NUCLEOPHILIC REACTIVITY IN 3-HYDROXYISOTHIAZOLE

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by

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AUTHOR'S STATEMENT

I declare that the research described in this
Thesis is my own except where the work of others is
specifically acknowledged.

ACKNOWLEDGMENTS

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CONTENTS

ABSTRACT

Synthetic approaches have been examined to the
preparation of N-substituted-3-isothiazolones, in which
the substituent chain carries a potential carbanion site.
The object of the work was to establish the geometry of
carbanion attack on the S-N bond, with a view to preparing
new S,N-heterocyclic systems.

PART I

Several techniques for acylation of 3-hydroxyisothia-
zole (XXXII) were examined. Reactions with acyl chlorides/
triethylamine in benzene were subject to kinetic control,
leading almost exclusively to the 3-acyloxyisothiazoles.
In the absence of triethylamine, the reaction with acid
chlorides yielded, in most cases, nearly equal amounts of
O- and N-acyl derivatives. With aliphatic acid anhydrides
N-acylation was the predominant reaction. The
differences were rationalized in terms of the steric
requirements in the transition state of both the acyl
group and the base catalyst (where present). Acylation
with isatoic anhydride gave 3-anthranoyloxyisothiazole
(LXXXVIII) and the new heterocyclic system isothiazolo-

[2,3-b]-4(3H)-quinazolinone (XCI). A proposed synthesis of (XCI) from the reaction of 3-chloroisothiazole with anthranilic acid was unsuccessful.

The existence of a reversible O→N migration of acyl groups was demonstrated. The use of isotopic labelling established that the acyl migration was intermolecular, and was catalysed by 3-hydroxyisothiazole and other nucleophiles. The rearrangement process ((XXXII) as catalyst) involved O→O, O→N, N→O and N→N acyl-transfer reactions. The position of equilibrium was rationalized in terms of steric demand by the acyl group (the larger groups being more stable on oxygen) and N-CO overlap in the N-acyl-3-isothiazolones.

The reaction of sodium hydride on a number of N-acyl-3-isothiazolones was examined. Where the 5-position was free, formation of the 5-anion led to the production of polymers, possibly through a thioketene intermediate. This effectively prevents examination of attack on the S-N bond by a carbanion site in the acyl chain unless the 5-position is blocked.

PART II

The reaction of 3-hydroxyisothiazole (XXXII) with diazomethane and with triethyloxonium fluoroborate was reinvestigated. In both cases a mixture of O- and N-alkyl

derivatives resulted. Michael reaction with acrylonitrile and with ethyl acrylate gave only the N-alkyl compounds. The absence of any O-substituted product was probably due to the greater tendency of the O-alkyl compound to undergo a reverse Michael reaction.

Alkylation of the metal salts of 3-hydroxyisothiazole was studied in relation to the effects of cation, solvent and alkyl halide structure on the alkylation site. The results showed that the product composition (O- and N-) was primarily a function of the size of the alkylating agent, with greater steric requirements in N-alkylation. Choice of solvents was important in the alkylation of (XXXII) using this method, since solvent participation was observed when acetone was used as a solvent. Hydroxylic solvent systems such as alcohol/alkoxide invariably led to dithietane formation by dimerization of the N-alkyl-3-isothiazolone.

Attempts to prepare 3-chloroisothiazole from (XXXII) were unsuccessful. This compound, prepared later by a published method,[104] was found to be inert towards alkoxide ions. Therefore the preparation of 3-alkyloxy-isothiazoles from 3-chloroisothiazole could not be effected.

<u>INTRODUCTION</u>

(I) <u>SYNTHESIS OF ISOTHIAZOLES</u>

Bicyclic and polycyclic systems containing the isothiazole structure have long been known; Bambas in 1952 fully reviewed the chemistry of such systems.[1] Adams and Slack prepared the first mononuclear isothiazole in 1956,[2] and since then several synthetic methods and a variety of derivatives of isothiazoles have been described. Literature up to 1964 has been reviewed by Slack and Wooldridge.[3] In this review, the authors mentioned that isothiazoles have considerable potential in the field of chemotherapy and pharmacology; a number of examples were quoted.

Formation of the S-N bond is a very important process in the synthesis of isothiazoles. Methods that have been reviewed include the following -

(a) oxidative ring closure of β-iminothioamides[4-8] or β-iminothioketones;[9]

(b) reaction of olefins with sulphur dioxide and ammonia in the presence of activated alumina;[10,11]

(c) cyclization with liquid ammonia of the addition product from acetylenic ketones and thiosulphate or

thiocyanate;[12-15]

(d) cyclization of dicyanoethylene-thiolate with sulphur, chlorine or chloramide.[16-20]

Examples of these methods are depicted on page 3.

A brief summary of more recent synthesis of isothiazoles is given below to illustrate the importance of S-N bond formation:

(A) REACTION OF DITHIOLIUM SALTS

Fanghaenel[21] reported that 1,3-dithiolium salts (I) reacted with sodium azide to give the unstable intermediate (II) which lost nitrogen to give the dithiazine derivatives (III). When R and R' were different, two isomers of (III) were isolated because the nitrene intermediate could attack either of the two sulphur atoms in the 1,3-dithiole system. A competing side reaction was the transformation of (II) to (IV). Isothiazoles (V) were obtained by heating (III) at 160°-180°. This is essentially a sulphur-extrusion reaction. Although the formation of the S-N bond by a nitrene insertion mechanism is novel, this method suffered from the disadvantages mentioned above.

OXIDATIVE RING CLOSURE OF β-IMINOTHIOAMIDES

REACTION OF OLEFINS WITH SULPHUR DIOXIDE AND AMMONIA

$$3CH_2=CHCH_3 + 4SO_2 + 3NH_3 \longrightarrow$$

$$3 \quad + \quad 8H_2O + H_2S$$
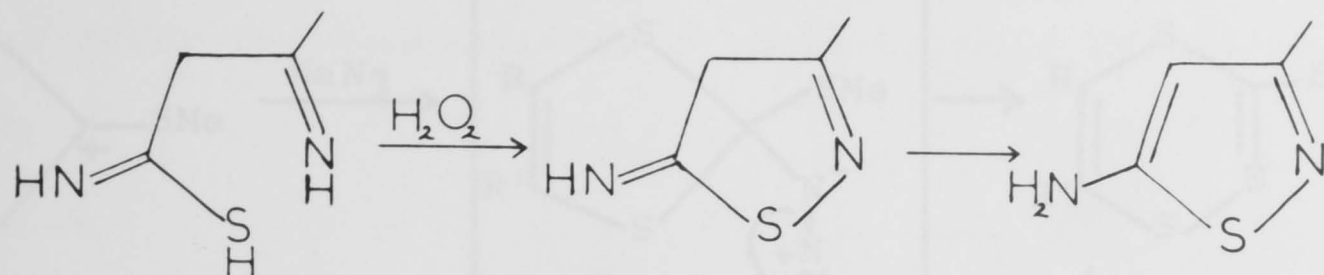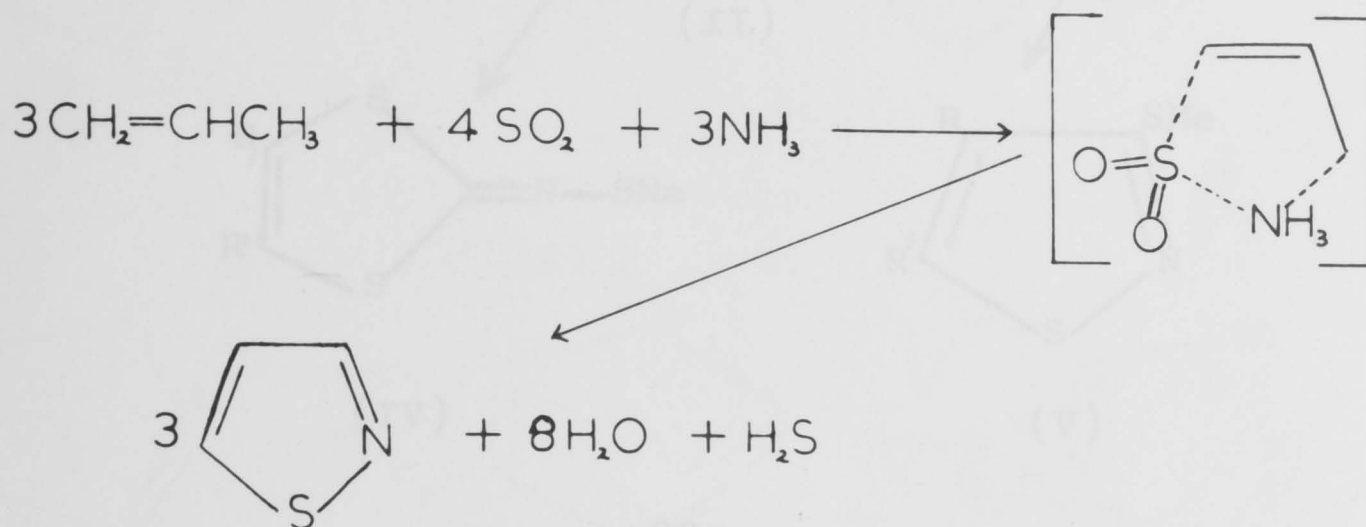
REACTION OF ACETYLENIC CARBONYL COMPOUNDS

$$\equiv-COR + Na_2S_2O_3 \longrightarrow$$
SCN
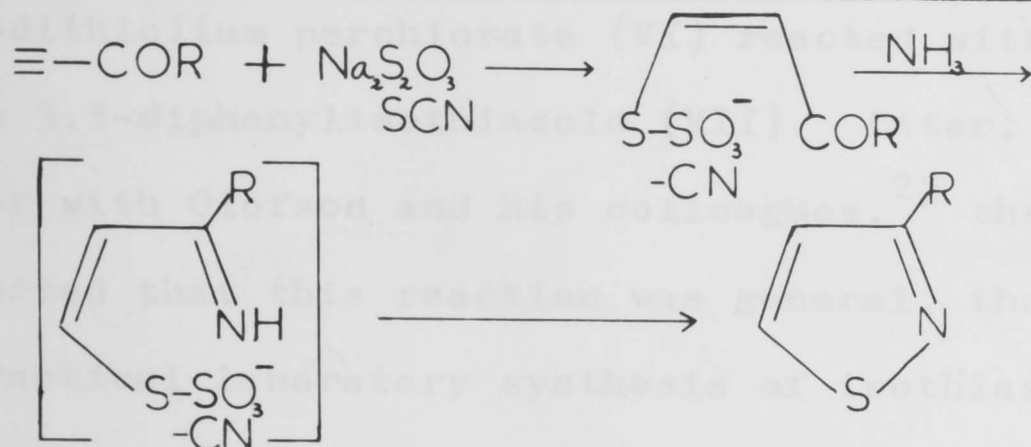
REACTION OF DICYANOETHYLENE—THIOLATE

NCCCN
‖
NaSCSNa
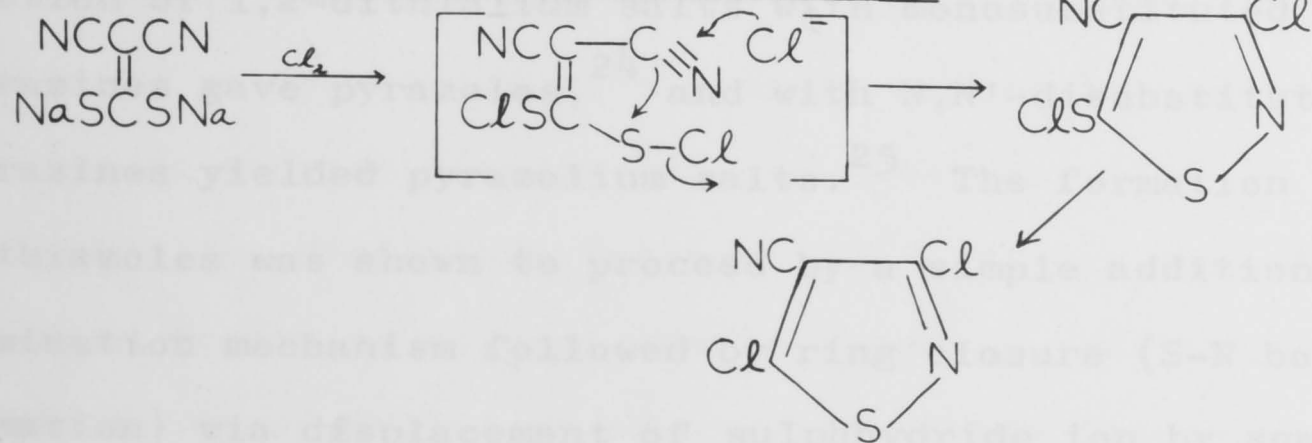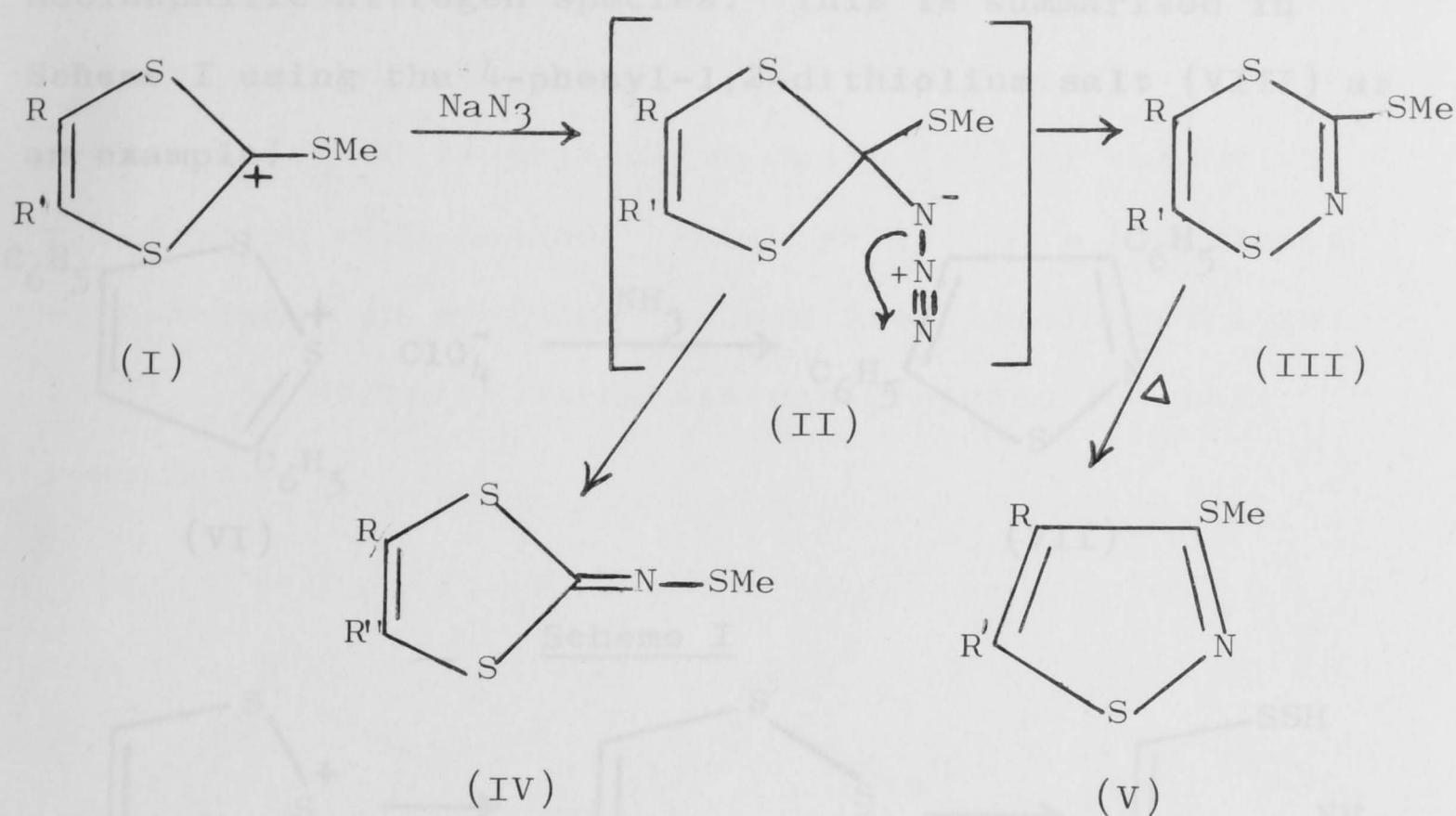
Leaver and his co-workers[22] found that 3,5-diphenyl
1,2-dithiolium perchlorate (VI) reacted with ammonia to
give 3,5-diphenylisothiazole (VII). Later, in a joint
paper with Olofson and his colleagues,[23] the same authors
reported that this reaction was general, thus constituting
a practical laboratory synthesis of isothiazoles. It is
of interest to note that Klingsberg first discovered that
reaction of 1,2-dithiolium salts with monosubstituted
hydrazines gave pyrazoles,[24] and with N,N'-disubstituted
hydrazines yielded pyrazolium salts.[25] The formation of
isothiazoles was shown to proceed by a simple addition-
elimination mechanism followed by ring closure (S-N bond
formation) via displacement of sulphhydride ion by some

nucleophilic nitrogen species. This is summarised in Scheme I using the 4-phenyl-1,2-dithiolium salt (VIII) as an example.

(VI)   (VII)
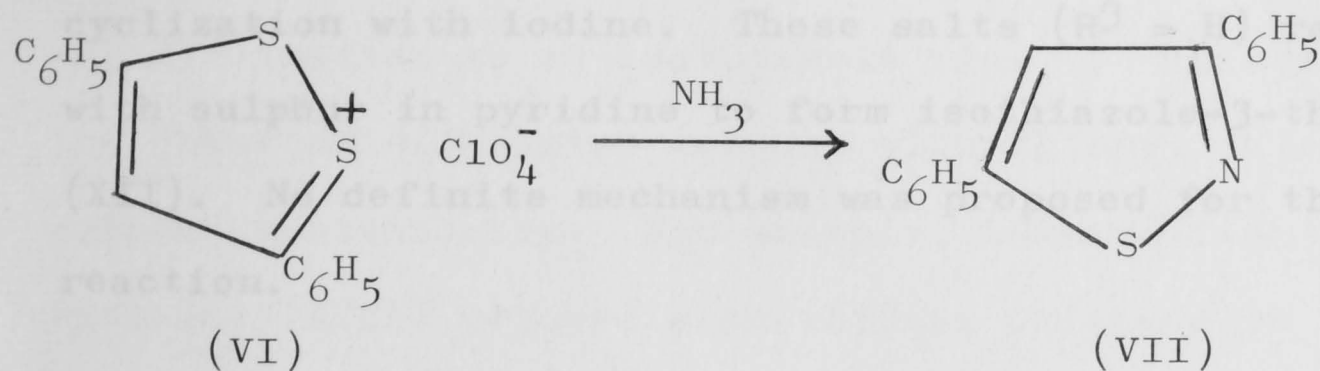
Scheme I

(VIII)
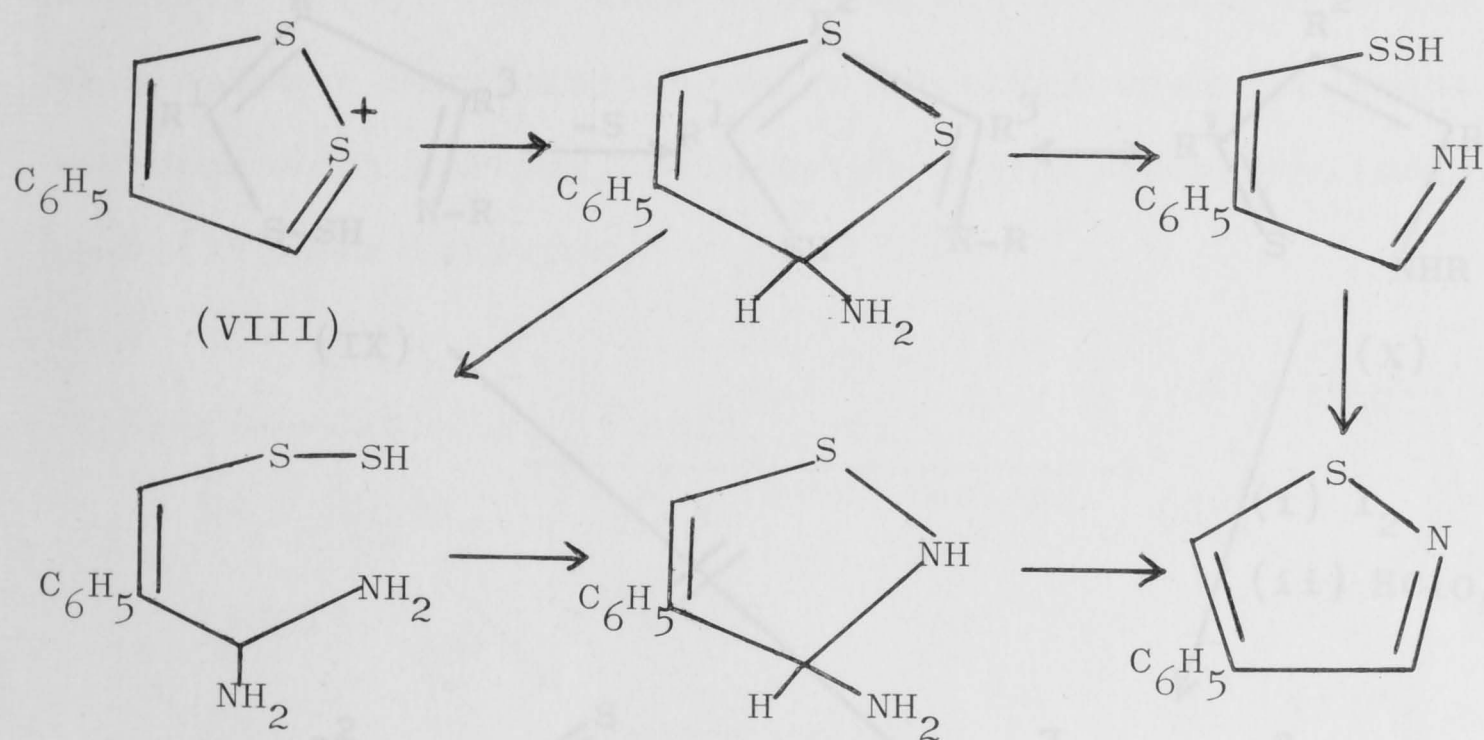
Recently McKinnon and Robak[26] found that certain 1,2-dithiolium salts reacted with primary amines in alcoholic solution to provide 1-amino-propene-3-thiones (X). Presumably the disulphide intermediate (IX) was formed by a similar mechanism as depicted in Scheme I, but instead of undergoing an overall loss of a sulphhydride ion to yield

the N-substituted isothiazolium system (XI), (IX) lost one

atom of sulphur to generate (X). Nevertheless (X) could

be converted to isothiazolium salts (XI) by oxidative

cyclization with iodine. These salts (R^3 = H) reacted

with sulphur in pyridine to form isothiazole-3-thiones

(XII). No definite mechanism was proposed for this

reaction.

(IX)   (X)

(i) I_2

(ii) $HClO_4$

(XII)   (XI)
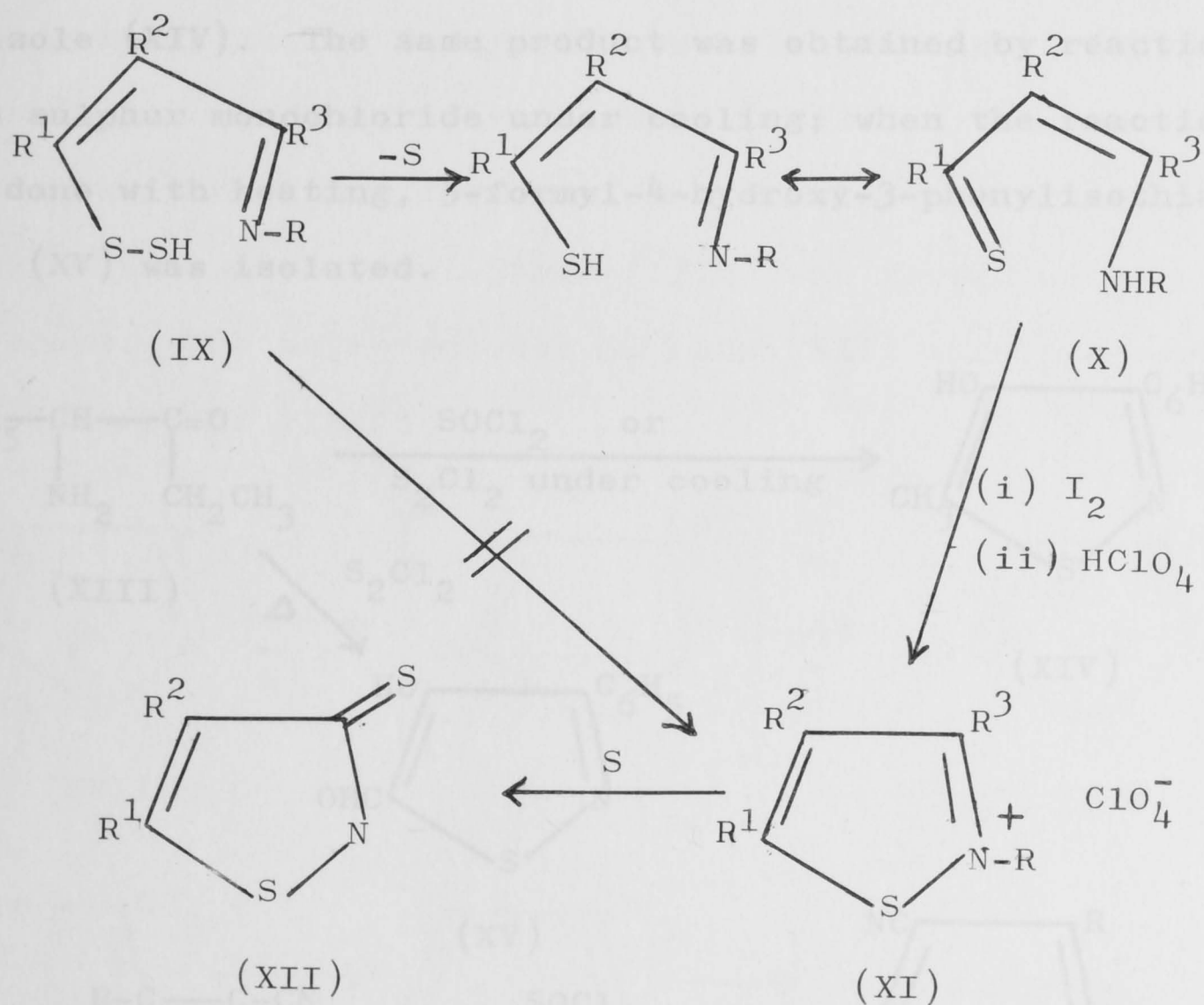
(B) <u>REACTION OF α-AMINO KETONES WITH
THIONYL CHLORIDE OR SULPHUR
MONOCHLORIDE</u>

Naito and his co-workers reported a novel procedure
for cyclization to an isothiazole ring.[27] This involved
the reaction of α-amino ketones with thionyl chloride or
sulphur monochloride. For example, 1-Amino-1-phenyl-2-
butanone (XIII) reacted with thionyl chloride in
dimethylformamide to give 4-hydroxy-5-methyl-3-phenyliso-
thiazole (XIV). The same product was obtained by reaction
with sulphur monochloride under cooling; when the reaction
was done with heating, 5-formyl-4-hydroxy-3-phenylisothia-
zole (XV) was isolated.

8
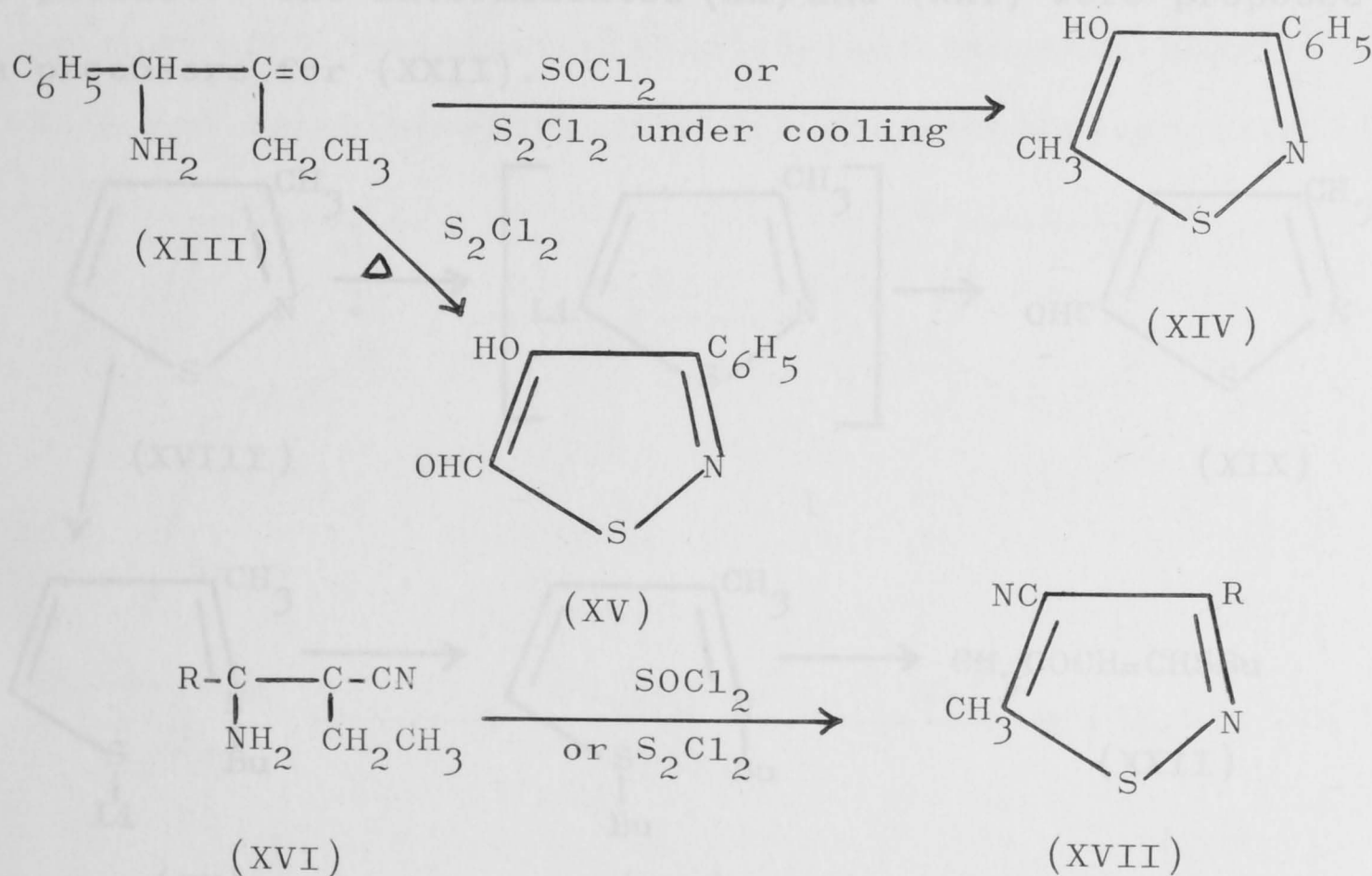
An extension of this method was the preparation of 4-cyanoisothiazoles (XVII) from reaction of β-cyano-enamines (XVI) with thionyl chloride or sulphur monochloride.[28]

(II) S-N BOND CLEAVAGE IN ISOTHIAZOLES

There have not been many observations of S-N bond cleavage in mononuclear isothiazoles. Slack and his co-workers[29] reported the first case of such a ring scission. In the preparation of 5-formyl-3-methyl-isothiazole (XIX) by lithiation of 3-methylisothiazole (XVIII) with n-butyl lithium and subsequent formylation with dimethylformamide, 4-butylmercapto-2-oxo-but-3-ene (XXII) was formed as a by-product. The intermediates (XX) and (XXI) were proposed as precusors for (XXII).

(XVIII) (XIX)

(XX) (XXI)

$CH_3COCH=CHSBu$
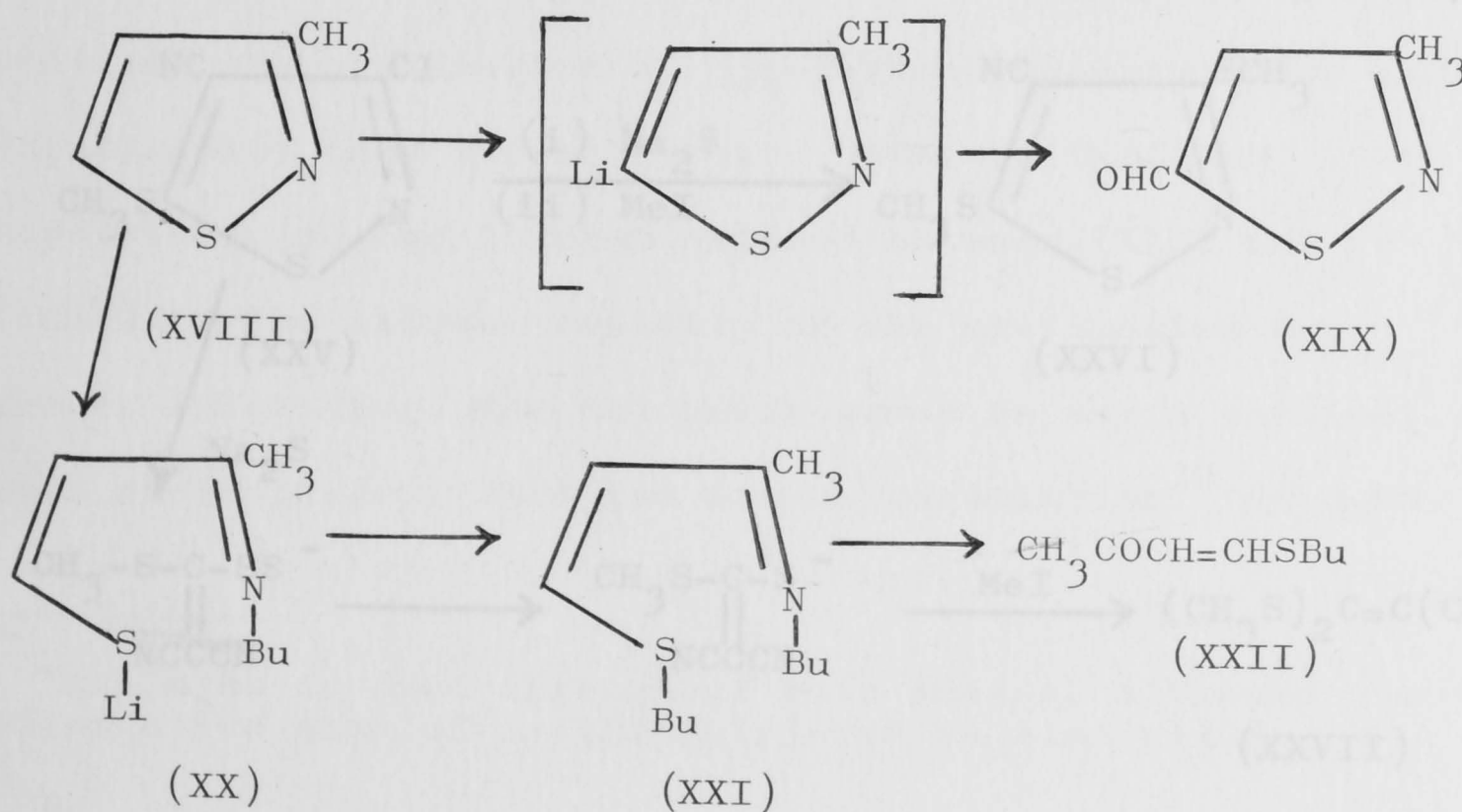
(XXII)

Hatchard[17] reported that Raney nickel desulphurization
of 5-anilino-3-chloro-4-isothiazolecarbonitrile (XXIII)
yielded anilinomethylenemalononitrile (XXIV). This could
arise only from a ring-opening reaction as shown below.

(XXIII)   (XXIV)
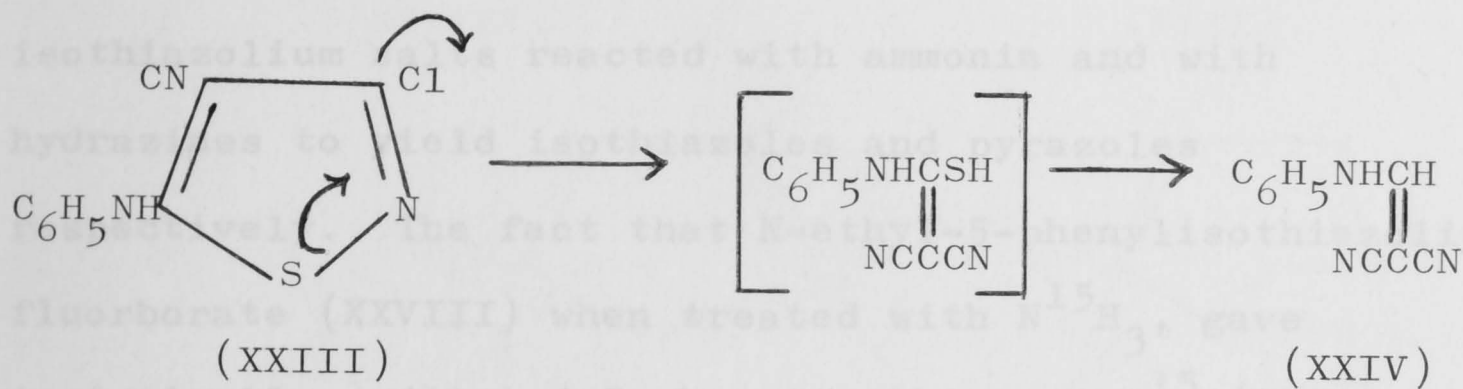
In the same paper an example of nucleophilic attack on the
sulphur atom was given: reaction of 3-chloro-5-methylthio-
4-isothiazolecarbonitrile (XXV) with sodium sulphide
followed by alkylation with methyl iodide was found to give
a mixture of 3,5-bis(methylthio)-4-isothiazolecarbonitrile
(XXVI) and 1,1-bis(methylthio)-2,2-dicyanoethylene (XXVII).

(XXV)   (XXVI)

(XXVII)
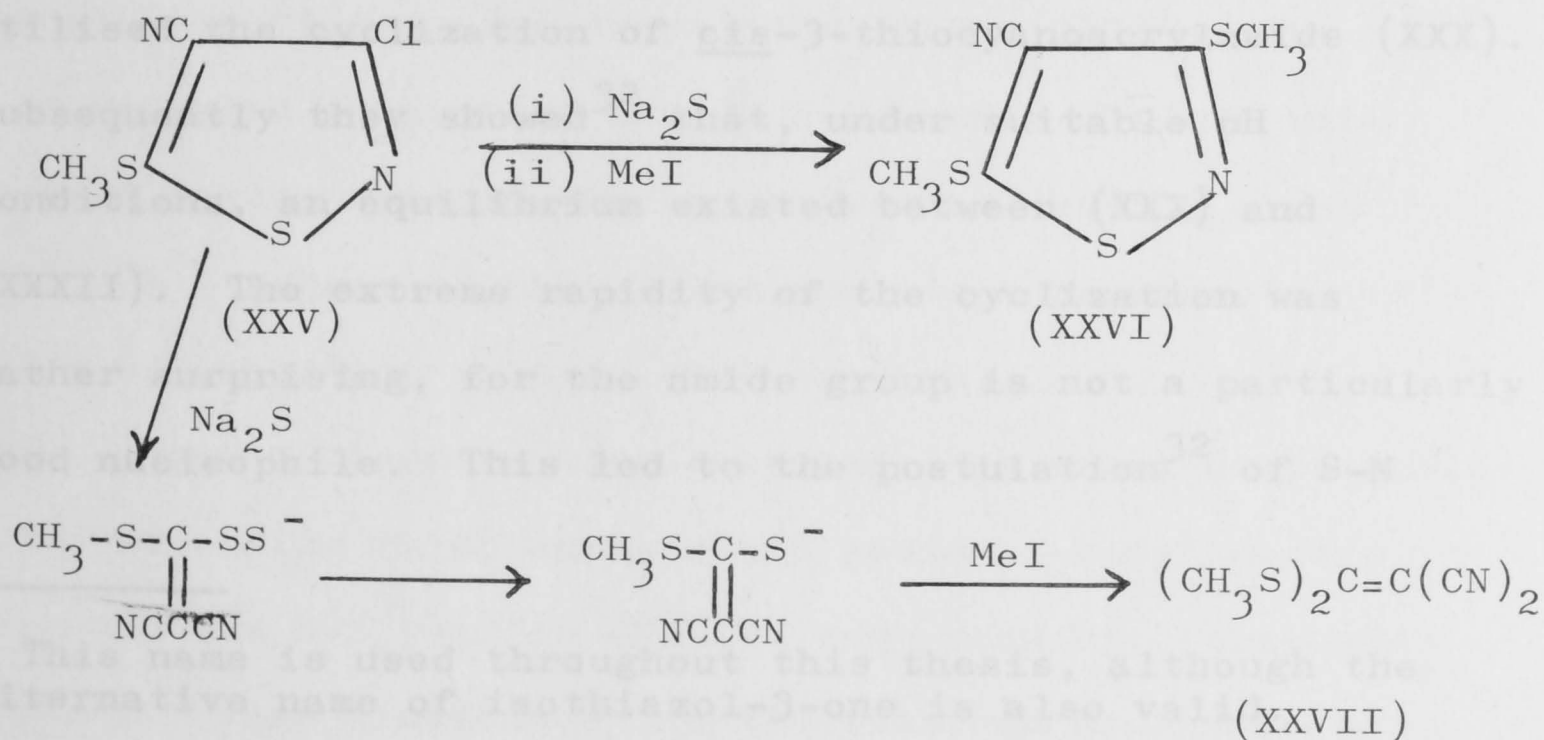
The formation of the dicyanoethylene apparently occurred by attack of the sulphide anion on the ring sulphur with ejection of chloride ion.

In 1966 Landesberg and Olofson[30] showed that isothiazolium salts reacted with ammonia and with hydrazines to yield isothiazoles and pyrazoles respectively. The fact that N-ethyl-5-phenylisothiazolium fluorborate (XXVIII) when treated with $N^{15}H_3$, gave isotopically undiluted 5-phenylisothiazole N^{15} (XXIX) indicated a somewhat unusual mechanism for the reaction. The authors favoured the addition-elimination mechanism (A), but mechanism (B) could not be ruled out though it might not be a dominant one.

The present work originated from the synthesis of 3-hydroxyisothiazole* (XXXII) by Crow and Leonard[31] who utilised the cyclization of cis-3-thiocyanoacrylamide (XXX). Subsequently they showed[32] that, under suitable pH conditions, an equilibrium existed between (XXX) and (XXXII). The extreme rapidity of the cyclization was rather surprising, for the amide group is not a particularly good nucleophile. This led to the postulation[32] of S-N

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* This name is used throughout this thesis, although the alternative name of isothiazol-3-one is also valid.

(XXVIII)   (XXIX)
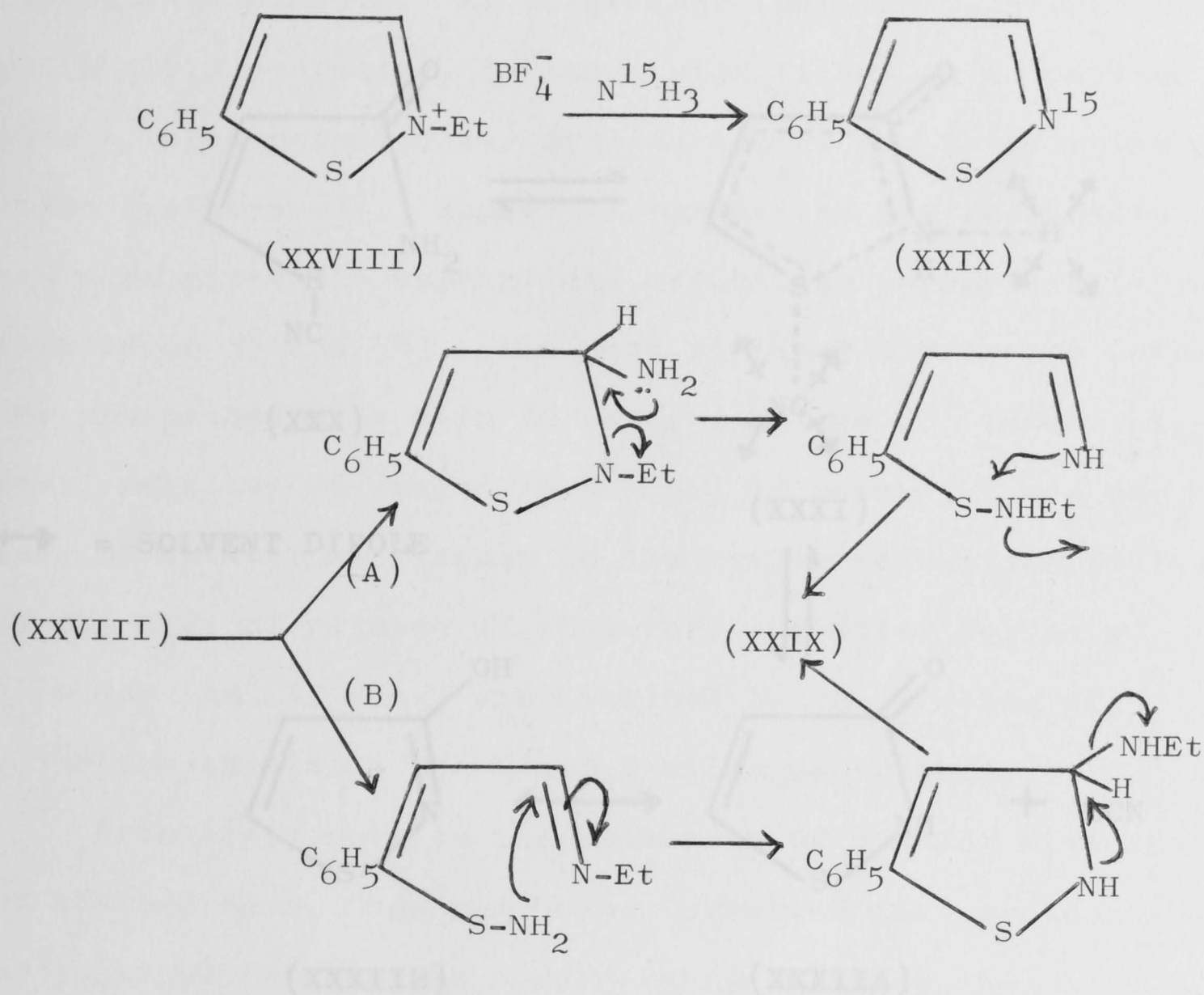
orbital overlap in the transition state (XXXI). The

accompanying stretching of the S-CN and N-H bonds with

charge development on the two potential leaving group

(H^+, CN^-) suggested that solvation might be expected to

play an important role in the reaction.

Crow and Leonard also observed that other nucleophiles

such as sodium thiophenolate and sodium t-butyl mercaptide

cleaved the S-N bond in (XXXII) very readily. Crow and

Gosney[33] then elucidated the kinetics and mechanism of

cyclization of cis-3-thiocyanoacrylamide. The reverse

reaction, namely, cyanide cleavage of the S-N bond, was also

studied.[34] They showed that the reactions were reversible.

The cyclization of cis-3-thiocyanoacrylamide was shown to

occur by two kinetically distinct mechanisms. At pH less

than 3.5 the amide itself underwent cyclization to the

conjugate acid of 3-hydroxyisothiazole at a rate independent

of pH, the product undergoing rapid loss of a proton to the

solvent (pathway I). At pH greater than 3.5 this mechanism, while still operative, became insignificant in comparison with a rapid unimolecular cyclization of the thioacrylamide anion (pathway II). Scheme II summarises the mechanisms and also gives the appropriate activation parameters (from references 33 and 34). The most striking difference between the two pathways is seen in the respective ΔS^* terms. The small negative ΔS^* value (9.5 e.u.) in pathway I was due to loss of rotational freedom in the cyclic transition state. In the case of pathway II, however, a greater degree of disorder ($\Delta S^* = 22$ e.u.) was ascribed to the freeing of solvation shells as the N and S atoms approached.
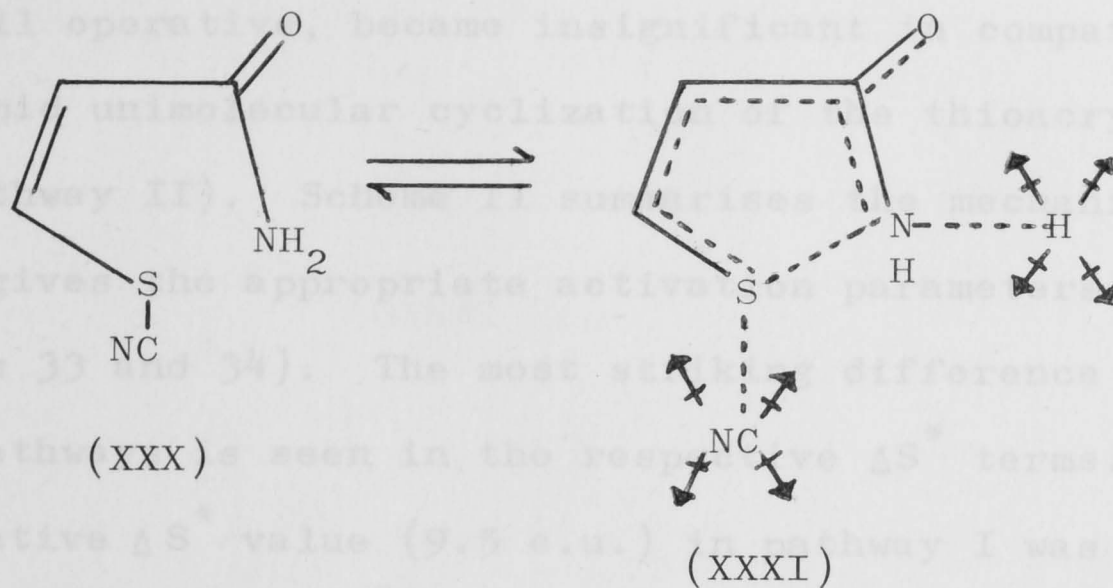
From their work on the mechanism of cyanide cleavage of the S-N bond, Crow and Gosney observed that protonation of 3-hydroxyisothiazole considerably enhanced the susceptibility of the S-N bond to nucleophilic attack. The rate constant was greater by a factor of 10^3 than that for attack on the neutral molecule. This is a direct consequence of weakening of the S-N bond by protonation. The site of protonation (oxygen or nitrogen) is immaterial, since it is expected there will be a decrease in electron density in the vicinity of the S-N bond. This means that the availability of electrons on nitrogen for any p_π-d_π overlap will be lowered, hence the weakening of the bond.

SCHEME II

Pathway I

Pathway II

—Cyclization mechanisms for *cis*-3-thiocyanoacrylamide. Pathway I: k_1 $4 \cdot 5 \times 10^{-5}$ sec^{-1}; pK_t $-0 \cdot 33 \pm 0 \cdot 03$; ΔH^* $20 \cdot 7$ kcal mole^{-1}; ΔS^* $-9 \cdot 5$ e.u. Pathway II: K_a assumed 10^{-9}, giving k_2 $10 \cdot 4$ sec^{-1}; ΔH^* $22 \cdot 6$ kcal mole^{-1}; ΔS^* $22 \cdot 0$ e.u.

A number of synthetic possibilities can be derived
theoretically by utilizing the nucleophilic attack on the
sulphur of the isothiazol-3-one moiety. The schemes (III
to V) shown below are self-explanatory.

Scheme III
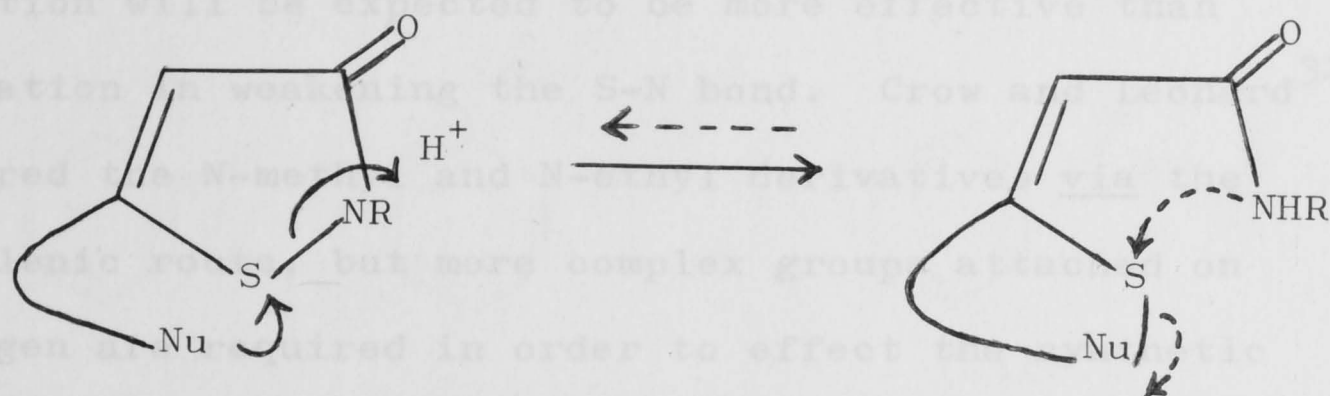
Scheme IV
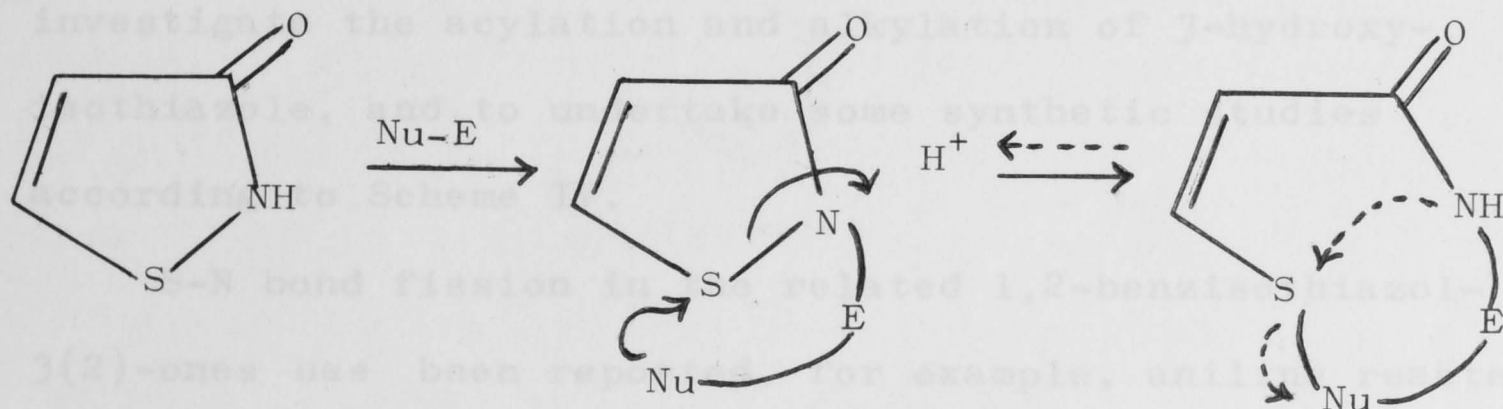
Scheme V
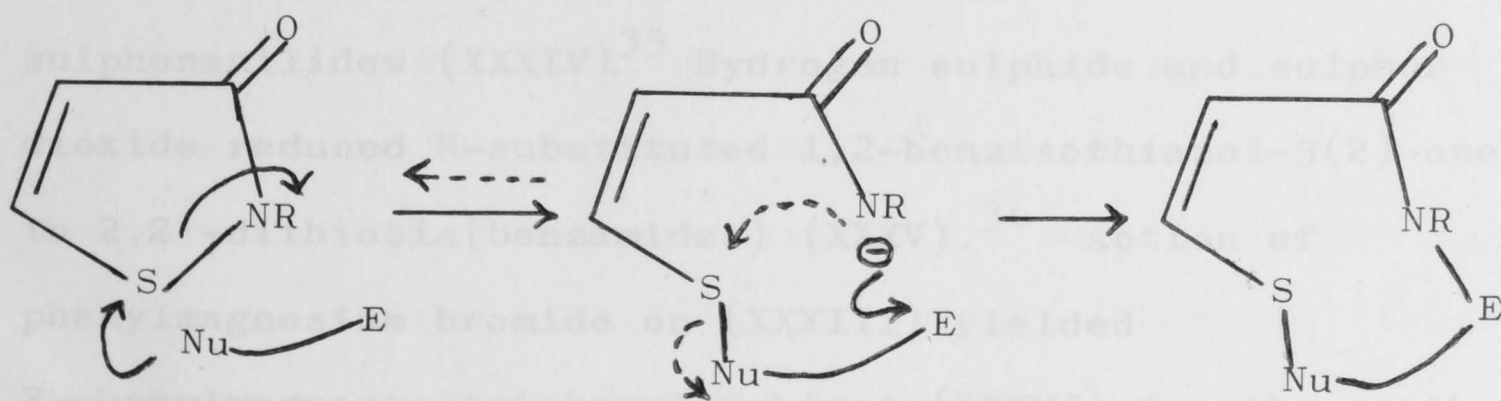
R=H, Alkyl, Acyl, Nu=Nucleophilic site, E=Electrophilic
site.

From the synthetic point of view, use of an acidic medium is not desirable, especially when the attacking nucleophile is a carbon acid (for example, in Scheme V). It is thought that N-alkylation and N-acylation of 3-hydroxyisothiazole might be an attractive alternative. Acylation will be expected to be more effective than alkylation in weakening the S-N bond. Crow and Leonard[32] prepared the N-methyl and N-ethyl derivatives via the acetylenic route, but more complex groups attached on nitrogen are required in order to effect the synthetic Scheme IV. The prime objective of this work is thus to investigate the acylation and alkylation of 3-hydroxy-isothiazole, and to undertake some synthetic studies according to Scheme IV.

S-N bond fission in the related 1,2-benzisothiazol-3(2)-ones has been reported, for example, aniline reacted with 2-benzenesulphonyl-1,2'-benzisothiazol-3(2)-one (XXXIII) to give 2-N-benzenesulphonylcarbamyl-phenyl-sulphenanilides (XXXIV).[35] Hydrogen sulphide and sulphur dioxide reduced N-substituted 1,2-benzisothiazol-3(2)-ones to 2,2'-dithiobis(benzamides) (XXXV).[36] Action of phenylmagnesium bromide on (XXXIII) yielded 2-phenylmercapto-triphenylcarbinol (XXXVI) together with benzenesulphonamide (XXXVII).[37]
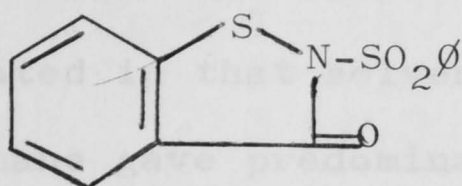
(XXXIII)
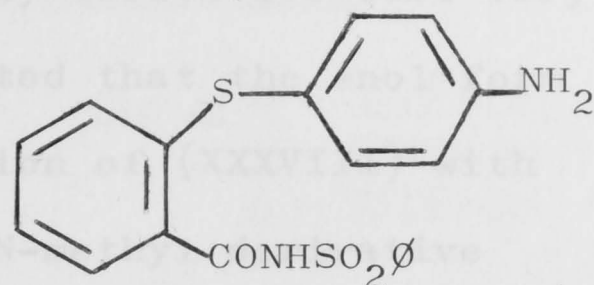
(XXXIV)
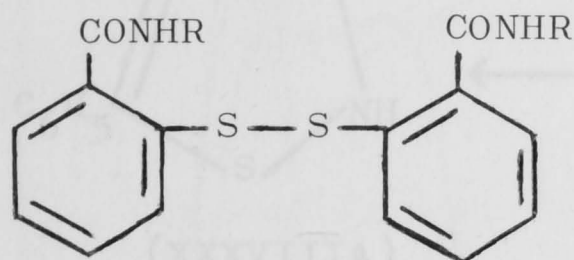
(XXXV)
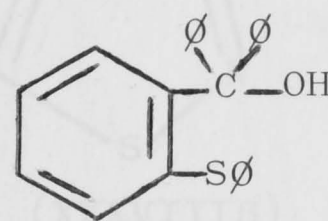
(XXXVI)
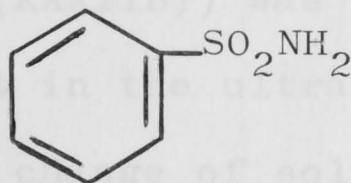
(XXXVII)

(III) ALKYLATION AND ACYLATION STUDIES

Isothiazoles containing a hydroxyl group in position 3 can theoretically exhibit lactam-lactim tautomerism. Goerdeler and Mittler[9] synthesized the methyl derivatives of both the lactam (XXXVIIIA) and lactim (XXXVIIIB) forms of 3-hydroxy-5-phenylisothiazole by ring closure of the appropriate intermediates. In methanolic solution, the U.V.

spectra of (XXXVIII) and its 3-methoxy derivative were very similar. From this Goerdeler suggested that the enol form predominated in that solvent. Reaction of (XXXVIII) with diazomethane gave predominantly the N-methyl derivative after 3 days.

(XXXVIIIA)   (XXXVIIIB)
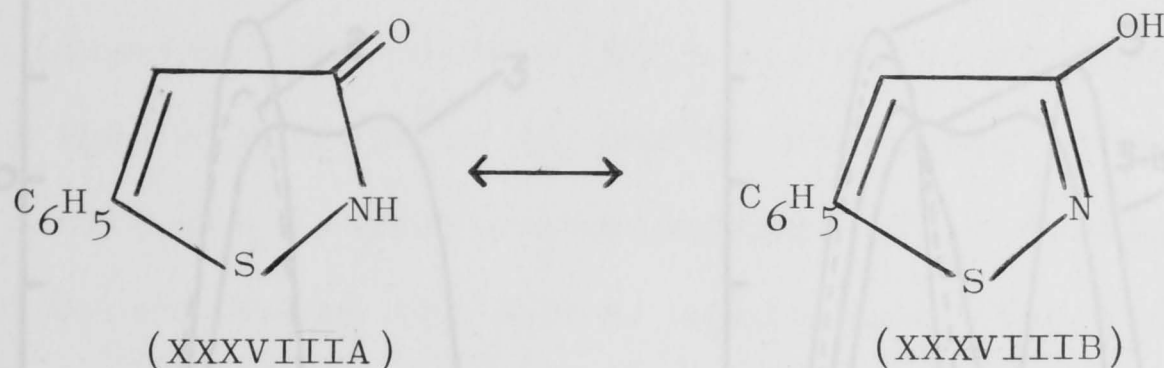
For 3-hydroxyisothiazole itself the same lactam-lactim tautomerism ((XXXIIA) ↔ (XXXIIB)) was investigated by Gosney.[38] A marked shift in the ultra-violet absorption spectrum for (XXXII) with change of solvent was observed (see Figure I - reference 38). This suggested the existence of tautomers. Subsequently Gosney used N-ethyl-3-isothiazolone (XXXIX) and a calculated spectrum for 3-ethoxyisothiazole (XL) as standards for the two tautomeric forms, and he compared these with the unsubstituted compound in various solvents. Results indicated that the lactim form existed almost exclusively in ether and other non-polar solvents, while in water, both forms were present in about the same proportions. The use of a calculated spectrum was inevitable because efforts in preparing the 3-methoxy- and 3-ethoxyisothiazoles were unsuccessful. Alkylation of

UV Spectra for 3-Isothiazolone in various solvents

Curve 1 — Et_2O

2 — MeOH

3 — H_2O

Curve 4 — abs.EtOH

5 — 50%EtOH

6 — 75%EtOH

N-ethyl 3-isothiazolone

$E \times 10^{-3}$

250   mμ 300

250   mμ 300

FIG. I

20
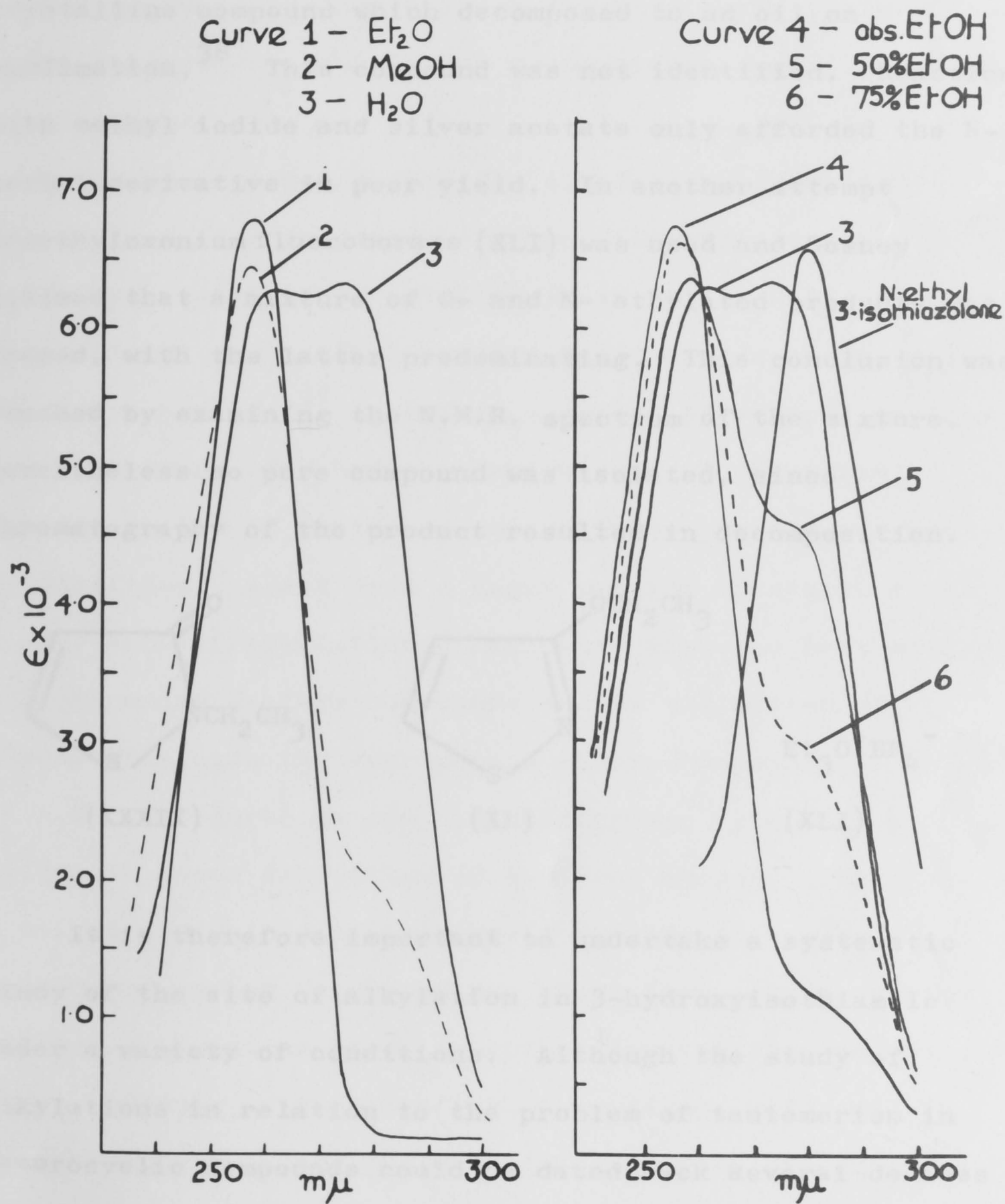
(XXXII) with diazomethane was reported to yield an unstable crystalline compound which decomposed to an oil on sublimation,[38] This compound was not identified. Reaction with methyl iodide and silver acetate only afforded the N-methyl derivative in poor yield. In another attempt triethyloxonium fluoroborate (XLI) was used and Gosney claimed that a mixture of O- and N- ethylated products was formed, with the latter predominating. This conclusion was reached by examining the N.M.R. spectrum of the mixture. Nevertheless no pure compound was isolated, since chromatography of the product resulted in decomposition.
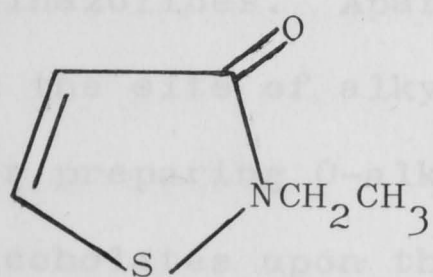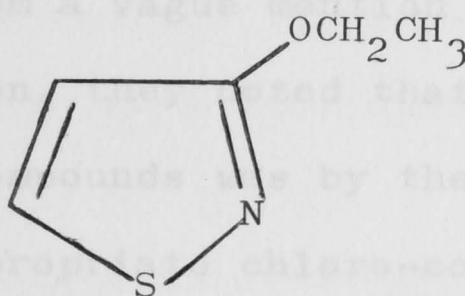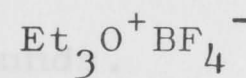
(XXXIX)   (XL)   (XLI)

It is therefore important to undertake a systematic study of the site of alkylation in 3-hydroxyisothiazole under a variety of conditions. Although the study of alkylations in relation to the problem of tautomerism in heterocyclic compounds could be dated back several decades ago, early workers were handicapped by technical difficulties associated with the separation and analysis of

resulting product mixtures. In many cases, degradative work had to be employed to establish the structure of a product. These rendered systematic and quantitative work impossible at that time.

The most common method for alkylation of ambident anions (i.e. anions possessing two different reaction positions) consists of reacting their metal salts, usually in a solvent, with alkyl or aryl halides. An early review by Bogert and Seil[39] contained a number of generalizations on alkylations of 2-hydroxy derivatives of the closely related series of pyridines, quinolines, pyrimidines and quinazolines. Apart from a vague mention of steric effect on the site of alkylation, they noted that the best method for preparing O-alkyl compounds was by the action of alcoholates upon the appropriate chloro-compounds.

In 1955 Kornblum and his colleagues[40] proposed a principle about alkylation of ambident anions. This provided a simple rationale for the hitherto unsolved problem of carbon versus oxygen alkylation, oxygen versus nitrogen alkylation etc., in anions derived from acetoacetic ester, phenols, nitroparrafins, α-pyridone, acid amides, thioamides etc. They proposed that when the SN1 character of the transition state was greater, there was a greater preference for covalency formation with the atom of higher

electronegativity; conversely, a greater SN2 contribution

to the transition state resulted in a greater preference

for bond formation to the atom of lower electronegativity.

Later work by Kornblum[41-44] provided useful information

concerning those factors which govern the site of

alkylation of ambident anions; these included steric

hindrance, heterogeneity, hydrogen-bonding with solvents,

and dielectric constants of solvents. Recently Tieckelmann

and his co-workers reported the alkylation of 2-hydroxy-

pyrimidine[45] and 2-pyridone salts.[46] In their work, factors

such as the cation, solvent, leaving group, and alkyl

halide structure were systematically varied. The ratios of

O- and N-alkylated products were determined by gas liquid

chromatography.

No systematic study of alkylation of 3-hydroxy-

isothiazoles has been reported. Reissert and Manns[47] found

that the silver salt of 1,2-benzisothiazol-3(2)-one (XLII)

reacted with methyl iodide to give a mixture of O- and N-

methyl derivatives. Normally N-alkyl and N-aryl-1,2-

benzisothiazol-3(2)-ones (XLIV) can be prepared more

conveniently by synthesis. McClelland's method was one of

many examples: this involved reaction of 2-chlorocarbonyl-

phenylsulphenyl chlorides (XLIII) with primary amines.[36]

(XLII)   (XLIII)   (XLIV)
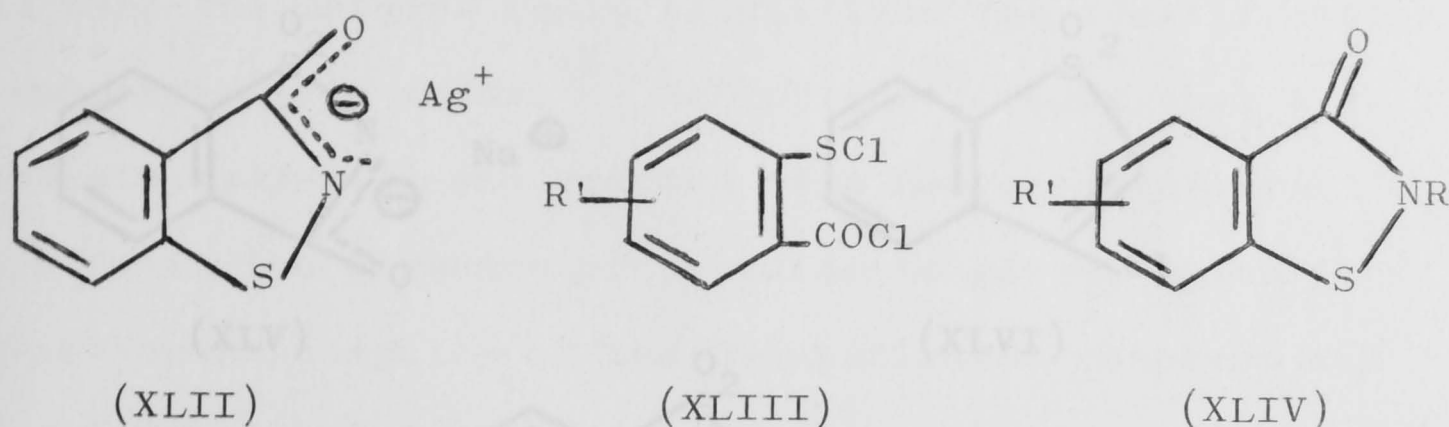
Bambas[1] has reviewed reactions of sodium saccharide
(XLV) with alkylating agents. In most cases only N-
substitution occurred; methylation yielded a mixture of O-
and N- products. In fact alkylation of saccharin was used
as a method of identifying alkyl iodides and bromides,
since the technique was simple and sharp melting points
were obtained for the derivatives.[48] 3-alkoxy and 3-
aryloxysaccharins (XLVII) could be prepared by heating 3-
chlorosaccharin (XLVI) with the appropriate alcohols.[49]
This was proposed as a good method of identifying alcohols.
The corresponding thioethers could be similarly prepared by
reaction of (XLVI) with thiols.[50] Hettler[51] recently
reported that some 3-alkoxysaccharins rearranged on heating
to the corresponding N-substituted derivatives. A four-
centre mechanism was suggested for this rearrangement, but
no evidence was presented to support it.

O_2

S

N

Na$\oplus$

$\ominus$

O

(XLV)

O_2

S

N

Cl

(XLVI)

O_2

S

N

OR

(XLVII)

R=alkyl or aryl
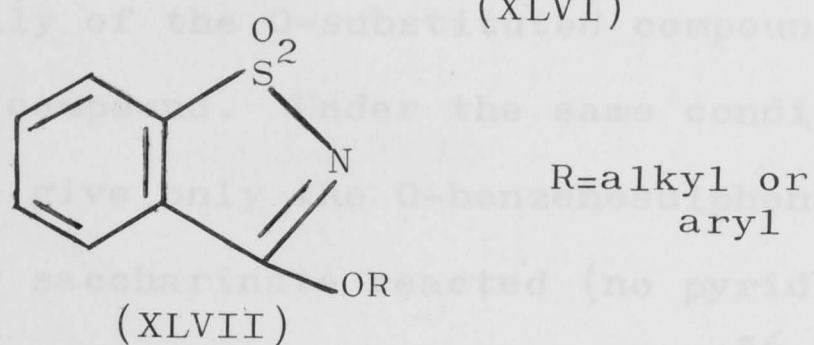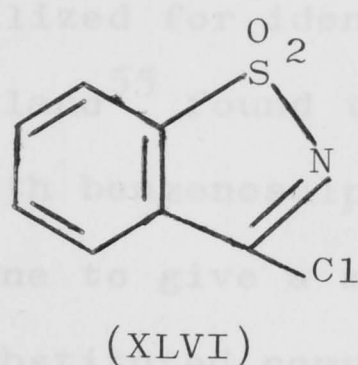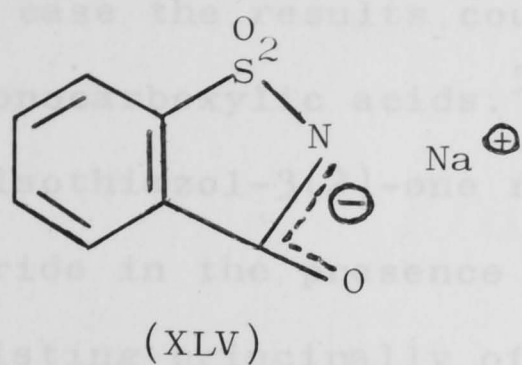
The site of acylation of 3-hydroxyisothiazole was not known. Goerdeler[9] reported that 5-methyl-3-hydroxyisothiazole (XLVIII) reacted with acetic anhydride to give an acetyl derivative, but the site of attack was not specified. It was presumably the N-acetyl derivative.

OH

CH_3

N

S

(XLVIII)
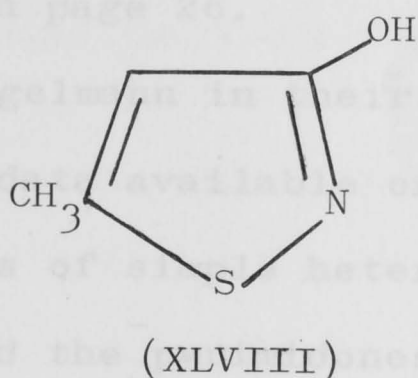
Reactions of the sodium salt of 1,2-benzisothiazol-3(2)-one ((XLII), Na instead of Ag) with acid chlorides and acid anhydrides gave only the N-acyl compounds.[52,53] Similar

results were obtained with the sodium salt of saccharin; in this case the results could be utilized for identification of monocarboxylic acids.[54] McClelland[55] found that 1,2-benzisothiazol-3(2)-one reacted with benzenesulphonyl chloride in the presence of pyridine to give a mixture consisting principally of the 0-substituted compound and some N-substituted compound. Under the same conditions saccharin reacted to give only the 0-benzenesulphonyl compound; but silver saccharinate reacted (no pyridine was used) to give only the N-substituted derivative.[56] Micheel and Lorenz[57] found that 3-chlorosaccharin (XLVI) reacted with protected amino acids (XLIX) to form the N-acylated compounds (L). Presumably these resulted from rearrangement of the initially formed 0-acylated compounds. A peptide synthesis could be effected from (L) via a transacylation process as shown on page 26.

Curtin and Engelmann in their recent paper[58] commented on the paucity of data available on pairs of isomeric N- and 0- acyl derivatives of simple heterocyclic systems such as the α-pyridones and the pyrimidones. In this paper the authors reported that benzoylation of the sodium salt of 6(5H)-phenanthridinone (LI) at -20° gave initially the 0-substituted product with a trace of the N-substituted compound present. On heating, 0- to N- benzoyl migration

rearrangement has not been elucidated. In the conclusion
of their paper, ... made the following
remark:

N-acyl isomers of simple heterocyclic systems
may be rather more accessible than is implied
by their almost complete absence from the
literature. In addition the ease of the O→N
benzoyl migration in the phenanthridinone
system indicates that such rearrangements may
be of general importance in the chemistry of
other heterocyclic compounds.

$$CbZO-NH-\underset{\underset{R^1}{|}}{CH}-COOH$$

(XLIX)

(L)

(L) $+$ $NH_2-\underset{\underset{R^2}{|}}{CH}-COOH$ $\xrightarrow[0^o]{KHCO_3}$

Acylation of 2(1H)-pyridone (LII) has been reviewed by
Meislich.[59] This was accomplished with difficulty because
the products were sensitive to moisture. In general only
O-acyl compounds were formed. The formation of the N-acyl
derivatives was doubtful, but recently Curtin and Miller
suggested that acylation of the sodium salt of the pyridone at
low temperature gave rise to both O- and N- acylated

$$CbZO-NH-\underset{\underset{R^1}{|}}{CH}-CO-NH-\underset{\underset{R^2}{|}}{CH}-COOH$$ $+$

was observed. The formation of the O-benzoyl compound was
thus kinetically controlled, but the N-benzoyl derivative
was thermodynamically more stable. The mechanism of this

rearrangement has not been elucidated. In the conclusion
of their paper, Curtin and Engelmann made the following
remark:

> N-acyl isomers of simple heterocyclic systems
> may be rather more accessible than is implied
> by their almost complete absence from the
> literature. In addition the ease of the O→N
> benzoyl migration in the phenanthridinone
> system indicates that such rearrangements may
> be of general importance in the chemistry of
> other heterocyclic compounds.
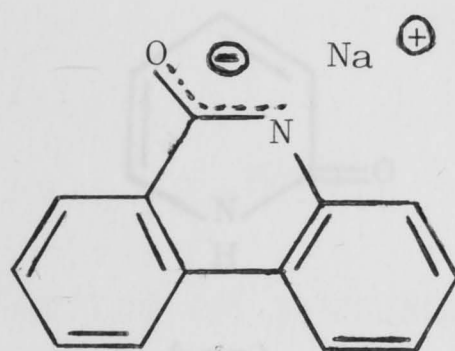
(LI)

Acylation of 2(<u>1H</u>)-pyridone (LII) has been reviewed by
Meislich.[59] This was accomplished with difficulty because
the products were sensitive to moisture. In general only
O-acyl compounds were formed. The formation of N-acyl
derivatives was doubtful, but recently Curtin and Miller[60]
suggested that acylation of the sodium salt of 2-pyridone at
low temperature gave rise to both O- and N- acylated
products. Evidence for this observation was drawn from the
infra-red carbonyl absorptions of the acylated product. A
rapid N- to O- acyl migration occurred at room temperature.

Similar results were reported by Taylor and his

collaborators[61] on acetylation of the thallium (I) salt of

(LII). At -40° both N- and O- acetyl derivatives were

formed, with the former present to the extent of about 40%.

This was estimated by N.M.R. spectroscopy. The N-acetyl

compound could not be isolated because of the rapid

rearrangement mentioned above.
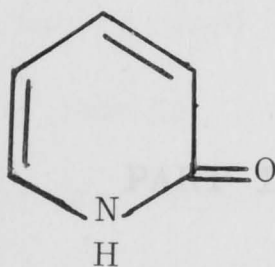
(LII)

From the foregoing discussion it is clear that the site

of acylation of 3-hydroxyisothiazole cannot be predicted

readily.

PART I

ACYLATION OF 3-HYDROXYISOTHIAZOLE

constants of the two pairs of doublets[*] confirmed the

preceding suggestion. The major pair had J=4.6 cps,

similar to that observed between H_4 and H_5 in isothiazoles,[62]

whereas the other pair showed J=6.6 cps, similar to that

observed in N-alkyl-3-isothiazolones.[32] This implied that

3-acetoxyisothiazole (LIII) was the major product and that

N-acetyl-3-isothiazolone (LIV) was the other product.
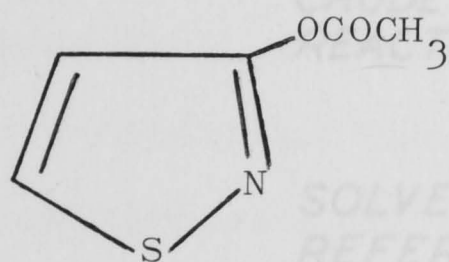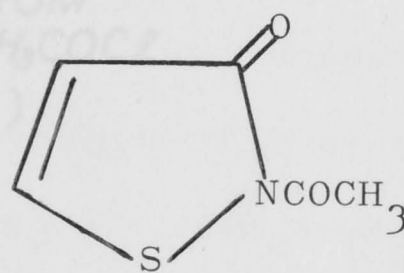
(LIII)   (LIV)

Further support for the foregoing conclusion came from

the following data. The I.R. spectrum of the liquid product

revealed a strong carbonyl absorption at about 1775 cm^{-1} and

two much less intense peaks at about 1665 cm^{-1} and 1705 cm^{-1}

respectively. The U.V. spectrum showed a major absorption

at 245 mμ and a minor one at 305 mμ. The intense peak at

1775 cm^{-1} in the I.R. spectrum was assigned to an ester-

carbonyl stretching frequency, confirming that 3-acetoxy-

isothiazole (LIII) was the major product. The other two

---

[*]

The term "ring doublets" will be used to denote doublets
due to the olefinic protons of 3-substituted isothiazoles.

bands were considered to be due to the presence of some N-
acetyl-3-isothiazolone (LIV). Separation of the mixture
could be effected by column chromatography on silica gel,
affording an oil (main product) and a solid. The former
possessed only one intense carbonyl absorption at 1775 cm^{-1},
while the latter had two carbonyl bands at 1665 and 1705 cm^{-1}.

A range of acyl halides was reacted with 3-hydroxy-
isothiazole under the same conditions. Analysis of the
total product mixtures in each case showed that the
site of electrophilic attack was predominantly at oxygen,
although products of attack at nitrogen could usually be
detected in low percentages. Reactions with methanesulphonyl
chloride and with p-toluenesulphonyl chloride were also
carried out for comparison, and resulted in the formation of
O-substituted compounds. No trace of the corresponding N-
substituted compounds could be detected in these

CRUDE MIXTURE FROM
REACTION WITH CH₃COCl
(METHOD A)

SOLVENT : CCl₄
REFERENCE : T.M.S.
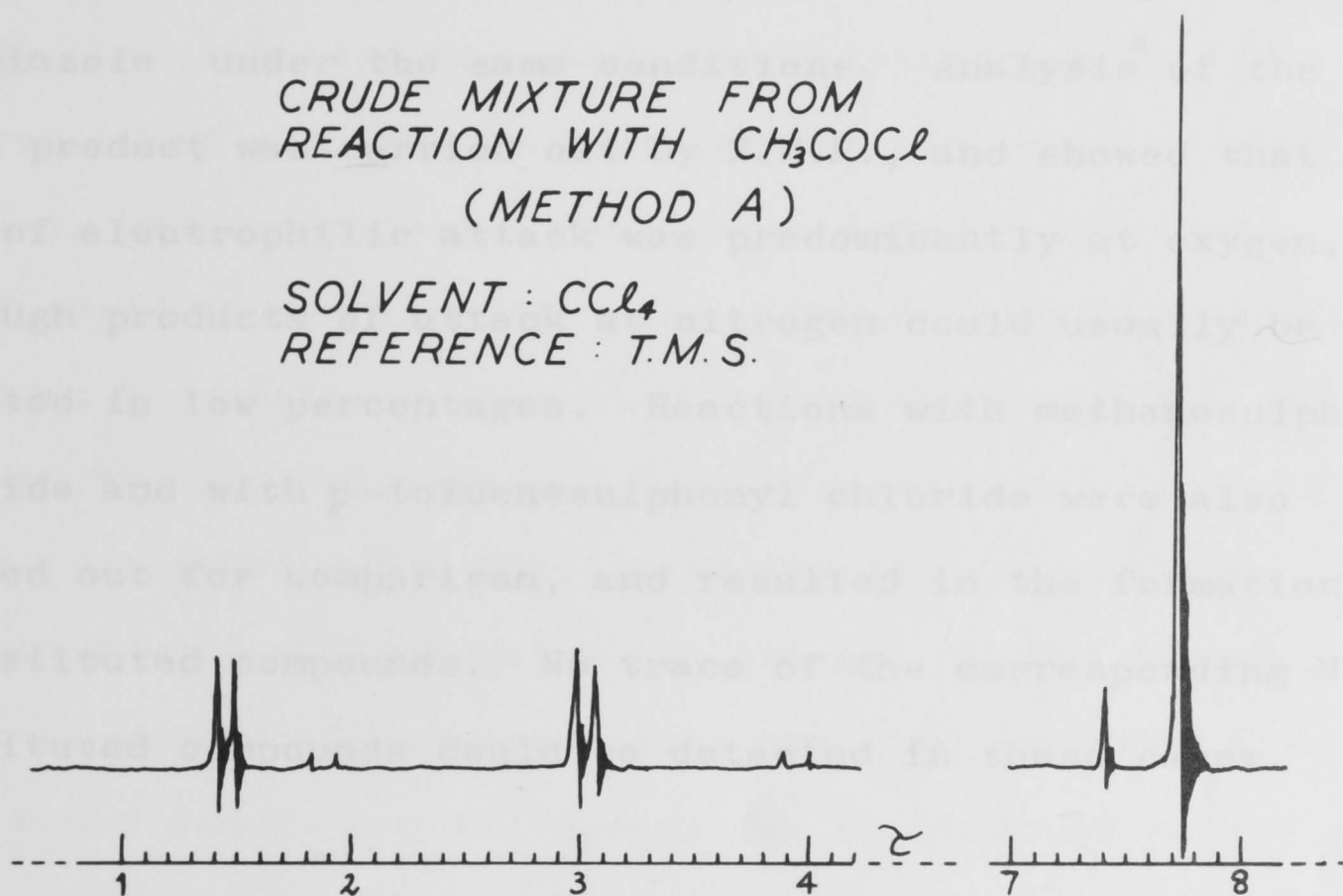
FIG. II

(B) 3-ACYLOXYISOTHIAZOLES

The original oil from the reaction with acetyl chloride
crystallised on standing. Accompanying changes in the
spectroscopic data left little doubt that acyl migration

_____

This was done immediately after work-up in order to
minimise the possibility of rearrangement.

bands were considered to be due to the presence of some N-acetyl-3-isothiazolone (LIV). Separation of the mixture could be effected by column chromatography on silica gel, affording an oil (main product) and a solid. The former possessed only one intense carbonyl absorption at 1776 cm^{-1}, while the latter had two carbonyl bands at 1665 and 1704 cm^{-1}.

A range of acyl halides was reacted with 3-hydroxy-isothiazole under the same conditions. Analysis[*] of the total product was carried out by N.M.R., and showed that the site of electrophilic attack was predominantly at oxygen, although products of attack at nitrogen could usually be detected in low percentages. Reactions with methanesulphonyl chloride and with p-toluenesulphonyl chloride were also carried out for comparison, and resulted in the formation of O-substituted compounds. No trace of the corresponding N-substituted compounds could be detected in these cases.

(B) 3-ACYLOXYISOTHIAZOLES

The original oil from the reaction with acetyl chloride crystallized on standing. Accompanying changes in the spectroscopic data left little doubt that acyl migration

---

[*] This was done immediately after work-up in order to minimise the possibility of rearrangement.

from oxygen to nitrogen was taking place. This indicated
that the isomer ratios initially measured were the result
of kinetic control of the acylation process, as might be
expected from the extreme speed of acylation. With the
exception of the trimethylacetyl derivative (LV), all 3-
acyloxyisothiazoles obtained from reaction with aliphatic
acid chlorides underwent such acyl migration. Rates varied
widely; in the case of 3-chloroacetoxyisothiazole (LVI),
rearrangement occurred so rapidly that isolation of the pure
O-isomer was impossible. Considerable difficulty was
experienced in handling the other liquid 3-acyloxyisothiazoles
until it was realised that high purity was essential to
prevent the acyl migration. Once they were purified and
dried, these compounds were quite stable, and could be
distilled without undergoing any change. Undue exposure of
the pure products, however, still resulted in rearrangement,
presumably due to partial hydrolysis by absorbed moisture
(this will be discussed in detail in Chapter II). It was
also found that a trace of acid (from unreacted acyl halide)
brought about a rapid acyl migration. Therefore in all
subsequent acylation reactions, a slight excess of
triethylamine was employed. In contrast to the behaviour
mentioned above, 3-acyloxyisothiazoles resulting from reaction
with aromatic acid chlorides did not exhibit O- to N- acyl
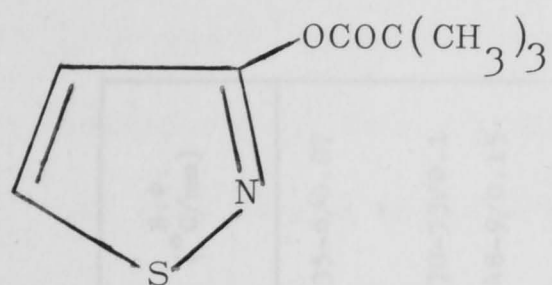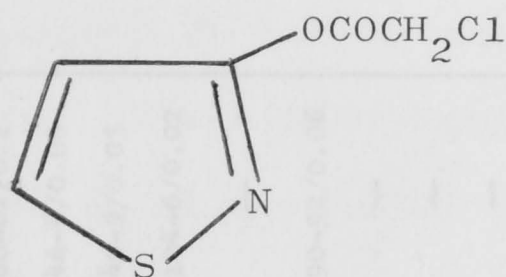
(LV)   (LVI)

migration.   Indeed in most cases very little or none of the
N-isomers was formed by method (a).   No change occurred on
exposure of these O-acyl compounds.

   Diagnostic physical data for a series of 3-acyloxy-
isothiazoles are summarised in Table I.   A few important
features are noted here:

(i)   Most of these compounds are liquids possessing
      characteristic ester stretching vibrations in the I.R.
      spectra.

(ii) Assignments of chemical shifts for H_4 and H_5 in the
      N.M.R. spectra were made by analogy with those assigned
      for 3-hydroxyisothiazole.[32]   This was confirmed by the
      preparation of 5-deutero-3-acetoxyisothiazole which
      showed a singlet $(\tau=3.02)$ in the aromatic region.

(iii) A coupling constant of 4.6 cps for the ring doublets
      was observed for nearly all of the compounds listed.
      This could be used for identification of unknown
      compounds.

TABLE I

3-ACYLOXYISOTHIAZOLES $(C_3H_2NOS)COR$

R	λ_{max} (mμ),(ε) in 95% EtOH	$\nu_{C=O}$** (cm^{-1})	60 Mc N.M.R. (τ; cps) IN CCl_4				M.P.($^{\circ}$C)	B.P. ($^{\circ}$C/mm)
			H_4	H_5	$J_{4,5}$	OTHER SIGNALS		
CH_3	254 (7870)	1776	3.02	1.42	4.6	7.73(3H)	—	35-6/0.07
$ClCH_2$*	244 —	1782	2.97	1.40	4.6	5.71(2H)	—	-
$CH=CH_2$	246 (10100)	1753	2.91	1.39	4.6	2.95-4.10 SEE FIGURE IVA	—	70-73/0.1
C_2H_5	245 (7880)	1780	3.02	1.41	4.6	7.44(2H,Q); 8.79(3H,T)	—	48-9/0.15
C_3H_7	245 (8140)	1766	3.03	1.49	4.6	7.45(2H,T); 8.93(3H,M) 7.9-8.6(2H,M)	—	49-51/0.1
$i-C_3H_7$	245 (7670)	1765	3.01	1.44	4.6	7.2(1H,M); 8.69(6H,D)	—	68-9/0.05
CH_2CH_2Br	244 (9460)	1770	2.96	1.35	4.6	6.36(2H,T); 6.81(2H,T)	—	55-7/0.1
$(CH_3)_3C$	245 (8430)	1760	2.99	1.38	4.6	8.63(9H)	—	60-62/0.1
CH_3O	244 (7480)	1789	3.01	1.42	4.6	6.16(3H)	—	46-8/0.08
C_2H_5O	244 (8030)	1772	3.00	1.42	4.6	5.72(2H,Q); 8.60(3H,T)	—	46-9/0.05
$\emptyset CH_2$	246 (8140)	1770	3.00	1.41	4.6	2.63(5H); 6.12(2H)	—	104-6/0.02
$\emptyset CH=CH$	286 (19750)	(1728)	2.83	1.34	4.7	2.06(1H,J=16); 3.41(1H,J=16); 2.25-2.72(5H)	82-3	—
$\emptyset$	244 (8030)	1750	2.82	1.40	4.6	1.7-2.0(2H); 2.3-2.7(3H)	—	90-92/0.06
$4-CH_3\emptyset$	249 (23700)	(1750)	2.80	1.32	4.6	1.89(2H); 2.70(2H); 7.53(3H)	31-33	—
$4-NO_2\emptyset$	254 (18100)	(1744)	2.78	1.23	4.6	1.61(4H)	130-32	—
$3,5-(NO_2)_2\emptyset$	236 (24300)	(1755)	2.76	1.21	4.6	0.67(3H)	120-21	—

* DATA OBTAINED FROM MIXTURE OF O- AND N-COMPOUNDS

** LIQUID FILM; NUJOL MULL IN PARENTHESES

D=DOUBLET   M=MULTIPLET   Q=QUARTET   T=TRIPLET

(iv) Reaction with β-bromopropionyl chloride using method

(a) gave, apart from the expected O- and N- acyl

compounds, two other products. The N.M.R. spectrum

of the crude mixture is shown in Figure IIIA; it

can be seen that each ring doublet appears to show

fine splitting. Since such splitting could not be due to

coupling with other protons, the most logical

explanation would be to assume that another pair of

O- and N- substituted compounds was present. The

presence of a series of peaks in the region $\tau = 2-4$ led

to the suggestion that these were due to dehydro-

brominated products (LVII) and (LVIII) of the

initially formed O- and N- (β-bromopropionyl) compounds.

Although the possibility of dehydrobromination of the

acid chloride taking place prior to acylation could

not be ruled out, this was considered unlikely.

Treatment of a solution of the crude reaction mixture

in benzene with the calculated amount of triethylamine

resulted in immediate precipitation of triethylamine

hydrobromide. The N.M.R. spectrum (Figure IIIB) of the

product now showed no absorption from $\tau 4.5-10$ (compare

Figure IIIA), and no fine structure in the ring

doublets. This demonstrated that complete dehydro-

bromination had now been achieved and that (LVII) and

(LVIII) were present in the original mixture. It was possible to obtain the mixture of (LVII) and (LVIII) directly by using two equivalents of triethylamine in the original reaction.

OCOCH=CH$_2$
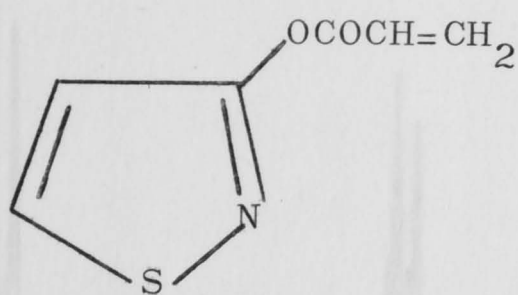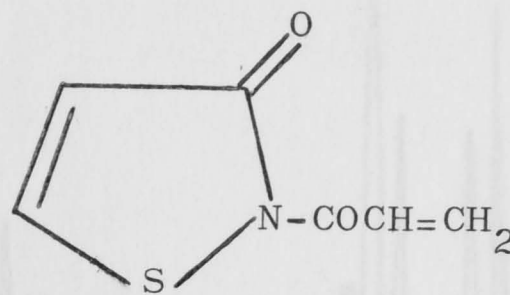
(LVII)

(LVIII)

The N.M.R. spectra of pure (LVII) and (LVIII) are shown in Figure IVA and Figure IVB respectively for comparison. Even the use of exactly one equivalent of triethylamine in the original reaction did not prevent the formation of some (LVII) and (LVIII). Separation of these four products proved impossible; the 3-(β-bromopropionyloxy)-isothiazole was obtained by another method, described in section (C).

(v) 3-Formyloxyisothiazole could not be prepared by method (a) for obvious reasons. Reaction with formic-acetic anhydride (see below) yielded only N-formyl-3-isothiazolone.

38

CRUDE MIXTURE FROM REACTION
WITH BrCH₂CH₂COCl (METHOD A)

SOLVENT : CDCl₃
REFERENCE : T.M.S.
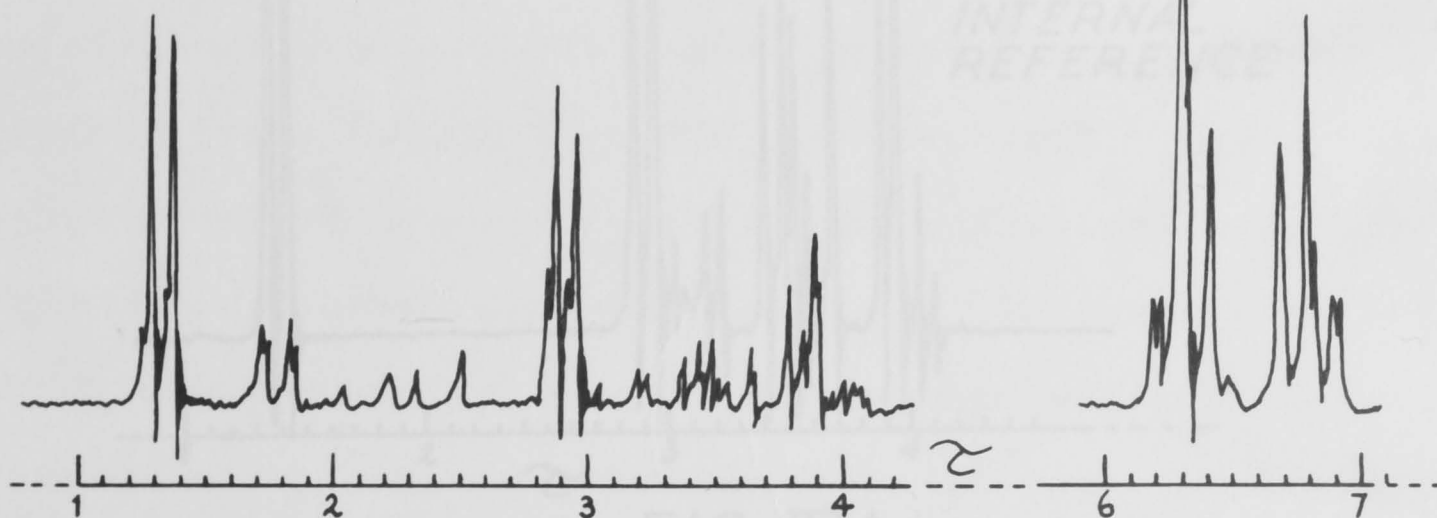
FIG. ⅢA

THE ABOVE MIXTURE TREATED WITH Et₃N

SOLVENT : CDCl₃   REFERENCE : T.M.S.

FIG. ⅢB

SOLVENT : CCl₄

T.M.S. AS INTERNAL REFERENCE

FIG. ⅣA

SOLVENT : CDCl₃

T.M.S. AS INTERNAL REFERENCE

FIG. Ⅳ B

(C) N-ACYL-3-ISOTHIAZOLONES

In view of the low yields of N-acyl-3-isothiazolones

obtained by method (a), a different procedure was sought to

afford a reasonable yield of these compounds. Rearrangement

of the corresponding 3-acyloxyisothiazoles proved

satisfactory, but only for those in which rapid migration

occurred (viz. R=COCH$_2$Cl, COCH$_3$, COOMe, COOC$_2$H$_5$). A better

method involved the reaction of 3-hydroxyisothiazole with

aliphatic acid anhydrides (method (b)). Excess of the

anhydride was used as solvent and no catalyst was necessary.

Reaction with formic-acetic anhydride at room temperature

yielded N-formyl-3-isothiazolone in quantitative yield.

Other aliphatic acid anhydrides (viz. acetic, propionic,

butyric and isobutyric) reacted at about 40° to give high

yields of the N-acyl compounds; a small percentage of the

respective O-acylated products could be detected by N.M.R.

Trimethylacetic anhydride was an exception, giving only 3-

trimethylacetoxyisothiazole (LV).

It was of some interest to examine the influence of

the triethylamine used in method (a) upon the course of the

acylation process. Accordingly, reaction with acid

chlorides in boiling benzene without the use of triethylamine

(method (c)) was investigated. With this technique, a

mixture of O- and N-acylated products was obtained in most

41

cases, but the proportion of N-acylation was increased

considerably.   This opened a simple route to the preparation

of N-acyl-3-isothiazolones with aromatic acyl groups. As

before, trimethylacetyl chloride gave only the O-substituted

compound.   Reaction with β-bromopropionyl chloride yielded

only the expected mixture of O- and N-acyl derivatives;

no dehydrobromination was observed.   Table II compares

results obtained from this method with those resulting from

method (a).   Product ratios were determined by integration

of the ring doublets.

In method (c) an initial formation of 3-hydroxy-

isothiazolium hydrochloride (LIX) occurred, but this

gradually decomposed on warming to the parent compound and

hydrogen chloride.   It was thought at first that increase

in the yields of N-acyl derivatives might have resulted

from an acid-catalysed O- to N-acyl migration, but the

following experiments indicated that this assumption was

not valid:

(i)   pure 3-benzoyloxyisothiazole (LXX), when treated with

3-hydroxyisothiazolium chloride in boiling benzene

over the same period did not show any change. The

same result was obtained when (LXX) was refluxed in

benzene with benzoyl chloride or with 3-hydroxy-

isothiazole.

TABLE II

PRODUCTS FROM REACTION WITH RCOCl

$$(C_3H_2NOS)COR$$
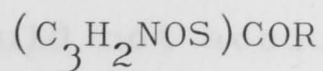
R	METHOD (a)		METHOD (c)	
	% O-	% N-	% O-	% N-
CH_3	92	8	49	51
C_2H_5	95	5	42	58
C_3H_7	95	5	46	54
C_2H_5O	98	2	0	100
$(CH_3)_3C$	100	0	100	0
$BrCH_2CH_2$	ca 80	ca 20	50	50
$MeOOC.CH_2CH_2$	89	11	42	58
$MeOOC(CH_2)_3$	88	12	53	47
$\emptyset$	ca 100	0-2	48	52
$4-CH_3\emptyset$	ca 100	0-2	70	30
$4-(NO_2)\emptyset$	ca 100	0	85	15

(ii) 3-acetoxyisothiazole (LIII) was treated similarly.

In each case only a little rearrangement (<10%)

occurred. This could not account for the proportion

of N-acetyl compound obtained by method (c).

Other aliphatic O-acyloxyisothiazoles showed the same

behaviour; an exception was O-trimethylacetoxyisothiazole

which behaved the same as (LXX).

(LIX)   (LXX)
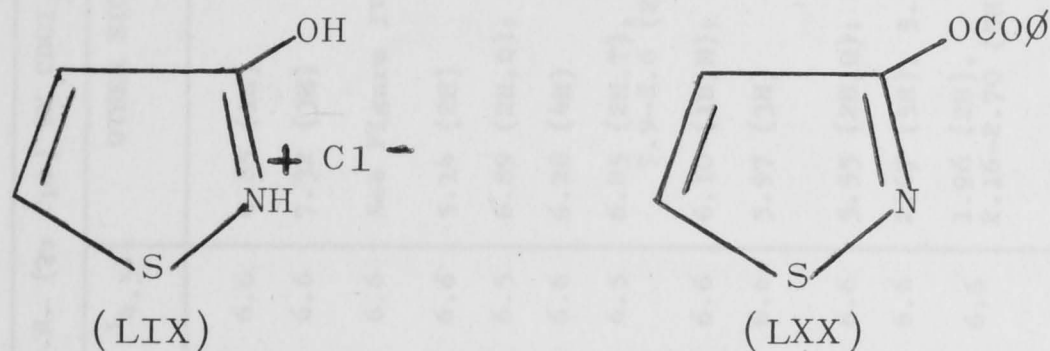
These results demonstrated that increase in yields of

N-acyl-3-isothiazolones was mainly a kinetic effect under

the conditions of experiment. Table III presents diagonstic

data for a range of N-acyl-3-isothiazolones. Important

features are outlined below:

(i) All the N-acylated compounds are solids.

(ii) A coupling constant of 6.6 cps between H_4 and H_5 was

observed for nearly all the compounds. (Compare $J_{4,5}=$

4.6 cps in 3-acyloxyisothiazoles). This, together with

the characteristic chemical shifts for the ring doublets,

provided a means for determining the identity of an un-

known product.

TABLE III

N-ACYL-3-ISOTHIAZOLONES $(C_3H_2NOS)COR$

R	λ_{max} (mμ), (ε) IN 95% EtOH	$\gamma_{C=O}$ (Cm^{-1})**	60 Mc N.M.R. (τ; Cps) IN CDCl$_3$				M.P. (°C)
			H_4	H_5	$J_{4,5}$	OTHER SIGNALS	
H	308 (6570)*	(1697,1724)	3.74	1.59[a]	6.6	0.65 (1H)	130-31
CH_3	305 (8530)	1665,1704	3.75	1.76	6.6	7.32 (3H)	89-91
$CH=CH_2$	226 (15500) 323 (14100)	1664,1692	3.80	1.73	6.6	See Figure IV B	130-31
$ClCH_2$	304 (7230)*	1680,1698	3.77	1.66	6.6	5.14 (2H)	99-100
C_2H_5	304 (7720)	1683,1706	3.80	1.78	6.5	6.89 (2H,Q); 8.75 (3H,T)	123-24
CH_2CH_2Br	305 (7990)	1680,1700	3.76	1.67	6.6	6.28 (4H)	86-7
C_3H_7	305 (8950)	1670,1704	3.81	1.73	6.5	6.85 (2H,T), 9.0 (3H,M) 7.9-8.6 (2H,M)	57-8
$i-C_3H_7$	305 (7610)	(1699,1708)	3.79	1.76	6.6	6.10 (1H,M); 8.73 (6H,D)	70-71
CH_3O	295 (8310)	1660,1758)	3.75	1.74	6.6	5.97 (3H)	155 (decomp.)
C_2H_5O	295 (8190)	1652,1752	3.82	1.82	6.6	5.55 (2H,Q); 8.58 (3H,T)	125-26
$\emptyset CH_2$	306 (7550)	1680,1690	3.80	1.83	6.6	2.67 (5H), 5.53 (2H)	104-5
$\emptyset CH=CH$	231 (12370) 306 (23120)	1660,1688	3.80	1.78	6.6	1.96 (2H), 2.16-2.70 (5H)	125-26
$\emptyset$	242 (10500)* 319 (3540)	1672	3.79	1.29	6.3	2.19-2.72 (b)	108-110
$4-CH_3\emptyset$	241 (10500)* 318 (3350)	1652,1682	3.69	1.31	6.3	2.02 (2H), 2.67 (2H) (b) 7.61 (3H)	103-4

* IN ETHER   ** NUJOL MULL; CHLOROFORM SOLUTION IN PARENTHESES

D=DOUBLET   M=MULTIPLET
Q=QUARTET   T=TRIPLET

(a) COUPLING OF H_5 WITH FORMYL PROTON: J=1 cps   (b) IN D^{6}DMSO

(iii) In N-formyl-3-isothiazolone (LXXI), coupling of H_5

with the formyl proton was observed (J=1 cps). An

analogous splitting pattern has been reported for 2-

formyl-thiophene (LXXII),[63] where a coupling constant

of 0.9 cps was observed between H_5 and the formyl

proton.
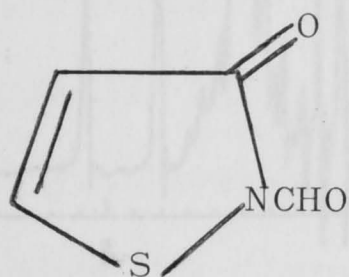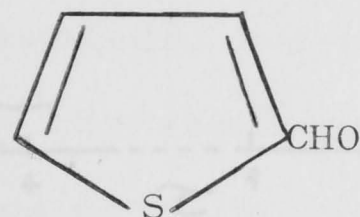
(LXXI)   (LXXII)

(iv) The N.M.R. spectrum of N-cinnamoyl-3-isothiazolone

(LXXIII) requires some comment. Unlike its O-isomer

and N,N-diethylcinnamamide, this compound did not

exhibit the expected AB splitting pattern for the

olefinic protons of the cinnamoyl group. Figure V

shows the N.M.R. spectra of these three compounds.

The observed difference is most likely due to an

anisotropic effect resulting from the steric

disposition of this compound. Such an effect caused

a downfield shift of the olefinic proton near the

phenyl ring. Elix[64] has observed an analogous

anisotropic effect with 2,5-bis(β-styryl)furan: in

the cis-cis isomer (LXXIV A) the olefinic protons in

the side chain showed only two closely-spaced singlets,
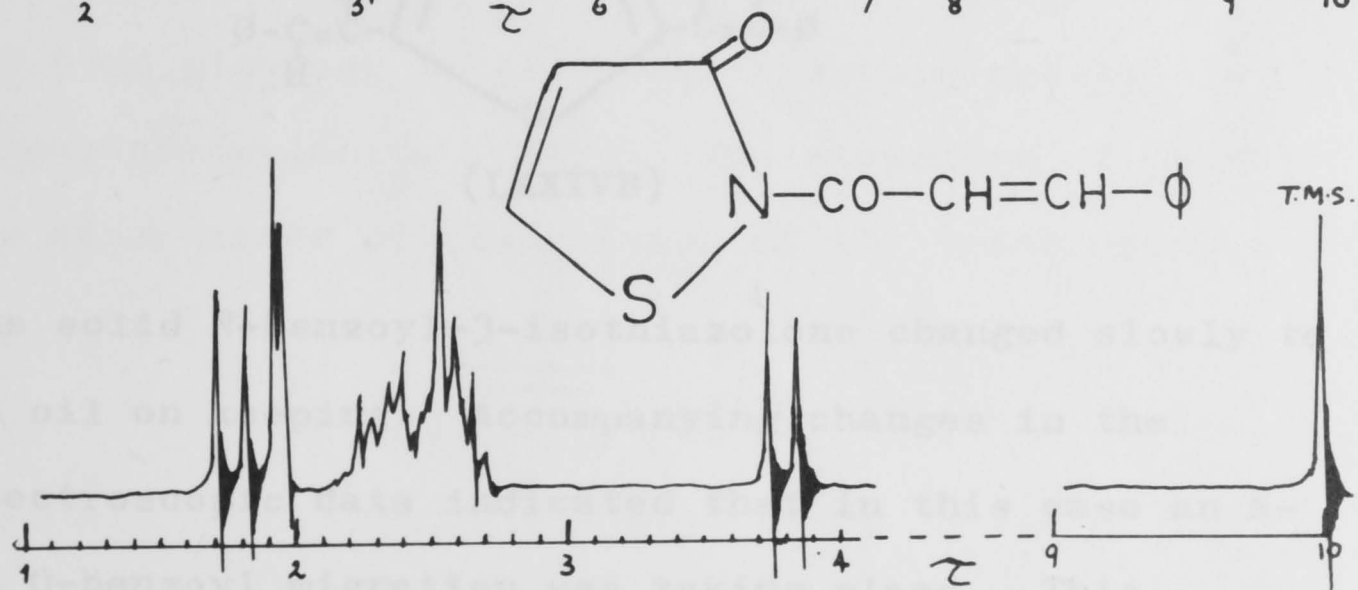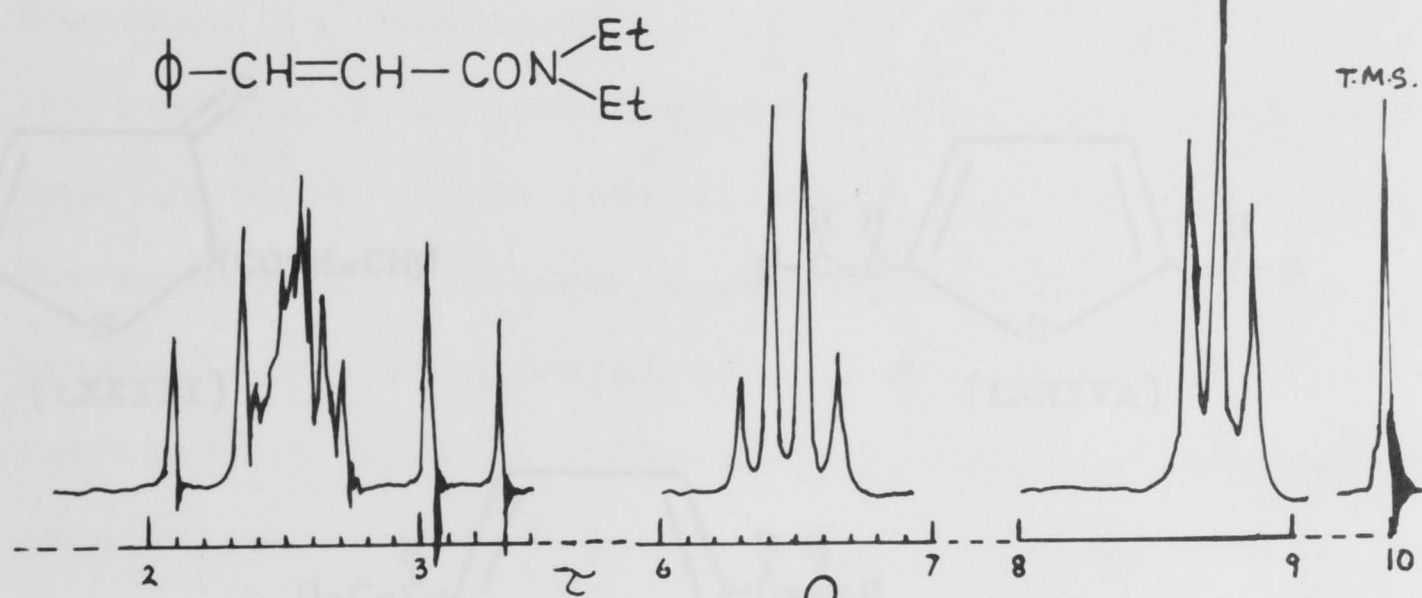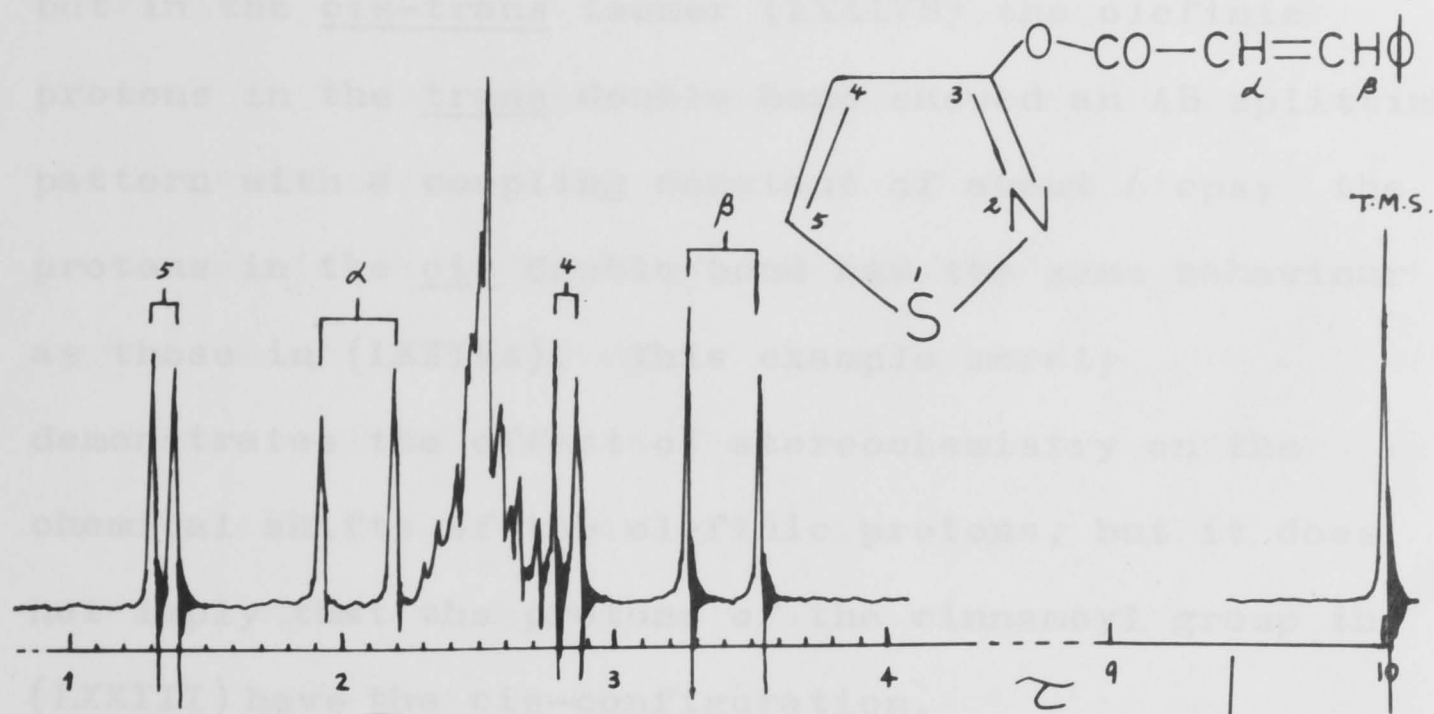
SOLVENT : CDCl₃

FIG. V

but in the <u>cis-trans</u> isomer (LXXIVB) the olefinic

protons in the <u>trans</u> double bond showed an AB splitting

pattern with a coupling constant of about 6 cps;   the

protons in the <u>cis</u> double bond had the same behaviour

as those in (LXXIVA).   This example merely

demonstrates the effect of stereochemistry on the

chemical shifts of the olefinic protons, but it does

not imply that the protons of the cinnamoyl group in

(LXXIII) have the <u>cis</u>-configuration.

(LXXIII)   (LXXIVA)

(LXXIVB)
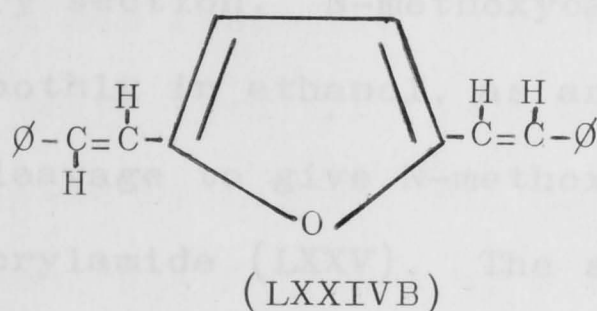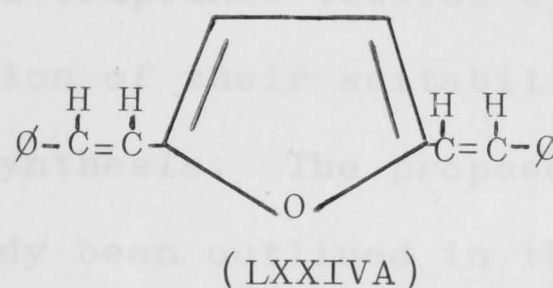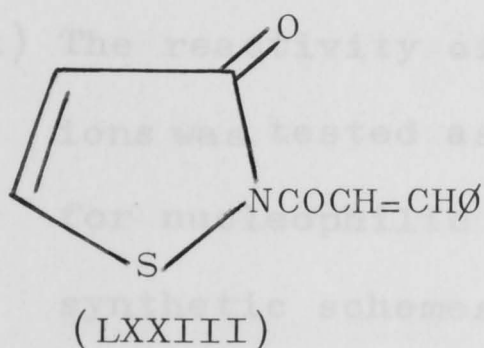
(v)   The solid N-benzoyl-3-isothiazolone changed slowly to

an oil on keeping.   Accompanying changes in the

spectroscopic data indicated that in this case an N-

to O-benzoyl migration was taking place.   This

rearrangement was essentially complete in about two

weeks with total conversion to the O-benzoyl compound.
A trace of 3-hydroxyisothiazole was also present in
the rearranged product. The significance of its
presence will be discussed later in relation to the
mechanism of rearrangement. This was the first
evidence to show that an N-acyl-3-isothiazolone would
rearrange to a 3-acyloxyisothiazole, and raised the
interesting question as to what factors influenced the
stability of the isomers. This aspect will be
discussed in Chapter II.

(vi) The reactivity of some N-acyl compounds towards cyanide
ions was tested as an indication of their suitability
for nucleophilic attack in synthesis. The proposed
synthetic schemes have already been outlined in the
introductory section. N-methoxycarbonyl-3-isothiazolone
reacted smoothly in ethanol, as anticipated, undergoing
S-N bond cleavage to give N-methoxycarbonyl-cis-3-
thiocyanoacrylamide (LXXV). The structure of (LXXV)
was ascertained by examination of its spectroscopic

SCN   CONH
              |
              COOMe
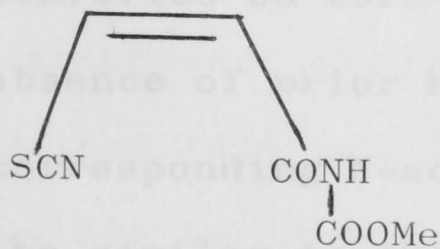
(LXXV)

data: the I.R. spectrum (Nujol mull) showed bands at

3230 (NH), 1662 (α,β-unsaturated amide), 1743 (N-COOMe),

and 2150cm^{-1} (S-C≡N), while the N.M.R. spectrum

(DMSO-d$_6$) showed signals at τ-1.12 (NH), 2.25 (doublet,

$\underline{H}_3$, J:9 c/s); 3.14 (doublet, $\underline{H}_2$,J:9 c/s), and 6.25

(singlet, $\underline{3H}$, COOMe). A similar reaction with N-acetyl-

3-isothiazolone (LIV) resulted in a very small yield

(<10%) of the expected product: the major product was

cis-3-thiocyanoacrylamide (XXX), which on work-up was

converted to 3-hydroxyisothiazole. This indicated that

either solvolysis of (LIV) (by ethanol) occurred prior

to attack by cyanide ions, or the resultant N-acyl-

thiocyanoacrylamide suffered solvolysis.

As a comparison, the reaction of 3-acyloxyisothiazoles

with cyanide ions was attempted only in the case of the

trimethylacetyl derivative (LV), which was known to be

relatively stable to hydrolysis and not to rearrange.

Reaction in ethanol was followed by U.V. spectroscopy, and

occurred relatively slowly, with the formation of cis-3-

thiocyanoacrylamide, converted on work-up into 3-hydroxy-

isothiazole. In the absence of prior hydrolysis or

rearrangement to the corresponding N-acyl compound, the

reaction sequence may be similar to that observed for the

attack of thiols on 3,5-dichloro-4-cyanoisothiazole[17]

(see page 9). This is summarised below: the intermediacy
of the nitrile (LXXVI), however, is speculative at this
stage.

OCOR ... OCOR

N

S

CN⁻

and/or

N⁻ OCOR

SCN

OCOR

NH

SCN

(LXXVI)

O

NH₂

SCN

O

NH

S
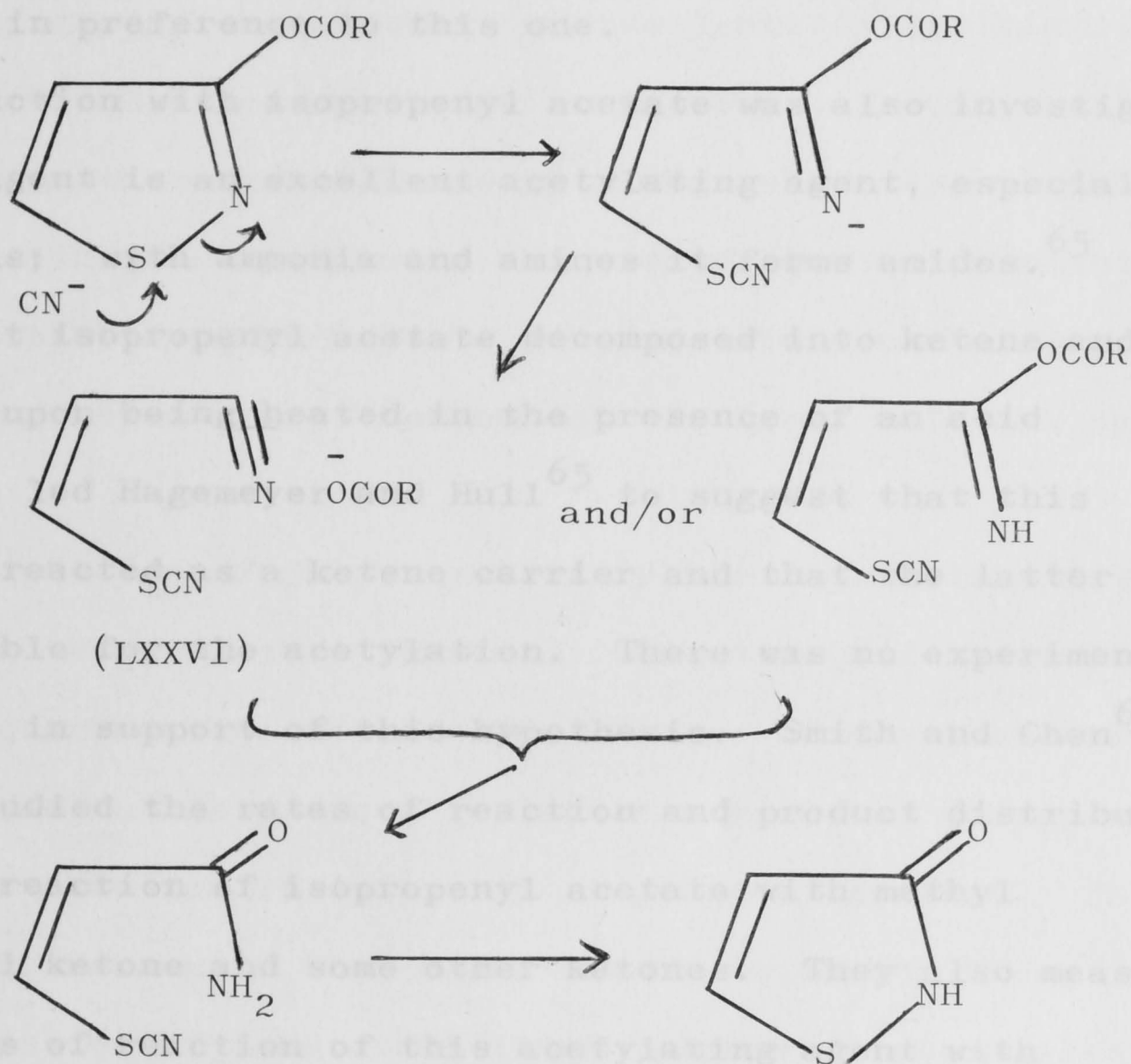
(D) OTHER ACYLATION REACTIONS

Reaction of the sodium salt of 3-hydroxyisothiazole
with acyl chlorides (Method (d)) was studied briefly. This
did not proceed as smoothly as in method (a). Yields were
not quantitative, with the result that some unchanged acid

chloride was always present. This led to rapid rearrangement of most of the aliphatic O-acyl compounds on work-up. The other methods mentioned earlier were adopted in preference to this one.

Reaction with isopropenyl acetate was also investigated. This reagent is an excellent acetylating agent, especially for enols; with ammonia and amines it forms amides.[65] The fact that isopropenyl acetate decomposed into ketene and acetone upon being heated in the presence of an acid catalyst led Hagemeyer and Hull[65] to suggest that this reagent reacted as a ketene carrier and that the latter was responsible for the acetylation. There was no experimental evidence in support of this hypothesis. Smith and Chen[66] later studied the rates of reaction and product distribution for the reaction of isopropenyl acetate with methyl isopropyl ketone and some other ketones. They also measured the rates of reaction of this acetylating agent with n-butyl, isobutyl and t-butyl alcohols. The resulting complex kinetic data led the authors to conclude that, most probably, ketene played no important role in these reactions.

With 3-hydroxyisothiazole, isopropenyl acetate reacted to give a mixture of O- and N-acetyl compounds. When excess of the acetylating agent was used as solvent, and concentrated sulphuric acid was employed as catalyst, the

percentage proportions of O- and N-acetyl compounds were

forty and sixty respectively. The yield was rather

unsatisfactory due to formation of some tarry material. In

addition, rapid rearrangement of the 3-acetoxyisothiazole

often occurred, presumably due to presence of acid. A

cleaner reaction was effected by using toluene-p-sulphonic

acid as catalyst; equimolar amounts of the two reactants

reacted in boiling benzene to give a mixture containing

76% N- and 24% O-acetyl compounds. No tarry material was

formed.

Acetylation of 3-hydroxyisothiazole with ketene itself

in carbon tetrachloride gave only N-acetyl-3-isothiazolone

in near quantitative yield. The absence of any 3-acetoxy-

isothiazole in the product reflected a somewhat different

course of reaction to that with isopropenyl acetate. This

is in agreement with the suggestion by Smith and Chen.[66]

Acylation of some substituted 3-hydroxyisothiazoles

was investigated briefly as a comparison. Unlike the

unsubstituted compound, the 4-bromo derivative reacted very

slowly under the conditions of method (a), so that the

reactions were performed under refluxing condition. In

spite of this variation, the product ratios obtained from

this method $(R = CH_3, COOC_2H_5, (CH_3)_3C, \emptyset)$ were virtually the

same as those resulting from 3-hydroxyisothiazole (XXXII)

itself, i.e., kinetic control of O-acylation. Acetylation

under the conditions of method (b) and (c) gave similar

results to those obtained for (XXXII). For the 5-methyl and

5-phenyl derivatives acylation $(R= CH_3, (CH_3)_3C)$ gave

exactly the same results as that observed for (XXXII) under

the conditions of methods (a) to (c). All the three

substituted 3-acetoxyisothiazoles underwent O→N acetyl

migration on standing, but the corresponding trimethylacetyl

derivatives were stable.

(E) DISCUSSION

The different results obtained from the various methods

of acylation required some rationalization. It has been

established that the mechanism of ester formation involves

addition to the carbonyl group of the acylating agent in a

rate-determining step with formation of a tetrahedral

intermediate.[67,68] When a tertiary base is used as a

catalyst, the acylating agent is the acylammonium cation,[69,70]

i.e., in method (a), N-acetyl-triethylammonium chloride.

O- and N-acylation would require formation of the

intermediates (LXXVIIA) and (LXXVIIB) respectively. Models

of these two intermediates indicated that in (LXXVIIB) there

was much overlapping of the alkyl groups with the isothiazole

ring atoms for nearly all conformations, but in (LXXVIIA),

some conformations were virtually free from any steric
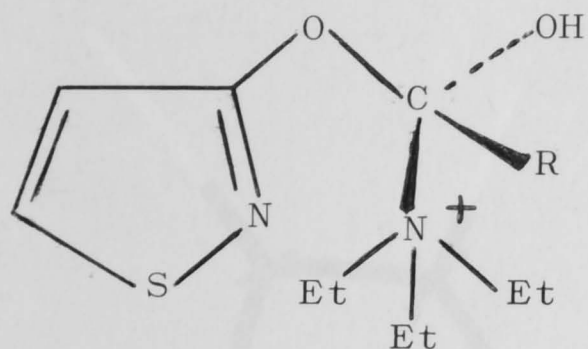
(LXXVIIA)
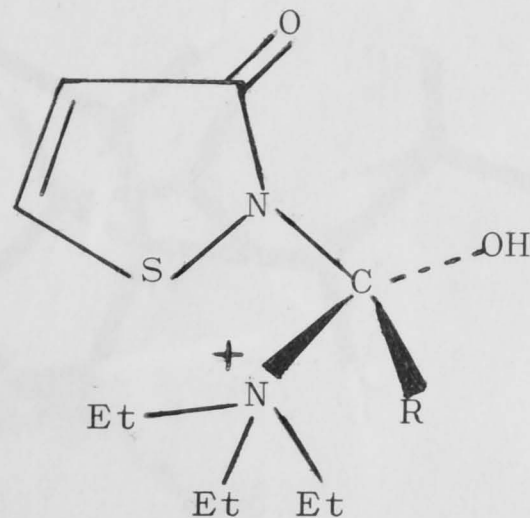
(LXXVIIB)

interaction. Photographs of these two models (see next page) clearly illustrate these effects. It can be seen that the ethyl groups in triethylamine are sufficiently bulky to favour the formation of (LXXVIIA) even in the case of acetylation $(R=CH_3)$, although it can be anticipated that the size of alkyl group R will also contribute to the general steric effect, particularly in cases where it is very bulky. This led to the observed kinetic preference for O-acylation irrespective of the acyl chlorides used. If this analysis of the situation were correct, then the use of a base catalyst with smaller steric requirements should lead to an increase in the extent of N-acylation. Such an increase (if any) would be most pronounced in acetylation, since a smaller alkyl group was involved. Reaction with acetyl
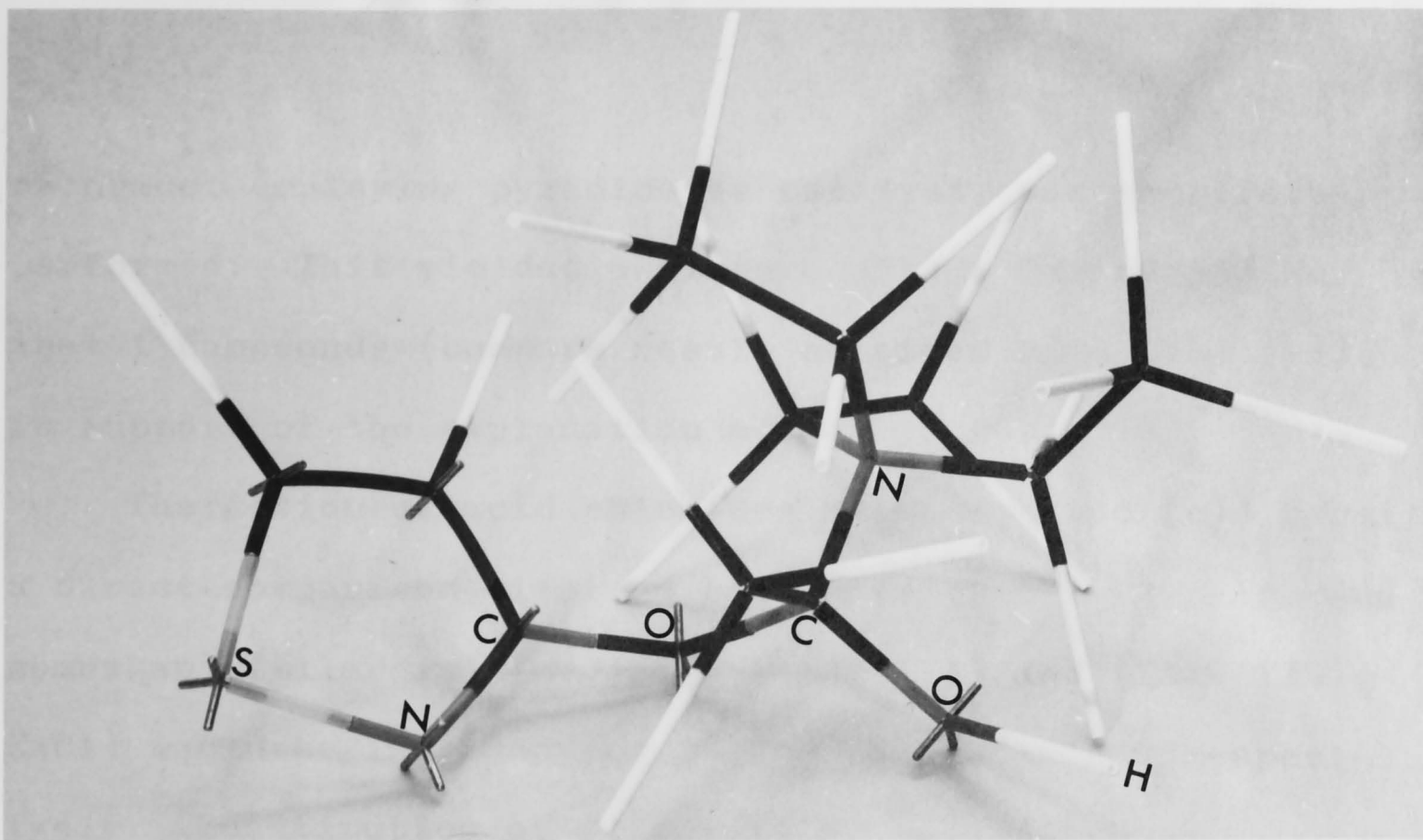
(LXXVIIA)
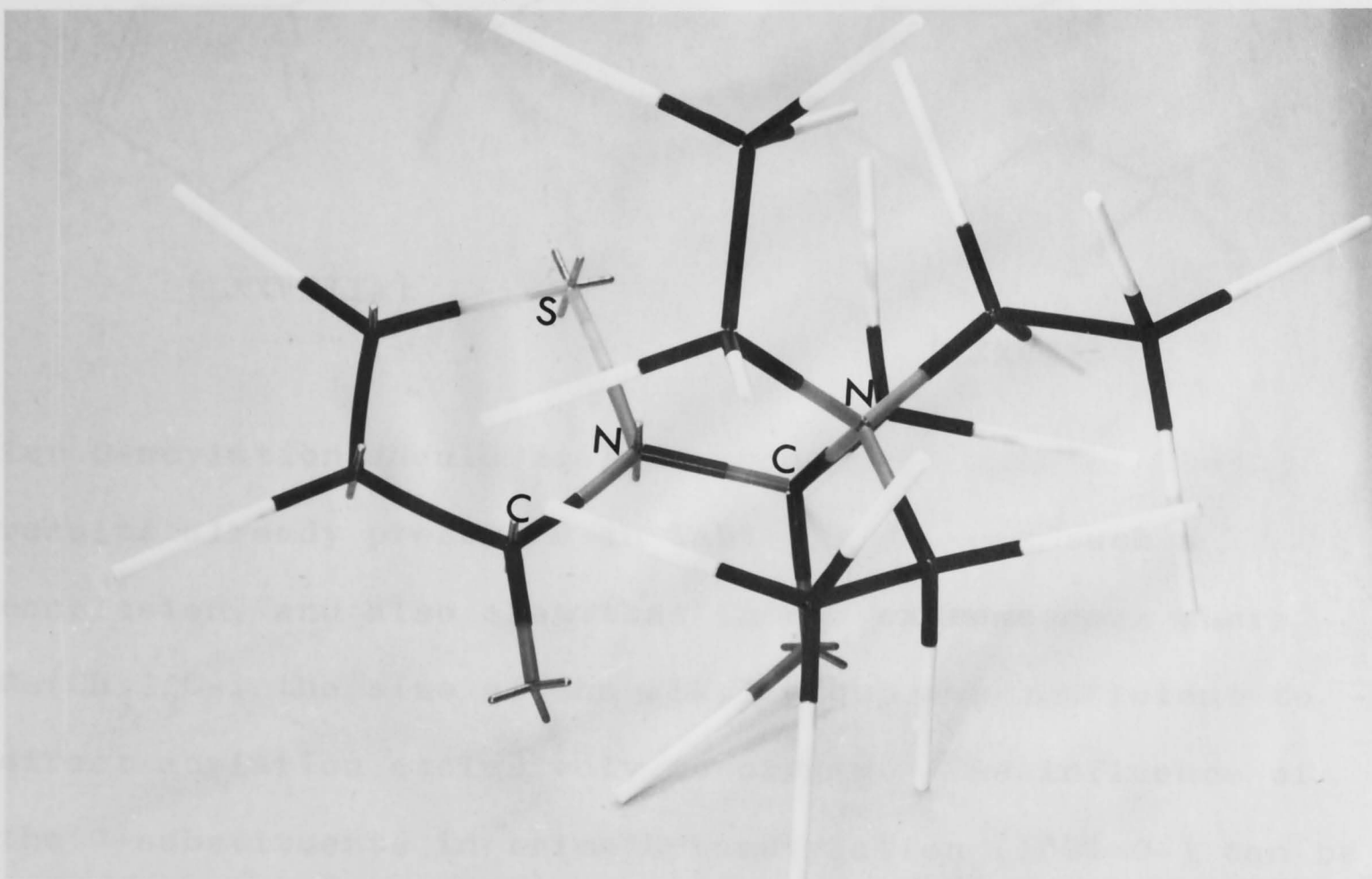
(LXXVIIB)

chloride, employing pyridine as catalyst, was therefore performed. This yielded a mixture of 45% O- and 55% N- acetyl compounds (compare result obtained by method (a)), in support of the explanation advanced.

The action of acid chlorides alone (method (c)) permits a direct comparison with the base-catalysed acylation, and somewhat similar intermediates (LXXVIIIA) and (LXXVIIIB), X=Cl) would be involved for O- and N-acylations respectively. Substitution of Cl for Et_3N^+ should lessen the steric problem considerably, and the kinetic preference
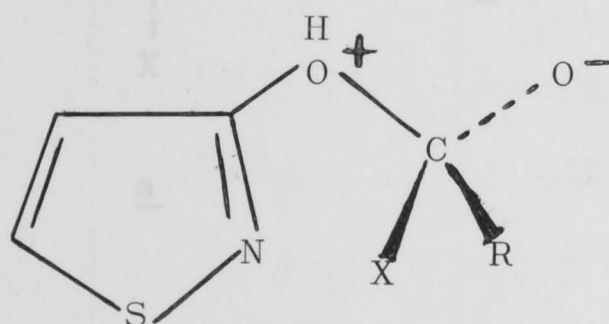
(LXXVIIIA)
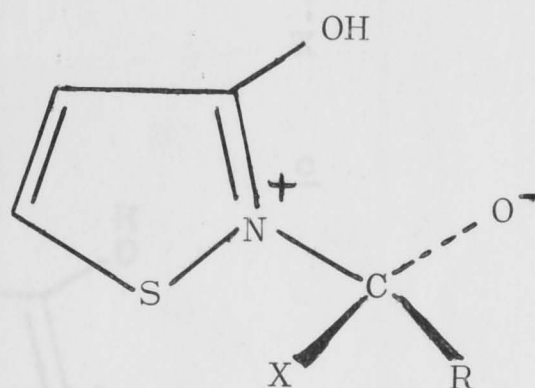
(LXXVIIIB)

for O-acylation should be less pronounced again. The results already presented in Table II support such a conclusion, and also show that in the extreme case where $R=(CH_3)_3C-$, the size of the alkyl group was sufficient to direct acylation exclusively to oxygen. The influence of the α-substituents in trimethylacetylation (100% O-) can be seen when comparison is made with, for example, the case

$R=MeO_2C(CH_2)_3-$ (53% O-). Newman projections ($\underline{a}$,$\underline{b}$,$\underline{c}$) show that in cases where only one α-substituent is present in the acyl group, two of the three conformations still show relatively small interactions; when three α-substituents are present it becomes impossible to avoid the most unfavourable conformation in $\underline{c}$.
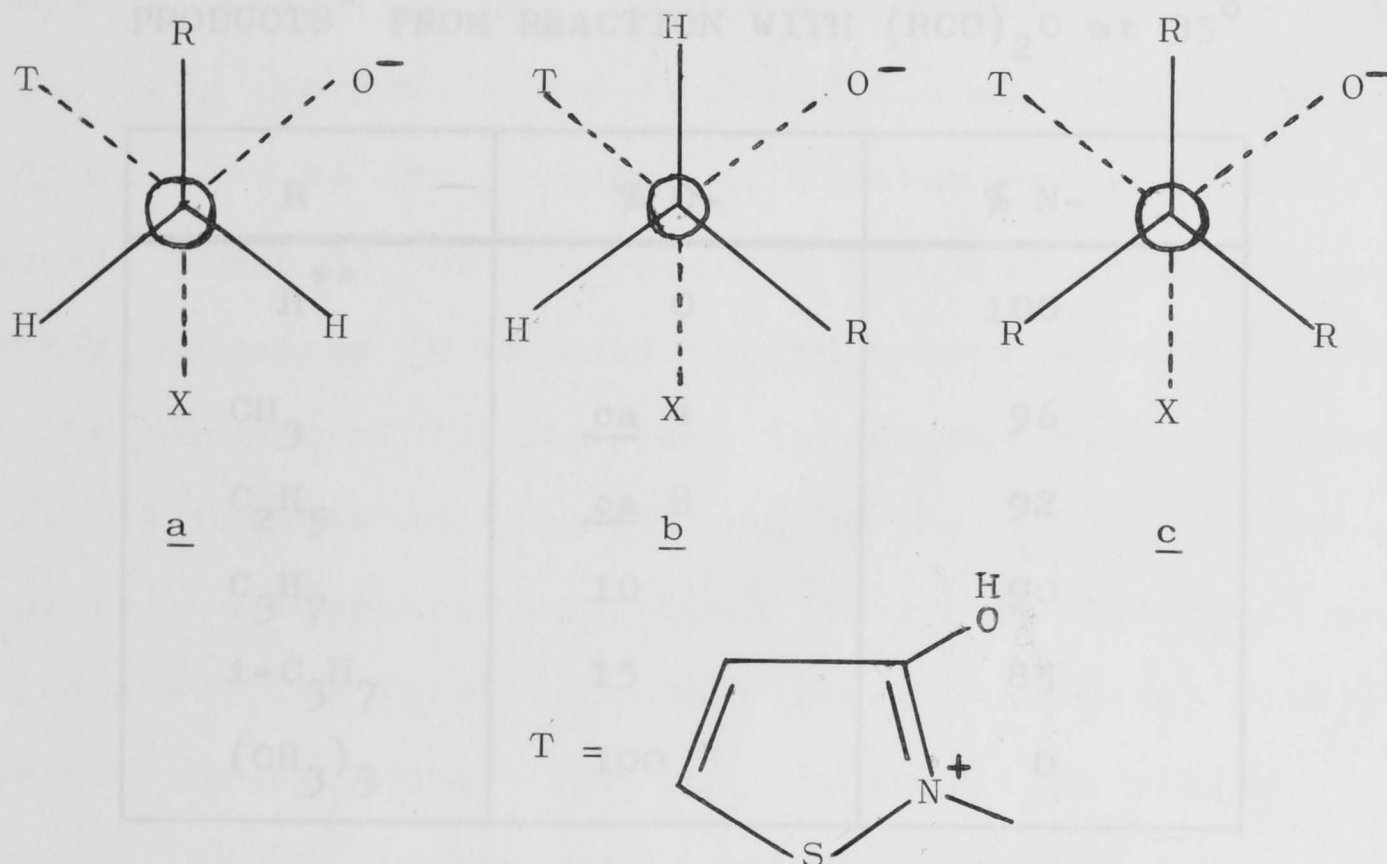
The major difficulty arises in comparing the results obtained by direct acylation with acid chlorides and acid anhydrides. In the latter case (method (b)) similar intermediates (X=OAcyl in (LXXVIII)) would be expected to form, and since a more bulky group was involved here, O-acylation should be more favoured. Nevertheless the results shown in Table IV suggest the contrary in most cases

except in the reaction with trimethylacetic anhydride where the extreme steric effect is again operative. Reaction with acetic anhydride in the presence of triethylamine as catalyst was performed in order to test the validity of the arguments on steric effects. This led to exclusive

<u>TABLE IV</u>

PRODUCTS[*] FROM REACTION WITH $(RCO)_2O$ at 35°

R	% O-	% N-
H[**]	0	100
CH_3	<u>ca</u> 4	96
C_2H_5	<u>ca</u> 8	92
C_3H_7	10	90
i-C_3H_7	15	85
$(CH_3)_3$	100	0

*   Reactions conducted in N.M.R. tubes with excess anhydrides as solvents. Product ratios were determined by integration of the ring doublets.

**   From formic-acetic anhydride.

formation of 3-acetoxyisothiazole (LIII) as anticipated, since the acylating agent was probably the bulky N-acetyl-triethylammonium cation. With pyridine (penta-deutero-pyridine was used) as catalyst, however, a mixture of 68% O-

and 32% N-acetyl compounds was formed. Reaction with

formic-acetic anhydride in the presence of triethylamine as

catalyst was also attempted, since this might open a route

to the preparation of 3-formyloxyisothiazole. The N.M.R.

spectrum of the reaction mixture immediately after mixing

indicated that, apart from the ring doublets due to the N-

formyl compound (ca 70%), there was present another pair

of doublets (ca 30%, J=4.6 cps) at τ 1.0 and 2.90. This was

evidently due to the presence of O-formyloxyisothiazole

(compare Table I), but the signals for this compound

quickly decreased in intensity, and a corresponding increase

for the signals of the N-formyl isomer was visible. After

about six minutes the signals due to the O-formyl compound

completely disappeared. Although this compound could not

be isolated, its formation under the experimental condition

provided strong support for the hypothesis on steric

effects. These results indicated that the intermediates

required for N-acylation in the absence of base catalysts

exhibited a high degree of tolerance for steric interaction.

In other words the data implied that N-substitution was

preferred to O-substitution in the absence of extreme steric

effects. The anhydrides, being somewhat less reactive than

the acid chlorides, would normally be expected to show a

greater selectivity, hence the preference for N-substitution

would be more evident. The reason for the somewhat

unexpected insensitivity to mild steric effects is not at

all clear. Since knowledge of the exact nature of the

intermediates is not available, a clear-cut rationalization

of the different results in methods (b) and (c) is therefore

not possible at this stage.

(F) <u>REACTION WITH ISATOIC ANHYDRIDE</u>[*]

The following introduction on the chemistry of isatoic

anhydride provides a background for investigation of its

reaction with 3-hydroxyisothiazole.

Isatoic anhydride (LXXIX) is a convenient reagent for

certain anthranoylations, serving as the unknown anthranoyl

chloride. Wagner and his co-workers initiated a systematic

---

[*] The current official name (ref. <u>Chemical Abstract</u>) is
2H-3,1-benzoxazine-2,4(1H)-dione.

study of the reactions of (LXXIX) with ammonia,[71] primary and secondary amines,[72] and amides.[73] Sheibley performed similar work on dihalogenoisatoic anhydrides.[74,75] Condensations of (LXXIX) with primary and secondary amines yielded the corresponding substituted anthranilamides (LXXX) as well as α-substituted o-ureidobenzoic acids (LXXXI). The latter, if derived from primary amines, could undergo cyclization to form the substituted quinazolines (LXXXII). Wagner[72] suggested that formation of these products involved two different cleavages, (a) and (b) of (LXXIX) as shown in Scheme VIA.

<u>Scheme VIA</u>
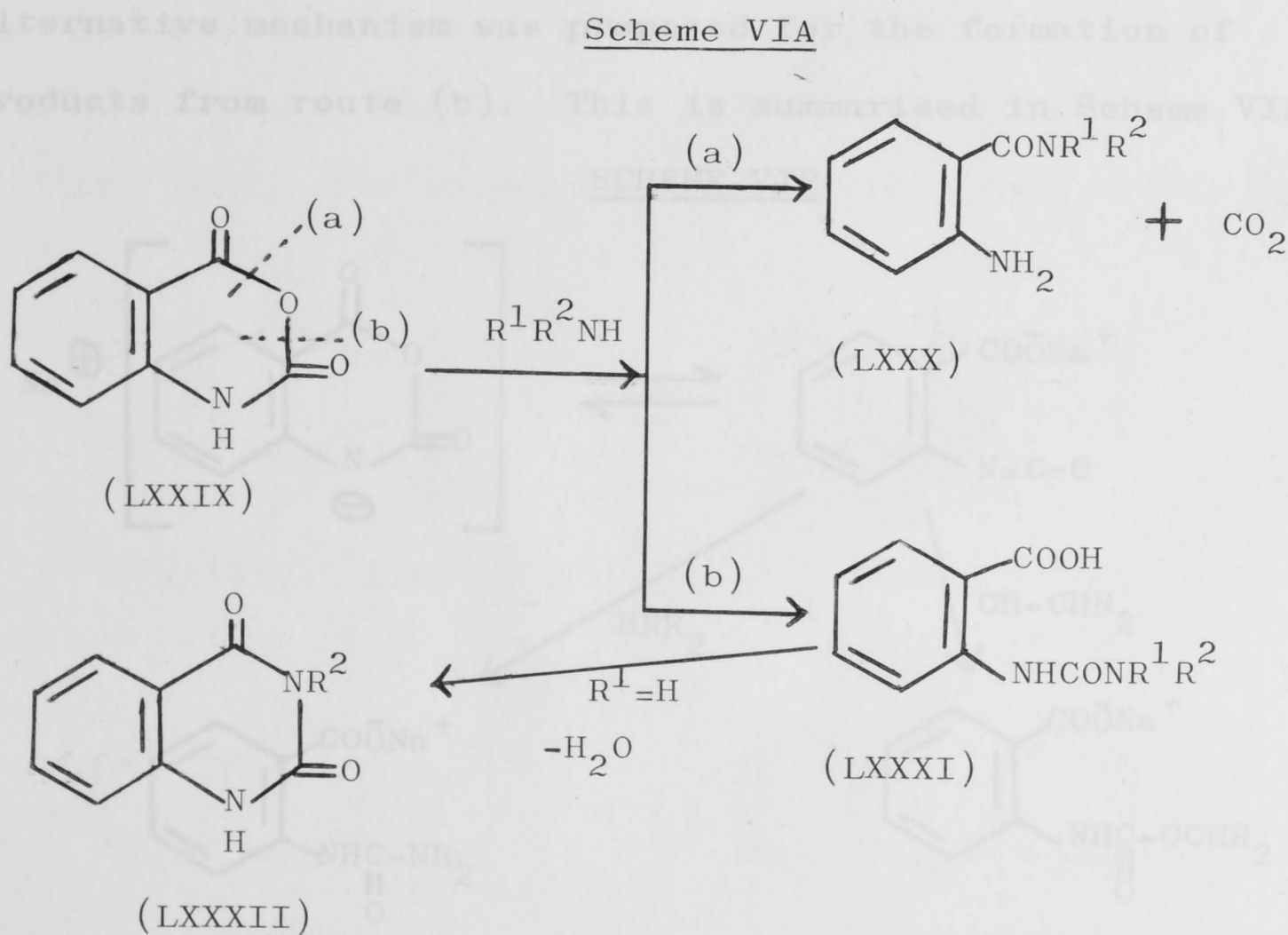
Staiger and Miller[76] then extended the reactions of isatoic

anhydride to include alcohols, phenols, mercaptans and

active methylene compounds. Sodium hydroxide was used as a

catalyst in these reactions which formed substituted esters,

carbamates, thioesters, thiocarbamates and quinolines

respectively. In most cases the reactions proceeded mainly

through route (a), but the authors pointed out that several

factors joined in varying degrees to control the route and

products in the reaction with any particular nucleophile.

The most important of these were the nature and activity of

the nucleophile, steric hindrance and concentration. An

alternative mechanism was proposed for the formation of

products from route (b). This is summarised in Scheme VIB.

<u>SCHEME VIB</u>
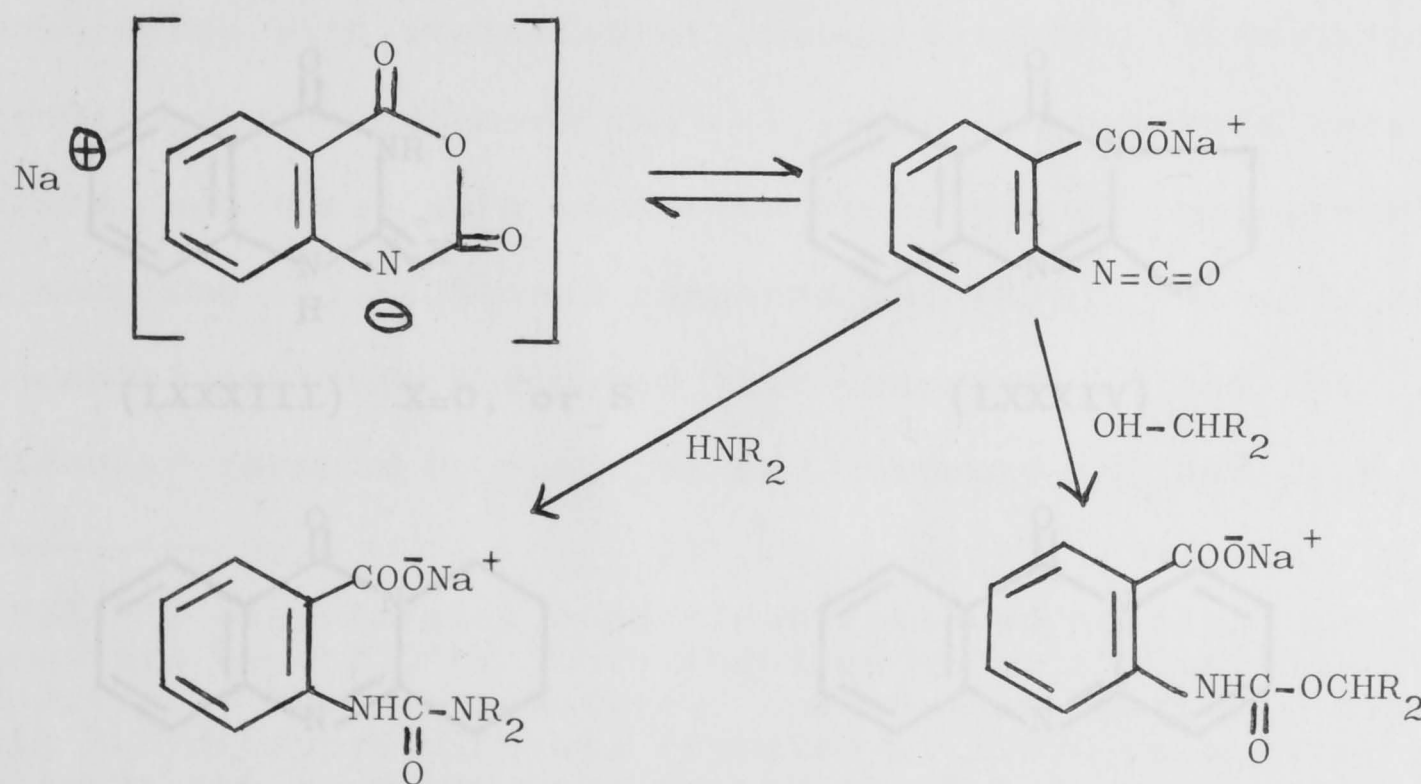
Isatoic anhydride (LXXIX) has been used in heterocyclic synthesis, particularly for substituted quinazolines, e.g., reaction with ureas and thioureas to form derivatives of tetrahydroquinazolines (LXXXIII).[77] Similar products could be obtained by reaction of (LXXIX) with isocyanates and isothiocyanates.[78] Späth and Platzer[79] found that (LXXIX) reacted with α-pyrrolidone and α-piperidone to give the substituted quinazolines (LXXXIV) and (LXXXV) respectively and later (Späth and Kuffner)[80] reported that the same reaction with 2-(1H)-pyridone (LII) yielded "pyracridone" (LXXXVI). Späth[79] proposed that formation of these compounds resulted from cyclization of the initially formed anthranilamides; for example, in the case of 2-(1H)-pyridone (LII), the intermediate (LXXXVII) (from attack via
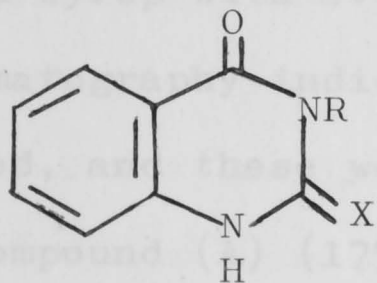
(LXXXIII) X=O, or S
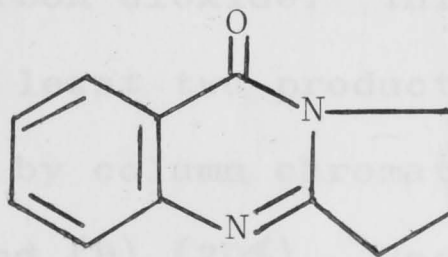
(LXXXIV)

(LXXXV)

(LXXXVI)

63
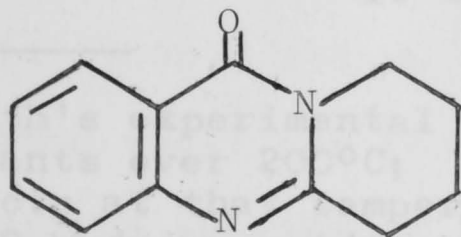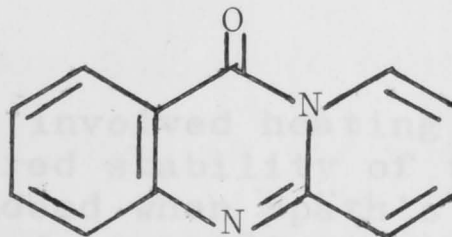
route (a) as suggested by Staiger) lost one molecule of

water to give (LXXXVI). The result of the reaction of

(LII) is particularly interesting, since (LII) normally

forms O-acylated products.[*]
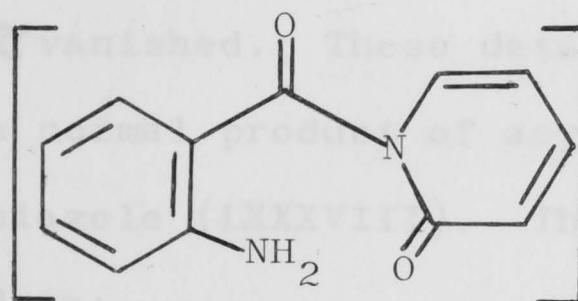
(LXXXVII)

In the light of the results obtained by Späth and his

colleagues, it was of considerable interest to examine the

reaction of isatoic anhydride with 3-hydroxyisothiazole

(XXXII). Heating a mixture of these two compounds just

above the melting point of (XXXII) for 3 hours yielded a

brown syrup with evolution of carbon dioxide. Thin-layer

chromatography indicated that at least two products were

formed, and these were separated by column chromatography

as compound (A) (17%) and compound (B) (20%). Results of

elemental analysis indicated that compound (A) had the

molecular formula $C_{10}H_8N_2O_2S$, and compound (B) had $C_{10}H_6N_2OS$.

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[*]
Späth's experimental conditions involved heating the
reactants over 200°C; this required stability of the
products at that temperature. Indeed when Späth's reaction
with 2-hydroxypyridine was repeated at 110°C, a mixture of
at least two products were formed (by T.L.C. examination),
but separation of this mixture could not be achieved.

Figure VI shows the N.M.R. spectrum of compound (A).
The chemical shifts and coupling constant for the ring
doublets were consistent with O-acylation of 3-hydroxy-
isothiazole (compare Table I). On addition of D_2O the
broad peak at 4.3τ vanished. These data implied that
compound (A) was a normal product of acylation — 3-
anthranoyloxyisothiazole (LXXXVIII). This was supported
by the following data:
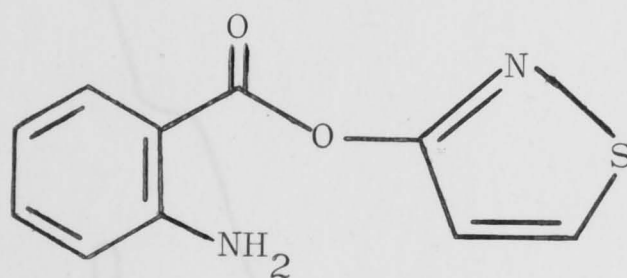
(LXXXVIII)

(i)   The I.R. spectrum (Nujol mull) of compound (A) showed
      bands at 1704 (C=O), 3420 and 3540 cm^{-1} (NH). The
      somewhat lower carbonyl absorption compared to that of
      3-benzoyloxyisothiazole (1750 cm^{-1}) was ascribed to
      hydrogen bonding with the amino group (intra- or
      intermolecular).

(ii) The U.V. spectrum in 95% EtOH showed maxima at 223.5 mμ
      (ε 27600), 248 mμ (ε 15970) and 351 mμ (ε 6690). A
      good model for comparison was found in the combination
      of the spectra of methyl anthranilate (λmax at 221 mμ
      (ε 28660), 248 mμ (ε 7560), 337 mμ (ε 5090)) and 3-
      acetoxyisothiazole (LIII) (λmax at 245 mμ (ε 7870)).

65

COMPOUND (A)

SOLVENT : CDCℓ₃
REFERENCE : T.M.S.

J=4·6 cps
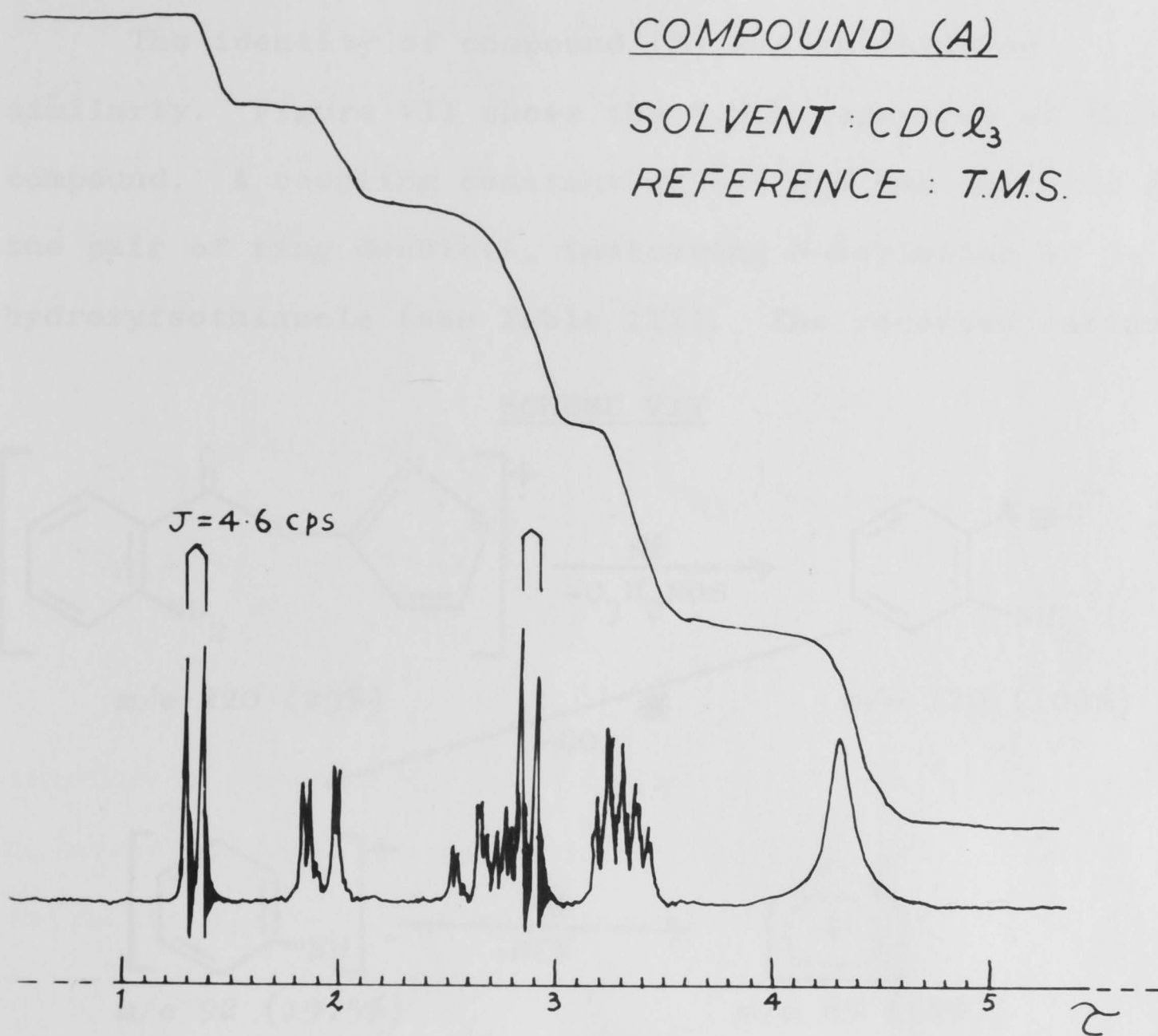
FIG. VI

(iii) The mass spectral fragmentation pattern, illustrated in Scheme VII,[*] was consistent with the structure (LXXXVIII).

The identity of compound (B) was established similarly. Figure VII shows the N.M.R. spectrum of this compound. A coupling constant of 6.4 cps was observed for the pair of ring doublets, indicating N-acylation of 3-hydroxyisothiazole (see Table III). The recorded ratios of

SCHEME VII

m/e 220 (23%) $-C_3H_2NOS$ m/e 120 (100%)

$-CO$

m/e 92 (19.5%) $-HCN$ m/e 65 (14%)

m/e 205 (5%) $-C_3H_2NOS$ m/e 105 (100%) $-CO$ m/e 77 (35%)

✳ = Metastable ion

_____
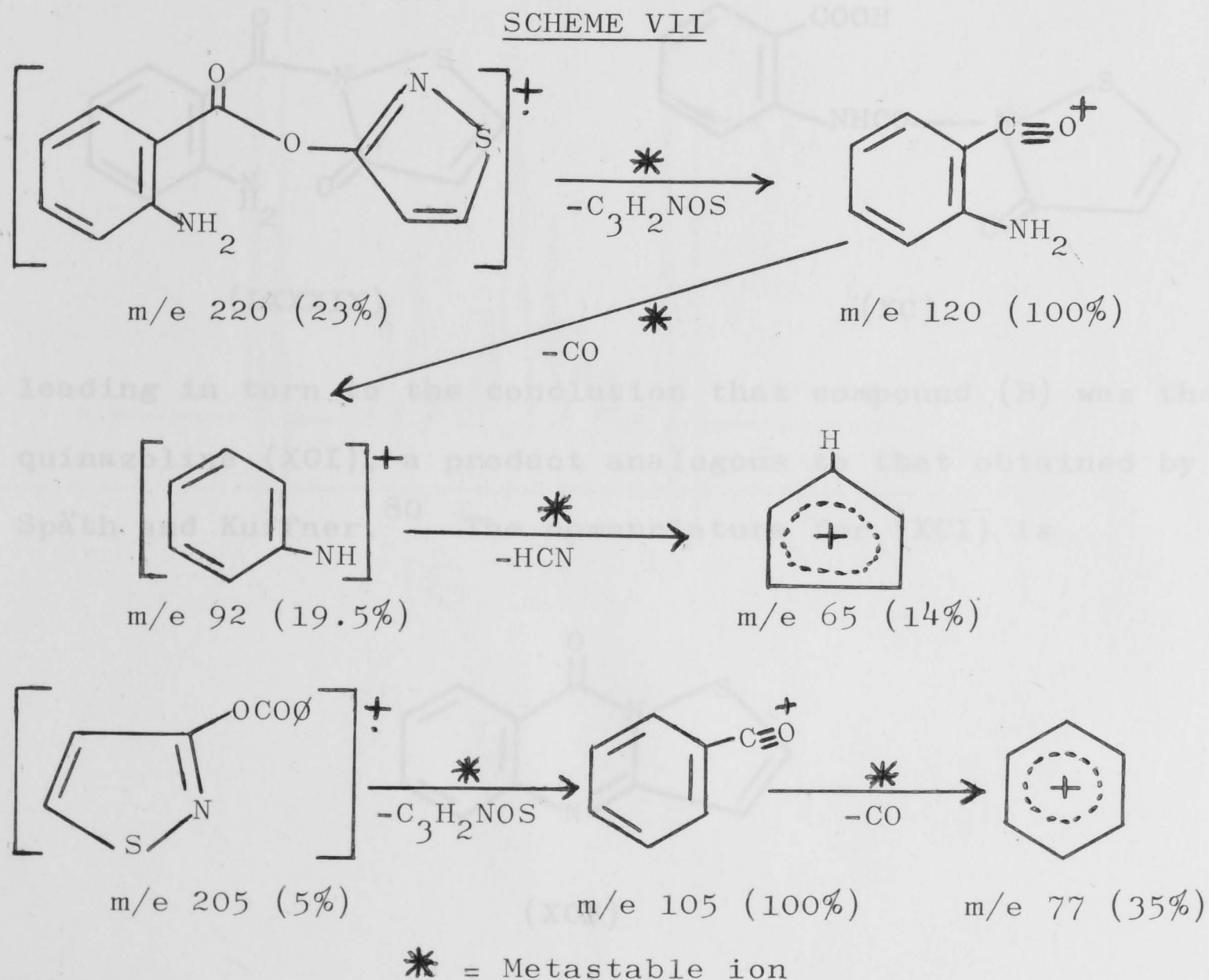
[*] The fragmentation pattern for 3-benzoyloxyisothiazole was included for comparison.

integration, and the absence of any absorption due to NH- or OH- protons excluded the possibility that it might be either of the two compounds (LXXXIX) or (XC); the former compound was a product analogous to the intermediate (LXXXVII) as suggested by Späth,[79] and the latter could be derived from nitrogen attack via route (b) as proposed by Staiger.[72] The molecular formula obtained for compound (B) also suggested that such structures were not possible,
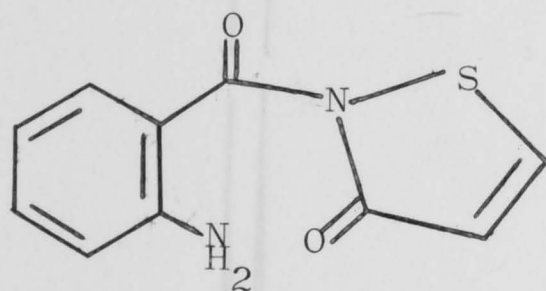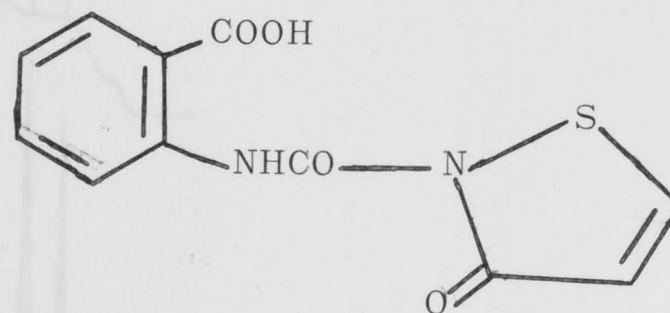
(LXXXIX)   (XC)

leading in turn to the conclusion that compound (B) was the quinazoline (XCI), a product analogous to that obtained by Späth and Kuffner.[80] The nomenclature for (XCI) is

(XCI)

COMPOUND (B)

SOLVENT : D⁶DMSO

REFERENCE : T.M.S.

J = 6.4 cps

FIG. VII

Log ∈

4·5
4·0
3·5
3·0
2·5

220   260   300   340   380   mμ

⊸⊙ COMPOUND (B)
→ (LXXXVI)

FIG. VIII A

Log ∈

4·5
4·0
3·5
3·0

220   260   300   340   mμ
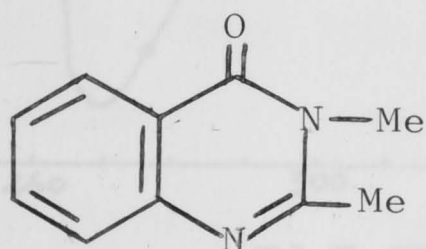
▲ (XCIII)
— (XCIV)

FIG. VIII B

71

(iii) The mass spectrum showed a parent ion (base peak) at

m/e 202, while all other peaks had relative abundances

of about 6% or less. The very low intensity of

fragment ions is consistent with the condensed

aromatic ring structure proposed. Scheme IXA depicts

some of the fragmentations, which evidently involved

rearrangements. The mass spectrum of "pyracridone"

(LXXXVI) was measured for comparison; the fragmen-

tations shown in Scheme IXB are fully resemblant to

those in Scheme IXA.

Control experiments with 3-anthranoyloxyisothiazole

(LXXXVIII) established that the quinazoline (XCI) was not

formed by rearrangement of (LXXXVIII). The formation of

(XCI) probably followed the mechanism suggested by Späth.[79]

So far it has not been possible to detect or isolate the

intermediate anthranilamide (LXXXIX) or any other product

resulting from attack via route (b) (for example, (XC)).

The experimental conditions were varied to examine the

effect on product ratios. When the reaction was performed

in refluxing acetonitrile for 35 hours, the major product

(75%) was (LXXXVIII); only very little (ca 5%) of the

quinazoline (XCI) could be isolated. Table V presents

results obtained by variation of the method which involved

heating the two reactants together in the absence of any

73
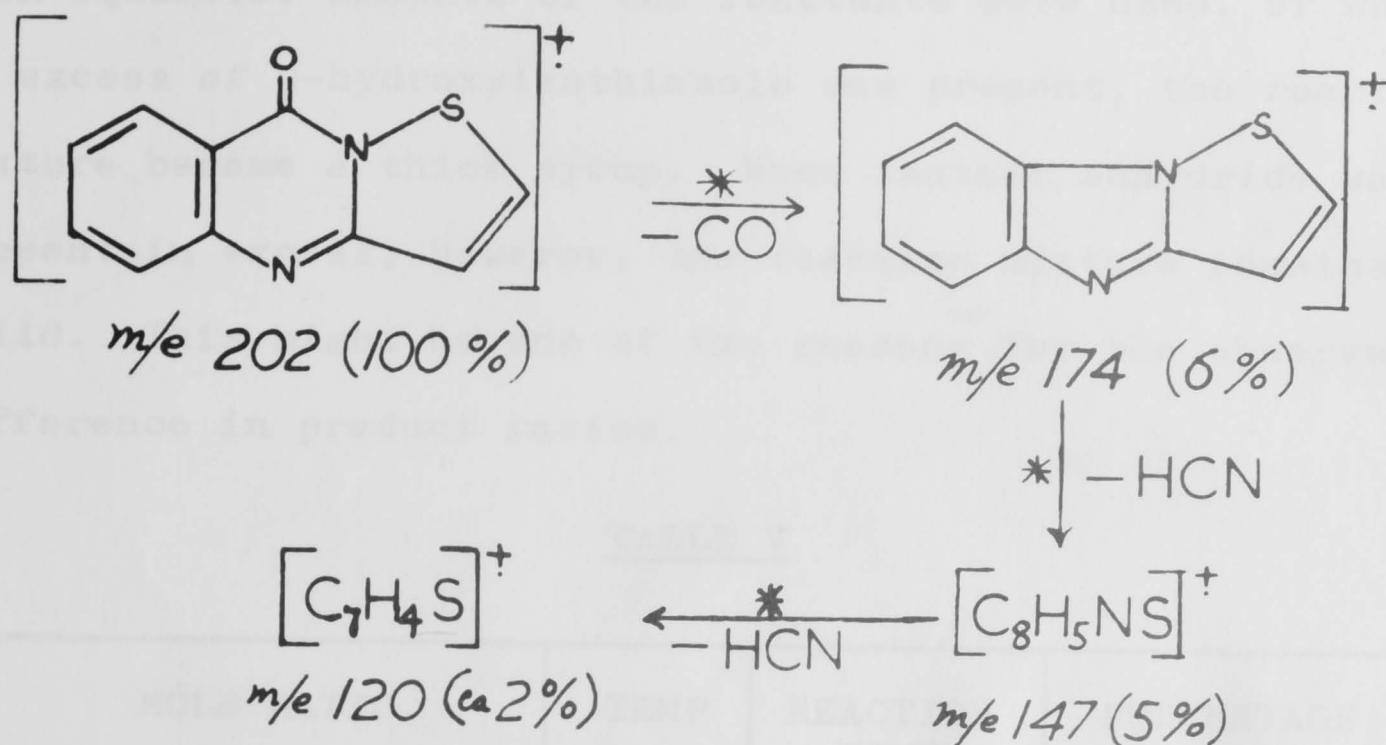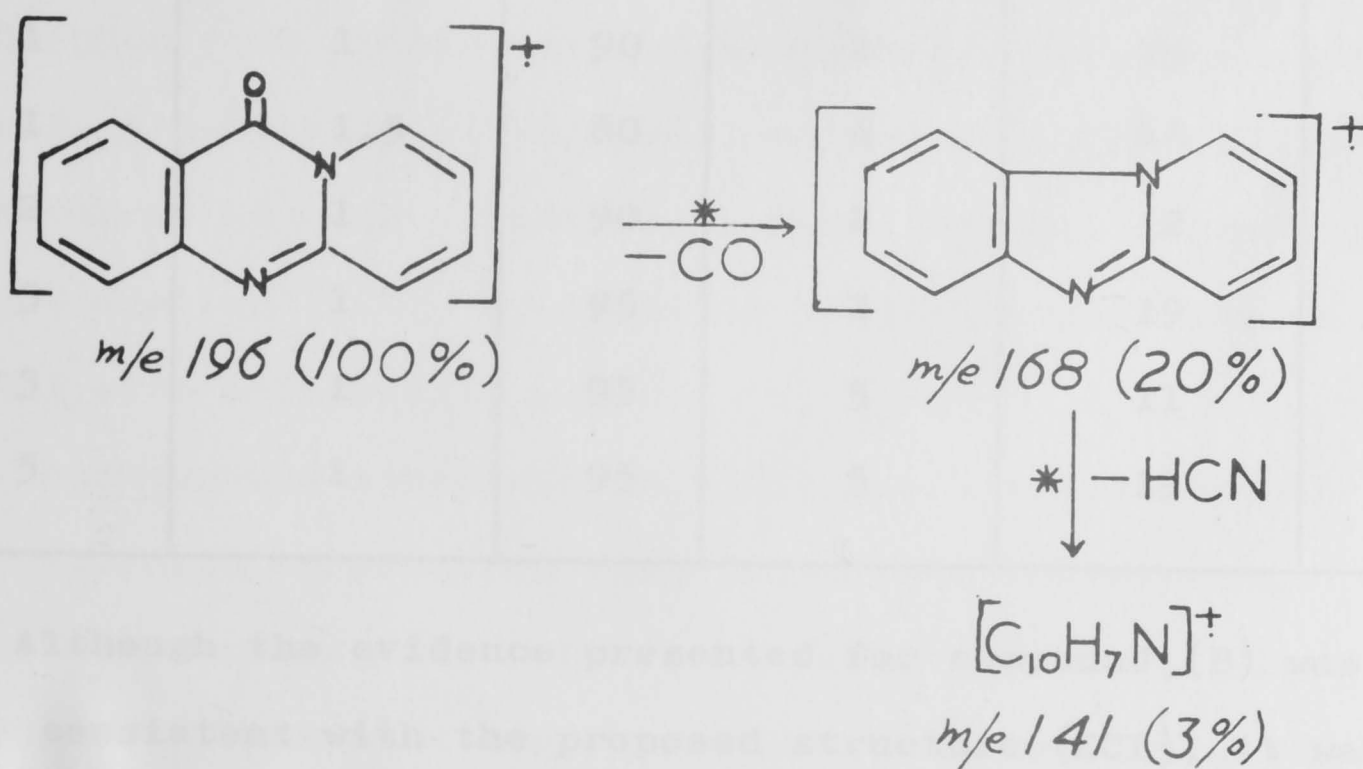
solvent. Yields were those obtained after chromatography.
When equimolar amounts of the reactants were used, or when
an excess of 3-hydroxyisothiazole was present, the reaction
mixture became a thick syrup. When isatoic anhydride was
present in excess, however, the reaction mixture remained
solid. This might be one of the reasons for the observed
difference in product ratios.

TABLE V

MOLE RATIO		TEMP ^{o}C	REACTION TIME	PERCENTAGE YIELD	
ISATOIC ANHYDRIDE	3-HYDROXY-ISOTHIAZOLE		(hours)	(LXXXVIII)	(XCI)
1	1	80	3	17	20
1	1	90	2	25	15
1	1.5	80	6	48	17
2	1	90	2	12	11
3	1	95	2	19	22
3	1	95	5	11	38
5	1	95	5	19	39

Although the evidence presented for compound (B) was
fully consistent with the proposed structure (XCI), it was
decided to synthesize this compound by an alternative route,
involving reaction of 3-chloroisothiazole with anthranilic
acid as depicted in Scheme X.

SCHEME X
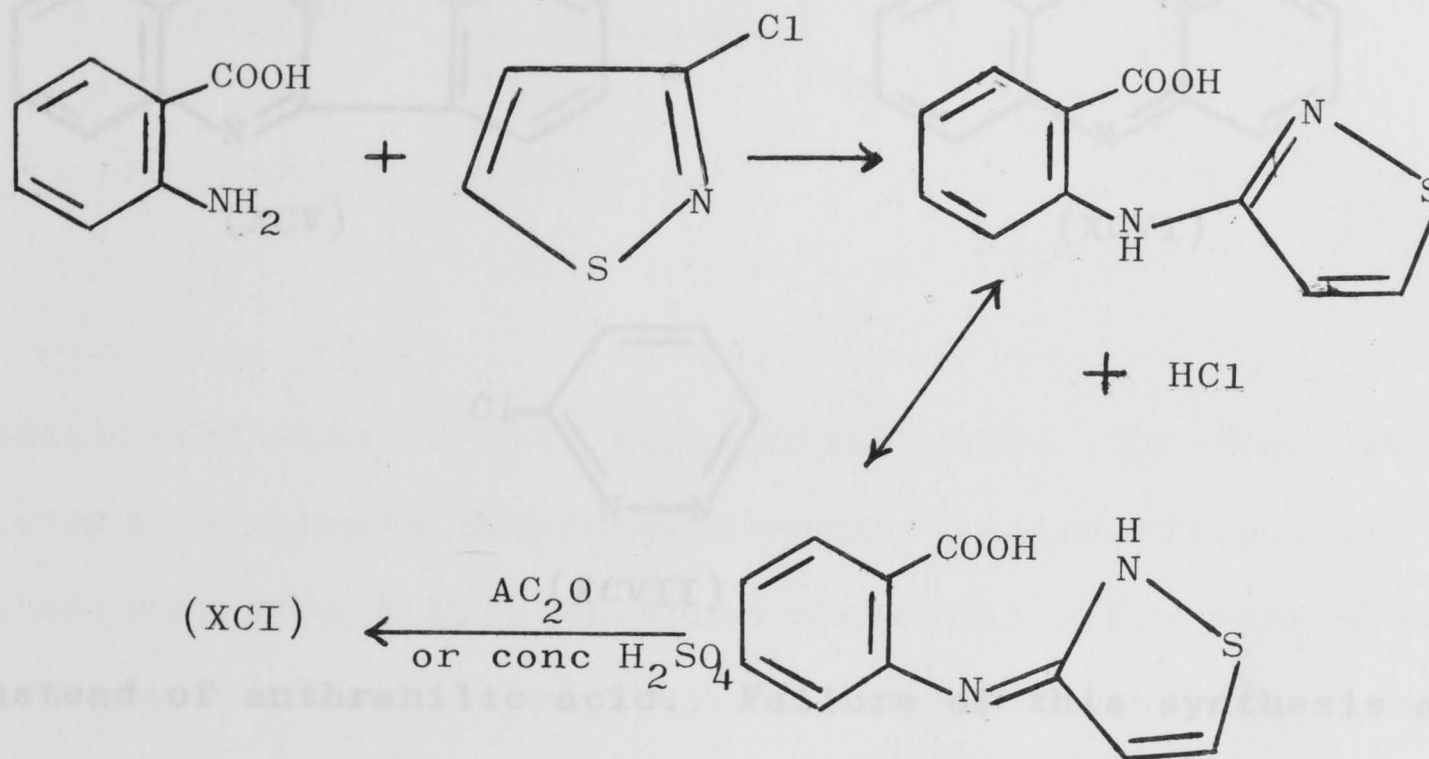
This type of synthesis was employed successfully by Stephen

and Stephen[83] in synthesizing 7-oxobenzo[d]-quinazo[3,2-b]-

thiazole 5:5-dioxide (XCV) from 3-chlorosaccharin (XLVI)

and anthranilic acid. Similarly, Yanai, et al.[84] prepared

the quinazoline (XCVI) by reaction of 3-chloropyridazine

(XCVII) with anthranilic acid.

The proposed synthesis of (XCI) was totally unsuccess-

ful. No reaction occurred when 3-chloroisothiazole was

heated with anthranilic acid in acetone, and in boiling

dimethylformamide only tarry products resulted. Similar

results were obtained when no solvent was used, or when

ammonium anthranilate or methyl anthranilate was used

(XCV)

(XCVI)

(XCVII)
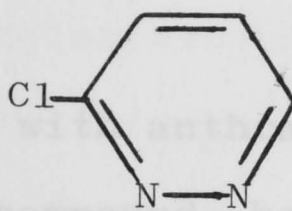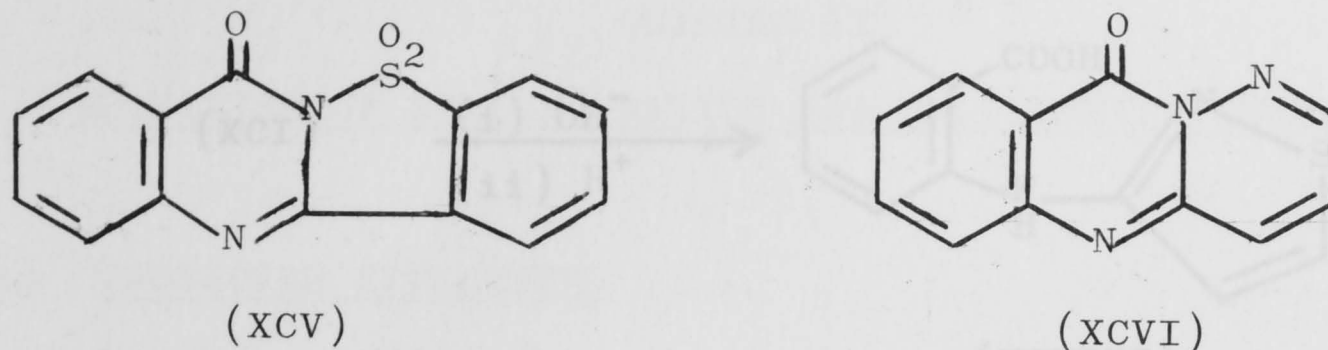
instead of anthranilic acid. Failure of this synthesis at
lower temperatures was probably due to the low reactivity
of 3-chloroisothiazole towards nucleophiles; under more
vigorous conditions S-N bond fission of the isothiazole ring
would be expected to interfere. Hatchard's work[17] on 3,5-
dichloroisothiazoles demonstrated that the 3-position was
inert to most nucleophiles; under vigorous conditions
reactions occurred but these were accompanied by S-N bond
fission. Smith[85] encountered the same sort of behaviour
with other substituted 3,5-dihaloisothiazoles.

Attempted chemical degradation of (XCI) was also
unsuccessful. It was hoped that hydrolysis of (XCI) might
result in the formation of the substituted anthranilic acid
(XCVIII), which was the product expected from reaction of

(XCI) $\xrightarrow{\text{(i) OH}^-}$ $\xrightarrow{\text{(ii) H}^+}$

(XCVIII)

3-chloroisothiazole with anthranilic acid.   The reaction

yielded an unknown compound, however, apparently polymeric

in nature.   The N.M.R. spectrum showed only two very broad

peaks in the aromatic region;   no ring doublet was visible.

So far it has not been possible to purify this compound.

Failure of this reaction might be due again to S-N bond

fission in (XCI).

CHAPTER II

MECHANISM OF ACYL MIGRATION AND EQUILIBRIUM STUDIES

(A) CROSSOVER EXPERIMENT

Initial difficulties encountered in the isolation and purification of 3-acyloxyisothiazoles suggested that some form of catalysis was involved in the rearrangement. While the possibility of a four-centre intramolecular mechanism, proceeding through the transition state (XCIX), could not be overlooked, a bimolecular mechanism seemed more likely. The following crossover experiment was designed to investigate this proposal. 3-acetoxyisothiazole (LIII)
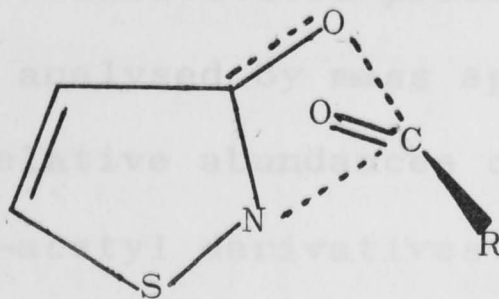
(XCIX)

and 5-D-3-trideuteroacetoxyisothiazole (C) were allowed to rearrange together. The use of a double-labelled molecule was essential in order that the effect of an intermolecular mechanism, if present, would be visible. If an intermolecular acyl migration were operative, one would expect scrambling of the acyl moieties as shown in Scheme XI.

Scheme XI

OCOCH$_3$ (LIII) M$^+$=143 + OCOCD$_3$ (C) M$^+$=147

↓

D/H N-COCH$_3$ M$^+$=143(5H) =144(5D) + D/H N-COCD$_3$ M$^+$=146(5H) =147(5D)
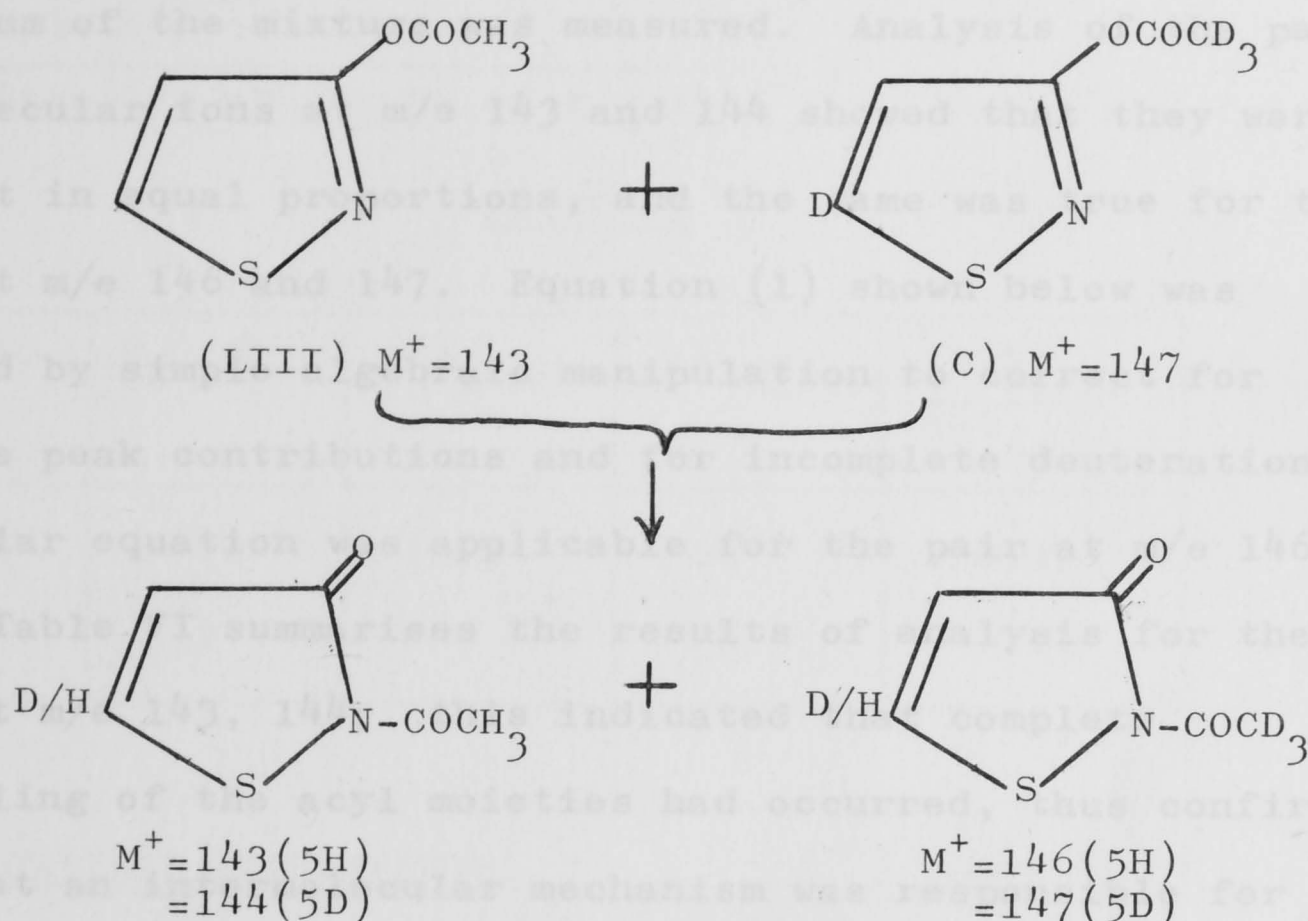
The mixture of N-substituted products from the cross-over experiment was analysed by mass spectrometry. This was done by comparing relative abundances of the molecular ions of the mixture of N-acetyl derivatives. It can be seen from Scheme XI that the mass spectrum of the products resulting from an intramolecular mechanism would show molecular ions at m/e 143 and 147; the peaks at much lower intensity at m/e 144 and 146 would be due only to natural isotope contributions and incomplete deuteration respectively. On the other hand, a mixture resulting from an intermolecular mechanism would show four molecular ions as depicted in

Scheme XI, and such was the result obtained when the spectrum of the mixture was measured. Analysis of the pair of molecular ions at m/e 143 and 144 showed that they were present in equal proportions, and the same was true for the pair at m/e 146 and 147. Equation (1) shown below was derived by simple algebraic manipulation to correct for isotope peak contributions and for incomplete deuteration. A similar equation was applicable for the pair at m/e 146, 147. Table VI summarises the results of analysis for the pair at m/e 143, 144; this indicated that complete scrambling of the acyl moieties had occurred, thus confirming that an intermolecular mechanism was responsible for the rearrangement.

$$\frac{143_{corr.}}{144_{corr.}} = \frac{143_{mixt.} - K_D \ 144_{mixt.}}{144_{mixt.} - K_H \ 143_{mixt.}} \tag{1}$$

where $143_{corr.}$ (or $144_{corr.}$) = corrected relative abundance of m/e 143 (or 144) in the mixture.

$143_{mixt.}$ (or $144_{mixt.}$) = observed abundance of m/e 143 (or 144) in the mixture.

K_H = correction factor for isotope peak contribution in pure N-acetyl-3-isothiazolone

$$= \frac{\text{Relative abundance of m/e 144}}{\text{Relative abundance of m/e 143}}$$

K_D = correction factor for incomplete deuteration in

5D-N-acetyl-3-isothiazolone

$$= \frac{\text{Relative abundance of m/e 143}}{\text{Relative abundance of m/e 144}}$$

TABLE VI

K_D %	K_H %	$143_{mixt.}$	$144_{mixt.}$	$\dfrac{143_{corr.}}{144_{corr.}}$
5.2	7.2	18.5	24	0.97
5.2	7.2	22	28.5	1.04

(B) CATALYSIS EXPERIMENTS

In the light of the foregoing information, a
concerted mechanism would necessarily involve an eight-
centre transition state such as (CI). A more attractive
possibility was the stepwise transacylation process
involving the intermediates (CII) and (CIII). As a strong
phenol, 3-hydroxyisothiazole would be expected to yield
esters which would act as transacylating agents. The
bimolecular transacylation would lead to the N-acyl-3-
acyloxyisothiazolium cation (CIII), which could undergo
attack on (CII) at either heteroatom to yield the observed
products. A major conceptual difficulty was, however,
apparent in the separation of the charged species (CII) and
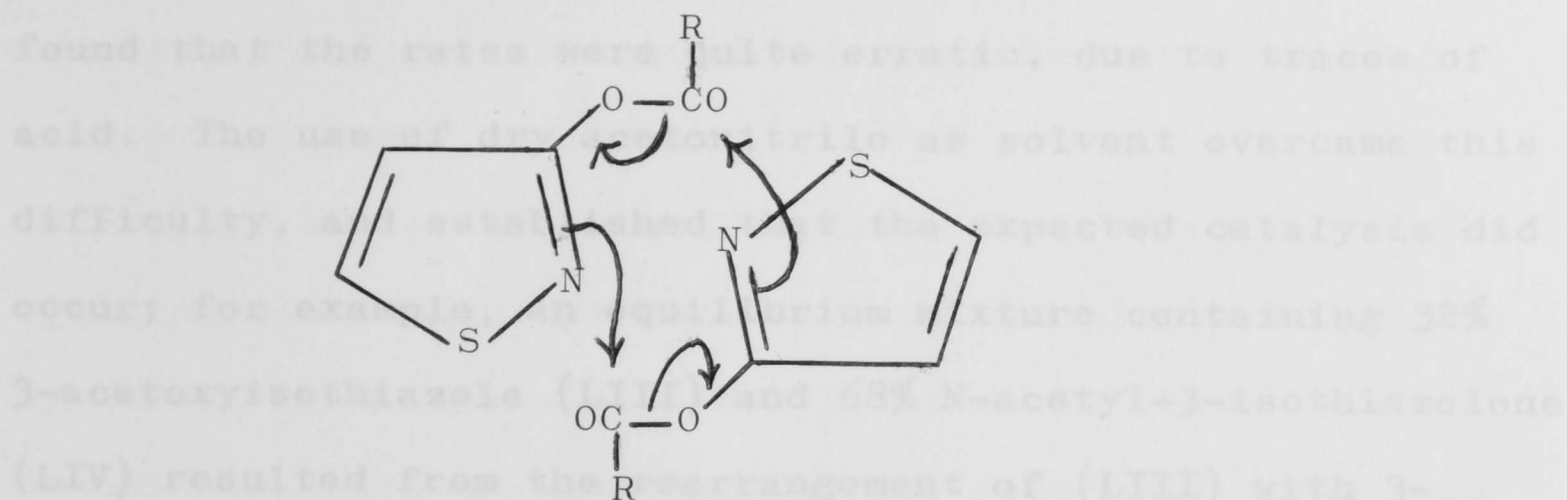
(CI)
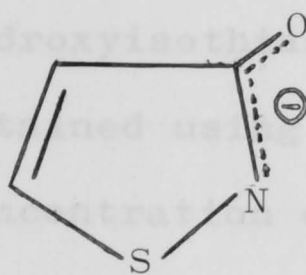
(CII)
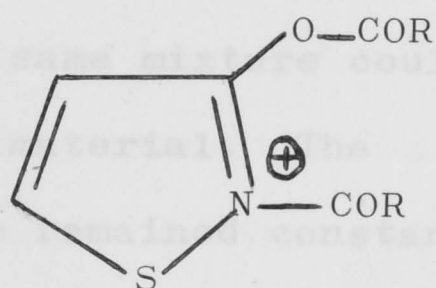
(CIII)

(CIII) from the transition state. The 3-oxyisothiazole

anion (CII) was known to undergo extremely rapid acylation

even at 0°, so that its separation from an efficient

acylating agent seemed rather anomalous. The hypothesis

was tested by treating pure 3-acetoxyisothiazole with dry

acetic anhydride, a process calculated to aid the

formation of (CIII). In fact the rearrangement was

suppressed, a result more in line with removal of the anion

(CII) than generation of (CIII). Such an observation was

also more in line with the effect of exposure (generation

of 3-hydroxyisothiazole by hydrolysis) in accelerating the

rearrangement. The effect of 3-hydroxyisothiazole itself

81

was examined by N.M.R., in deuterochloroform, but it was

found that the rates were quite erratic, due to traces of

acid. The use of dry acetonitrile as solvent overcame this

difficulty, and established that the expected catalysis did

occur; for example, an equilibrium mixture containing 32%

3-acetoxyisothiazole (LIII) and 68% N-acetyl-3-isothiazolone

(LIV) resulted from the rearrangement of (LIII) with 3-

hydroxyisothiazole as catalyst. The same mixture could be

obtained using (LIV) as the starting material. The

concentration of 3-hydroxyisothiazole remained constant

throughout the experiment. The rearrangement was still

further accelerated by a trace of dry hydrogen chloride,

presumably due to enhanced polarisation of the carbonyl

group, which in turn facilitated nucleophilic attack by

3-hydroxyisothiazole. Control experiments, omitting 3-

hydroxyisothiazole, indicated that pure 3-acetoxyisothiazole

in acetonitrile did not show any rearrangement even after

several days at 35°. With other aliphatic 3-acyloxy-

isothiazoles (except the trimethylacetoxy derivative) 3-

hydroxyisothiazole also catalysed the O→N acyl migration,

and control experiments with the pure compounds again

showed no rearrangement. This offered a clear demonstration

that the intramolecular mechanism (XCIX) and the self-

acylation mechanism were not operative. The transacylation

mechanism thus requires a suitable substrate before it can operate, the 3-acyloxyisothiazoles apparently being too weakly nucleophilic to serve.

A variety of other nucleophiles were effective in bringing about the acyl migration; these included phenol, pyrazole, benzimidazole, alcohol, etc. In the case of phenol and 3-acetoxyisothiazole, the generation of phenyl acetate and 3-hydroxyisothiazole could be seen by N.M.R. to occur prior to rearrangement. The final result was a complete conversion to phenyl acetate and 3-hydroxy-isothiazole. A control experiment showed that no transacylation occurred between phenyl acetate and 3-hydroxyisothiazole.

In view of the ability of 3-hydroxyisothiazole to undergo O- and N-acylation, it was to be expected that a portion of the total transacylation would involve O-acyl transfer rather than O→N transfer. A series of experiments was designed to demonstrate this point. 3-trimethylacetoxy-isothiazole (LV), which did not undergo O→N migration, was allowed to react with 5D-3-hydroxyisothiazole in acetonitrile, whereupon rapid scrambling of the isothiazole moieties was observed. No trace of the N-substituted isomer could be detected. Figure IX shows the N.M.R. measurements of this process. The results clearly showed

that the O-substituted isomer was exclusively preferred thermodynamically. A similar experiment was performed on 3-butyryloxyisothiazole, in which the overall rate of migration to nitrogen was slow. Figure X depicts results of this experiment. It can be seen that O→O transfer was much faster than O→N transfer, although the latter was observable. Another case examined was that of N-formyl-3-isothiazolone (LXXI), which did not undergo N→O formyl migration even in the presence of 3-hydroxyisothiazole, and which might therefore be expected to be the most likely case to show N→N transacylation. When (LXXI) was treated with 5D-3-hydroxyisothiazole, rapid scrambling of the formyl group occurred, and equilibrium was reached in about two hours in D^6DMSO. The result showed clearly that the N-substituted isomer was exclusively favoured thermodynamically.

The somewhat rapid rate of scrambling observed for the N-formyl compound raised the interesting question of the relative rates of the four possible exchange reactions (O→O, O→N, N→O, N→N) in those compounds that underwent reversible acyl migration. This was examined in the case of O→N acetyl migration. In early trials, the incorporation of 5-D-3-hydroxyisothiazole was examined while O→N migration was in progress, i.e., incorporation into a system moving towards equilibrium. This seemed to indicate that O→O

85
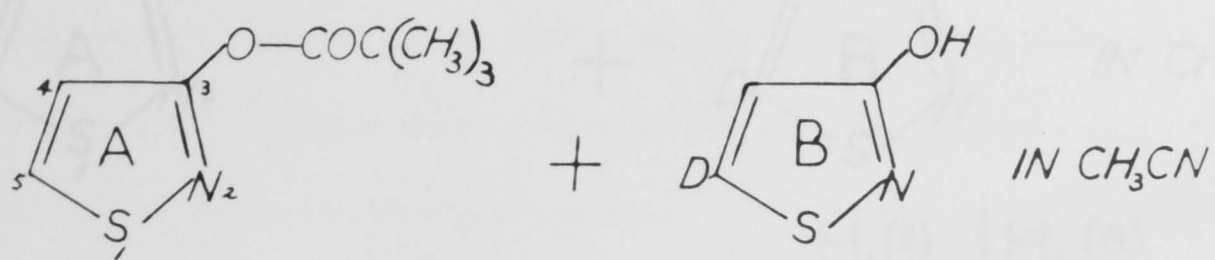
FIG. IX
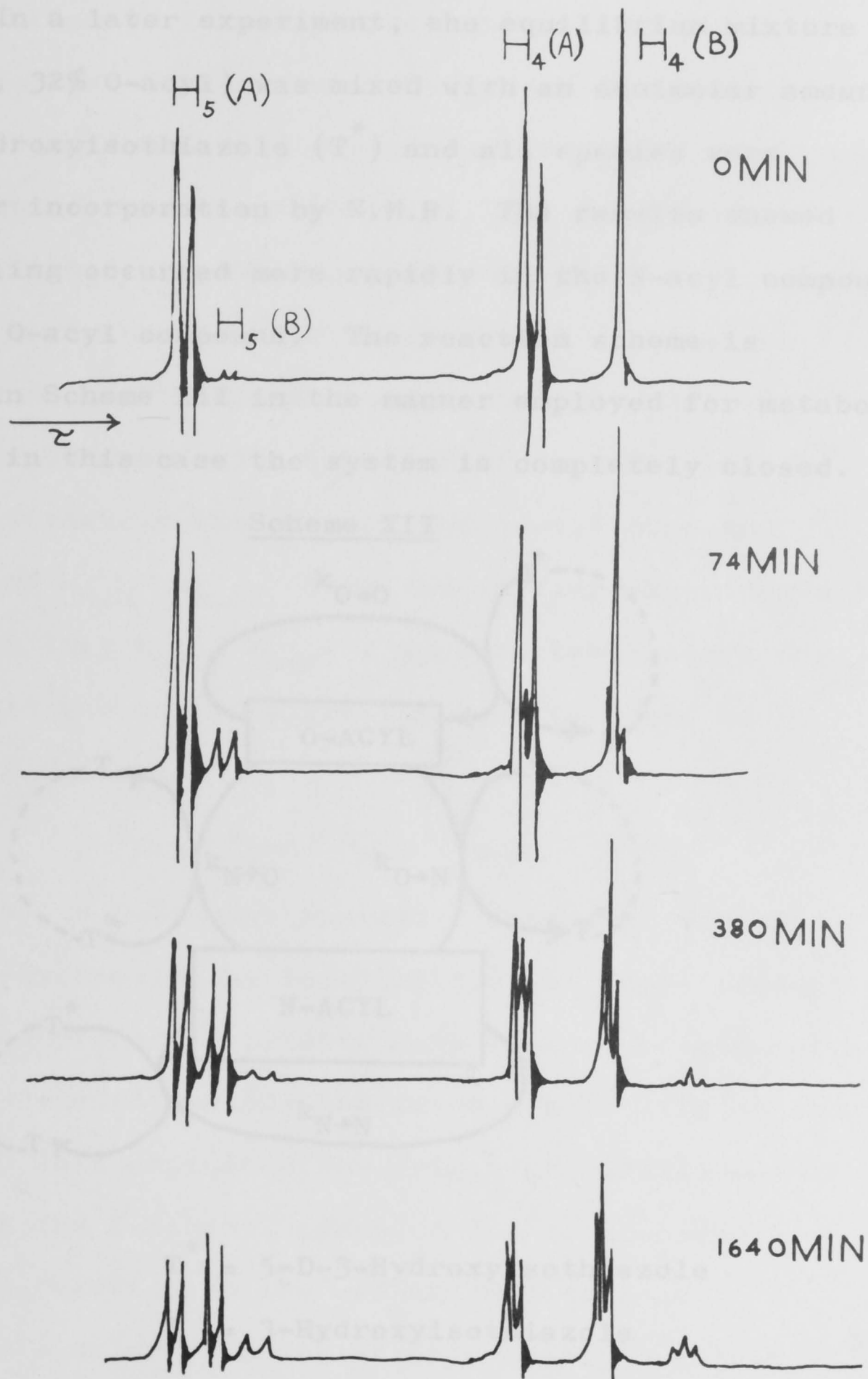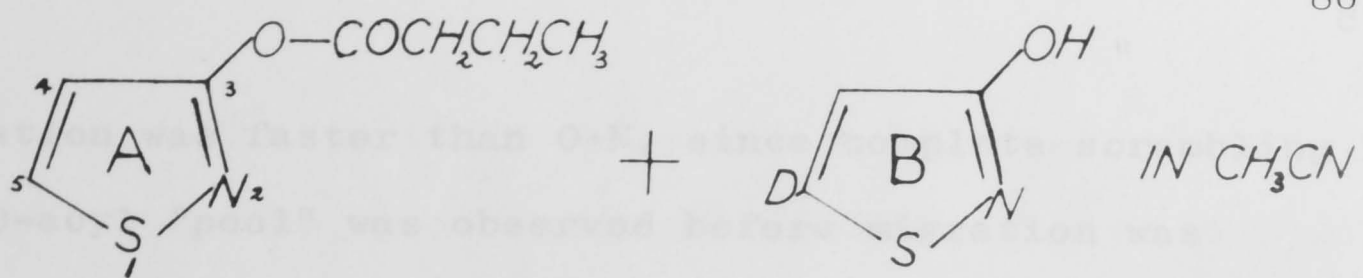
FIG. X

migration was faster than O→N, since complete scrambling in

the O-acyl "pool" was observed before migration was

complete. In a later experiment, the equilibrium mixture

(68% N-acyl, 32% O-acyl) was mixed with an equimolar amount

of 5-D-3-hydroxyisothiazole (T^*) and all species were

examined for incorporation by N.M.R. The results showed

that scrambling occurred more rapidly in the N-acyl compound

than in the O-acyl compound. The reaction scheme is

summarised in Scheme XII in the manner employed for metabolic

processes; in this case the system is completely closed.

Scheme XII

$$k_{O \to O} \qquad T^*$$

$$O\text{-}ACYL \qquad T$$

$$T \qquad T$$

$$k_{N \to O} \qquad k_{O \to N}$$

$$T^* \qquad T^*$$

$$N\text{-}ACYL$$

$$T^*$$

$$k_{N \to N}$$

$$T \qquad T$$
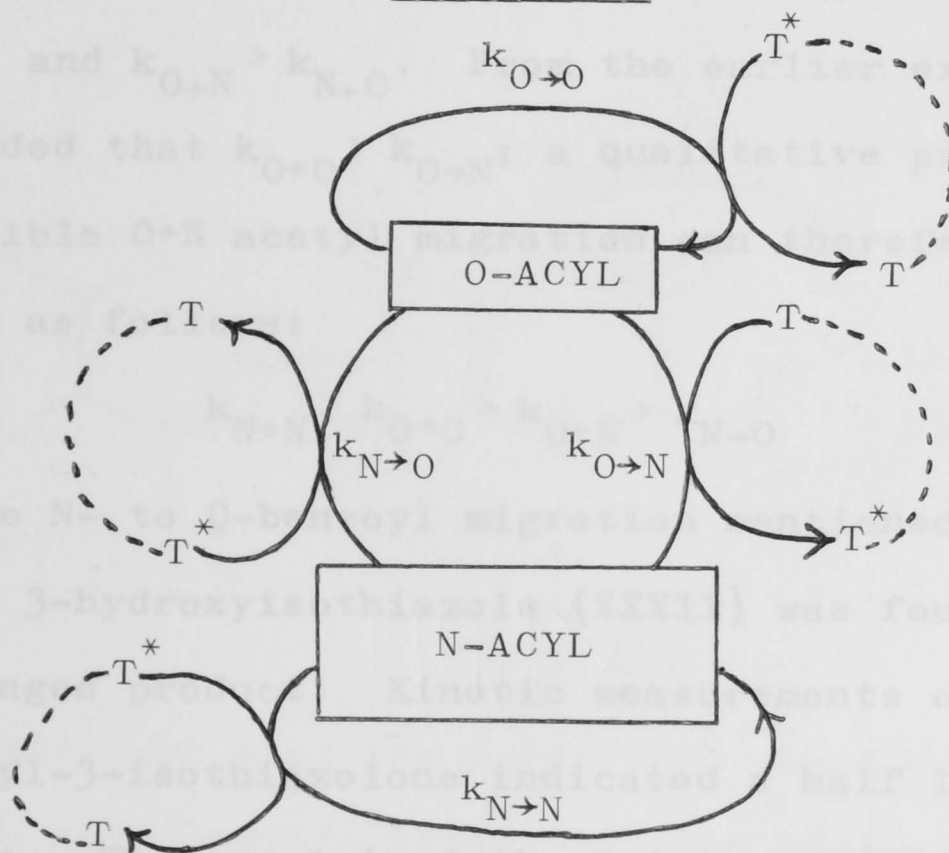
$$T^* = 5\text{-}D\text{-}3\text{-Hydroxyisothiazole}$$

$$T = 3\text{-Hydroxyisothiazole}$$

Since the T—T* "pool" is the same at all times for all
cycles, it can be ignored; its isotopic concentration will
be equally reflected in all. Since the mass flow in the
$O \rightarrow N/N \rightarrow O$ cycle must be constant (the system is at equilibrium),
the smaller "pool" (O-acyl) must show the faster turnover
(with respect to this reaction only), and should therefore
equilibrate with the T—T* "pool" more rapidly. This is
directly in contrast with the experimental results, so it
follows that the $N \rightarrow N$ cycle not only outweighs this effect,
but also the added effect of the $O \rightarrow O$ cycle. Thus the
conclusion is that in the case of the acetyl compound
$k_{N \rightarrow N} > k_{O \rightarrow O}$, and $k_{O \rightarrow N} > k_{N \rightarrow O}$. From the earlier experiments it
was concluded that $k_{O \rightarrow O} > k_{O \rightarrow N}$; a qualitative picture for
the reversible $O \rightarrow N$ acetyl migration can therefore be
summarised as follows:

$$k_{N \rightarrow N} > k_{O \rightarrow O} > k_{O \rightarrow N} > k_{N \rightarrow O}$$

In the N- to O-benzoyl migration mentioned in Chapter I,
a trace of 3-hydroxyisothiazole (XXXII) was found present in
the rearranged product. Kinetic measurements of ethanolysis
of N-benzoyl-3-isothiazolone indicated a half life of about
100 minutes. This explained the origin of (XXXII) —— by
hydrolysis of the N-benzoyl compound due to absorbed
moisture. In relation to the mechanism discussed
previously, a similar transacylation probably occurred in

this case with the complete conversion to the thermo-
dynamically more stable 3-benzoyloxyisothiazole (LXX). This
was confirmed by a catalysis experiment involving addition
of 3-hydroxyisothiazole to a solution of N-benzoyl-3-
isothiazolone in DMSO; the expected rearrangement occurred
with total conversion to (LXX).

A similar mechanism has recently been reported[86] for
the methyl migration observed in 2,6-dimethylthio-4-
thiapyrones (CIV)→(CVI). It was found that the reaction
was accelerated by the addition of methyl iodide, and that
the thiapyrilium salt (CV) was involved. However, it was

(CIV)   (CV)   (CVI)
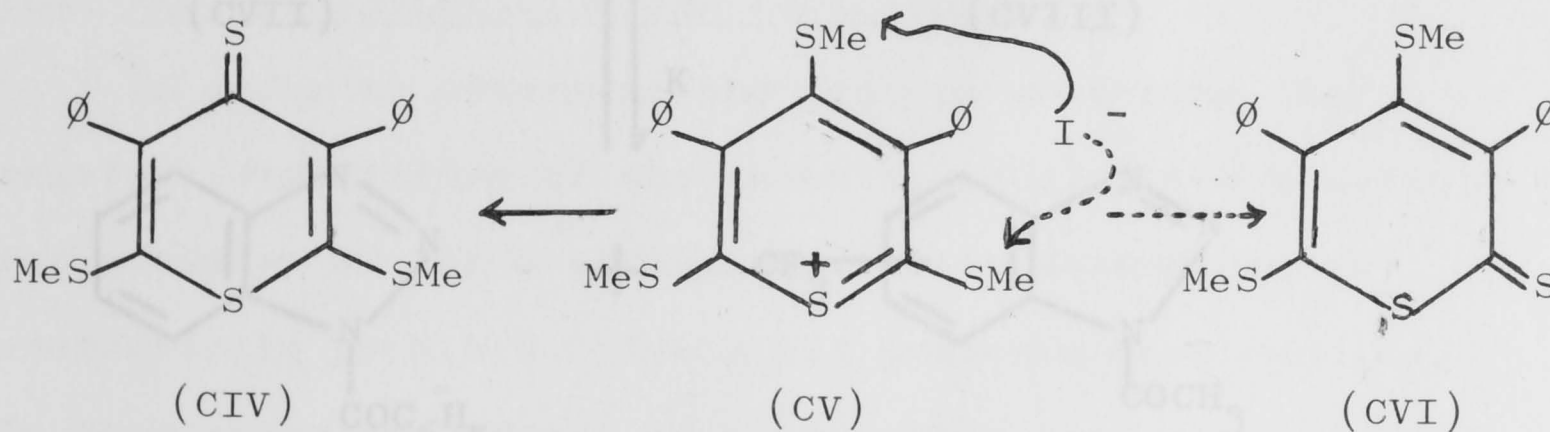
subsequently shown that the iodide ion was the necessary
reagent; a nucleophilic attack by this species was the
essential step. In the acyl migration discussed earlier,
the necessity for generating a cationic species correspond-
ing to (CV) does not seem to arise, presumably because the

3-acyloxyisothiazoles are already sufficiently susceptible to nucleophilic attack without such activation. However, the effect on the rate shows that protonation does assist the migration.

Recently Druliner[87] reported a thermal intermolecular acyl exchange reaction between the N-acylbenzotriazoles (CVII) and (CVIII). The author pointed out that a referee had suggested that a trace of acid chloride could cause

(CVII)   +   (CVIII)

↑↓ K

(CIX)   +   (CX)
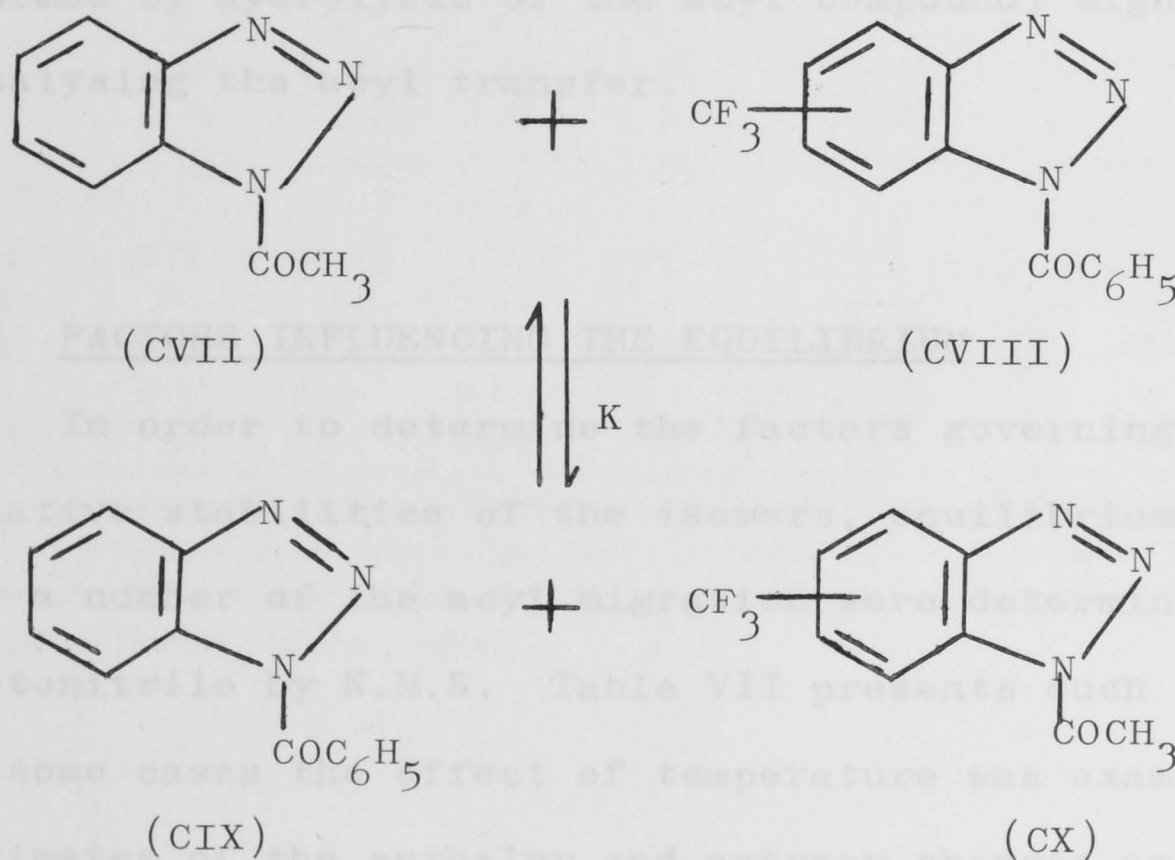
transacylation $\underline{via}$ an intermediate such as (CXI); but when a mixture of (CIX) and (CX) was treated with a trace of benzoyl chloride, the rate of transacylation was found to be measurably retarded rather than enhanced. This result was comparable to the effect of acetic anhydride on 3-

COR
|
N⁺
‖
N
|
N
|
COR
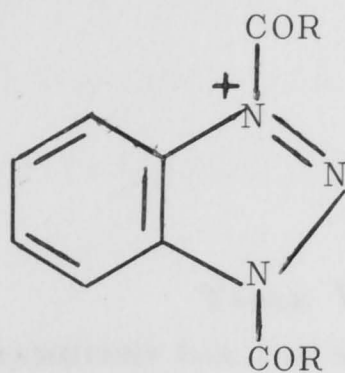
(CXI)

acetoxyisothiazole mentioned already. However, Druliner

did not explore the possibility that benzotriazole itself

(formed by hydrolysis of the acyl compound) might be

catalysing the acyl transfer.

(C) FACTORS INFLUENCING THE EQUILIBRIUM

In order to determine the factors governing the

relative stabilities of the isomers, equilibrium constants

for a number of the acyl migration were determined in

acetonitrile by N.M.R. Table VII presents such results.

In some cases the effect of temperature was examined, and

estimates of the enthalpy and entropy changes are included.

The proportion of the 3-acyloxyisothiazoles increases with

temperature at a rather less rapid rate than is required

for a linear plot of logK $\underline{vs}$ $^1/_T$, so that the results

presented are averaged over the temperature range 20—35°.

TABLE VII

EQUILIBRIUM PARAMETERS FOR THE MIGRATION IN ACETONITRILE:
3-ACYLOXYISOTHIAZOLE $\rightleftarrows$ N-ACYL-3-ISOTHIAZOLONE

$$K = [N\text{-acyl}]/[O\text{-acyl}]$$

R in RCO	K^a				ΔG_{302} (kcal mole^{-1})	ΔH^b (kcal mole^{-1})	ΔS^b (e.u.)
	24·4°	29·2°	34·5	50·0°			
H	α	α	α	α	—	—	—
Me	3·02	2·44	2·14	1·88	−0·54	−5·4	−16
Et	2·00	1·64	1·53	1·36	−0·30	−4·3	−13
Pr	1·62	1·46	1·23	1·14	−0·22	−4·2	−13
Pr^i	—	—	0·56	—	—	—	—
Me$_3$C	0·0	0·0	0·0	0·0	—	—	—
MeO	—	—	2·88	—	—	—	—
EtO	3·00	2·66	2·20	2·00	−0·59	−4·8	−14
Ph	0·0	0·0	0·0	0·0	—	—	—
PhCH$_2$	—	—	1·49	—	—	—	—

^{a} Determined by n.m.r. integration ratios—mean of at least three runs.

^{b} Averaged over the range 24–35°, within which reasonable linearity was observed. The negative values for ΔS are consistent with the greater restriction of rotational freedom in the product.

Examination of the equilibrium constants for the series R=acetyl, propionyl, butyryl etc. suggests the operation of a simple steric effect with less hindrance in the O-sbustituted isomer. The situation is evidently not quite so simple, since the formyl derivative exists entirely in the N-form. Models indicated that coplanarity of the acyl carbonyl with the ring was permitted in N-formyl-3-isothiazolone, thus allowing full N-CO interaction, whereas in the case of larger acyl groups an increasing amount of out-of-plane twisting was enforced. Comparison of the infrared stretch frequencies (in chloroform) of N-formyl-3-isothiazolone (1724 cm^{-1}) and N-acetyl-3-isothiazolone (1711 cm^{-1}) with those of the corresponding dimethylamides (formyl: 1680 cm^{-1}, acetyl: 1636 cm^{-1}) indicated a greater difference in the acetyl case. This was taken as good evidence for out-of-plane twisting in N-acetyl-3-isothiazolone. The presence of larger acyl groups on the nitrogen resulted in similar carbonyl frequencies at about 1710 cm^{-1}. In the absence of steric factors it is apparent that the N-acylated isomer is probably the more stable, due to the enhanced interaction with the carbonyl group. Where the necessary coplanarity is sterically forbidden, the choice between stability of the O- and N-substituted isomers becomes somewhat more complex,

involving consideration of the conformation around the
ester C-O bond. In order to achieve O-CO interaction two
conformations are possible, the s-trans (CXII) and the s-cis
(CXIII), the former being preferred on account of the lesser
lone-pair interaction between oxygen atoms. Karabatsos[88]
has estimated an enthalpy difference between the conformers
of more than 2.5 kcal mole^{-1} for ethyl formate, and 3.7 kcal
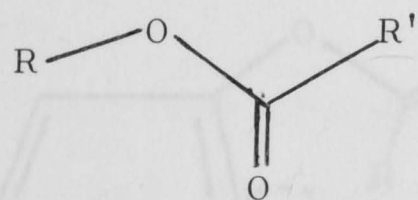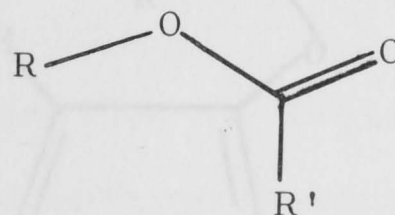
(CXII)   (CXIII)

mole^{-1} for isopropyl formate. The corresponding structures
for 3-acyloxyisothiazoles, (CXIV) and (CXV), and for N-acyl-
3-isothiazolones, (CXVI), are shown on page 95.

The acidity of 3-hydroxyisothiazole, and the
susceptibility of its esters to nucleophilic attack at the
carbonyl group, are indicative of enhanced interaction
between the 3-oxygen and the ring system. This would be
expected to lower the electron density on the 3-oxygen,
thus lowering the lone-pair interactions and bringing (CXIV)
and (CXV) closer together in energy. The system should
thus be more susceptible to purely steric effects of the
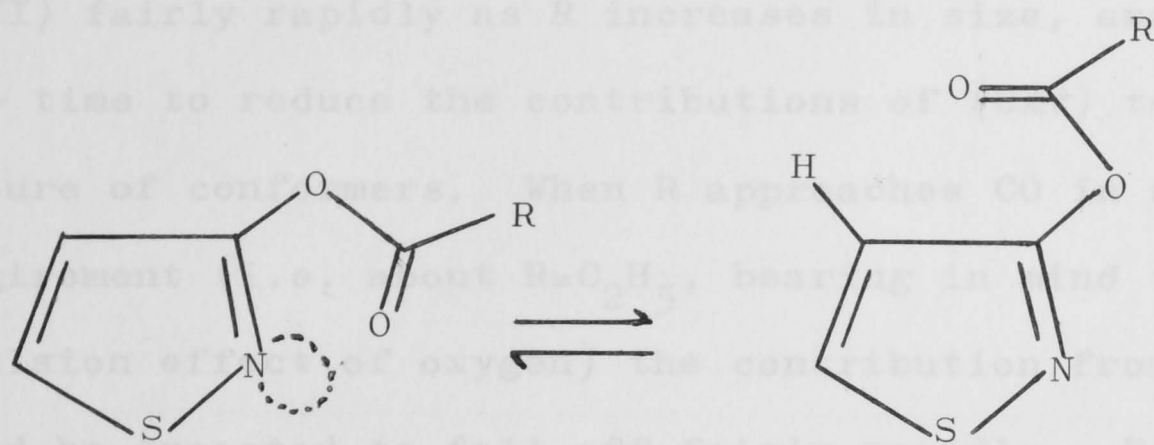
(CXIV)
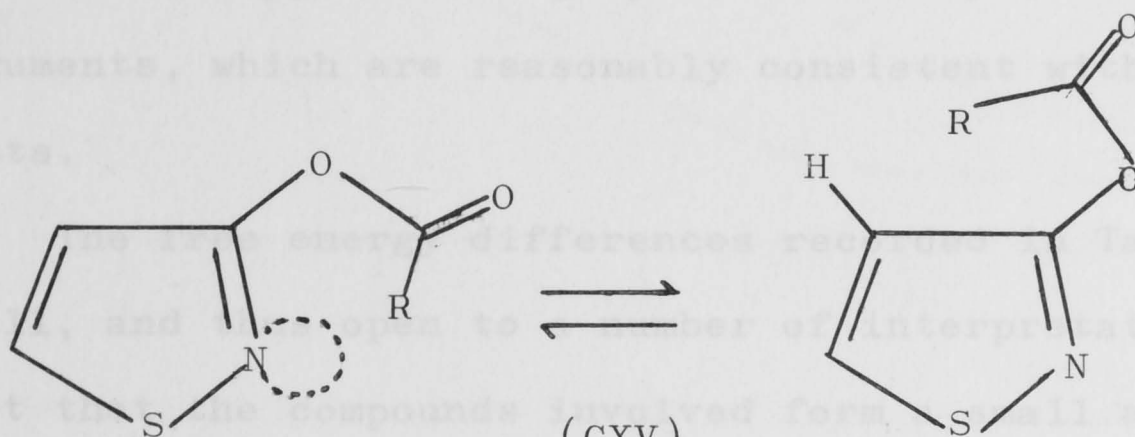
(CXV)
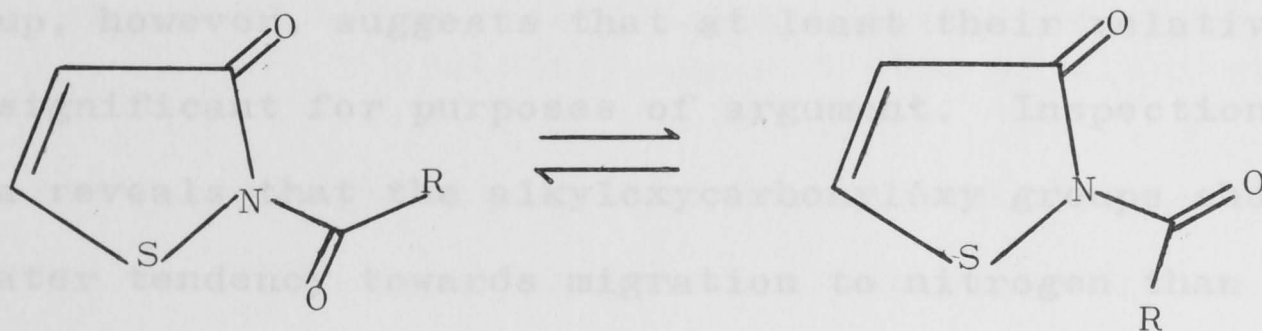
(CXVI)

acyl group. The stability of the s-trans conformer (CXIV)

will be largely unaffected by increase in the size of the

alkyl group R, since only the carbonyl group is likely to

encounter ring atoms, whereas the reverse holds for the

s-cis conformer (CXV) and the N-acyl conformer (CXVI). The

effect should thus be to reduce the relative stability of

(CXVI) fairly rapidly as R increases in size, and at the

same time to reduce the contributions of (CXV) to the O-acyl

mixture of conformers. When R approaches CO in steric

requirement (i.e. about $R=C_2H_5$, bearing in mind the dipole

repulsion effect of oxygen) the contribution from (CXV)

would be expected to fall off fairly rapidly. Figure XI

presents an approximate graphical summary of these

arguments, which are reasonably consistent with the observed

facts.

The free energy differences recorded in Table VII are

small, and thus open to a number of interpretations. The

fact that the compounds involved form a small and distinct

group, however, suggests that at least their relative order

is significant for purposes of argument. Inspection of the

data reveals that the alkyloxycarbonyloxy groups show a

greater tendency towards migration to nitrogen than would

appear to be warranted by their spatial requirements (i.e.

compared with propionyl and butyryl). In these cases

electron donation from oxygen would have the effect of

decreasing the electron-withdrawing power of the acyl

carbonyl, thus decreasing the necessity for N-CO overlap.

Lack of coplanarity in (CXVI) would thus be less serious.

In addition to this, it would be no longer possible to

avoid lone-pair interactions in the esters (CXIV) and (CXV),
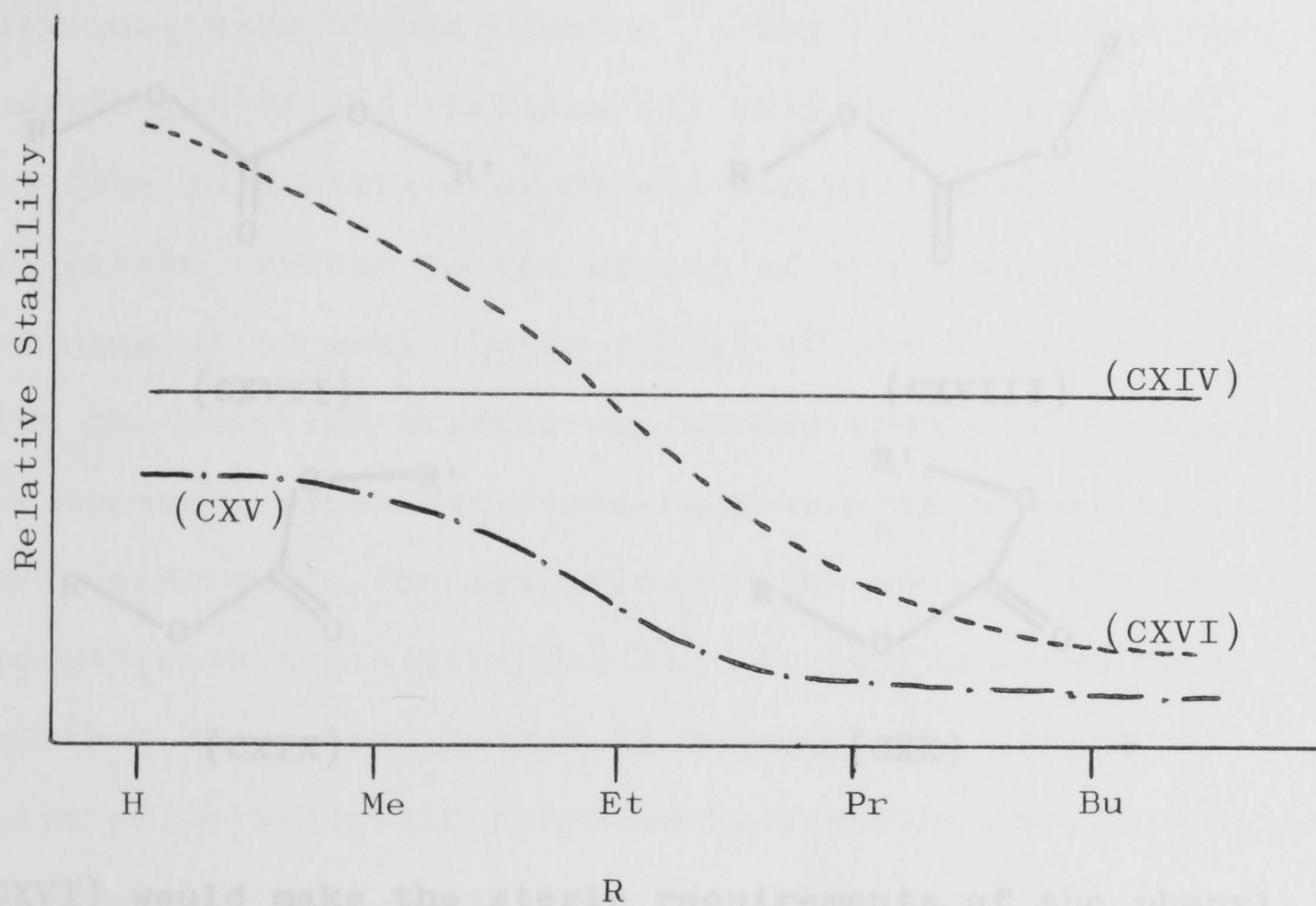
Figure XI — Graphical representation of relative
stability against size of alkyl group R

so that the energy distinction between the four conformers

(CXVII) to (CXX) is no longer so clear-cut. The benzoyl

derivatives, regardless of the nature of the substituent,

show a clear preference for O-substitution, and in this

respect may be compared with the trimethylacetyl

derivative. Models indicated that N-CO interaction is not

possible without a certain amount of overlapping between

the ortho hydrogens of the phenyl ring with either the

sulphur atom or the carbonyl group in the isothiazole ring.

The desirability of maintaining CO-phenyl interaction in
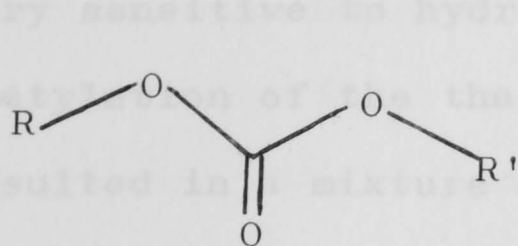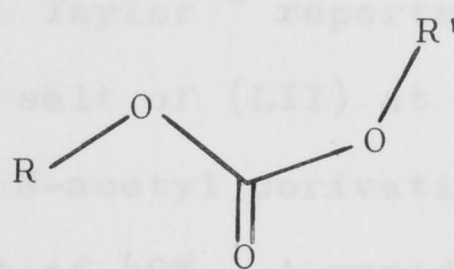
(CXVII)   (CXVIII)
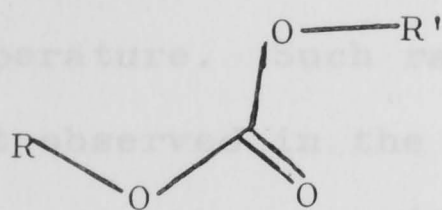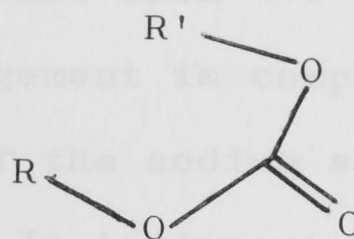
(CXIX)   (CXX)

(CXVI) would make the steric requirements of the phenyl
ring similar to that of the trimethylacetyl group. Thus the
stability of the s-trans ester conformer (CXIV) would again
be the deciding factor in the equilibrium.

(D) ACYLATION OF 2-(IH)-PYRIDONE

Ascertainment of the mechanism of acyl migration in
3-acyloxyisothiazoles has led to the hypothesis that a
similar trans-acylation process might be responsible for the
N→O acyl migration in N-acyl-2-(IH)-pyridones reported by
Curtin[58] and Taylor.[61] This is not unexpected since the
acyl derivatives of 2-(IH)-pyridone (LII) were found to be

very sensitive to hydrolysis.[59] Taylor[61] reported that

acetylation of the thallium (I) salt of (LII) at -40°

resulted in a mixture of O- and N-acetyl derivatives, with

the latter present to the extent of 40%. A rapid re-

arrangement of most (but not all) of the N-isomer occurred

when the reaction mixture was warmed from -40° to room

temperature. Such rapid rearrangement is comparable to

that observed in the acylation of the sodium salt of 3-

hydroxyisothiazole (Chapter I). It is important to point

out that the common method of reacting the alkali metal

salts of heterocyclic compounds possessing ambident sites

is unsatisfactory when there is a likelihood of acyl

migration. This is because the method involves a hetero-

geneous reaction, and invariably results in the presence

of some unchanged acid chlorides which subsequently enhance

rearrangement.

In order to substantiate the above statements, acety-

lation of 2-(IH)-pyridone was attempted using the conditions

of method (a) employed for the acylation of 3-hydroxy-

isothiazoles. Upon work-up, the crude product was

immediately analysed by N.M.R. at 35° which revealed a

mixture of 46% O- and 54% N-acetyl derivatives. In contrast

to Taylor's observations, a relatively slow N→O acetyl

rearrangement occurred in D^6DMSO, and an equilibrium

mixture containing 92% O- and 8% N-acetyl derivatives was obtained only after more than 24 hours. In another experiment, 2-(IH)-pyridone (LII) was added to the crude mixture in D^6DMSO, and the rate of rearrangement was seen to increase slightly (about 5—10%) over the control run with no (LII) added. This suggested that an intermolecular transacylation process was operative. The experiment would have been more convincing if pure N-acetyl-2-(IH)-pyridone were used as the starting material, but so far it has not been possible to separate the crude mixture into pure components, due to rapid hydrolysis of the acyl derivatives. For the same reason, it was impossible to exclude the possibility of hydrolysis of the crude acetylated mixture, with the result that (LII) was always present in the control run. Nevertheless, the result of the catalysis experiment, and the much slower migration rate observed for the crude mixture (due to absence of acid chloride or hydrogen chloride) as compared to that observed by Taylor, offered good circumstantial evidence for the hypothesis mentioned earlier.

CHAPTER III

ATTEMPTED SYNTHESIS WITH N-ACYL-3-ISOTHIAZOLONES

The possibility of forming heterocyclic systems by utilising the facile S-N bond cleavage in 3-isothiazolones has already been outlined in the Introduction (Schemes III → V). This chapter deals with results obtained from preliminary investigations based on the proposed Scheme IV. Acylation studies on 3-hydroxyisothiazole had shown that it was possible to prepare in reasonable yields (from method (c) about 50-60%) the N-acyl-3-isothiazolones required for this investigation.

Fava and Ilceto[89] showed that the preferred transition-state geometry for nucleophilic substitution at sulphenyl sulphur was the same as that at sp^3 carbon, namely, a trigonal bipyramid with the entering and leaving groups occupying the apical positions. Since in SN2 displacements at sp^3 carbon bond-making and bond-breaking are synchronous, the same could well be true for nucleophilic displacements at sulphenyl sulphur. Kice and Anderson[90] demonstrated that, at least in the reaction of aryl Bunte salts with cyanide ions (equation (2)), the extent of bond-making was the same as that of bond-breaking in the transition state, and concluded that the d-orbitals of sulphur were not involved. A similar conclusion was reached by Brown and Hogg[91]

$$\text{CN}^- + \text{[aryl ring, X substituted]}-\text{S}-\text{SO}_3^- \xrightarrow{(2)} \text{[aryl ring, X substituted]}-\text{S}-\text{CN} + \text{SO}_3^{2-}$$
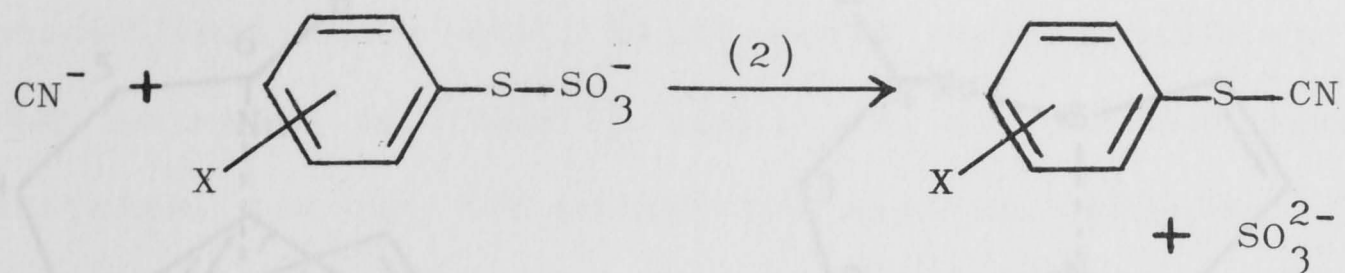
in their investigation on nucleophilic substitution involving aryl sulphenyl compounds (equation (3)).

$$\text{OH}^- + \text{[aryl ring, X substituted]}-\text{SOEt} \xrightarrow{(3)} \text{[aryl ring, X substituted]}-\text{SOH} + \text{EtO}^-$$
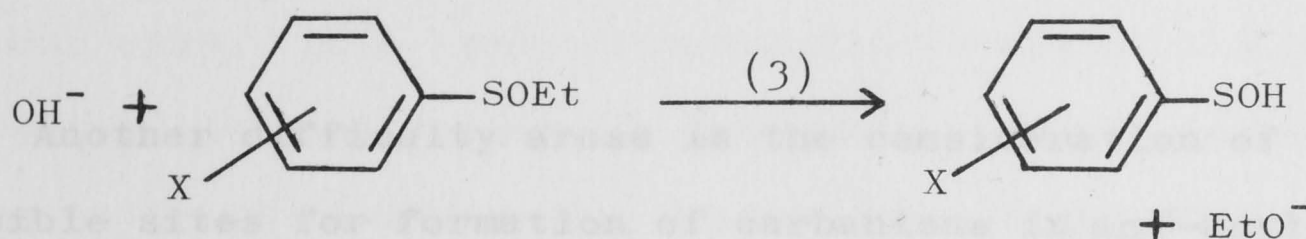
In order to effect an internal nucleophilic attack (using a carbanion as the nucleophile) on the sulphur of N-acyl-3-isothiazolones, a trigonal bipyramidal transition state would require the nucleophilic site be developed on the sixth carbon of the acyl chain as shown in (CXXI). On the other hand edge-attack would require the nucleophilic site be formed on the fourth carbon in the acyl chain as illustrated in (CXXII). From the thermodynamic point of view these two syntheses are expected to be achieved only with difficulty, since they involve formation of larger

heterocyclic rings (11- and 9-membered respectively.)

R
6
5
Nu
4
3
S
2
N
1
O   O

(CXXI)

R
4
Nu —— S
3
5
2
N
1
O   O
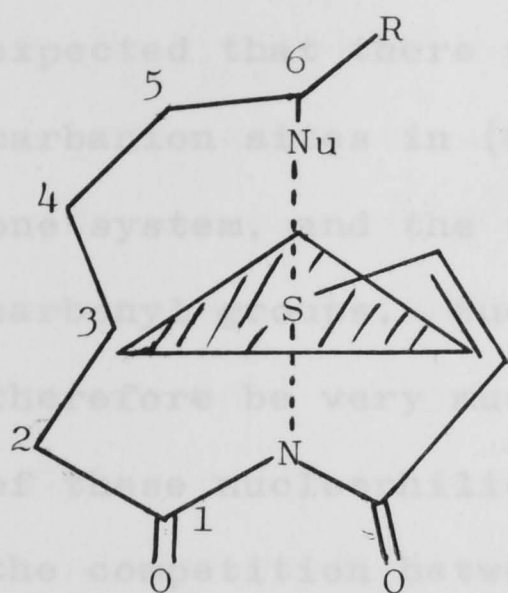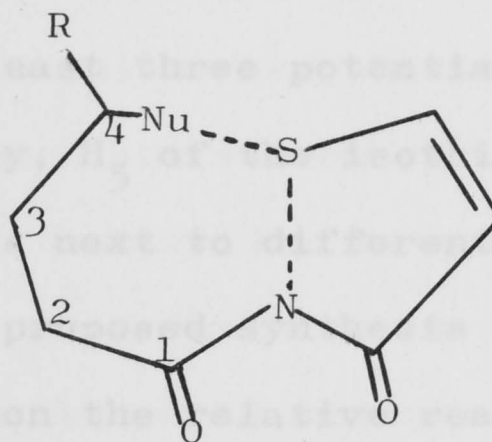
(CXXII)

Nu = Nucleophilic site

Another difficulty arose in the consideration of possible sites for formation of carbanions in an N-acyl-3-isothiazolone such as (CXXIII). Woodward[92] and Olofson[93] have found that the proton in position-5 of isothiazoles

O

N —— COCH$_2$(CH$_2$)$_n$CH$_2$COOR

S
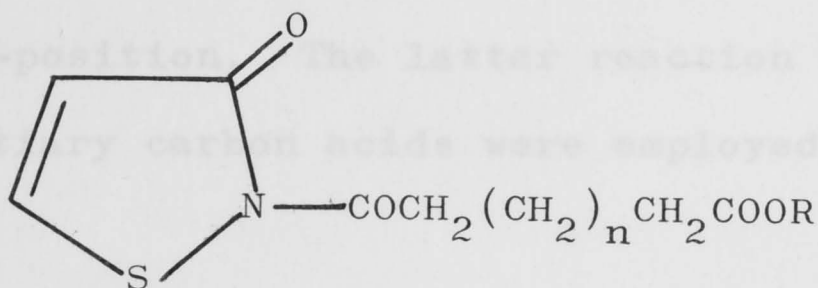
(CXXIII)

underwent deuterium exchange in the presence of trideutero sodium methoxide. The rate of deprotonation increased when there was an electron-withdrawing group present in the ring,

but the opposite effect was observed in the presence of an electron-donating substituent. It was therefore to be expected that there would be at least three potential carbanion sites in (CXXIII), namely, H_5 of the isothiazol-3-one system, and the two methylenes next to different carbonyl groups. Success of the proposed synthesis would therefore be very much dependent on the relative reactivity of these nucleophilic sites. Another important factor is the competition between the amide nitrogen atom and the entering nucleophile for overlap with the electron-deficient sulphur atom. In a study of carbanion attack of the S-N bond in N-ethyl-3-isothiazolone (a synthetic approach based on the steps outlined in Scheme V), Gosney[94] has found that with primary and secondary carbon acids, the expected attack on sulphur (equation 4)) occurred in preference to a competing reaction (dimer formation) which was initiated by formation of an anion at the 5-position. The latter reaction occurred exclusively when tertiary carbon acids were employed in the
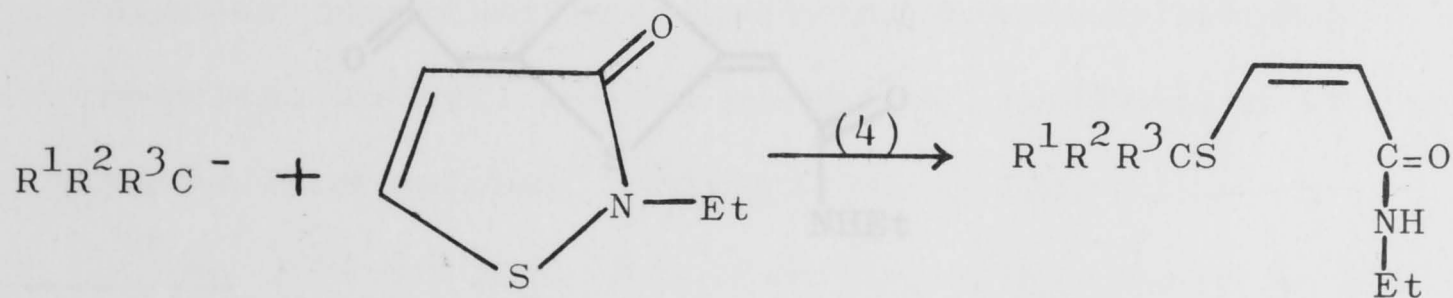
nucleophilic attack. In this case the tertiary carbon acid

was recovered unchanged, and a highly insoluble dimer

$(C_{10}H_{12}N_2O_2S_2)$ of N-ethyl-3-isothiazolone was obtained.

The ready reactivity of primary and secondary carbon

acids was explained[94] in terms of the ability to stabilize

the products by carbanion formation in the basic medium.

The presence of hydrogen on the carbon atom adjacent to

sulphur rendered carbanion formation possible, and the

resultant overlap with the adjacent sulphur atom more or less

effectively prevents S-N overlap which led to reversion to

starting materials. The product from attack by a tertiary

carbon acid, being unable to stabilize itself in a similar

fashion, was usually ejected by the amide nitrogen, i.e.

no effective reaction was observed.

Gosney[94] proposed that the dimer had the dithietane

structure (CXXIV), and this was well-supported by the

following physical evidence:
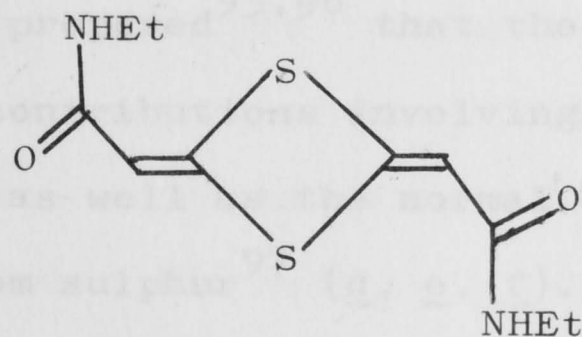
(CXXIV)

(i) The I.R. spectrum (nujol mull) showed bands at 1630 α,β-unsaturated amide) and 3244 cm^{-1} (NH).

(ii) N.M.R. signals[*] at τ: 1.90 (broad triplet, 2 x NH), 3.80 (singlet, 2 x CH), 6.86 (multiplet, 2 x $2CH_2$), and 8.96 (triplet, 2 x CH_3). The values of the chemical shifts were close to those observed in a series of alkylmercaptoacrylamides.[95]

(iii) A molecular ion at m/e 258 (100%) was present in the mass spectrum. Other fragmentations shown on page 107 were consistent with the proposed structure. The dithietane derived from 4D-N-ethyl-3-isothiazolone had a molecular ion at m/e 260.

(iv) The U.V. spectrum showed λmax at 304 mμ (ε 31000), 318 mμ (ε 25000) and an inflection at about 290 mμ. The substantial bathochromic shift and intensity increase compared to the alkylmercaptoacrylamides[95] was to be expected for the dithietane structure. It has been proposed[95,96] that these effects are due to dipolar contributions involving transannular S-S overlap, as well as the normal delocalisation of lone pairs from sulphur[97] (d, e, f).

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[*] Because of the low solubility of the dithietane an average spectrum (using P.D.P.8S-CAT, 250 scans) was determined in DMSO-d_6.

m/e 258 (100%)

-EtNH

de-dimerisation
&
H-transfer

m/e 214 (89%)

m/e 130 (77%)

-CO

※ = Metastable ion

m/e 186 (8%)
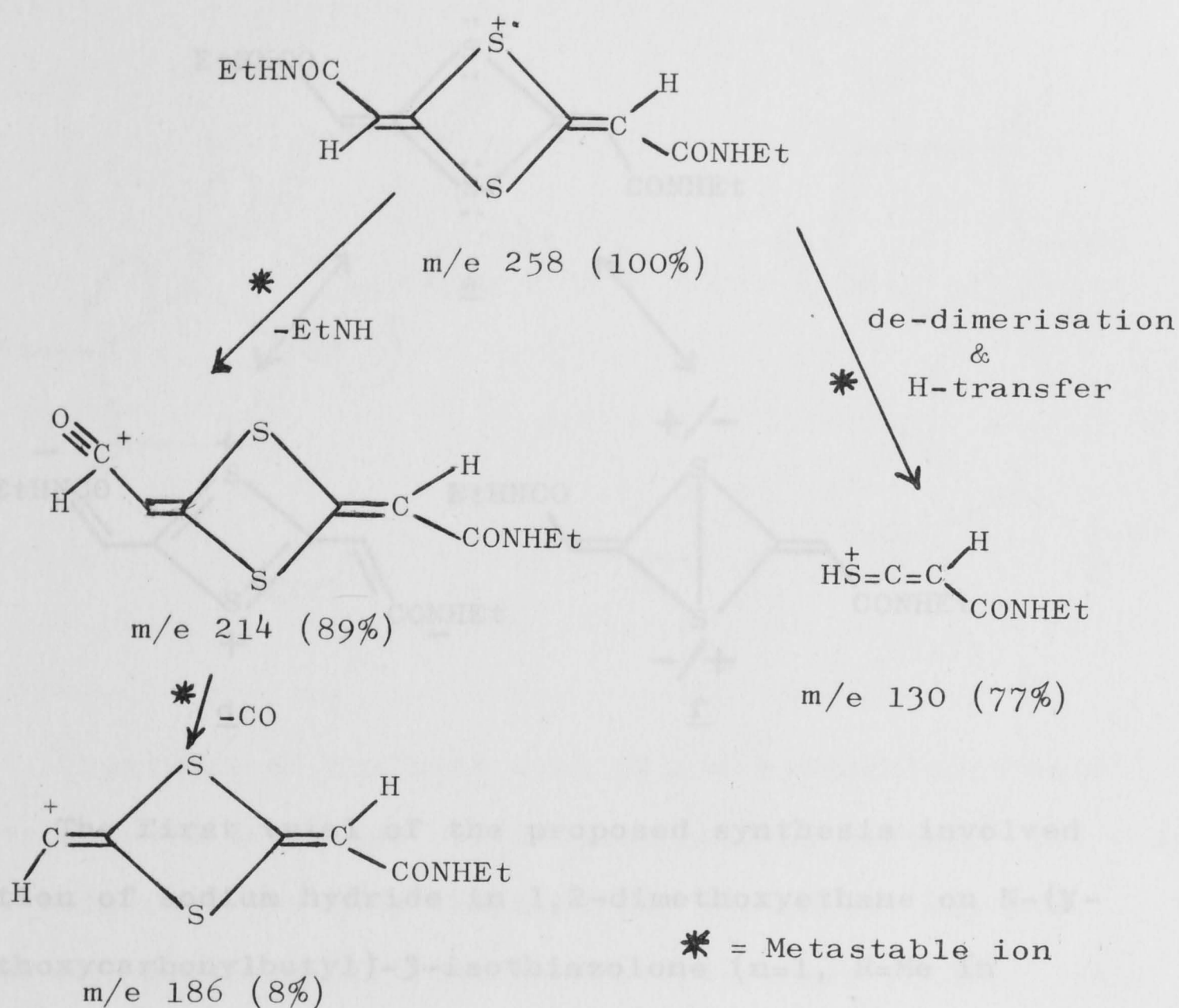
5-Phenyl-N-ethyl-3-isothiazolone did not give a
dithietane when treated under the same condition, in support
of the hypothesis that the 5-anion was responsible for the
dimerisation. Formation of the dithietane might involve a
concerted process as depicted in (CXXV), or it might occur
via the thioketene intermediate (CXXVI). Dickoré and
Wegler[98] have reported the formation of dithietanes by
dimerisation of thioketenes.
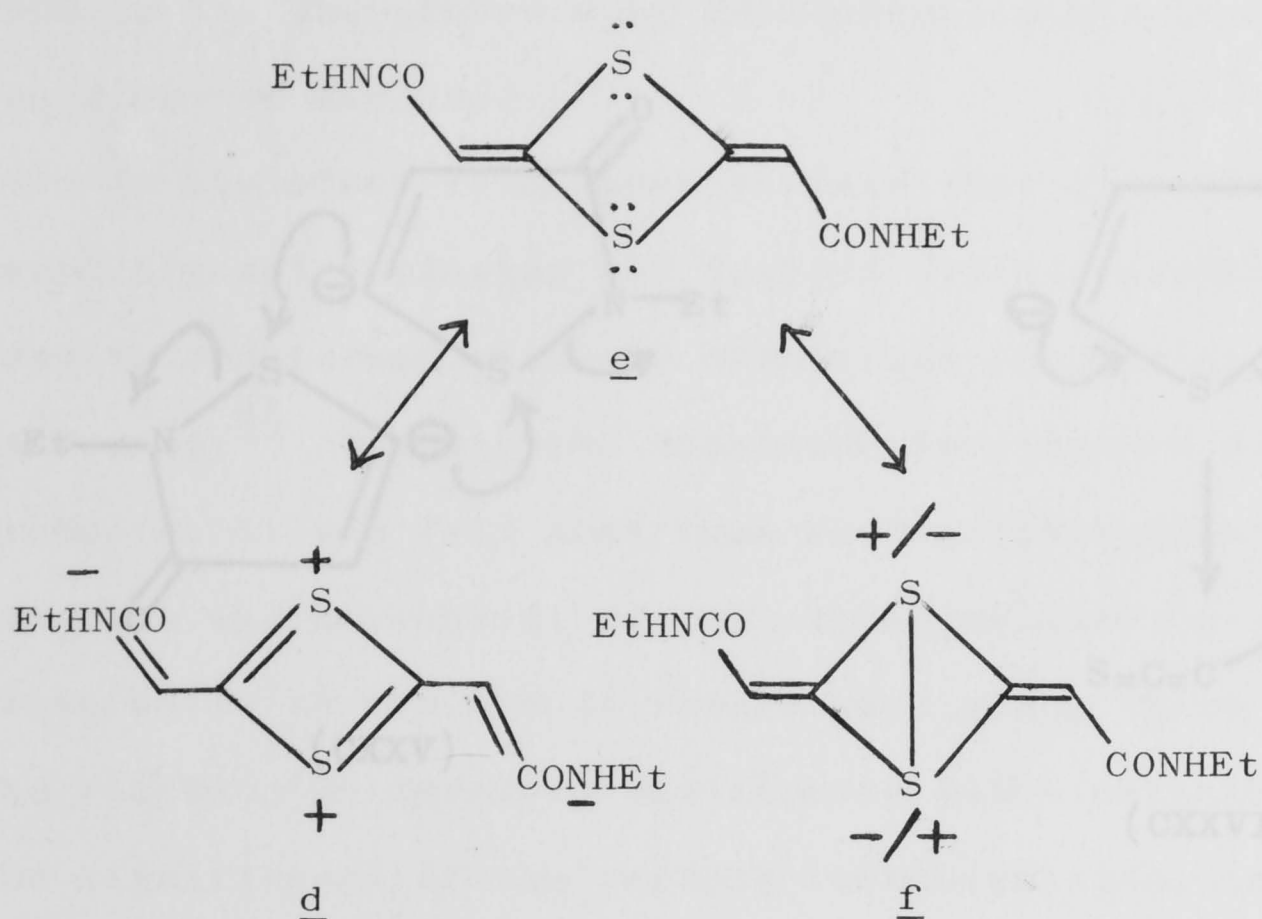
The first trial of the proposed synthesis involved action of sodium hydride in 1,2-dimethoxyethane on N-(γ-methoxycarbonylbutyl)-3-isothiazolone (n=1, R=Me in (CXXIII)). This yielded a red-brown precipitate. The ready solubility of this product in water suggested it was a sodium salt, and this was supported by results of elemental analysis which showed 8.6% sodium (the mono-sodium salt of the parent acyl compound required 9.2% for sodium). Other results of the analysis were similarly not consistent with values expected for the monosodium salt of the original acyl compound, e.g., the observed OCH_3 composition was 7.7% compared to a calculated value of 12.4%.

(CXXV)

(CXXVI)
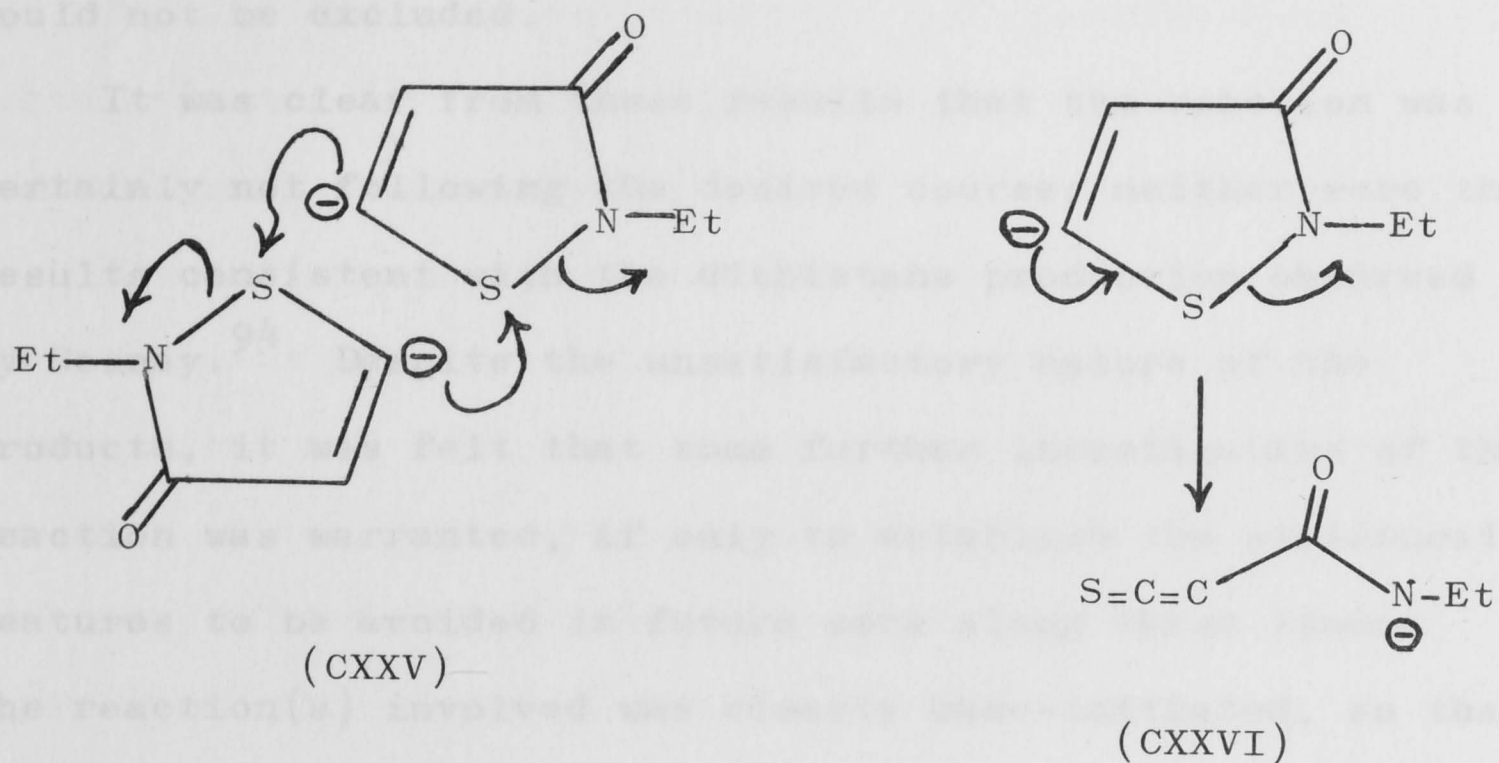
Treatment of the salt with dilute hydrochloric acid

gave a brownish-orange solid containing no sodium. The very

low volatility of this compound did not permit any mass

spectral measurement. Unlike the dithietane (CXXIV), this

compound was soluble in dilute sodium hydroxide to give a

very viscous dark-coloured solution, the N.M.R. of which did

not reveal any peak from τ 0-5. This indicated that it did

not have the dithietane structure (expected singlet at τ 3.8)

or that expected from the attack of carbanion on sulphur

(expected pair of olefinic doublets). The U.V. spectrum

showed only a very broad peak centred at about 300 mμ, and

the I.R. spectrum was poorly resolved (due to inability to

purify this compound), showing a broad carbonyl band at about

1700 cm^{-1}. The presence of NH-absorption was doubtful, but could not be excluded.

It was clear from these results that the reaction was certainly not following the desired course; neither were the results consistent with the dithietane production observed by Gosney.[94] Despite the unsatisfactory nature of the products, it was felt that some further investigation of the reaction was warranted, if only to establish the structural features to be avoided in future work along these lines. The reaction(s) involved was clearly base-initiated, so that the significance of the various carbanion sites in the starting acyl compound was an obvious point for examination. The effect of varying the position of the carbanion site at the terminus of the acyl chain was first examined (e.g. reaction with N-(β-methoxycarbonylpropyl)-3-isothiazolone (n=0, R=Me in (CXXIII)), and it was found that the same type of polymeric material resulted. Complete removal of the terminal carbanion site (e.g. reactions with N-acetyl- and N-ethoxycarbonyl-3-isothiazolones) was similarly without effect on the formation of the red-brown polymer. The final case examined was on the N-formyl compound, and this also gave a similar red-brown polymer, thus establishing that the reaction was not associated with the carbanion site(s) in the acyl residue. The significance of the 5-anion in the reaction

pathway was therefore obvious. This was substantiated by the recovery of unchanged 5-phenyl- and 5-methyl-N-acetyl-3-isothiazolones (over 80%) after treatment with sodium hydride under the same conditions.

The difference in products obtained from the N-alkyl (N-methyl- and N-benzyl-3-isothiazolones also gave the dithietanes) and N-acyl derivatives seemed to be due to presence of the acyl-carbonyl group in the latter compounds. Treatment of 5-D-N-ethyl-3-isothiazolone with dilute NaOH established that rapid scrambling at the 5-position (detected by N.M.R.) occurred together with dithietane formation. This indicated that the rate of deprotonation at the 5-position was faster than that of dithietane formation; in other words the 5-anion actually existed as an intermediate. This is in contrast to the finding of Woodward and Olofson[99] on the action of base on isoxazolium salts (CXXVII) in which the authors established that the ylide (CXXVIII) was only part of a transition state in a concerted elimination of the proton at C-3 and the ring scission to form the ketenimine (CXXIX). The result seemed to suggest that the mechanism of dithietane formation was as depicted in (CXXV) other than proceeding via a thioketene intermediate. The presence of an electron-withdrawing acyl group would increase the rate of deprotonation in the 5-position.[93] For the same

(CXXVII)

(CXXVIII)

(CXXIX)
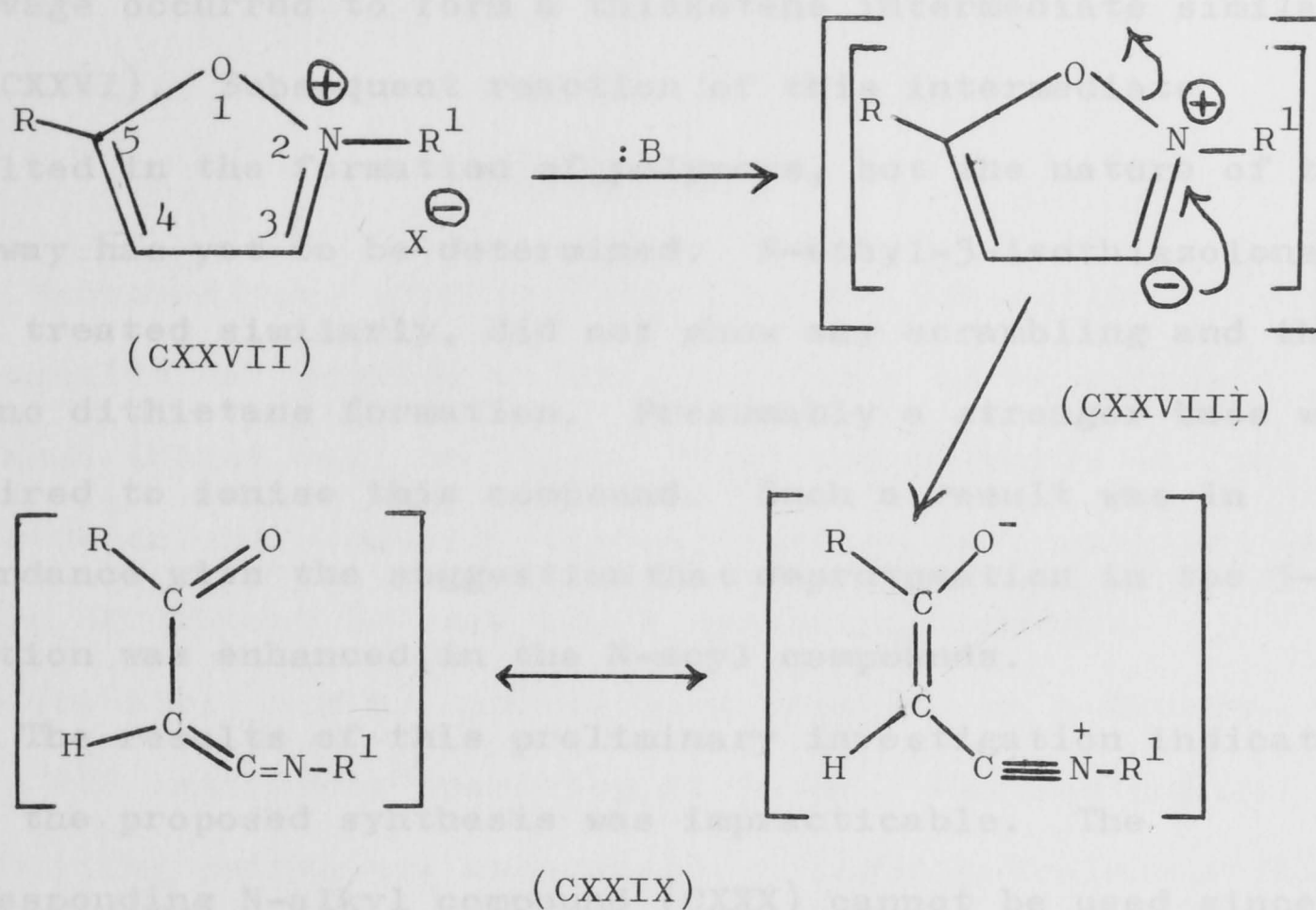
reason S-N bond cleavage was expected to be enhanced. When

a solution of N-ethoxycarbonyl-3-isothiazolone in D^6DMSO was

treated with triethylamine, (the use of an aqueous base

resulted in rapid hydrolysis of the acyl compound) the same

polymer formation occurred but no scrambling at the 5-position

could be detected by N.M.R. Instead the intensity of the

pair of olefinic doublets decreased quickly and the signals

completely vanished in less than an hour. This result was

comparable to that observed by Woodward and Olofson[99] with

isoxazolium salts, and therefore led to the conclusion that

a concerted elimination of the proton at C-5 and S-N bond

cleavage occurred to form a thioketene intermediate similar to (CXXVI). Subsequent reaction of this intermediate resulted in the formation of polymers, but the nature of the pathway has yet to be determined. N-ethyl-3-isothiazolone, when treated similarly, did not show any scrambling and there was no dithietane formation. Presumably a stronger base was required to ionise this compound. Such a result was in accordance with the suggestion that deprotonation in the 5-position was enhanced in the N-acyl compounds.

The results of this preliminary investigation indicated that the proposed synthesis was impracticable. The corresponding N-alkyl compound (CXXX) cannot be used since dithietane formation will interfere. Future work along this line will therefore have to be conducted on the 5-substituted N-acyl or N-alkyl compounds.
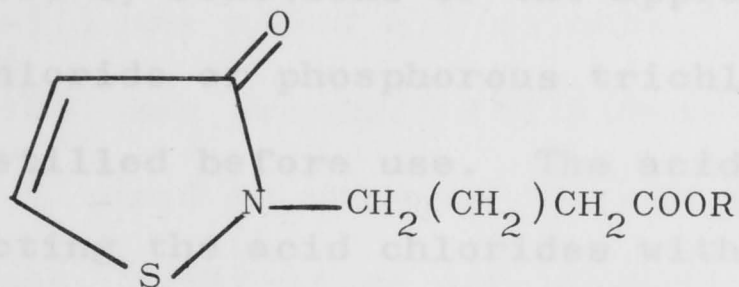
(CXXX)

CHAPTER IV

EXPERIMENTAL

Microanalyses were performed by the Australian
Microanalytical Service at the University of Melbourne.
Infrared (Nujol mull or liquid film) and ultraviolet (in
95% EtOH unless otherwise stated) spectra were measured on
Unicam SP200G and Beckman DK-2A spectrophotometers
respectively; N.M.R. spectra were recorded on a Perkin-
Elmer R10 instrument operating at 60 Mc. Melting points
and boiling points are uncorrected. Light petroleum refers
to a hydrocarbon fraction b.p. 60-80°. Microanalytical
results for the 3-acyloxyisothiazoles and the N-acyl-3-
isothiazolones are summarised in Table VIII. Mass spectra
were recorded on an A.E.I. MS9 instrument.

Most of the acid chlorides used in the acylation
reactions were prepared by reactions of the appropriate
acids with thionyl chloride or phosphorous trichloride, and
the products were distilled before use. The acid anhydrides
were prepared by reacting the acid chlorides with the
corresponding acids; formic-acetic anhydride was obtained by
reaction of formic acid with acetic anhydride. All the
compounds gave the correct boiling points as quoted in the
literature. Other compounds prepared are as follows:-

115

Name of Compound	Reference Number
N,N-diethylcinnamamide	100
β-methoxycarbonyl-propionyl chloride	101
γ-methoxycarbonyl-butyryl chloride	102
β-mercaptopropionitrile	103
(for preparation of 3-chloro- isothiazole)	
3-chloroisothiazole	104

(1) Preparation of 3-Acyloxyisothiazoles (method (a))

3-Hydroxyisothiazole (1.01g, 0.01 mole) in benzene (50 ml.) was treated with triethylamine (1.01g, 0.01 mole) and cooled to incipient crystallization of the solvent. An ice-cold solution of the appropriate acid chloride (0.01 mole) in benzene (25ml.) was added all at once. Triethylamine hydrochloride (over 98%) was precipitated almost immediately, and the solution was allowed to warm up to room temperature with occasional shaking. Filtration and concentration of the filtrate on a rotary film evaporator at low temperature afforded the 3-acyloxyisothiazole as a light yellow oil, containing some (0-10%) of the corresponding N-acyl-3-

isothiazolone. (In the reaction with 4-nitrobenzoyl chloride
and with 3,5-dinitrobenzoyl chloride only the solid 3-
acyloxyisothiazoles were obtained.) The mixture was at once
chromatographed on a silica gel column (30 x $1\frac{1}{2}$ cm) in a
mixture of ether (20%) and carbon tetrachloride (80%),
which rapidly eluted the 3-acyloxyisothiazole, obtained as a
colourless oil on distillation under reduced pressure. It
was stored immediately in a sealed ampoule to prevent
contact with moisture. The solid 3-acyloxyisothiazoles were
purified by sublimation under vacuum at temperatures near
their melting points. Further elution of the column with
chloroform resulted in the recovery of any N-acyl-3-
isothiazolone formed during the acylation, but this
invariably contained some 3-hydroxyisothiazole due to
hydrolysis by the ethanol present in chloroform.

(2) Preparation of 3-Sulphonyloxyisothiazoles

This was carried out as described in (1). Reaction with
methanesulphonyl chloride yielded 3-methanesulphonyloxy-
isothiazole (> 95%) as an oil which crystallized on standing.
After being washed with cold carbon tetrachloride (15 ml),
the product was purified by sublimation (60°/0.1 mm) to give
colourless prisms, m.p. 43-4°.

Infrared : no carbonyl absorption

Ultraviolet : 245 mμ (ε 7520)

N.M.R. (CDCl$_3$) : τ 1.34 (doublet, J=4.8 cps) (1H)

3.04 (doublet, J=4.8 cps) (1H)

6.56 (singlet) (3H)

Analysis : C$_4$H$_5$NO$_3$S$_2$ requires C : 26.8%, H : 2.8%, N : 7.8%

Found : C : 26.8%, H : 2.8%, N : 7.7%

For the reaction with 4-toluenesulphonyl chloride a slight excess of 3-hydroxyisothiazole was employed, and the reaction was carried out in chloroform for 30 hr at 30-35°. The resultant 3-(4-toluenesulphonyloxy)isothiazole (90%), after purification by chromatography on alumina in ether (3): carbon tetrachloride (2): chloroform (1) mixture, was distilled under reduced pressure, b.p. 65-8°/0.01 mm.

Infrared : no carbonyl absorption

Ultraviolet : 231 mμ (ε 13300)

N.M.R. (CCL$_4$) : τ 1.42 (doublet, J=4.8 cps) (1H)

3.11 (doublet, J=4.8 cps) (1H)

2.23 (2H), 2.70 (2H), 7.60 (3H)

Analysis : C$_{10}$H$_9$NO$_3$S$_2$ requires C : 47.1%, H : 3.6%, N : 5.5%

Found : C : 47.4%, H : 3.7%, N : 5.7%

(3) Preparation of N-Acyl-3-isothiazolones

(i) By rearrangement : The reaction mixture as obtained in (1) was allowed to stand in air for 1-2 days. Light petroleum (50 ml) was added and the solid N-acyl-3-isothiazolone was isolated by filtration.

This was washed with cold carbon tetrachloride (20 ml) and the product was purified by sublimation (80°/0.1 mm). This method was effective for R=CH_3, OCH_3, OC_2H_5 and CH_2Cl, but was too slow in other cases.

(ii)   By reaction with acid anhydrides (method (b)):
3-Hydroxyisothiazole (1.0g) was dissolved in the appropriate anhydride (2ml) and warmed at $40-50^{\circ}$ for 0.5-2 hr with accasional swirling. Light petroleum (200 ml) was added and the solution cooled. The N-acyl-3-isothiazolone crystallized in up to 85% yield. The compound was washed with cold carbon tetrachloride (20ml) and was purified as above. This method was effective in the cases R=CH_3, C_2H_5, C_3H_7, i-C_3H_7; in the case R=$C(CH_3)_3$, only the O-acyl derivative resulted.

Reaction with acetic anhydride in the presence of an equimolar amount (w.r.t. 3-hydroxyisothiazole) of triethylamine was performed at room temperature. This yielded only 3-acetoxyisothiazole. A similar experiment with pentadeutero-pyridine as catalyst 68% O-acetyl and 32% N-acetyl compounds.

N-Formyl-3-isothiazolone (LXXI) was prepared in quantitative yield by allowing 3-hydroxyisothiazole to stand at room temperature (1 hr) in excess formic-acetic

anhydride. Evaporation of the excess anhydride under reduced pressure afforded (LXXI), which was purified in the usual way.

In another experiment equimolar amounts of triethylamine and 3-hydroxyisothiazole were dissolved in excess formic-acetic anhydride. Reaction occurred instantaneously; the results have been described in Chapter I (E) (page 58).

(iii) <u>By reaction with acid chlorides (method (c))</u>: 3-Hydroxyisothiazole (1.0 g, 0.01 mole) in benzene (50 ml) was refluxed (2 hrs) with the appropriate acid chloride (0.01 mole). The initially formed precipitate of 3-hydroxyisothiazolium chloride decomposed gradually, and an intermittent stream of nitrogen was employed to facilitate removal of the HCl. After evaporation of the solvent under vacuum, light petroleum (400 ml) or carbon tetrachloride (80 ml) was added to the crude oil. On cooling the N-acyl-3-isothiazolone crystallized. The method of purification was the same as described before.

(iv) <u>By reaction with ketene</u>: Ketene, generated by pyrolysis of acetone, was introduced into a cold solution of 3-hydroxyisothiazole in carbon tetrachloride. After $\frac{1}{2}$ hr the solution was evaporated to give a quantitative yield of N-acetyl-3-isothiazolone.

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(4)   Sodium Salt of 3-Hydroxyisothiazole

An ethanolic solution of 3-hydroxyisothiazole (0.01 mole in 20 ml) was added dropwise with stirring to a solution of sodium ethoxide in ethanol (0.01 g atom Na in 30 ml). After 5 minutes the solvent was removed under vacuum to give the sodium salt in quantitative yield, m.p. 250-51° (decomp.). It was dried at 110° for 1 hr and was used without further purification.

3-Hydroxyisothiazole could be recovered by dissolution of the salt in excess dilute HCl followed by continuous extraction with ether (over 95% recovery).

(5)   Reaction of Sodium Salt of 3-Hydroxyisothiazole with Acid Chlorides

The sodium salt (0.62 g, 0.005 mole) was suspended in benzene (25 ml), and an equivalent amount of the appropriate acid chloride was added. The mixture was refluxed 2-3 hr. Filtration and evaporation of the filtrate yielded, in most cases, a mixture of O- and N-acyl derivatives, but rapid rearrangement generally occurred where aliphatic acid chlorides were used. In such cases only the N-acyl-3-isothiazolone could be isolated.

(6)   Reaction with Isopropenyl Acetate

(i)   3-Hydroxyisothiazole (0.5 g) was dissolved in the minimum amount of isopropenyl acetate (ca 3 ml).

Concentrated sulphuric acid (4 drops) was added. The
reaction flask was stoppered and the mixture was
warmed at 50°, whereby a vigorous reaction occurred.
After ½ hr the brown tarry material left in the flask
was extracted with boiling benzene (60 ml). Filtration
and evaporation of the benzene extract afforded a
mixture of 3-acetoxyisothiazole (LIII) (40%) and N-
acetyl-3-isothiazolone (LIV) (60%); total yield was
about 40%.

(ii) Equimolar amounts of 3-hydroxyisothiazole (XXXII)
and isopropenyl acetate were dissolved in benzene
(50 ml). Toluene-p-sulphonic acid (2% by weight of
(XXXII)) was added, and the solution was refluxed 6 hr.
Evaporation of the solvent under reduced pressure
yielded a mixture (total yield >90%) containing (LIII)
(24%) and (LIV) (76%).

(7) 4-Bromo-3-hydroxyisothiazole

Excess bromine (3 ml) was added to a stirred solution
of (XXXII) (1 g) in carbon tetrachloride (60 ml). This
resulted in an immediate formation of a fine precipitate.
Stirring was continued for 12 hrs, whereby more precipitate
was formed, and this settled at the bottom of the flask as a
solid layer. After decantation of the carbon tetrachloride,
water (100 ml) was added and the solid was ground in a

mortar. The resulting yellow solid was removed by filtration and was washed with more water. This on sublimation (110°/0.1 mm) gave light yellow crystals, m.p. indefinite, decomposing at about 150°.

Infrared : 1632 cm^{-1} (C=O)

2500, 2590, 2680, 2780 cm^{-1} (NH)

Ultraviolet : 266 mμ (ε 7540), 288 mμ (shoulder, ε 1920)

N.M.R. (DMSO) 1.08 ᴚ(1H), -0.93 ᴚ(broad singlet, (1H))

Analysis : C$_3$H$_2$NOSBr requires C : 20.01%, H : 1.12%, N : 7.78%

Found : C : 20.29%, H : 1.23%, N : 7.9%

(8) 4-Bromo-N-acetyl-3-isothiazolone

4-Bromo-3-hydroxyisothiazole was reacted with acetic anhydride as described in (3) (ii). The N-acetyl compound was obtained in 90% yield, and was purified by sublimation (110°/0.3 mm) to give colourless crystals, m.p. 134-5°.

Infrared : 1680, 1700 cm^{-1} (C=O)

N.M.R. (CDCl$_3$) : ᴚ : 1.80 (singlet, 1H), 7.32 (singlet, 3H)

Analysis : C$_5$H$_4$NO$_2$SBr requires C : 27.04%, H : 1.82%, N : 6.31%

Found : C : 27.08%, H : 1.83%, N : 6.15%

(9) 5-Phenyl-N-acetyl-3-isothiazolone

5-Phenyl-N-acetyl-3-isothiazolone[9] was similarly treated with acetic anhydride to give yellow crystals of the N-acetyl compound (85% yield). It was purified by

sublimation (90°/0.05 mm), m.p. 128-30° (decomp.)

Infrared : 1666, 1684 cm^{-1} (C=O)

Ultraviolet : 281 mμ (ε 19600), 316 mμ (ε 7130)

N.M.R. (CDCl$_3$) : 𝜏 : 2.48 (singlet, 5H), 3.55 (singlet, 1H), 7.31 (singlet, 3H)

Analysis : C$_{11}$H$_9$NO$_2$S requires C : 60.27%, H : 4.14%, N : 6.39%

Found : C : 60.32%, H : 4.08%, N : 6.5%.

(10) 5-Methyl-N-acetyl-3-isothiazolone

This was similarly prepared from 5-methyl-3-hydroxy-isothiazole.* The N-acetyl compound was obtained as colourless crystals, m.p. 154-5°, identical with that reported by Goerdeler.[9]

Infrared : 1666, 1684 cm^{-1} (C=O)

Ultraviolet : 228 mμ (ε 6810), 301 mμ (ε 7210)

N.M.R. (CDCl$_3$) : 𝜏 : 3.99 (fine quartet, 1H), 7.34 (singlet, 3H), 7.59 (doublet, J=0.9 cps, 3H).

(11) Action of Cyanide Ion on 3-Trimethylacetoxyisothiazole

The substrate (0.001 mole) was dissolved in 95% MeOH (5 ml). Pure KCN (0.001 mole) was added all at once. The U.V. peak at 245 mμ decreased, and a new peak at 278 mμ (cis-3-thiocyanoacrylamide) developed. After 15 minutes the

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* This compound was supplied by Mr Gosney of this department.

solution was acidified, and the solvent was removed on a

rotary film evaporator. Extraction with chloroform yielded

3-hydroxyisothiazole (85%).

(12) Action of Cyanide Ion on N-Methoxycarbonyl-3-

isothiazolone

The substrate (0.0015 mole) in ethanol (20 ml) was

treated with pure KCN (0.0015 mole) and stirred. After 3 hr

the crystalline N-methoxycarbonyl-cis-3-thiocyanoacrylamide

(LXXV) was collected, washed and dried, m.p. indefinite,

decomposing at about 130°. The physical data for this

compound has been mentioned on page 49.

Analysis : $C_6H_6N_2O_3S$ requires C : 38.72%, H : 3.25%, N : 15.1%

Found : C : 38.85%, H : 3.30%, N : 14.9%

(13) 3-Anthranoyloxyisothiazole (LXXXVIII)

Isatoic anhydride (LXXIX) (2g, 0.012 mole) and 3-

hydroxyisothiazole (XXXII) (0.413g, 0.004 mole) were

dissolved in acetonitrile (80 ml). The solution was

refluxed for 35 hr. After evaporation of the solvent, the

residue was extracted with two 50 ml portions of chloroform.

Most of the unchanged (LXXIX) remained undissolved.

Filtration and evaporation of the chloroform extract

afforded a red-brown syrup. This was chromatographed on

alumina using a mixture of ether (3): carbon tetrachloride (2):

chloroform (1). The faint yellow band first eluted

contained (LXXXVIII) (yield 75%). It was purified by

sublimation (75°/0.15 mm) to give yellow crystals, m.p.

68-9°. (See pages 64-66 for physical data.)

   Analysis : $C_{10}H_8N_2O_2S$ requires C : 54.55%, H : 3.66%, N : 12.72%

                              Found : C : 54.71%, H : 3.75%, N : 12.72%

(14) Isothiazolo-[2,3-b]-4(3H)-quinazolinone (XCI)

   Isatoic anhydride (1.63g, 0.01 mole) and (XXXII) (0.3g,

0.03 mole) were mixed thoroughly in a mortar, and the

mixture was transferred almost quantitatively into a test

tube. The mixture was warmed at 95° for 5 hr, and the

resulting solid material was extracted with chloroform

(2 x 60 ml). The mixture from the extract was chromato-

graphed as described in (13), affording (LXXXVIII) in

11% yield. Further elution of the column with chloroform

moved a bright yellow band which contained (XCI) (yield 38%).

This was purified by sublimation (115°/0.05 mm) to give faint

yellow crystals, m.p. indefinite, decomposing at 155°. (See

pages 68-72 for physical data.)

   Analysis : $C_{10}H_6N_2OS$ requires C : 59.41%, H : 2.99%, N : 13.86%

                              Found : C : 59.51%, H : 3.11%, N : 13.5%

(15) Attempted synthesis of (XCI)

   3-Chloroisothiazole[104] (0.01 mole) and anthranilic acid

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(0.01 mole) were dissolved in A.R. acetone (50 ml). The solution was refluxed for 24 hr. No reaction occurred, and the starting materials could be recovered.

A similar experiment with dimethylformamide as solvent yielded tarry materials only. Extraction of the residue with hot ethanol gave a little dark brown gum, the N.M.R. of which (in D^6DMSO) showed only two very broad peaks in the aromatic region.

Other trials included heating an equimolar mixture of the two reagents in sealed tubes at temperatures ranging from 80° to 160°. Only tarry materials were formed in all cases. Similar results were obtained when ammonium anthranilate or methyl anthranilate was used instead of anthranilic acid.

(16) Attempted Hydrolysis of (XCI)

The substrate (XCI) (0.15g) was suspended in 10% KOH (5 ml), and the mixture was refluxed gently, whereby (XCI) gradually dissolved. The solution quickly changed from light orange to dark reddish-brown. After 1 hr the solution was acidified with 20% acetic acid, resulting in the precipitation of a brownish orange material (0.12g). This was collected and washed well with cold water. The N.M.R. spectrum in D^6DMSO showed only two very broad peaks in the aromatic region. Attempted recrystallization of this compound was unsuccessful.

(17) Pyracridone (LXXXVI)

The reaction conditions were the same as described by Späth,[80] but the procedure for purification was modified in order to remove some unidentified impurity which was invariably present if Späth's method (sublimation) was followed. This was effected by column chromatography of the crude product on alumina using ether (1) : carbon tetra-chloride (3) as eluant. (LXXXVI) was eluted as a faint yellow band while the impurity was strongly adsorbed on the column. It was then further purified by sublimation $(110^{o}/0.1 \text{ mm})$, giving sulphur-yellow crystals, m.p. $205-6^{o}$ (Späth reported $213-4^{o}$).

(18) 5-Deutero-3-hydroxyisothiazole

Propiolamide was dissolved in excess (15 mole) D_2O in the presence of a trace of anhydrous potassium carbonate. After 1 hr the solvent was removed under reduced pressure. Appropriate measures were taken to prevent back-diffusion of water vapour. After repeating the process twice, transformation of the product to the corresponding 3-hydroxyisothiazole was carried out as described previously.[32] Analysis by N.M.R. indicated that the deuterium content at the 5-position was 97-98%. This material was used for the preparation of labelled derivatives by the normal methods.

(19) <u>Mixed Migration Experiments</u>

5-D-3-Trideuteroacetoxyisothiazole and 3-acetoxy-

isothiazole (equimolar proportions) were mixed together with

a small amount of acetone, which was subsequently removed by

evaporation under reduced pressure. This resulted in the

presence of a catalytic amount of water in the mixture,

which was necessary to accelerate the rate of migration.

After 2-3 days in a sealed flask at room temperature, light

petroleum was added, and the N-acylated fraction was

isolated as in (3) (i). The total fraction was analysed by

mass spectrometry, indicating the presence of equal amounts

of N-acetyl-3-isothiazolone (m/e 143), 5-D-N-acetyl-3-

isothiazolone (m/e 144), N-trideuteroacetyl-3-isothiazolone

(m/e 146), and 5-D-N-trideuteroacetyl-3-isothiazolone (m/e

147). The mass spectrum of each of the pure compounds was

measured, and appropriate corrections were made for

incomplete deuteration and for isotopic peak contributions.

In a similar experiment, reaction was stopped after 12

hr, during which time only partial conversion into the N-

acyl-derivatives had occurred. The O-acylated compounds

were isolated. Similar analysis showed that even at this

stage equal amounts of the four possible O-acylated

derivatives (m/e 143, 144, 146, and 147) were present.

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Equimolar amounts of 3-trimethylacetoxyisothiazole and
5-D-3-hydroxyisothiazole were dissolved in dry acetonitrile
(0.5 ml). The resulting solution was transferred into an
N.M.R. tube which was sealed immediately. N.M.R.
measurements (see Chapter II) revealed scrambling of the
isothiazole moieties. Other similar experiments described
in Chapter II (B) were performed in the same way.

(20) Equilibrium Studies by N.M.R.

All solvents were purified and dried by the normal
recommended procedures. 3-Hydroxyisothiazole was purified
by sublimation, and the required 3-acyloxyisothiazoles were
used immediately after purification. N.M.R. tubes were
washed with chromic acid to remove basic surface effects,
and thoroughly washed with distilled water to remove any
remaining acid. The reactants were introduced to the dried
tubes, which were immediately sealed. The course of
rearrangement was followed by integration (300 cps sweep
width) of the ring doublets for each species, and expression
as % total. The concentration of 3-hydroxyisothiazole
remained constant throughout the experiments, and no
generation of other compounds was detected. Runs were
performed in duplicate or better, and control tubes (no
catalyst) were used in each case. The same results could be

obtained starting with the appropriate N-acyl-3-isothiazolone.

Table VII (page 92) summarises the results.

(21) <u>Acetylation of 2-(1H)-Pyridone (LII)</u>

The reaction of (LII) with acetyl chloride was performed

exactly as described in (1), and the results of the

rearrangement study on the crude product have already been

described in Chapter II (D).

(22) <u>Action of Sodium Hydride on N-(γ-Methoxycarbonyl-
    butyl)-3-isothiazolone</u>

To a stirred suspension of sodium hydride in 1,2-

dimethoxyethane (0.004 mole in 10 ml) was added a solution

of the N-acyl compound in the same solvent (0.004 mole in

15 ml). The reaction was conducted in a nitrogen atmosphere.

The mixture quickly turned from yellow to brownish orange

and after a while, a brown precipitate (sodium salt) began

to form. Stirring was continued for 12 hr and the mixture

became dark red-brown. The sodium salt (about 92% of

original weight) was removed by filtration and the free

compound was obtained by treatment of the salt with dilute

HCl. The properties of this compound have already been

described in Chapter III (page 109).

(23) <u>Action of Sodium Hydride on other N-Acyl-3-isothiazolones</u>

The same procedure was followed and in all cases red-brown polymers were obtained. The following N-acyl derivatives were examined: (i) formyl-, (ii) acetyl-, (iii) ethoxy-carbonyl-, (iv) (β-methoxycarbonylpropyl)-

(24) <u>Action of Sodium Hydride on 5-Substituted N-Acetyl-3-isothiazolones</u>

5-Methyl- and 5-phenyl-N-acetyl-3-isothiazolones were each subjected to the same treatment as described in (22), and in each case no polymer was formed. After quenching the reaction mixture with dilute HCl, the solution was extracted with chloroform. The organic layer was dried over magnesium sulphate. Evaporation of the chloroform yielded the unchanged acetyl compound (over 80% recovery).

(25) <u>Dithietane formation from N-ethyl-3-isothiazolone</u>

N-Ethyl-3-isothiazolone[32] was treated with sodium hydride as described in (22). A light yellow precipitate (sodium salt of the dithietane) was formed slowly. The mixture was stirred for 12 hr. Dilute HCl was added and the dithietane (90%) was filtered and washed well with water, then with DMSO. It was dried at 120°, m.p.>250°.

When sodium ethoxide in ethanol was used, formation of the dithietane was very much quicker; the reaction was completed in about $\frac{1}{2}$ hr.

TABLE VIII

ANALYTICAL RESULTS FOR ACYLATED 3-HYDROXYISOTHIAZOLE $(C_3H_2NOS)COR$

R	Required %			Found % (O-compd)			Found % (N-compd)		
	C	H	N	C	H	N	C	H	N
H	37.2	2.3	10.8	-	-	-	37.2	2.4	10.5
CH_3	42.0	3.5	9.8	41.9	3.6	10.1	42.2	3.6	9.5
CH_2Cl	33.8	2.3	7.9	-	-	-	33.8	2.5	8.1
$CH_2=CH$	46.5	3.3	9.0	46.4	3.4	9.2	46.5	3.3	8.9
C_2H_5	45.9	4.5	8.9	45.9	4.7	8.8	46.0	4.6	8.9
CH_2CH_2Br	30.5	2.6	5.9	30.3	2.7	5.7	30.4	2.6	6.0
C_3H_7	49.1	5.3	8.2	49.2	5.1	8.4	48.9	5.4	8.2
$i-C_3H_7$	49.1	5.3	8.2	49.3	5.4	8.3	49.0	5.2	8.1
$C(CH_3)_3$	51.9	6.0	7.6	51.5	6.0	7.4	-	-	-
$\varnothing CH_2$	60.3	4.1	6.4	60.4	4.3	6.0	60.4	4.2	6.2
$\varnothing-CH=CH$	62.3	3.9	6.1	62.4	4.0	5.8	62.4	3.9	6.0
CH_3O	37.7	3.2	8.8	37.9	3.4	8.9	38.0	3.3	9.0
C_2H_5O	41.6	4.1	8.1	41.8	4.0	8.6	41.8	4.0	8.1
$COOMe(CH_2)_2$	44.7	4.2	6.5	44.9	4.1	6.7	44.7	4.4	6.4
$COOMe(CH_2)_3$	47.2	4.8	6.1	47.1	4.9	6.3	46.9	5.0	5.8
$\varnothing$	58.5	3.4	6.8	58.6	3.6	7.0	58.7	3.6	6.7
$4-CH_3-\varnothing$	60.3	4.1	6.4	60.4	4.1	6.4	60.2	4.0	6.6
$4-NO_2-\varnothing$	48.0	2.4	11.2	48.2	2.5	11.0	-	-	-
$3,5-(NO_2)_2-\varnothing$	40.7	1.7	14.2	40.5	1.9	13.5	-	-	-

PART II

ALKYLATION OF 3-HYDROXYISOTHIAZOLE

CHAPTER V

RESULTS AND DISCUSSION

(A) REACTION WITH DIAZOMETHANE AND WITH TRIETHYLOXONIUM
FLUOROBORATE

The unsuccessful attempts by Gosney[38] to prepare 3-
aklyloxyisothiazoles have already been mentioned in the
Introduction (page 20). Decomposition of the products was
suggested to account for the failure to isolate any
alkylated derivative from the reactions with diazomethane and
with triethyloxonium fluoroborate. This was somewhat
surprising since Goerdeler[9] reported that 5-phenyl-3-
hydroxyisothiazole (XXXVIII) reacted with diazomethane to
give predominantly the N-methyl derivative (the presence of
some O-methyl derivative was inferred from its characteristic
smell). The successful synthesis of 5-phenyl-3-methoxy-
isothiazole[9] clearly indicates the stability of this type of
compound. It was therefore necessary to reinvestigate the

reaction of 3-hydroxyisothiazole with diazomethane and with
triethyloxonium fluorborate.

3-Hydroxyisothiazole (XXXII) reacted rapidly with
ethereal diazomethane at 0° to give a mixture of O- and N-
methyl compounds. The ratio of the two isomers was found to
vary with repeated experiments, and it soon became apparent

that loss of some 3-methoxyisothiazole during work-up
(evaporation of solvent under reduced pressure) was the
cause of such variations. This was the first indication
that 3-methoxyisothiazole was rather volatile, and probably
explained the failure of Gosney[38] to isolate the O-alkyl
compound from the reaction of (XXXII) with methyl iodide
and silver acetate. The procedure described in the
Experimental was designed to effect maximum yields of the
two isomers. N.M.R. measurements of the reaction mixture
(before work-up) showed the presence of 55% O- and 45% N-
methyl compounds. The fact that about 43% yield was obtained
(after separation of the mixture by column chromatography)
for the N-methyl compound confirmed that the observed
product ratio was genuine.

Reaction with triethyloxonium fluoroborate gave a mixture
of 70% O- and 30% N-ethyl compounds. 3-Ethoxyisothiazole was
likewise quite volatile, but no difficulty was encountered
in separating the mixture.

(B) REACTION WITH ACRYLONITRILE AND WITH ETHYL ACRYLATE

The possibility of effecting alkylation of 3-hydroxy-
isothiazole (XXXII) by Michael addition was examined in the
case of acrylonitrile. Initially, solid sodium hydroxide
was used as a catalyst with excess acrylonitrile as solvent.

This gave a very small yield (ca 15%) of a solid product,
and the physical data suggested that it was N-(β-cyano-
ethyl)-3-isothiazolone (CXXXI). There was no formation of
the corresponding O-adduct. The highest yield (ca 40%) was
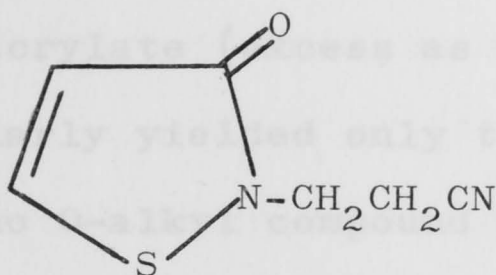
(CXXXI)

achieved using Triton B as catalyst, but again no O-alkylated
product was detected. The complete absence of any product
from O-attack by (XXXII) was in contrast to the results
observed in acylation and alkylation by direct nucleophilic
displacement (vide infra). In these cases kinetic control
resulted in a preponderance of attack by the oxygen centre,
except in the case of small electrophiles. The results
obtained in the Michael addition to acrylonitrile were
strongly suggestive of a reversible reaction, and this was
readily confirmed. Addition of sodium methoxide to a
methanolic solution of (CXXXI) resulted in disappearance of
the ring doublets for (CXXXI) and simultaneous appearance of
the ring doublets for 3-hydroxyisothiazole (confirmed by

control experiment). It is to be expected that the oxygen

atom of 3-hydroxyisothiazole would constitute a better

leaving group than the nitrogen atom, and that consequently

the rate of the reverse Michael reaction would be greater

in the O-substituted compound than in (CXXXI). Michael

addition to ethyl acrylate (excess as solvent) using Triton

B as catalyst similarly yielded only the product of N-attack

(38% yield), with no O-alkyl compound detectable. This

product similarly underwent a reverse Michael reaction when

treated with sodium methoxide.

Although it was of some interest to observe that

exclusive N-alkylation of 3-hydroxyisothiazole apparently

could be effected by this method, the susceptibility of the

product to reverse Michael reaction was regarded as a draw-

back.

(C) ALKYLATION OF METAL SALTS OF 3-HYDROXYISOTHIAZOLE

The objective of this study was to examine the

sensitivity of the alkylation site of metal salts of 3-

hydroxyisothiazole towards a number of factors known to have

influence in other ambident anion systems.[40-46] These

included the cation, solvent and alkyl halide structure, which

have been varied systematically. Tieckelmann and his co-

workers[46] found that alkylation of 2(1H)-pyridone (LII) by

in situ generation of the silver salt with silver carbonate
gave results similar to those obtained with the isolated
silver salt. This method was therefore adopted in this
alkylation study.

The first trial involved the in situ generation of the
potassium salt of 3-hydroxyisothiazole (XXXII) with
potassium carbonate. A mixture of (XXXII), anhydrous
potassium carbonate and benzyl chloride was refluxed in
acetone. Chromatography of the resulting mixture gave two
products, an oil and a solid. The following N.M.R. data
(in CCl_4) clearly indicated that the liquid product was 3-
benzyloxyisothiazole:

τ : 1.70 (doublet, J=4.6 cps, 1H)

2.51-2.91 (multiplet, 5H)

3.50 (doublet, J=4.6 cps 1H)

4.67 (singlet, 2H)

This was supported by the absence of carbonyl absorption and
the presence of ether group absorptions in the I.R. spectrum.
Unlike 3-methoxy-and 3-ethoxyisothiazoles, the benzyloxy
compound has a relatively low volatility and consequently
was much easier to handle.

The identity of the solid compound proved to be rather
unexpected, since the N.M.R. spectrum (Figure XII) was
nothing like that anticipated for N-benzyl-3-isothiazolone.

Nevertheless, interpretation of the spectrum was straight-
forward and the data were consistent with the structure of
(N-benzyl-<u>cis</u>-3-acrylamido)mercaptoacetone (CXXXII). The
assignment of peaks is included in Figure XII. Other
support came from the U.V. and I.R. data (see Experimental).

$$CH_3COCH_2S \qquad\qquad CONH$$
$$CH_2\emptyset$$

(CXXXII)
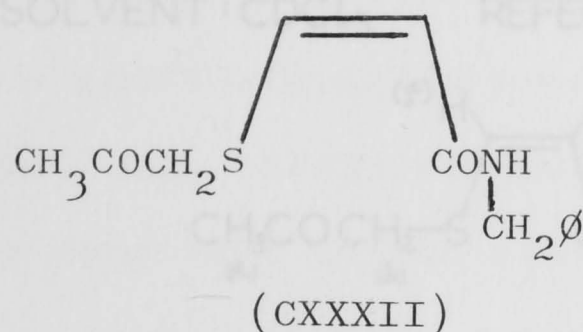
Formation of this unexpected product was easily rationalized
in terms of nucleophilic attack by the acetonide ion on N-
benzyl-3-isothiazolone. This was confirmed by a control
experiment in which the N-benzyl compound (prepared as
described later) was treated with acetone and potassium
carbonate as in the alkylation reaction. This afforded
(CXXXII) in almost quantitative yield. Other experiments
outlined below confirmed that formation of (CXXXII) arose
solely from the proposed pathway:

(i) 3-hydroxyisothiazole showed no reaction when it was
     treated similarly with potassium carbonate/acetone.
     Therefore (CXXXII) could not have been formed by
     benzylation of the unsubstituted acrylamide (H instead
     of $\emptyset CH_2$ in (CXXXII)).

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SOLVENT : CDCl₃   REFERENCE : T.M.S.

FIG. XII

(ii) pure 3-benzyloxyisothiazole was recovered almost

quantitatively when similarly treated. The result

indicated that N-benzyl-3-isothiazolone was not formed

by an O- to N-alkyl migration.

Benzylation in acetonitrile as solvent instead of

acetone was quite straightforward, giving the expected

mixture of O- and N-alkylated products, with no evidence of

ring cleavage. This result further stressed that choice of

solvents was important in the alkylation of 3-hydroxy-

isothiazole. It was already known that hydroxylic systems

such as ethanol/ethoxide could not be used because of

dithietane formation, and it was now apparent that carbanion

attack by the solvent represented another potential

difficulty. The present study was therefore confined to the

use of polar and non-polar aprotic solutions which did not

participate in carbanion attack on the S-N bond. The

success of benzylation mentioned above indicated that the

use of a metal carbonate did not result in dithietane

formation.

To effect the proposed alkylation study required a

method of measuring quantitatively the resulting mixture of

O- and N-alkylated products. N.M.R. measurements proved to

be rather convenient since the chemical shifts for the ring

doublets of the O- and N-alkyl compounds were different,

but the close proximity of chemical shifts of the ring

doublets in the O-alkyl compounds and 3-hydroxyisothiazole

itself required that 100% reaction be attained. Fortunately,

this was the case in nearly all the alkylations investigated,

although the time required to achieve 100% reaction varied

with individual alkylating reagents. In cases where the

presence of unchanged 3-hydroxyisothiazole (XXXII) was

suspected, a check on the presence of any downfield

absorption (due to OH of (XXXII)) could be made.

Alternatively, other signals could be analysed, e.g. in

benzylation, the benzyl methylene absorptions could be

utilized in the determination of product ratios (τ 4.67 for

O-compound, and τ 5.08 for N-compound). A final check was

made by isolation of the pure O- and N-alkyl compounds. In

order to eliminate the possibility of loss of products

(especially in methylation and ethylation) by evaporation,

the alkylation was conducted in sealed ampoules.

The following is a summary of the general spectroscopic

properties for 3-alkoxyisothiazoles and N-alkyl-3-

isothiazolones; data for individual compounds are given in

the Experimental.

<u>3-ALKOXYISOTHIAZOLES</u>

<u>N.M.R.</u> : H$_5$: τ 1.6-1.7 $\qquad$ H$_4$: τ 3.4-3.5

<u>U.V.</u> : 255 mμ; ε about 7500

<u>I.R.</u> : no carbonyl absorption.

N-ALKYL-3-ISOTHIAZOLONES

N.M.R. : H_5: ~ 1.8-2.0 H_4: ~ 3.7-3.8

U.V. :   278 mµ;   ε about 7000

I.R. :   carbonyl band at about 1630 cm^{-1}.

Results of the alkylation study are summarised in Table IX. The reactions were conducted by in situ generation of the potassium salt with potassium carbonate, and 50% excess of alkylating reagents were employed. Rates of alkylation were rapid in dimethylsulphoxide and dimethylformamide, intermediate in acetonitrile, and slow in 1,2-dimethoxyethane. In non-polar aprotic solvents such as benzene there was little or no reaction. Variations of temperature of a number of alkylation reactions (e.g. with ØCH$_2$Cl in DMSO from 35 to 75°) had no effect on the observed product ratios, and the same was therefore assumed for the other cases. The

products of alkylation were stable toward rearrangement

(O → N or N → O) and decomposition under the conditions

employed. Therefore the observed product ratios did not

result from thermodynamic control. Changes in product ratios

with alkylating agents can therefore be attributed directly

to changes in the relative rates of alkylation at nitrogen

and oxygen. As in acylation, nitrogen alkylations would be

expected to have greater steric requirements than oxygen

alkylations. The observed increase of oxygen alkylation with

increase of the size of the alkyl group supported this

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expectation. It can be seen from Table IX that, except in the case of 1,2-dimethoxyethane, there was little solvent effect on product distributions. The effect of changing the cation on the product ratios could only be examined in a limited way, since little or no reaction occurred in acetonitrile and 1,2-dimethoxyethane when the silver salt or lithium salt was used. However the limited data shown in Table X indicated that the silver salt favoured O-alkylation and the lithium salt favoured N-alkylation. Such results are comparable to those reported for other ambident anion systems.[45,46] In conclusion the site of alkylation of 3-hydroxyisothiazole appeared to be primarily a function of the alkylating agent, and the steric factors discussed for acylation were again seen to be in operation.

TABLE IX

EFFECT OF ALKYLATING AGENT ON PRODUCT DISTRIBUTIONS

RESULTING FROM ALKYLATION OF THE POTASSIUM SALT AT 35°-80°

ALKYL HALIDE	PRODUCT COMPOSITION (%)[*]							
	A		B		C		D	
	O	N	O	N	O	N	O	N
MeI	46	54	41	59	40	60	20	80
EtI	75	25	77	23	70	30	50	50
n-PrBr	78	22	80	20	80	20	-	-
n-BuBr	80	20	81	19	80	20	78	22
i-PrBr	88	12	-	-	86	14	-	-
$\emptyset CH_2Cl$	68	32	59	41	45	55	34	66
$COOMe(CH_2)_3Br$	77	23	-	-	78	22	-	-
$CH_3CH_2CHBrCOOC_2H_5$	87	13	-	-	84	16	-	-

[*] All reactions were 100% complete; duplicate runs were performed.

A: in dimethylsulphoxide

B: in dimethylformamide

C: in acetonitrile

D: in 1,2-dimethoxyethane.

TABLE X

EFFECT OF CATION ON THE ALKYLATION SITE
OF 3-HYDROXYISOTHIAZOLE

ALKYL HALIDE	CATION	SOLVENT	PRODUCT COMPOSITION (%)	
			O	N
MeI	K	DMSO	46	54
MeI	Ag	DMSO	68	32
MeI	Li	DMSO	34	66
MeI	K	DMF	40	60
MeI	Li	DMF	17	83
EtI	K	DMF	70	30
EtI	Li	DMF	55	45

(D) ATTEMPTED PREPARATION OF 3-CHLOROISOTHIAZOLE

An obvious method of synthesis of 3-alkyloxyisothiazoles
involves treatment of 3-chloroisothiazole with the desired
alkoxide. This method, if successful, would have the
advantage of forming only the O-alkyl compounds. The work
of Hatchard[17] indicated that the 3-chloro group in 3,5-

dichloroisothiazoles was inert to most nucleophiles. There-
fore the same behaviour might be expected for 3-chloro-
isothiazole itself. Another possible difficulty is anion
formation in the 5-position and this might lead to a
concerted elimination of chloride ion as depicted below to
form the interesting thioketene intermediate (CXXXIII). At
the commencement of this work no synthesis of 3-chloro-
isothiazole was known. It was thought that 3-hydroxy-
isothiazole (XXXII) could be converted to 3-chloroisothiazole

$$\left[S=C=C-C\equiv N \right] + Cl^-$$

(CXXXIII)
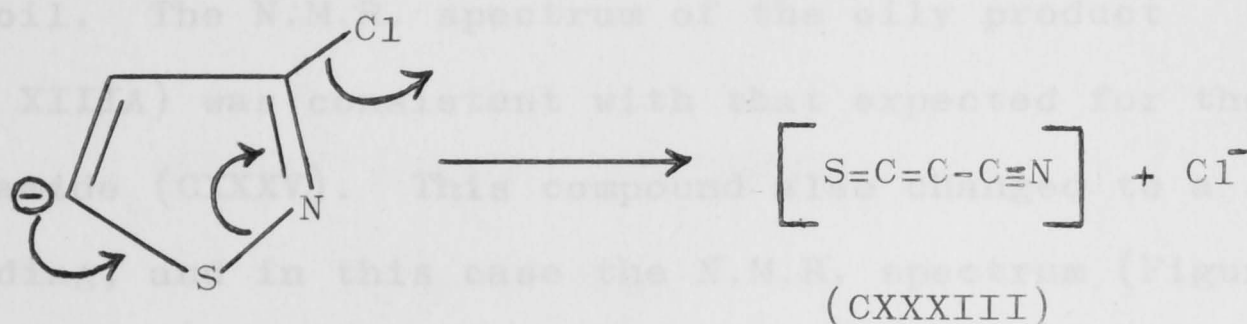
by reaction with thionyl chloride or phosphorus halides, a
method which has been employed successfully to prepare a
large number of 2-chloropyridines from the corresponding
2(1H)-pyridones.[59]

Reaction of (XXXII) with thionyl chloride in the
presence of an equivalent of pyridine resulted in the
precipitation of pyridine hydrochloride in near quantitative
yield and the formation of an oil which quickly changed to a
solid on standing, the N.M.R. spectrum (CCl_4) of the original

oil showed ring doublets at τ1.35 and 3.15, with a coupling

constant of 4.6 cps. The I.R. spectrum of the solid was

identical with that of 3-hydroxyisothiazolium hydrochloride

(LIX). These data suggested that the initially formed oil

was the chlorosulphite (CXXXIV), and that this was probably

decomposed by moisture to give (LIX) and SO_2. The existence

of (CXXXIV) was further supported by addition of aniline (2

equivalents) to the solution resulting from the reaction with

thionyl chloride as described above. This led to the

formation of aniline hydrochloride (about 98% theoretical)

and an oil. The N.M.R. spectrum of the oily product

(Figure XIIIA) was consistent with that expected for the

sulphinamide (CXXXV). This compound also changed to a solid

on standing, and in this case the N.M.R. spectrum (Figure

XIIIB) clearly showed that the product was a cis-3-

mercaptoacrylamide (cis-3-thiocyanoacrylamide (XXX)[32] has

doublets at τ 2.79 and 3.59, J=9 cps), and its structure

(CXXIV)   (CXXXV)

was tentatively assigned to 5-phenyl-1-carbamoylpropenyl-sulphonamide (contains...) which... (XXX) shows a carbonyl band at ~~~ cm^{-1} (XXX) ... (XXX) and at

SOLVENT: CCl$_4$ REFERENCE: T.M.S.

FIG. XIII A

bands at 3350 and 3150 cm^{-1}. Confirmation of the postulated structure was obtained by shaking a solution of this compound in methanol-d_4 with sodium deuterooxide and... the N.M.R. spectrum showed... the appearance of the olefinic doublets of the cis-... protons, and the resulting spectrum was identical with... tautomeric mixture of 3-hydroxyisothiazole and maleamide in the same solvent system. This transformation was also effected on a preparative scale by treating (XXXVII) with sodium at room temperature... work-up, boiling and hydrolytic extraction... Similarly the mass spectrum confirmed... (XXXVII) had an open structure showing no molecular ion (XXX) ... decompose during slight warming) and the mass spectrum... that of maleic together with the less intense fragmentation of...

SOLVENT: DMSO   REFERENCE: T.M.S.

FIG. XIII B

isothiazole. The mechanism of formation of compound (XXXV) has yet to be elucidated.

was tentatively assigned as S-(<u>cis</u>-3-acrylamido)-N-phenyl-

sulphenamide (CXXXVI). The I.R. spectrum (Nujol mull) showed

a carbonyl band at 1636 cm^{-1} (1636 cm^{-1} in (XXX)) and NH

$$\phi NH-S \quad CONH_2$$
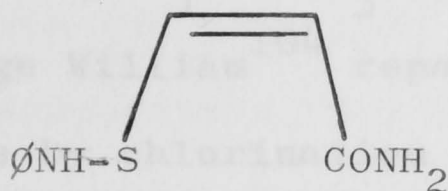
(CXXXVI)

bands at 3380 and 3500 cm^{-1}. Confirmation of the proposed

structure was obtained by treating a solution of this

compound in methanol-d$_4$ with sodium trideuteromethoxide:

the N.M.R. spectrum showed an immediate disappearance of the

olefinic doublets of the acrylamide moiety, and the resulting

spectrum was identical with that of a synthetic mixture of

3-hydroxyisothiazole and aniline in the same solvent system.

This transformation was also conducted on a preparative scale

by treating (CXXXVI) with 2N NaOH at room temperature. After

work-up, aniline and 3-hydroxyisothiazole were isolated. The

mass spectrum was also consistent with the proposed structure,

showing no molecular ion (the compound decomposed even on

slight warming) and the spectrum was mainly that of aniline

together with the less intense fragmentations of 3-hydroxy-

isothiazole. The mechanism(s) of formation of (CXXXVI) from

(CXXXV) has yet to be elucidated.

Reaction with thionyl chloride alone as solvent was unsuccessful — 3-hydroxyisothiazole was recovered on work-up. Similar results were obtained in reactions with phosphorus halides (PCl_3, $POCl_3$).

At this stage William[104] reported the synthesis of 3-chloroisothiazole by chlorination of β-mercaptopropionitrile. It was therefore possible to test the reaction of this compound with a sodium alkoxide. It was found that no reaction occurred with sodium methoxide, and there was no evidence of formation of the thioketene (CXXXIII) or any product resulting from it. Therefore 3-alkyloxyisothiazoles could not be prepared by the proposed route.

CHAPTER VI

EXPERIMENTAL

The statements (on page 114) concerning spectroscopic measurements, microanalysis, melting points and boiling points also apply to the experiments described in this chapter.

(1)   Reaction with Diazomethane

A freshly distilled ethereal solution of diazomethane was prepared (from 21g of nitrosomethylurea) as described by Vogel.[105] This was added in small portions to an ice-cooled ethereal solution of 3-hydroxyisothiazole (3g in 20 ml). Reaction occurred instantaneously with evolution of nitrogen. A slight excess of diazomethane was added and the mixture was allowed to stand for 40 minutes at 0°. The solution was then concentrated to a small volume (ca 10-15 ml) by warming on a water bath maintained at 45°. The resulting mixture was immediately chromatographed on alumina. Elution with ether yielded 3-methoxyisothiazole; after removal of the ether at 45°, the remaining oil was distilled to give the pure 0-methyl compound as a colourless oil, b.p. 142-4° (yield 48%).

N.M.R. (CCl_4) : τ: 1.62 (doublet, J=4.6 cps, 1H)

3.49 (doublet, J=4.6 cps, 1H)

6.00 (singlet, 3H)

U.V. : 255 mμ (ε 7300)

I.R. : 664, 746, 811, 839, 921, 1020, 1052, 1231,
1380, 1401, 1452, 1500, 1539, 2880, 2960,
3000, 3130 cm^{-1}

Analysis : C_4H_5NOS requires : C: 41.74%, H: 4.38%,
N: 12.17%
Found : C : 41.69%, H: 4.40%,
N: 12.4%

Further elution of the column with chloroform afforded

N-methyl-3-isothiazolone in 43% yield. It was purified by

sublimation (55°/0.4 mm). The spectroscopic data were

identical with those described by Crow and Leonard.[32]

(2) Reaction with Triethyloxonium Fluoroborate

The reagent in methylene chloride was prepared as

described by Paquette.[106] This solution (ca 0.035 mole) was

added gradually with stirring to a cold solution of 3-

hydroxyisothiazole in dry methylene chloride (3g in 60 ml).

The resulting mixture was stirred overnight and allowed to

stand for 10 hr. To the stirred solution was added slowly

5N K_2CO_3 solution. The precipitated solid was removed by

filtration, and the organic layer was collected. The

aqueous layer was then extracted with ether (2 X 50 ml), and

the combined organic extract (ether and methylene chloride)

was concentrated on a water bath maintained at 55°.

Chromatography of the mixture of O- and N-ethyl compounds

was performed as in (1). 3-Ethoxyisothiazole was purified

by distillation, b.p. 147-9° (yield 60%).

N.M.R. (CCl_4) :τ: 1.60 (doublet, J=4.6 cps, 1H)

3.46 (doublet, J=4.6 cps, 1H)

5.58 (quartet, 2H)

8.61 (triplet, 3H)

U.V. : 255 mμ (ε 7350)

I.R. : 664, 682, 744, 810, 840, 881, 980, 1035, 1055,

1230, 1350, 1381, 1424, 1480, 1531, 2880,

3000, 3130 cm^{-1}

Analysis : C_5H_7NOS requires : C: 46.51%, H: 5.47%,

N: 10.85%

Found : C: 46.7%, H: 5.42%, N: 10.9%

N-Ethyl-3-isothiazolone was obtained in 30% yield, and

was purified in the usual way.[32]

(3) N-(β-Cyanoethyl)-3-isothiazolone (CXXXI)

3-Hydroxyisothiazole (1g) was dissolved in acrylonitrile

(3.5 ml), and 2 drops of Triton B were added. The reaction

flask was stoppered and the mixture was warmed at 50° for

36 hr. The resulting mixture was chromatographed on alumina.

Elution with 1:1 mixture of ether and carbon tetrachloride

removed the excess acrylonitrile. This was followed by

elution with chloroform, which afforded (CXXXI) in 40% yield.

Sublimation $(80^\circ/0.3 \text{ mm})$ of the product gave white crystals,

m.p. 85°.

> N.M.R. $(CDCl_3)$: τ : 1.79 (doublet, J=6.4 cps, 1H)
>
> 3.72 (doublet, J=6.4 cps, 1H)
>
> 5.93 (triplet, 2H)
>
> 7.17 (triplet, 2H)
>
> U.V. : 278 mμ (ε 7800)
>
> I.R. : 1658 (C=O), 2230 cm^{-1} (C≡N)
>
> Analysis : $C_6H_6N_2OS$ requires C: 46.76%, H: 3.92%,
>
> N: 18.18%
>
> Found : C: 46.69%, H: 3.96%,
>
> N: 18.4%

(4) N-(β-Carboethoxyethyl)-3-isothiazolone

This was prepared as in (3) from 3-hydroxyisothiazole

(1g) and ethyl acrylate (5 ml). The product was obtained as

a light yellow oil which did not crystallize. An attempt to

distil the compound under reduced pressure was unsuccessful,

since it decomposed above 130°.

> N.M.R. $(CDCl_3)$: τ : 1.81 (doublet, J=6.5 cps, 1H)
>
> 3.77 (doublet, J=6.5 cps, 1H)
>
> 5.6-6.1 (two superimposable quartets,
>
> 4H)

7.25 (triplet, 2H)

8.73 (triplet, 3H)

U.V. : 278 mμ (ε 7720)

I.R. : 676, 779, 1021, 1041, 1080, 1110, 1180,

1242, 1319, 1379, 1441, 1639, 1730, 2940,

3000, 3100 cm^{-1}.

(5) Reaction with Benzyl Chloride

(i) A mixture of 3-hydroxyisothiazole (1g), anhydrous

potassium carbonate (0.7g) and benzyl chloride (1.6 ml)

in acetone (15 ml) was refluxed for 40 hr. The

mixture was filtered and washed well with acetone.

Evaporation of the filtrate yielded a mixture of oil

and solid, and these were chromatographed on alumina.

Elution with ether : carbon tetrachloride (1:1 mixture)

gave a mixture of 3-benzyloxyisothiazole and unchanged

benzyl chloride. The latter could be removed by

chromatography on silica gel using benzene as solvent,

and the O-alkyl compound was eluted later with the same

solvent. Distillation of the product gave a colourless

oil (b.p. 102-4°/0.9 mm) in 60% yield.

N.M.R. : as described in page 137

U.V. : 255 mμ (ε 8500)

I.R. : 670, 685, 699, 731, 750, 818, 826, 840, 910,

977, 1010, 1060, 1070, 1218, 1230, 1358, 1398,

1420, 1460, 1502, 1528, 2890, 2950, 3040,

3100 cm^{-1}

<u>Analysis</u> : $C_{10}H_9NOS$ requires C: 62.82%, H: 4.75%,

N: 7.33%

Found : C: 62.93%, H: 4.73%,

N: 7.5%

Elution of the original alumina column with chloroform

gave (<u>N-benzyl-cis-3-acrylamido</u>)mercaptoacetone

(CXXXII) as an oil which crystallized on standing.

(CXXXII) was dissolved in the minimum amount of

chloroform, and light petroleum was slowly added with

swirling until the solution became turbid. On cooling

(CXXXII) crystallized in pale yellow plates, m.p. 120-

21° (yield 28%).

<u>N.M.R.</u> : as described on page 139

<u>U.V.</u> : 278 mμ (ε 14100)

<u>I.R.</u> : 1632, 1700 (C=O), 3330 cm^{-1} (NH)

<u>Analysis</u> : $C_{13}H_{15}NO_2S$ requires : C: 62.64%, H: 6.07%,

N: 5.62%

Found : C: 62.60%, H: 6.15%,

N: 5.83%

(ii) When the benzylation was performed in acetonitrile

instead of acetone, chromatography of the products on

alumina (as above) gave 3-benzyloxyisothiazole (40%)

and N-benzyl-3-isothiazolone (53%).   The latter

compound was obtained as an oil which crystallized on

standing.   It was purified by sublimation (80°/0.1 mm)

to give white places, m.p. 76-77°.

N.M.R. :   (CDCl$_3$): $\mathcal{T}$: 1.98 (doublet, J=6.3 cps, 1H)

3.77 (doublet, J=6.3 cps, 1H)

2.69 (singlet, 5H)

5.08 (singlet, 2H)

(8)   Preparation of (CXXXII) from N-Benzyl-3-isothiazolone

N-Benzyl-3-isothiazolone was similarly reacted with

acetone/K$_2$CO$_3$ for 12 hr.   The procedure for isolating

(CXXXII) was the same as described in (5) (i).   The yield

was about 95%.

(9)   Reaction with Thionyl Chloride

(i) A solution of 3-hydroxyisothiazole (0.483g) and

pyridine (0.378 g) in anhydrous ether (15 ml) was cooled

in a dry ice-acetone bath.   A cold ethereal solution of

thionyl chloride (0.569g in 4 ml) was added all at once.

An immediate precipitation of pyridine hydrochloride

occurred.   The mixture was allowed to warm up to room

temperature with occasional swirling.   Filtration and

evaporation of the filtrate gave an oil which quickly
deposited some solid. On standing more solid was
formed. The I.R. spectrum of this solid was identical
with that of 3-hydroxyisothiazolium hydrochloride.

(ii) The above experiment was repeated and the
resulting mixture (without removal of pyridine
hydrochloride) was refluxed 6 hr. The same product was
obtained on work-up.

(iii) 3-Hydroxyisothiazole (XXXII) (0.5g) was
dissolved in excess thionyl chloride (5 ml). There
was an immediate formation of some 3-hydroxyisothiazolium
hydrochloride. The mixture was refluxed for 6 hr, and
the resulting solution was then poured carefully with
stirring into a beaker of ice. Continuous extraction
with ether gave (XXXII) (ca 95% recovery).

(10) S-(cis-3-Acrylamido)-N-Phenylsulphenamide (CXXXVI)

The reaction of 3-hydroxyisothiazole (0.527g) and
pyridine (0.412g) with thionyl chloride (0.620g) was
performed as described in (9)(i). After removing the
pyridine hydrochloride, aniline (0.96g) was added to the
filtrate (or alternatively, it was added directly into the
reaction mixture prior to filtration). An immediate
precipitation of aniline hydrochloride resulted. The

mixture was stirred for 10 minutes. Filtration and evaporation of the filtrate gave a light brown oil with a pungent smell. On standing, a solid compound (CXXXVI) began to appear; this was isolated and washed well with ether. The N.M.R. and I.R. data have been mentioned on page 148.

(11) Reaction of (CXXXVI) with Sodium Hydroxide

(CXXXVI) (0.5g) was added in small amounts to a stirred 2N NaOH solution (10 ml) at room temperature. Oily droplets (aniline) appeared almost at once. After 10 minutes the alkaline solution was extracted with ether, and the organic layer was evaporated to give aniline (88%; confirmed by I.R. spectrum). The aqueous layer was acidified with 2N HCl, and this was then subjected to continuous extraction with ether. This afforded 3-hydroxyisothiazole in 90% yield.

(12) Reaction with Phosphorous Trichloride

This was conducted as described in (10)(iii) with excess phosphorous trichloride (5 ml). A similar work-up resulted in a 92% recovery of 3-hydroxyisothiazole.

The same result was obtained in a similar experiment with phosphorus oxychloride.

(13) Alkylation of the Potassium Salt of 3-Hydroxyisothiazole

3-Hydroxyisothiazole (0.5g) and anhydrous potassium

carbonate (0.36g) were introduced into a dry ampoule. The appropriate solvent (3 ml) and alkyl halide (50% excess) were then added. The ampoule was sealed immediately, and it was half-immersed into a warm water bath maintained at a constant temperature ($\pm$ 3°). The rate of methylation or ethylation in DMSO and in DMF was rapid (100% complete in 24 hr at 35°), but other alkylation reactions in the same solvents required a longer reaction time (48-60 hr at 50°). Methylation and ethylation in acetonitrile or 1,2-dimethoxyethane were conducted at 40° for 48 hr, and the other reactions were performed at 65° for 55-70 hr.

Analysis of product ratios was done immediately after opening the ampoule by integration (300 c/s sweep width) of the ring doublets, and expression as percentage of the total. Individual products could be isolated by column chromatography as described in (5).

Table XI summarises the N.M.R. data of some of the 3-alkyoxyisothiazoles and N-alkyl-3-isothiazolones that were isolated.

Alkylation of the lithium (and silver) salt of 3-hydroxy-isothiazole was performed in exactly the same manner.

TABLE XI

N.M.R. DATA (τ, cps) OF 3-ALKYLOXYISOTHIAZOLES* AND
N-ALKYL-3-ISOTHIAZOLONES**

R	H_4	H_5	Other Signals	B.P. $0^{o}/mm$
			O-Alkylation	
n-Pr	3.48	1.64	5.67 (T,2H), 7.86-8.45 (M,2H), 8.95 (T,3H)	58/2
i-Pr	3.51	1.64	4.51-5.12 (M,1H), 8.66 (D,6H)	53/1
n-Bu	3.49	1.68	5.66 (T,2H), 7.97-9.2 (M,7H)	60/2
COOMe(CH$_2$)$_3$	3.50	1.61	5.61 (T,2H), 6.37 (S,3H), 7.38-8.18 (M,4H)	92-94/0.3
COOEtCHCH$_2$CH$_3$	3.40	1.64	4.92 (T,1H), 5.87 (Q,2H), 7.81 8.32 (M,2H), 8.6-9.14 (2T,6H)	91-93/0.6
			N-Alkylation	
n-Pr	3.75	1.81	6.22 (T,2H), 7.9-8.6 (M,2H), 9.04 (T,3H)	* * *
i-Pr	3.75	1.83	4.85-5.5 (M,1H), 8.59 (D,6H)	* * *
n-Bu	3.77	1.84	6.21 (T,2H), 7.96-9.2 (M,7H)	* * *
COOMe(CH$_2$)$_3$	3.74	1.82	6.13 (T,2H), 6.30 (3H,S), 7.35-8.2 (M,4H)	* * *
COOEtCHCH$_2$CH$_3$	3.75	1.82	5.52-5.95 (1Q & 1T, 3H) 7.8-8.3 (M,2H) 8.55-9.2 (2H,6H)	* * *

Notes for Table on page 162

NOTES TO TABLE XI

*   in CCl_4 ($J_{4,5}$ = 4.6 cps)   ** in $CDCl_3$($J_{4,5}$ = 6.4 cps)

*** B.P. above 130°/0.1 mm; decomposed above this
    temperature.

D = Doublet   M = Multiplet,   Q = Quartet

S = Singlet   T = Triplet

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