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Chemistry

SYNTHESES IN THE THIAZOLOBENZIMIDAZOLE SERIES

Syntheses in the Thiazolobenzimidazole Series

by

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List of Roman Numerals and the Compounds or Structures They Represent.

Roman Numeral	Compound or Structure
I	Thiazolo[3,2-a]benzimidazole
II	2-Benzimidazolinethione
III	3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole
IV	3-Acetoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole
V	3-Ethoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole
VI	2-Ethylthiobenzimidazole
VII	Thiazolo[3,2-a]benzimidazole methiodide
VIII	(2-Benzimidazolylthio)acetic acid.
IX	3(2H)-Thiazolo[3,2-a]benzimidazolone.
X	2-Benzimidazolinone.
XI	2-(2-Benzimidazolylthio)ethanol
XII	5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole
XIII	2-Chlorocyclohexanone
XIV	5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole methiodide
XV	2-Mercapto-4,5,6,7-tetrahydrobenzimidazole
XVI	6,7-Dimethylthiazolo[3,2-a]benzimidazole
XVII	5,6-Dimethyl-2-benzimidazolinethione
XVIII	4,5-Dimethyl-2-nitroacetanilide
XIX	4,5-Dimethyl-2-nitroaniline
XX	4,5-Dimethyl-o-phenylenediamine
XXI	6,7-Dimethyl-3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole

XXII	5,8-Dimethylthiazolo[3,2-a]benzimidazole
XXIII	3,6-Dimethyl-o-phenylenediamine
XXIV	2,3-Dinitro-p-xylene
XXV	5-Amino-2-nitro-p-xylene
XXVI	4,7-Dimethyl-2-benzimidazolinethione
XXVII	5,8-Dimethyl-3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole
XXVIII	2-Methylthiazolo[3,2-a]benzimidazole
XXIX	2-Chloropropionaldehyde
XXX	3-Hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole
XXXI	3-Acetoxy-2-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole
XXXII	3-Phenylthiazolo[3,2-a]benzimidazole
XXXIII	(2-Benzimidazolylthio)acetophenone
XXXIV	3-Methylthiazolo[3,2-a]benzimidazole
XXXVa	3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole
XXXVb	(2-Benzimidazolylthio)propan-2-one
XXXVI	2-Acetylthiazolo[3,2-a]benzimidazole
XXXVII	2-Hydroxymethyl-3-methylthiazolo[3,2-a]benzimidazole
XXXVIII	Ethyl 2-(2-benzimidazolylthio)acetoacetate
XXXIX	2-Carbethoxy-3-methylthiazolo[3,2-a]benzimidazole
XL	2-(1-Hydroxyethyl)thiazolo[3,2-a]benzimidazole
XLI	2-(1-Acetoxyethyl)thiazolo[3,2-a]benzimidazole
XLII	2-Acetyl-3-methylthiazolo[3,2-a]benzimidazole
XLIII	(2-N-Acetylbenzimidazolylthio)propan-2-one
XLIV	3-Chloro-2,4-pentanedione

XLV	3-(2-Benzimidazolylthio)-2,4-pentanedione
XLVI	2-(1-Hydroxyethyl)-3-methylthiazolo[3,2-a]-benzimidazole
XLVII	6-(or 7-)Nitrothiazolo[3,2-a]benzimidazole
XLVIII	2-Methylimidazo[2,1-b]benzothiazole
XLIX	2-Acetamidobenzothiazole
L	Imidazo[2,1-b]thiazole
LI	Imidazo[2,1-b]benzothiazole
LII	2-Phenylimidazo[2,1-b]benzothiazole
LIII	3-Methylimidazo[2,1-b]benzothiazole
LIV	α-Bromopropionaldehyde diethyl acetal
LV	6-Methylimidazo[2,1-b]thiazole
LVI	2-Imino-3-(2-propanone)thiazole hydrochloride
LVII	(2-N-Acetylbenzimidazolylthio)acetophenone
LVIII	(2-Benzimidazolylthio)-1-propen-2-ol acetate

GENERAL INTRODUCTION

This dissertation reports the syntheses of three classes of aromatic heterocycles having a bridgehead nitrogen namely, the thiazolo[3,2-a]benzimidazoles, the imidazo-[2,1-b]benzothiazoles and the imidazo[2,1-b]thiazoles. Although various derivatives of these compounds were known, the parent compound of each series had not been synthesized. Therefore, this investigation was undertaken.

No study of the spectra of these three types of compounds had been made. Therefore, it was of interest to examine their infrared, ultraviolet and N.M.R. spectra and to report the main spectral characteristics of these compounds.

The direction of the condensation reaction between 2-benzimidazolinethione and alpha-halocarbonyl compounds forming thiazolo[3,2-a]benzimidazoles had not been shown unambiguously. It seemed significant to establish the course of this reaction in order to assign the structures of the substituted thiazolo[3,2-a]benzimidazoles prepared from 2-benzimidazolinethiones.

The intermediate reaction products formed in the syntheses of the thiazolo[3,2-a]benzimidazoles, e.g. (2-benzi-midazolylthio)propan-2-one, are potentially tautomeric. Hence, it was of interest to study the structure of these compounds. Spectral data would be most useful in this investigation.

Confusion existed as to the structure of the product obtained when (2-benzimidazolylthio)propan-2-one reacted with acetic anhydride in pyridine. Determination of the structure of this product and a study of the scope of this reaction seemed in order.

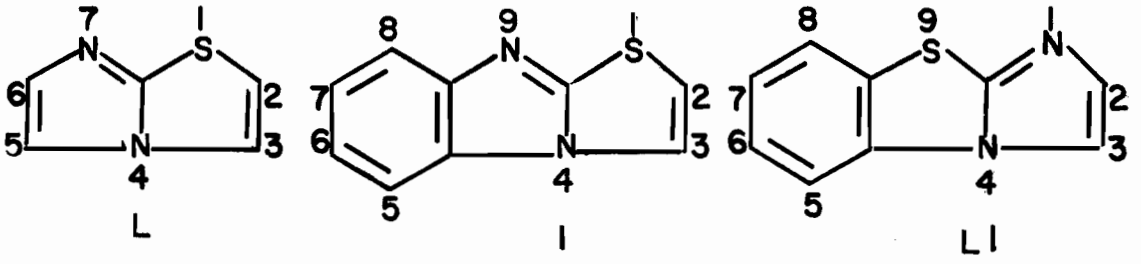
HISTORICAL INTRODUCTION

I. General

The ring systems investigated, namely thiazolo-[3,2-a]benzimidazole (I), imidazo[2,1-b]benzothiazole (LI) and imidazo[2,1-b]thiazole (L) were first synthesized between 1936 and 1940. The imidazo[2,1-b]thiazole and the thiazolo-[3,2-a]benzimidazoles found interest as model compounds in the elucidation of the structure of thiochrome, obtained from the alkaline oxidation of thiamine (Vitamin B_1) (30). However, the parent compound of each series has not been reported and no study of the spectra of such compounds has been made. Also, ambiguity exists concerning the structure of some products which have been obtained in the thiazolo-[3,2-a]benzimidazole series. This introduction summarizes the available information on the three ring systems to this time.

II. Nomenclature and Structure

The compounds are named and numbered according to the rules on nomenclature given in the Ring Index (26) and correspond with the names used in Chemical Abstracts.



The imidazo[2,1-b]thiazole system (L), R.R.I.* 904, consists of a thiazole ring fused to an imidazole ring with a common or bridgehead nitrogen in the 4-position.

The thiazolo[3,2-a]benzimidazole system (I), R.R.I. 2342, consists of a thiazole ring fused to the benzimidazole system forming a tricyclic compound, having a bridgehead nitrogen at position 4.

Imidazo[2,1-b]benzothiazole (LI), R.R.I. 2343, is also a tricyclic system with a bridgehead nitrogen in position 4 but the imidazole ring is fused onto the benzothiazole system.

III. Imidazo[2,1-b]thiazoles

This ring system is treated first since it forms the nucleus of the two other systems. Compounds of this type may be prepared by building a thiazole ring onto an imidazole ring or vice versa (27).

A. Annelation of a thiazole ring to an imidazole ring

Treatment of 2(3H)-imidazolethiones with alpha-haloketones gives (2-imidazolylthio)ketones which are cyclized with phosphorus oxychloride (31,35,37) or a mineral acid (32,33,34) to form imidazo[2,1-b]thiazoles. Acetals obtained

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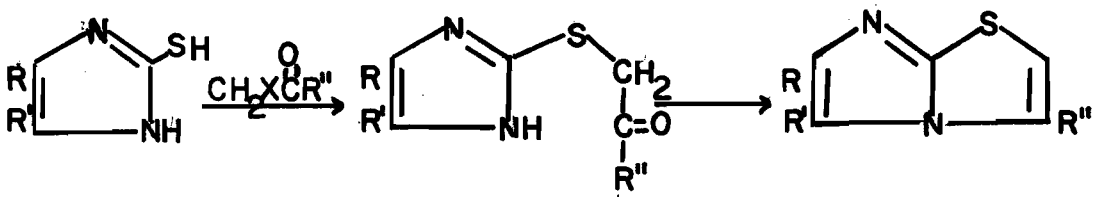
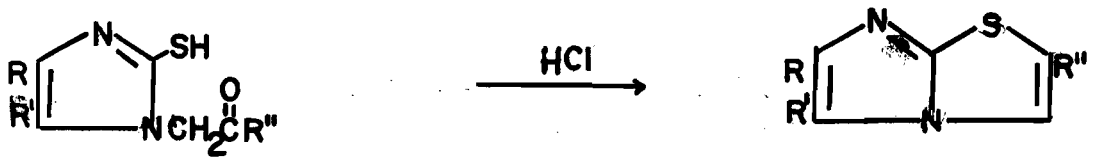
*R.R.I. - The R.R.I. number is the serial number assigned to the ring system in the revised edition of The Ring Index (26).



from 2(3H)-imidazolethiones and bromoacetals are cyclized by phosphorus oxychloride to 3-alkoxy-2,3-dihydro-imidazo-[2,1-b]thiazoles (36).

Lawson and Morley (38,39) prepared several imidazo[2,1-b]thiazoles by cyclizing 2-mercaptoglyoxalines obtained from alpha-amino acid esters.

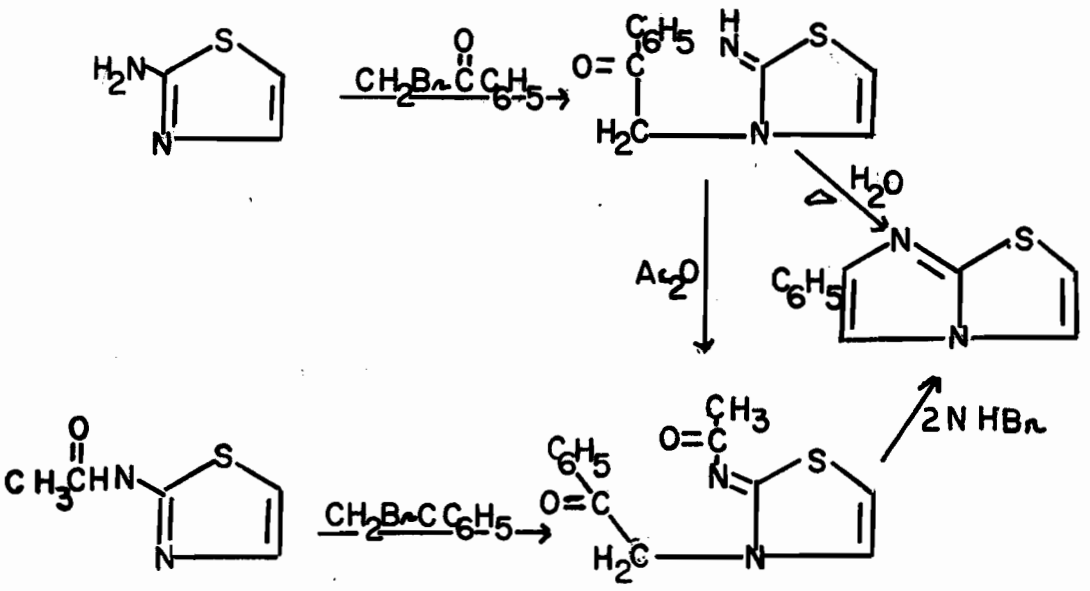


B. Annelation of an imidazole ring to a thiazole ring.

2-Aminothiazoles have been condensed with phenacyl halides to prepare several 6-phenylimidazo[2,1-b]thiazoles (25,40-47).

Kickhöfen and Kröhnke (43) have demonstrated the direction of this condensation by showing that 6-phenylimidazo-[2,1-b]thiazole was formed from either 2-aminothiazole or

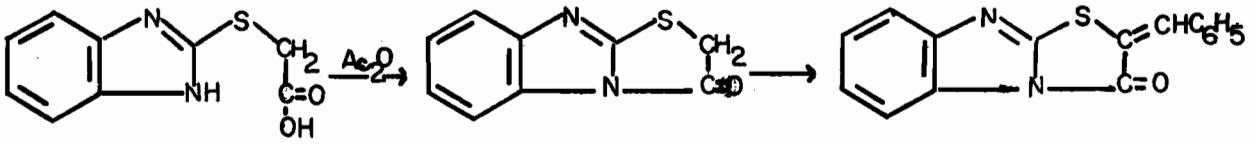
2-acetamidothiazole.



Pyl and his co-workers (44-46) have reported that the imidazo[2,1-b]thiazole system shows typical aromatic behaviour towards electrophilic substitution. Nitrosation (44,45) and bromination (44) occur in the 5-position. 5-Aminoimidazo-[2,1-b]thiazoles, obtained by reduction of the 5-nitro compounds, undergo reactions typical of aromatic amines (46).

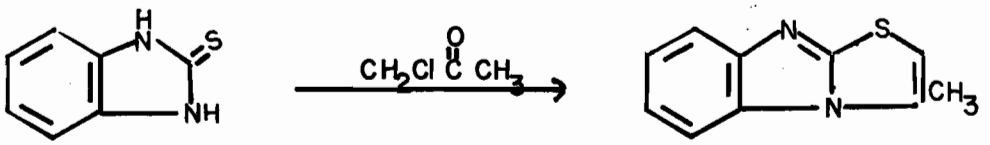
IV. Thiazole[3,2-a]benzimidazoles

Syntheses of compounds of this type usually involve annelation of a thiazole ring to the benzimidazole system. 3(2H)-Thiazolo[3,2-a]benzimidazolone has been known since 1926 (48) and is most conveniently prepared by dehydration of (2-benzimidazolylthio)acetic acid with acetic anhydride (5).



The activated 2-position condenses with a variety of reagents and numerous derivatives of this type have been prepared (5,49-55).

The reaction of 2-benzimidazolinethione and chloroacetone has been reported to give 3-methylthiazolo[3,2-a]-benzimidazole (32,28). However, no intermediate was isolated

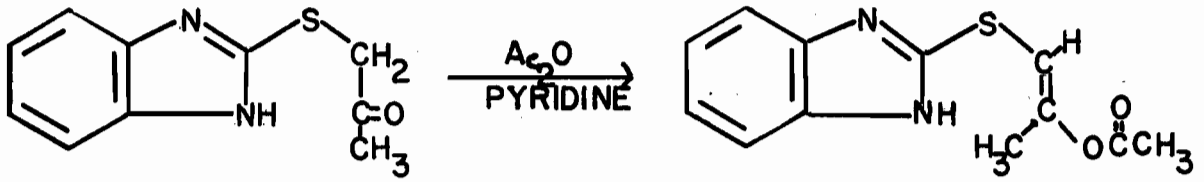


and the possibility that the product is the isomeric 2-methyl compound cannot be totally excluded. Similarly, De Stevens and Halamandaris (3) obtained 2,3-dimethylthiazolo[3,2-a]benzimidazole from 2-benzimidazolinethione and 3-bromo-2-butanone.

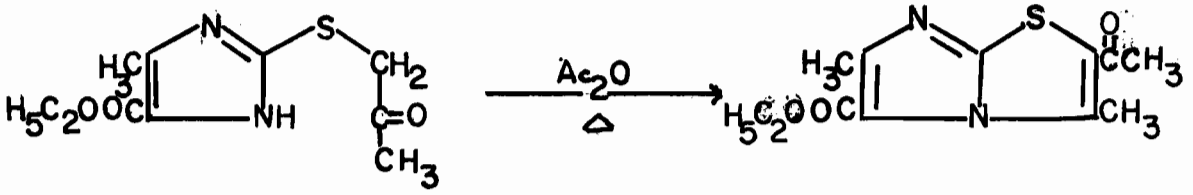
A different approach to the thiazolo[3,2-a]benzimidazole system has been patented by Rudner (56) who condensed 2-aminothiazole and p-quinone to yield the 6- or 7-hydroxy compound. This is analogous to the formation of pyrido[1,2-a]-benzimidazoles from 2-aminopyridine and p-quinone (57).

During the course of this investigation a paper appeared by D'Amico (17) on the synthesis of several 3-methylthiazolo[3,2-a]benzimidazoles from 2-benzimidazolinethione and alpha-haloketones through the intermediate (2-benzimidazolylthio)-

ketones. D'Amico reported that treatment of 1-(2-benzimidazolylthio)-2-propanone with acetic anhydride in pyridine gave an enol acetate.

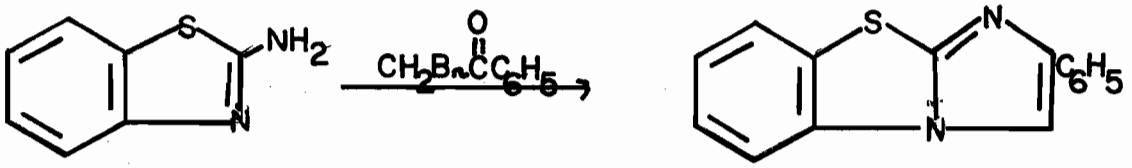


However, in the imidazo[2,1-b]thiazole series, Ochiai (31) had found that the similar compound 2-acetylthio-5-methyl-4-carbethoxyimidazole when heated in acetic anhydride formed a ketone which, he postulated, was a 2-acetylimidazo[2,1-b]thiazole.



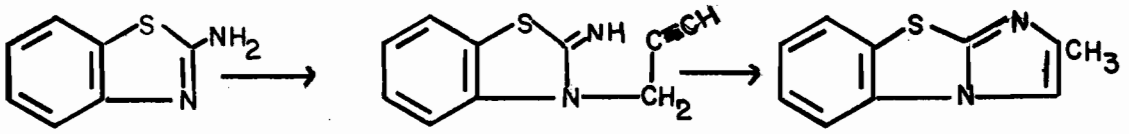
V. Imidazo[2,1-b]benzothiazoles

Ochiai and Nizisawa have synthesized 6-phenyl-imidazo[2,1-b]benzothiazole from 2-aminobenzothiazole and bromoacetophenone (29).



Recently, another method for fusing an imidazole ring to a thiazole ring has been reported (58). Propynyl bromide and 2-aminobenzothiazole form 2-imino-3-(2-propynyl)-2,3-dihydrobenzothiazole hydrobromide. Its free base is

cyclized by sodium ethoxide to give 2-methylimidazo[2,1-b]-benzothiazole. This method is generally applicable for the



synthesis of methyl-substituted heteroaromatics.

DISCUSSION

I. Syntheses of Thiazolo[3,2-a]benzimidazoles

Thiazolo[3,2-a]benzimidazoles were synthesized by annelation of a thiazole ring to various benzimidazoles. The intermediates formed were isolated and characterised and some of their reactions were studied.

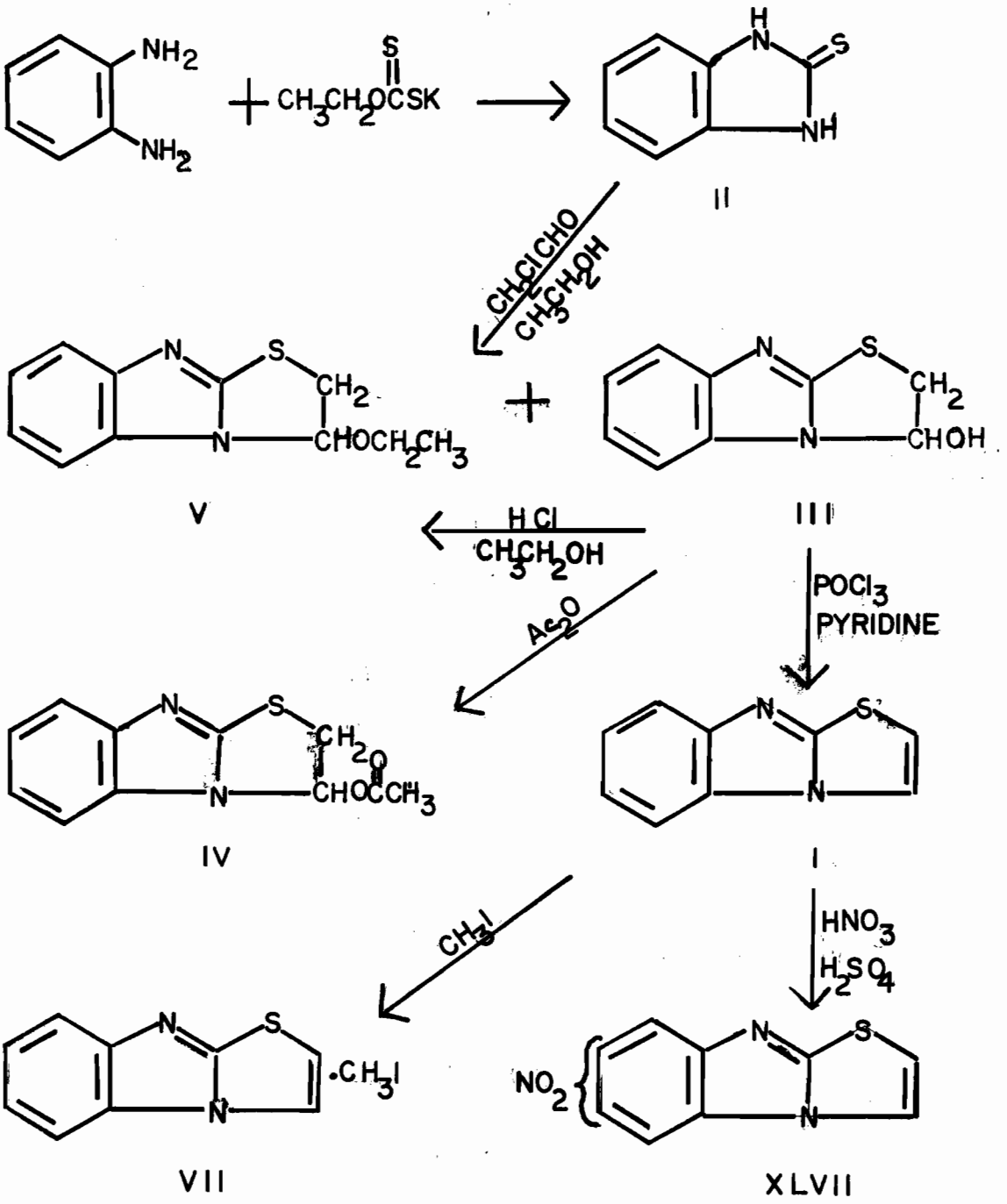
Attempts to form thiazolo[3,2-a]benzimidazoles by the method described in Rudner's patent (56) were unsuccessful and no product was obtained. Attempted dehydrogenation of 5,6,7,8-tetrahydrothiazolo[3,2-a]benzimidazole was also unsuccessful.

A. Synthesis of Thiazolo[3,2-a]benzimidazole (I).

The synthesis of I is outlined in Scheme 1. In this investigation, reaction of o-phenylenediamine with potassium ethyl xanthate, after Van Allan and Deacon (1), gave an 88% yield of 2-benzimidazolinethione (II).

The thiazole ring was formed using the sulfur and nitrogen atoms of 2-benzimidazolinethione (II) by reaction of II with chloroacetaldehyde. This is an application of the Hantzsch thiazole synthesis from a thioamide and an alpha-halocarbonyl compound (60). 2,3-Dimethylthiazole[3,2-a]-benzimidazole had been similarly prepared from II and 3-bromo-2-butanone (3).

SCHEME I


NH2
NH2
S
CH3CH2OCSK
H
N
S
NH
II
CH2ClCHO
CH3CH2OH
N
S
CH2
CHOCH2CH3
V
CHOH
III
HCl
CH3CH2OH
Ac2O
POCl3
PYRIDINE
CH2
O
CHOCCH3
IV
I
CH3I
HNO3
H2SO4
·CH3I
VII
NO2
XLVII

Condensation of 2-benzimidazolinethione and chloroacetaldehyde in 2-butanone, however, gave not I but the intermediate 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III). (The location of the hydroxyl group in III will be proved in Section B of this discussion.) III was identified by elemental analysis and spectral data.

Compound III analyzed for $C_9H_8N_2OS$ one mole of water more than the formula of thiazolo[3,2-a]benzimidazole. Its infrared spectrum (Fig. 1) showed three broad bands of medium intensity at 3050, 2844 and 2736 with a shoulder at 2672 $cm.^{-1}$ (hydrogen-bonded O-H stretch); and strong bands at 1040 $cm.^{-1}$ (C-O stretch for a secondary cyclic alcohol (61)) and 742 $cm.^{-1}$ (C-H out-of-plane deformation for the ortho-disubstituted benzene ring). The extreme insolubility of III prevented the study of the O-H stretching vibration in solution.

The nuclear magnetic resonance (N.M.R.) spectrum of III (DMSO-d_6) is complex. It showed a multiplet between 7.6 and 7.0 p.p.m., a broad unresolved multiplet at 6.30 p.p.m., a quartet at 4.3 p.p.m. (J = 12.0 cps* and J = 6.0 cps), a quartet at 3.69 p.p.m. (J = 12.0 cps and J = 2.1 cps) in the ratio 5:1:1:1. After addition of two drops of trifluoroacetic acid the entire spectrum was shifted slightly downfield. It now showed (Fig. 2) a complex multiplet between 7.3 and 7.9 p.p.m. for the four aromatic protons, a quartet at 6.62

*Unless otherwise noted only the absolute values of the coupling constants are given.

p.p.m. for the hydrogen alpha to the hydroxyl group, and two quartets at 4.52 and 3.92 p.p.m. for the methylene protons.

In dimethyl sulfoxide, hydrogen bonding to the solvent shifts the hydroxyl resonance downfield and reduces its rate of exchange sufficiently to observe splitting (62). In this spectrum the hydroxyl proton of III was obscured by the multiplet for the aromatic protons. When trifluoroacetic acid was added the hydroxyl proton underwent rapid exchange with the acidic proton and its signal disappeared. Also, the unresolved multiplet for the proton alpha to the hydroxyl group became a distinct quartet, since there was no longer coupling with the hydroxyl proton. The downfield shift of the entire spectrum after addition of trifluoroacetic acid is due to intermolecular interaction between the solute and this polar solvent (63).

The three quartets, for the three protons on the thiazolidine ring, form an AMX spectrum with J_{AM} = 12.0 cps, J_{AX} = 2.1 cps and J_{MX} = 6.0 cps. Since the proton at C_2 coupled to X by 2.1 cps is cis to X, and that coupled to X by 6.0 cps is trans to it (71) the quartet at lower field (4.52 p.p.m., J = 12.0 and J = 6.0 cps), must be assigned to the proton at C_2 cis to the hydroxyl group. Deshielding of a proton by an electronegative substituent has also been observed in the N.M.R. spectra of steroids (64,66-69). An

axial hydroxyl group deshields a proton occupying a 1,3-diaxial position with respect to it by 0.5 to 0.39 p.p.m. (64). This effect has been attributed to an intramolecular Van der Waal's interaction (69). Calculations based on the known intermolecular relationship have given results in good agreement with the observed shifts (64,69).

De Stevens and Halamandaris (3) had carried out the condensation of 3-bromo-2-butanone and 2-benzimidazolinethione (II) in ethanol. However, when ethanol was used as a solvent for the reaction of II with chloroacetaldehyde the N.M.R. spectrum of the crude product indicated that approximately 10% of 3-ethoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (V) was also formed. This ether had resulted from an acid-catalyzed exchange between the product and the solvent. Therefore, 2-butanone was chosen as a solvent for this reaction because it has good dissolving properties and a boiling point close to that of ethanol, and can dissolve the water used in the reaction.

3-Ethoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (V) was prepared from III by refluxing III in ethanol containing a slight excess of hydrochloric acid. V absorbed in the infrared region at 1065 $cm.^{-1}$ (asym. C-O stretch). Its N.M.R. spectrum ($CDCl_3$) showed a complex multiplet between 7.1 and 7.7 p.p.m. for the four aromatic protons, three quartets, an AMX spectrum, for the three protons on the thiazolidine ring, as well as a quartet at 3.5 p.p.m. (J = 7.1 cps) and a triplet at 1.2 p.p.m.

(J = 7.1 cps) for the ethoxy group (71). In the AMX spectrum the quartet at 5.96 p.p.m. (J = 2.3 and J = 5.7 cps) is assigned to the proton alpha to the ethoxy group at C_3, that at 4.16 p.p.m. (J = 5.7 and J = 11.7 cps) to the proton at C_2 cis to the ethoxy group, and the quartet at 3.7 p.p.m. (J = 2.3 and J = 11.7 cps) to the remaining proton at C_2. The ethoxy group deshielded the proton "opposite" to it as was observed for the hydroxy substituent.

The condensation of II with chloroacetaldehyde was also carried out in aqueous sodium hydroxide and III was obtained in excellent yield.

Chloroacetaldehyde is extremely reactive and cannot be stored in pure form. In these reactions a 40-45% solution of chloroacetaldehyde in water was found to be a suitable reagent. When α,β-dichloroethyl ether was used as a source of the aldehyde an additional product, 2-ethylthiobenzimidazole (VI), was obtained in 4% yield. VI was formed from a by-product of the cleavage of the α,β-dichloroethyl ether (91,92). Its melting point 170-172° agreed with the value 170-170.5° reported in the literature (20) for 2-ethylthiobenzimidazole. Its infrared spectrum showed broad absorption between 2500 $cm.^{-1}$ and 3200 $cm.^{-1}$ for the hydrogen-bonded N-H stretch. The N.M.R. spectrum of VI had a complex multiplet between 7.0 and 7.6 p.p.m. for the four aromatic

protons, a quartet at 3.4 p.p.m. (J = 7.2 cps) for the methylene protons, and a triplet at 1.4 p.p.m. (J = 7.2 cps) for the methyl group.

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) forms the 3-acetoxy derivative in 92% yield when treated with acetic anhydride at room temperature. 3-Acetoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (IV) absorbed in the infrared at 1732 $cm.^{-1}$ (C=O stretch of an ester), 1239 $cm.^{-1}$ (C-O stretch of the ester) and 1019 $cm.^{-1}$ (C-O stretch of the alcohol residue). In chloroform solution, the carbonyl stretching absorption occurred at 1750 $cm.^{-1}$ This lowering of the carbonyl frequency in the condensed phase is due to lattice field effects and possibly association (70).

The N.M.R. spectrum of IV ($CDCl_3$) showed a complex multiplet between 7.0 and 7.7 p.p.m. for the four aromatic protons, and the proton alpha to the acetoxy group (acetylation of secondary alcohols shifts the signal for the alpha proton downfield by 1.0 to 1.1 p.p.m. (71)), a quartet at 4.29 p.p.m. (J = 13.5 and J = 5.0 cps) and a doublet at 3.7 p.p.m. (J = 13.5 cps) for the hydrogens at C_2 and a singlet at 2.05 p.p.m. for the methyl protons of the acetyl group (71). The quartet (4.29 p.p.m.) is assigned to the proton at C_2 cis to the acetoxy group and the doublet at higher field (3.7 p.p.m.) to the remaining proton at C_2. It shows an additional splitting of approximately 1.0 cps from coupling with the proton cis to it at C_3.

Thiazolo[3,2-a]benzimidazole (I) was obtained from 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) by dehydration with sulfuric acid or with phosphorus oxychloride in pyridine (see Scheme 1). The latter method was preferred as it gave a higher yield (77%) and a purer product. The infrared spectrum of the product showed no absorption for the hydroxyl group in the 3000 $cm.^{-1}$ region or at 1040 $cm.^{-1}$ Its N.M.R. spectrum in $CDCl_3$ (Fig. 4) showed a complex multiplet between 7.1 and 7.9 p.p.m. for H_3, H_5, H_6, H_7, and H_8 and a doublet at 6.7 p.p.m. (J = 4.7 cps) assigned to H_2. (See Section G for further discussion of the N.M.R. spectrum of I).

Thiazolo[3,2-a]benzimidazole formed a quaternary methiodide (VII), m.p. 237-239°, which was stable and could be recrystallized from boiling ethanol.

Thiazoles undergo nitration and other electrophilic substitution in the 5-position (65). However, for benzothiazoles nitration occurs in the benzene ring to give mainly 6-nitrobenzothiazole (72), Benzimidazole is also nitrated in the benzene ring yielding 5-nitrobenzimidazole (73). Therefore it was of interest to study the nitration of thiazolo[3,2-a]benzimidazole (I).

I was readily nitrated with a sulfuric-nitric acid mixture at 0°. Thin layer chromatography (T.L.C.) indicated that three products had been formed. The main product, isolated

by T.L.C., was identified as either 6- or 7-nitrothiazolo-[3,2-a]benzimidazole (XLVII) from its infrared and N.M.R. spectra.

XLVII absorbed in the infrared at 3144, 3098, and 3039 $cm.^{-1}$ (aromatic C-H stretch), at 1513 and 1324 $cm.^{-1}$ (asym. and sym. NO_2 stretch, respectively (70)), at 832 and 880 $cm.^{-1}$ (C-H out-of-plane bending for a 1,2,4-trisubstituted benzene ring). Its N.M.R. spectrum (DMSO) (Fig. 5) showed two doublets at 7.45 and 8.6 p.p.m. (J = 4.0 cps) which were assigned to H_2 and H_3; a doublet at 9.1 p.p.m. (J = 2.0 cps), a quartet at 8.2 p.p.m. (J = 2.0 cps and J = 9.5 cps) and a doublet 7.70 p.p.m. (J = 9.5 cps) for the three protons on the benzene ring. The coupling constants (71) indicate that there are two protons ortho to each other (8.2 and 7.70 p.p.m. J = 9.5 cps) one of which (8.2 p.p.m.) is meta to the third proton (9.1 p.p.m., J = 2.0 cps). Therefore the nitro group is either at C_6 or C_7. Due to the complexity of the N.M.R. spectrum of the unsubstituted thiazolo[3,2-a]benzimidazole (see discussion Section G) and the effect of the nitro group on the chemical shift of the adjacent protons, it is impossible to unequivocably assign the position of the nitro group from the N.M.R. spectrum. Also, an unambiguous synthesis of either the 6- or 7-nitro derivative is impossible as it would involve the symmetrical 5-nitro-2-benzimidazolinethione.

Nitration of I actually occurred on the protonated species. When the reaction mixture was worked up without

basification nitrate salts of the products were obtained. The infrared spectrum showed strong bands at 1400 and 850 $cm.^{-1}$ for the nitrate ion vibrations in organic nitrates (59).

B. Chemical Proof for the Structure of 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III).

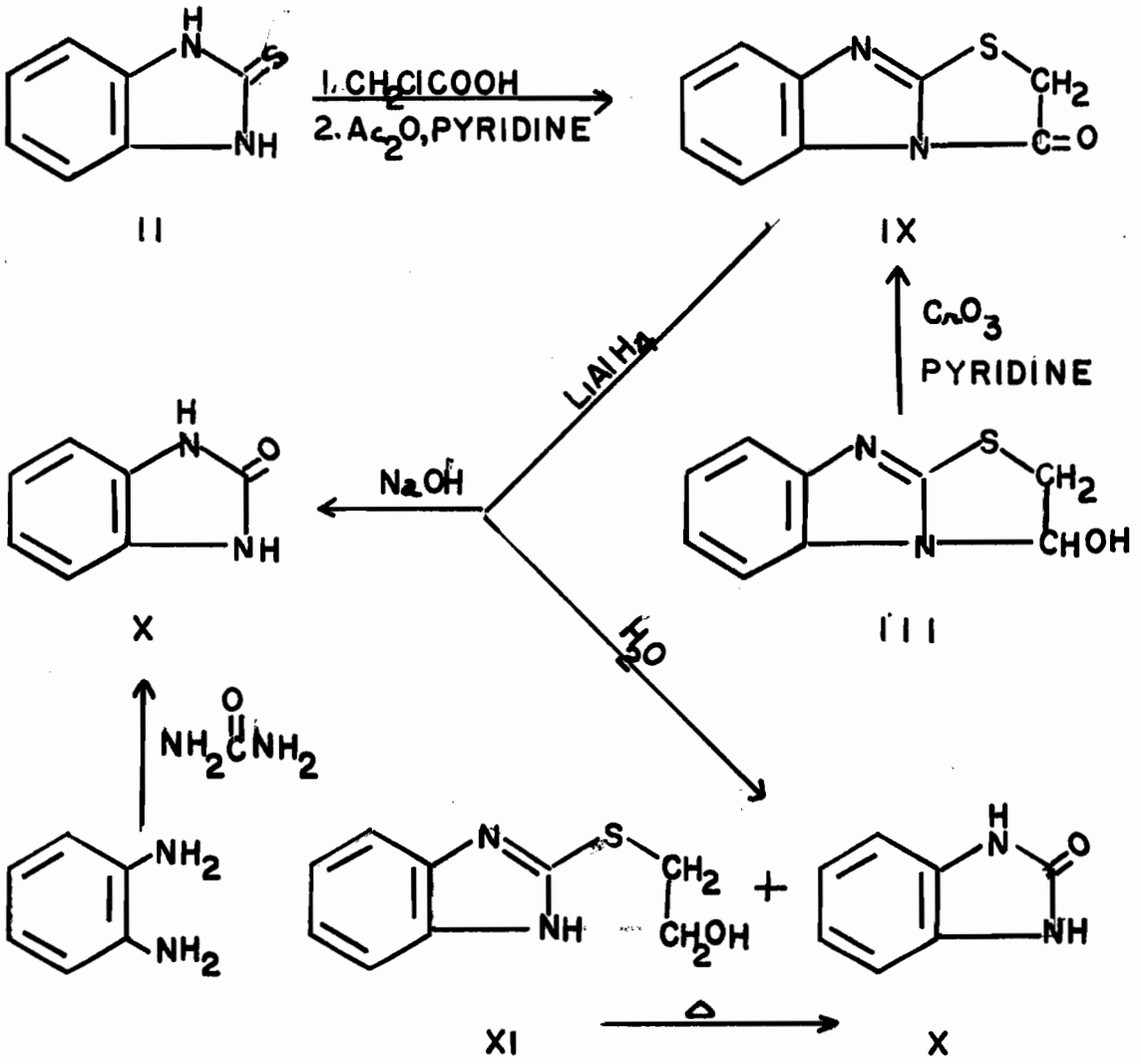
Previously, it was assumed that chloroacetaldehyde had reacted with 2-benzimidazolinethione (II) to form 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole and not the 2-hydroxy compound. The condensation product was proved to have the hydroxyl group in the 3-position by relating it to the known 3(2H)-thiazolo[3,2-a]benzimidazolone (IX).

IX was prepared according to Duffin and Kendall (5) as shown in Scheme 2. In this investigation 2-benzimidazolinethione (II) and chloroacetic acid gave a 94% yield of (2-benzimidazolylthio)acetic acid (VIII). Dehydration of VIII with acetic anhydride gave 3(2H)-thiazolo[3,2-a]benzimidazolone (IX) in 76% yield. Duffin and Kendall (5) concluded that the chloroacetic acid had reacted with the sulfur and not a nitrogen of II. The ultraviolet spectrum of VIII having λ_{max} 248.0 mμ (log ε = 3.79)*, 283.0 mμ (log ε = 4.11) and 291.0 mμ (log ε = 4.11) resembled that of 1-methyl-2-methylthiobenzimidazole (λ_{max} 285 mμ and 292.0 mμ) and not that of 1,3-dimethylbenzimidazolinethione (λ_{max} 321.0 mμ) (5).

In the ultraviolet spectrum of VIII between 400 and 200 mμ there was, in addition to the maxima noted by

*Obtained from the original data by using four-figure logarithms.

SCHEME 2


1. CH2ClCOOH
2. Ac2O, PYRIDINE
II
IX
CrO3
PYRIDINE
LiAlH4
NaOH
X
III
H2O
NH2CNH2
XI
Δ
X

Duffin and Kendall, a band at 209 mμ (log ε = 4.61). A similar band at 209 mμ (log ε = 4.47) not reported by Duffin and Kendall (5) was also observed in the ultraviolet spectrum of the 3(2H)-thiazolo[3,2-a]benzimidazolone (IX).

The infrared and N.M.R. spectra of IX were also recorded. Its infrared spectrum showed strong bands at 1742 $cm.^{-1}$ (C=O stretch of a fused γ-lactam) and 760 $cm.^{-1}$ (C-H out-of-plane bending for a 1,2-disubstituted benzene ring). The N.M.R. spectrum (DMSO - d_6) showed a complex multiplet between 8.0 and 7.0 p.p.m. for the four aromatic protons and a singlet at 4.5 p.p.m. for the methylene protons.

3(2H)-Thiazolo[3,2-a]benzimidazolone (IX) was reduced with lithium aluminum hydride as shown in Scheme 2. Using neutral work-up conditions 2-(2-benzimidazolylthio)-ethanol (XI) (50% yield) and benzimidazolinone (X) (39.6% yield) were obtained. The structure of XI was deduced from elemental analysis and spectral data. XI analyzed for $C_9H_{10}N_2OS$. Its infrared spectrum showed broad absorption between 3144 and 2720 $cm.^{-1}$ (hydrogen-bonded O-H and N-H stretch), a strong band at 1050 $cm.^{-1}$ (C-O stretch of a primary alcohol) and 745 and 735 $cm.^{-1}$ (C-H out-of-plane bending of a 1,2-disubstituted benzene). The infrared spectrum in chloroform solution showed a sharp band at 3447 $cm.^{-1}$ and a broad band at 3200 $cm.^{-1}$ for the bonded O-H and N-H stretching. The position and shape of the two bands

did not change on dilution. This indicates that there is intramolecular hydrogen bonding (59).

The N.M.R. spectrum of XI (DMSO-d_6-$CDCl_3$, 1:3) showed a complex multiplet between 7.4 and 6.6 p.p.m. assigned to the four aromatic protons, a singlet at 7.8 p.p.m. for the hydroxyl and amino protons, a triplet centered at 3.8 p.p.m. (J = 4.9 cps) for the methylene protons alpha to the hydroxyl group (71) and a triplet centered at 3.5 p.p.m. (J = 4.9 cps) for the methylene protons adjacent to the sulfur atom. The hydroxyl and amino protons occur together and it is probable that rapid exchange is taking place making them magnetically equivalent. After exchange with deuterium oxide the signal at 7.8 p.p.m. disappeared. In the N.M.R. spectrum of 2-ethylthiobenzimidazole the methylene protons adjacent to the sulfur gave a signal at 3.4 p.p.m. The additional shift of 0.1 p.p.m. to lower field in the N.M.R. spectrum of XI is due to the effect of the β-hydroxyl group (71). The ultraviolet spectrum of XI showed absorption maxima at 291 mμ (log ε = 4.29), 283 mμ (log ε = 4.28) and 210.5 mμ (log ε = 4.60). It closely resembled the ultraviolet spectrum of 2-ethylthiobenzimidazole which had maxima at 291 mμ, 283 mμ and 211 mμ.

2-(2-Benzimidazolylthio)ethanol (XI) when heated in air below its melting point was observed to change at 110° and a disagreeable mercaptan odor was noted. The new product

was identified as 2-benzimidazolinone (X) by comparison with an authentic sample. X had been prepared in 92% yield from o-phenylenediamine and urea (6). A sample of 2-(2-benzimidazolylthio)ethanol was dried in vacuo at 60° for 48 hours and then was heated at 110° under nitrogen. Transformation to X also occurred under these conditions. This would indicate that 2-benzimidazolinone is formed as a result of nucleophilic attack at the 2-position by the hydroxyl group of another molecule of XI.

In addition to 2-(2-benzimidazolylthio)ethanol (XI), 2-benzimidazolinone (X) was obtained in 40% yield. Hydrolysis of the thiol linkage of XI occurred in aqueous solution. Duffin and Kendall (5) had noted that compounds of this type were readily hydrolyzed.

When the lithium aluminum hydride reduction mixture was worked up with strong base, 2-benzimidazolinone was the only product isolated. The hydroxide ion increases the rate of hydrolysis by nucleophilic attack at C_2.

Reduction of an amide with lithium aluminum hydride usually gives the corresponding amine. However, when the amide has large bulky substituents on the nitrogen, or the nitrogen atom is part of a heteroaromatic system, reductive decomposition can occur (82). In 3(2H)-thiazolo[3,2-a]-benzimidazolone the nitrogen atom of the thiazolidone is part of the benzimidazole system and cleavage of the carbon-

nitrogen bond to give 2-(2-benzimidazolylthio)ethanol was observed.

The formation of 2-(2-benzimidazolylthio)ethanol from the reduction of 3(2H)-thiazolo[3,2-a]benzimidazolone (IX) is further proof that the carbonyl group of IX is adjacent to the bridgehead nitrogen.

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) was oxidized with chromic oxide in pyridine (Scheme 2). After twenty-two hours at room temperature 3(2H)-thiazolo-[3,2-a]benzimidazolone (IX) was isolated in 24% yield and 63% of the starting material was recovered. Chromic oxide in pyridine was selected as the oxidizing agent since it is sufficiently mild at room temperature not to affect olefinic double bonds, thioethers and other easily oxidizable linkages (7).

When the reaction time was extended to forty-eight hours (2-benzimidazolylthio)acetic acid (VIII) was also obtained in 8.4% yield with 0.6% of 2-benzimidazolinone (X). X was probably formed by hydrolysis of the acid VIII when the reaction mixture was dissolved in base. In his investigation of the oxidation of several alcohols in this manner Holum (7) usually detected trace amounts (3-10%) of the corresponding carboxylic acid in the product.

This oxidation of 3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (III) to the known 3(2H)-thiazolo[3,2-a]-

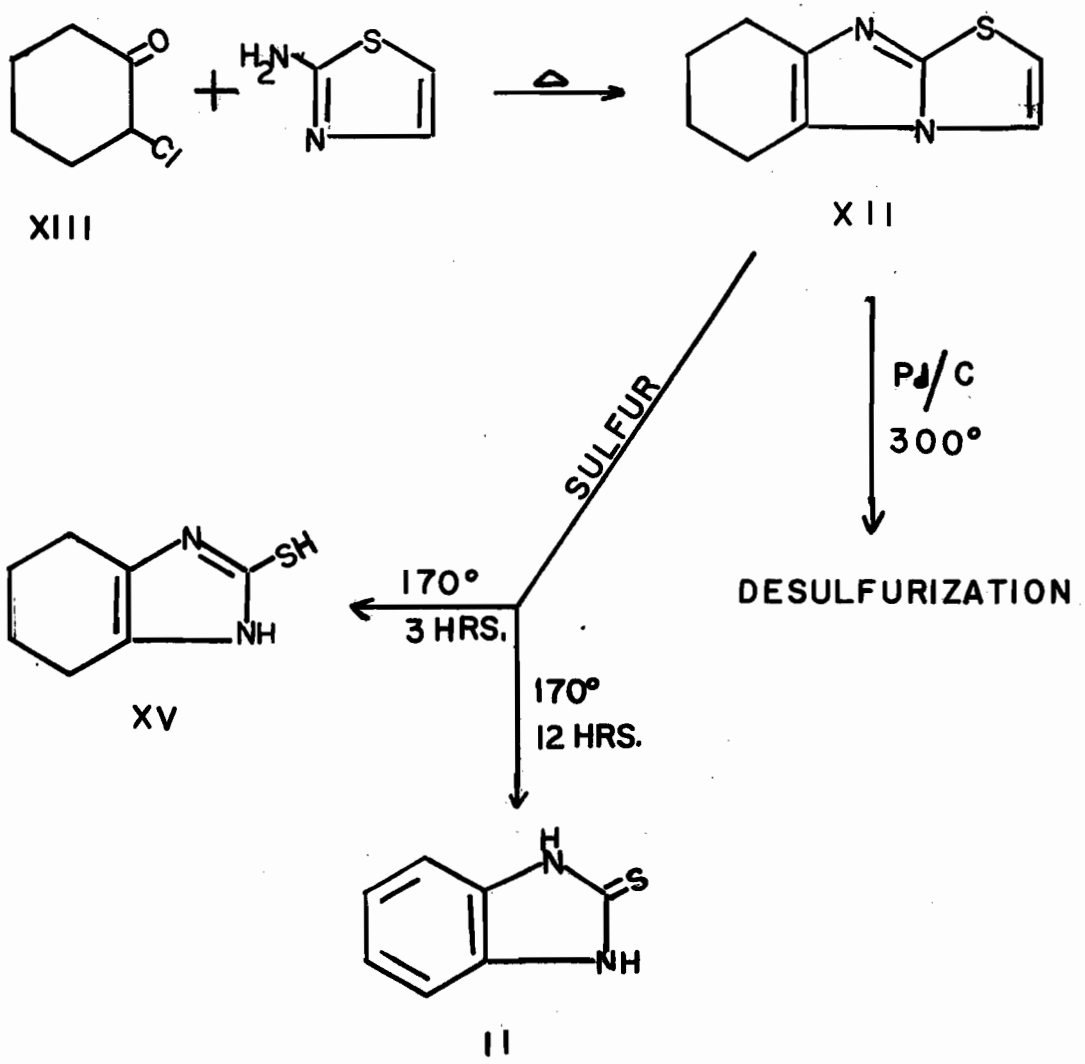
benzimidazolone (IX) is definite proof that the hydroxyl group is in the 3-position in III. Therefore, in the reaction of 2-benzimidazolinethione with an alpha-halocarbonyl compound the sulfur displaces the halide and the carbonyl group reacts with a nitrogen. Now that the direction of this condensation has been established, it will be possible to unambiguously assign the structures of the thiazolo[3,2-a]-benzimidazoles, substituted on the thiazole ring, synthesized in this investigation (see Section D).

C. Synthesis of 5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole (XII).

6,7,8,9-Tetrahydropyrido[1,2-a]benzimidazole, which can be dehydrogenated to pyrido[1,2-a]benzimidazole, was synthesized from 2-aminopyridine and 2-chlorocyclohexanone (74). 2-Aminopyridine and 2-aminothiazole are known to react similarly under many conditions (43,93). Therefore, this method was applied to the synthesis of thiazolo[3,2-a]benzi-midazoles as shown in Scheme 3.

2-Chlorocyclohexanone (XIII) was prepared in 58% yield by chlorination of cyclohexanone (2). Condensation of 2-amino-thiazole with 2-chlorocyclohexanone in the absence of solvent gave a 22% yield of 5,6,7,8-tetrahydrothiazolo[3,2-a]benzi-midazole (XII). The infrared spectrum of the product showed no absorption for the amino group, the carbonyl group, or the C-Cl bond. It did show, however, bands at 3116, 3090 and

SCHEME 3


XIII
XII
SULFUR
Pd/C
300°
DESULFURIZATION
170°
3 HRS.
XV
170°
12 HRS.
II

3043 $cm.^{-1}$ for the C-H stretch of the thiazole ring (75) as well as at 2937, 2916 and 2848 $cm.^{-1}$ for the C-H stretch of the methylene groups. The N.M.R. spectrum (CCl_4) showed a pair of doublets at 6.56 and 7.12 p.p.m. (J = 4.8 cps) for H_2 and H_3 respectively, a singlet at 2.43 p.p.m. for the four methylene protons adjacent to the imidazole ring; and a singlet at 1.75 p.p.m. for the four remaining methylene protons. No splitting was observed for the protons of the cyclohexane ring. The two singlets represent the average positions of two complex multiplets not resolved at 60 Mc. 5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole formed a stable, although very hygroscopic, quaternary methiodide.

Preparation of thiazolo[3,2-a]benzimidazole (I) was attempted by dehydrogenation of XII. Treatment of XII with palladium on charcoal at 300°, the conditions used for dehydrogenation of 6,7,8,9-tetrahydropyrido[1,2-a]benzimidazole (74), resulted in desulfurization. There are many examples in the literature of desulfurization of sulfur-heterocycles and other sulfur-containing compounds in the presence of such catalysts as palladium, platinum, and Raney nickel (76-79). It has been postulated (78) that the hydrogen liberated reacts with the sulfur in the presence of these catalysts to form hydrogen sulfide.

However, 3-thiazolines have been successfully dehydrogenated to thiazoles in the presence of sulfur at

120-140° (80) and tetralin and decalin have been converted to naphthalene with sulfur at higher temperatures (81). Treatment of 5,6,7,8-tetrahydrothiazolo[3,2-a]benzimidazole (XII) with sulfur at 170° for twenty hours resulted in decomposition as well as dehydrogenation to give 2-benzimidazolinethione. Heating XII with sulfur at 170° for three hours gave a product, m.p. 278-280°. This compound was tentatively identified as 2-mercapto-4,5,6,7-tetrahydrobenzimidazole (XV). Its infrared spectrum* showed bands at 2950 and 2850 $cm.^{-1}$ for the C-H stretch of the methylene groups, a band at 1440 $cm.^{-1}$ for the C-H deformation of the methylene groups, and a strong band at 1195 $cm.^{-1}$ for the C=S stretching but no bands in the 700-900 $cm.^{-1}$ region, for the C-H out-of-plane bending of hydrogens on a benzene ring or a double bond.

The N.M.R. spectrum (DMSO) of this product showed no signals for aromatic or olefinic protons. The broad hump at 11.6 p.p.m. was assigned to the two amino protons. In the N.M.R. spectra of other benzimidazoles in DMSO the protons on nitrogen occurred at low field (12.0-12.5 p.p.m.). It also showed a singlet at 3.6 p.p.m. for four methylene protons. Any further signals were hidden beneath the dimethyl sulfoxide bands.

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*This infrared spectrum was recorded on the Perkin-Elmer Model 137 instrument.

Therefore, decomposition of XII must occur prior to its dehydrogenation. Hence 5,6,7,8-tetrahydrothiazolo-[3,2-a]benzimidazole was not suitable for the synthesis of thiazolo[3,2-a]benzimidazole.

D. Syntheses of Substituted Thiazolo[3,2-a]benzimidazoles

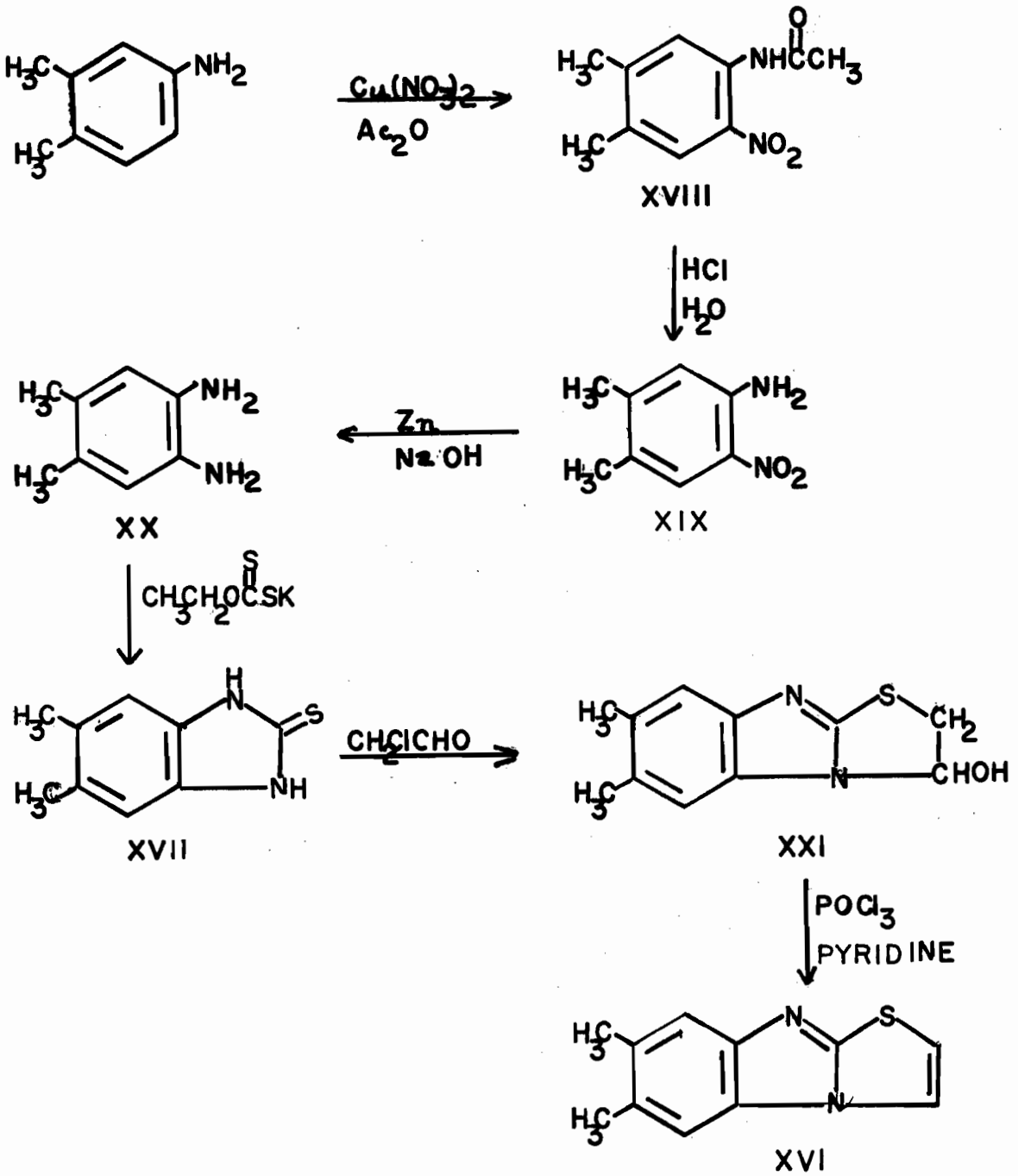
1. Substituted on the benzene ring

Thiazolo[3,2-a]benzimidazoles substituted on the benzene ring were synthesized by annelation of a thiazole ring to a suitably substituted 2-benzimidazolinethione.

(a) Synthesis of 6,7-Dimethylthiazolo[3,2-a]benzimidazole (XVI).

The synthesis of XVI from 3,4-dimethylaniline is outlined in Scheme 4. The method of Takatori and his co-workers (8) was followed to prepare the 5,6-dimethyl-2-benzimidazolinethione (XVII). In the present investigation nitration of 3,4-dimethylaniline in acetic anhydride gave 4,5-dimethyl-2-nitroacetanilide (XVIII) in 71% yield. Hydrolysis of XVIII to 4,5-dimethyl-2-nitroaniline (XIX) followed by reduction with zinc in sodium hydroxide gave an 81% yield of 4,5-dimethyl-o-phenylenediamine (XX). Reaction of XX with potassium ethyl xanthate gave 5,6-dimethylbenzimidazoline-thione (XVII) in 90% yield. The N.M.R. spectrum of XVII (DMSO-d_6) showed a singlet at 12.3 p.p.m. for the two amino protons, a singlet at 6.96 p.p.m. for the two protons on the benzene ring and a singlet at 2.25 p.p.m. for the two methyl groups. The equivalence of the two protons on the benzene ring and

SCHEME 4


Cu(NO3)2
Ac2O
XVIII
HCl
H2O
Zn
NaOH
XIX
XX
CH3CH2OC(=S)SK
XVII
CH2ClCHO
XXI
POCl3
PYRIDINE
XVI

the two methyl groups indicates that the two nitrogens are equivalent as in benzimidazole itself (83).

5,6-Dimethyl-2-benzimidazolinethione (XVII) was condensed with chloroacetaldehyde in 2-butanone to give 6,7-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXI) in 88% yield. Its infrared spectrum showed broad absorption between 3100 and 2500 $cm.^{-1}$ (hydrogen-bonded O-H stretch) and strong bands at 1046 and 1054 $cm.^{-1}$ (C-O stretch) and 848 $cm.^{-1}$ (C-H out-of-plane bending of a 1,2,4,5-tetrasubstituted benzene ring).

The N.M.R. spectrum of XXI (DMSO-d_6) showed two singlets at 7.26 and 7.12 p.p.m. for the two protons on the benzene ring. Superimposed on the singlet at 7.26 p.p.m. was a doublet ($J \approx 4$ cps) for the hydroxyl proton. The proton alpha to the hydroxyl group gave a multiplet at 6.30 p.p.m. At higher field the N.M.R. spectrum showed two quartets at 4.24 p.p.m. ($J = 12.0$ and $J = 5.9$ cps) and 3.64 p.p.m. ($J = 12.0$ and 2.3 cps) for the protons at C_2 cis and trans to the hydroxyl group at C_3 respectively, and a singlet at 2.28 p.p.m. for the two methyl groups. It is not unexpected that the individual coupling constants cannot be measured from the multiplet for the proton alpha to the hydroxyl group since the remainder of the spectrum has shown this proton to be split by the hydroxyl proton (4.0 cps) and by both hydrogens at C_2 (5.9 and 2.3 cps). Hence, the lines would be close

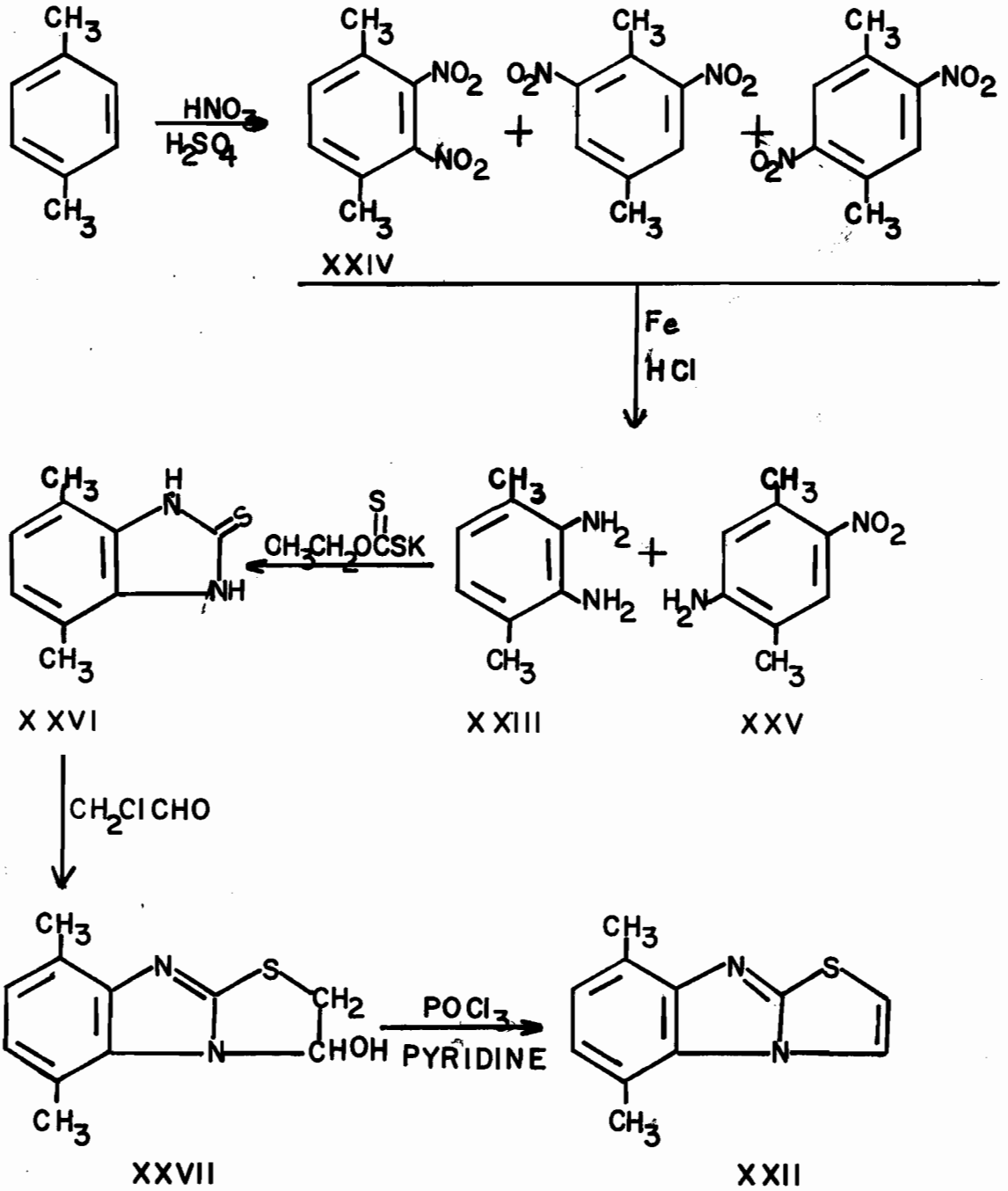
together and indistinguishable as observed. Addition of trifluoroacetic acid removed the hydroxyl proton. The aromatic region then showed only two singlets at 7.50 and 7.43 p.p.m. and the signal for proton alpha to the hydroxyl group became a distinct quartet (J = 2.3 and J = 5.9 cps).

6,7-Dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (XXI) was dehydrated with phosphorus oxychloride in pyridine to give 6,7-dimethylthiazolo[3,2-a]benzimidazole (XVI) in 78% yield. The infrared spectrum of the product showed no absorption due to the hydroxyl group. It did show a strong band at 840 $cm.^{-1}$ for the C-H out-of-plane bending of a 1,2,4,5-tetrasubstituted benzene ring. The N.M.R. spectrum of XVI ($CDCl_3$) showed two singlets at 7.52 and 7.26 p.p.m. for the protons on the benzene ring, a doublet at 7.46 p.p.m. (J = 4.6 cps) and a doublet at 6.63 p.p.m. (J = 4.6 cps) for H_3 and H_2 respectively, and a singlet at 2.3 p.p.m. for the two methyl groups.

(b) Synthesis of 5,8-Dimethylthiazolo[3,2-a]benzimidazole (XXII).

The synthesis of XXII from p-xylene is outlined in Scheme 5. The method of Smith (84) was used to prepare 3,6-dimethyl-o-phenylenediamine (XXIII) from p-xylene. The dinitration of p-xylene with a nitric-sulfuric acid mixture according to the procedure of Kobe (13) gave an 88.5% yield of a mixture of dinitro-p-xylenes. The N.M.R. spectrum of

SCHEME 5


HNO3
H2SO4
XXIV
Fe
HCl
CH3CH2OCSK
XXVI
XXIII
XXV
CH2ClCHO
XXVII
POCl3
PYRIDINE
XXII

the mixture ($CDCl_3$) showed three singlets at 7.94, 7.82 and 7.44 p.p.m. for aromatic protons. The signal at 7.44 p.p.m. accounted for 55% of the product and was assigned to H_5 and H_6 of the 2,3-dinitro-p-xylene which would be expected to occur at highest field as the nitro groups are meta and para to these protons. The singlet at 7.82 p.p.m. was tentatively assigned to H_3 and H_6 of 2,5-dinitro-p-xylene having nitro groups ortho and meta to them. The signal at lowest field (7.94 p.p.m.) probably arose from H_3 and H_5 of the 2,6-dinitro isomer deshielded by both ortho and para nitro groups. Assignments are not definite as the N.M.R. spectra of the separate isomers were not available for comparison and previous workers had not found 2,5-dinitro-p-xylene among the products of this nitration.

No attempt was made to separate the 2,3-dinitro-p-xylene. Reduction of the mixed dinitro-p-xylenes would give a mixture of amino compounds of which only the ortho diamine could condense with potassium ethyl xanthate to give a 2-benzimidazolinethione. A similar approach had been followed by Smith (84) in the preparation of 4,7-dimethylbenzimidazole. However, when the mixture of dinitro-p-xylenes was reduced with iron and hydrochloric acid the 3,6-dimethyl-o-phenylenediamine (XXIII) was easily separated in 41% yield. It was identified by its melting point, 72-74° (lit. m.p. 75°(12)), and spectral data.

XXIII absorbed in the infrared at 3360 and 3287 $cm.^{-1}$ (N-H stretch of a primary amine), 1612 $cm.^{-1}$ (N-H deformation) 1271 $cm.^{-1}$ (C-N stretch for a primary aromatic amine) and 791 $cm.^{-1}$ (C-H out-of-plane bending of a 1,2,3,4-tetrasubstituted benzene ring). Its N.M.R. spectrum ($CDCl_3$) showed a singlet at 6.52 p.p.m. for the aromatic protons, a singlet at 3.28 p.p.m. for the four amino protons and a singlet at 2.12 p.p.m. for the two methyl groups. It also showed that no other isomer was present.

A second product was isolated from the reduction mixture in 5% yield. It was identified as 2-amino-5-nitro-p-xylene (XXV) from its melting point, 142-144° (lit. m.p. 142° (21)), and spectral data. It exhibited infrared absorption at 3470 and 3375 $cm.^{-1}$ (N-H stretch of a primary amine), 1630 $cm.^{-1}$ (N-H deformation), 1516 $cm.^{-1}$ (NO_2 asym. stretch), 1360 $cm.^{-1}$ (sym. NO_2 stretch), and 858 $cm.^{-1}$ (C-H out-of-plane bending). The N.M.R. spectrum showed a singlet at 7.94 p.p.m. for the proton ortho to the nitro group, a singlet at 6.45 p.p.m. for the proton ortho to the amino group, a broad band centered at 4.08 p.p.m. for the amino protons, a singlet at 2.55 p.p.m. for the methyl group ortho to the nitro group and a singlet at 2.15 p.p.m. for the methyl protons ortho to the amine function. Isolation of XXV from the reduction of the mixture of dinitro-p-xylenes confirmed the presence of 2,5-dinitro-p-xylene in the mixture.

In the N.M.R. spectrum of a crude sample of XXV a contaminant was present having singlets at 7.26, 2.28 and 2.08 p.p.m. These signals are tentatively assigned to the two equivalent aromatic protons and two different methyl groups of 2,6-diamino-p-xylene. However, this compound was not isolated and identified.

2,3-Diamino-p-xylene (XXIII) was condensed with potassium ethyl xanthate to give 4,7-dimethyl-2-benzimidazoline-thione (XXVI) in 81% yield. The infrared spectrum of XXVI showed broad absorption between 3300 and 3100 $cm.^{-1}$ (hydrogen-bonded N-H stretch), a strong band at 1154 $cm.^{-1}$ (C=S stretch) and a strong band at 793 $cm.^{-1}$ (C-H out-of-plane bending for a 1,2,3,4-tetrasubstituted benzene ring). The N.M.R. spectrum (DMSO-d_6) showed singlets at 12.54 p.p.m. for the two amino protons, 6.70 p.p.m. for the two aromatic protons and 2.30 p.p.m. for the two methyl groups.

XXVI was condensed with chloroacetaldehyde in 2-butanone to give an 89% yield of 5,8-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXVII). The infrared spectrum of XXVII showed broad absorption between 3200 and 2700 $cm.^{-1}$ (hydrogen bonded O-H stretch), and strong bands at 1049 $cm.^{-1}$ (C-O stretch) and 810 $cm.^{-1}$ (C-H out-of-plane bending).

The N.M.R. spectrum of XXVII showed a singlet at 6.80 p.p.m. for the two aromatic protons superimposed on a broad signal for the hydroxyl group, an unresolved multiplet

for the proton alpha to the hydroxyl group, a quartet at 4.25 p.p.m. (J = 5.0 and J = 11.9 cps) for the proton at C_2 cis to the hydroxyl group, a doublet at 3.65 p.p.m. (J = 11.9 cps) for the other proton at C_2 and two singlets at 2.53 and 2.42 p.p.m. for the two methyl groups. The doublet at 3.65 p.p.m. showed some additional splitting in the order of 1 cps. After addition of trifluoroacetic acid the broad signal disappeared from the aromatic region and the multiplet at 6.32 p.p.m. became a quartet (J = 5.0 and J = 1.5 cps).

The hydroxyl proton appeared as a broad singlet although the spectrum was measured in DMSO. However, some coupling was occurring as evidenced by the effect of the hydroxyl proton on the shape of the signal for the proton alpha to it. Recently Tranynham and Knesel (87) have pointed out that the splitting of the hydroxyl proton in DMSO is not general. The failure to observe splitting may often be due to the presence of trace amounts of moisture. However even after drying over sodium carbonate they found that several alcohols gave a singlet for the hydroxyl proton.

5,8-Dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (XXVII) was dehydrated with phosphorus oxychloride in pyridine. The intermediate phosphate ester was the main product isolated after one hour. It gave a positive test for the presence of phosphorus and its infrared spectrum showed broad absorption between 2400 and 2700 $cm.^{-1}$ (P-OH stretch (59)).

This phosphate was converted quantitatively into 5,8-dimethyl-thiazolo[3,2-a]benzimidazole (XXII) by stirring in pyridine at room temperature. The infrared spectrum of the product showed no absorption for the hydroxyl group but did show a strong doublet at 808 and 844 $cm.^{-1}$ (C-H out-of-plane bending of a 1,2,3,4-tetrasubstituted benzene ring). The N.M.R. spectrum of XXII (Fig. 6) showed a doublet at 7.70 p.p.m. (J = 4.8 cps) and a doublet 6.68 p.p.m. (J = 4.8 cps) for the two protons on the thiazole ring. The aromatic region of the spectrum also showed an AB quartet for the two protons on the benzene ring. This AB spectrum was solved according to the method described by Roberts (85) locating the two protons at 7.02 and 6.82 p.p.m. (δ_{AB} = 11.1 cps) with J_{AB} = 7.5 cps. J_{AB} is comparable with the usual value for ortho coupling. (71). At higher field the N.M.R. spectrum showed two singlets at 2.64 and 2.55 p.p.m. for the two methyl groups.

2. Substitution on the Thiazole Ring

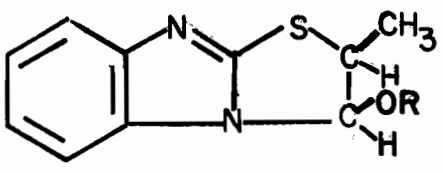
In addition to the thiazolo[3,2-a]benzimidazoles substituted on the benzene ring, derivatives substituted in the 2 or 3 position were prepared by condensation of 2-benzimidazolinethione (II) with the appropriate alpha-haloaldehyde or ketone. The position of the substituent could be given with certainty since the direction of the condensation reaction had been previously established. (See Section B).

(a) Synthesis of 2-Methylthiazolo[3,2-a]benzimidazole (XXVIII).

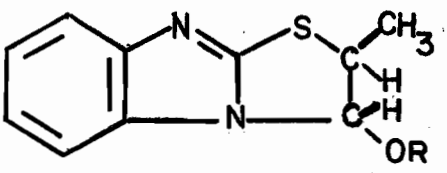
2-Methylthiazolo[3,2-a]benzimidazole (XXVIII) was synthesized as outlined in Scheme 6. An alpha-halopropionaldehyde was necessary for this synthesis. Chlorination of n-propyl ether, according to the procedure of Cusmano (15) and cleavage of the chlorinated products with sulfuric acid gave a 5% yield of alpha-chloropropionaldehyde. The yield was low since, as Summers (86) has shown, the main product obtained from chlorination of n-propyl ether is not α,β-dichloropropyl ether but rather α,β,β-trichloropropyl ether.

Condensation of 2-benzimidazolinethione (II) with the alpha-chloropropionaldehyde in 2-butanone gave 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXX) in quantitative yield. The infrared spectrum of XXX showed broad absorption between 3100 and 2800 $cm.^{-1}$ (hydrogen-bonded O-H stretch) and strong bands at 1039 $cm.^{-1}$ (C-O stretch) and 750 $cm.^{-1}$ (C-H out-of-plane deformation).

The N.M.R. spectrum (DMSO-d_6) of the crude product indicated that isomers A and B were present in the ratio 5:4. After purification the isomer distribution had not changed.



A

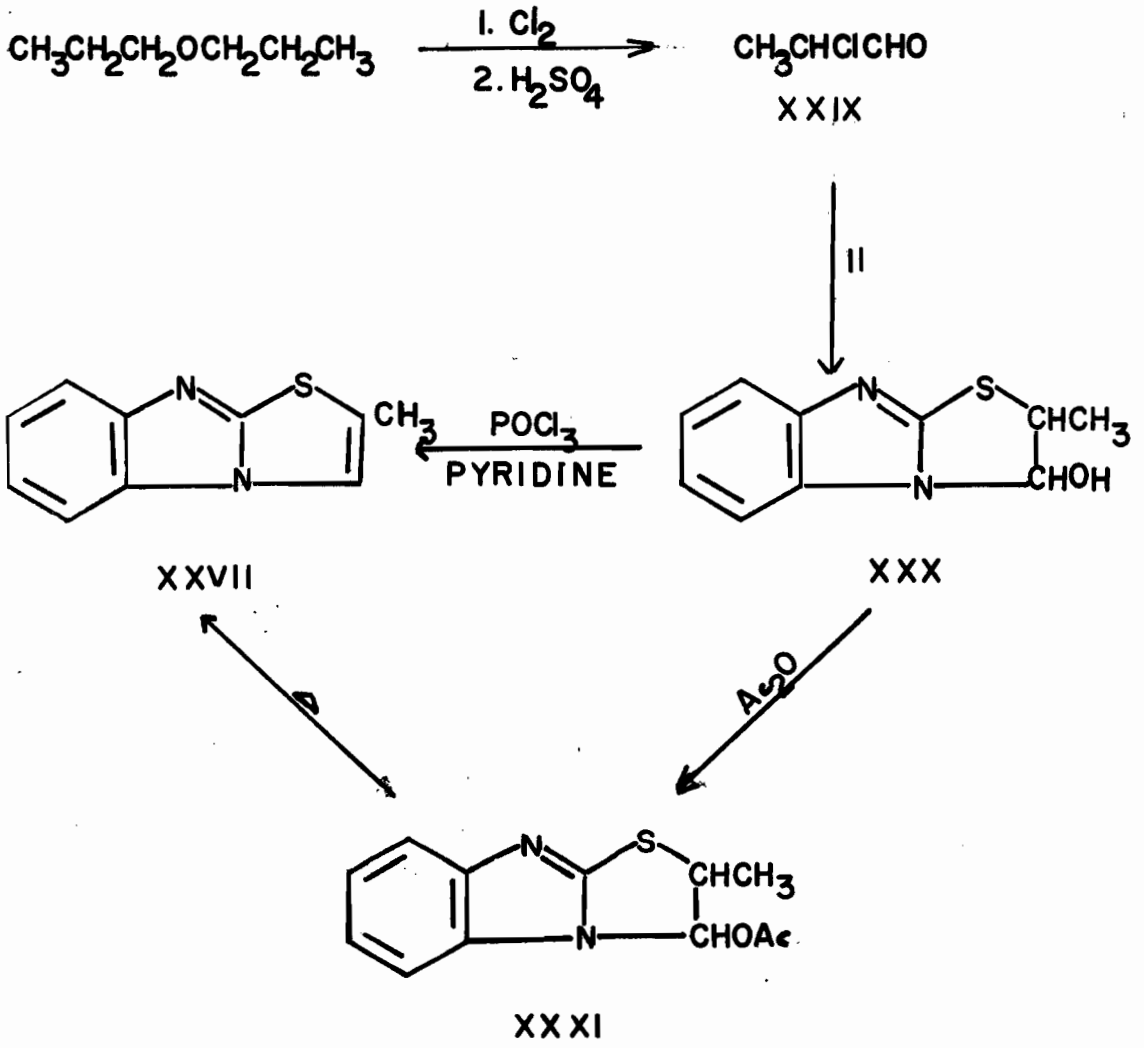


B

XXX R=H

XXXI R=C(=O)CH3

SCHEME 6


CH3CH2CH2OCH2CH2CH3
1. Cl2
2. H2SO4
CH3CHClCHO
XXIX
II
POCl3
PYRIDINE
CH3
CHCH3
CHOH
XXVII
XXX
Δ
Ac2O
CHCH3
CHOAc
XXXI

The complex multiplet between 7.6 and 6.9 p.p.m. is assigned to the aromatic protons of both isomers and the broad signal at 6.65 p.p.m. to their hydroxyl groups. The doublet at 5.98 p.p.m. is assigned to the proton alpha to the hydroxyl group in B coupled with the proton at C_2 (J = 5.2 cps) and the doublet at 5.82 p.p.m. (J = 2.0 cps) to the proton alpha to the hydroxyl group in A. The multiplet at 4.65 p.p.m. is for the proton at C_2 in B and the octet at 4.12 p.p.m. is for the C_2 proton of A coupled with the methyl group (J = 7.0 cps) and the proton at C_3 (J = 2.0 cps). The doublet at 1.4 p.p.m. is assigned to the methyl group of both isomers split by the proton alpha to it. After exchange with trifluoroacetic acid the signal at 6.65 p.p.m. disappeared.

The signal for the proton cis to the methyl group (isomer B) occurred 0.16 p.p.m. to lower field than that for the proton trans to the methyl group (isomer A). A similar effect was noted by Abraham (69). The N.M.R. spectrum of 2α-bromo-4,4,6-trimethylcholest-5-en-3-one showed that the methyl group at C_4 deshields the proton at C_2 by 0.17 p.p.m. Also, the signal for the proton at C_2, cis to the hydroxyl group (isomer B) occurred 0.53 p.p.m. to lower field than the corresponding proton in isomer A which is trans to the hydroxyl group. This effect of the hydroxyl group was already noted in the N.M.R. spectra of other 3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazoles.

Formation of this mixture of isomers indicated that the condensation reaction occurred non-stereospecifically as would be expected. In previous products this was not evident as there was no substituent at C_2 and the cis and trans products were not distinguishable. A suitable method for separation of isomers A and B was not found.

Acetylation of XXX gave the corresponding mixture of 3-acetoxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazoles (XXXI) which could not be separated. In an attempt to purify the acetate by distillation elimination of acetic acid occurred and 2-methylthiazolo[3,2-a]benzimidazole (XXVIII) was formed.

The infrared spectrum ($CHCl_3$ solution) of XXXI showed a strong band at 1748 $cm.^{-1}$ (C=O stretch of an ester). The N.M.R. spectrum of XXXI showed that A and B were present in the ratio 5:4. The signals were assigned as follows: the complex multiplet between 7.1 and 7.8 p.p.m. to the four aromatic protons of both isomers; the doublet at 7.0 p.p.m. to the proton alpha to the acetoxy group in isomer B coupled with the proton trans to it at C_2 by 5 cps; the singlet at 6.75 p.p.m. to the proton alpha to the acetoxy group in A; the octet at 4.78 p.p.m. to the proton at C_2 in B split by the methyl group (J = 7.0 cps) and further split by the proton at C_3 (5 cps); the quartet at 4.2 p.p.m. to the proton at C_2

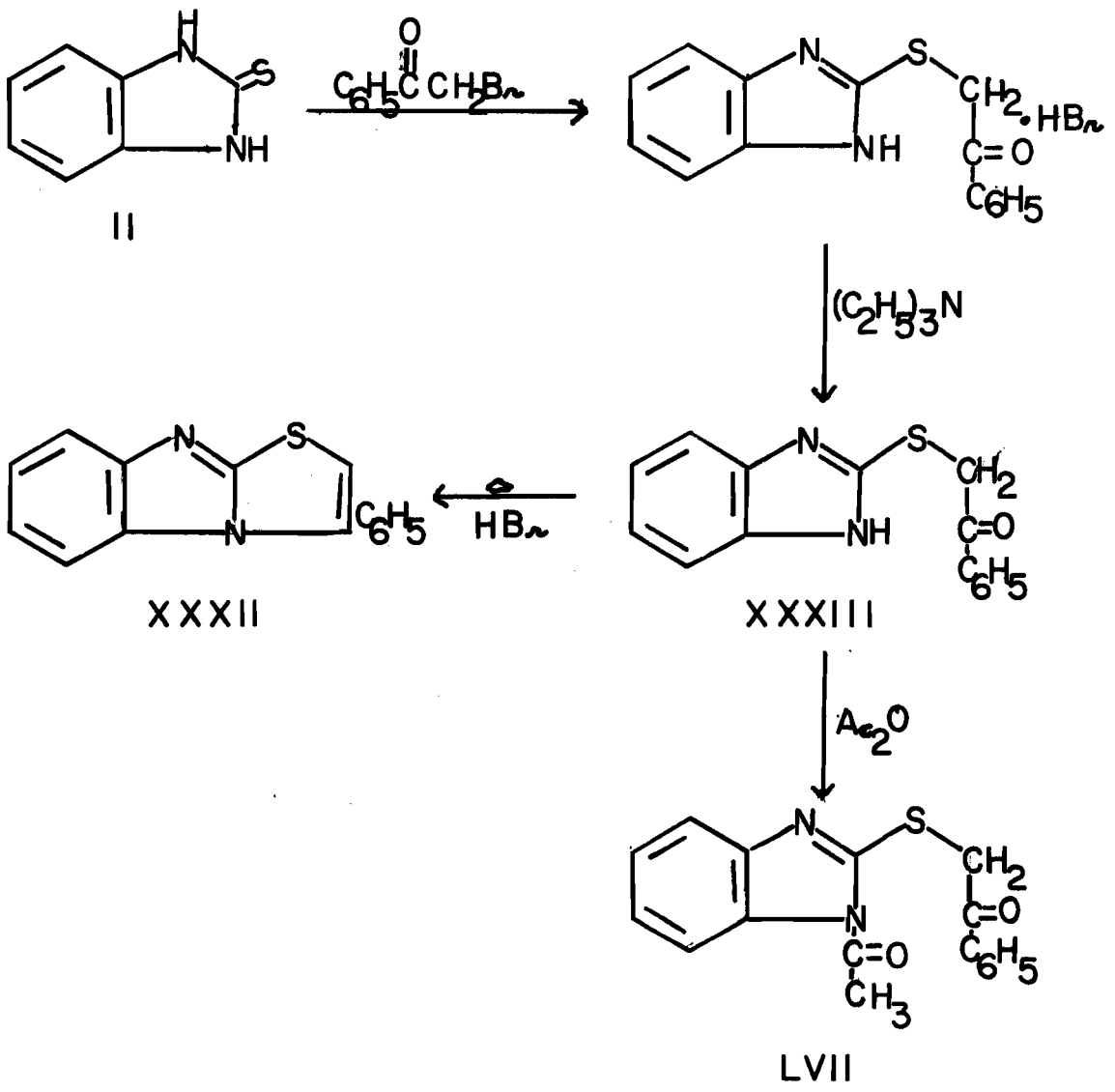
in A coupled with the adjacent methyl group (J = 7 cps); the singlet at 2.1 p.p.m. to the methyl protons of the acetate and the two doublets at 1.69 p.p.m. (J = 7.0 cps) and 1.63 p.p.m. (J = 7.0 cps) to the methyl groups at C_2 in A and B respectively.

Dehydration of 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXX) with phosphorus oxychloride in pyridine gave 2-methylthiazolo[3,2-a]benzimidazole (XXVIII) in 93% yield. The infrared spectrum of the product showed the absence of any absorption due to the hydroxyl group. The N.M.R. spectrum of XXVIII in $CDCl_3$ showed a doublet at 2.40 p.p.m. (J = 1.5 cps) assigned to the methyl group in the 2-position and a complex multiplet between 7.9 and 7.15 p.p.m. for the five aromatic protons. The strong signal for H_3 at 7.3 p.p.m. can be distinguished from this multiplet. The splitting of the methyl signal (J = 1.5 cps) is the result of coupling between the methyl protons and H_3. Similar splitting of the signals for the methyl protons in the N.M.R. spectra of 4-methyl- and 5-methylthiazole was observed by Taurins and Schneider (88).

2. Synthesis of 3-Phenylthiazolo[3,2-a]benzimidazole (XXXII)

The synthesis of 3-phenylthiazolo[3,2-a]benzimidazole (XXXII) is outlined in Scheme 7. Condensation of 2-benzimidazolinethione (II) and bromoacetophenone gave (2-benzimidazolylthio)acetophenone hydrobromide in quantitative yield.

SCHEME 7



This hydrobromide was insoluble in water. (2-Benzimidazolylthio)acetophenone (XXXIII) was obtained by treatment of the hydrobromide with triethylamine in ethanol. The infrared spectrum of XXXIII showed a broad absorption between 3100 and 2500 $cm.^{-1}$ (hydrogen-bonded N-H stretch) and strong bands at 1690 $cm.^{-1}$ (C=O stretch of an aryl ketone (59)), 739 $cm.^{-1}$ (C-H out-of-plane bending of the 1,2-disubstituted benzene) and 750 $cm.^{-1}$ (C-H out-of-plane bending for the phenyl group). In chloroform solution XXXIII absorbed in the infrared at 3458 $cm.^{-1}$ (non-bonded N-H stretch), at 3250 $cm.^{-1}$ (hydrogen-bonded N-H stretch) and 1683 $cm.^{-1}$ (C=O stretch).

The N.M.R. spectrum (DMSO-d_6) showed a complex pattern between 8.2 and 7.0 p.p.m. for the five protons of the phenyl group and the four protons of the benzimidazole system, a singlet at 5.06 p.p.m. for the methylene protons and a broad singlet at 4.6 p.p.m. for the amino proton. Comparison of the region between 8.2 and 7.0 p.p.m. with the N.M.R. spectra of other benzimidazoles and acetophenone (95) indicated that the ortho protons of the phenyl group gave a multiplet at 8.2 p.p.m. The signals for the remaining three phenyl protons were superimposed on the multiplet for the benzimidazole protons at approximately 7.6 p.p.m.

Treatment of XXXIII with acetic anhydride gave (2-N-acetylbenzimidazolylthio)acetophenone (LVII). The infrared spectrum of LVII showed the carbonyl absorption of the

amide as a doublet at 1700 and 1704 $cm.^{-1}$ The C=O stretch of the aryl ketone was essentially unchanged from the unacetylated product occurring at 1687 $cm.^{-1}$ In chloroform solution the amide carbonyl absorption occurred at 1716 $cm.^{-1}$ and that of the aryl ketone at 1683 $cm.^{-1}$ The high frequency of the amide carbonyl absorption may be due to the unavailability of the lone pair of electrons on the nitrogen atom (59,145). The N.M.R. spectrum of LVII ($CDCl_3$-DMSO-d_6) showed a complex multiplet between 8.2 and 7.1 p.p.m. for the nine aromatic protons with the signals for the ortho phenyl protons occurring at 8.16 p.p.m.; a singlet at 4.85 p.p.m. for the methylene protons and a singlet at 2.81 p.p.m. for the methyl protons of the acetyl group.

(2-Benzimidazolylthio)acetophenone (XXXIII) was resistant to cyclization and refluxing in fuming hydrobromic acid was necessary to give a 43% yield of 3-phenylthiazolo-[3,2-a]benzimidazole (XXXII). 2-Benzimidazolinethione (II) was also formed. This was not unexpected as thio ethers are known to cleave to mercaptans and alkyl halides when heated with hydrogen halides (94). The infrared spectrum of the product showed no carbonyl or N-H absorption indicating that cyclization had occurred. The N.M.R. spectrum ($CDCl_3$) showed a singlet at 6.6 p.p.m. assigned to H_2 and a complex multiplet between 7.0 and 8.1 p.p.m. for the four protons on the benzene ring. Superimposed on this multiplet was the strong signal for the five protons of the phenyl group at 7.5 p.p.m.

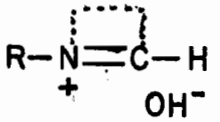
(c) Synthesis of 3-Methylthiazolo[3,2-a]benzimidazole (XXXIV).

The preparation of XXXIV is outlined in Scheme 8. Condensation of 2-benzimidazolinethione (II) and chloroacetone in 2-butanone gave a 97% yield of 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXXV). The condensation was also carried out in ethanolic potassium hydroxide to give an 85% yield of the same product. XXXV is actually a tautomeric mixture. Its structure and spectra are discussed in detail in Section E.

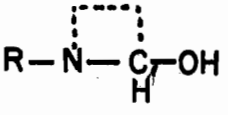
XXXV was readily cyclized to 3-methylthiazolo[3,2-a]-benzimidazole (XXXIV) by either phosphorus oxychloride (85% yield) or dilute hydrochloric acid (quantitative yield). The N.M.R. spectrum ($CDCl_3$) of XXXIV showed a complex multiplet between 7.9 and 7.0 p.p.m. for the four protons on the benzene ring, a quartet at 6.11 p.p.m. (J = 1.5 cps) for H_2 coupled with the adjacent methyl group and a doublet at 2.59 p.p.m. (J = 1.5 cps) for the methyl group at C_3.

E. Tautomerism of 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazoles.

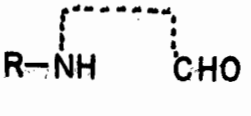
The 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazoles are potentially tautomeric carbinol amines. Three structures have been postulated for tautomeric systems of



1
quaternary ammonium hydroxide

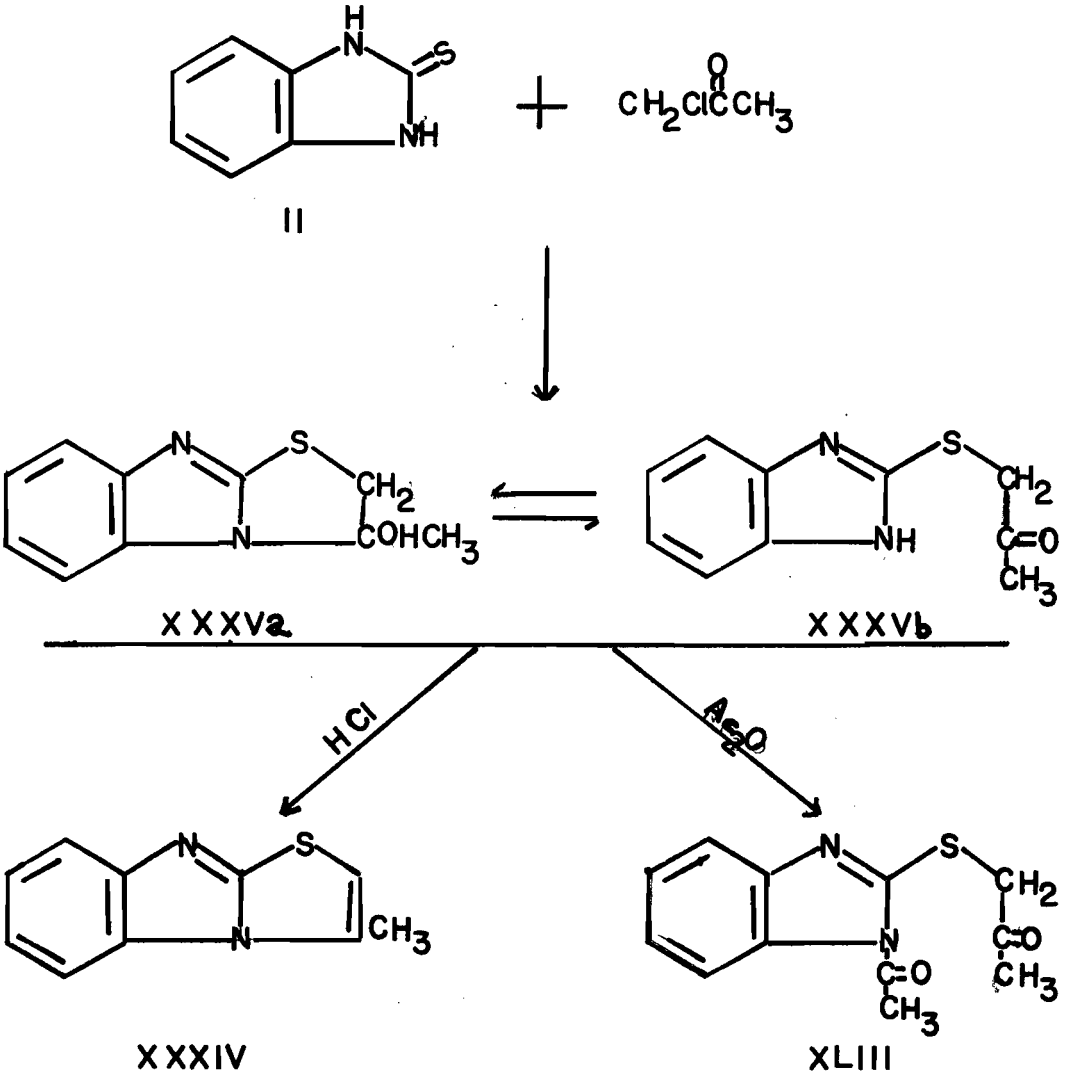


2
pseudo base carbinol amine



3
amino aldehyde

SCHEME 8



this type. However, the three tautomers have never been shown to exist simultaneously (89).

The structures of the carbinol amines obtained in the syntheses of thiazolo[3,2-a]benzimidazoles were studied mainly by spectral methods. The infrared spectra of the compounds as potassium bromide discs unambiguously determined their structure in the solid state. However, tautomeric equilibria of this type occur only in solution or in the liquid or gaseous states (89). Infrared spectra measured in solution were helpful but N.M.R. spectra were found most useful in these investigations. A few derivatives were prepared. However, it is essential to note that a derivative can be produced from a very minor tautomer and therefore its formation cannot be the only criterion in establishing the structure of the carbinol amine.

The hydroxy compounds unsubstituted on the thiazole ring, i.e. 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III), 5,8-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXVII) and 6,7-dimethyl-3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (XXI) as well as 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXX) exist only in the carbinol amine form. The infrared spectra of these compounds in the solid state (Table I) showed broad absorption between 3200 and 2600 $cm.^{-1}$ for the hydrogen bonded O-H stretch and a strong band between 1040 and 1050 $cm.^{-1}$ for the C-O stretch.

A broad band of medium intensity between 1300 and 1337 $cm.^{-1}$ was tentatively assigned to the O-H deformation. Deuterium studies would confirm this assignment. These alcohols also showed intense absorption 100-130 $cm.^{-1}$ above the C-O stretching frequency, however, the origin of this band is unknown. The low frequency of the C-O stretching vibration (below 1050 $cm.^{-1}$) indicated that these were cyclic, secondary alcohols (61,117).

TABLE I

Infrared Absorption ($cm.^{-1}$) of the 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazoles as KBr Pellets

Compound	O-H Stretch	O-H Deformation	C-O Stretch	?
Unsubstituted (III)	3200-2600	1320	1040	1167
5,8-Dimethyl (XXVII)	3200-2600	1308	1049	1177
6,7-Dimethyl* (XXI)	3200-2600	1319	1046,1054	1178,1166
2-Methyl (XXX)	3200-2600	1337	1039	1137
3-Methyl (XXXV)	3200-2600	1345	1085	1206

*The C-O stretching vibration and the band at 1178 $cm.^{-1}$ were split. This may be due to intermolecular association occurring in the solid state (70).

None of these alcohols was sufficiently soluble to permit the study of their infrared spectra in solution.

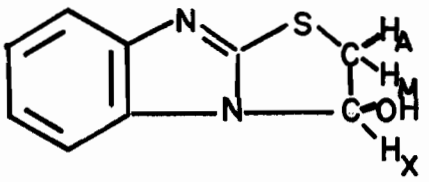
The N.M.R. spectra of III, XXVII, XXI and XXX in DMSO-d_6 demonstrated that these carbinol amines existed only as cyclic alcohols in this solvent. No other tautomer was

present in an amount detectable by N.M.R. (< 5%). After exchange with trifluoroacetic acid (to remove the hydroxyl proton) the spectra of III, XXVII and XXI showed an AMX pattern for the three protons on the thiazolidine ring (Table II).

The protons at C_2 are non-equivalent and couple with each other by -12.0 cps (geminal couplings are usually negative (64)), indicating a cyclic structure. The methylene protons in the N.M.R. spectra of 2-ethylthiobenzimidazole (VI), 2-(2-benzimidazolylthio)ethanol (XI) and (2-benzimidazolylthio)acetic acid (VIII) are equivalent and occur as a singlet in each case. Further evidence for the cyclic structure is the fact that H_A and H_M couple differently with the vicinal proton, H_X, due to the different dihedral angles each makes with H_X, indicating a cis and trans relationship.

TABLE II

Chemical Shifts and Coupling Constants of the Non-aromatic Protons of some 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazoles. (Spectra measured in DMSO-d_6.)



H_A is cis to OH

H_M is trans to OH

Compound	H_X	H_A	H_M	J_{AX}	J_{MX}	J_{AM}
	(p.p.m.)*			(cps)		
Unsubstituted (III)	6.30	4.30	3.69	6.0	2.1	-12.0
5,8-Dimethyl (XXVII)	6.32	4.25	3.65	5.0	1.5	-11.9
6,7-Dimethyl (XXI)	6.30	4.24	3.64	5.9	2.3	-12.0

*The values for the chemical shifts are those observed prior to exchange with trifluoroacetic acid. On addition of trifluoroacetic acid the entire spectrum was shifted to lower field.

The N.M.R. spectrum of 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXX) was discussed in Section D. The fact that two isomers existed, one having the methyl and hydroxyl substituents cis and the other having these groups trans indicated that XXX must have a thiazolidine ring.

The ultraviolet spectra of these compounds are not suitable for studying the tautomerism between the carbinol amine and amino aldehyde forms. The open-chain 2-substituted benzimidazoles, e.g. 2-ethylthiobenzimidazole (VI) and the cyclic 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazoles have ultraviolet absorption maxima at the same positions.

The reactions of the 3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazoles were, in general, typical of the carbinol amine structure. 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) and the 2-methyl derivative (XXX) were readily acetylated with acetic anhydride at room temperature to give the O-acetyl derivatives IV and XXXI, respectively, and not N-acetylated products. The infrared spectrum of IV ($CHCl_3$ solution) had carbonyl absorption at 1750 $cm.^{-1}$ and that of XXXI at 1748 $cm.^{-1}$ for the C=O stretching of an ester. The N-acetyl derivative would be expected to have a lower carbonyl stretching frequency.

The N.M.R. spectra of the acetates also indicated that the cyclic O-acetyl derivatives had been formed. The N.M.R. spectrum of IV showed an AMX pattern for the three protons on the thiazolidine ring and that of XXXI indicated that it was a mixture of cis and trans isomers.

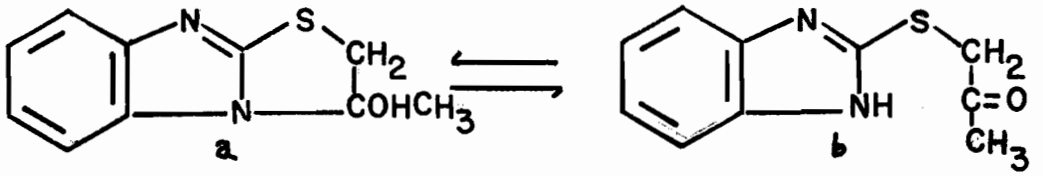
Carbinol amines are known to form alkyl ethers easily with alcohols (89). The ethyl ethers corresponding to

3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) and 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXX) were formed as by-products (indicated by the N.M.R. spectrum of the crude products) in the preparation of III and XXX in ethanol solution. Refluxing III in ethanol containing hydrochloric acid gave 3-ethoxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (V).

Further proof for the cyclic carbinol amine structure of III was its oxidation with chromic oxide and pyridine (Section B) to 3(2H)-thiazolo[3,2-a]benzimidazolone (IX). The only evidence of III being potentially tautomeric is the fact that in acetic anhydride and pyridine it underwent N-acetylation as the first step in the formation of 2-acetyl-thiazolo[3,2-a]benzimidazole (XXXVI) (Section F).

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXXV) was also synthesized. The infrared spectrum of XXXV as a KBr pellet indicated that it existed in the cyclic carbinol amine form in the solid state. It showed broad absorption between 3200 and 2600 $cm.^{-1}$ for the O-H stretch of the hydrogen-bonded hydroxyl group, a strong band at 1085 $cm.^{-1}$ for the C-O stretch of a tertiary alcohol, a broad band of medium intensity at 1345 $cm.^{-1}$ for the in-plane O-H deformation and a strong band at 1206 $cm.^{-1}$ of unknown origin.

In solution, however, XXXV was a mixture of the carbinol amine (a) and the open-chain ketone (b). The infra-



XXXV

red spectrum of XXXV in chloroform solution showed a sharp band at 3650 $cm.^{-1}$ (free O-H stretch), a broad band at 3554 $cm.^{-1}$ (bonded O-H stretch), a sharp band at 3448 $cm.^{-1}$ (free N-H stretch), a broad band at approximately 3250 $cm.^{-1}$ (bonded N-H stretch) and a band of medium intensity at 1715 $cm.^{-1}$ (C=O stretch). The free N-H stretch of benzimidazoles usually occurs between 3470 and 3400 $cm.^{-1}$ (96).

The N.M.R. spectrum (DMSO-d_6) indicated that the tautomers XXXVa and XXXVb were present in a 1:2 ratio in this solvent (Fig. 7). It showed a complex multiplet for the four aromatic protons of both forms and the hydroxyl proton of XXXVa between 7.72 and 6.95 p.p.m., a singlet at 4.35 p.p.m. for the methylene protons of XXXVb, a quartet centered at 3.94 p.p.m. for the protons at C_2 in XXXVa, a singlet at 2.32 p.p.m. for the methyl protons of the keto form and a singlet at 1.94 p.p.m. for the methyl protons of XXXVa. The quartet at 3.94 p.p.m. is an AB pattern for the non-equivalent methylene protons of the cyclic form XXXVa. The chemical shift and coupling constant were calculated in the usual manner (85) to give δ_{AB} = 8.8 cps and J_{AB} = 11.5 cps. Therefore the two protons absorb at 4.08 and 3.79 p.p.m. It is impossible to determine unambiguously which proton gave which signal. However, it is

probable, from the effects of opposite substituents observed in these compounds, that the proton cis to the hydroxyl group gives the signal at lower field (4.08 p.p.m.).

D'Amico (17) had reported the preparation of (2-benzimidazolylthio)propan-2-one (XXXVb) from 2-benzimidazolinethione (II) and chloroacetone but gave no evidence for its tautomerism. A sample of D'Amico's product, which he was kind enough to send, was proved to be identical in all respects with our product XXXV and hence a mixture of tautomers (a) and (b).

Treatment of XXXV with acetic anhydride at room temperature gave (2-N-acetylbenzimidazolylthio)propan-2-one (XLIII) by acetylation of the open chain ketone, XXXVb. The infrared spectrum of XLIII in the solid state indicated that it was the N-acetyl derivative. It showed no absorption above 3100 $cm.^{-1}$ for the N-H stretch but it did show a strong band at 1707 $cm.^{-1}$ (C=O stretch). In chloroform solution the carbonyl stretching vibration appeared at 1716 $cm.^{-1}$ The carbonyl absorption would occur at higher frequency ca. 1750 $cm.^{-1}$ in the O-acetyl compound. Nevertheless, for the N-acetyl derivative two bands were expected in this region, one for the C=O stretch of the amide occurring at lower frequency and one for the C=O stretch of the ketone. For this amide the frequency of the carbonyl stretch is raised as the lone pair of electrons on the nitrogen is involved in the aromatic benzimidazole system and

cannot take part in resonance with the adjacent carbonyl group (59,145). The carbonyl stretch for the acetyl group in (2-N-acetylbenzimidazolylthio)acetophenone occurred at 1716 $cm.^{-1}$ in chloroform solution and the keto form of XXXV showed carbonyl stretching at 1715 $cm.^{-1}$ in chloroform solution. Therefore, XLIII is the N-acetyl derivative having the carbonyl stretching of the amide superimposed on that of the keto group at 1716 $cm.^{-1}$ Also, a strong band at 1250 $cm.^{-1}$ would be expected for the C-O stretch of the O-acetyl derivative but no strong absorption was found in this region.

The N.M.R. spectrum ($CDCl_3$) confirmed that XLIII was the N-acetyl compound. It showed a complex multiplet between 7.7 and 7.1 p.p.m. for the four aromatic protons, a singlet at 4.10 p.p.m. for the methylene protons, a singlet at 2.75 p.p.m. for the acetyl group and a singlet at 2.40 p.p.m. for the methyl group of the ketone. The methyl protons of the unacetylated keto form (XXXVb) gave a signal at 2.32 p.p.m. in its N.M.R. spectrum (in DMSO) supporting the assignment of the signals at high field. The fact that the methylene protons gave a singlet indicated that XLIII was the N-acetyl derivative. There was no evidence for the cyclic O-acetate even in the N.M.R. spectrum of the crude reaction product. Acetylation of carbinol amines can result in the formation of both O- and N-acetylated products as was observed for the alkaloid Contarnin (90).

When 2-benzimidazolinethione was condensed with bromoacetophenone, (2-benzimidazolylthio)acetophenone (XXXIII) was formed (Section E). This product existed only as the open-chain ketone both in the solid state and in solution. It showed no evidence of tautomerism with the cyclic carbinol amine or the quaternary hydroxide. Its infrared spectrum as a KBr pellet showed absorption between 3100 and 2500 $cm.^{-1}$ (bonded N-H stretch) and a strong band at 1690 $cm.^{-1}$ (C=O stretch of the phenyl ketone). In chloroform solution the infrared spectrum showed a sharp band at 3458 $cm.^{-1}$ (free N-H stretch) and a strong band at 1683 $cm.^{-1}$ (C=O stretch). The N.M.R. spectrum of XXXIII (DMSO-d_6) also showed no evidence for tautomerism. Besides the complex signal for the nine aromatic protons it showed a singlet at 5.06 p.p.m. for the methylene protons.

Treatment of XXXIII with acetic anhydride at room temperature gave the corresponding N-acetyl derivative (LVII). The infrared and N.M.R. spectra of LVII confirmed its open-chain structure. The infrared spectrum of (2-N-acetylbenzimidazolylthio)acetophenone (LVII) showed carbonyl absorption at 1704 and 1700 $cm.^{-1}$ for the N-acetyl group and at 1687 $cm.^{-1}$ for the phenyl ketone. In chloroform solution the carbonyl stretch of the amide occurred at 1717 $cm.^{-1}$ and that of the ketone at 1685 $cm.^{-1}$ The methylene protons of LVII gave a singlet at 4.85 p.p.m. and its methyl protons a singlet at

2.81 p.p.m. in the N.M.R. spectrum ($CDCl_3$).

The compounds studied in this investigation existed mainly in the carbinol amine form; however, substitution alpha to the hydroxyl group increased their tendency to tautomerize to an amino aldehyde. No evidence for the quaternary ammonium hydroxide was noted. This is not unexpected as the tautomerism depends on the strength of the C-N and O-H bonds. Electron-repelling substituents on the nitrogen increase the strength of the C-N bond and favor tautomerism to the hydroxide. Electron-withdrawing substituents on the nitrogen, however, weaken the C-N bond and ring opening can occur. In the 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazoles the nitrogen atom of the carbinol amine is part of the benzimidazole system and the latter effect predominates. Substituents on the carbon atom can also influence the electron density. The methyl and phenyl substituents in XXXV and XXXIII can supply electrons to the carbon atom and hence aid the cleavage of the C-N bond.

This tautomerism can be viewed as the equilibrium reaction in the condensation of an amine with an aldehyde or a ketone. The methyl group and even more the phenyl group stabilize the carbonyl form, the former by the inductive effect and the latter to a greater extent by the resonance effect (109).

F. Rearrangement of the 3-Hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazoles Under Acetylating Conditions.

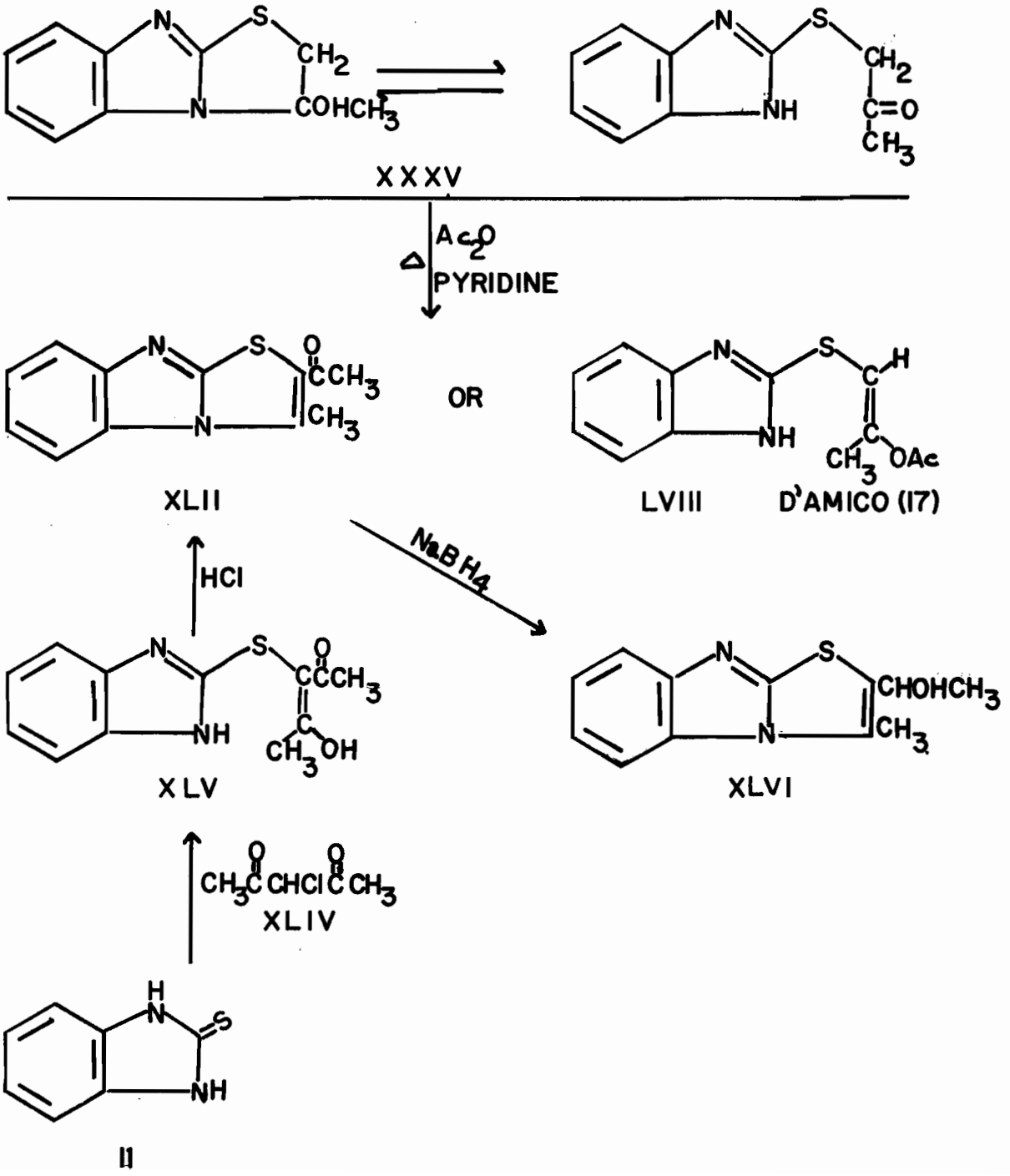
The 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazoles were readily acetylated with acetic anhydride at room temperature (Section E). However, treatment with acetic anhydride and pyridine at higher temperatures gave different products for 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) and 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole (XXXV). The products were identified and the mechanism of this reaction was established.

1. 3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole XXXV.

Treatment of XXXV with acetic anhydride and pyridine gave a white solid XLII, m.p. 164-165° (Scheme 9). D'Amico (17) had reported that this reaction gave the enol acetate (2-benzimidazolylthio)-1-propen-2-ol acetate (LVIII). XLII was identified as 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole and not the enol acetate from spectral data, chemical reactions and synthesis.

The infrared spectrum of the product showed no absorption above 3100 $cm.^{-1}$ It did show strong bands at 1646 $cm.^{-1}$ (C=O stretch of a conjugated ketone), 1483 $cm.^{-1}$ (the thiazolo-[3,2-a]benzimidazole ring system) and 746 and 740 $cm.^{-1}$ (C-H out-of-plane deformation of a 1,2-disubstituted benzene ring). Also, the intensities of the bands between 1500 and 1600 $cm.^{-1}$, for the C=C and C=N stretching, were greatly enhanced compared

SCHEME 9


XXXV
Ac2O
PYRIDINE
OR
XLII
LVIII
D'AMICO (17)
NaBH4
HCl
XLV
XLVI
XLIV
II

to those in the infrared spectrum of thiazolo[3,2-a]benzimidazole (I), indicating conjugation of the heteroaromatic system with the carbonyl group (59). In chloroform solution the carbonyl absorption occurred at 1672 $cm.^{-1}$ The enol acetate (LVIII) would be expected to show bands for the N-H stretch and C-O stretch which were not observed and the carbonyl absorption would occur above 1700 $cm.^{-1}$ (70).

In the N.M.R. spectrum of XLII ($CDCl_3$) there was a complex multiplet between 7.8 and 7.0 p.p.m. for the four aromatic protons, a singlet at 2.95 p.p.m. for the methyl group at C_3, and a singlet at 2.47 p.p.m. for the methyl protons of the acetyl group. The methyl group in 2-acetylthiazolo[3,2-a]benzimidazole (XXXVI) gave a signal at 2.45 p.p.m. in the N.M.R. spectrum, confirming the assignment of the two singlets at high field.

XLII formed a 2,4-dinitrophenylhydrazone, m.p. 271-273°, indicating an aldehyde or a ketone. Also, iodoform was precipitated when XLII was treated with sodium hypoiodite which indicated that it was a methyl ketone.

2-Acetyl-3-methylthiazolo[3,2-a]benzimidazole was reduced with sodium borohydride to give the secondary alcohol 2-(1-hydroxyethyl)-3-methylthiazolo[3,2-a]benzimidazole (XLVI) in 80% yield. Its infrared spectrum showed a broad band centered at 3221 $cm.^{-1}$ (bonded O-H stretch), a strong band at 1477 $cm.^{-1}$ (the thiazolo[3,2-a]benzimidazole ring system), a

strong band at 1081 $cm.^{-1}$ (C-O stretch of a secondary alcohol) and two strong bands at 753 and 745 $cm.^{-1}$ (C-H out-of-plane bending for a 1,2-disubstituted benzene ring). The ultraviolet spectrum of XLVI showed absorption maxima at 270 mμ (log ε = 4.14), 247 mμ (log ε = 4.40), 240 mμ (log ε = 4.41) and 214 mμ (log ε = 4.55) indicating that the thiazolo[3,2-a]-benzimidazole ring system was present in this alcohol and therefore in the ketone (XLII). The parent compound thiazolo [3,2-a]benzimidazole (I) showed ultraviolet absorption (Fig. 8) at 273 mμ (log ε = 3.99), 247 mμ (log ε = 4.16), 241 mμ (log ε = 4.19) and 214 mμ (log ε = 4.47).

D'Amico and his co-workers (17) had prepared 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole, however, they had not identified it with their product from the reaction of XXXV with acetic anhydride in pyridine. Therefore 2-acetyl-3-methyl-thiazolo[3,2-a]benzimidazole was synthesized according to their procedure as shown in Scheme 9 to ascertain whether the two products were identical.

In this investigation 3-chloro-2,4-pentanedione (XLIV) was obtained in 80% yield by chlorination of acetylacetone. Condensation of XLIV with 2-benzimidazolinethione (II) gave a 90% yield of 3-(2-benzimidazolylthio)-2,4-pentanedione (XLV). XLV was cyclized either with hydrochloric acid or on treatment with acetic anhydride in pyridine to give 2-acetyl-3-methyl-thiazolo[3,2-a]benzimidazole in 93% yield. The infrared spectrum

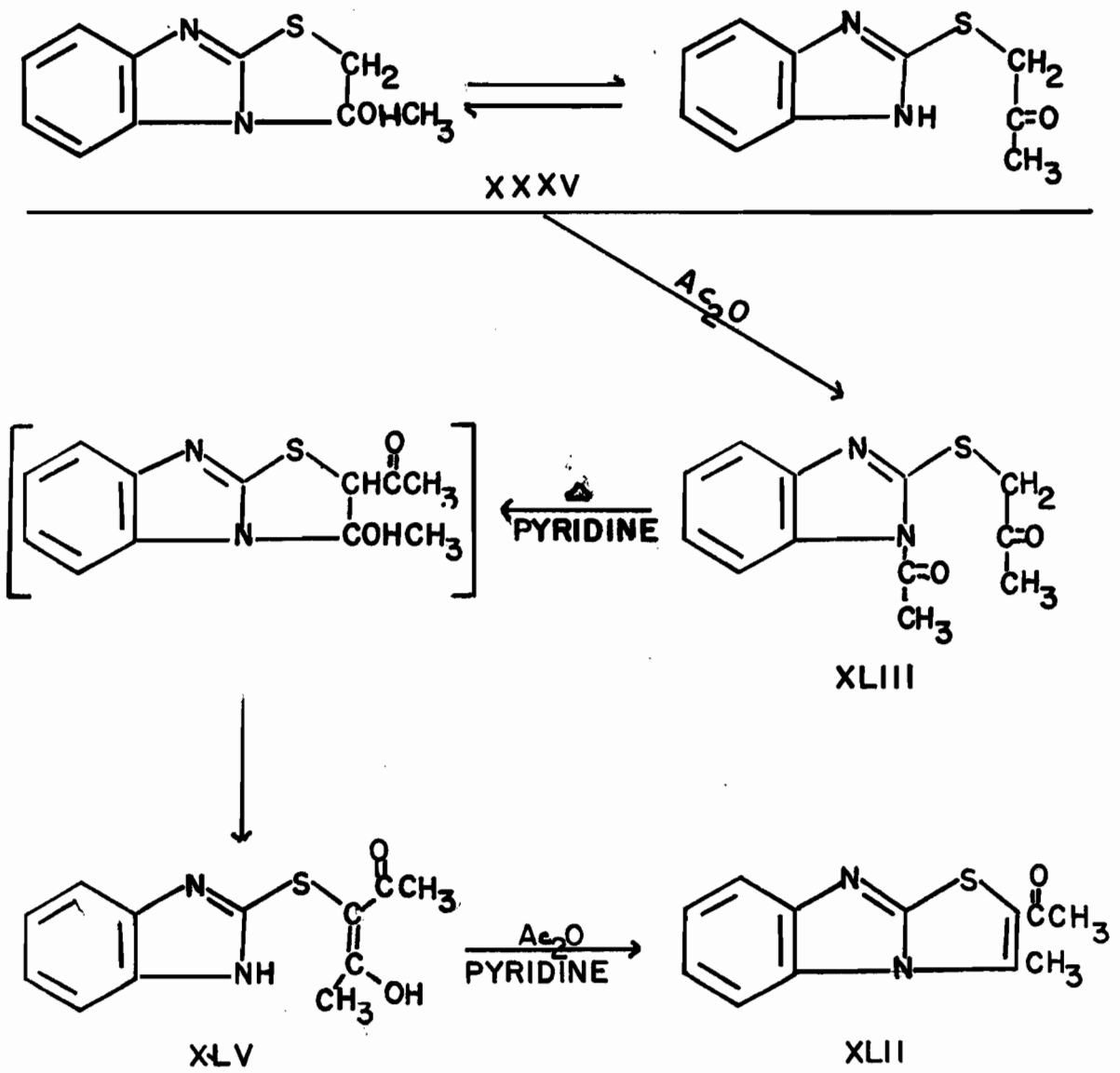
of this compound was superimposable on that of XLII obtained from the reaction of 3-hydroxy-3-methyl-2,3-dihydrothiazolo-[3,2-a]benzimidazole (XXXV) with acetic anhydride and pyridine. Also, admixture with XLII did not depress its melting point. Therefore 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole had been obtained from XXXV.

Ochiai (31) had reported a similar reaction. When 2-acetylthio-5-methyl-4-carbethoxyimidazole was heated in acetic anhydride a ketone was obtained which he postulated was a 2-acetylimidazo[2,1-b]thiazole.

A possible explanation for the formation of XLII from XXXV is outlined in Scheme 10. The open-chain keto form (XXXVb) is acetylated to give (2-N-acetylbenzimidazolylthio)-propan-2-one (XLIII). XLIII can undergo internal condensation between the methylene protons and the carbonyl group of the amide. The carbinol amine formed is the cyclic tautomer of 3-(2-benzimidazolylthio)-2,4-pentanedione (XLV). The open chain form is definitely favored for this compound due to the stabilizing influence of the keto-enol tautomerism of its β-diketone. XLV then undergoes cyclodehydration to form 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole.

This reaction sequence was proved. It was shown (Section E) that treatment of XXXV with acetic anhydride gave the N-acetyl derivative (XLIII). When XLIII was heated in pyridine, 3-(2-benzimidazolylthio)-2,4-pentanedione (XLV) was

SCHEME 10



obtained in 90% yield. It was identical in all respects with the product from the condensation of 3-chloro-2,4-pentanedione and 2-benzimidazolinethione. As shown above XLV was cyclized with acetic anhydride and pyridine to give 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole (XLII).

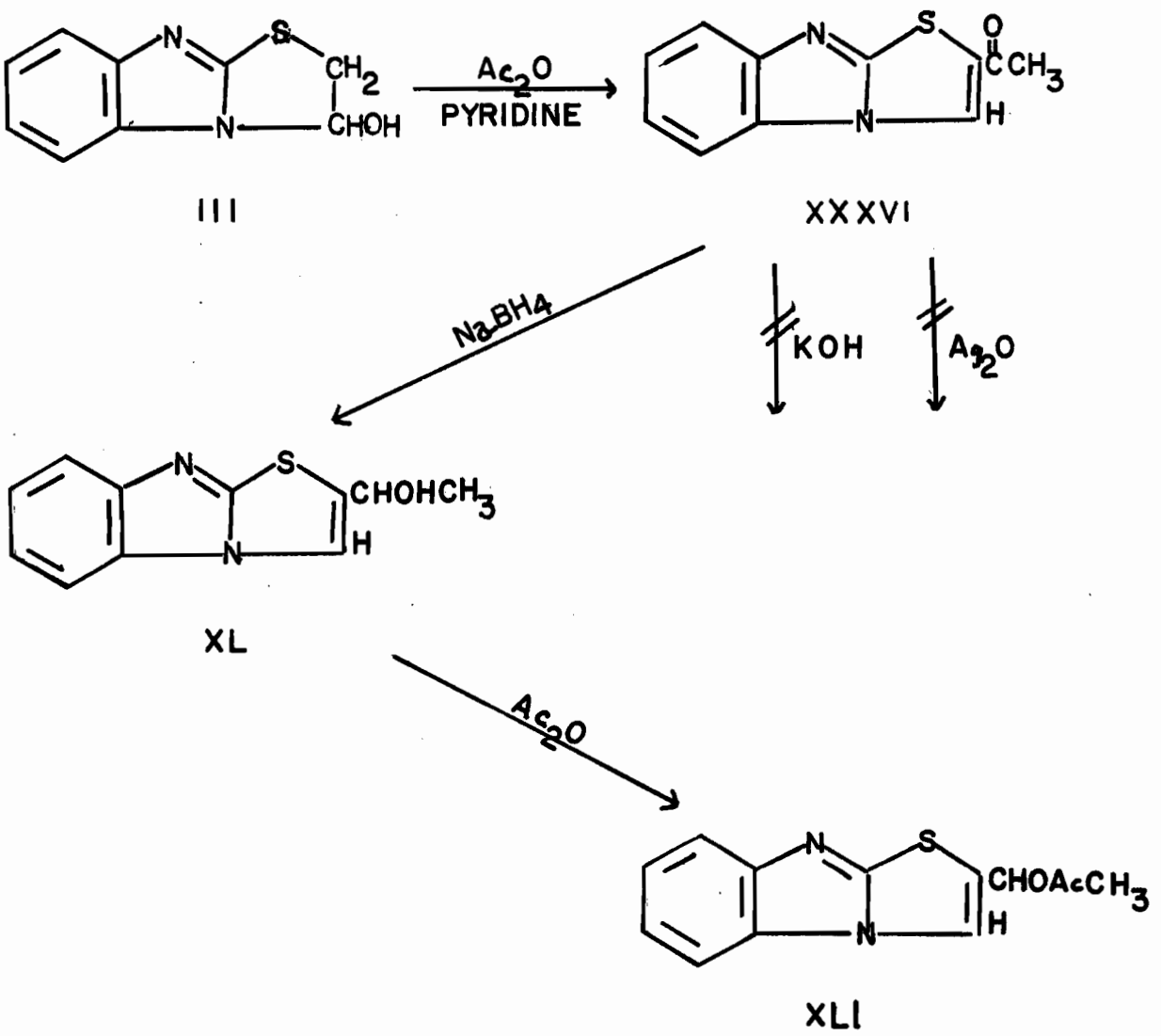
2. 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III).

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXXV) had undergone acetylation and rearrangement to give an acetylthiazolo[3,2-a]benzimidazole through its open-chain ketone form (XXXVb). It was of interest to examine the scope of this reaction and in particular to determine if the hydroxy compounds for which no open-chain tautomer was detected (Section E) would react in the same manner.

Refluxing III in acetic anhydride and pyridine gave a pale yellow carbonyl compound XXXVI, m.p. 227-228^{o} (Scheme 11). When 3-acetoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (IV) was treated under the same conditions it was recovered unchanged indicating that the O-acetyl derivative was not an intermediate in this reaction. Similarly, refluxing thiazolo[3,2-a]benzimidazole (I) in acetic anhydride and pyridine gave no reaction. Therefore it appeared that the reaction of III did proceed via cleavage of the C-N bond.

It was not unexpected that III reacted in this manner. Gaylord (97) had shown that stable carbinolamines of this type (having their nitrogen atom part of a heteroaromatic system)

SCHEME II



III

XXXVI

XL

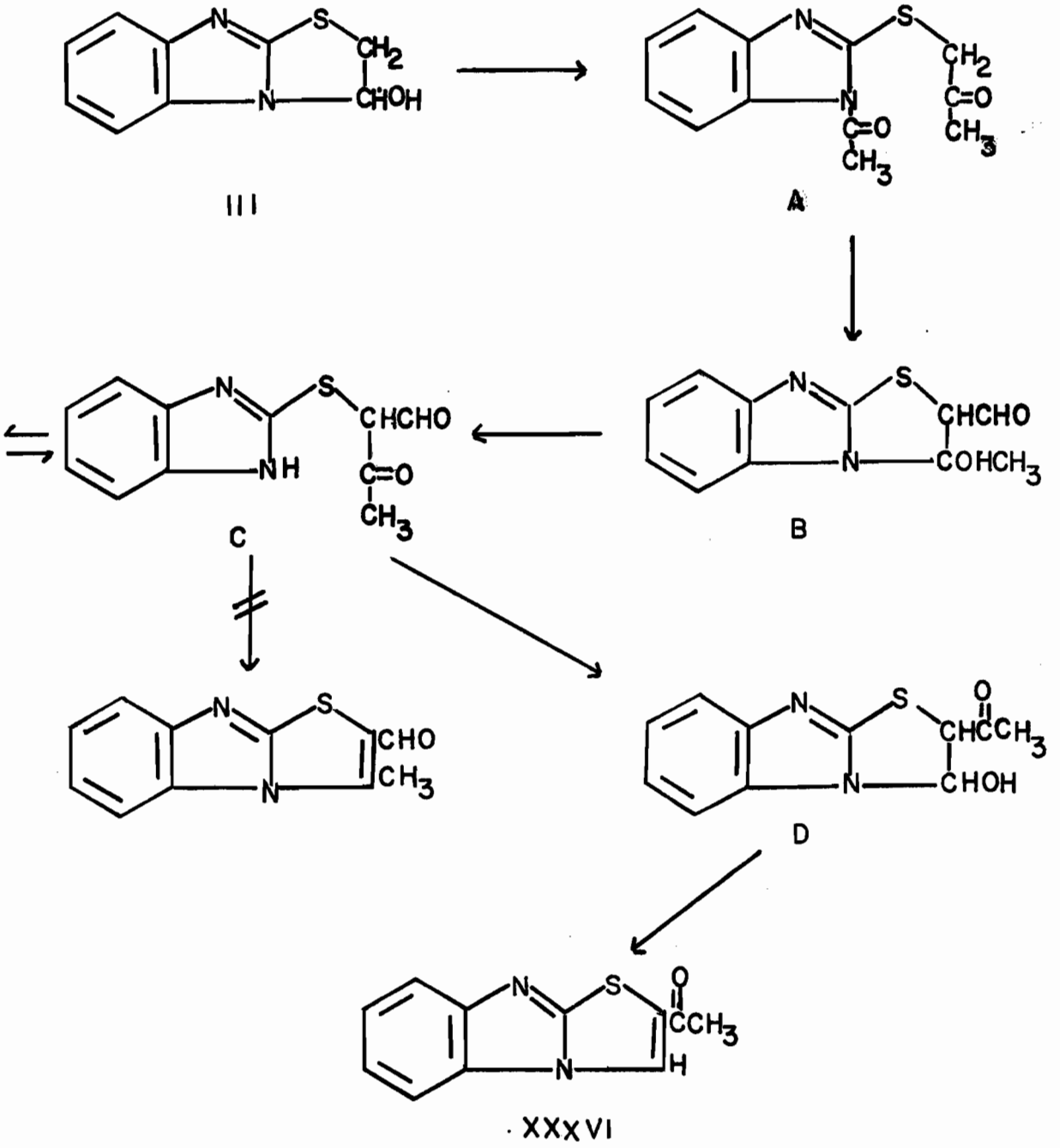
XLI

can be cleaved under similar conditions to form N-acylated products. 1-Hydroxymethyl-1H-benzotriazole with benzoic anhydride gave the O-benzoyl derivative but on treatment with pyridine and benzoylchloride in refluxing dioxane 1-benzoyl-1H-benzotriazole was formed.

Following a reaction path analogous to that for the 3-methyl compound either 3-methylthiazolo[3,2-a]benzimidazole-2-aldehyde or 2-acetylthiazolo[3,2-a]benzimidazole may result as shown in Scheme 12. Proof of the structure of XXXVI came from elemental analysis, spectral evidence and chemical reactions.

Compound XXXVI analyzed for $C_{11}H_8N_2OS$. Its infrared spectrum showed strong bands at 1660 $cm.^{-1}$ (C=O stretch), 1487 $cm.^{-1}$ (the thiazolo[3,2-a]benzimidazole ring system) and 765 $cm.^{-1}$ (C-H out-of-plane deformation of the 1,2-disubstituted benzene ring). The intensity of the bands between 1600 and 1500 $cm.^{-1}$ for the C=C and C=N stretching was enhanced compared with the intensity of those in the infrared spectrum of thiazolo[3,2-a]benzimidazole (I), indicating that the carbonyl group was conjugated with the ring system. The carbonyl stretching occurred at 1668 $cm.^{-1}$ in chloroform solution. The infrared spectrum did indicate a substituted thiazolo[3,2-a]-benzimidazole. Although the position of the carbonyl stretching did not help to differentiate between the conjugated aldehyde or ketone structure, the absence of absorption between 2900 and 2700 $cm.^{-1}$, the region in which aldehydes usually show two weak bonds for the C-H stretch (59), supported the ketone structure.

SCHEME 12



However, the N.M.R. spectrum (DMSO-d_6) showed a singlet at 9.3 p.p.m. for one proton. A signal for a single proton at such low field in the N.M.R. spectrum usually indicates the aldehyde function (71). A complex multiplet between 8.0 and 7.1 p.p.m. for the four aromatic protons and a singlet at 2.45 p.p.m. for a methyl group also appeared.

The ultraviolet spectrum of XXXVI (Fig. 9) indicated that it was a conjugated thiazolo[3,2-a]benzimidazole. Absorption maxima occurred at 271 mμ (log ϵ = 4.62) and 212 mμ (log ϵ = 4.67). 2-Acetyl-3-methylthiazolo[3,2-a]benzimidazole (XLII) showed absorption bands at 273 mμ (log ϵ = 4.64) and 213 mμ (log ϵ = 4.62) while 2-carbethoxy-3-methylthiazolo-[3,2-a]benzimidazole (XXXIX) absorbed at 266 mμ (log ϵ = 4.49) and 212 mμ (log ϵ = 4.49). Thus spectral data indicated that XXXVI was a carbonyl substituted thiazolo[3,2-a]benzimidazole but did not unambiguously differentiate between the aldehyde and ketone structures.

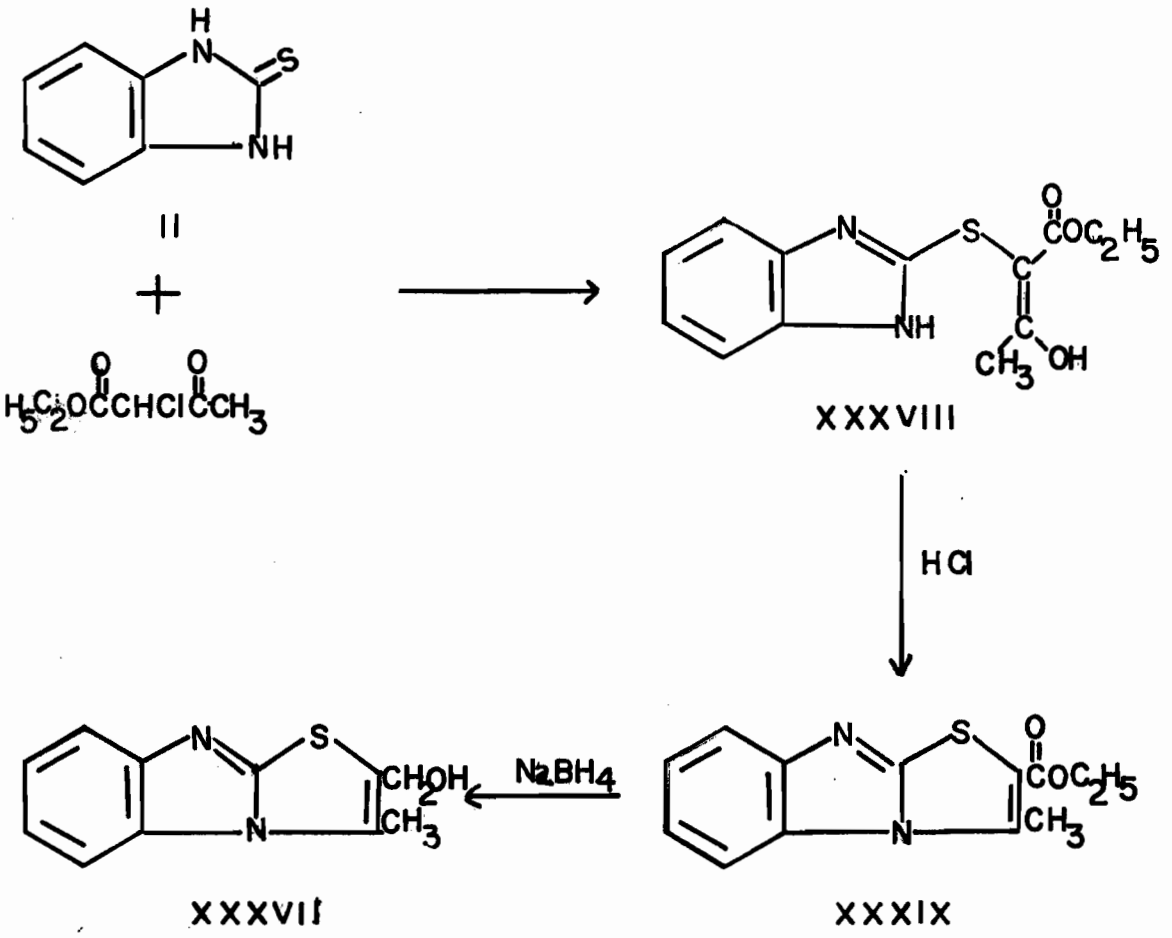
Aldehydes are known to disproportionate in the presence of strong base giving equal amounts of the corresponding carboxylic acid and alcohol (Cannizzaro Reaction)(109). 2-Phenylthiazole-4-aldehyde on treatment with potassium hydroxide gave 2-phenyl-4-hydroxymethylthiazole and 2-phenylthiazole-4-carboxylic acid (98). However, when XXXVI was treated with potassium hydroxide under the same conditions no reaction occurred. Also, aldehydes are readily oxidized

to carboxylic acids but reaction of XXXVI with silver oxide gave only recovered starting material.

Conclusive proof for the structure of XXXVI was obtained by sodium borohydride reduction (Scheme 11). Reduction of the proposed ketone would give 2-(1-hydroxyethyl)thiazolo-[3,2-a]benzimidazole (XL). Reduction of the proposed aldehyde would give 2-hydroxymethyl-3-methylthiazolo[3,2-a]benzimidazole (XXXVII).

2-Hydroxymethyl-3-methylthiazolo[3,2-a]benzimidazole (XXXVII) was synthesized as outlined in Scheme 13. 2-Carbethoxy-3-methylthiazolo[3,2-a]benzimidazole (XXXIX) was prepared according to the procedure of D'Amico (12). In this investigation condensation of 2-benzimidazolinethione (II) and ethyl-2-chloroacetoacetate gave ethyl-2-(2-benzimidazolylthio)-acetoacetate (XXXVIII) in 82% yield. By the cyclization of XXXVIII either with acetic anhydride and pyridine or with hydrochloric acid, 2-carbethoxy-3-methylthiazolo[3,2-a]benzimidazole (XXXIX) was formed in quantitative yield. The infrared spectrum of XXXIX showed strong bands at 1711 $cm.^{-1}$ (C=O stretch of the conjugated ester) 1611, 1591 and 1572 $cm.^{-1}$ (C=C and C=N stretch), 1488 $cm.^{-1}$ (the thiazolo[3,2-a]benzimidazole system), 1221 $cm.^{-1}$ (C-O stretch of an ester), 1078 $cm.^{-1}$ (O-CH_2 stretch) and 738 $cm.^{-1}$ (C-H out-of-plane bending of the 1,2-disubstituted benzene ring). The N.M.R. spectrum ($CDCl_3$) of 2-carbethoxy-3-methylthiazolo[3,2-a]benzimidazole

SCHEME 13



showed a complex multiplet between 7.9 and 7.0 p.p.m. for the four aromatic protons, a quartet at 4.38 p.p.m. (J = 7.2 cps) for the methylene protons of the ethyl group, a singlet at 3.0 p.p.m. for the methyl group in the 3-position and a triplet at 1.4 p.p.m. (J = 7.2 cps) for the methyl protons of the ethyl group.

Carboxylic acid esters are not usually reduced by sodium borohydride. Brown has shown recently (101) that these esters are not resistant to reduction but that the rate of reduction by this agent is much slower than that for aldehydes and ketones. Using a ten to twenty-fold excess of sodium borohydride esters are smoothly reduced to primary alcohols in good yields. 2-Carbethoxy-3-methylthiazolo[3,2-a]-benzimidazole was reduced using a ten-fold excess of sodium borohydride, to give an 80% yield of 2-hydroxymethyl-3-methyl-thiazolo[3,2-a]benzimidazole (XXXVII). Its infrared spectrum showed broad absorption between 3600 and 3000 $cm.^{-1}$ (bonded O-H stretch) and strong bands at 1472 $cm.^{-1}$ (the thiazolo-[3,2-a]benzimidazole system), 1019 $cm.^{-1}$ (C-O stretch of a primary alcohol), and 734 $cm.^{-1}$ (C-H out-of-plane deformation of the benzenoid hydrogens). The N.M.R. spectrum (DMSO-d_6) of XXXVII showed a complex multiplet for the four protons on the benzene ring between 7.9 and 7.0 p.p.m., a broad band at approximately 5.5 p.p.m. for the hydroxyl proton, a singlet

at 4.55 p.p.m. for the methylene protons and a singlet at 2.52 p.p.m. for the methyl group. After exchange with trifluoroacetic acid the broad signal at 5.5 p.p.m. disappeared.

Reduction of the product XXXVI with sodium borohydride gave an alcohol XL (Scheme 11) which was not identical with 2-hydroxymethyl-3-methylthiazolo[3,2-a]benzimidazole (XXXVII). XL was shown to be 2-(1-hydroxyethyl)thiazolo-[3,2-a]benzimidazole. Therefore XXXVI must be the ketone, 2-acetylthiazolo[3,2-a]benzimidazole. The infrared spectrum of XL showed broad absorption at approximately 3228 $cm.^{-1}$ and strong bands at 1475 $cm.^{-1}$ (the thiazolo[3,2-a]benzimidazole ring system), 1079 $cm.^{-1}$ (C-O stretch of a secondary alcohol) and 752 and 740 $cm.^{-1}$ (C-H out-of-plane bending for the 1,2-disubstituted benzene ring). In general the infrared spectrum was similar to that of the secondary alcohol, 2-(1-hydroxyethyl)-3-methylthiazolo[3,2-a]benzimidazole. In the N.M.R. spectrum of XL ($CDCl_3$) there was a complex multiplet between 7.9 and 7.0 p.p.m. for the five aromatic protons, a broad singlet at 5.7 p.p.m. for the hydroxyl proton, a quartet at 5.0 p.p.m. (J = 6.5 cps) for the proton alpha to the hydroxyl group coupled with the methyl protons and a doublet at 1.59 p.p.m. (J = 6.5 cps) for the methyl group. The N.M.R. spectrum also showed signals at 4.15 and 1.2 p.p.m. for an unidentified minor impurity (ca. 5%).

An analytically pure sample of XL was not obtained. Therefore XL was acetylated to give 2-(1-acetoxyethyl)thiazolo-[3,2-a]benzimidazole (XLI) which, after purification by thin layer chromatography analyzed for $C_{13}H_{12}N_2O_2S$. Its infrared spectrum showed strong bands at 1734 $cm.^{-1}$ (C=O stretch of the ester), 1225 $cm.^{-1}$ (C-O stretch of the acetate) and 1062 $cm.^{-1}$ (C-O stretch of the alcohol residue). The N.M.R. spectrum of XLI ($CDCl_3$) had a complex multiplet between 7.9 and 7.1 p.p.m. for the five aromatic protons from which H_3 could be distinguished as a sharp singlet at 7.75 p.p.m. It also showed a quartet at 6.13 p.p.m. (J = 6.5 cps) for the proton alpha to the acetoxy group, coupled with the adjacent methyl group, a singlet at 2.08 p.p.m. for the methyl protons of the acetyl group and a doublet at 1.67 p.p.m. (J = 6.5 cps) for the other methyl group. Acetylation of the secondary alcohol had shifted the signal for the alpha proton 1.13 p.p.m. to lower field, as expected (71).

Also, XXXVI produced iodoform when treated with sodium hypoiodite supporting the methyl ketone structure. Since XXXVI has been identified as 2-acetylthiazolo[3,2-a]benzimidazole the signal at 9.3 p.p.m. in its N.M.R. spectrum must be assigned to H_3. This low field position for a proton on a heteroaromatic nucleus is not without analogy. The N.M.R. spectrum of nicotinamide shows a signal at 9.04 p.p.m. for H_2 (102).

The formation of the ketone XXXVI and not the aldehyde from III is not too surprising. In the intermediate C (Scheme 12) the nitrogen would condense more readily with the aldehyde function than with the ketone. Also, the carbinol amine D, resulting from the aldehyde condensation, would be more stable than that from the ketone condensation.

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) was allowed to stand in pyridine and acetic anhydride at room temperature. The infrared spectrum of the crude product indicated that it was a mixture of approximately equal amounts of XXXVI and 3-acetoxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (IV). Therefore higher temperatures must facilitate cleavage of the C-N bond of III.

Also, it was noted that some 2-acetylthiazolo[3,2-a]-benzimidazole (XXXVI) was formed when recrystallization of III from ethyl acetate* was attempted. Refluxing 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) in ethyl acetate for three days gave 2-acetylthiazolo[3,2-a]benzimidazole in 64% yield. The ethyl acetate must react with the nitrogen to give the intermediate N-acetyl compound which undergoes internal condensation as before (Scheme 12).

---

*The ethyl acetate had been purified to remove traces of water, ethanol and acetic acid according to the procedure of Vogel (18).

Although III and XXXV had been observed to react at the nitrogen atom with acetic anhydride in pyridine, 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXX) gave only the O-acetyl derivative (XXXI) when reacted with acetic anhydride under similar conditions. This indicated that the carbon-nitrogen bond had not been cleaved and hence the 2-methyl compound must be more stable than the unsubstituted 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole.

G. Spectra of Thiazolo[3,2-a]benzimidazoles.

Although some thiazolo[3,2-a]benzimidazoles had been previously synthesized no report on their spectra was made. Therefore, the infrared, ultraviolet and N.M.R. spectra of these compounds were recorded. The main absorption bands in the infrared and ultraviolet spectra characteristic of this ring system are pointed out and the signals in their N.M.R. spectra are assigned in the following discussion.

1. Ultraviolet Spectra

The ultraviolet spectra of thiazolo[3,2-a]benzimidazoles between 400 and 200 mμ consist of two moderate intensity bands followed at shorter wavelength by a high intensity band (Table III). These are named the α-, p- and β-bands respectively analogous to the classification of Clar for aromatic and six-membered heteroaromatic rings extended by Mason (112) to the benzoderivatives of five-membered heteroaromatic molecules.

TABLE III

Ultraviolet Absorption Maxima (in mμ) and Corresponding log ε Values of Some Thiazolo[3,2-a]benzimidazoles in Ethanol

Compound	α-band	p-band	β-band
Thiazolo[3,2-a]-benzimidazole (I)	282(3.89) 273(3.99)	247(4.16) 241(4.19)	214(4.47)
2-Methyl- (XXVIII)	275(4.12) 286(3.95)	248(4.40) 242(4.36)	215(4.63)
3-Methyl- (XXXIV)	277(4.15) 288 sh.	245.5(4.40) 238.5(4.40)	213(4.58)
2-(1-Hydroxyethyl)-3-methyl- (XLVI)	288(3.74) 279(4.14)	247(4.40) 240.5(4.41)	214(4.55)
2-(1-Acetoxyethyl) (XLI)	275(4.10)	248(4.35)	213.5(4.57)
2-(1-Hydroxyethyl) (XL)	275(4.15)	248(4.36)	215(4.64)
2-Hydroxymethyl-3-methyl- (XXXVII)	288(3.99) 279(4.09)	247(4.36) 242(4.36)	213.5(4.49)
3-Phenyl- (XXXII)	283(4.01) 268(4.10)	248(4.10) 235(4.26)	
5,8-Dimethyl-(XXII)	277(4.05)	241(4.16)	221(4.57)
6,7-Dimethyl- (XVI)	277(4.05)	245(4.28)	215(4.59)
6 or 7-Nitro- (XLVII)	262(4.02)	231.5(4.34)	205(4.29)
Methiodide VII	288(4.03) 279(3.98)	-	211(4.63)
2-Acetyl-3-methyl- (XLII)	273(4.64)	-	213(4.62)
2-Acetyl- (XXXVI)	271(4.62)	-	212(4.67)
2-Carbethoxy-3-methyl- (XXXIX)	266(4.49)	-	212(4.49)

Thiazolo[3,2-a]benzimidazole (I) has its main absorption maxima at 282 mμ (log ε = 3.89), 273 mμ (log ε = 3.99) (α-band); 247 mμ (log ε = 4.16), 241 mμ (log ε = 4.19) (p-band); and 214 mμ (log ε = 4.47) (β-band). (Fig. 8). In general its substituted derivatives show bands in the same positions. However, when a carbonyl substituent in the 2-position is conjugated with the ring, the p-band undergoes a bathochromic shift of approximately 30 mμ to overlap the α-band. (Fig. 9). In these compounds a band of low intensity occurs at longer wavelengths for the carbonyl group. It is interesting to note that formation of the quaternary methiodide of I results in the disappearance of the p-band.

Alkyl substitution at any position in the thiazolo-[3,2-a]benzimidazole system causes a small bathochromic shift of the α-band. The ultraviolet spectrum of the nitrothiazolo-[3,2-a]benzimidazole (XLVII) shows a band at 347 mμ for the nitro group and a marked hypsochromic shift of the entire spectrum of 10-13 mμ. This effect was also noted for 5(6)-nitrobenzimidazole (111).

The ultraviolet spectra of several substituted benzimidazoles have been reported (111,110 and 103). They exhibit two main bands between 400 and 230 mμ, the band at longer wavelengths usually showing some fine structure. Although these workers did not report a third band at shorter wavelengths Steck (106) noted an increase in intensity before

cut-off at 215 mμ. The ultraviolet spectra of the 2-substituted benzimidazoles prepared in this investigation show the two bands corresponding to those previously reported as well as a band of high intensity between 209 and 211 mμ. The β-band has also been observed for similar benzofused heterocycles (112,107).

In general the ultraviolet spectra of the benzo-derivatives of five-membered heteroaromatics resemble those for carbocyclic compounds (112,65). The three bands observed correspond to the α-, p- and β-bands of these compounds with reduction in fine structure and intensification of the α-band. Recently Ellis and Griffiths (107) have interpreted the ultraviolet spectrum of benzothiazole by its relationship to naphthalene and benzothiophene and ascribed the changes in the α-band to the reduced symmetry of the heterocyclic compound compared to naphthalene. However, Rabiger and Jouillié (103) have stated that the p-band for benzimidazoles is related to "excitations in the amidine ring" and that "excitations of both rings" may intensify the α-band.

Thiazole shows absorption maxima at 231 mμ and 205 mμ in the ultraviolet and its spectrum has been compared to those of thiophene, pyrrole and cyclopentadiene (107).

The spectra of thiazolo[3,2-a]benzimidazoles and its derivatives show marked similarities to the spectra of benzimidazoles and other benzoderivatives of five-membered

heteroaromatics. The spectra of the 2,3-dihydrothiazolo-[3,2-a]benzimidazoles are identical to those of the 2-substituted benzimidazoles. However, introduction of a double bond into the thiazole ring to form the heteroaromatic thiazolo-[3,2-a]benzimidazoles causes a hypsochromic shift of the α-band by approximately 10 mμ in all cases.

In general, linear or angular annelation of aromatic hydrocarbons and their aza analogues results in a bathochromic shift of the three main absorption bands (112). Fusion of a thiazole ring to quinoline, naphthalene or benzene displaces all the bands of the parent compound to longer wavelengths (107,118). However, when a thiazole ring is fused to the benzimidazole system to give thiazolo[3,2-a]-benzimidazole the positions of the p- and β-bands remain unchanged and the α-band undergoes a hypsochromic shift.

2. Infrared Spectra

The infrared spectra of the thiazolo[3,2-a]benzimidazoles were studied between 4000 and 650 $cm.^{-1}$ The main regions of the spectra are discussed and the principal bands are classified according to the type of vibration they represent.

The 3100-3000 $cm.^{-1}$ region

Multiple weak bands are found in this region for the aromatic C-H stretching vibrations of carbocyclic and heterocyclic systems (70). Thiazole shows a single strong band in this region at 3090 $cm.^{-1}$ overlapping a second band (75).

The C-H stretching vibrations of benzimidazole cannot be distinguished from the bonded N-H stretching which occurs in this region (103).

The infrared spectrum (Fig. 3) of the unsubstituted thiazolo[3,2-a]benzimidazole (I) has bands at 3112 (w), 3054 (m) and 3030 (w) $cm.^{-1}$ The various substituted thiazolo[3,2-a]-benzimidazoles show from one to five bands in this region. Substituents do affect these vibrations but no correlations have been made between the nature of the substituent and the position and intensity of the C-H stretching (70).

The 1650-1500 $cm.^{-1}$ region

Aromatic heterocyclic compounds show absorption in this region for the C=C and C=N stretching modes. These vibrations usually cannot be distinguished due to their complete interaction (70). The bands in this region have been found to vary in intensity and position with the nature and position of substituents; however, it is difficult to make definite conclusions concerning the substitution pattern from this region of the spectrum. Thiazole shows one band in this region at 1615 $cm.^{-1}$ (75). Bassignana and his co-workers have found that substituted thiazoles usually show two bands between 1625 and 1605 $cm.^{-1}$ and 1550 and 1505 $cm.^{-1}$ designated as Thiazole I and Thiazole II. The band at higher frequency arises mainly from a C=N stretching vibration (131). Benzimidazole has bands at 1622 (m), 1591 (m) and 1604 (w) $cm.^{-1}$ (103). Most substituted benzimidazoles also show three bands

in this region at 1610-1640 $cm.^{-1}$, 1585-1605 $cm.^{-1}$ and 1560-1520 $cm.^{-1}$ (134).

Thiazolo[3,2-a]benzimidazole shows four bands in this region at 1619 (w), 1539 (w), 1544 (m) and 1511 (w) $cm.^{-1}$ All the substituted thiazolo[3,2-a]benzimidazoles exhibit absorption between 1624 and 1608 $cm.^{-1}$ (Table IV). Those substituted on the benzene ring absorb at the higher frequencies and those with conjugating substituents at the 2-position at lower frequencies. Thiazolo[3,2-a]benzimidazoles substituted on the benzene ring show three bands between 1500 and 1600 $cm.^{-1}$ and those substituted on the thiazole ring show two or less. The positions and intensities of these bands do vary with substituents; however, no definite correlations could be made for the compounds studied. The intensity of at least one of the bands between 1500 and 1600 $cm.^{-1}$ is greatly enhanced for thiazolo[3,2-a]benzimidazoles substituted with a conjugating substituent. A similar effect due to conjugation is observed on the 1580 $cm.^{-1}$ band of carbocyclic aromatic compounds (59).

The 1500-1300 $cm.^{-1}$ region.

Heteroaromatic compounds show in-plane skeletal vibrations between 1500 and 1300 $cm.^{-1}$ Care must be taken in assigning bands of substituted compounds as C-H deformations of alkyl groups occur in this region (59). Thiazoles show bands between 1500 and 1485 $cm.^{-1}$ and 1375 and 1385 $cm.^{-1}$ (75) while benzimidazoles absorb strongly at 1460 and 1420 $cm.^{-1}$ (104).

TABLE IV

Ring-stretching Vibrations (1650-1300 $cm.^{-1}$ region) in the Infrared Spectra of Thiazolo[3,2-a]benzimidazoles as KBr Pellets

Compound							
Thiazolo[3,2-a]-benzimidazole (I)	1619 w	1593w		1544 m	1511 w	1459 vs	1310 m
6,7-Dimethyl- (XVI)	1622 w		1570 w	1546 m	1539 m	1462 vs	1314 m
5,8-Dimethyl- (XXII)	1616 w	1598 w		1546 s	1517 m	1471 vs	1304 m
6- or 7-Nitro- (XLVII)	1620 w	1589 m	1552 w	1542 w		1455 vs	1302 m
2-Methyl- (XXVIII)	1613 m	1599 m	1572 w			1461 vs	1320 m
3-Methyl- (XXXIV)	1610 m	1590 w	1572 w			1463 vs	1307 m
3-Phenyl- (XXXII)	1611 m		1557 w			1478 vs	1303 m
2-Carbethoxy-3-methyl (XXXIX)	1611 w	1591 s	1572 w			1490 vs	1310 m
2-Acetyl-3-Methyl- (XLII)	1608 w	1582 m	1564 s			1483 vs	1306 m
2-Acetyl- (XXXVI)	1614 w		1579 w	1556 s		1487 vs	1307 m
2-Hydroxymethyl-3-methyl- (XXXVII)	1624 m					1472 vs	1312 m
2-(1-Hydroxyethyl)- (XL)	1616 w	1591 m	1576 m			1477 vs	1305 m
2-(1-Acetoxyethyl)- (XLI)	1617 m	1598 m	1576 w			1467 vs	1320 m
2-(1-Hydroxyethyl)-3-methyl (XLVI)	1617 m					1477 vs	-

w = weak m = medium s = strong vs = very strong

Thiazolo[3,2-a]benzimidazole (I) shows a very strong band at 1459 $cm.^{-1}$ and a band of weak to medium intensity at 1310 $cm.^{-1}$ All the thiazolo[3,2-a]benzimidazoles studied show very strong absorption between 1490 and 1455 $cm.^{-1}$ (Table IV). This intense band is very characteristic of the thiazolo[3,2-a]benzimidazole system and was useful in identifying several products formed. This strong band occurs at highest frequency when a substituent is conjugated with the ring system. Many of the thiazolo[3,2-a]benzimidazoles studied show a second weaker band between 1325 and 1300 $cm.^{-1}$ (Table IV).

The 1250-1000 $cm.^{-1}$ region

Heterocyclic compounds show a series of characteristic bands in the 1250 to 1000 $cm.^{-1}$ region which may be assigned to in-plane C-H deformations and ring-breathing modes (70). Simple benzimidazoles usually show bands near 1000 and 960 $cm.^{-1}$ (103), however, these bands are not of much value for the characterization and identification of the molecules.

The 950-650 $cm.^{-1}$ region

Strong absorption in this region is attributed to the C-H out-of-plane deformation vibrations of aromatic compounds both benzenoid and heterocyclic (59,70). The position of these bands depends on the number of adjacent hydrogens and hence they are extremely useful in characterizing

substitution patterns (59,105). Bands of variable intensity also occur in this region for the heterocyclic ring-breathing vibrations (103).

The C-H bending frequencies of several benzimidazoles have been assigned (103,105) and usually occur within the ranges given by O'Sullivan for various substituted benzenes fused to five-membered rings (105,113). Thiazoles and substituted thiazoles show strong absorption in this region assigned to the C-H out-of-plane deformations, however, there appeared to be no correlation between the number of hydrogens and the number of bands (75). Thiazoles generally show a band of strong to medium intensity between 885 and 855 $cm.^{-1}$ for the ring-breathing mode (131). Confusion exists as to the frequency of this vibration in the infrared spectra of benzimidazoles. Morgan (104) assigned bands at 760 $cm.^{-1}$ and 880 $cm.^{-1}$ to ring-breathing vibrations. However, more recently, Bassignana reported that the ring-breathing modes of benzimidazoles occur between 920 and 960 $cm.^{-1}$

Thiazolo[3,2-a]benzimidazole (I) shows a strong doublet at 740 and 726 $cm.^{-1}$ for the C-H out-of-plane deformation of the four adjacent hydrogens on the benzene ring. Bands in this region often show splitting in solid state spectra due to intermolecular attraction (70). I also shows bands of weak to medium intensity at 760, 754, 825 and 665 $cm.^{-1}$ The thiazolo[3,2-a]benzimidazoles unsubstituted

on the benzene ring show strong absorption between 735 and 765 $cm.^{-1}$; usually in the form of a doublet, for the C-H bending of the hydrogens on the benzene ring. 5,8-Dimethylthiazolo[3,2-a]benzimidazole has a strong doublet at 844 and 808 $cm.^{-1}$ for the C-H out-of-plane deformation of the two adjacent hydrogens. 6,7-Dimethylthiazolo[3,2-a]-benzimidazole shows a strong band at 840 $cm.^{-1}$ which is assigned to the C-H deformation of the isolated hydrogens. However, this band occurs outside the range of 945 to 860 $cm.^{-1}$ proposed for this type of substitution (105). Several of the substituted benzimidazoles studied by Jouillié (103) also have C-H deformations which do not occur within the ranges given by O'Sullivan. 2-Phenylthiazolo[3,2-a]benzimidazole has an intense band at 694 $cm.^{-1}$ which is assigned to the C-H deformations of the five hydrogens on the phenyl group (59). Many of the thiazolo[3,2-a]benzimidazoles also show a band of medium intensity between 630 and 650 $cm.^{-1}$

In addition to the vibrations typical of the thiazolo[3,2-a]benzimidazole ring system vibrations for the substituents attached to the ring are also present. In general, these occur within the regions characteristic for the particular substituent. However, these vibrations may be modified if strong interaction with the heterocyclic nucleus can take place. For example, conjugation of the carbonyl

group with the ring system results in lowering the frequency of the carbonyl stretching in the 2-acetyl- and 2-carbethoxy-thiazolo[3,2-a]benzimidazoles.

The substituent vibrations of the 2,3-dihydro-thiazolo[3,2-a]benzimidazoles have been discussed (Section E). However, these compounds show characteristic vibrations in other spectral regions. The C-H stretching both of the aromatic and alicyclic hydrogens are masked by absorption for the bonded O-H stretch. The 2,3-dihydrothiazolo[3,2-a]-benzimidazoles unsubstituted on the benzene ring show absorption of weak to medium intensity between 1610 and 1615 $cm.^{-1}$ and in most cases a weak band between 1595 and 1585 $cm.^{-1}$ In the infrared spectra of the 5,8-dimethyl- and 6,7-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazoles bands appear at 1619 (w), 1593 (m), and 1519 (m) $cm.^{-1}$ and 1621 (w), 1573 (m), and 1512 (w) $cm.^{-1}$ respectively. These bands are assigned to the C=C and C=N stretching of the benzimidazole ring and occur in the positions noted by Jouillié characteristic of 2-substituted benzimidazoles (103). These compounds all show strong absorption between 1400 and 1200 $cm.^{-1}$ for the in-plane vibrations of the heterocyclic ring system at approximately 1475, 1450 and 1380 $cm.^{-1}$ These bands overlap the C-H deformations of the thiazolidine ring. In addition to these vibrations, the out-of-plane bending of the hydrogens on the benzene ring give the characteristic strong bands between 950 and 650 $cm.^{-1}$

3. The N.M.R. Spectra of Thiazolo[3,2-a]benzimidazoles

Thiazolo[3,2-a]benzimidazole (I) has six aromatic protons which will give signals in its N.M.R. spectrum. The two protons on the thiazole ring will give a separate pattern from that for the four protons on the benzene ring since the two groups are separated by the imidazole nucleus and coupling cannot occur.

The protons on the thiazole ring H_2 and H_3 give two doublets at 7.6 and 6.7 p.p.m. (J = 4.7 cps), in the N.M.R. spectrum of I in $CDCl_3$ (Fig. 4). For thiazole H_4 which is adjacent to the nitrogen atom gives a signal at lower field (7.6 p.p.m.) than H_5 (7.1 p.p.m.) (88). Therefore the doublet at 7.6 p.p.m. is assigned to H_3 in I.

The doublet at lower field is superimposed on the multiplet for the benzene-ring protons; however, it is readily distinguished as the strongest signal. Also, when the N.M.R. spectrum of I is taken in dioxane or acetone the chemical shifts of H_2 and H_3 are affected to a greater extent than those for the benzenoid protons (Table V) and the doublet for H_3 no longer overlaps the other signals. This solvent-dependent shift to lower field of the signals for the protons on an aromatic ring either benzenoid (115,123,125) or heterocyclic (119-122) has been noted previously. The effect for thiazole itself is larger than for other five-membered rings. The signal for H_4 is shifted by 5.9 cps

TABLE V

Chemical Shifts of H_2 and H_3 in the N.M.R. Spectrum of I in Various Solvents (p.p.m. from TMS)

Solvent	H_2	H_3	Δ
Chloroform-d	6.7	7.6	54 cps
Dioxane	6.9	7.9	59 cps
Acetone	7.2	8.2	61 cps

while that for H_5 is shifted 27.3 cps in changing the solvent from hexane to acetone (119). However, in the N.M.R. spectrum of thiazolo[3,2-a]benzimidazole (I) the effect of change in solvent on the doublets for H_2 and H_3 is approximately equal.

In general, the effect of solvent on the chemical shift may be due to long-range bulk diamagnetic susceptibility or to short-range interactions between the solute and the solvent (63). The former generally has a small effect but the variation in chemical shift caused by the latter depends on the nature of the interaction. The short-range interactions which may affect the chemical shift are (1) the Van der Waal's forces between the solute and the solvent, (2) a polar effect caused by charge distribution in the neighboring solvent molecule, (3) a ring current effect in aromatic molecules or (4) hydrogen bonding or other specific solute-solvent inter-

actions (124). Schaefer and Schneider (119,121,123) ascribed the large solvent-induced shifts observed in the N.M.R. spectra of aromatic compounds to a specific interaction which they picture as preferential hydrogen bonding of a proton of the solute to the solvent. More recently, Suhr (125) has suggested that solvents such as acetone, acetonitrile, pyridine and dimethylformamide form π complexes with aromatic solutes, which are responsible for these shifts, but does not elaborate concerning the nature of these complexes. No theory has been advanced, however, which satisfactorily explains which protons of a given molecule will be most affected.

The change in solvent, however, does not alter the coupling constant. It is interesting to note that the coupling constant J_{23} (4.7 cps) for thiazolo[3,2-a]benzimidazole (I) is larger than J_{45} (3.1 cps) for thiazole (88). This may result from change in the bond angles on fusion of the thiazole ring to the benzimidazole system or a change in the electron density at the adjacent atoms (141).

In the N.M.R. spectrum of 2-methylthiazolo[3,2-a]-benzimidazole (XXVIII) H_3 gives a signal at 7.30 p.p.m. while the band for H_2 of 3-methylthiazolo[3,2-a]benzimidazole (XXXIV) occurs at 6.11 p.p.m. This confirms the assignment of the doublets for H_2 and H_3 in the spectrum of I. It was noted

that H_2 and H_3 couple with the adjacent methyl group in these compounds by 1.5 cps. Similar coupling was observed in the N.M.R. spectra of the methyl thiazoles (88). It has been shown recently that π-electron interactions make a large contribution to such side-chain couplings (144).

Comparison of the N.M.R. spectra of I, XXXIV, and XXVIII indicates that a methyl group in the 3-position of the thiazolo[3,2-a]benzimidazole ring system has a greater effect on the chemical shift of the adjacent proton than a methyl substituent in the 2-position. A qualitative explanation may be that the effect of the methyl group at C_3 in XXXIV is partly due to hyperconjugation with the heterocyclic molecule increasing the electron density at C_2 and hence shielding H_2. A similar effect is not possible in 2-methylthiazolo[3,2-a]benzimidazole (XXVIII) and only the positive inductive effect would operate here.

The four protons on the benzene ring are non-equivalent and give a complicated pattern. The N.M.R. spectra of the dimethylthiazolo[3,2-a]benzimidazoles indicates this. H_5 and H_8 give two singlets at 7.52 and 7.26 p.p.m. in the N.M.R. spectrum of 6,7-dimethylthiazolo[3,2-a]benzimidazole (XVI). H_6 and H_7 give an AB quartet having the signal for H_A at 7.02 p.p.m. and that for H_B at 6.82 p.p.m. with J_{AB} = 7.5 cps in the spectrum of 5,8-dimethylthiazolo[3,2-a]benzi-

midazole (XXII). As expected the signals for H_6 and H_7 occur at higher field than those for H_5 and H_8. The protons at C_5 and C_8 are deshielded by the adjacent imidazole ring as in the N.M.R. spectrum of benzimidazole (83). However, it is impossible to differentiate between H_5 and H_8 or between H_6 and H_7.

The N.M.R. spectra of four non-equivalent nuclei are in general very complex. The simplest example is an AMRX system in which the chemical shifts are large compared to the coupling constants. This system gives a 32-line spectrum of four octets which may be solved by first-order analysis. The N.M.R. spectrum of indazole at 100 megacycles is an AMRX spectrum (114). However, as the ratios of the chemical shifts to the coupling constants approach unity the spectrum becomes more complicated and combination lines, arising from the simultaneous change of spin of more than two nuclei, acquire measurable intensity (108). The most general case is that of an ABCD system in which the four interacting nuclei have coupling constants nearly equivalent to the chemical shifts. 24 combination lines and 32 fundamental lines can appear (115). Acridine gives an ABCD spectrum (116). An intermediate case is the ABXY system in which the internal chemical shift between A or B and X or Y is large compared to the coupling constant. The AB and XY parts of such a spectrum each consists of 16 fundamental and 8 combination lines and therefore theoretically could give a 48-line spectrum (138,142).

In the N.M.R. spectrum ($CDCl_3$) of thiazolo-[3,2-a]benzimidazole the four benzenoid protons give an ABXY spectrum in which 17 separate lines are distinguished (Fig. 4). The signals for the two protons adjacent to the heterocyclic ring occur at lower field between 7.8 and 7.5 p.p.m. and H_6 and H_7 give lines between 7.5 and 7.0 p.p.m.

The analyses of such complex N.M.R. spectra are usually carried out by computer methods utilizing an iterative technique for calculation of the line positions and their intensities (127). However, it is first necessary to assign the spectral lines to the various transitions. If the pattern is well spread out such an assignment is relatively simple (114,128). The more complex patterns, however, can often be simplified by solvent effects (115), spin decoupling experiments (128) or measurement of the spectrum at higher field strength (114,136). For the last method, since the chemical shifts are field dependent but the coupling constants are not the ratio of chemical shift to coupling constant can be increased by increasing the applied field and hence the appearance of the spectrum is altered (63). Also, a second-order approximation method is sometimes useful in assigning the spectral lines (136,137). Otherwise, the only remaining method is calculation of the energy levels on a computer using various reasonable values for the chemical shift and coupling constant parameters (136). Here a knowledge of

the spectra of similar compounds is helpful. The computer program then operates on the energy levels, derived from the assigned transitions, and calculates the changes in parameters necessary to adjust these approximate energy levels towards the experimental ones. This process is repeated until parameters are calculated which give a good fit to the experimental spectrum.

The pattern for the benzenoid protons in the N.M.R. spectrum of I is greatly affected by solvent. In dioxane solution the spectrum of the benzenoid protons itself is not affected but the signals for the thiazole ring protons no longer overlap it. In acetone solution the pattern for the two benzenoid protons at lower field (H_5 and H_8) is more spread out but still highly perturbed. At 100 megacycles in acetone the signals for H_5 and H_8 are well separated and the spectrum has become essentially an ABMX system (Fig. 10). However, it is impossible to say which of these protons (H_5 or H_8) gives a signal at lower field.

It is interesting to note that in the N.M.R. spectrum of thiazolo[3,2-a]benzimidazole (I) the signal for H_2 occurs at higher field (6.7 p.p.m.) than the signal for the corresponding proton (H_5) of the thiazole (7.1 p.p.m.) Also, the signals for protons on the benzene ring, in particular the two alpha to the heterocyclic ring, are shifted downfield compared to the signals for the benzenoid protons of

2-ethylthiobenzimidazole (VI) (7.6-7.0 p.p.m.). It has been shown that ring currents in one ring of a fused carbocyclic aromatic system affect the line positions for protons in the other ring (63). Albert has noted that imidazole has a greater π-electron density than thiazole (65). Hence, the ring current of the electron-rich imidazole ring may cause the upfield shift of the signals for the protons on the thiazole ring and the ring current of the thiazole ring may deshield the protons of the benzene ring through the imidazole ring.

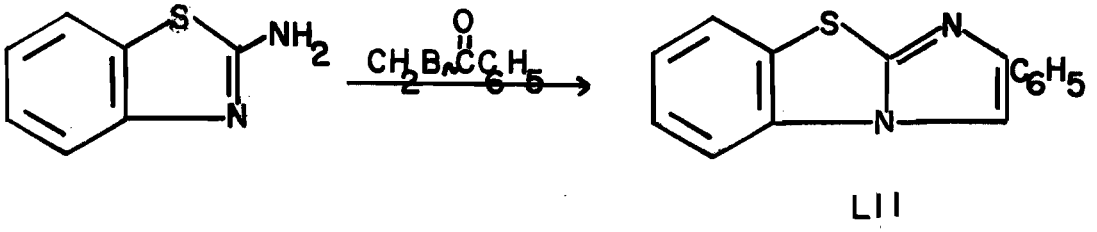
II. Synthesis of Imidazo[2,1-b]benzothiazoles

The imidazo[2,1-b]benzothiazoles were synthesized by annelation of an imidazole ring to benzothiazole by the condensation of 2-aminobenzothiazole with an alpha-haloaldehyde or ketone. Ochiai had synthesized 2-phenylimidazo[2,1-b]-benzothiazole in this manner (29). This method is an application of the widely used synthesis of 2-arylimidazoles from an alpha-haloketone and a benzamidine (129).

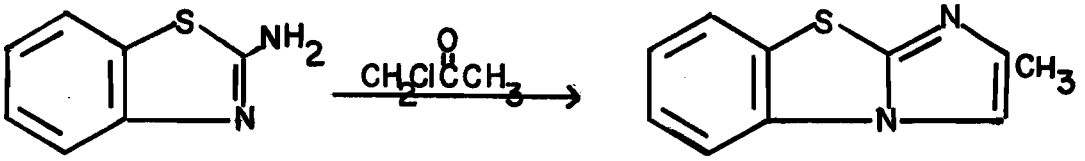
A. Syntheses of Imidazo[2,1-b]benzothiazole and Derivatives Substituted on the Imidazole Ring

2-Phenylimidazo[2,1-b]benzothiazole (LII) was synthesized according to Ochiai (29). In this investigation (Scheme 14) condensation of 2-aminobenzothiazole and bromo-

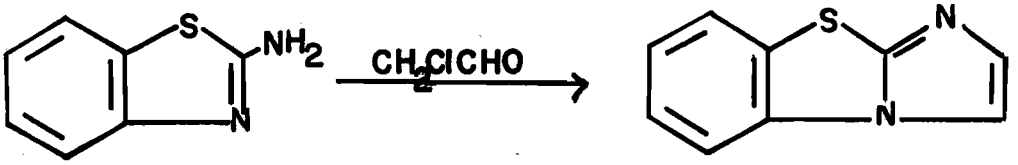
SCHEME 14



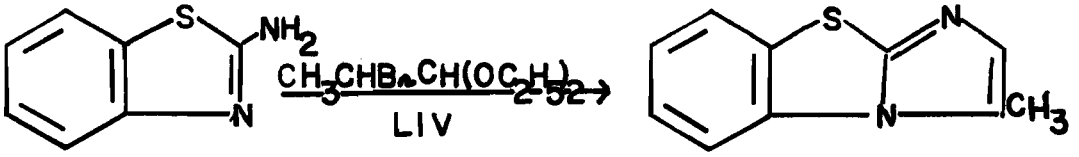
LII



XLVIII



LI



LIII

acetophenone gave a 90% yield of the hydrobromide salt of LII which was only sparingly soluble in water. 2-Phenylimidazo[2,1-b]benzothiazole (LII) was obtained by treatment of the hydrobromide in ethanol with triethylamine. The N.M.R. spectrum of LII in $CDCl_3$ showed a multiplet between 7.99 and 7.81 p.p.m. for the phenyl protons and a multiplet between 7.08 and 7.75 p.p.m. for the five aromatic protons of the imidazo[2,1-b]benzothiazole system. The sharp singlet at 7.31 p.p.m. is assigned to the proton at C_3. The low field position of the phenyl protons is the result of conjugation with the heterocyclic ring.

Ochiai (29) had stated that the 2-phenylimidazo-[2,1-b]benzothiazole (LII) formed but gave no proof that the product was not the 3-phenyl isomer. However, Krönke and Kickhöfen (43) had shown the direction of the annelation of an imidazole ring by this method in the imidazo[2,1-b]thiazole series. They found that 6-phenylimidazo[2,1-b]thiazole was obtained from either 2-aminothiazole or 2-acetamidothiazole and bromoacetophenone. However, an attempt to show unequivocally that the condensation proceeded in this direction in the imidazo[2,1-b]benzothiazole series was unsuccessful. Treatment of 2-acetoamidobenzothiazole with chloroacetone in refluxing toluene gave no product.

2-Methylimidazo[2,1-b]benzothiazole (XLVIII) was synthesized (Scheme 14) by the condensation of 2-aminobenzo-

thiazole and chloroacetone in ethanol. In all instances the condensation was not complete. The N.M.R. spectrum of the crude product indicated that a 1:1 mixture of XLVIII and 2-aminobenzothiazole was present. The ratio of the aromatic protons to methyl protons was 3:1 and there was a broad signal for the amino group of 2-aminobenzothiazole at 6.2 p.p.m. which disappeared on exchange with deuterium oxide. XLVIII was separated from the recovered starting material by treatment of the crude product with acetic anhydride. 2-Acetamidobenzothiazole was formed which was insoluble in dilute acid. The acid-soluble 2-methylimidazo-[2,1-b]benzothiazole (XLVIII) was obtained on basification. The N.M.R. spectrum of XLVIII showed a complex multiplet between 7.80 and 7.15 p.p.m. for the five aromatic protons and a singlet at 2.4 p.p.m. for the methyl group. The signal for the proton at C_3 could be distinguished from the other aromatic protons at 7.42 p.p.m. This signal and that of the methyl group showed a weak coupling of approximately 1 cps. The infrared spectra of XLVIII and the other imidazo[2,1-b]-benzothiazoles will be discussed together (Section B).

3-Methylimidazo[2,1-b]benzothiazole (LIII) was also synthesized. An alpha-halopropionaldehyde was necessary for this synthesis. Due to the low yield of chloropropionaldehyde obtained previously (Part I, Section D) from chlorination of n-propyl ether, other procedures were investigated. Alpha-

bromopropionaldehyde diethyl acetal (LIV) was prepared in good yield by the method of Chastrette (23). In this investigation propionaldehyde diethyl acetal was obtained from propionaldehyde in 73% yield. Bromination of the acetal gave a 61% yield of LIV. Alpha-bromopropionaldehyde diethyl acetal was hydrolyzed with hydrobromic acid. The alpha-bromopropionaldehyde was not isolated but was used in the reaction with 2-aminobenzothiazole to give an 80% yield of 3-methylimidazo-[2,1-b]benzothiazole (LIII). In the N.M.R. spectrum of LIII (in $CDCl_3$), a complex multiplet appeared between 7.93 and 7.26 p.p.m. for the five aromatic protons and a singlet occurred at 2.66 p.p.m. for the methyl group. The signal for H_2 could be distinguished as a sharp singlet at 7.66 p.p.m. No coupling between the methyl group and the adjacent proton was observed in this spectrum.

The parent compound of the imidazo[2,1-b]benzothiazole series was synthesized by condensation of 2-aminobenzothiazole and chloroacetaldehyde. The crude product was a mixture of starting material and imidazo[2,1-b]benzothiazole (LI) which were separated by acetylation of the 2-aminobenzothiazole. The N.M.R. spectrum of LI in $CDCl_3$ (Fig. 13) showed a complex pattern between 7.75 and 7.16 p.p.m. for the six aromatic protons. Two doublets for the protons on the imidazole ring could be distinguished from the pattern for the benzenoid protons at 7.66 and 7.40 p.p.m. (J = 1.5 cps).

It was observed that when an alpha-bromoketone or aldehyde was used in the preparation of imidazo[2,1-b]benzothiazoles no unreacted starting material was recovered. The failure to obtain complete reaction with the chloro compounds may be due to their lesser reactivity. The halogen of the bromocarbonyl compounds is known to be more easily displaced than that of the chlorocompounds.

B. Spectra of Imidazo[2,1-b]benzothiazoles

The spectra of the imidazo[2,1-b]benzothiazoles had not been previously reported. Therefore, the infrared, ultraviolet and N.M.R. spectra of these compounds were recorded.

1. Infrared Spectra

The absorption bands in the infrared spectra of the imidazo[2,1-b]benzothiazoles, typical of such a heteroaromatic compound, are classified and discussed according to the main spectral regions in which they occur.

The 3000-3100 $cm.^{-1}$ region.

The imidazo[2,1-b]benzothiazoles show absorption in this region for the C-H stretching vibrations of the benzene and imidazole rings. In the infrared spectrum of imidazole the C-H stretching absorption is masked by that of the hydrogen-bonded N-H groups. However, in N-substituted imidazoles bands at 3060 and 3040 $cm.^{-1}$ have been assigned to C-H stretching vibrations (132). Imidazo[2,1-b]benzothia-

zole (LI) has bands of weak to medium intensity at 3134 and 3111 $cm.^{-1}$ and a weaker band at 3062 $cm.^{-1}$ (Fig. 11). The 3-methyl compound shows no absorption above 3100 $cm.^{-1}$ and has only a single weak band at 3060 $cm.^{-1}$ In the infrared spectra of the substituted derivatives there is weak absorption at 3122 $cm.^{-1}$ and a more intense band near 3055 $cm.^{-1}$ However, the number of compounds studied was too small to make any definite correlation between the number of bands and positions of the substituents. Metzger and his co-workers have assigned bands at 2940 and 2875 $cm.^{-1}$ in the infrared spectrum of 2-mercaptobenzothiazole to the aromatic C-H stretching of the benzene ring (133). However, no absorption was noted between 3000 and 2800 $cm.^{-1}$ in the spectrum of LI.

The 1650-1500 $cm.^{-1}$ region.

The C=C and C=N stretching vibrations occur between 1650 and 1500 $cm.^{-1}$ Bassignana and his co-workers have studied the infrared spectra of a number of substituted benzothiazoles and found that they usually exhibit three bands in this region at 1600-1592 $cm.^{-1}$, 1570-1550 $cm.^{-1}$ and 1540-1525 $cm.^{-1}$ (131) which they assign to the C=N stretching of the thiazole ring, a C=C stretching and a thiazole ring vibration respectively. Imidazoles show a weak band in this region at approximately 1605 $cm.^{-1}$ and one of greater intensity between 1550 and 1531 $cm.^{-1}$ designated as the Imidazole I (C=N stretching) and

Imidazole II vibrations respectively (134). In fused ring systems the C=C and C=N vibrations are strongly coupled and cannot be distinguished (59).

Imidazo[2,1-b]benzothiazole (LI) shows three bands in this region at 1625 (w), 1592 (m) and 1573 (w) $cm.^{-1}$ The derivatives of LI substituted on the imidazole ring show no absorption above 1600 $cm.^{-1}$ 3-Methylimidazo[2,1-b]benzothiazole has a band of medium intensity at 1581 $cm.^{-1}$ and a weaker band at 1556 $cm.^{-1}$ The 2-substituted compounds showed absorption at 1595, 1578 and 1545 $cm.^{-1}$

The 1500-1350 $cm.^{-1}$ region.

Absorption occurs in this region for the in-plane skeletal vibrations of heteroaromatic compounds. Imidazole has two bands at 1492 and 1451 $cm.^{-1}$ (130), however, substituted imidazoles absorb at 1460 and 1420 $cm.^{-1}$ (134). 2-Substituted benzothiazoles show two very strong bands between 1450 and 1425 $cm.^{-1}$ characteristic of the benzothiazole ring system (133). The imidazo[2,1-b]benzothiazoles all have a very strong band at 1490 ± 2 $cm.^{-1}$ Imidazo[2,1-b]benzothiazole (LI) has three additional bands in this region at 1478 (s), 1449 (m) and 1377 (m) $cm.^{-1}$ The substituted derivatives, however, showed no absorption between 1350 and 1400 $cm.^{-1}$

The 950-650 $cm.^{-1}$ region

Aromatic compounds both heterocyclic and carbocyclic show strong absorption for the C-H out-of-plane bending

vibrations between 950 and 650 $cm.^{-1}$ Heterocyclic ring-breathing modes also occur in this region (170).

The imidazo[2,1-b]benzothiazoles studied show very strong bands between 760 and 735 $cm.^{-1}$ the region given by O'Sullivan for the C-H out-of-plane deformation of the four adjacent hydrogens on a benzene ring fused to a five-membered ring (105). 2-Phenylimidazo[2,1-b]benzothiazole also has a strong band at 712 $cm.^{-1}$ for the out-of-plane bending of the five phenyl hydrogens.

Imidazo[2,1-b]benzothiazole shows absorption of medium intensity at 854 $cm.^{-1}$ and four bands of strong to medium intensity at 733, 717, 707 and 675 $cm.^{-1}$ The substituted derivatives also have bands of variable intensity in this region. These bands probably arise from ring-breathing modes and C-H out-of-plane deformations of the imidazole ring. However, since the positions and intensities vary greatly in the spectra studied no definite correlations can be made.

Otting has assigned bands at 659, 738 and 758 $cm.^{-1}$ to the C-H out-of-plane deformations of imidazole (135) but no assignments have been made for bands in this region in the infrared spectra of substituted imidazoles. Benzothiazoles and imidazoles show absorption of variable intensity between 920 and 860 $cm.^{-1}$ and 970 and 930 $cm.^{-1}$ respectively, for the ring-breathing vibrations (131,134).

2. Ultraviolet Spectra

The imidazo[2,1-b]benzothiazoles show four main absorption maxima in the ultraviolet between 400 and 200 mμ (Table VI). They are classified as the α-, p-, β- and β'-bands, as were the bands in the ultraviolet spectra of the thiazolo[3,2-a]benzimidazoles, in analogy with the carbocyclic compounds.

TABLE VI

Ultraviolet Absorption Maxima (mμ) and Corresponding Log ε Values of the Imidazo[2,1-b]benzothiazoles in Ethanol

Compound	α-Band	p-Band	β-Band	β'-Band
Imidazo[2,1-b] Benzothiazole (LI)	292(3.42) 283(3.44)	236(4.29)	218(4.37)	*
3-Methyl-(LIII)	290(3.08) 283(3.15)	231(3.92)	217.5(4.11)	205(4.29)
2-Methyl-(XLVIII)	294(3.36) 286(3.44)	240(4.18)	220(4.28)	204(4.54)
2-Phenyl-(LII)	263 (4.44)	244(4.44)	215(4.58)	205(4.59)
Benzothiazole (107)	292.3 283.2 276.7	256.5 250.6	215.7	+

\+ Solvent absorption is high.

* Intensity still increasing at 200 mμ.

The spectrum of benzothiazole has recently been interpreted by Ellis and Griffiths (107) by comparison to

that of naphthalene and benzothipphene. The α-, p-, β- and β'-bands were observed and related to those for naphthalene. The β'-band of benzothiazole is only observed in hexane and water solutions. In general the spectrum of imidazo-[2,1-b]benzothiazole (Fig. 12) resembles that of benzo-thiazole (Table VI). The only effect on the ultraviolet absorption spectrum by annelation of an imidazole ring is a shift of the p-band to shorter wavelengths.

3. N.M.R. Spectra

Imidazo[2,1-b]benzothiazole (LI) has six aromatic protons which will give signals in its N.M.R. spectrum. The four protons on the benzene ring are independent of the two on the imidazole ring as they are separated by the thiazole nucleus.

The N.M.R. spectrum of imidazo[2,1-b]benzothiazole (LI) in $CDCl_3$ (Fig. 13) shows a complex multiplet between 7.83 and 7.11 p.p.m. for its six protons. The two imidazole-ring protons are distinguished as sharp doublets at 7.66 and 7.40 p.p.m. The assignment of these signals to the protons on the heterocyclic ring is confirmed by their preferential solvent shift. The two doublets appear 17 cps apart and are masked by the signals for the benzenoid protons in the N.M.R. spectrum in deuterated chloroform. However, in the N.M.R. spectrum of LI in dioxane solution the two doublets appear

at 7.53 and 7.01 p.p.m. separated by 31 cps and in acetone solution at 8.1 and 7.39 p.p.m. with an internal chemical shift of 44 cps, completely separated from the signals of the benzene ring protons. A similar solvent effect was noted on the chemical shift of the thiazole-ring protons of thiazolo[3,2-a]benzimidazole (I); however, the internal chemical shift between H_2 and H_3 was not greatly affected.

The N.M.R. spectrum of 3-methylimidazo[2,1-b]-benzothiazole shows a signal at 7.66 p.p.m. for H_2; H_3 gives a signal at 7.42 p.p.m. in the N.M.R. spectrum of 2-methyl-imidazo[2,1-b]benzothiazole (XLVIII). Therefore, the doublet at lower field in the N.M.R. spectrum of LI is assigned to H_2. Comparison of the positions of the signals for H_2 and H_3 in these three spectra indicates that a methyl group has little effect on the chemical shfft of the adjacent proton.

The fact that the proton adjacent to the bridgehead nitrogen atom gives a signal at higher field (7.44 p.p.m.) in the N.M.R. spectrum of LI than H_2 (7.66 p.p.m.) indicates that the two nitrogens are non-equivalent. The bridgehead nitrogen atom acts similarly to the nitrogen of pyrrole and the other nitrogen behaves as a pyridine nitrogen.

The coupling constant (J_{23}) between the protons on the imidazole ring is small in comparison to that for the ortho protons of six-membered aromatics (J = 8-10 cps)(71)

and even compared to that for other five-membered heterocycles. Corresponding results have been noted in the N.M.R. spectra of 1-substituted imidazoles for which J_{45} is between 1.4 and 1.8 cps. This effect is due to the electronegativity of the adjacent atoms and the bond angle between the adjacent C-H bonds in the different systems (83,126).

The four benzenoid protons give a complex ABCD pattern between 7.75 and 7.16 p.p.m. in the N.M.R. spectrum of LI in $CDCl_3$ (Fig. 13). Fifteen lines are distinguished; however, some are masked by the signals of the imidazole-ring protons. In acetone the spectrum is more spread out and the four benzenoid protons show two separate patterns between 8.08 and 7.75 p.p.m. and between 7.75 and 7.39 p.p.m. However, the system is still complex and it is impossible to assign any lines with certainty.

It is interesting to note the effect of annelation of an imidazole ring to the benzothiazole system on the chemical shifts of the protons. When the N.M.R. spectrum of imidazo[2,1-b]benzothiazole is compared to the spectra of imidazole and benzothiazole in $CDCl_3$ (95) it can be seen that the signals for the imidazole-ring protons are shifted downfield from their position in the spectrum of unsubstituted imidazole (7.14 p.p.m. to 7.66 and 7.40 p.p.m.) and that the signals for the benzenoid protons adjacent to the heterocyclic ring in benzothiazole are shifted to higher field to overlap the signals for the other two benzenoid protons in the N.M.R.

spectrum of the tricyclic compound. The ring current of the imidazole ring increases the shielding of the protons of benzothiazole. A similar effect of the imidazole ring was observed on the chemical shifts of the protons of the thiazole ring in thiazolo[3,2-a]benzimidazole.

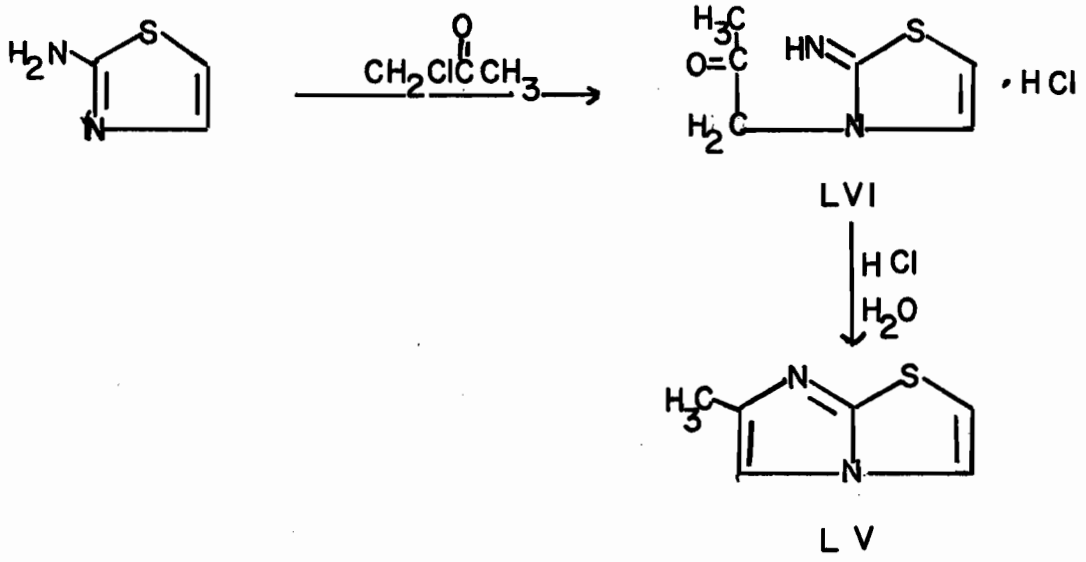
III. Syntheses of Imidazo[2,1-b]thiazoles

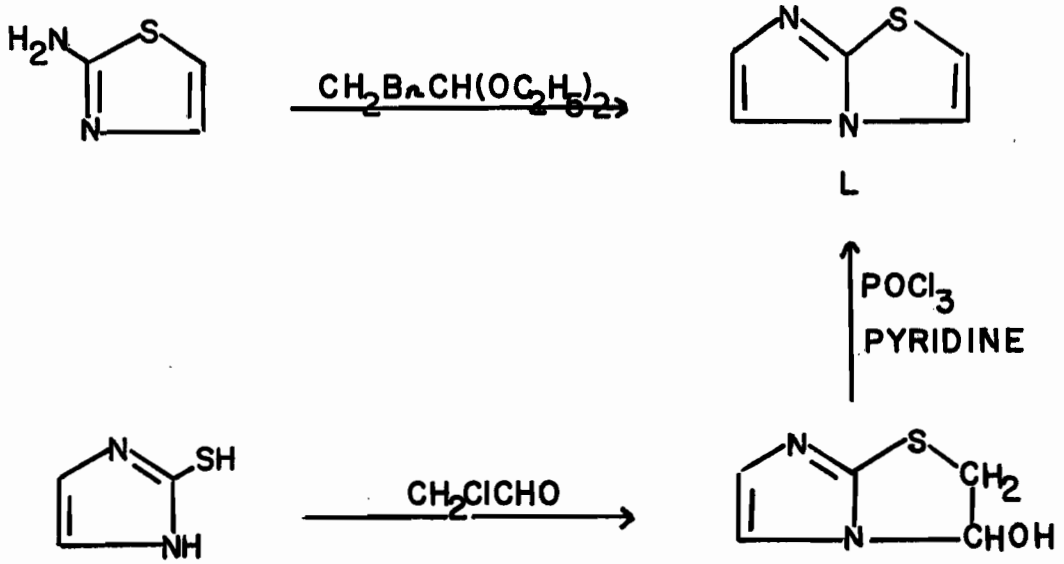
The methods of synthesis for thiazolo[3,2-a]benzimidazoles and imidazo[2,1-b]benzothiazoles described in Parts I and II of this discussion were applied in the imidazo[2,1-b]thiazole series. The 6-methyl derivative was prepared from 2-aminothiazole and chloroacetone. The parent compound, which had not been previously reported, was synthesized by annelation of a thiazole ring to 2(3H)-imidazolethione as well as by annelation of an imidazole ring to 2-aminothiazole.

A. Syntheses of Imidazo[2,1-b]thiazole and 6-Methylimidazo-[2,1-b]thiazole

Treatment of 2-aminothiazole with chloroacetone in 2-butanone at room temperature gave 2-imino-3-(2-propanone)-thiazole hydrochloride (LVI) in 80% yield (Scheme 15). The infrared spectrum of the product indicated that condensation had occurred as there was no absorption for a primary amine and a strong band appeared at 1710 $cm.^{-1}$ for the carbonyl stretch of the ketone. On standing at room temperature LVI spontaneously underwent cyclodehydration to give the hydrochloride salt of 6-methylimidazo[2,1-b]thiazole. Also, all

SCHEME 15


CH2ClCCH3
O
HCl
LVI
HCl
H2O
LV


CH2BrCH(OC2H5)2
L
POCl3
PYRIDINE
CH2ClCHO

attempts to isolate the free base 2-imino-3-(2-propanone)-thiazole were unsuccessful and resulted in cyclodehydration. Pyl (44) had noted spontaneous ring closure of thiazolyl ketones of this type and ascribed it to the fact that the salts are in the correct pH range for the acid-catalyzed ring closure. Treatment of LVI with dilute hydrochloric acid followed by basification gave 6-methylimidazo[2,1-b]thiazole (LV). Three distillations of the product gave an analytically pure sample (b.p. 102-104°/1.5 m.m., ($C_6H_6N_2S$) which failed to crystallize. However, after standing for four months, fine needles began to form.

The N.M.R. spectrum of 6-methylimidazo[2,1-b]thiazole (LV) in $CDCl_3$ showed a pair of doublets at 7.30 and 6.60 p.p.m. (J = 4.5 cps) for H_3 and H_2, respectively, and a signal at 7.16 p.p.m. for the proton on the imidazole ring (H_5) and a doublet at 2.33 p.p.m. (J = 1.0 cps) for the methyl group. The signal at 7.16 p.p.m. did show some splitting due to coupling with the adjacent methyl protons but was not well resolved.

The methyl group is located in the 6-position by analogy with the work of Krönke and Kickhöfen (43) who showed the direction of the condensation reaction between 2-aminothiazole and bromoacetophenone.

Treatment of 2-aminothiazole with bromoacetaldehyde, obtained from the hydrolysis of bromoacetaldehyde diethyl acetal, in ethanol gave imidazo[2,1-b]thiazole (L) (Scheme 15). No intermediate condensation product was isolated in this reaction. This is not surprising due to the greater reactivity of the aldehyde compared to the methyl ketone. In the N.M.R. spectrum of L in $CDCl_3$ (Fig. 14) the quartet at 6.78 p.p.m. is assigned to H_2 (J = 4.5 cps and J = 1 cps), the doublet at 7.38 p.p.m. (J = 4.5 cps) to H_3, the doublet at 7.41 p.p.m. (J = 1.2 cps) to H_6 and the triplet at 7.30 p.p.m. (J ≈ 1 cps) to H_5. Of the two signals for the imidazole-ring protons (7.41 and 7.30 p.p.m.) the signal at higher field (7.30 p.p.m.) is assigned to H_5 in analogy with the positions of the signals for H_2 and H_3 in the N.M.R. spectrum of imidazo-[2,1-b]benzothiazole. The long-range coupling of H_2 with H_5 occurs across five bonds. Similar long-range coupling has been observed for other bicyclic heteroaromatics (139,140) and is accounted for by π-electron interactions (141).

From the N.M.R. spectrum of (L) and that of the 6-methyl derivative it is noted that the signals for the protons on the imidazole ring occur at lower field than in the spectrum of imidazole itself (95) and the thiazole ring protons give signals at higher field than those of the unsubstituted thiazole (88). A similar effect was noted on fusion of an imidazole ring to benzothiazole (Part II) and on fusion of an imidazole ring to pyridine (99).

If these shifts in the line positions in the N.M.R. spectrum occurring on fusion of another ring can be attributed to ring current effects then this is evidence for the aromaticity of the three heterocyclic systems studied in this investigation. Elvidge and Jackman have defined an aromatic compound as one which will sustain ring current (143). This would mean that the bridgehead nitrogen atom contributes two electrons to the aromatic systems. Therefore it has sp^2 bonding and is similar to the nitrogen atom in pyrrole.

Imidazo[2,1-b]thiazole was also synthesized from 2(3H)-imidazolethione (Scheme 15). Condensation of chloroacetaldehyde and 2(3H)-imidazolethione in 2-butanone gave a product in low yield which was tentatively identified as 3-hydroxy-2,3-dihydroimidazo[2,1-b]thiazole. The infrared spectrum of this product indicated the alcohol structure. There was broad absorption between 3120 and 2600 $cm.^{-1}$ (bonded O-H stretch), a strong band at 1051 $cm.^{-1}$ (C-O stretch) and a band of medium intensity at 1339 $cm.^{-1}$ (O-H deformation). This product was not further characterized due to the low yield. Treatment of the hydrochloride salt of this condensation product with phosphorus oxychloride in pyridine gave imidazo-[2,1-b]thiazole (L). Its infrared spectrum was superimposable on that of (L) obtained from 2-aminothiazole.

B. Spectra of Imidazo[2,1-b]thiazoles

The absorption bands appearing in the ultraviolet and infrared spectra characteristic of the imidazo[2,1-b]-thiazole ring system are pointed out. The spectra of 5,6,7,8-tetrahydrothiazolo[3,2-a]benzimidazole (XII), which is actually a derivative of imidazo[2,1-b]thiazole, are included in this discussion.

1. Infrared Spectra

The typical vibrations of aromatic heterocycles give bands in the infrared spectra of the imidazo[2,1-b]-thiazoles.

The 3100-3000 $cm.^{-1}$ region

The infrared spectrum of imidazo[2,1-b]thiazole (L) (Fig. 15) has a band of medium intensity at 3054 $cm.^{-1}$ with a shoulder at 3080 $cm.^{-1}$ The 6-methyl compound, however, shows absorption only above 3100 $cm.^{-1}$ (Table VII) and 5,6,7,8-tetrahydrothiazolo[3,2-a]benzimidazole (XII) has three bands at 3116, 3090 and 3043 $cm.^{-1}$ These bands are assigned to the C-H stretching vibrations. Substitution seems to affect their positions to some extent. Thiazole itself and the methylthiazoles all showed a band at 3090 $cm.^{-1}$ for the C-H stretching vibrations (75).

The 1600-1500 $cm.^{-1}$ region

Bassignana and his co-workers have studied this region in the infrared spectra of imidazoles (134) and thia-

TABLE VII

Absorption Maxima ($cm.^{-1}$) in the Infrared Spectra of Imidazo[2,1-b]thiazoles as KBr Pellets

Region	Imidazo-[2,1-b]thiazole (L)	6-Methyl-imidazo-[2,1-b]thia-zole (LV)	5,6,7,8-Tetra-hydrothiazolo-[3,2-a]benzimi-dazole (XII)
3100-3000	3080 w	3137 m	3116 w
	3053 m	3111 m	3090 m
			3043 w
1500-1600	1575 w	1687 w	1588 m
	1548 m	1679 w	1553 w
		1561 m	1532 s
		1554 m	
1500-1350	1460 s	1466 s	1445 s
	1378 w	1370 m	1381 s
1350-1050	1332 m	1334 m	1310 s
	1288 s	1292 s	1251 m
	1243 m	1248 m	1225 s
	1130 m	1163 m	1124 m
	1120 m		
950-650	920 m	998 w	849 s
	842 m	968 m	821 m
	744 m	953 m	749 s
	732 m	794 w	718 m
	713 s		708 w
	652 w		681 m
			660 s

w = weak; m = medium; s = strong.

zoles (131). Thiazoles show weak absorption between 1625 and 1601 $cm.^{-1}$ and a more intense band between 1550 and 1505 $cm.^{-1}$ Imidazoles also have two bands in this region, the weaker near 1605 $cm.^{-1}$ and the more intense between 1531 and 1550 $cm.^{-1}$ The absorption at higher frequency in each case is assigned to the C=N stretching.

Imidazo[2,1-b]thiazoles showed at least two bands between 1590 and 1530 $cm.^{-1}$ with that at lower frequency being more intense. The 6-methyl compound showed weaker absorption as well at 1679 and 1687 $cm.^{-1}$ It is impossible to assign these bands to specific vibrations of either ring as strong coupling of C=C and C=N vibrations occurs in such hetero-aromatic systems (59).

The 1500-1350 $cm.^{-1}$ region.

Imidazo[2,1-b]thiazole (L) has a strong band at 1460 $cm.^{-1}$ and a weaker band at 1378 $cm.^{-1}$ These are assigned to the in-plane skeletal vibrations characteristic of this system. LV and XII show these two bands (Table VII) as well as absorption for the methyl and methylene deformation vibrations, respectively. Imidazole shows intense absorption at 1451 $cm.^{-1}$ (130) and thiazoles have a band of strong to medium intensity between 1385 and 1375 $cm.^{-1}$ (75) for the skeletal vibrations of these five-membered rings.

The 1350-1050 $cm.^{-1}$ region

The C-H in-plane deformation vibrations of hetero-aromatics occur in this region(70). The imidazo[2,1-b]thiazoles studied show similar patterns of bands (Table VII). Although the absorption in this region is usually characteristic of the ring system more compounds must be investigated before definite conclusions can be made for this series.

The 950-650 $cm.^{-1}$ region

The C-H out-of-plane deformation vibrations occur in this region (59). Although the position of these bands is characteristic of the substitution pattern for six-membered rings (70,150) no correlations have been made for these vibrations of substituted five-membered rings. Taurins and his co-workers assigned the bands at 880, 860, 800 and 720 $cm.^{-1}$ in the infrared spectrum of thiazole to C-H out-of-plane bending (75). Imidazole shows bands at 659, 738 and 758 $cm.^{-1}$ for its C-H bending vibrations (135).

The infrared spectra of imidazo[2,1-b]thiazoles show several bands between 950 and 650 $cm.^{-1}$ (Table VII). All absorption bands in this region do not arise from C-H deformations. Heterocyclic ring-breathing modes give bands of varying intensity between 1000 and 850 $cm.^{-1}$ Thiazoles absorb between 885 and 855 $cm.^{-1}$ (131) while imidazoles have a band of medium intensity between 970 and 930 $cm.^{-1}$ (134).

However, it would be necessary to study the spectra of more derivatives to decide where the ring-breathing modes of this fused-ring system absorb.

2. Ultraviolet Spectra

In general the interpretations of the ultraviolet spectra of five-membered heteroaromatic compounds are not satisfactory. These compounds are divided into two classes (107) according to their ultraviolet spectra. Class I includes thiophene, pyrrole and thiazole which show spectra similar to that of cyclopentadiene having two bands in the regions 240-250 mμ and 204-200 mμ. Class II of which imidazole is typical includes furan, pyrazole and oxazole and has one band with a maximum between 212 and 200 mμ. Furan, imidazole and thiophene have very weak bands between 269 and 250 mμ which Mason suggests may be due to the presence of impurities (112). Recently this suggestion has been confirmed for thiophene and furan (100).

It is evident from the data in Table VIII that the ultraviolet spectrum of imidazo[2,1-b]thiazole (Fig. 16) resembles that of cyclopentadiene and thiazole. Ellis and Griffiths have assigned both Bands A and B for thiazole to $\pi \rightarrow \pi^*$ transitions (10). Mason (112) has pointed out that $n \rightarrow \pi^*$ transitions have not been located in the absorption spectra of heteroaromatic five-membered ring compounds even

TABLE VIII

Ultraviolet Absorption Maxima (in mμ) and Corresponding log ε Values for Imidazo[2,1-b]thiazoles and Some Related Compounds.

Compound	B and A	B and B	Solvent
Imidazo[2,1-b]-thiazole (L)	248(3.62)	201(4.11)	Ethanol
6-Methylimidazo-[2,1-b]thiazole (LV)	244(3.59)	205(4.17)	Ethanol
5,6,7,8-Tetra-hydrothiazolo-[3,2-a]benzimi-dazole (XII)	260(3.98)	213(4.35)	Ethanol
Cyclopentadiene (112)	238.5(3.53)*	200(4.00)	Hexane
Thiazole (107)	231(3.53)	+	Methanol
Imidazole (112)	265(0.17)	206(3.53)	Water

+ High solvent absorption prevented accurate determination of ν_{max} (107).

* Converted from the original data using four-figure logarithms.

though such transitions would be expected to be relatively strong and of high energy. However Ellis and Griffiths (107) suggested since Band A in the ultraviolet spectra of thiazole is fairly broad it would probably overlap the absorption due to an $n \rightarrow \pi^*$ transition of high energy.

The effect of fusing the imidazole ring to thiazole on the ultraviolet spectrum of the latter was a marked intensification and bathochromic shift of Band A. Fusion of an imidazole ring to pyridine resulted in a similar bathochromic shift and intensification of the ultraviolet absorption maxima of pyridine (99).

An insufficient number of substituted imidazo[2,1-b]-thiazoles have been studied to permit consideration of substituent effects on the absorption maxima.

Figure 1

Infrared Spectrum of 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (III) in a KBr pellet

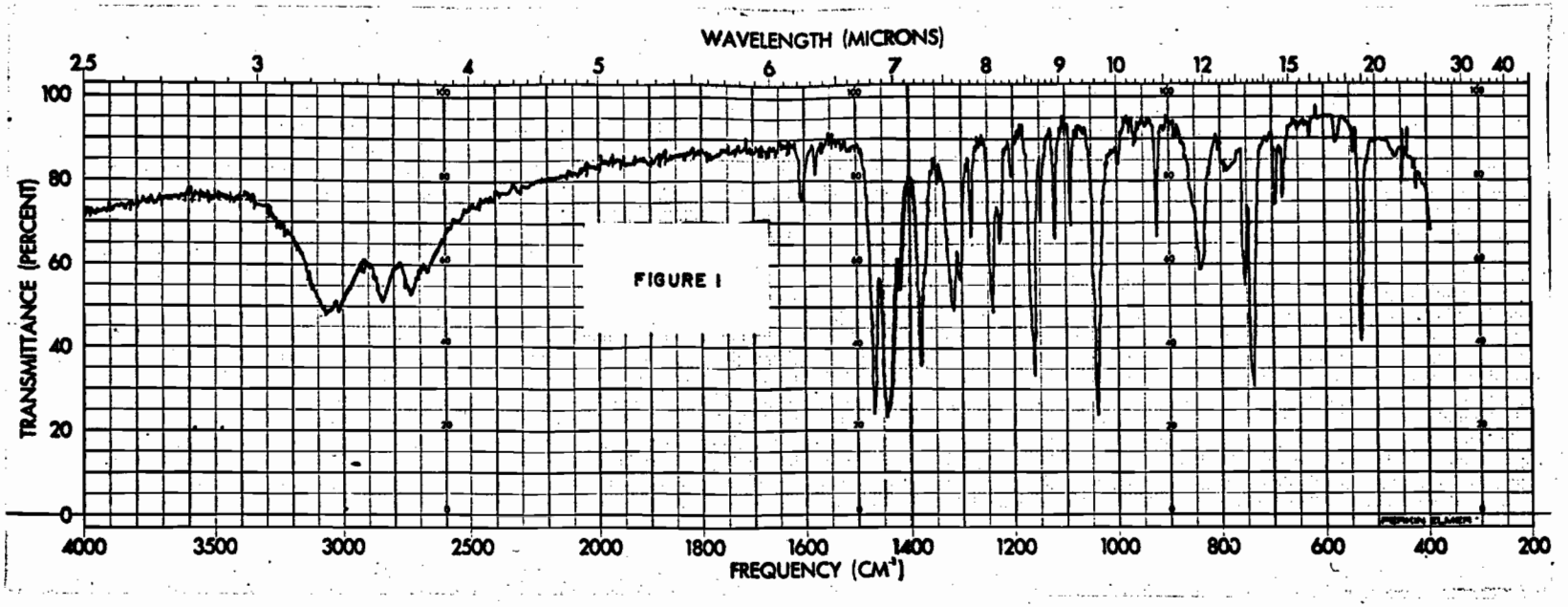

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)

FIGURE I

Figure 2

N.M.R. Spectrum of 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (III) in DMSO-d_6 (after exchange with trifluoroacetic acid)

FIGURE 2

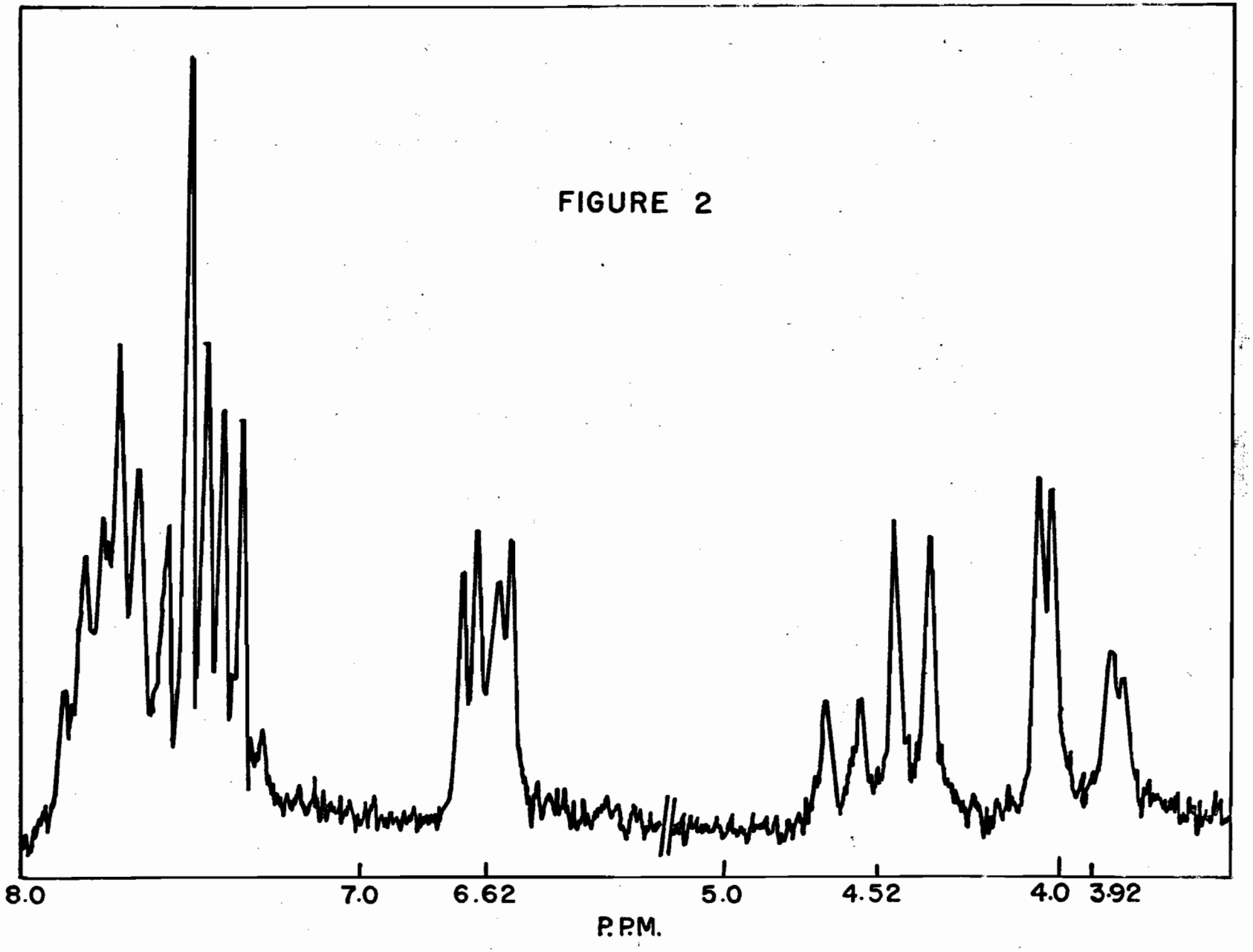


Figure 3

Infrared Spectrum of Thiazolo[3,2-a]benzimidazole (I)in a KBr pellet

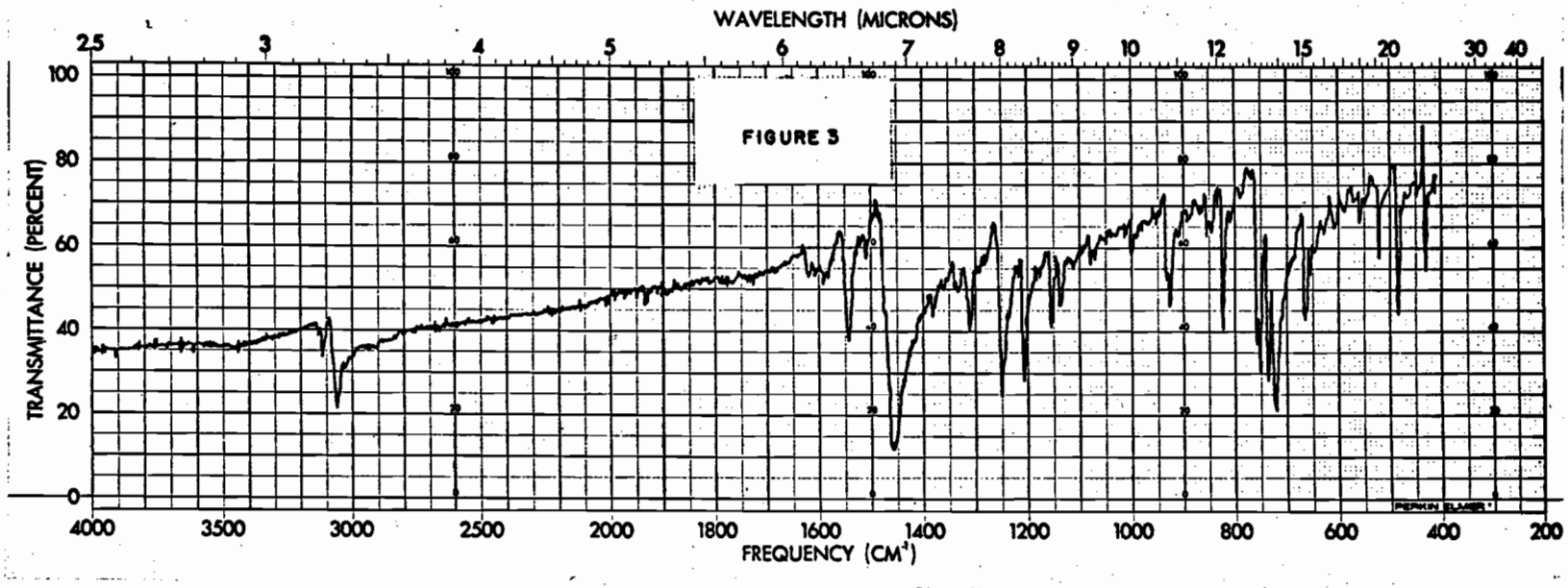

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
TRANSMITTANCE (PERCENT)
FIGURE 3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)

Figure 4

N.M.R. Spectrum of Thiazolo[3,2-a]benzimidazole (I) in $CDCl_3$

FIGURE 4

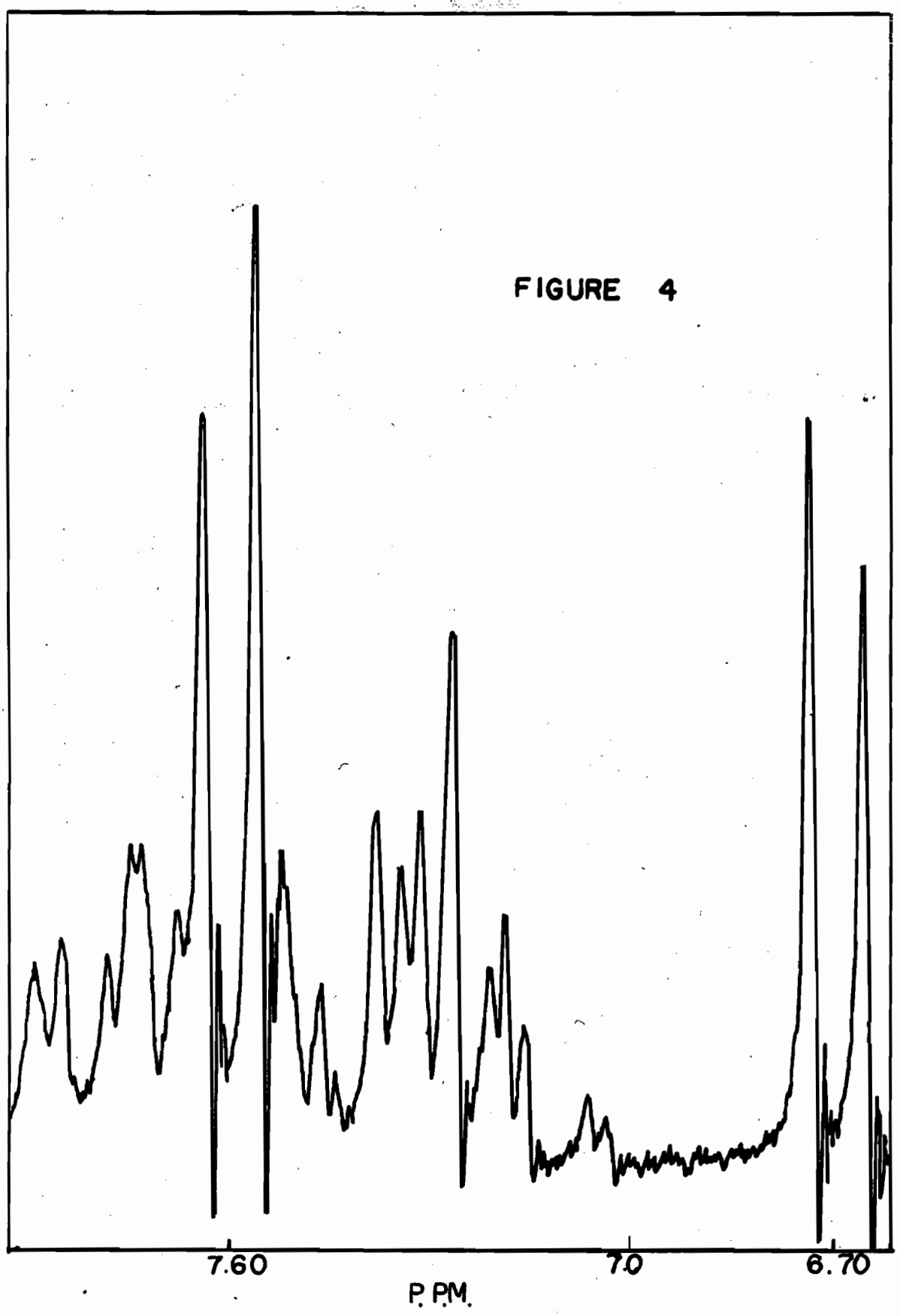


Figure 5

N.M.R. Spectrum of 6- (or 7-)Nitrothiazolo[3,2-a]benzimidazole (XLVII) in DMSO

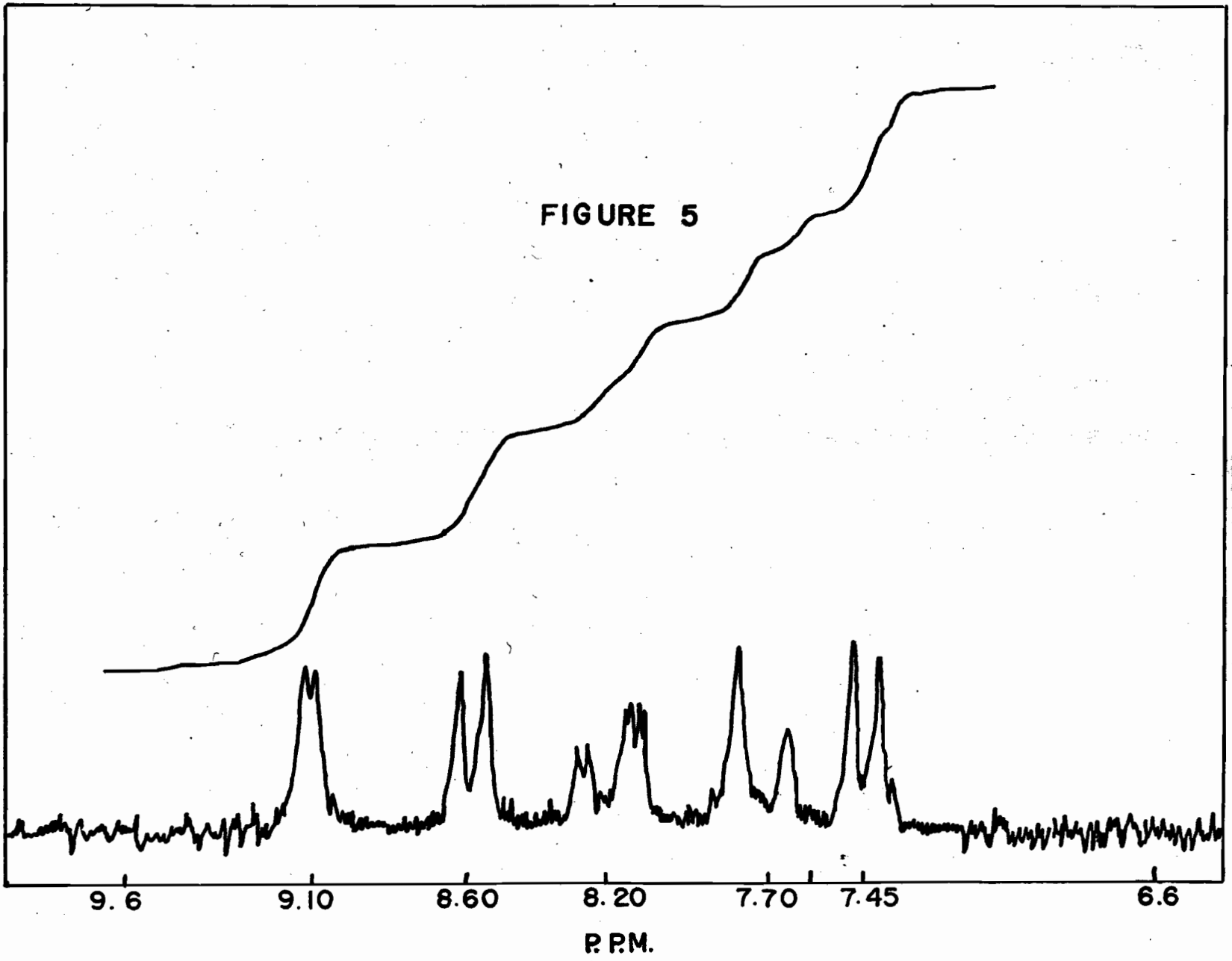


FIGURE 5

Figure 6

N.M.R. Spectrum of 5,8-Dimethylthiazolo[3,2-a]benzimidazole (XXII) in $CDCl_3$

FIGURE 6

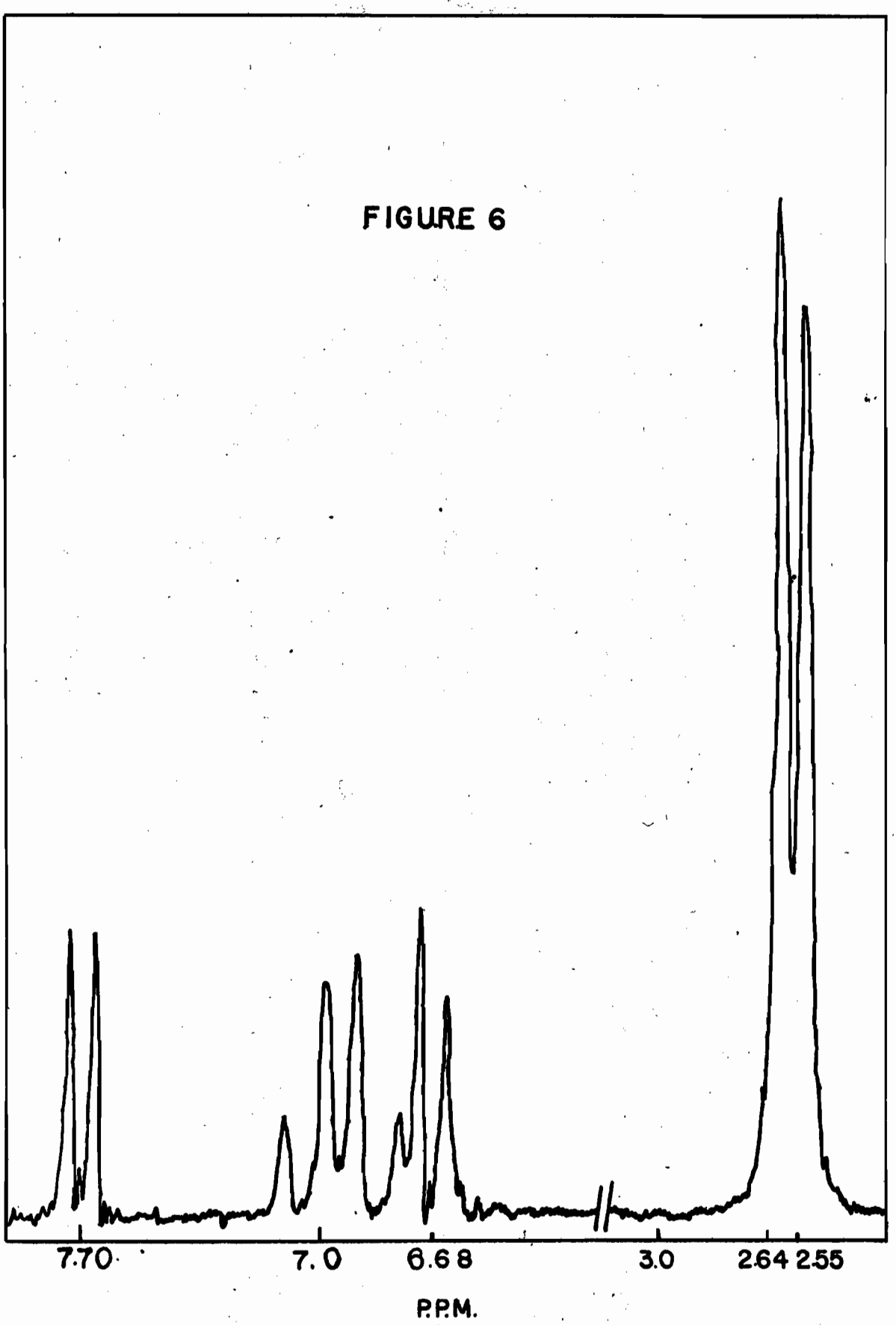


Figure 7

N.M.R. Spectrum of 3-Hydroxy-3-methyl-2,3-dihydrothiazolo-[3,2-a]benzimidazole (XXXV) in DMSO-d_6

FIGURE 7

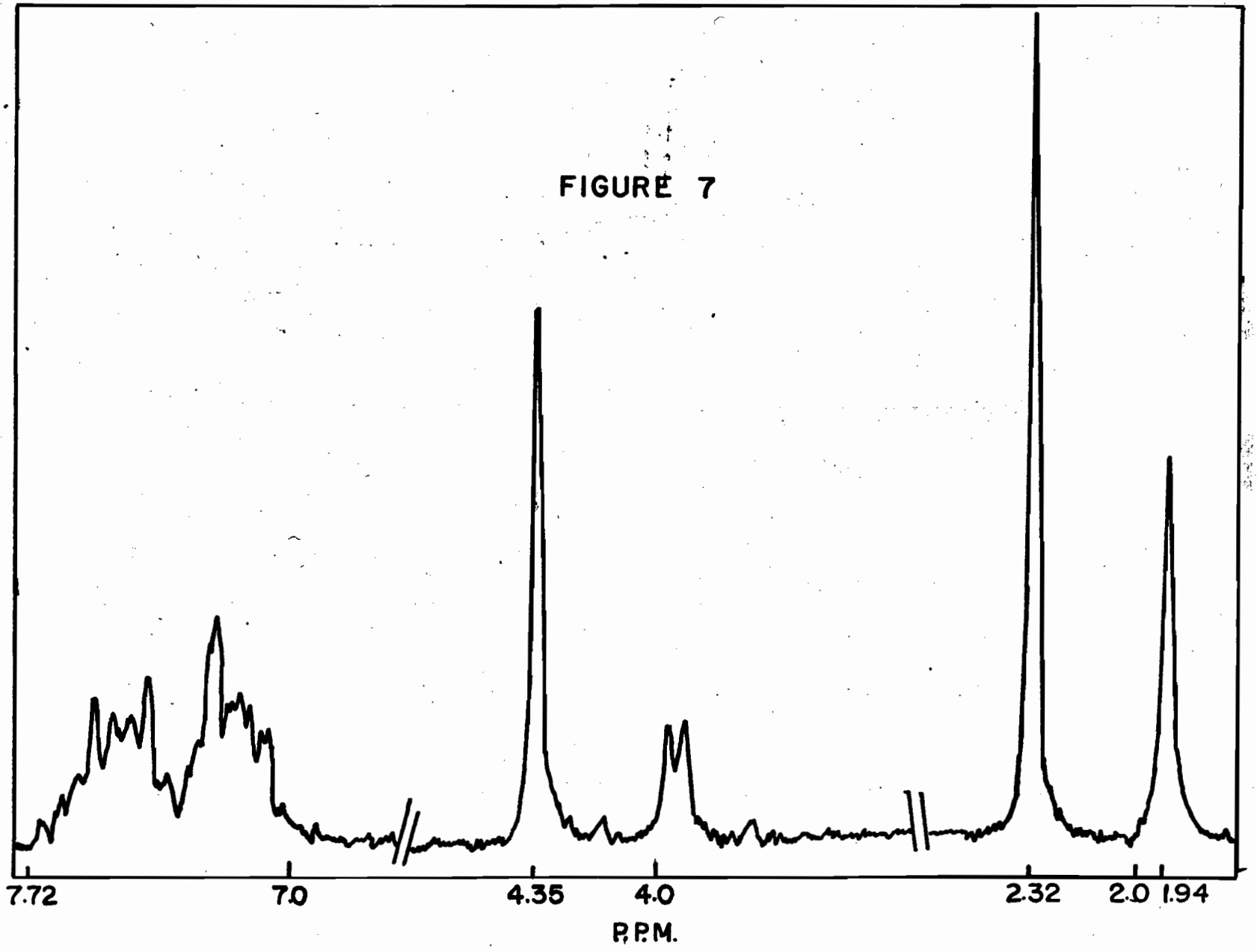


Figure 8

Ultraviolet spectrum of thiazolo[3,2-a]benzimidazole (I) in ethanol

_____ 0.056 mg./ml.

\- - - - - - 0.112 mg./ml.

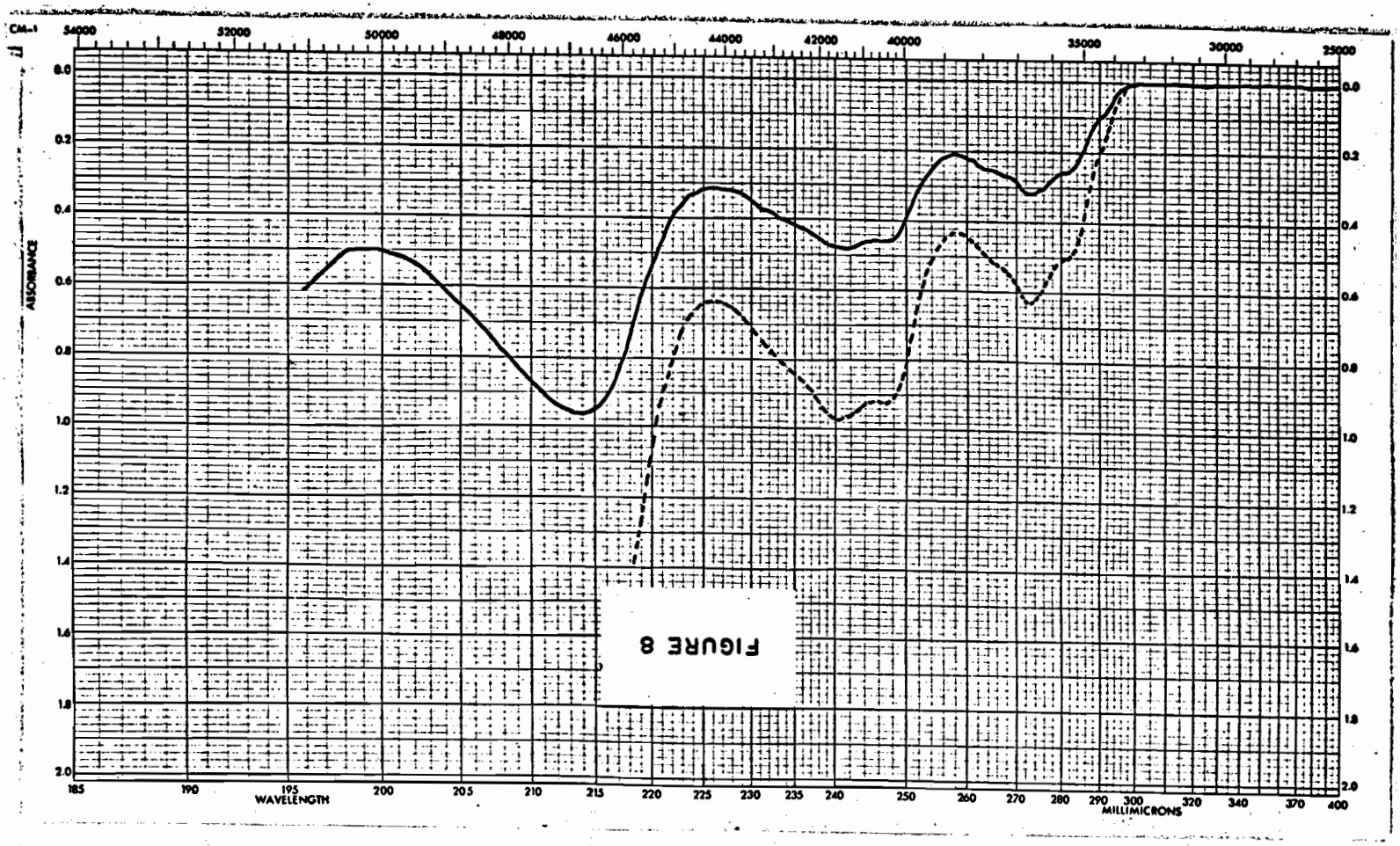

CM-1
54000
52000
50000
48000
46000
44000
42000
40000
35000
30000
25000
ABSORBANCE
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
185
190
195
200
205
210
215
220
225
230
235
240
250
260
270
280
290
300
320
340
370
400
WAVELENGTH
MILLIMICRONS

FIGURE 8

Figure 9

Ultraviolet Spectrum of 2-Acetylthiazolo[3,2-a]benzimidazole (XXXVI) in Ethanol (0.075 mg./ml.)

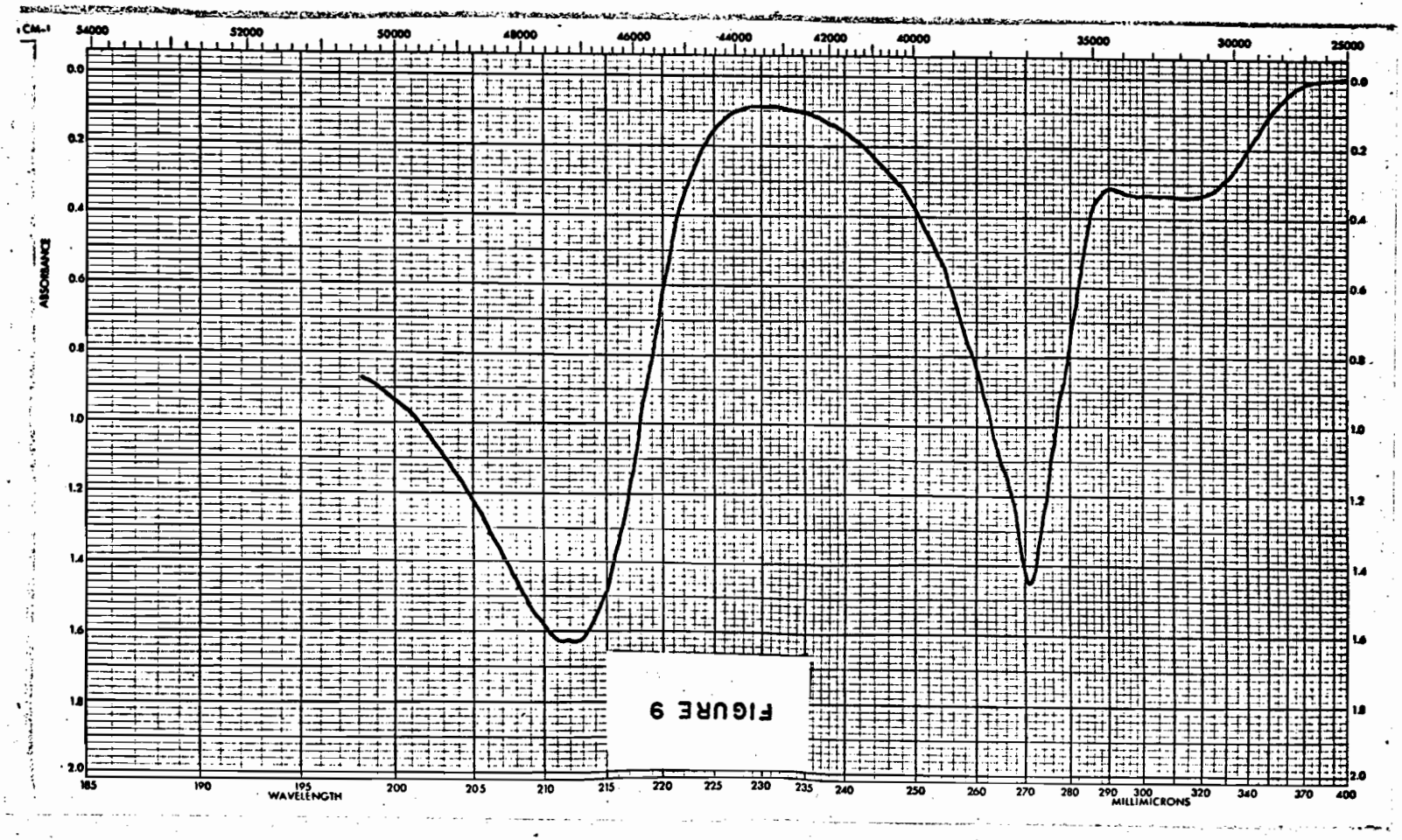

CM.-1
54000
52000
50000
48000
46000
44000
42000
40000
35000
30000
25000
ABSORBANCE
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
185
190
195
200
205
210
215
220
225
230
235
240
250
260
270
280
290
300
320
340
370
400
WAVELENGTH
MILLIMICRONS

FIGURE 9

Figure 10

N.M.R. Spectrum of Thiazolo[3,2-a]benzimidazole (I) in Acetone at 100 Megacycles

FIGURE 10

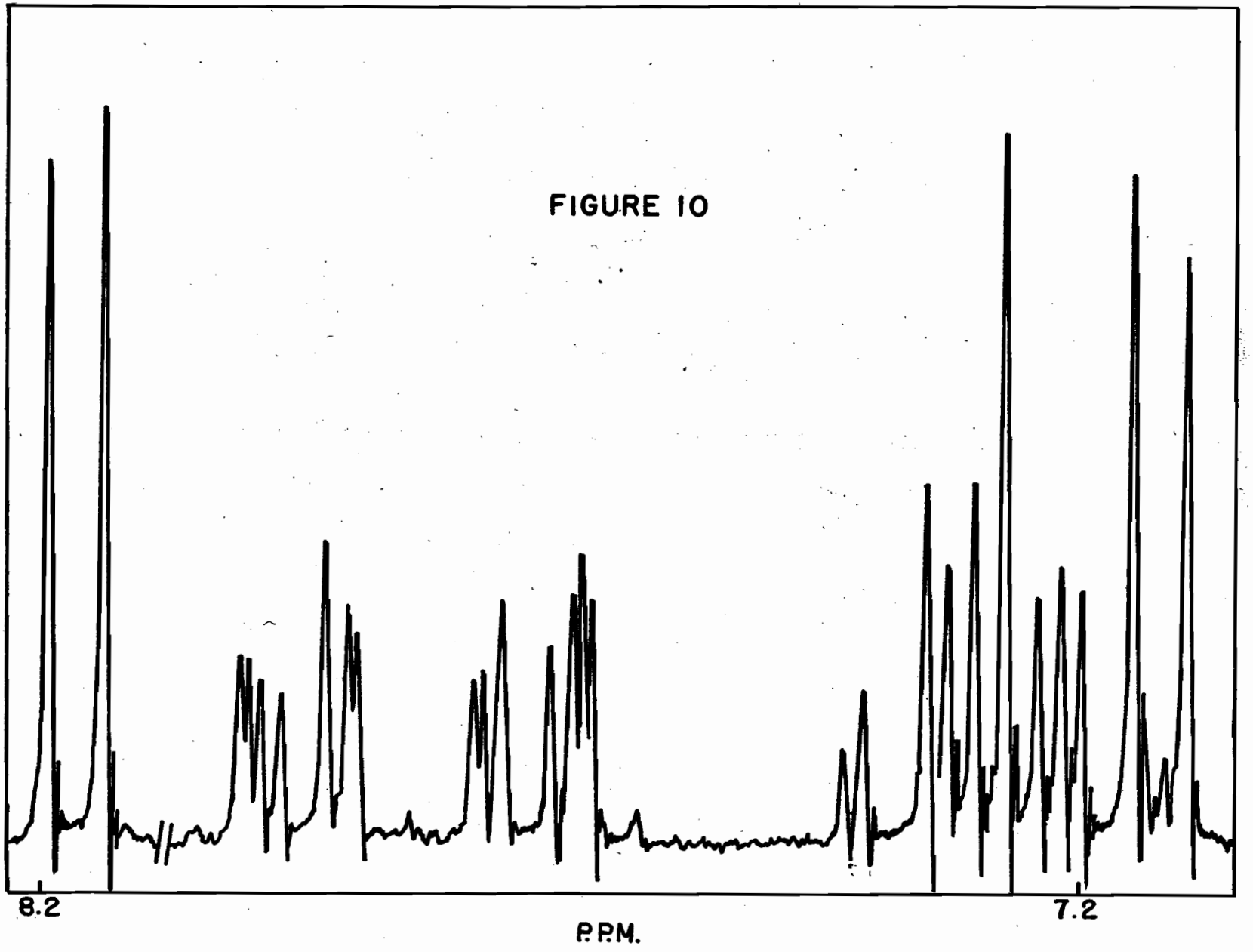


Figure 11

Infrared Spectrum of Imidazo[2,1-b]benzothiazole (LI) in a KBr Pellet

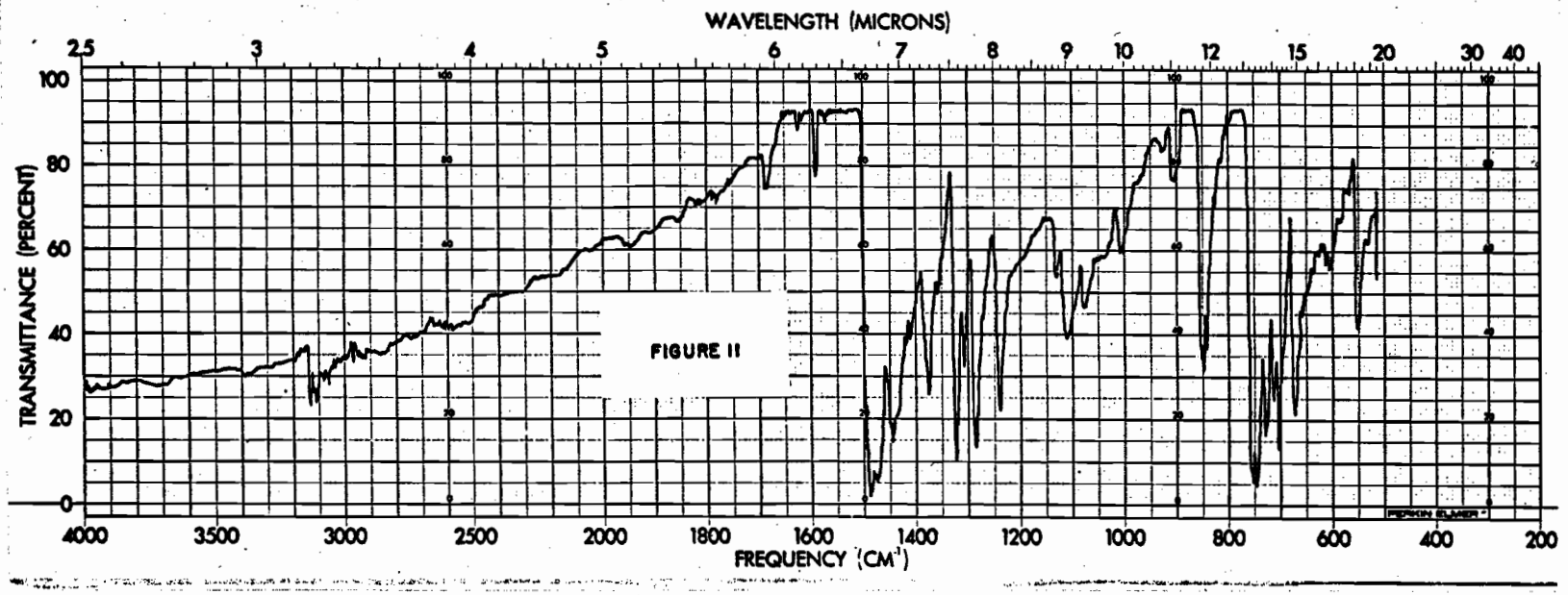

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
TRANSMITTANCE (PERCENT)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)
PERKIN ELMER

FIGURE II

Figure 12

Ultraviolet Spectrum of Imidazo[2,1-b]benzothiazole (LI) in Ethanol

_____ 0.290 mg./ml.

_ _ _ _ _ _ _ 0.058 mg./ml.

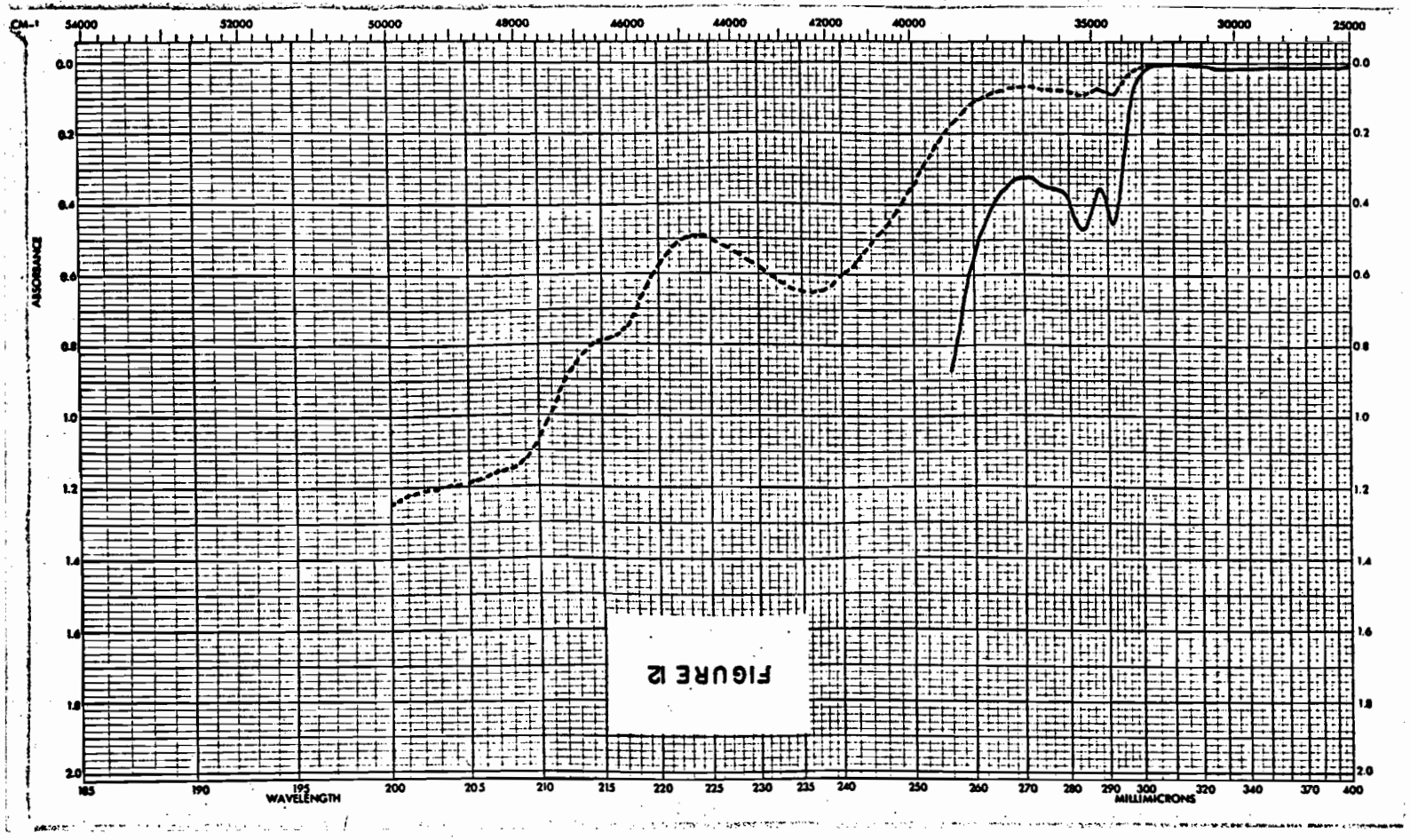

CM.-1
54000
52000
50000
48000
46000
44000
42000
40000
35000
30000
25000
ABSORBANCE
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
185
190
195
200
205
210
215
220
225
230
235
240
250
260
270
280
290
300
320
340
370
400
WAVELENGTH
MILLIMICRONS

FIGURE 12

Figure 13

N.M.R. Spectrum of Imidazo[2,1-b]benzothiazole (LI) in $CDCl_3$

FIGURE 13

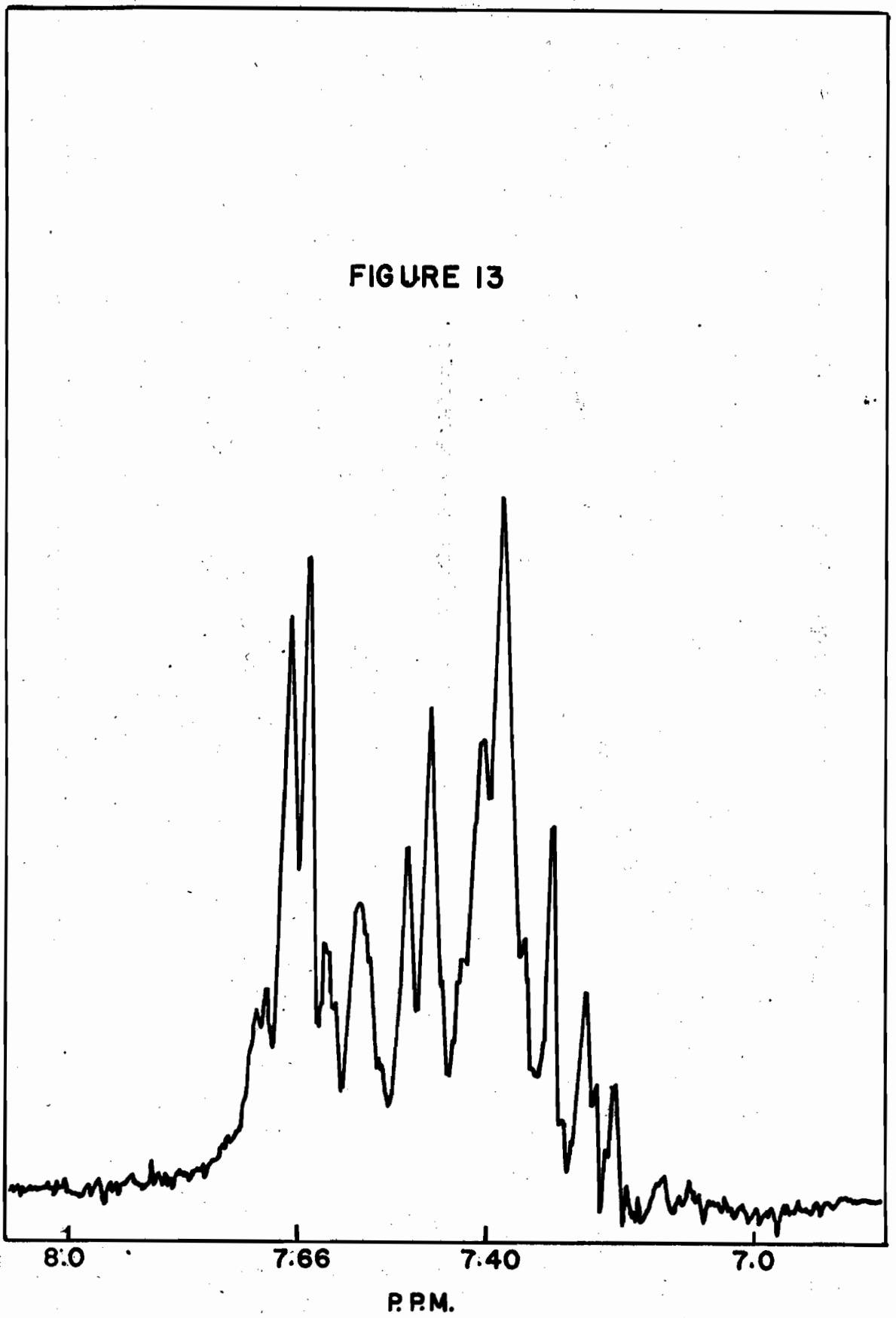


Figure 14

N.M.R. Spectrum of Imidazo[2,1-b]thiazole (L) in $CDCl_3$

FIGURE 14

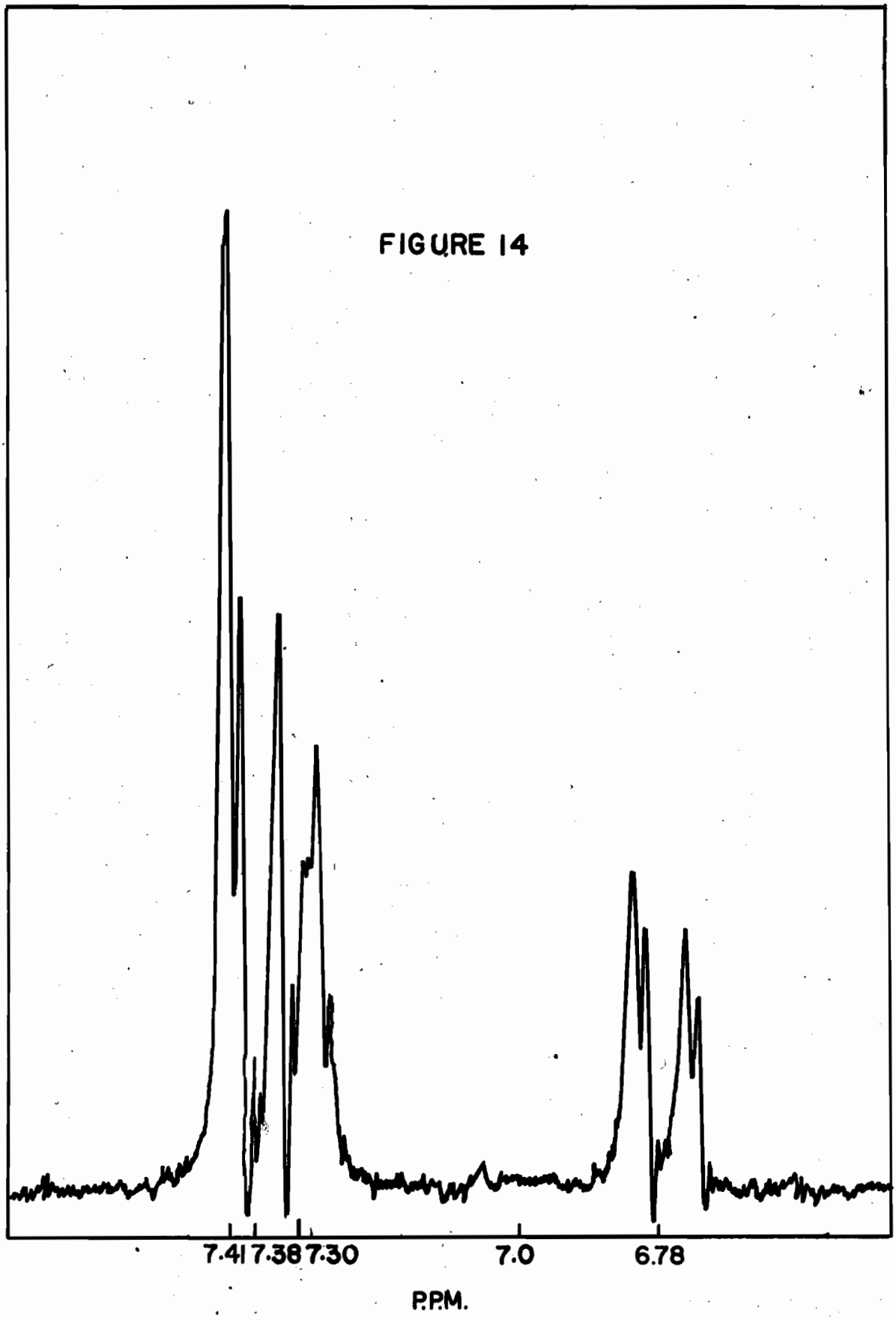


Figure 15

Infrared Spectrum of Imidazo[2,1-b]thiazole (L) in a KBr Pellet

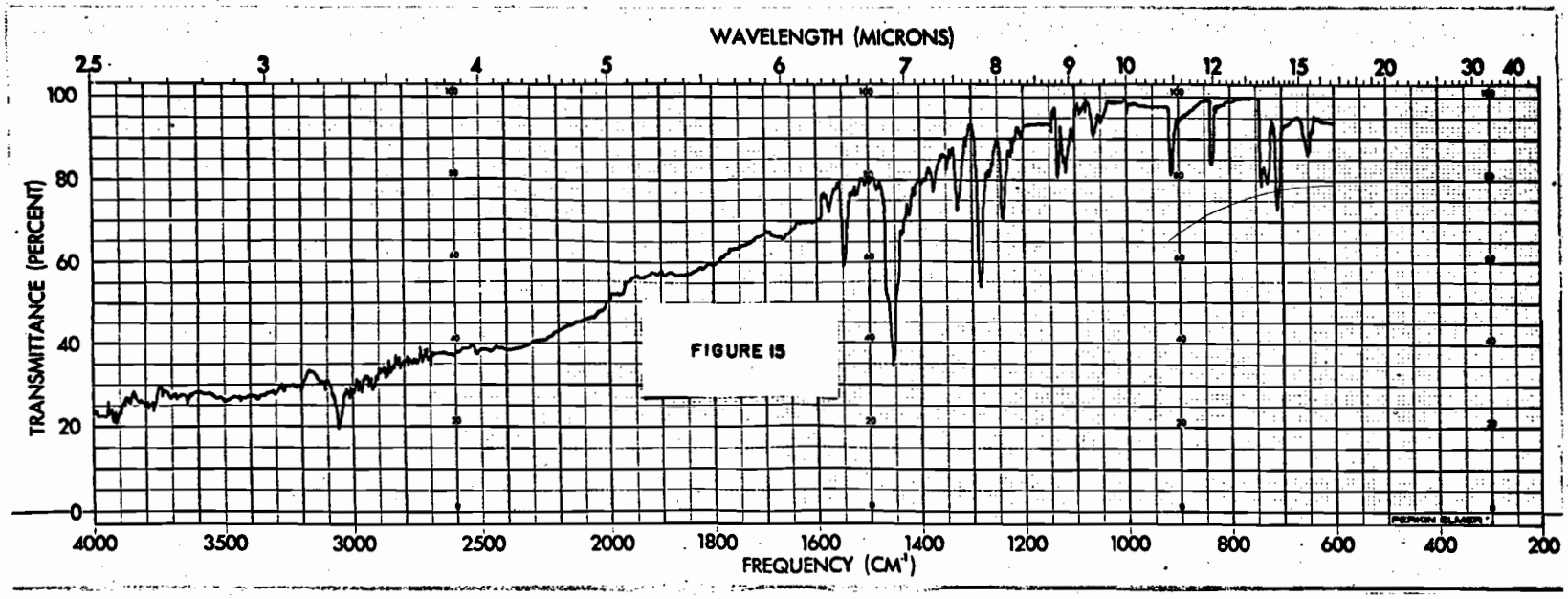

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
TRANSMITTANCE (PERCENT)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)
PERKIN ELMER

FIGURE 15

Figure 16

Ultraviolet Spectrum of Imidazo[2,1-b]thiazole (L) in Ethanol

_____ 0.180 mg./ml.

- - - - - - 0.072 mg./ml.

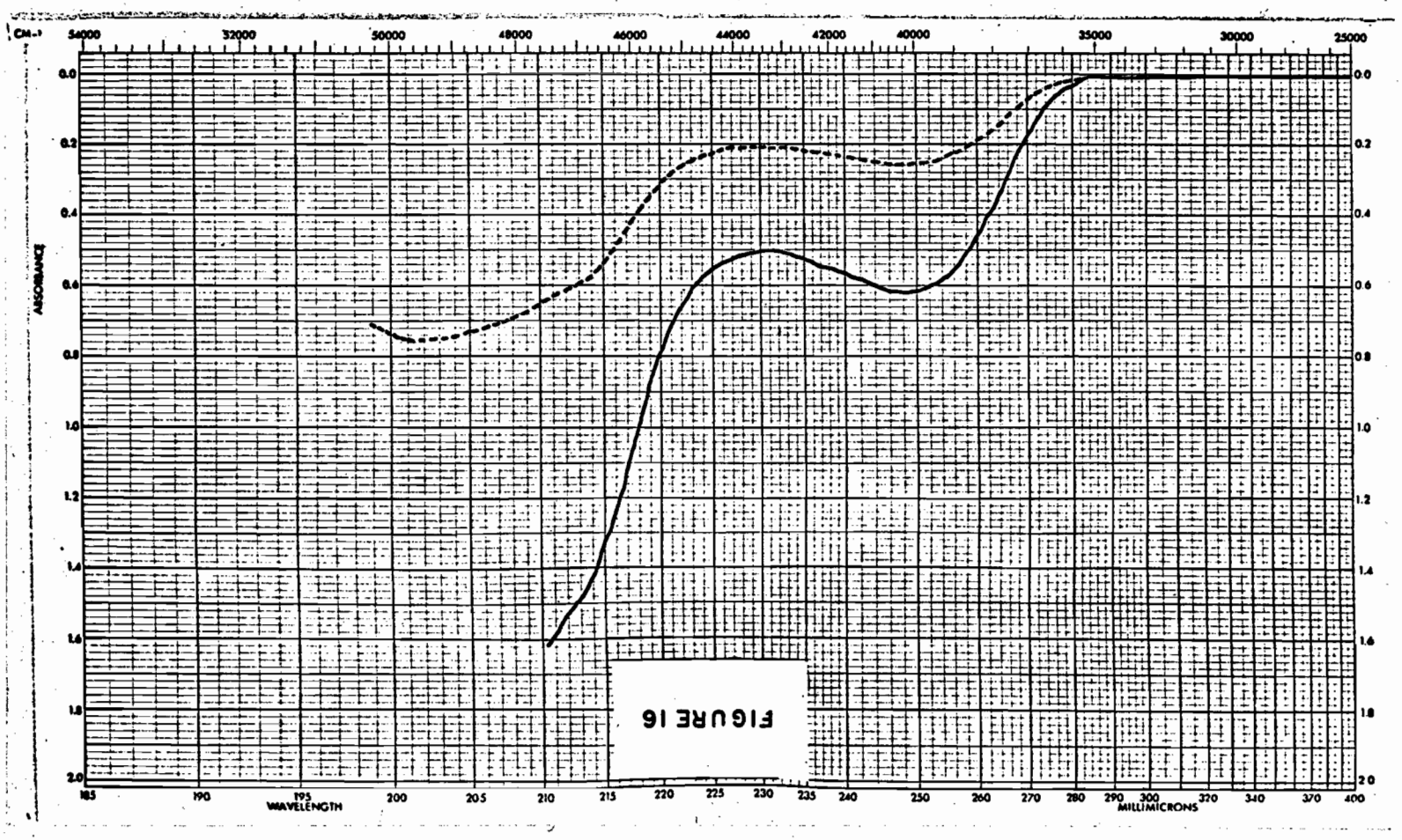

CM-1
54000
32000
50000
48000
46000
44000
42000
40000
35000
30000
25000
ABSORBANCE
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
185
190
195
200
205
210
215
220
225
230
235
240
250
260
270
280
290
300
320
340
370
400
WAVELENGTH
MILLIMICRONS

FIGURE 16

EXPERIMENTAL

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

Infrared spectra were recorded on a Perkin-Elmer model 521 grating spectrophotometer. Unless otherwise indicated the measurements of the spectra were made on solid compounds as potassium bromide pellets and on liquids between two sodium chloride plates. The infrared spectra of some reaction products were recorded on a Perkin-Elmer model 137 or model 337 spectrophotometer and these are indicated by the notation PE-137 or PE-337.

Ultraviolet spectra were measured on a Perkin-Elmer model 350 spectrophotometer using absolute ethanol as solvent.

Nuclear magnetic resonance spectra were determined on a Varian High Resolution Nuclear Magnetic Resonance Spectrometer, model HR-60 or model A-60. Solvents used were deuterated chloroform ($DCCl_3$), carbon tetrachloride (CCl_4), dimethylsulfoxide (DMSO), dimethylsulfoxide-d_6 (DMSO-d_6), dioxane and acetone. Tetramethylsilane (TMS) was used as an internal standard.

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

I. Syntheses of Thiazolo[3,2-a]benzimidazoles

A. Synthesis of thiazolo[3,2-a]benzimidazole (I).

1. Preparation of 2-Benzimidazolinethione (II)

The procedure of Van Allan and Deacon (1) was used to prepare this compound. o-Phenylenediamine (16.2g., 0.15 moles) gave 20.0 g. (89% yield) of 2-benzimidazolinethione as colorless platelets, m.p. 302-304°; (lit. value 303-304°(1)).

2. Preparation of 3-Hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (III)

(a) Condensation of 2-benzimidazolinethione (II) and chloroacetaldehyde in ethanol.

To 2.5 g. (0.016 mole) of benzimidazolinethione dissolved in 40 ml. of ethanol was added 3.2 ml. of a 40-45% solution of chloroacetaldehyde in water (approx. 0.016 mole of chloroacetaldehyde). The resulting solution was refluxed for four hours. The white solid, which separated out on cooling, was filtered and dried to give 1.4 g. of a hydrochloride, m.p. 179-181° (decomp.). Concentration of the filtrate gave an additional 1.0 g., m.p. 178-180° (decomp.). Total yield: 80%. The crude hydrochloride was dissolved in water, the solution was filtered by gravity, and the filtrate basified with sodium bicarbonate. The resulting white precipitate was filtered and dried in vacuo over phosphorus pentoxide giving 3.0 g. of a white solid, m.p. 180-200° (decomp.). The N.M.R. spectrum of the crude product in DMSO-d_6 showed that it contained approximately 10% 3-ethoxy-2,3-dihydrothiazolo[3,2-a]-

benzimidazole. On standing the basic filtrate gave 50 mg. of pale yellow needles, m.p. 97-99°; mixed melting point with an authentic sample of 3-ethoxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (V) was 98-100°. The infrared spectra (PE-137) of the two compounds were identical.

(b) Condensation of 2-benzimidazolinethione (II) and chloroacetaldehyde in 2-butanone.

2-Benzimidazolinethione (1.5 g., 0.01 mole) was suspended in 30 ml. of 2-butanone and 1.9 ml. of a 40-45% solution of chloroacetaldehyde in water was added. The mixture was refluxed for four hours. As the remaining 2-benzimidazolinethione went into solution a new substance precipitated out. After cooling, the white solid was filtered and dried to give 2.2 g. (quantitative yield) of 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole hydrochloride, m.p. 178-180° (decomp.). Two recrystallizations from ethanol gave an analytical sample, m.p. 180.0-180.5° (decomp.).

Anal. calcd. for $C_9H_9N_2OSCl$: C, 47.44; H, 3.92; N, 12.26.

Found: C, 47.68; H, 3.95; N, 12.14.

The crude hydrochloride (1.1 g.) was dissolved in water and filtered by gravity to remove any unreacted 2-benzimidazolinethione. The filtrate was basified with sodium bicarbonate. The resulting white precipitate was filtered and dried to give 0.93 g. of 3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (III), m.p. - decomposes gradually beginning to darken at 180° and finally becoming a black

liquid at 205°. Repeated recrystallizations from tetrahydrofuran did not improve the melting point. However, the infrared spectrum (PE137) did not change and the N.M.R. spectrum showed the absence of any contaminant.

Anal. calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57.
Found: C, 56.18; H, 4.22; N, 14.48.

The acetyl derivative of III was prepared by allowing 1.0 g. (0.0052 mole) of III to stand overnight at room temperature in 30 ml. of acetic anhydride. The acetic anhydride solution was added to 150 ml. of water and neutralized with sodium bicarbonate. An oil separated which crystallized on standing. This slightly yellow solid was filtered and dried giving 1.1 g. (92% yield) of 3-acetoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (IV), m.p. 94-96°. Recrystallization from hexane gave colorless crystals, m.p. 102-103°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96.
Found: C, 56.52; H, 4.50; N, 11.86.

(c) Preparation of 3-Ethoxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (V).

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) (0.2 g., 0.001 mole) was dissolved in 25 ml. of ethanol. Ten drops of concentrated hydrochloric acid were added and the solution was refluxed for four hours. The ethanol was evaporated and the residue was dissolved in 100 ml. of water and basified with sodium bicarbonate. The resulting precipitate was filtered and dried giving 0.17 g. (80% yield) of slightly colored crystals, m.p. 97.5-99.5°. Crystallizations from benzene gave

colorless needles of 3-ethoxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole, m.p. 101-102°.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.44; N, 12.72.

Found: C, 59.86; H, 5.38; N, 12.86.

(d) Condensation of 2-benzimidazolinethione (II) and chloroacetaldehyde in aqueous sodium hydroxide.

To 2-benzimidazolinethione (3.7 g., 0.025 mole) in 35 ml. of water, containing 1.0 g. of sodium hydroxide, heated to 40° was added 5.5 ml. of a 40-45% solution of chloroacetaldehyde in water. An exothermic reaction occurred immediately as evidenced by a rise in temperature to 55°. A solid precipitated out of solution. The reaction mixture was cooled and filtered giving 4.2 g. (93% yield) of a pale yellow powder, m.p. 174-202° (decomp.). Its infrared spectrum (PE-137) was superimposable on that of 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III).

(e) Condensation of 2-benzimidazolinethione (II) and α,β-dichloroethyl ether in ethanol.

To 8.4 g. (0.056 mole) of 2-benzimidazolinethione dissolved in 70 ml. of ethanol was added 8.0 g. (0.056 mole) of α,β-dichloroethyl ether and 1 ml. of water. The reaction mixture was refluxed for four hours and then concentrated to give 9.0 g. of a white solid. The crude product was dissolved in water. The solution was filtered to give 1.13 g. of a water-insoluble substance. Its infrared spectrum (PE-137) indicated that it was unreacted starting material (14.1%).

The filtrate was basified with sodium bicarbonate and an oily substance separated. The oily suspension was extracted with three 60 ml. portions of ether. A white solid (2.47 g., 6% yield) separated out and remained insoluble in ether or water. Its infrared spectrum (PE-137) was identical with that of 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III). The combined ether extract was dried over anhydrous sodium sulfate and the solvent evaporated leaving a yellow oil. The oil slowly crystallized giving 4.4 g. of a yellow solid. Crystallization from benzene gave 2.4 g. (24% yield) of colorless crystals m.p. 166-169°. Concentration of the benzene solution gave 1.6 g. (13% yield) of needles, m.p. 94-97°. The infrared spectrum of this compound (PE-137) identified it as 3-ethoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (V). Two further recrystallizations of the fraction having m.p. 166-169° gave colorless crystals of 2-ethylthiobenzimidazole (VI), m.p. 170-172°; (lit. m.p. 170-170.5° (20)).

3. Preparation of Thiazolo[3,2-a]benzimidazole (I)

(a) Dehydration of III with sulfuric acid.

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) (250 mg., 0.0013 mole) was refluxed in 30 ml. of a 2:1 sulfuric acid-water solution for five hours. The reaction mixture was added to 50 ml. of water and basified with sodium carbonate to give a cloudy solution. This basic solution was extracted with three 20 ml. portions of ether. The combined

ether extract was washed once with water, dried over anhydrous sodium sulfate and filtered. The ether was evaporated leaving 100 mg. (45% yield) of a yellow solid, m.p. 125-130°. Recrystallization from carbon tetrachloride gave slightly yellow crystals, m.p. 129-133°. A mixed melting point with thiazolo-[3,2-a]benzimidazole (I) was 130-133°.

(b) Dehydration of III with phosphorus oxychloride in pyridine.

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) was dissolved in 40 ml. of freshly-distilled pyridine in a three-necked, round-bottomed, 100 ml. flask equipped with a magnetic stirrer, a dropping funnel and a reflux condenser. Phosphorus oxychloride (6 ml.-this large excess is necessary) was added from the dropping funnel over a 45-minute period. The reaction mixture was stirred at room temperature for one hour then treated cautiously with ice chips to remove any unreacted phosphorus oxychloride. After the vigorous reaction had subsided the mixture was poured into 200 ml. of water. The aqueous solution was extracted with three 50 ml. portions of ether. The combined ether extract was washed once with water and dried over anhydrous sodium sulfate. The ether was evaporated and any remaining pyridine removed leaving 1.5 g. of a tan-colored crystalline mass, m.p. 130-135°. After treatment with charcoal recrystallization from hexane gave 1.3 g. (77% yield) of colorless crystals of thiazolo[3,2-a]benzimidazole (I).

Three further recrystallizations gave an analytical sample, m.p. 135.5-136.5°.

Anal. Calcd. for $C_9H_6N_2S$: C, 62.04; H, 3.47; N, 16.09.

Found: C, 61.84; H, 3.59; N, 16.24.

The methiodide of thiazolo[3,2-a]benzimidazole was prepared. Thiazolo[3,2-a]benzimidazole (III) (250 mg., 0.014 mole) was dissolved in 1 ml. of methyl iodide in a test tube. On standing a white solid precipitated out. The reaction mixture was cooled and then filtered to give 0.31 g. (70% yield) of a white powder. Crystallization from ethanol gave thiazolo-[3,2-a]benzimidazole methiodide (VII), m.p. 237-239° (decomp.).

4. Nitration of Thiazolo[3,2-a]benzimidazole (I).

Thiazolo[3,2-a]benzimidazole (I) (0.3 g., 0.0017 mole) was dissolved in 0.5 ml. of concentrated sulfuric acid at 0°. Nitric acid (0.25 ml.; sp. g. 1.4) was added dropwise to the solution at 0°. The reaction mixture was stirred at room temperature for one hour and poured into 100 ml. of ice. A yellow solid separated. The suspension was treated with dilute ammonium hydroxide until reaching a pH of approximately 2. The solid was filtered and dried in vacuo to give 0.36 g. (quantitative yield) of a yellow product. Thin layer chromatography (TLC) on silica gel, developed with a 70:30 tetrahydrofuran-benzene solution, indicated that there was one main product and two minor products. Separation of 100 mg. of the crude product in this manner gave 60 mg. of the major product, m.p. 252-255°. Recrystallization from benzene gave yellow

needles, m.p. 254-255°. The N.M.R. spectrum of this product indicated that it was either the 6- or 7-nitrothiazolo[3,2-a]-benzimidazole (XLVII).

Anal. Calcd. for $C_9H_5N_3O_2S$: C, 49.35; H, 2.30.

Found: C, 49.32; H, 2.39.

B. Chemical Proof for the Structure of 3-Hydroxy-2,3-dihydro-thiazolo[3,2-a]benzimidazole (III).

1. Preparation of (2-Benzimidazolylthio)acetic acid (VIII)

The procedure of Everett (4) was used to prepare this compound from 2-benzimidazolinethione (II). A 93.7% yield of (2-benzimidazolylthio)acetic acid was obtained, m.p. 200-201°; (lit. m.p. 190°(4)).

2. Preparation of 3(2H)-Thiazolo[3,2-a]benzimidazolone (IX).

The procedure given by Duffin and Kendall (5) was followed with some modification.

(2-Benzimidazolylthio)acetic acid (15.0 g., 0.073 mole) was suspended in 15 ml. of acetic anhydride and 23 ml. of pyridine. As the acid dissolved the solution turned yellow, heat was evolved and yellow needles formed. The reaction mixture was allowed to stand at room temperature for 24 hours and then was filtered to give yellow needles, m.p. 174-176.5°. Recrystallization from ethanol gave 11.3 g. (76% yield) of 3(2H)-thiazolo[3,2-a]benzimidazolone, m.p. 176-177°; (lit. m.p. 181° (5)).

3. Lithium Aluminum Hydride Reduction of 3(2H)-Thiazolo-[3,2-a]benzimidazolone (IX).

a. Using basic work-up conditions.

Lithium aluminum hydride (0.17 g., 0.004 mole) was dissolved in 200 ml. of sodium-dried diethyl ether in a 500 ml., three-necked flask fitted with a mechanical stirrer, a soxhlet extractor and a reflux condenser protected by a calcium chloride drying tube. The 3(2H)-thiazolo[3,2-a]-benzimidazolone (0.76 g., 0.004 mole) was placed in the thimble of the soxhlet extractor and the ether solution was refluxed until all the yellow ketone had reacted (approx. 7 hours). The reaction mixture was cooled and water was cautiously added dropwise to decompose any unreacted hydride. The ether suspension was treated with 80 ml. of a 30% sodium hydroxide solution, to dissolve the precipitated salts, and the organic layer was separated. The aqueous basic layer was extracted with three 30 ml. portions of amyl alcohol. The combined amyl alcohol extract was washed once with water and dried over anhydrous magnesium sulfate. The amyl alcohol was evaporated leaving 0.28 g. (53% yield) of a white solid, m.p. 310-313° (decomp.). Mixed melting point with an authentic sample of 2-benzimidazolinone (X) was 310-312° (decomp.).

(b) Using neutral work-up conditions.

After decomposition of the excess lithium aluminum hydride with water the reaction mixture was poured into 150 ml. of ice water. The ether layer was separated and dried

over anhydrous magnesium sulfate. Evaporation of the ether gave 0.39 g. (50% yield) of white crystals, m.p. 120-121.5°. Two recrystallizations from chloroform gave an analytical sample of 2-(2-benzimidazolylthio)ethanol (XI).

Anal. Calcd. for: $C_9H_{10}N_2OS$: C, 55.64; H, 5.19; N, 14.42.

Found: C, 55.61; H, 5.30; N, 14.35.

Determination of the melting point of the pure 2-(2-benzimidazolylthio)ethanol showed that at approximately 110° it coalesced to form a new white substance which did not melt at 121° but began to sublime at 260° and melted with decomposition at 302-305°.

The aqueous suspension remaining after separation of the ether layer was continuously extracted with amyl alcohol. The amyl alcohol extract was dried over anhydrous magnesium sulfate and the solvent was evaporated leaving 0.21 g. (39.6% yield) of 2-benzimidazolinone (X), m.p. 309-310° (decomp.).

(c) Pyrolysis of 2-(2-benzimidazolylthio)ethanol (XI).

2-(2-Benzimidazolylthio)ethanol (XI) (20 mg.) was heated (under nitrogen) in a pear-shaped flask in an oil bath. At 110° XI was observed to change. On further heating to 135° the new substance did not melt. Its infrared spectrum (PE-137) was identical with that of 2-benzimidazolinone (X). Also, it did not depress the melting point of an authentic sample of X.

4. Preparation of 2-Benzimidazolinone (X).

The procedure of Mistry and Guha (6) was followed

to prepare this compound from o-phenylenediamine. 2-Benzimidazolinone (X) was obtained in 92% yield as white crystals, m.p. 311-312° (decomp.); (lit. m.p. 311° (6)).

5. Oxidation of 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (III) with Chromic Oxide in Pyridine

(a) For 22 hours

The chromic oxide-pyridine complex was prepared according to Holum (7). Chromic oxide (1.5 g., 0.015 mole) was added in small portions, over a thirty-minute period, to 20 ml. of chilled pyridine with vigorous stirring, to give an orange-yellow suspension. 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III) (0.95 g., 0.005 mole) was then added and the mixture stirred for 15 minutes. The resulting red-orange solution was allowed to stand at room temperature for 22 hours. The reaction mixture was added to 200 ml. of water and extracted continuously with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, concentrated to approximately 15 ml., and filtered to give 0.6 g. of a white solid, m.p. 170-202° (decomp.). Its infrared spectrum (PE-137) was identical with that of the starting material. (63% yield). Evaporation of the remaining chloroform solution gave 0.23 g. of yellow needles (24% yield), m.p. 177-179°. Mixed melting point with an authentic sample of 3(2H)-thiazolo[3,2-a]benzimidazolone was 178-179.5°.

(b) For 48 hours

When the reaction mixture was allowed to stand at room temperature for 48 hours the chloroform extract gave

0.42 g. (70% yield) of crystalline material. Its infrared spectrum (PE-137) indicated that the solid was a mixture of IX having carbonyl absorption at 1740 $cm.^{-1}$ and (2-benzimidazolylthio)acetic acid (VIII). The mixture was dissolved in 5% sodium hydroxide and filtered. A yellow substance (0.2 g.) did not dissolve in the sodium hydroxide. Its infrared spectrum indicated that it was 3(2H)-thiazolo[3,2-a]benzimidazolone. The basic solution was carefully acidified with 10% acetic acid. At the neutral point a white precipitate formed and was filtered to give 40 mg. (0.6% yield) of a white solid, m.p. 311-313° which did not depress the melting point of an authentic sample of 2-benzimidazolinone (X). Further acidification of the filtrate gave 0.12 g. (8.4% yield) of white needles, m.p. 198-202°. Mixed melting point with (2-benzimidazolylthio)acetic acid (VIII) was 200-202°.

C. Synthesis of 5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole (XII).

1. Preparation of 2-chlorocyclohexanone (XIII)

2-Chlorocyclohexanone was prepared by the chlorination of cyclohexanone following the procedure of Newman (2). From 98 g. (1 mole) of cyclohexanone 78.2 g. (58% yield) of XIII, b.p. 75-77°/7-8 mm.; (lit. b.p. 90-91°/14-15 mm. (2)) was obtained.

2. Preparation of 5,6,7,8-Tetrahydrothiazolo[3,2-a]-benzimidazole (XII)

2-Aminothiazole (10 g., 0.1 mole) and 2-chlorocyclohexanone (12 g., 0.10 mole) were fused together in the

absence of solvent and refluxed for 15 minutes. The resulting dark mass was taken up in 500 ml. of water and this aqueous solution was extracted with three 50 ml. portions of ether to remove any unreacted 2-chlorocyclohexanone. The aqueous solution was basified with a 10% sodium hydroxide solution and the resulting cloudy solution was extracted with three 100 ml. portions of chloroform. The combined chloroform extract was washed once with water, dried over sodium sulfate and the solvent evaporated to give a yellow oil. Distillation of the oil in vacuo gave 3.7 g. (22.5% yield) of a colorless liquid, b.p. 146°/1-2 mm. On standing the liquid slowly crystallized to give pale yellow needles, m.p. 61-65°. Crystallization from petroleum ether (b.p. 30-60°) gave 3.2 g. of 5,6,7,8-tetrahydrothiazolo[3,2-a]benzimidazole (XII), m.p. 71-73°. Two further recrystallizations from petroleum ether gave an analytical sample, m.p. 72-73°.

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.63; H, 5.65; N, 15.71.

Found: C, 60.64; H, 5.56; N, 15.56.

The methiodide of 5,6,7,8-tetrahydrothiazolo[3,2-a]-benzimidazole was prepared. 5,6,7,8-Tetrahydrothiazolo-[3,2-a]benzimidazole (0.5 g., 0.003 mole) was added to 1 ml. of methyl iodide in a test tube. The solid went into solution as the methyl iodide was warmed slightly. On standing at room temperature for 30 minutes a white solid precipitated. The solid was filtered, washed with ether and dried in vacuo to

give a 0.74 g. (76% yield) of 5,6,7,8-tetrahydrothiazolo-[3,2-a]benzimidazole methiodide (XIV), m.p. 247-249°. Five recrystallizations from absolute ethanol gave an analytical sample, m.p. 244-245°. This methiodide is very hygroscopic.

Anal. Calcd. for $C_{10}H_{13}N_2SI$: C, 37.50; H, 4.09; N, 8.74.

Found: C, 37.79; H, 4.27; N, 8.53.

3. Attempted Dehydrogenation of XII

(a) With palladium on charcoal at 300°.

5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole (XII) (0.5 g., 0.0027 mole) was heated with palladium on charcoal (0.25 g.) in a sublimation tube in a small oven at 300° for six hours. The residue was extracted with boiling acetone. Evaporation of the acetone gave 150 mg. of a yellow solid. When this product was tested for the presence of sulfur it gave no precipitate of lead sulfide. No attempt was made to further characterize this product.

(b) With sulfur

5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole (0.36 g., 0.002 mole) was heated with sulfur (0.128 g., 0.004 mole) at 125-130°. After two hours the reaction mixture was cooled and it solidified to give a dark-colored solid. This residue was extracted with chloroform. The chloroform extract gave 0.35 g. of a yellow oil. Its infrared spectrum (PE-137) was identical with that of the starting material. Sulfur (0.128 g.) was added to this yellow oil and the mixture heated at 125-130° for ten hours. The reaction mixture was

worked up as before. The infrared spectrum (PE-137) of the product obtained indicated that it was recovered starting material. The recovered 5,6,7,8-tetrahydrothiazolo[3,2-a]-benzimidazole and 0.12 g. of sulfur was heated together at 170° for 20 hours. When the reaction was worked up as before, the chloroform extract gave 0.17 g. of a brown solid, m.p. 290° (decomp.). Crystallization of 120 mg. of this solid from ethanol gave 10 mg. of red needles, m.p. 113-115°. This product was not further characterized. Concentration of the ethanol solution gave 100 mg. of slightly yellow platelets, m.p. 298-303°. Mixed melting point with an authentic sample of 2-benzimidazolinethione (II) was 299-303°. Its infrared spectrum (PE-137) was identical with that of II.

5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole (0.35 g., 0.002 mole) was heated with sulfur (0.12 g.) at 170° for 3 hours. Chloroform extraction gave 166 mg. of a dark solid. Crystallization from ethanol gave yellow crystals, m.p. 278-282°. This product was tentatively identified as 2-mercapto-4,5,6,7-tetrahydrobenzimidazole (XV); (lit. m.p. 282-283° (3)).

D. Synthesis of 6,7-Dimethylthiazolo[3,2-a]benzimidazole (XVI)

1. Synthesis of 5,6-Dimethyl-2-benzimidazolinethione (XVII)

(a) Preparation of 4,5-Dimethyl-2-nitroacetanilide (XVIII)

This compound was prepared by nitration of 3,4-dimethylacetanilide with cupric nitrate in acetic anhydride following the procedure of Takatori (8).

4,5-Dimethyl-2-nitroacetanilide was obtained in 71% yield as orange-yellow needles (from ethanol), m.p. 106-107°; (lit. m.p. 108° (8)).

(b) Preparation of 4,5-Dimethyl-2-nitroaniline (XIX)

4,5-Dimethyl-2-nitroacetanilide (6.9 g., 0.003 mole) was dissolved in 60 ml. of concentrated hydrochloric acid and the solution was heated on a steam bath for five minutes. The reaction mixture was diluted with 150 ml. of water and neutralized with ammonium hydroxide. The resulting orange solid was filtered and dried in vacuo giving 5.0 g. (95% yield) of 4,5-dimethyl-2-nitroaniline, m.p. 138-140°; (lit. m.p. 140° (8)).

(c) Preparation of 4,5-Dimethyl-o-phenylenediamine (XX)

(i) Attempted Reduction of XIX with zinc in water

The procedure of Noelting (9) was followed for the reduction of 4,5-dimethyl-2-nitroaniline. However, after several attempts only unreacted starting material was recovered.

(ii) Reduction of XIX with zinc in sodium hydroxide solution.

The procedure of Martin (10) for the reduction of o-nitroaniline to o-phenylenediamine using zinc in sodium hydroxide solution was followed. 4,5-Dimethyl-2-nitroaniline gave an 81% yield of 4,5-dimethyl-o-phenylenediamine (XX), m.p. 124-126°; (lit. m.p. 125-126° (11)).

(d) Preparation of 5,6-dimethyl-2-benzimidazolinethione (XVII)

The procedure of Takatori (8) was followed to prepare XVII from 4,5-dimethyl-o-phenylenediamine (XX). 5,6-Dimethyl-2-benzimidazolinethione (XVII) was obtained as sparkling colorless platelets in 90% yield, m.p. 331-335°; (lit. m.p. 328° (8)). This product was not further purified before use in the next step of the synthesis.

2. Preparation of 6,7-Dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXI)

5,6-Dimethyl-2-benzimidazolinethione (4.0 g., 0.022 mole) was suspended in 160 ml. of 2-butanone and 4 ml. of a 40-45% solution of chloroacetaldehyde in water was added. The mixture was refluxed for four hours. The condensation product precipitated during the course of the reaction. The reaction mixture was cooled and the hydrochloride salt filtered and dried in vacuo. The crude hydrochloride was dissolved in 250 ml. of water and the solution was basified with sodium bicarbonate. The resulting precipitate was filtered and dried in vacuo giving 4.3 g. (88% yield) of 6,7-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXI), m.p. 185-202° (gradual decomp.). Two recrystallizations from tetrahydrofuran did not improve the melting point.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72

Found: C, 60.10; H, 5.59; N, 12.67.

3. Preparation of 6,7-Dimethylthiazolo[3,2-a]benzimidazole (XVI).

6,7-Dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]-

benzimidazole (0.8 g., 0.004 mole) was dissolved in 40 ml. of freshly-distilled pyridine in a 100 ml., three-necked flask equipped with a magnetic stirrer, a dropping funnel and a reflux condenser. Phosphorus oxychloride (3 ml.) was added from the dropping funnel over a half-hour period. The reaction mixture was stirred at room temperature for one hour. Ice chips were added cautiously to decompose any unreacted phosphorus oxychloride and after this reaction had subsided the mixture was poured into 100 ml. of water. The resulting aqueous solution was extracted with three 50 ml. portions of ether. The combined ether extract was washed once with water and dried over anhydrous sodium sulfate. The ether was evaporated and any remaining pyridine was removed leaving 0.62 g. (78% yield) of tan crystals, m.p. 160-163°. Crystallization from benzene, after treatment with charcoal, gave 0.59 g. of colorless crystals, m.p. 163-166°. Two further recrystallizations from benzene gave an analytical sample of 6,7-dimethylthiazolo[3,2-a]benzimidazole (XVI), m.p. 164-165°.

Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.31; H, 4.98; N, 13.85.

Found: C, 65.22; H, 5.10; N, 13.77.

E. Synthesis of 5,8-Dimethylthiazolo[3,2-a]benzimidazole (XXII)

1. Preparation of 3,6-Dimethyl-o-phenylenediamine (XXIII)

(a) Dinitration of p-xylene.

The procedure of Kobe (13) was followed; however, the mononitration products were not isolated but were further

nitrated directly. Nitration of 106 g. (1.0 mole) of p-xylene gave 169.5 g. (188.5% yield) of slightly yellow crystals, m.p. 77-82°. Crystallization from ethanol gave colorless crystals, m.p. 82-86°. No attempt was made to isolate 2,3-dinitro-p-xylene (XXIV) and the mixture of dinitro-p-xylenes was reduced.

The N.M.R. spectrum ($CDCl_3$) of the mixture, to be used in the reduction, indicated that approximately 55% of XXIV was present together with two other products. Kobe had reported 60-80% of XXIV in his product mixture (13).

(b) Reduction of the dinitro-p-xylene mixture.

The procedure of Mahood and Schaffner (14) for the reduction of 2,4-dinitrotoluene to 2,4-diaminotoluene with iron in hydrochloric acid was followed with some modification in the work-up. Reduction of 48.0 g. of the dinitro-p-xylene mixture gave an 86% yield of amino compounds, isolated as their sulfates (51.5 g.). This mixture of sulfates was dissolved in water and basified with a saturated sodium hydroxide solution. The basic suspension was continuously extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and the benzene evaporated to give 14.2 g. (41% yield) of a yellow solid. After treatment with charcoal, two recrystallizations from petroleum ether (b.p. 60-80°) gave fine white needles of 3,6-dimethyl-o-phenylene-diamine, m.p. 72-74°; (lit. m.p. 75° (12)). The basic solution was then continuously extracted with chloroform.

The chloroform extract was dried over anhydrous sodium sulfate and the solvent evaporated to give 2.0 g. (5.3% yield) of a dark crystalline mass. Its infrared spectrum (PE-137) indicated that this was a nitroaniline. Recrystallization from chloroform gave yellow needles, m.p. 142-144°, tentatively identified as 2-amino-5-nitro-p-xylene (XXV); (lit. m.p. 142° (21)).

2. Synthesis of 4,7-Dimethyl-2-benzimidazolinethione (XXVI)

A mixture of 2,3-diamino-p-xylene (6.8 g., 0.05 mole) potassium hydroxide (2.8 g., 0.05 mole) and 10 ml. of carbon disulfide (0.05 mole) was refluxed in 50 ml. of ethanol and 10 ml. of water for three hours. During the course of the reaction hydrogen sulfide was evolved and a solid precipitated. The reaction mixture was diluted with 30 ml. of water and acidified with 10-12 ml. of a 1:2 acetic acid-water solution. The resulting precipitate was filtered and dried in vacuo to give 7.2 g. (81% yield) of slightly yellow crystals which did not melt below 350°. Two recrystallizations from ethanol gave sparkling colorless platelets of 4,7-dimethyl-2-benzimidazolinethione (XXVI).

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.71.

Found: C, 60.72; H, 5.78; N, 15.67.

3. Synthesis of 5,8-Dimethyl-3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (XXVII).

To 4,7-dimethyl-2-benzimidazolinethione (4.45 g., 0.025 mole) suspended in 100 ml. of 2-butanone was added

4.5 ml. of a 40-45% solution of chloroacetaldehyde in water. The mixture was refluxed for four hours. The reaction mixture was cooled and the precipitated white solid was filtered and dried in vacuo. This crude hydrochloride salt was dissolved in 200 ml. of water and the solution was basified with sodium bicarbonate. The resulting precipitate was filtered and dried in vacuo giving 4.9 g. (88.9% yield) of 5,8-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXVII) as a white powder, m.p. 191.5-193.5° (decomp.). Two recrystallizations from tetrahydrofuran gave an analytical sample.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72

Found: C, 59.85; H, 5.38; N, 12.57.

4. Preparation of 5,8-Dimethylthiazolo[3,2-a]benzimidazole (XXII).

5,8-Dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (3.3 g., 0.015 mole) was dissolved in 70 ml. of freshly-distilled pyridine in a 100 ml., three-necked flask equipped with a magnetic stirrer, a reflux condenser and a dropping funnel. Phosphorus oxychloride (9 ml.) was added from the dropping funnel over a one-hour period. The reaction mixture was stirred at room temperature for an additional one hour. Ice chips were added cautiously to decompose any unreacted phosphorus oxychloride and the reaction mixture was poured into 250 ml. of water. The resulting precipitate was filtered and dried in vacuo to give 3.2 g. of a tan-colored solid, m.p. 250° (sublimes). The filtrate was extracted with three 50 ml. portions of ether. The combined ether extract

was washed once with water and dried over anhydrous sodium sulfate. The ether was evaporated and any remaining pyridine removed to give 0.8 g. of a slightly yellow solid. Its infrared spectrum (PE-137) was identical with that of the precipitated solid. The total product (4.0 g.) was extracted with 200 ml. of boiling hexane. A dark solid (0.8 g.) was insoluble in hexane. Vacuum sublimation (2 mm.) at 140-150° gave 0.5 g. of white crystals, m.p. 245° (sublimes) 280° (decomp.). Its infrared spectrum (PE-137) showed a broad band between 2400 and 2700 $cm.^{-1}$ indicating the possible presence of an intermediate phosphate ester. This substance gave a positive reaction with an ammonium molybdate solution verifying the presence of phosphorus.

The phosphorus-containing compound (160 mg.) was stirred in 30 ml. of pyridine for ten hours at room temperature. The pyridine solution was added to 100 ml. of water and the aqueous solution was extracted with three 30 ml. portions of ether. The combined ether extract was washed once with water and dried over anhydrous sodium sulfate. The ether was evaporated and any remaining pyridine was removed to give 120 mg. of slightly yellow crystals, m.p. 132-135°. Mixed melting point with 5,8-dimethylthiazolo[3,2-a]benzimidazole was 132-135°.

The hexane extract, after treatment with charcoal was concentrated to give 2.8 g. (93% yield) of 5,8-dimethylthiazolo[3,2-a]benzimidazole (XXII) as colorless crystals, m.p. 132-135°. Two recrystallizations from hexane gave an

analytical sample, m.p. 134-135°.

Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.31; H, 4.98; N, 13.85.

Found: C, 65.29; H, 5.09; N, 13.77.

F. Synthesis of 2-Methylthiazolo[3,2-a]benzimidazole (XVIII)

1. Preparation of 2-Chloropropionaldehyde (XXIX)

(a) Chlorination of di-n-propyl ether.

The procedure of Oddo and Cusmano (15) was followed. Chlorination of 51.5 g. of di-n-propyl ether gave 42.7 g. (50% yield) of a colorless liquid, b.p. 80-82° at 12 mm.

(b) Cleavage of the chlorinated propyl ether mixture.

The procedure of Moelants was followed. The chlorination product (40.7 g.) was heated with 82 g. of 5% sulfuric acid to give 2.1 g. (10% yield) of 2-chloropropionaldehyde, b.p. 84-86°; (lit. b.p. 85-86° (16)).

2. Synthesis of 3-Hydroxy-2-methyl-2,3-dihydrothiazolo-[3,2-a]benzimidazole (XXX).

A mixture of 2-benzimidazolinethione (II) (1.5 g., 0.01 mole) and 2-chloropropionaldehyde (2.0 g., 0.02 mole) was refluxed in 40 ml. of 2-butanone for four hours. During the course of the reaction a white solid precipitated. The reaction mixture was cooled and filtered. The crude hydrochloride salt was dissolved in 100 ml. of water and the solution basified with sodium bicarbonate. The resulting white precipitate was filtered and dried in vacuo giving 2.1 g. (quantitative yield) of 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole, m.p. 201-203°. Recrystalliza-

tion from tetrahydrofuran did not change the melting point of the product.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58.

Found: C, 58.38; H, 5.02; N, 13.47.

This product is a mixture of isomeric alcohols (cis and trans). Separation was attempted by thin layer chromatography (TLC); however, a suitable system was not found.

The acetyl derivative of III, 3-acetoxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXXI) was prepared by allowing 500 mg. (0.0024 mole) of XXX to stand overnight at room temperature in 10 ml. of acetic anhydride. The reaction mixture was added to 300 ml. of water and neutralized with sodium bicarbonate. The cloudy solution which resulted was extracted with three 50 ml. portions of ether. The combined ether extract was washed once with water and dried over anhydrous sodium sulfate. The ether was evaporated to give 0.56 g. (95% yield) of a white oil. When purification of the crude 3-acetoxy-2-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole was attempted by distillation in vacuo at 170-174°/3 mm. a liquid distilled which crystallized spontaneously in the condenser. Its infrared spectrum (PE-337) was identical with that of 2-methylthiazolo[3,2-a]benzimidazole (XXVIII). The 3-acetoxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole obtained was also a mixture of isomers (cis and trans); however, a suitable method of separation was not found.

3. Preparation of 2-Methylthiazolo[3,2-a]benzimidazole (XXVIII).

3-Hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXX) (0.82 g., 0.004 mole) was dissolved in 30 ml. of freshly-distilled pyridine in a 100 ml., three-necked flask equipped with a magnetic stirrer, a reflux condenser, and a dropping funnel. Phosphorus oxychloride (3 ml.) was added from the dropping funnel over a 30-minute period. The reaction mixture was stirred for one hour at room temperature. Ice chips were added cautiously to decompose any unreacted phosphorus oxychloride and the reaction mixture was poured into 150 ml. of water. The aqueous solution was extracted with three 50 ml. portions of ether. The combined ether extract was washed once with ether and dried over anhydrous sodium sulfate. The ether was evaporated and any remaining pyridine was removed to give 0.7 g. (93% yield) of nearly colorless crystals, m.p. 156-158°. Recrystallization from hexane gave an analytical sample of 2-methylthiazolo[3,2-a]-benzimidazole (XXVIII), m.p. 158-159°.

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63.79; H, 4.27; N, 14.88.

Found: C, 63.62; H, 4.42; N, 14.67.

G. Synthesis of 3-Phenylthiazolo[3,2-a]benzimidazole (XXXII).

1. Synthesis of (2-Benzimidazolylthio)acetophenone (XXXIII)

2-Benzimidazolinethione (0.37 g., 0.0025 mole) and bromoacetophenone (0.50 g., 0.0025 mole) were suspended in

40 ml. of 2-butanone and the mixture was refluxed for four hours. The reaction mixture was cooled and filtered to give 0.85 g. (quantitative yield) of (2-benzimidazolylthio)acetophenone hydrobromide, m.p. 205-207°. When this product was added to 250 ml. of water 0.8 g. did not dissolve and was filtered. The filtrate was basified with sodium bicarbonate and a small amount of precipitate formed. The solution was filtered to give 30 mg. of a white solid, m.p. 160-162°. Its infrared spectrum (PE-337) was identical with that of (2-benzimidazolylthio)acetophenone (XXXIII).

To obtain the free base the hydrobromide salt was treated with triethylamine. (2-Benzimidazolylthio)acetophenone hydrobromide (0.6 g., 0.00075 mole) was suspended in 10 ml. of ethanol and the mixture was heated to reflux. Freshly-distilled triethylamine was added dropwise to the mixture until all the salt had dissolved (approximately 1 ml. was necessary). The solution was refluxed for 10 minutes and poured into 100 ml. of water. The resulting white precipitate was filtered and dried in vacuo giving 0.45 g. of (2-benzimidazolylthio)acetophenone (XXXIII), m.p. 164-167°. Two recrystallizations from benzene gave colorless needles, m.p. 166.5-167.5°.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44

Found: C, 67.23; H, 4.51; N, 10.27.

The acetyl derivative of (2-benzimidazolylthio)acetophenone (XXXIII) was prepared. A solution of 0.5 g. of XXXIII in

15 ml. of acetic anhydride was allowed to stand at room temperature overnight. White needles had precipitated out of solution. The solution was filtered and the product was dried in vacuo to give 0.49 g. of white needles, m.p. 168-172°. Two crystallizations from a mixture of benzene and petroleum ether (b.p. 60-80°) gave an analytical sample of (2-N-acetylbenzimidazolylthio)acetophenone (LVII), m.p. 167-168°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.78; H, 4.55; N, 9.03.

Found: C, 65.67; H, 4.49; N, 9.25.

2. Preparation of 3-Phenylthiazolo[3,2-a]benzimidazole (XXXII)

(a) Attempted cyclization of XXXIII with phosphorus oxychloride in pyridine

(2-Benzimidazolylthio)acetophenone (0.8 g., 0.003 mole) was dissolved in 20 ml. of freshly-distilled pyridine in a 100 ml., three-necked flask equipped with a magnetic stirrer, a dropping funnel and a reflux condenser. Phosphorus oxychloride (4 ml.) was added from the dropping funnel over a 30 minute period. The reaction mixture was stirred for one hour at room temperature. Ice chips were added cautiously to decompose any unreacted phosphorus oxychloride and the reaction mixture was poured into 150 ml. of water. The aqueous solution was extracted with three 50 ml. portions of ether. The combined ether extract was washed once with water and dried over anhydrous sodium sulphate. The ether was evaporated and any remaining pyridine was removed to give 0.5 g. of a dark-colored

solid. Its infrared spectrum (PE-337) indicated this was mainly 2-benzimidazolinethione with some unreacted starting material.

(b) Cyclization of (2-benzimidazolylthio)acetophenone with hydrobromic acid.

(2-Benzimidazolylthio)acetophenone (1.0 g., 0.0038 mole) was refluxed in 30 ml. of fuming hydrobromic acid for three and a half hours. The reaction mixture was added to 400 ml. of water and filtered to give 0.34 g. of a white precipitate. Its infrared spectrum (PE-337) indicated that this product was 2-benzimidazolinethione (II). The filtrate was basified with sodium bicarbonate. The resulting precipitate was filtered and dried in vacuo giving 0.4 g. (43% yield) of a white solid. Two recrystallizations from hexane gave 3-phenylthiazolo[3,2-a]benzimidazole (XXXII), m.p. 140-142°.

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19.

Found: C, 72.17; H, 4.17; N, 11.16.

H. Synthesis of 3-Methylthiazolo[3,2-a]benzimidazole (XXXIV)

1. Preparation of 3-Hydroxy-3-methyl-2,3-dihydrothiazolo-[3,2-a]benzimidazole (XXXV).

(a) Condensation of 2-benzimidazolinethione (II) and chloroacetone in neutral medium.

A mixture of 2-benzimidazolinethione (1.5 g., 0.01 mole) and chloroacetone (0.93 g., 0.01 mole) was refluxed in 40 ml. of 2-butanone for four hours. During the course of the reaction a white solid precipitated. The reaction mixture

was cooled and filtered. The crude hydrochloride salt obtained was dissolved in 100 ml. of water. The solution was basified with sodium carbonate. An oily white substance separated which solidified on scratching. The solid was filtered and dried in vacuo giving 2.0 g. (97% yield) of 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXXV) m.p. 110-112°. Crystallization from diethyl ether gave a white powder, m.p. 111-112°.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58.

Found: C, 58.42; H, 5.05; N, 13.44.

(b) Condensation of 2-benzimidazolinethione and chloroacetone in ethanolic potassium hydroxide.

From 1.5 g. of 2-benzimidazolinethione 1.7 g. (85% yield) of a white powder, m.p. 111-112° was obtained. The mixed melting point with 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole was 111-112°. The infrared spectra (PE-337) of both products were identical.

D'Amico sent us a crude sample of his reaction product, named by him (2-benzimidazolylthio)-2-propanone, m.p. 110-113°. Recrystallization from ethanol gave a white solid, m.p. 112-113°. The mixed melting point with our product was 112-113°.

(c) Acetylation of 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXXV).

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole (0.5 g., 0.0028 mole) was allowed to stand at

room temperature overnight in 20 ml. of acetic anhydride. The reaction mixture was added to 250 ml. of water. An oil separated which immediately crystallized. The solution was filtered to give 0.75 g. (quantitative yield) of almost colorless crystals, m.p. 115.5-118.5°. Three recrystallizations from hexane gave an analytical sample of (2-N-acetylbenzimidazolylthio)propan-2-one (XLIII), m.p. 121-122°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28.

Found: C, 58.24; H, 5.02; N, 11.42.

After standing for 12 months XLIII had become brown in color and smelt of acetic acid. The infrared spectrum (PE-337) of the changed product indicated that it was mainly 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole with some unchanged (2-N-acetylbenzimidazolylthio)propan-2-one.

2. Preparation of 3-Methylthiazolo[3,2-a]benzimidazole (XXXIV).

(a) Dehydration with phosphorus oxychloride in pyridine.

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole (1 g., 0.005 mole) was dissolved in 40 ml. of freshly-distilled pyridine in a 100 ml., 3-necked flask equipped with a dropping funnel, a reflux condenser, and a magnetic stirrer. Phosphorus oxychloride (4 ml.) was added from the dropping funnel and the reaction mixture was stirred at room temperature for one hour. Ice chips were added to decompose any unreacted phosphorus oxychloride. The reaction

mixture was poured into 150 ml. of water and extracted with three 50 ml. portions of ether. The combined ether extract was washed once with water, and dried over anhydrous sodium sulfate. The ether was evaporated and any remaining pyridine was removed leaving 1.0 g. of a slightly yellow solid, m.p. 109-110°. Its infrared spectrum (PE-137) indicated that it was unreacted starting material. The 1.0 g. of recovered 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole was again dissolved in pyridine and treated with phosphorus oxychloride. The reaction mixture was stirred at room temperature for fifteen hours. The reaction was worked up as before and the ether extract gave 0.8 g. (85% yield) of 3-methylthiazolo[3,2-a]benzimidazole (XXXIV), m.p. 153-156°. Two recrystallizations from hexane gave white crystals, m.p. 160-161°, (lit. m.p. 165-166° (17)).

(b) Dehydration of XXXV with hydrochloric acid.

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (0.6 g., 0.003 mole) was refluxed in 70 ml. of 4% hydrochloric acid for 15 hours. The reaction mixture was diluted with 100 ml. of water and basified with sodium bicarbonate. Filtration of the precipitated product gave 0.55 g. (quantitative yield) of white crystals of 3-methylthiazolo-[3,2-a]benzimidazole (XXXIV), m.p. 159-161°. Recrystallization from hexane raised the melting point to 160-161°. Its infrared spectrum (PE-137) was identical with that of the

product obtained from the phosphorus oxychloride dehydration of XXXV.

J. Rearrangement of the Hydroxydihydrothiazolo[3,2-a]benzimidazoles under Acetylating Conditions

1. Formation of 2-Acetylthiazolo[3,2-a]benzimidazole (XXXVI) from III.

(a) Reaction of 3-hydroxy-2,3-dihydrothiazolo[3,2-a] benzimidazole (III) with ethyl acetate.

Reagent grade (Fisher certified) ethyl acetate was purified according to the procedure given by Vogel (18) and a boiling point of 77-78° was observed for the purified form. 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (1.0 g., 0.0052 mole) was refluxed in 200 ml. of purified ethyl acetate for 12 hours. The solution, which had turned yellow, was concentrated to approximately 30 ml. The precipitated product was filtered and dried in vacuo. Its infrared spectrum (PE-137) indicated that it was a mixture of starting material and a new product (XXXVI) having carbonyl absorption at 1660 $cm.^{-1}$ Additional freshly-purified ethyl acetate was added to the product and the mixture was refluxed for 15 hours. Concentration of the reaction mixture and filtration gave a solid the infrared spectrum (PE-137) of which indicated that it was a mixture containing mainly XXXVI with some unreacted starting material. Purified ethyl acetate (200 ml.) was added to the product and refluxing was continued for 12 hours. Concentration of the reaction mixture to approximately 30 ml. and filtration of the precipitated product gave 0.7 g.

of a yellow solid, m.p. 224-227°. Its infrared spectrum (PE-137) indicated that no starting material remained. Recrystallization from ethanol gave sparkling pale yellow crystals of XXXVI, m.p. 226-228°. Two further recrystallizations from ethanol gave an analytical sample, m.p. 227-228°. Anal. Found: C, 61.09; H, 3.70; N, 3.07. The calculated formula was $C_{11}H_8N_2OS$.

(b) Reaction of 3-Hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole with acetic anhydride in pyridine.

(i) At reflux temperature

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (1.0 g., 0.005 mole) was refluxed for three hours in 25 ml. of acetic anhydride and 50 ml. of pyridine. The reaction mixture was added to 800 ml. of water. After basification with dilute ammonium hydroxide a yellow solid precipitated. The solution was filtered to give 0.8 g. (72% yield) of a yellow product, m.p. 222-226°. Crystallization from ethanol gave yellow needles, m.p. 226-227°. The infrared spectrum (PE-137) of this product was identical with that of XXXVI and a mixed melting point with XXXVI was 226-227°.

(ii) At room temperature.

3-Hydroxy-2,3-dihydrothiazolo[3,2-a]benzi-

midazole (III) (1.0 g., 0.005 mole) in 25 ml. of acetic anhydride and 50 ml. of pyridine was allowed to stand at room temperature for 24 hours. The reaction mixture was poured into 800 ml. of water and basified with dilute ammonium hydroxide. The basic solution was extracted with three 100 ml. portions of ether. The combined ether extract was washed once with water and was dried over anhydrous sodium sulfate. Evaporation of the ether and removal of any remaining pyridine gave 0.9 g. of a slightly yellow solid. The infrared spectrum (PE-137) of this product indicated that it was a mixture of approximately equal amounts of XXXVI and 3-acetoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (IV).

(c) Treatment of thiazolo[3,2-a]benzimidazole (I) with acetic anhydride in pyridine.

Thiazolo[3,2-a]benzimidazole (0.1g.) was refluxed for three hours in 5.0 ml. of pyridine and 2.5 ml. of acetic anhydride. The reaction mixture was added to 100 ml. of water and the aqueous solution was extracted with three 20 ml. portions of ether. The combined ether extract was washed once with water and was dried over anhydrous sodium sulfate. Evaporation of the ether and removal of any remaining pyridine

gave 0.1 g. of slightly colored crystals. The infrared spectrum (PE-137) of the product indicated that it was unreacted thiazolo[3,2-a]benzimidazole (I),

(d) Treatment of 3-acetoxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (IV) with pyridine.

3-Acetoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (IV) (47 mg.) was refluxed in pyridine for three hours. The pyridine solution was added to 100 ml. of water and the aqueous solution was extracted with three 20 ml. portions of ether. The combined ether extract was washed once with water and was dried over anhydrous sodium sulfate. Evaporation of the ether and removal of any remaining pyridine gave a slightly yellow solid. Its infrared spectrum (PE-137) indicated that it was unreacted 3-acetoxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole.

2. Determination of the Structure of XXXVI

(a) Attempted oxidation of XXXVI with silver oxide.

XXXVI (0.205 g., 0.001 mole) in 40 ml. of ethanol was added to a solution of 0.340 g. (0.002 mole) of silver nitrate in 5 ml. of water. Sodium hydroxide (0.240 g.) in 6 ml. of water was added dropwise to the reaction mixture with vigorous stirring. The solution, which had darkened and finally turned black, was stirred for four hours. The reaction mixture was filtered and the filtrate was acidified with hydrochloric acid. The acidic solution was extracted with three 10 ml. portions of chloroform. The combined

chloroform extract was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.15 g. of a yellow solid. Its infrared spectrum (PE-137) indicated that it was recovered starting material.

(b) Attempted Cannizzaro Reaction on XXXVI

XXXVI (0.20 g., 0.001 mole) was added to 0.2 g. of potassium hydroxide in 4 ml. of water and the mixture stirred at room temperature for twelve hours. The reaction mixture was filtered to give 0.19 g. of a solid. Its infrared spectrum (PE-137) indicated that it was unreacted XXXVI.

(c) Synthesis of 2-hydroxymethyl-3-methylthiazolo-[3,2-a]benzimidazole (XXXVII).

(i) Preparation of ethyl 2-(2-benzimidazolylthio) acetoacetate (XXXVIII)

The procedure of D'Amico (17) was followed to prepare this compound. Ethyl 2-(2-benzimidazolylthio)acetoacetate was obtained in 82% yield, m.p. 148-149°; (lit. m.p. 149-150° (17)).

(ii) Preparation of 2-carbethoxy-3-methylthiazolo-[3,2-a]benzimidazole (XXXIX).

This compound was prepared by cyclization of XXXVIII following the procedure of D'Amico (17). 2-Carbethoxy-3-methylthiazolo[3,2-a]-benzimidazole was obtained in quantitative yield, m.p. 120-122°; (lit. m.p. 122-123° (17)).

(iii) Preparation of 2-hydroxymethyl-3-methylthiazolo-[3,2-a]benzimidazole (XXXVII).

2-Carbethoxy-3-methylthiazolo[3,2-a]benzimida-

zole (XXXIX) (1.0 g., 0.004 mole) was dissolved in 20 ml. of ethanol. A solution of 1.6 g. (0.04 mole) of sodium borohydride in 160 ml. of ethanol was added all at once. After the initial exothermic reaction had subsided the mixture was refluxed for two hours and then poured into 900 ml. of water. On standing the solution gave 0.75 g. of a white precipitate, m.p. 181-185°. Crystallization from ethanol and water gave 0.7 g. (82% yield) of 2-hydroxymethyl-3-methylthiazolo[3,2-a]benzimidazole (XXXVII), m.p. 186-189°. Two further recrystallizations from dioxane gave an analytical sample, m.p. 194-195°.

Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.52; H, 4.62; N, 12.83.

Found: C, 60.44; H, 4.67; N, 12.95.

(d) Treatment of XXXVI with sodium hypoiodite.

The iodoform test was carried out on XXXVI according to the procedure of Shriner and Fuson (22). Treatment of XXXVI in sodium hydroxide solution with iodine gave iodoform, a yellow solid, m.p. 118-121°.

(e) Sodium borohydride reduction of 2-acetylthiazolo-[3,2-a]benzimidazole (XXXVI)

(XXXVI) (1.2 g., 0.0058 mole) was dissolved in 200 ml. of ethanol. A solution of 0.3 g. (0.006 mole) of sodium borohydride in 100 ml. of ethanol was added all at

once and the mixture was refluxed for two hours. The ethanol solution was concentrated to approximately 50 ml. and was added to 300 ml. of water. The aqueous solution was extracted with three 60 ml. portions of chloroform. The combined chloroform extract was washed once with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a pale yellow oil. Treatment with benzene gave 1.1 g. (80% yield) of nearly colorless crystals of 2-(1-hydroxyethyl)thiazolo[3,2-a]benzimidazole (XL), m.p. 112-114°. Two recrystallizations from benzene raised the melting point to 116-118°. However, an analytical sample of XL was not obtained since no method of purification was found to remove the minor impurity which was observed in its N.M.R. spectrum in $CDCl_3$.

The acetyl derivative of 2-(1-hydroxyethyl)thiazolo[3,2-a]benzimidazole was prepared. Crude XL, m.p. 116-118° (0.22 g., 0.001 mole) was allowed to stand in 10 ml. of acetic anhydride for 24 hours at room temperature. The reaction mixture was added to 200 ml. of water and the solution basified with sodium bicarbonate. A white solid separated which was filtered and dried in vacuo to give 75 mg. of product. The filtrate was extracted with three 50 ml. portions of ether. The combined ether extract was dried over anhydrous sodium sulfate. The solvent was evaporated to give 0.17 g. of a yellow oil. Its infrared spectrum (PE-137) was identical with that of the solid product. The crude

acetate was purified by thin layer chromatography (TLC) on silica gel, developing with ether. The main band gave 0.16 g. of colorless crystals, m.p. 94-96°. Recrystallization from hexane gave an analytical sample of 2-(1-acetoxyethyl)-thiazolo[3,2-a]benzimidazole (XLI), m.p. 104-105°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.99; H, 4.63; N, 10.76.
Found: C, 60.07; H, 4.70; N, 10.88.

3. Formation of 2-Acetyl-3-methylthiazolo[3,2-a]-benzimidazole (XLII) from 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (XXXV).

(a) Reaction of XXXV with acetic anhydride in pyridine.

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole (4 g., 0.019 mole) in 100 ml. of pyridine and 50 ml. of acetic anhydride was heated at 100° for three hours. The reaction mixture was added to 350 ml. of water. The resulting white precipitate was filtered and dried in vacuo giving 4.1 g. (95% yield) of white needles, m.p. 162-165°. Two recrystallizations from benzene gave an analytical sample, m.p. 164-165°. The mixed melting point with an authentic sample of 2-acetyl-3-methylthiazolo-[3,2-a]benzimidazole was 163-165°.

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.62; H, 4.37; N, 12.17.
Found: C, 62.33; H, 4.35; N, 12.28.

The 2,4-dinitrophenylhydrazone of 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole (XLII) was prepared. To a solution of 50 mg. of XLII in 5 ml. of ethanol was added 5 ml. of a saturated solution of 2,4-dinitrophenyl-

hydrazine in ethanol and one drop of concentrated sulfuric acid. A yellow solid, m.p. 271-273°, precipitated.

Also, treatment of XLII in sodium hydroxide solution with iodine precipitated iodoform, m.p. 118-121°.

(b) Rearrangement of (2-N-acetylbenzimidazolylthio)-propan-2-one (XLIII) in pyridine.

(2-N-Acetylbenzimidazolylthio)propan-2-one (XLIII) (50 mg., 0.0002 mole) was heated in 3 ml. of pyridine for three hours at 100°. The reaction mixture was added to 100 ml. of water. On standing it gave 45 mg. (90% yield) of a white precipitate, m.p. 176-177°. The mixed melting point of this product with 3-(2-benzimidazolylthio)-2,4-pentanedione (XLV) was 177-179°. The infrared spectra (PE-337) of the two compounds were identical.

(c) Preparation of 2-(1-hydroxyethyl)-3-methylthiazolo-[3,2-a]benzimidazole (XLVI).

This compound was prepared by sodium borohydride reduction of 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole following the procedure of D'Amico (17). XLVI was obtained in 80% yield, m.p. 210-212°, (lit. m.p. 227-228° (17)).

4. Preparation of 2-Acetyl-3-methylthiazolo[3,2-a]-benzimidazole (XLII).

(a) Preparation of 3-chloro-2,4-pentanedione (XLIV).

This compound was prepared by chlorination of acetylacetone following the procedure of Buchanan and Richardson (19). 3-Chloro-2,4-pentanedione, b.p. 48-50°/

20-22 mm., was obtained in 80% yield; (lit. b.p. 56-59°/ 28 mm. (19)).

(b) Condensation of 3-chloro-2,4-pentanedione and 2-benzimidazolinethione.

A mixture of 2-benzimidazolinethione (1.5 g., 0.01 mole) and 3-chloro-2,4-pentanedione was refluxed for four hours in 2-butanone. The solid which had precipitated from the reaction mixture was filtered and dried in vacuo. Part of this product dissolved in water giving an acidic solution. A white solid (1.8 g.), m.p. 178-179° (decomp.), remained undissolved. The acidic solution was basified with sodium bicarbonate. The resulting white precipitate was filtered and dried in vacuo giving 0.3 g. of a white solid, m.p. 178-179° (decomp.). Mixed melting point with the water-insoluble portion was 178-179° (decomp.). A total yield of 2.1 g. (90%) of 3-(2-benzimidazolylthio)-2,4-pentanedione (XLV) was formed; (lit. m.p. 185-186° (17)).

(c) Cyclization of XLV.

(i) With acetic anhydride in pyridine

The procedure of D'Amico (17) was followed. 3-(2-Benzimidazolylthio)-2,4-pentanedione (XLV) gave 2-acetyl-3-methylthiazolo[3,2-a]-benzimidazole (XLII) in 97% yield, m.p. 163-165°; (lit. m.p. 167-168° (17)).

(ii) With hydrochloric acid.

3-(2-Benzimidazolylthio)-2,4-pentanedione

(30 mg.) was dissolved in 5 ml. of 5% hydrochloric acid and the solution was refluxed for three hours. The reaction mixture was added to 100 ml. of water. The solution was basified with sodium bicarbonate and a white product precipitated. The solution was filtered and dried to give a white solid, m.p. 160-163°. Its infrared spectrum (PE-337) was identical with that of 2-acetyl-3-methylthiazolo[3,2-a]benzimidazole (XLII) and a mixed melting point with an authentic sample of XLII was 160-163°.

5. Treatment of 3-Hydroxy-2-methyl-2,3-dihydrothiazolo [3,2-a]benzimidazole (XXX) with Acetic Anhydride in Pyridine.

3-Hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole (XXX) (0.4 g.) in 5 ml. of acetic anhydride and 10 ml. of pyridine was refluxed for three hours. The reaction mixture was added to 250 ml. of water to give an oily suspension. This suspension was extracted with three 50 ml. portions of ether. The combined ether extract was washed once with water and dried over anhydrous sodium sulfate. Evaporation of the ether and removal of any remaining pyridine gave 0.35 g. of a slightly colored oil. Its infrared spectrum (PE-337) was identical with that of 3-acetoxy-2-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole.

II. Syntheses of Imidazo[2,1-b]benzothiazoles

A. Preparation of 2-Phenylimidazo[2,1-b]benzothiazole (LII)

2-Phenylimidazo[2,1-b]benzothiazole was prepared according to Ochiai (29). 2-Aminobenzothiazole (0.2 g., 0.0013 mole) and 0.3 g. (0.0013 mole) of bromoacetophenone were refluxed in 5 ml. of absolute ethanol for three hours. The resulting white precipitate was filtered and dried to give 0.4 g. (90% yield) of 2-phenylimidazo[2,1-b]benzothiazole hydrobromide, m.p. 258-260°; (lit. m.p. 263° (29)). This hydrobromide was insoluble in water.

The hydrobromide (0.3 g.) was suspended in 4 ml. of ethanol and the mixture was heated to reflux. Freshly-distilled triethylamine was added dropwise to the hot mixture until all the salt had dissolved. The mixture was refluxed for ten minutes and was added to 100 ml. of cold water. The resulting oily suspension was extracted with three 20 ml. portions of ether. The combined ether extract was washed once with water and was dried over anhydrous sodium sulfate. The solvent was evaporated leaving a colorless oil which, on treatment with hexane, slowly crystallized to give 0.2 g. of colorless needles. Two recrystallizations from hexane gave 2-phenylimidazo[2,1-b]benzothiazole, m.p. 98-99°; (lit. m.p. 100° (29)).

B. Synthesis of 2-Methylimidazo[2,1-b]benzothiazole (XLVIII).

1. Preparation of 2-Acetamidobenzothiazole (XLIX).

2-Aminobenzothiazole (0.22 g., 0.0015 mole) was

allowed to stand in 5 ml. of acetic anhydride overnight at room temperature. A solid precipitated out. The reaction mixture was filtered and the white solid was dried in vacuo at 120° to give 0.2 g. (80% yield) of 2-acetamidobenzothiazole, m.p. 187-189°; (lit. m.p. 189° (24)).

2. Preparation of 2-Methylimidazo[2,1-b]benzothiazole (XLVIII)

2-Aminobenzothiazole (6.0 g., 0.04 mole) and 7.6 g. (0.08 mole) of chloroacetone were refluxed in 100 ml. of absolute ethanol for three hours. The solution was evaporated nearly to dryness and the residue was added to 200 ml. of water. On standing a solid precipitated which was filtered and dried in vacuo to give 2.6 g. of a slightly yellow product, m.p. 130-133°. The filtrate was basified with sodium carbonate. The resulting precipitate was filtered and dried in vacuo to give 2.4 g. of a white solid, m.p. 131-134°. Its infrared spectrum (PE-337) was identical with that of the product obtained before treatment with sodium carbonate. The N.M.R. spectrum in $CDCl_3$ of this product indicated that it was a 1:1 mixture of 2-aminobenzothiazole and 2-methylimidazo[2,1-b]-benzothiazole. The estimated yield of crude 2-methylimidazo-[2,1-b]benzothiazole was 2.7 g. (36% yield).

The mixture (2.4 g.) was allowed to stand in 15 ml. of acetic anhydride at room temperature overnight. The acetic anhydride solution was added to 200 ml. of water. The resulting white precipitate was filtered and was dried in vacuo

giving 1.2 g. of a white solid, m.p. 180-185°. Its infrared spectrum (PE-337) indicated that it was mainly 2-acetamidobenzothiazole. The filtrate was basified with sodium carbonate and a white solid separated. The solution was filtered and the solid was dried in vacuo giving 1.0 g. of white needles, m.p. 89-90°. Two recrystallizations from hexane gave an analytical sample of 2-methylimidazo[2,1-b]benzothiazole (XLVIII), m.p. 91-92°; (lit. m.p. 89-90° (58)).

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63.79; H, 4.27; N, 14.88.

Found: C, 63.66; H, 4.37; N, 14.67.

3. Attempted Condensation of 2-Acetamidobenzothiazole with Chloroacetone.

A mixture of 2-acetamidobenzothiazole (0.76 g., 0.004 mole) and 0.4 g. (0.004 mole) of chloroacetone was refluxed in 20 ml. of toluene for 20 hours. The reaction mixture was cooled and a solid precipitated. The product was filtered and dried to give 0.6 g. of a white solid. Its infrared spectrum (PE-337) indicated that it was recovered 2-acetomidobenzothiazole.

C. Synthesis of Imidazo[2,1-b]benzothiazole (LI)

A mixture of 2-aminobenzothiazole (6.0 g., 0.04 mole) and 9 ml. of a 40-45% solution of chloroacetaldehyde in water was refluxed in 50 ml. of ethanol for three hours. The ethanol was evaporated and the dark residue was taken up in 250 ml. of water. A dark oil, smelling of chloroacetaldehyde, separated out. The oily suspension was extracted with

three 50 ml. portions of ether to remove any unreacted chloroacetaldehyde. The aqueous layer was basified with sodium carbonate and the basic solution was continuously extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and the benzene was evaporated leaving a yellow oil. Treatment of the oil with benzene and hexane gave a yellow solid. Its infrared spectrum (PE-337) indicated that it was a mixture of 2-aminobenzothiazole and imidazo[2,1-b]benzothiazole. (Approximately a 25% yield of crude imidazo[2,1-b]benzothiazole).

The mixture (0.5 g.) was allowed to stand overnight at room temperature in 4 ml. of acetic anhydride. The reaction mixture was added to 100 ml. of water and a solid separated. The solution was filtered to give 0.22 g. of a white solid. Its infrared spectrum (PE-337) indicated that it was 2-acetomidobenzothiazole. The filtrate was basified with sodium carbonate to give an oily suspension. This basic suspension was extracted with three 30 ml. portions of ether. The combined ether extract was dried over anhydrous sodium sulfate. The solvent was evaporated leaving 0.27 g. of an oil which failed to crystallize. Its infrared spectrum (PE-337) indicated that it was mainly imidazo[2,1-b]benzothiazole with a small amount of 2-acetamidobenzothiazole also present. This oil was taken up in 10 ml. of 0.4% hydrochloric acid and the solution was diluted with 70 ml. of water. The acidic solution was extracted with three 15 ml. portions of ether to remove the

remaining 2-acetomidobenzothiazole. The aqueous layer was basified with sodium carbonate and a solid slowly separated. The solution was filtered to give 0.20 g. of imidazo[2,1-b]-benzothiazole (LI), m.p. 53-55°. Two recrystallizations from hexane gave colorless needles, m.p. 53.5-54.5°.

Anal. Calcd. for $C_9H_6N_2S$: C, 62.04; H, 3.47; N, 16.08.

Found: C, 62.03; H, 3.52; N, 15.97.

D. Synthesis of 3-Methylimidazo[2,1-b]benzothiazole (LIII)

1. Preparation of α-Bromopropionaldehyde diethyl acetal (LIV).

(a) Preparation of propionaldehyde diethyl acetal.

The procedure of Chastrette (23) was followed to prepare this acetal from propionaldehyde. Propionaldehyde diethyl acetal, b.p. 123-124°, was obtained in 73% yield; (lit. b.p. 123-124° (23)).

(b) Bromination of propionaldehyde diethyl acetal.

The procedure of Chastrette (23) was followed to prepare α-bromopropionaldehyde diethyl acetal (LIV). Propionaldehyde diethyl acetal (48.2 g., 0.37 mole) gave 80.8 g. (61% yield) of LIV, b.p. 67-69°/10-12 mm; (lit. b.p. 70-71°/16 mm. (23)).

2. Preparation of 3-Methylimidazo[2,1-b]benzothiazole (LIII).

α-Bromopropionaldehyde diethyl acetal (2.1 g., 0.01 mole) was gently refluxed in 0.5 ml. of concentrated hydrobromic acid and 0.5 ml. of water for 30 minutes. The mixture was added to 20 ml. of ethanol and was treated with sodium

bicarbonate until the evolution of carbon dioxide had stopped. The mixture was filtered and 2-aminobenzothiazole (0.6 g., 0.004 mole) was added to the filtrate. The solution was refluxed for four hours and then was concentrated to one-half its volume. The resulting precipitate was filtered and was dried to give 0.8 g. (80% yield) of 3-methylimidazo[2,1-b]-benzothiazole hydrobromide. The crude hydrobromide was dissolved in 100 ml. of water and the solution was basified with sodium bicarbonate. The resulting white precipitate was filtered and dried to give 0.6 g. (80% yield) of 3-methylimidazo[2,1-b]-benzothiazole (LIII), m.p. 97-98°. Two recrystallizations from hexane gave colorless needles, m.p. 98-99°.

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63179; H, 4.27; N, 14.88.

Found: C, 64.01; H, 4.49; N, 14.85.

III. Syntheses of Imidazo[2,1-b]thiazoles

A. Synthesis of 6-Methylimidazo[2,1-b]thiazole (LV).

... 1. Condensation of 2-Aminothiazole and Chloroacetone

A mixture of 1.0 g. (0.01 mole) of 2-aminothiazole and 0.9 g. (0.01 mole) of chloroacetone was allowed to stand in 30 ml. of 2-butanone at room temperature for 48 hours. The resulting white precipitate was filtered and was dried to give 1.5 g. of 2-imino-3-(2-propanone)thiazole hydrochloride (LVI), m.p. 117-121°. It was noted that on standing this product changed first to a semi-solid, then to a liquid, and finally to a solid. Infrared spectra (PE-337) indicated that cyclodehydration to form 6-methylimidazo[2,1-b]thiazole hydrochloride was occurring.

2. Attempted Formation of 2-Imino-3-(2-propanone)thiazole

(a) With sodium bicarbonate in water.

The hydrochloride (LVI) (100 mg.) was dissolved in water and the solution was basified with sodium bicarbonate. The basic solution was extracted with three 10 ml. portions of ether. The combined ether extract was dried over anhydrous sodium sulfate and the solvent was evaporated leaving a slightly yellow oil. Its infrared spectrum (PE-337) indicated that cyclodehydration had occurred.

(b) With triethylamine.

The hydrochloride (LVI) (0.3 g.) was suspended in 5 ml. of ethanol and the mixture was heated to reflux. Freshly-distilled triethylamine was added dropwise to the hot solution until all the hydrochloride had dissolved. The reaction mixture was refluxed for 5 minutes and was added to 100 ml. of water. The aqueous solution was extracted with three 20 ml. portions of ether and the combined ether extract was washed once with water and was dried over anhydrous sodium sulfate. The ether was evaporated to give a slightly yellow oil. Its infrared spectrum (PE-337) indicated that cyclodehydration had occurred.

(c) Preparation of 6-methylimidazo[2,1-b]thiazole (LV).

2-Imino-3-(2-propanone)thiazole hydrochloride (LVI) (3.1 g., 0.016 mole) was refluxed in 60 ml. of 10% hydrochloric acid for three hours. The reaction mixture was added to 200 ml.

of water and the solution was basified with sodium bicarbonate. The basic solution was extracted with three 50 ml. portions of ether and the combined ether extract was dried over anhydrous sodium sulfate. The solvent was evaporated to give 2.2 g. of a yellow oil. Its infrared spectrum (PE-337) indicated that this was mainly 6-methylimidazo[2,1-b]thiazole (LV) but that some 2-aminothiazole was also present. The oil was allowed to stand for three hours in 10 ml. of acetic anhydride at room temperature. The mixture was added to 200 ml. of water and then was basified with sodium bicarbonate. The basic solution was extracted with three 50 ml. portions of ether and the combined ether extract was dried over anhydrous sodium sulfate. Evaporation of the ether gave 2.4 g. of a mixture of an oil and some crystalline material. This mixture was distilled in vacuo to give 1.5 g. (70% yield) of a colorless liquid, b.p. 102-104°/1.5 mm. Two successive redistillations gave an analytical sample of 6-methylimidazo[2,1-b]thiazole (LV).

Anal. Calcd. for $C_6H_6N_2S$: C, 52.14; H, 4.38; N, 20.27.

Found: C, 52.02; H, 4.18; N, 20.13.

After standing at room temperature for four months LV slowly began to crystallize.

B. Synthesis of Imidazo[2,1-b]thiazole (L)

1. From 2-Aminothiazole

Bromoacetaldehyde diethyl acetal (3.8 g., 0.018 mole) was refluxed in 1 ml. of concentrated hydrobromic acid and 1 ml. of water for 30 minutes. The mixture was poured into

20 ml. of ethanol and was basified with sodium bicarbonate until the evolution of carbon dioxide had ceased. The mixture was filtered and 1.0 g. (0.01 mole) of 2-aminothiazole was added to the filtrate. The resulting solution was allowed to stand at room temperature for 72 hours. The reaction mixture was added to 150 ml. of water and the aqueous solution was extracted with three 30 ml. portions of ether to remove any unreacted bromoacetaldehyde. The aqueous layer was basified with sodium bicarbonate and the basic solution was extracted with three 50 ml. portions of ether. The combined ether extract was dried over anhydrous sodium sulfate and the solvent was evaporated to give 0.8 g. of a nearly colorless oil. Its infrared spectrum (PE-337) indicated that this was a mixture of 2-aminothiazole and imidazo[2,1-b]-thiazole. The combined yield from three runs was 2.1 g. The mixture (2.1 g.) was allowed to stand in 10 ml. of acetic anhydride for three hours at room temperature. The reaction mixture was added to 150 ml. of water. The aqueous solution was basified with sodium carbonate and was extracted with three 50 ml portions of ether. The combined ether extract was dried over anhydrous sodium sulfate and the solvent was evaporated to give 2.3 g. of a semi-solid mass. This mixture of 2-acetamidothiazole and imidazo[2,1-b]thiazole was distilled in vacuo to give 0.8 g. of a clear liquid, b.p. 100-102^{o}/1.5 mm.

Redistillation at this temperature and pressure gave a colorless liquid which crystallized on scratching. Crystallization from hexane gave needles, m.p. 55-65°. Two recrystallizations from hexane gave an analytical sample, m.p. 62-64°.

Anal. Calcd. for $C_5H_4N_2S$: C, 48.36; H, 3.25; N, 22.56.
Found: C, 48.38; H, 3.24; N, 22.43.

2. From 2(3H)-imidazolethione.

(a) Condensation of 2(3H)-imidazolethione and chloroacetaldehyde.

A mixture of 2(3H)-imidazolethione (0.5 g., 0.005 mole) and 1 ml. of a 40-45% solution of chloroacetaldehyde in water was refluxed in 20 ml. of 2-butanone for three hours. The reaction mixture was filtered to give 0.95 g. (quantitative yield) of a hydrochloride salt. This crude hydrochloride was dissolved in 100 ml. of water and the solution was basified with sodium bicarbonate. The basic solution was extracted with three 20 ml. portions of ether. The combined ether extract was dried over anhydrous sodium sulfate and the solvent was evaporated to give 50 mg. of a yellow oil. Treatment of this oil with tetrahydrofuran gave 40 mg. of tan-colored crystals. The infrared spectrum (PE-337) of this solid indicated that it was a cyclic alcohol. However, continuous extraction of the basic solution with ether, chloroform or amyl alcohol gave no further product.

(b) Preparation of Imidazo[2,1-b]thiazole (L).

The crude hydrochloride (6.5 g., 0.033 mole) was dissolved in 250 ml. of freshly-distilled pyridine in a 500 ml. three-necked flask equipped with a dropping funnel, a reflux condenser and a magnetic stirrer. Phosphorus oxychloride (27 ml.) was added from the dropping funnel over a one hour period. The reaction mixture was stirred for an additional one hour at room temperature and then was added to 900 ml. of water. The aqueous solution was extracted with three 200 ml. portions of ether. The combined ether extract was washed once with water and was dried over anhydrous sodium sulfate. The ether was evaporated to give 1.0 g. of a very dark oil. Distillation at reduced pressure gave 0.1 g. of a colorless liquid, b.p. 98-100°/1.5 mm. Its infrared spectrum (PE-337) was identical with that of imidazo[2,1-b]thiazole.

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. The synthesis of thiazolo[3,2-a]benzimidazole from 2-benzimidazolinethione was accomplished.

2. The 2-methyl-, 3-phenyl-, 6,7-dimethyl-, and 5,8-dimethylthiazolo[3,2-a]benzimidazoles were synthesized in a similar manner.

3. The intermediate 3-hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazoles were isolated in the above syntheses and were characterized.

4. The position of the hydroxyl group in 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole was shown unambiguously.

5. Tautomerism of the 3-hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazoles was investigated.

6. Contrary to published reports treatment of 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole with acetic anhydride in pyridine gave 2-acetyl-3-methylthiazol⊕[3,2-a]benzimidazole.

7. A mechanism for the formation of 2-acetyl-3-methylthiazol⊕[3,2-a]benzimidazole was suggested and was proved.

8. 2-Acetylthiazolo[3,2-a]benzimidazole was formed from 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole under acetylating conditions.

9. A mechanistic interpretation of the formation of 2-acetylthiazolo[3,2-a]benzimidazole was proposed.

10. Nitration of thiazolo[3,2-a]benzimidazole gave the 6- or 7-nitro derivative as the main product.
11. Lithium aluminum hydride reduction of 3(2H)-thiazolo-[3,2-a]benzimidazolone gave 2-(2-benzimidazolylthio)ethanol.
12. 5,6,7,8-Tetrahydrothiazolo[3,2-a]benzimidazole was synthesized and its dehydrogenation was investigated.
13. Imidazo[2,1-b]benzothiazole and its 2-methyl and 3-methyl derivatives were synthesized.
14. The syntheses of imidazo[2,1-b]thiazole and 6-methyl-imidazo[2,1-b]thiazole from 2-aminothiazole were achieved.
15. Imidazo[2,1-b]thiazole was synthesized from 2(3H)-imidazolethione.
16. The following new compounds were prepared and characterized:
    (i) 3-hydroxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (III)
    (ii) 3-ethoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (V)
    (iii) 3-acetoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (IV)
    (iv) 6- (or 7-)nitrothiazolo[3,2-a]benzimidazole (XLVII)
    (v) thiazolo[3,2-a]benzimidazole (I)
    (vi) thiazolo[3,2-a]benzimidazole methiodide (VII)
    (vii) 5,6,7,8-tetrahydrothiazolo[3,2-a]benzimidazole (XII)
    (viii) 5,6,7,8-tetrahydrothiazolo[3,2-a]benzimidazole methiodide (XIV)
    (ix) 2-(2-benzimidazolylthio)ethanol (XI)
    (x) 6,7-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3,2-a]-benzimidazole (XXI)

(xi) 6,7-dimethylthiazolo[3,2-a]benzimidazole (XVI)

(xii) 4,7-dimethyl-2-benzimidazolinethione (XXVI)

(xiii) 5,8-dimethyl-3-hydroxy-2,3-dihydrothiazolo-[3,2-a]benzimidazole (XXVII)

(xiv) 5,8-dimethylthiazolo[3,2-a]benzimidazole (XXII)

(xv) 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole (XXX)

(xvi) 3-acetoxy-2-methyl-2,3-dihydrothiazolo[3,2-a]-benzimidazole (XXXI)

(xvii) 2-methylthiazolo[3,2-a]benzimidazole (XXVIII)

(xviii) (2-benzimidazolylthio)acetophenone (XXXIII)

(xix) 3-phenylthiazolo[3,2-a]benzimidazole (XXXII)

(xx) (2-N-acetylbenzimidazolylthio)acetophenone (LVII)

(xxi) (2-N-acetylbenzimidazolylthio)propan-2-one (XLIII)

(xxii) 2-hydroxymethyl-3-methylthiazolo[3,2-a]-benzimidazole (XXXVII)

(xxiii) 2-acetylthiazolo[3,2-a]benzimidazole (XXXVI)

(xxiv) 2-(1-hydroxyethyl)thiazolo[3,2-a]benzimidazole (XL)

(xxv) 2-(1-acetoxyethyl)thiazolo[3,2-a]benzimidazole (XLI)

(xxvi) 3-methylimidazo[2,1-b]benzothiazole (LIII)

(xxvii) imidazo[2,1-b]benzothiazole (LI)

(xxviii) imidazo[2,1-b]thiazole (L).

17. The N.M.R. spectra of the new compounds and some previously known compounds were recorded and correlated with structure.

18. The infrared spectra of the thiazolo[3,2-a]benzimidazoles, the imidazo[2,1-b]benzothiazoles and the imidazo[2,1-b]-thiazoles were recorded and discussed in some detail.

19. The ultraviolet absorption spectra of the three classes of compounds investigated were given.

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