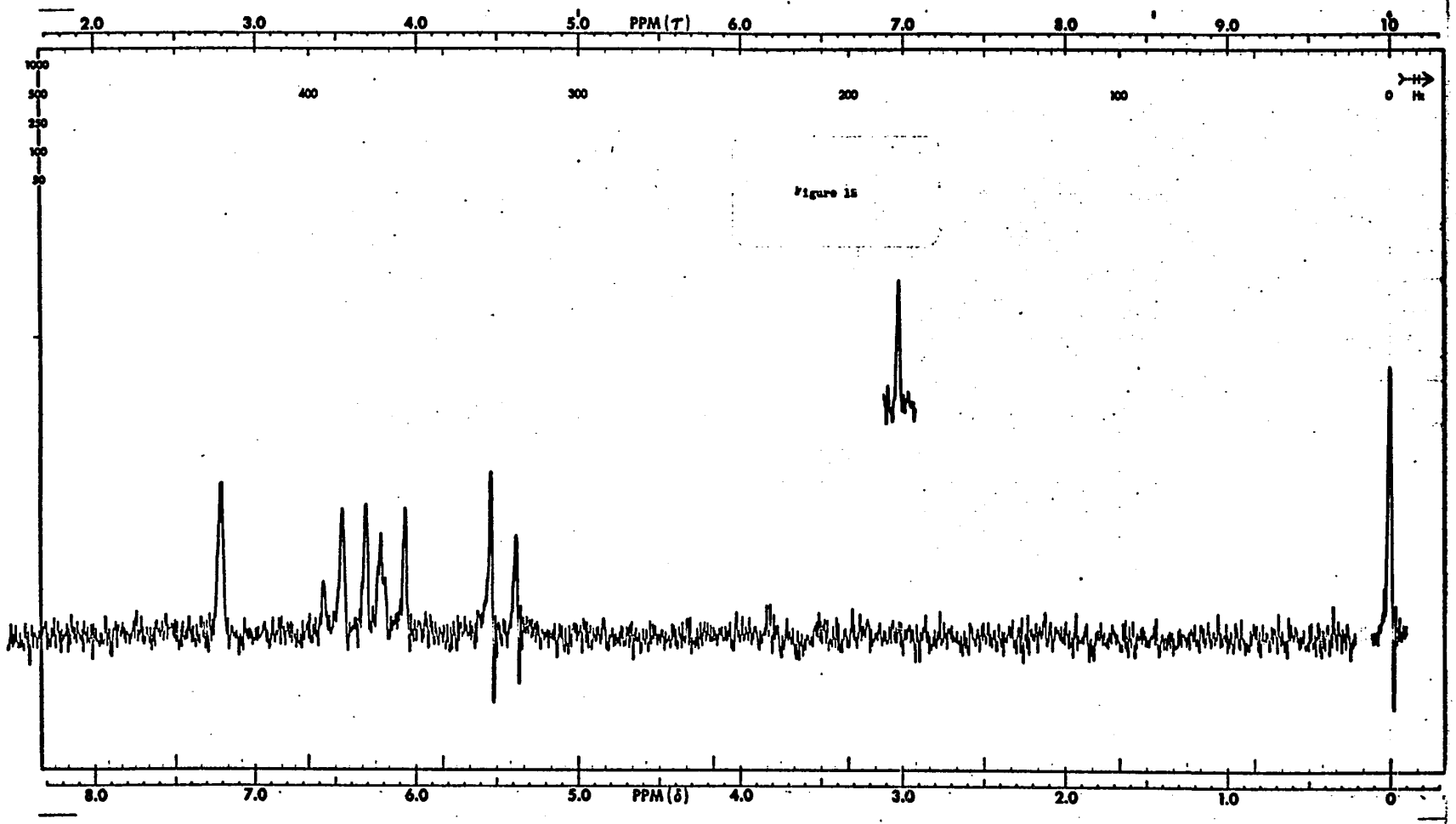


Figure 15

Sweep Offset 120 Hz.

Figure 13

NMR Spectrum of 2-Aminothiazolo(5,4-f)-isoquinoline (XVII) in DMSO-d_6

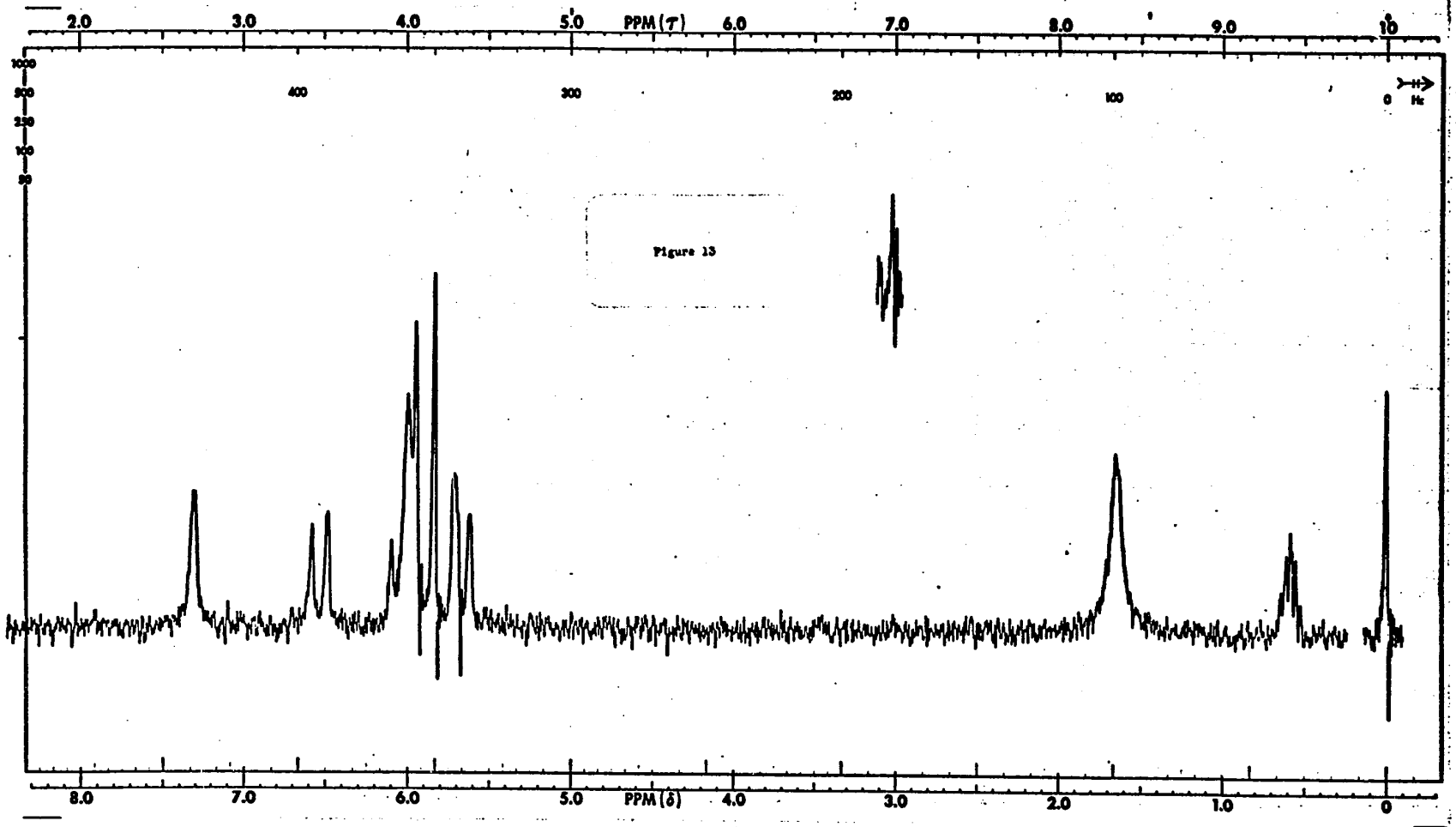


Figure 13

Sweep Offset 120 Hz.

Figure 14

NMR Spectra of 2,5-Diaminothiazolo(5,4-h)-isoquinoline (XVll) in DMSO-d_6

a) Before exchange with D_2O

b) After exchange with D_2O

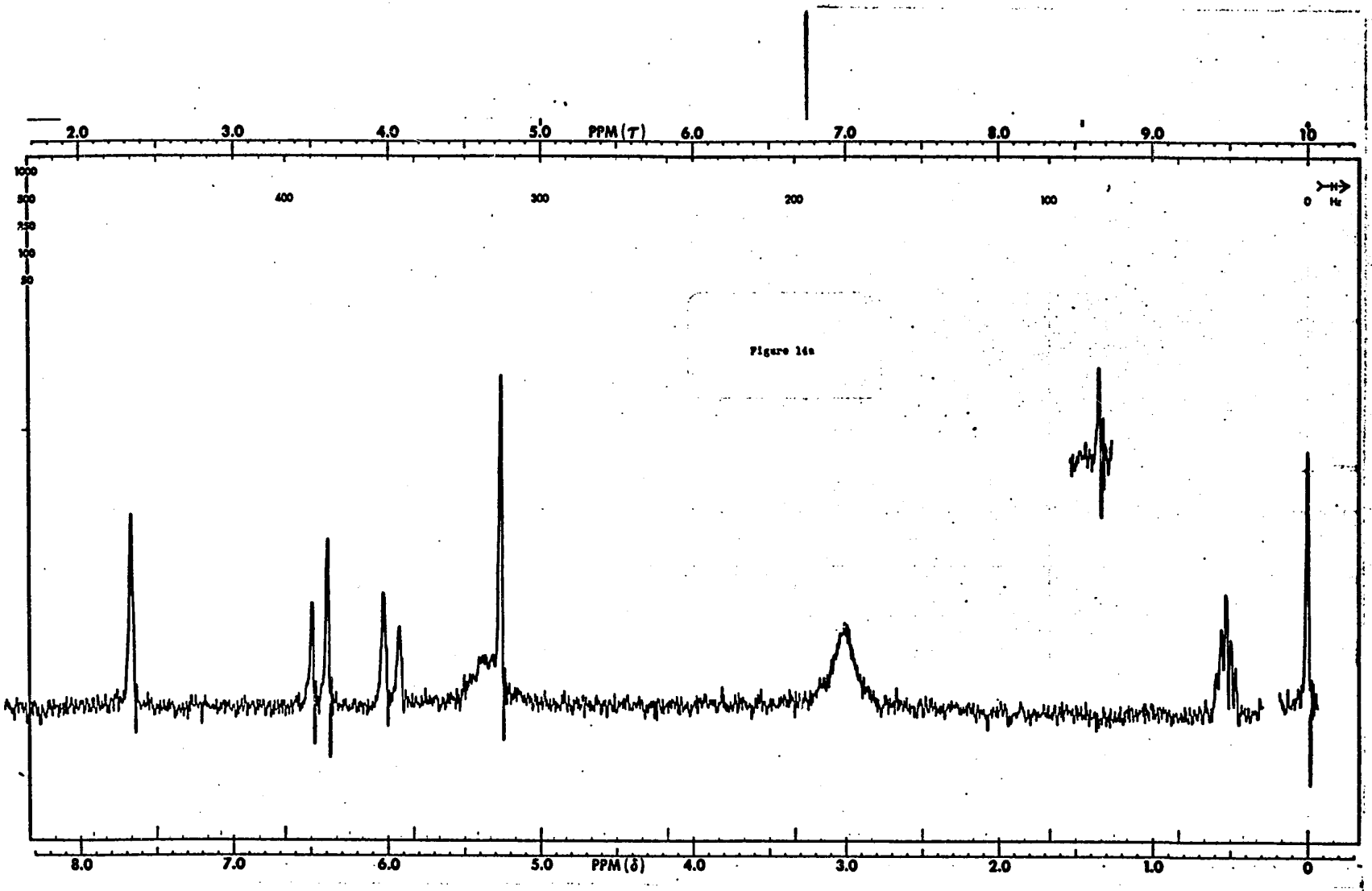


Figure 14a

Sweep Offset 120 Hz.

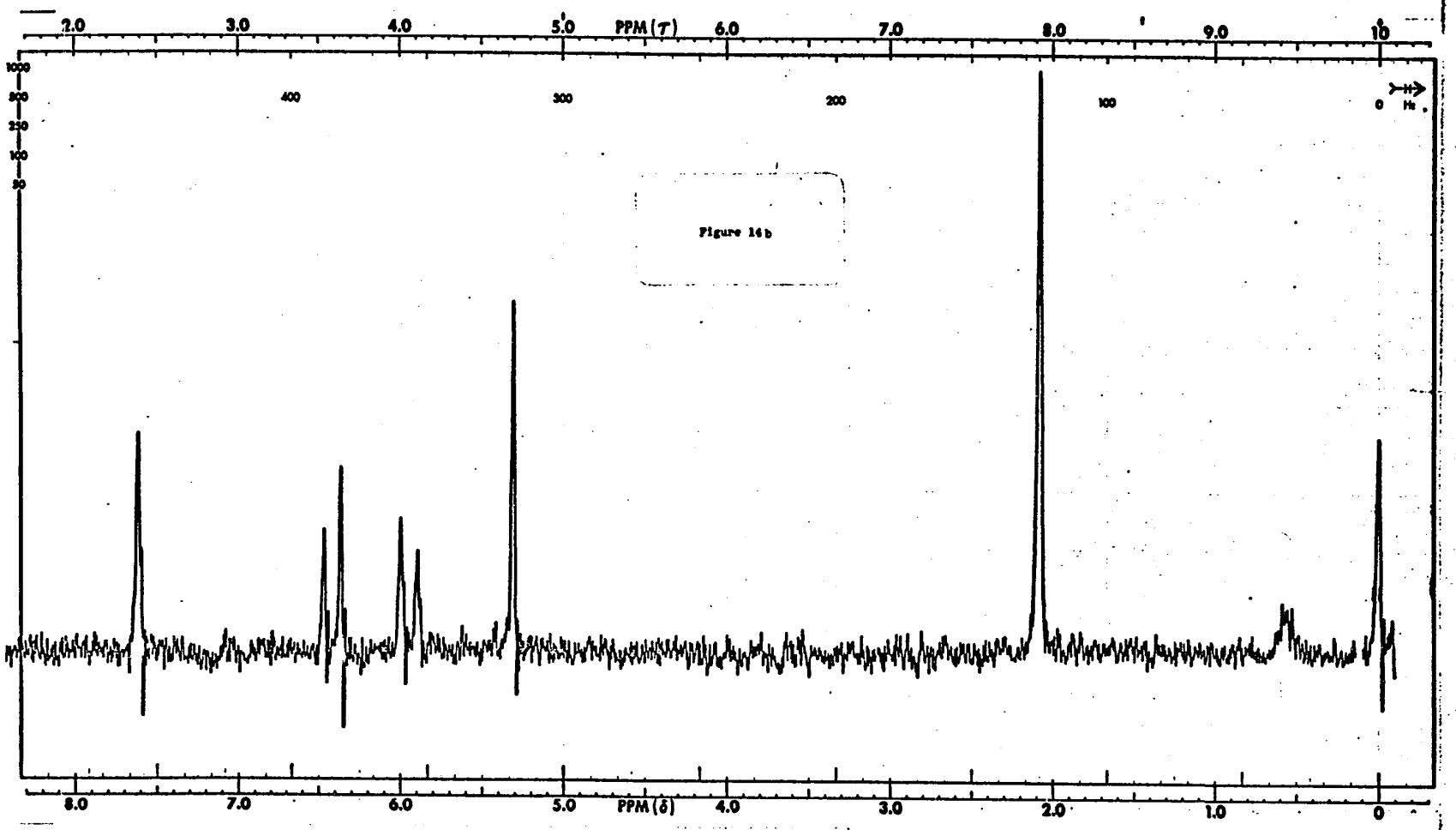


Figure 14b

Sweep Offset 120 Hz.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are corrected.

Infrared spectra were recorded on a Perkin-Elmer model 521 and a model 337 spectrophotometer. Unless otherwise indicated the measurements of the spectra of solid compounds were made on potassium bromide pellets and of liquids between two sodium chloride plates. Ultraviolet spectra were measured on a Perkin-Elmer model 350 spectrophotometer using absolute ethanol as the solvent.

Nuclear magnetic resonance spectra were determined on a Varian High Resolution Nuclear Magnetic Resonance Spectrometer, model A-60. Solvents used were carbon tetrachloride, deuteriochloroform, dimethylsulfoxide-d_6, acetic acid-d_4 and deuterium oxide. Tetramethylsilane (TMS) and 3-(trimethylsilyl)1-propanesulfonic acid sodium salt were used as an internal standard.

Elemental analyses were carried out by Dr. A. Bernhardt, Germany and by Dr. C. Daessle, Montreal.

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Infrared spectra were recorded on a Perkin-Elmer model 521 and a model 337 spectrophotometer. Unless otherwise indicated the measurements of the spectra of solid compounds were made on potassium bromide pellets and of liquids between two sodium chloride plates. Ultraviolet spectra were measured on a Perkin-Elmer model 350 spectrophotometer using absolute ethanol as the solvent.

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Elemental analyses were carried out by Dr. A. Bernhardt, Germany and by Dr. C. Daessle, Montreal.

1. SYNTHESIS OF THIAZOLO(4,5-h)ISOQUINOLINE (V11)

(a) Preparation of m-Hydroxybenzylidene aminoacetal (XXX1V)

The procedure of Woodward and Doering (17) was followed to prepare this compound from m-hydroxybenzaldehyde (XXX111). A yield of 85% of m-hydroxybenzylidene aminoacetal (XXX1V), m.p. 67-68.8°, was obtained; lit. value 67.2-67.8°(17).

(b) Preparation of 7-Hydroxyisoquinoline (XXXV)

The procedure of Woodward and Doering (17) was also followed in preparing 7-hydroxyisoquinoline (XXXV) from m-hydroxybenzylidene aminoacetal (XXX1V). A yield of 60% of 7-hydroxyisoquinoline was obtained, m.p. 229.5-231°; lit. value 229-231° (17).

This compound was purified through its sodium salt. Twenty grams of the crude material was dissolved in 100 ml of water containing 40 g of sodium hydroxide. The yellow plates which separated from the cooled solution were recrystallized from concentrated sodium hydroxide solution. On regeneration and recrystallization from ethanol, 16.5 g of 7-hydroxyisoquinoline was obtained.

(c) Preparation of 7-Aminoisoquinoline (XXXV1)

The procedure of Osborn et al. (19) was followed to prepare this compound. A yield of 85% of 7-aminoisoquinoline (XXXV1) was obtained, m.p. 203-205°; lit. value 203-205° (19).

(d) Preparation of 2-Aminothiazolo(4,5-h)isoquinoline (X)

7-Aminoisoquinoline (XXXVl) (2.88 g, 0.02 mole) and potassium thiocyanate (8.0 g, 0.063 mole) were dissolved in 80 ml of 95% glacial acetic acid in a 250 ml three necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. Absolute methanol (8 ml) was also added into the solution. The resulting solution was cooled to 0° to 5° and bromine (1.2 ml, 0.02 mole) in 10 ml of 95% glacial acetic acid was added dropwise to the stirred solution over a period of twenty minutes. The reaction mixture was poured into 100 ml of water after being stirred for another hour. The acid solution was neutralized with saturated sodium carbonate solution. The orange precipitated crude 7-amino-8-thiocyanoisoquinoline (XXXVll) was filtered and dried overnight. The yield was 78%.

A solution of 3.2 g of crude 7-amino-8-thiocyanoisoquinoline in 150 ml of 4N hydrochloric acid and 150 ml of ethanol was refluxed for two hours. The hot acid solution was filtered and left to stand overnight. A yellow crystalline compound precipitated and was filtered. This substance proved to be 2-aminothiazolo(4,5-h)-isoquinoline hydrochloride. Neutralization of the aqueous solution of the hydrochloride salt with dilute sodium carbonate solution precipitated the free base in 90% yield. The substance crystallized from aqueous alcoholic solution as pale yellow needles, m.p. 303.5-305.5°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.92;

Found: C, 59.60; H, 3.67; N, 20.74; S, 16.01;

(e) Preparation of 2-Chlorothiazolo(4,5-h)isoquinoline (1X)

Cuprous chloride was prepared in the usual way. Three grams of copper sulfate pentahydrate and 0.66 g of sodium chloride was dissolved in 30ml of hot water. A solution of 0.54 g of sodium bisulfite and 0.36 g of sodium hydroxide in 20 ml of water was added with constant stirring. The mixture was cooled to room temperature and the supernatant liquid was washed twice with water after being decanted from the colorless cuprous chloride. The cuprous chloride was dissolved in 10 ml of concentrated hydrochloric acid and cooled while the diazotization of the amino compound was being carried out.

2-Aminothiazolo(4,5-h)isoquinoline (X) (1.2 g, 6.0 millimole) was added to 40 ml of 85% phosphoric acid with mechanical stirring. It was then cooled and maintained at 5-10° and 10 ml of 70% nitric acid was added. The resulting solution was cooled to 0-5° and sodium nitrite (0.44 g, 6.5 millimole) in 4 ml of water was added with constant stirring over a period of fifteen minutes. The reaction mixture was stirred for another fifteen minutes at this temperature, and was then added over a period of twenty minutes to the stirred solution of cuprous chloride in concentrated hydrochloric acid at 0-5°. The reaction mixture was stirred for another hour at room temperature. It was made basic with 20% sodium hydroxide solution, with cooling and stirring. The basic mixture was extracted with three 250 ml portions of diethyl ether. The ether extract was washed with water, dried over magnesium sulfate, and filtered. The ether

solution was evaporated to dryness leaving a pale yellow solid. The crude 2-chlorothiazolo(4,5-h)isoquinoline (1X) was sublimed at 2 mm (bath temperature 98°). The sublimate (0.52 g) was recrystallized from n-hexane to give 0.45 g of pure colorless chloro compound, m.p. 130-131°.

Anal. Calcd. for $C_{10}H_5N_2SCl$ C, 54.42; H, 2.28; N,12.70; S, 14.53;

Found: C, 54.33; H, 2.32; N, 12.85; S, 14.57;

(f) Preparation of Thiazolo(4,5-h)isoquinoline (V11)

2-Chlorothiazolo(4,5-h)isoquinoline (1X) (0.5 g, 2.3 millimole) was dissolved in a mixture of 8 ml of 47% hydriodic acid, 4 ml of 95% glacial acetic acid and 4 ml of water, and 0.28 g of red phosphorus was added. The resulting mixture was refluxed for three hours and filtered while hot. The volume was reduced to 6 ml and allowed to stand for cooling. The orange-red crystalline precipitate was filtered and neutralized with dilute sodium carbonate solution. The resulting precipitate was filtered off, washed with water and dried. Recrystallization from n-hexane gave colorless needles of thiazolo-(4,5-h)isoquinoline (V11) in 58% yield, m.p. 138-139°.

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.05 S, 17.21;

Found: C, 64.34; H, 3.32; N, 14.93; S, 17.08;

(g) Preparation of 2-Acetamidothiazolo(4,5-h)isoquinoline (X11)

2-Aminothiazolo(4,5-h)isoquinoline (X) (0.5 g, 2.5 millimole) was refluxed in a mixture of 8 ml of acetic anhydride and 4 ml of pyridine for two hours. Filtration of the cooled reaction mixture gave 0.55 g of 2-acetamidothiazolo(4,5-h)isoquinoline (XII) (91% yield). Recrystallization from absolute alcohol gave colorless crystals, m.p. 350°.

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.08;

Found: C, 59.46; H, 3.37; N, 17.29; S, 13.29;

(b) Preparation of 2-Hydroxythiazolo(4,5-h)isoquinoline (XI)

2-Chlorothiazolo(4,5-h)isoquinoline (IX) (0.3 g, 1.48 millimole) was refluxed in 30 ml 0.5N sodium hydroxide solution for three hours. The solution was cooled to room temperature and acidified with dilute acetic acid to pH 6. The resulting precipitate was filtered off, washed with water and dried to give a 65% yield of 2-hydroxythiazolo(4,5-h)isoquinoline (IX). Recrystallization from aqueous alcoholic solution gave fine yellow needles, m.p. 296-297.5°.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.38; H, 2.99; N, 13.85;

Found: C, 59.62; H, 2.81; N, 13.96;

2. ATTEMPTED SYNTHESIS OF THIAZOLO(4,5-f)ISOQUINOLINE (IV)

(a) Preparation of 5-Nitroisoquinoline (XXXIX)

5-Nitroisoquinoline (XXXIX) was prepared by following the procedure of Le Fèvre and his co-workers (20). From 12 g of

freshly distilled isoquinoline (XXXVIII), 13.6 g of 5-nitroisoquinoline was obtained in 82% yield, m.p. 104-106°; lit. value 106-108°(20).

(b) Preparation of 5-Aminoisoquinoline (XL)

The method of Osborn and Madeleine (19) was followed to prepare 5-aminoisoquinoline (XL) from 5-nitroisoquinoline (XXXIX) in 85% yield, m.p. 128-130°; lit. value 129-131° (19).

(c) Thiocyanation of 5-Aminoisoquinoline (XL)

5-Aminoisoquinoline (XL) (2.88 g, 0.02 mole) and potassium thiocyanate (8.0 g, 0.063 mole) were dissolved in 60 ml of 95% glacial acetic acid in a 250 ml three necked flask equipped with a thermometer and a dropping funnel and 8 ml of absolute methanol was also added. The resulting solution was cooled to 0° to 5° and bromine (1.2 ml, 0.02 mole) in 10 ml of glacial acetic acid was added dropwise to the stirred solution for another hour. It was then poured into 100 ml of water and the acid solution was neutralized with sodium carbonate solution. The orange crude product was filtered, washed with water and dried overnight. Recrystallization from a large volume of benzene gave yellow needles (2.4 g). It was later established that the structure of this compound was 5-amino-8-thiocyanoisoquinoline (XLII), m.p. 181-183°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.57; H, 3.51; N, 20.88; S, 15.94;

Found: C, 59.60; H, 3.59; N, 20.88; S, 15.92;

(d) Acid hydrolysis of 5-amino-8-thiocyanoisoquinoline (XLII)

A solution of 2.0 g of 5-amino-8-thiocyanoisoquinoline (XLII) (0.01 mole) in 120 ml of 8N hydrochloric acid and 150 ml of ethanol was refluxed for four hours. The acid solution was evaporated to dryness on a water bath leaving only a yellow solid. Neutralization of the aqueous solution of the yellow salt with dilute sodium carbonate solution produced a precipitate which was filtered and dried. Recrystallization from ethanol gave 1.5 g of 5-amino-8-mercaptoisoquinoline (XLIII) (87% yield), m.p. 260-262°.

Anal. Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.54; N, 15.91
S, 18.19;

Found: C, 61.60; H, 4.48; N, 15.71; S, 18.11;

3. ATTEMPTED SYNTHESIS OF THIAZOLO(5,4-h)ISOQUINOLINE (VIII)

(a) Preparation of 5-Bromoisoquinoline (XLIV)

The procedure given by Osborn and Madeleine (19) for the preparation of 5-bromoisoquinoline (XLIV) from 5-aminoisoquinoline (XL) was followed and a 77% yield of 5-bromoisoquinoline was obtained, m.p. 82.5-84°, lit. value 82-84° (19).

(b) Preparation of 5-Bromo-8-nitroisoquinoline (XLV)

5-Bromo-8-nitroisoquinoline (XLV) was prepared by the nitration of 5-bromoisoquinoline (XLIV) following the procedure of Osborn and Madeleine (19). The yield was 70%; yellow needles, m.p. 138-139.5°; lit. value 139-141° (19).

(c) Preparation of 8-Aminoisoquinoline (XLVI)

The method used by Gordon and Pearson (26) for the reduction of 5-bromo-8-nitroisoquinoline (XLV) to 8-aminoisoquinoline (XLVI) was followed. A 72% yield of the amino compound was obtained, m.p. 172-174°; lit. value 170-172° (26).

(d) Thiocyanation of 8-Aminoisoquinoline (XLVI)

8-Aminoisoquinoline (XLVI) (3.35 g, 0.015 mole) and potassium thiocyanate (6.0 g, 0.047 mole) were dissolved in 90 ml of 95% glacial acetic acid in a 250 ml three necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. 6 Ml of absolute methanol was also added. The resulting solution was cooled to 0-5°, and bromine (0.9 ml, 0.015 mole) in 10 ml of 95% glacial acetic acid was added dropwise to the stirred solution over a period of twenty minutes. After the reaction mixture was stirred for an additional hour at room temperature, it was poured into 100 ml of water. The acid solution was neutralized with sodium carbonate solution. The yellow precipitate was filtered and dried to give 2.4 g (79% yield) of 8-amino-5-thiocyanoisoquinoline (XLVIII). Recrystallization from benzene yielded yellow needles, m.p. 209-211°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.57; H, 3.51; N, 20.88;

Found: C, 59.27; H, 3.83; N, 20.66;

(e) Acid hydrolysis of 8-Amino-5-thiocyanoisoquinoline (XLVIII)

8-Amino-5-thiocyanoisoquinoline (XLVIII) (2.0 g, 0.01 mole)

was dissolved in 100 ml of ethanol and 100 ml of 8N hydrochloric acid. The resulting solution was refluxed for three hours. After refluxing, the volume was reduced to 50 ml by evaporating on a water bath. The acid solution was neutralized with sodium carbonate solution. The yellow precipitate was filtered, washed with water, and let stand overnight. Recrystallization from ethanol gave 1.8 g of 8-amino-5-mercapto isoquinoline (XLIX) (90% yield), yellow needles, m.p. 244-246°.

Anal. Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.54; N, 15.91; S, 18.19;

Found: C, 61.77; H, 4.05; N, 16.09; S, 18.13;

(f) Preparation of 5-Acetamidoisoquinoline (L)

The procedure given by Craig and Case (14) for the preparation of 5-acetamidoisoquinoline (L) from 5-aminoisoquinoline (XL) was followed, and a 85% yield of this compound was obtained, m.p. 161-163°; lit. value 163-164° (14).

(g) Preparation of 5-Acetamido-8-nitroisoquinoline (LI)

5-Acetamido-8-nitroisoquinoline (LI) was prepared in 61% yield by the procedure of Keilin and Cass (29), m.p. 224-226°; lit. value 225-227° (29).

(h) Preparation of 5-Acetamido-8-aminoisoquinoline (LII)

5-Acetamido-8-nitroisoquinoline (LI) (4.6 g, 0.02 mole) was reduced for two hours in absolute ethanol with 5% palladium on charcoal and hydrogen. The catalyst was filtered

was dissolved in 100 ml of ethanol and 100 ml of 8N hydrochloric acid. The resulting solution was refluxed for three hours. After refluxing, the volume was reduced to 50 ml by evaporating on a water bath. The acid solution was neutralized with sodium carbonate solution. The yellow precipitate was filtered, washed with water, and let stand overnight. Recrystallization from ethanol gave 1.8 g of 8-amino-5-mercapto isoquinoline (XLIX) (90% yield), yellow needles, m.p. 244-246°.

Anal. Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.54; N, 15.91; S, 18.19;

Found: C, 61.77; H, 4.05; N, 16.09; S, 18.13;

(f) Preparation of 5-Acetamidoisoquinoline (L)

The procedure given by Craig and Case (14) for the preparation of 5-acetamidoisoquinoline (L) from 5-aminoisoquinoline (XL) was followed, and a 85% yield of this compound was obtained, m.p. 161-163°; lit. value 163-164° (14).

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(h) Preparation of 5-Acetamido-8-aminoisoquinoline (LII)

5-Acetamido-8-nitroisoquinoline (LI) (4.6 g, 0.02 mole) was reduced for two hours in absolute ethanol with 5% palladium on charcoal and hydrogen. The catalyst was filtered

off and the filtrate was evaporated to dryness. The resulting yellow solid substance was recrystallized from ethanol to give 3.4 g (85% yield) of 5-acetamido-8-aminoisoquinoline (L11) as yellow needles, m.p. 270.5-272.5°.

Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.74;

Found: C, 65.77; H, 5.75, N, 20.74;

(1) Preparation of 2,5-Diaminothiazolo(5,4-h)isoquinoline (XX11)

5-Acetamido-8-aminoisoquinoline (L11) (3.02 g, 0.015 mole) and potassium thiocyanate (6.0 g, 0.047 mole) were dissolved in 120 ml of 95% glacial acetic acid in a 250 ml three necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. Absolute methanol (10 ml) was also added. The resulting solution was cooled to 0-5° and bromine (0.9 ml, 0.015 mole) in 15 ml of glacial acetic acid was added dropwise to the stirred solution over a period of twenty minutes. The reaction mixture was poured into 100 ml of water after being stirred for another hour. The acid solution was neutralized with sodium carbonate solution. The orange crude precipitate was filtered off and dried overnight. The crude product (5-acetamido-8-amino-7-thiocyano-isoquinoline) weighed 3.2 g.

A solution of 3.0 g of crude product in 150 ml of ethanol and 150 ml of 4N hydrochloric acid was refluxed for three hours. The acid solution was filtered and the volume of the

filtrate was reduced to 50 ml. The acid solution was poured onto cracked ice and neutralized with sodium carbonate solution. The dark green precipitate was filtered and recrystallized from aqueous alcoholic solution as yellowish green needles, m.p. 274-276°. The total yield of 2,5-diaminothiazolo(5,4-h)isoquinoline (XXII) was 60%.

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.54; H. 3.73; N, 25.91;

Found: C, 55.68; H, 3.77; N, 25.74;

(j) Preparation of 2,5-Diacetamidothiazolo(5,4-h)isoquinoline (XVIII)

2,5-Diaminothiazolo(5,4-h)isoquinoline (XVII) (0.3 g, 1.4 millimole) was refluxed in a mixture of 4 ml of acetic anhydride and 2 ml of pyridine for one hour. Filtration of the cooled reaction mixture gave 0.35 g(84% yield) of 2,5-diacetamidothiazolo-(5,4-h)isoquinoline (XVIII). The product was recrystallized from N,N-dimethylformamide to obtain colorless fine needles, m.p. >350°.

Anal. Calcd. for $C_{14}H_{12}N_4O_2S$: C, 55,98; H, 4.03; N, 18.64; S, 10.68;

Found: C, 55.79; H, 4.10; N, 18.78; S, 10.61;

4. SYNTHESIS OF THIAZOLO(5,4-f)ISOQUINOLINE (IV)

(a) Preparation of m-Methoxybenzaldehyde (LIII)

m-Methoxybenzaldehyde was prepared in 75% yield by the procedure of Icke et al. (27) from m-hydroxybenzaldehyde; (XXXIII), b.p. 84-87°/ 2 mm; lit. value 88-90°/ 3 mm (27).

(b) Preparation of m-Methoxy-ω-nitrostyrene (LIV)

m-Methoxybenzaldehyde (LIII) (6.75 g, 0.05 mole) was dissolved in 100 ml of ethanol at room temperature and the solution was cooled to 5-10° after nitromethane (6.0 g, 0.0985 mole) was added. Then 100 ml of a solution of 5 g sodium hydroxide in 100 ml of ethanol, cooled to 5-10°, was then added from a dropping funnel at a rate of 5 ml per minute. The reaction mixture was stirred vigorously and kept below 15° during the addition of the ethanolic sodium hydroxide solution. The insoluble sodium salt of the condensation product precipitated as the reaction proceeded. After the alkali had been added and with the temperature kept below 10°, ice water was slowly added until all the sodium salt dissolved. The resulting basic solution was poured through a glass-sintered funnel to remove the small amount of undissolved material, and this solution was then added to hydrochloric acid (60 ml of concentrated hydrochloric acid + 90 ml of water) with stirring during the addition but with no attempt being made to control the temperature. A fine yellow precipitate formed immediately. After standing for half an hour it was filtered, washed with water and dried to give 6.4 g (79% yield) of yellow needles of m-methoxy-ω-nitrostyrene (LIV), m.p. 88.5-90°; lit. value 91-92° (19).

(c) Preparation of ω-3-Methoxyphenethylamine (LV)

In an atmosphere of dry nitrogen, 12 g of lithium aluminum hydride was suspended in 250 ml of tetrahydrofuran previously dried and distilled over lithium aluminum hydride. While stirring, a

solution of 17.9 g (0.1 mole) of m-methoxy-ω-nitrostyrene (LIV) in 180 ml of purified tetrahydrofuran was added dropwise at such a rate that the refluxing did not become too vigorous. After the addition, the reaction mixture was stirred for an additional hour. While cooling, 40 ml of 1:1 ratio water-tetrahydrofuran mixture was slowly added with stirring to decompose the excess reagent. The mixture was then slowly treated with 125 ml of 30% sodium hydroxide solution. The tetrahydrofuran layer was separated and dried over anhydrous sodium sulfate. Aster distilling off the tetrahydrofuran, the product was distilled under reduced pressure and the fraction boiling at 108-110°/ 2 mm (lit. value 118-119°/ 6 mm (26) was collected to give 10.8 g (71.5% yield).of ω-3-methoxyphenethylamine (LV). The product rapidly forms a solid carbonate in the air.

(d) Preparation of 6-Methoxy-1,2,3,4-tetrahydroisoquinoline (LVI)

The procedure of Helfer (30) was followed to prepare this compound from ω-3-methoxyphenethylamine (LV). 6-Methoxy-1,2,3,4-tetrahydroisoquinoline (LVI) was obtained in 64% yield as a colorless oil, b.p. 128-130°/ 2 mm; lit. value 143-144°/ 6 mm (30).

(e) Preparation of 6-Methoxyisoquinoline (LVII)

6-Methoxy-1,2,3,4-tetrahydroisoquinoline (LVI (10.0 g, 0.0614 mole) and 10% palladium on charcoal (3 g) in 50 ml of

decalin were placed in a three necked flask equipped with a mechanical stirrer, a nitrogen inlet and a reflux condenser with a calcium chloride tube. The mixture was heated at 180-190° for three hours. After cooling, the solution was diluted with 100 ml of diethyl ether and filtered to remove the catalyst. The ether solution was extracted with three portions of 3N hydrochloric acid. The remaining acid solution was shaken with fresh ether to remove impurities from the acid solution. The acid solution was evaporated into dryness and neutralized with sodium carbonate solution. A layer of oil was formed. Isolation by ether-extraction gave 6-methoxyisoquinoline (LVII) in 61% yield; the hydrochloride salt melting at 216°; lit. value m.p. 220° (5).

(f) Preparation of 6-Hydroxyisoquinoline (LVIII)

The procedure of Robinson (16) was followed to prepare this compound and a yield of 80% of 6-hydroxyisoquinoline (LVIII) was obtained, m.p. 220-222° ; lit. value 220° (16).

(g) Preparation of 6-Aminoisoquinoline (LIX)

The method used by Robinson (16) for the preparation of this compound from 6-hydroxyisoquinoline (LVIII) was followed and a 80% yield of 6-aminoisoquinoline (LIX) was obtained, m.p. 216-218° ; lit. value 217-218° (16).

(h) Preparation of 6-Amino-5-thiocyanoisoquinoline (LX)

6-Aminoisoquinoline (LIX) (2.88 g, 0.02 mole) and

potassium thiocyanate (8.0 g, 0.063 mole) were dissolved in 100 ml of 95% glacial acetic acid in a 250 ml three necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. The resulting solution was cooled to 0° to 5° and bromine (1.2 ml, 0.02 mole) in 10 ml of glacial acetic acid was added dropwise to the stirred solution over a period of twenty minutes. The reaction mixture was poured into 100 ml of water after being stirred for an additional hour. The acid solution was neutralized with sodium carbonate solution. The orange precipitate was filtered and dried overnight. The crude product was obtained in 85% yield. Recrystallization from a large volume of benzene gave yellow needles, of 6-amino-5-thiocyanoisoquinoline (LX), m.p. 159.5-161°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.92;

Found: C, 59.59; H, 3.52; N, 20.99; S, 15.76;

(i) Preparation of 2-Aminothiazolo(5,4-f)isoquinoline (XlV)

A solution of 6-amino-5-thiocyanoisoquinoline (LX) (2.0 g, 0.01 mole) in 120 ml of 4N hydrochloric acid and 120 ml of ethanol was refluxed for two hours. The acid solution was evaporated in order to remove the ethanol and was neutralized with sodium carbonate solution. The yellow precipitate was filtered, washed with water and dried to give 1.82 g (91% yield) of 2-aminothiazolo(5,4-f)isoquinoline (XlV). Recrystallization from aqueous alcoholic solution gave yellow needles, m.p. 251-253°.

Anal. Calc. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.92;

Found: C, 59.66; H, 3.61; N, 20.73; S, 15.80;

(j) Preparation of 2-Chlorothiazolo(5,4-f)isoquinoline (XIII)

The preparation of cuprous chloride was made in the same manner as mentioned previously. A warm solution of 3.0 g of cupric sulfate pentahydrate and 0.66 g of sodium chloride, was added to a warm solution containing 0.54 g of sodium bisulfite and 0.36 g of sodium hydroxide. The white precipitate of cuprous chloride was dissolved in 10 ml of concentrated hydrochloric acid.

2-Aminothiazolo(5,4-f)isoquinoline (XIV) (1.2 g, 6 millimole) was added with mechanical stirring to 40 ml of 85% phosphoric acid cooled and maintained at 5-10°, and 10 ml of 70% nitric acid was then added. The resulting solution was cooled to 0-5° and sodium nitrite (0.44 g, 6.5 millimole) in 4 ml of water was added with constant stirring over a period of fifteen minutes. The reaction mixture was stirred for another fifteen minutes at this temperature, and was then added to the stirred solution of cuprous chloride in hydrochloric acid at 0-5° over a period of twenty minutes. The reaction mixture was stirred for another hour at room temperature. It was then made basic with 20% sodium hydroxide solution, with cooling and stirring. The basic mixture was extracted with three portions of 250 ml diethyl ether. The ether extract was washed

with water, dried over magnesium sulfate, and evaporated to dryness, leaving a pale yellow solid. The crude 2-chlorothiazolo(5,4-f)isoquinoline (XIII) was sublimed at 2 mm (bath temperature 110°). The sublimate (0.52 g, 38% yield) was recrystallized twice from n-hexane giving 0.45 g of colorless needles of chloro-compound, m.p. 170° (decomp.).

Anal. Calcd. for $C_{10}H_5N_2SCl$: C, 54.42; H, 2.28; N, 12.70; Cl, 16.07;

Found: C, 54.03; H, 2.70; N, 12.81; Cl, 16.10;

(k) Preparation of Thiazolo(5,4-f)isoquinoline (IV)

2-Chlorothiazolo(5,4-f)isoquinoline (XIII) (0.5 g, 2.3 millimole) was dissolved in a mixture of 8 ml of 47% hydriodic acid, 4 ml of 95% glacial acetic acid, 4 ml of water and 0.28 g of red phosphorus were added. The resulting mixture was refluxed for three hours and filtered while hot. The volume was reduced to 6 ml and allowed to stand for cooling. The orange-red crystalline substance was filtered and neutralized with dilute sodium carbonate solution. The resulting compound was filtered off, washed with water, and dried. Recrystallization from n-hexane gave colorless needles of thiazolo-(5,4-f)isoquinoline (IV) in 55% yield, m.p. 174-175.5°.

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.05; S, 17.21;

Found: C, 64.76; H, 3.29; N, 14.92; S, 17.08;

(l) Preparation of 2-Acetamidothiazolo(5,4-f)isoquinoline (XVl)

2-Aminothiazolo(5,4-f)isoquinoline (XlV) (0.3 g, 1.5 millimole) was refluxed in a mixture of 5 ml of acetic anhydride and 2.5 ml of pyridine for one hour and allowed to cool to room temperature. The white precipitate was filtered off and washed with water to give 0.24 g (81% yield) of 2-acetamidothiazolo(5,4-f)isoquinoline (XVl). Recrystallization from absolute ethanol gave colorless needles, m.p. $> 350^{\circ}$.

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.08;

Found: C, 59.64; H, 3.31; N, 17.32; S, 13.33;

(m) Preparation of 2-Hydroxythiazolo(5,4-f)isoquinoline (XV)

2-Chlorothiazolo(5,4-f)isoquinoline (Xlll) (0.3 g, 1.48 millimole) was refluxed in 30 ml of 0.5N sodium hydroxide solution for three hours. The solution was cooled to room temperature and acidified with dilute acetic acid to pH 6. The resulting precipitate was filtered off, washed with water and dried to give a 65% yield of 2-hydroxythiazolo(5,4-f)isoquinoline (XV). Recrystallization from aqueous ethanolic solution gave fine yellow needles, m.p. $> 350^{\circ}$.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.38; H, 2.99; N, 13.85;

Found: C, 59.41; H, 3.37; N, 13.73;

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. The synthesis of thiazolo(4,5-h)isoquinoline from 7-amino-isoquinoline was accomplished in three steps:

   a) Thiocyanation of 7-aminoisoquinoline with bromine and potassium thiocyanate, followed by cyclization of 7-amino-8-thiocyanoisoquinoline yielded 2-aminothiazolo(4,5-h)isoquinoline.

   b) Diazotization of 2-aminothiazolo(4,5-h)isoquinoline and subsequent reaction with cuprous chloride produced 2-chlorothiazolo(4,5-h)isoquinoline.

   c) Reduction of 2-chlorothiazolo(4,5-h)isoquinoline with hydriodic acid and red phosphorus yielded thiazolo(4,5-h)isoquinoline.

2. Thiocyanation of 5-aminoisoquinoline gave 5-amino-8-thiocyanoisoquinoline as the only reaction product.

3. Acid hydrolysis of 5-amino-8-thiocyanoisoquinoline using 8N hydrochloric acid and ethanol produced 5-amino-8-mercaptoisoquinoline.

4. Thiocyanation of 8-aminoisoquinoline with thiocyanogen gave 8-amino-5-thiocyanoisoquinoline.

5. Acid hydrolysis of 8-amino-5-thiocyanoisoquinoline with 8N hydrochloric acid and ethanol gave 8-amino-5-mercaptoisoquinoline.

6. A plausible mechanism for the conversion of a thiocyano compound into a thiol using concentrated hydrochloric acid and ethanol was proposed.

7. Catalytic hydrogenation of 5-acetamido-8-nitroisoquinoline using 5% palladised charcoal produced 5-acetamido-8-aminoisoquinoline.

8. Thiocyanation of 5-acetamido-8-aminoisoquinoline, followed by cyclization of 5-acetamido-8-amino-7-thiocyanoisoquinoline produced 2,5-diaminothiazolo(5,4-h)isoquinoline.

9. Thiocyanation of 6-aminoisoquinoline with thiocyanogen gave 6-amino-5-thiocyanosioquinoline. Ring closure of 6-amino-5-thiocyanoisoquinoline produced 2-aminothiazolo(5,4-f)isoquinoline.

10. The synthesis of thiazolo(5,4-f)isoquinoline from 2-aminothiazolo(5,4-f)isoquinoline was achieved by diazotization, Sandmeyer reaction and reduction of the 2-chloro derivative.

11. Acetylation of 2-amino-thiazolo(4,5-h)- and 2-aminothiazolo-(5,4-f)isoquinolines with acetic anhydride in pyridine gave 2-acetamidothiazolo(4,5-h) and 2-acetamidothiazolo(5,4-f)-isoquinolines respectively.

12. The reaction of 2-chlorothiazolo(4,5-h)- and 2-chlorothiazolo-(5,4-f)isoquinolines with dilute sodium hydroxide solution produced 2-hydroxythiazolo(4,5-h) and 2-hydroxythiazolo(5,4-f)-isoquinolines respectively.

13. Dehydrogenation of 6-methoxy-1,2,3,4-tetrahydroisoquinoline using 10% palladised charcoal in decalin gave 6-methoxyisoquinoline.

14. The following new compounds were prepared and characterized:
    (a) 2-aminothiazolo(4,5-h)isoquinoline
    (b) 2-chlorothiazolo(4,5-h)isoquinoline
    (c) thiazolo(4,5-h)isoquinoline
    (d) 2-acetamidothiazolo(4,5-h)isoquinoline
    (e) 2-hydroxythiazolo(4,5-h)isoquinoline
    (f) 5-amino-8-thiocyanoisoquinoline
    (g) 5-amino-8-mercaptoisoquinoline
    (h) 8-amino-5-thiocyanoisoquinoline
    (i) 8-amino-5-mercaptoisoquinoline
    (j) 5-acetamido-8-aminoisoquinoline
    (k) 2,5-diaminothiazolo(5,4-h)isoquinoline
    (l) 2,5-diacetamidothiazolo(5,4-h)isoquinoline
    (m) 6-amino-5-thiocyanoisoquinoline
    (n) 2-aminothiazolo(5,4-f)isoquinoline
    (o) 2-chlorothiazolo(5,4-f)isoquinoline
    (p) thiazolo(5,4-f)isoquinoline

(q) 2-acetamidothiazolo(5,4-f)isoquinoline

(r) 2-hydroxythiazolo(5,4-f)isoquinoline

15. The nuclear magnetic resonance spectra of all the new compounds were recorded and correlated with the structure.

16. The ultraviolet spectra of all the new compounds were recorded and discussed briefly.

17. The infrared spectra of all the new compounds were recorded and discussed in some detail.

18. The infrared, ultraviolet and nuclear magnetic resonance spectra of previously known isoquinolines were investigated.

BIBLIOGRAPHY

1. Patterson, A. M., Capell, L. T. and Walker, D. F., The ring Index, Reinhold Publishing Corp., New York, N. Y., second edition, 1959.

2. Hall, C. E. and Taurins, A., Can. J. Chem., 44, 2465 (1966).

3. Hall, C. E. and Taurins, A., Can. J. Chem., 44, 2473 (1966).

4. Hugerschoff, A., Ber., 36, 3121 (1903).

5. Robinson, R. A., J. Am. Chem. Soc., 69, 1939 (1947).

6. Jacobson, P., Ber., 19, 1067 (1886).

7. Lankelma, H. P. and Knauf, A. E., J. Am. Chem. Soc., 53, 309 (1931).

8. Lankelma, H. P. and Sharnoff, P. X., J. Am. Chem. Soc., 53, (1931).

9. Dessai, R. D., Hunter, R. F. and Kureishy, M. A., J. Chem. Soc., 1668 (1936).

10. Erlenmeyer, H. and Ueberwasser, H., Helv. Chim. Acta.,

23, 328 (1940).

11. Kaufmann, H. P., Oehring, W. and Clauberg, A., Arch. Pharm., 266, 197 (1928).

12. Koshida, Y., Yokota, K. and Hai, S. H., J. Pharm. Soc., (Japan) 71, 533 (1951).

13. Manske, R. H. F. and Kulka, M., Can. J. Res., 27 B, 161 (1949).

14. Craig, J. J. and Cass, W. E., J. Am. Chem. Soc., 64, 783 (1942).

15. Manske, R. H. F. and Kulka, M., J. Am. Chem. Soc., 72, 4997 (1950)

16. Robinson, R. A., J. Am. Chem. Soc., 69, 1944 (1947).

17. Woodward, R. B. and Doering, W. Von. E., J. Am. Chem. Soc., 67, 860 (1945).

18. Kaufmann, H. P. and Küchler, K., Ber., 67, 944 (1934).

19. Osborn, A. R., Schofield, K. and Short, L. N., J. Chem. Soc., 4191 (1956).

23, 328 (1940).

11. Kaufmann, H. P., Oehring, W. and Clauberg, A., Arch. Pharm., 266, 197 (1928).

12. Koshida, Y., Yokota, K. and Hai, S. H., J. Pharm. Soc., (Japan) 71, 533 (1951).

13. Manske, R. H. F. and Kulka, M., Can. J. Res., 27 B, 161 (1949).

14. Craig, J. J. and Cass, W. E., J. Am. Chem. Soc., 64, 783 (1942).

15. Manske, R. H. F. and Kulka, M., J. Am. Chem. Soc., 72, 4997 (1950)

16. Robinson, R. A., J. Am. Chem. Soc., 69, 1944 (1947).

17. Woodward, R. B. and Doering, W. Von. E., J. Am. Chem. Soc., 67, 860 (1945).

18. Kaufmann, H. P. and Küchler, K., Ber., 67, 944 (1934).

19. Osborn, A. R., Schofield, K. and Short, L. N., J. Chem. Soc., 4191 (1956).

20. Le Fèvre C. G. and Le Fèvre, R. J. W., J. Chem. Soc., 1470 (1935).

21. Cheronis, N. D. and Ma, T. S., Organic Functional Group Analysis, Interscience Publishers, New York, N. Y., 1964, p. 323.

22. Kaufmann, H.P., Ber., 62, 390 (1929).

23. Suhr, H., Mol. Phys., 6, 153 (1963).

24. Riemschneider, R., J. Am. Chem. Soc., 78, 844 (1956).

25. Riemschneider, R., Wojahn, F. and Orlick, G., J. Am. Chem. Soc., 73, 5905 (1951).

26. Gordon, M. and Pearson, D. E., J. Org. Chem., 29, 329 (1964).

27. Icke, R. N., Redmann, C. E., Wisegarver, B. B. and Alles, G. A., Organic Synthesis, Collective Volume 111, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 564.

28. Marchant, A. and Pinder, A. R., J. Chem. Soc., 327 (1956)

29. Keilin, B. and Cass, W. E., J. Am. Chem. Soc., 64,

20. Le Fèvre C. G. and Le Fèvre, R. J. W., J. Chem. Soc., 1470 (1935).

21. Cheronis, N. D. and Ma, T. S., Organic Functional Group Analysis, Interscience Publishers, New York, N. Y., 1964, p. 323.

22. Kaufmann, H.P., Ber., 62, 390 (1929).

23. Suhr, H., Mol. Phys., 6, 153 (1963).

24. Riemschneider, R., J. Am. Chem. Soc., 78, 844 (1956).

25. Riemschneider, R., Wojahn, F. and Orlick, G., J. Am. Chem. Soc., 73, 5905 (1951).

26. Gordon, M. and Pearson, D. E., J. Org. Chem., 29, 329 (1964).

27. Icke, R. N., Redmann, C. E., Wisegarver, B. B. and Alles, G. A., Organic Synthesis, Collective Volume III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 564.

28. Marchant, A. and Pinder, A. R., J. Chem. Soc., 327 (1956)

29. Keilin, B. and Cass, W. E., J. Am. Chem. Soc., 64,

2443 (1942).

30. Helfer, L., Helv. Chim. Acta., 7, 945 (1924).

31. Robinson, R. A., J. Am. Chem. Soc., 69, 1940 (1947).

32. Luther, H., Mootz, D. and Radwitz, F., J. Prakt. Chem., ser. 4, 5, 242 (1958).

33. Bassignana, P., Cogrossi, C. and Gandino, M., Spectrochim. Acta., 19, 1885 (1963).

34. Katritzky, A. R., Physical Methods in Heterocyclic Chemistry, volume 2, Academic Press, New York. N. Y., 1963, pp. 35-62

35. Ellis, B. and Griffiths, P. J. P., Spectrochim. Acta., 21, 1881 (1965).

36. Boggust, W. A., Cocker, W., Schwarz, J. C. P. and Stuart, E. R., J. Chem. Soc., 680 (1950).

37. Rao, C. N. R., Ultraviolet and Visible Spectroscopy, Butterworths, London, second edition 1967.

38. Kato, H., Tanaka, K. and Ohta, M., Bull. Chem. Soc., (Japan) 35, 1901 (1962).

39. Kerstein, H. and Hoffmann, R., Ber., 57, 491 (1924).

40. Fraser, J. and Hamer, F. M., J. Chem. Soc., 507 (1936).

41. Bogert, M. T. and Husted, H. G., J. Am. Chem. Soc., 54, 3394 (1932).

42. Bellamy, L. J., The infra-red Spectra of Complex Molecules, Methuen and Co. Ltd., London, second edition, 1959.

43. Dyson, G. M., Hunter, R. F. and Morris, R. W., J. Chem. Soc., 1186 (1927).

44. Modica, G. D., Barni, E. and Monache, F. D., J. Hetero. Chem., 2, 242 (1965).

45. Brown, R. F. C., Radom, L., Sternhell, S. and Rae, I. D., Can. J. Chem., 46, 2576 (1968).

46. Pople, J. A., Schneider, W. G. and Bernstein, H. J., High-Resolution Nuclear Magnetic Resonance, McGraw-Hill Book Co. Inc., New York, N. Y., 1959.

47. Brügel, W., Ankel, T. and Kruckeberg, F., Zeitschrift fur Elektrochemie, 64, 1121 (1960).

48. Tori, K., Ogata, M. and Kano, H., Chem. Pharm. Bull., 71, 681 (1963).

49. Pohl, L. and Wiegreba, W., Zeitschrift für Naturforschung, 20 B, 1032 (1965).

50. Jackman, L. M., Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, New York, N. Y., 1965.

51. Bible, R. H., Interpretation of N. M. R. Spectra, Plenum Press, New York, N. Y., 1965.

52. Wells, P. R. and Alcorn, P. G. E., Aust. J. Chem., 16, 1108 (1963).

53. Platt, J. R., J. Chem. Phys., 17, 484 (1949).

54. Cerniani, A. and Passerini, R., J. Chem. Soc., 2261 (1954).

55. Black, P. J. and Heffernan, M. L., Aust. J. Chem., 19, 1287 (1966).

56. Rao, C. N. R. and Venkataraghavan, R., Can. J. Chem., 42, 43 (1964).

48. Tori, K., Ogata, M. and Kano, H., Chem. Pharm. Bull., 71, 681 (1963).

49. Pohl, L. and Wiegreba, W., Zeitschrift für Naturforschung, 20 B, 1032 (1965).

50. Jackman, L. M., Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, New York, N. Y., 1965.

51. Bible, R. H., Interpretation of N. M. R. Spectra, Plenum Press, New York, N. Y., 1965.

52. Wells, P. R. and Alcorn, P. G. E., Aust. J. Chem., 16, 1108 (1963).

53. Platt, J. R., J. Chem. Phys., 17, 484 (1949).

54. Cerniani, A. and Passerini, R., J. Chem. Soc., 2261 (1954).

55. Black, P. J. and Heffernan, M. L., Aust. J. Chem., 19, 1287 (1966).

56. Rao, C. N. R. and Venkataraghavan, R., Can. J. Chem., 42, 43 (1964).

57. Maggiolo, A., J. Am. Chem. Soc., 73, 5815 (1951).

58. Matteson, D. S. and Synder, H. R., J. Am. Chem. Soc., 79, 3610 (1957).

59. Bentley, F. F., Smithson, L. D. and Rozek, A. L., Infrared Spectra and Characteristic Frequencies 700-300 cm^{-1}, Interscience Publishers, Inc., New York, N. Y., 1968. pp. 65-84.

60. Person, W. B., Pimentel, G. C and Schnepp, O., J. Chem. Phys., 23, 230 (1955).

61. Lippincott, E. R. and O'Reilly, E. J. Jr., J. Chem. Phys., 23, 238 (1955).

62. Jakobson, R. J. and Bentley, F. F., Appl. Spectry., 18, 88 (1964).

63. Clar, E., Polycyclic Hydrocarbons, Academic Press, New York, N. Y. 1964, Vol. 1, pp. 40-69.

64. Joseph, P. K. and Joullie', M. M., J. Med. Chem., 7, 801 (1964).

65. Baumgarten, H. E. and Dirks, J. E., J. Org. Chem., 23, 900 (1958).

66. De La Mare, P. B. D. and Bolton, R., Electrophilic Additions to Unsaturated systems, Elsevier Publishing Company, New York, N. Y., 1966, p. 174.

67. Desai, R. D. and Mehta, C. V., Indian J. pharm., 13, 205 (1951).

68. Bhargava, P. N. and Boliga, B. T., J. Indian Chem. Soc., 35, 807 (1958).

69. Hirshberg, Y. and Jones, R. N., Can. J. Res., 27 B, 437 (1949).

70. Vogel, A. L., Elementary Practical Organic Chemistry, Partl, John Wiley & Sons, Inc., New York, N. Y. 1966, pp. 280-281.

71. Cox, J. M., Elvidge, J. A. and Jones, D. E. H., J. Chem. Soc., 1423 (1964).

72. Jaffe, H. H., Theory and Applications of Ultraviolet Spectroscopy, John Wiley and Sons, Inc., New York, N. Y. 1962, pp. 345-383.

73. Gold, V. and Whittaker, M., J. Chem. Soc., 1184 (1951).

74. Brennan, D. and Ubbelohde, A. R., J. Chem. Soc., 3011 (1956).

75. Kaufmann, H. P., Angew. Chem., 54, 195 (1941).

76. Kaufmann, H. P., Angew. Chem., 54, 168 (1941).

77. Kröhnke, F. and Stevernagal, H., Angew. Chem., 73, 26 (1961).

78. Elderfield, R. C., Heterocyclic Compounds, Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 344-454.

79. Fairfull, A. E. S. and Peak, D. A., J. Chem. Soc., 796 (1955).

80. O'Sullivan, D. G., J. Chem. Soc., 3279 (1960).

81. Adams, R., Organic Reactions, Vol. 111, John Wiley and Sons, Inc., 1947, pp. 240-266.

82. Kaufmann, H. P. and Kögler, F., Ber., 58, 1553 (1925).

83. Elderfield, R. C., Heterocyclic Compounds, Vol. 5, John Wiley and Sons, Inc., New York, N. Y. 1957, pp. 484-613.

84. Hrutford, B. F. and Bunnett, J. E., J. Am. Chem. Soc., 80, 2021 (1958).

85. Hrutford, B. F. and Bunnett, J. E., J. Am. Chem. Soc.,

83, 1691 (1961).

86. Jones, G., J. Chem. Soc., 1896 (1960).

87. Fichter, Fr. and Schömann, P., Helv. Chem. Acta., 19, 1411 (1936).

88. Takahashi, T., Yatsuka, Y. and Onuma, Y., J. Pharm. Soc., (Japan) 64, 235 (1944).

89. Adams, R., Organic Reactions, Vol. Vl, John Wiley and Sons, Inc., 1951, pp. 191-206.

90. Takahashi, T., Ueda, K. and Ichimoto, T., Pharm. Bull (Japan) 2, 196 (1954).

91. Kharash, N., Organic Sulfur Compound, Vol. 1, Pergamon Press, New York, N. Y. 1961, pp. 306-323.