A STUDY OF THE REACTIVITY OF METHYLTHIAZOLES

A Thesis

by

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GENERAL INTRODUCTION

The increasing importance of thiazole derivatives in biochemical, pharmaceutical and also in technical fields makes it highly desirable to know as much as possible about them. The penicillins, produced by a mold, the first antibiotics to be used in medicine, contain the thiazole ring system. Sulfathiazole, that is p-aminobenzenesulfanilamidothiazole, is still very widely used as an effective bactericide. Thiazole derivatives, namely 2-, 4- and 5-phenylthiazole, 2-, 4- and 5-(p-aminophenyl)-thiazole, 2-, 4- and 5-(p-hydroxyphenyl)-thiazole, are known, besides other thiazole-containing compounds, as active antitubercular drugs. 4-Methyl-5-(β-hydroxyethyl)-thiazole is the thiazole half of thiamine chloride, otherwise known as vitamin B_1. Derivatives of 2-mercaptothiazole, such as 2-mercaptobenzothiazole, commonly known as captax, or 2-cyclohexaminomercaptothiazole along with many other thiazole derivatives, are used as valuable rubber accelerators. Heilbron (1) mentioned in his review article the use of the derivatives of 5-amino-2-mercaptothiazole and 2-mercapto-5-thiazolone in the synthesis of amino acids and peptides.

The objective of the present work was firstly, to investigate the reactivity of the methylthiazoles in certain condensation reactions. The first group of reactions involved the condensation of methylthiazoles with anhydrides of aromatic dicarboxylic acids, such as phthalic, naphthalic, diphenic and pyromellitic anhydrides. The reactions were carried out by heating the mixtures of the components for several hours. The second group of reactions used in this investigation was the Mannich condensation, in which methylthiazoles were taken into reaction with formaldehyde and secondary amines (morpholine, piperidine and dimethylamine).

The second objective of this work was to measure for the first time the infrared spectra of unsubstituted thiazole and methylthiazoles, and to find the correlation between the structure of these compounds and their spectra.

HISTORICAL INTRODUCTION

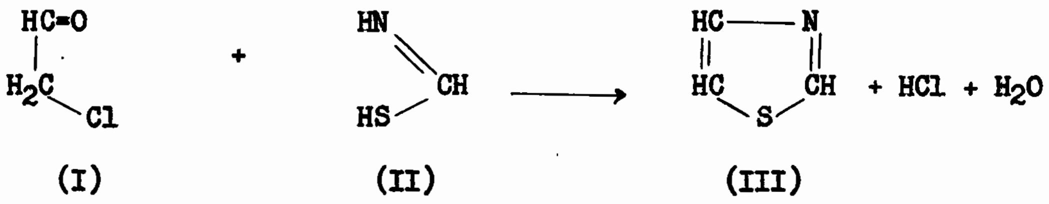
The physical and chemical properties of thiazole and methylthiazoles are similar to those of pyridine and methylpyridines. The nearness in boiling points of thiazole (116.8°)(2) and pyridine (115.5°)(3) is shown also by the methyl derivatives of these compounds. The similarity in the physical properties of 2-methylthiazole (b.p. 127.5-128) and 2-methylpyridine (128° ± 0.7°)(4) was first reported by Arapides (5), Hantzsch (6) and Popp (7). The odours of the thiazoles are frequently similar to those of the corresponding compounds in the pyridine series. The solubility of the thiazoles in water may be compared with that of pyridines. Pyridine and the three picolines are miscible in all proportions in water; thiazole is very hygroscopic, and 2-methylthiazole and 4-methylthiazole are miscible in all proportions. Similarly to the dimethylpyridines, 2,4-dimethylthiazole and 2,5-dimethylthiazole are more soluble in cold than in warm water.

Thiazole, like pyridine, is resistant to substitution reactions. Bromination in both cases can be accomplished only in the vapour phase at a temperature of about 300° (8, 9, 10, 11) and nitration and sulphonation (12) can be effected only under drastic conditions. By analogy with pyridine, thiazoles, for example 4-methylthiazole, add sodamide to form 2-amino-4-methylthiazole (13, 14).

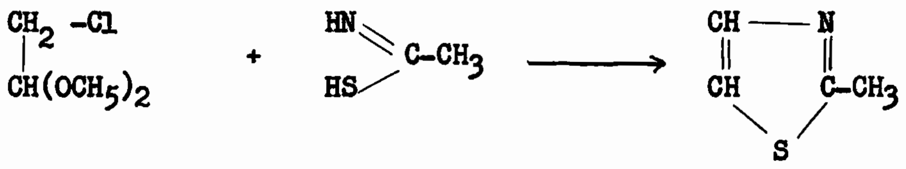
Synthesis of Thiazole and Methylthiazoles

Thiazole and its methyl and dimethyl homologues are considered to be rare chemicals. The preparation of these compounds is cumbersome. Their syntheses involve the use of some lachrimatory haloketones or haloaldehydes and phosphorus pentasulphide or thioamides of carboxylic acids possessing an unpleasant smell. Methylthiazoles themselves are skin-irritating and poisonous substances, therefore their preparation and handling require great care.

Thiazole (III) was first prepared by Popp (7) by diazotizing 2-aminothiazole and decomposing the diazotized product. The disadvantage of this method - besides the poor yield - is that, due to side reactions, only small amounts of 2-aminothiazole can be diazotized at a time. Synthesis of thiazole, condensing thioformamide (II) with chloroacetaldehyde (I) was first reported by Willstätter and Wirth (2) in 1909. The method affords only a very low yield. McLean and Muir (15) obtained thiazole in an excellent yield by zinc dust distillation of 2-chlorothiazole



Hantzsch (16) condensed α,β-dichlorodiethylether with thioacetamide (IV) and obtained some 2-methylthiazole (V) in very poor yield. The poor yield can be attributed to the fact that hydrochloric acid, which decomposes the thioacetamide, is liberated during the reaction. Hantzsch (6) later improved this method by using monochloroacetal (VI) instead of dichloroether. The yield was a little better.

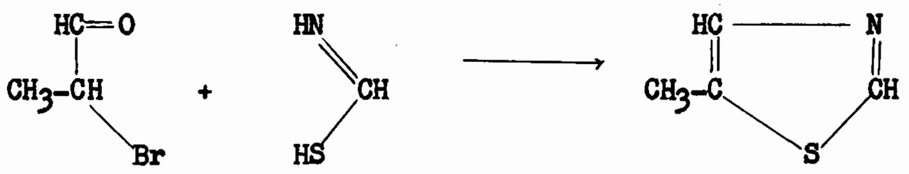


(VI) (IV) (V)

Erlenmeyer and Prijs (17) greatly improved the yield by condensing thioacetamide with chloroacetaldehyde hydrate ($2CH_2Cl\text{-}CHO + H_2O$) in the presence of acetic anhydride and benzene.

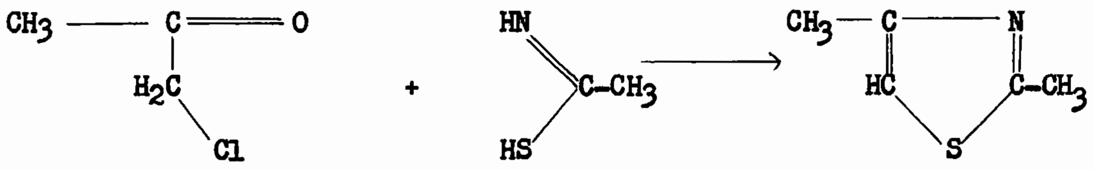
Arapides (5) prepared 4-methylthiazole (VII) by reduction of 4-methyl-2-hydroxythiazole and Popp (7) by diazotization of 4-methyl-2-aminothiazole. These methods are cumbersome and afford only very poor yields. A convenient method of preparation is given by Clarke and Gurin (18). They refluxed a mixture of thioformamide (II) in absolute alcohol and chloroacetone (VIII) for one hour. The yield of 4-methylthiazole is, however, low. Ganapathi and Venkataraman (19) synthesized thiazole derivatives, unsubstituted in position 2, by condensing an α-chloroketone with a mixture of formamide and phosphorus pentasulphide. This method can be used for the preparation of 4-methylthiazole and the yield is considerably better than any previously reported methods.

When α-chloro or α-bromopropionaldehyde (IX) is heated with thioformamide (II) in absolute ether, condensation occurs and 5-methylthiazole (X) is formed. Erlenmeyer and Schmidt (20) observed that the use of α-bromopropionaldehyde assures a considerably higher yield. McLean and Muir (15) used thiourea instead of thioformamide and the resulting 2-amino-5-methylthiazole was diazotized and transformed by subsequent treatment with concentrated hydrochloric acid into 2-chloro-5-methylthiazole from which they obtained 5-methylthiazole by heating it with glacial acetic acid in the presence of zinc dust.

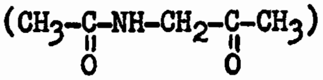


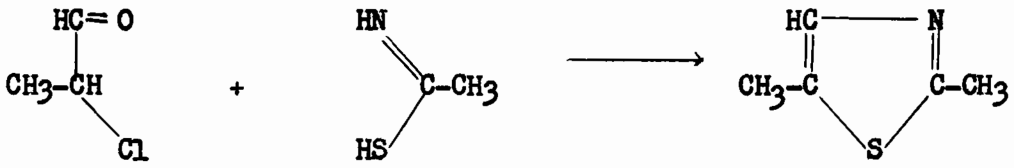
(IX) (II) (X)

The preparation of 2,4-dimethylthiazole (XI) was given by Hantzsch (6,16) in 1888. This compound was obtained in a rather poor yield by gentle heating of a mixture of thioacetamide (IV) and chloroacetone (VIII). An improved method for the preparation of (XI) where phosphorus pentasulphide, acetamide and chloroacetone were allowed to react in benzene as solvent, was presented by Schwartz (21).



(VIII) (IV) (XI)

The condensation of α-chloropropionaldehyde (XII) with thioacetamide (IV) resulted in the formation of 2,5-dimethylthiazole (XIII). This method, first reported by Hubacher (22), gave a trifling yield. Gabriel's (23) method of heating acetylaminoacetone ( $CH_3-\underset{\overset{\|}{O}}{C}-NH-CH_2-\underset{\overset{\|}{O}}{C}-CH_3$) with phosphorus pentasulphide also leads to the formation of (XIII)



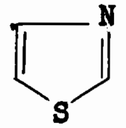
(XII) (IV) (XIII)

Improved methods for the preparation of thiazole and of some methylthiazoles will be described in this presentation in the "Experimental".

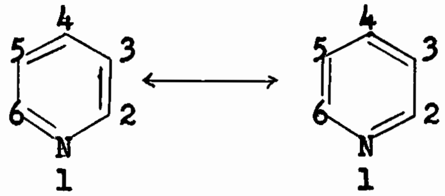
The Structure of Thiazole

Thiazole and its derivatives seem to possess aromatic character by virtue of their general properties. Like other aromatic compounds, thiazole exhibits great stability and also exhibits an unusual resistance to chemical attack, despite the fact that multiple linkages are present. Their characteristic reactions - as is the case in other aromatic compounds, are substitutions rather than additions.

Erlenmeyer and his coworkers (24, 25) studied the structure of thiazole in order to find a satisfactory explanation for the reactivity of substituents of C_2, C_4 and C_5 of the thiazole nucleus. The classical formula of thiazole (III) was found to be inadequate to explain the experimental facts. Taking pyridine (XIV) as an example, the symmetrical arrangement of the C-N-C group can easily be demonstrated, not only by the fact that there is no difference of reactivity of a substituent - for example methyl group - attached to the carbon atoms on either side of the nitrogen atom, but also by the fact that the 2- and 6-derivatives of pyridine are identical. On the other hand, a comparison of the chemical properties of the 2- (III) and 4 (IV)-derivatives of the thiazole shows the lack of symmetry of the C-N-C group in the thiazole nucleus. In the structural formula (I) the distribution of

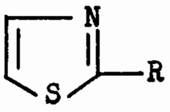


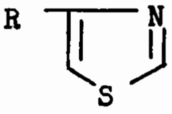
(III)

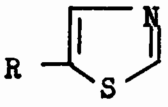


(XIV)

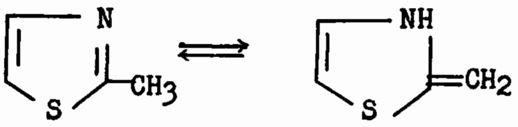
valences excludes the possible "oscillation" of bonds, as is assumed in pyridine, and leads to the fixing of single and double bonds. Considering this structural formula, the properties of 2-thiazole derivatives (XV) evidently will differ from the properties and behaviour of the corresponding isomers containing the same groups in position 4 (XVI) and 5 (XVII).

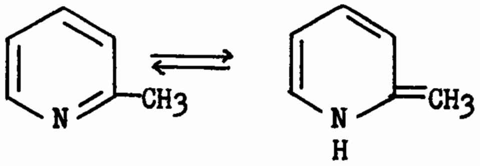

(XV)

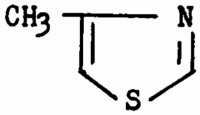

(XVI)


(XVII)

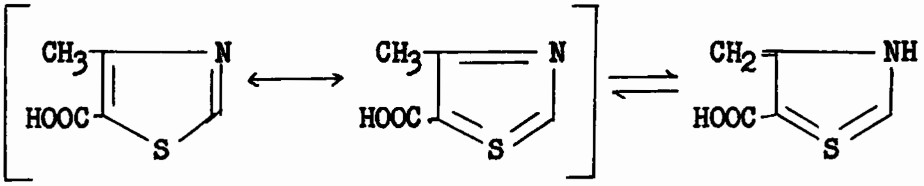
Characteristic differences could especially be shown by a comparison of behaviour of a 2-thiazole derivative with the corresponding 4-thiazole derivative. The tautomeric equilibrium of 2-methylthiazole (V) can be formulated in a similar manner to that postulated by Chichibabin (13) for 2-methylpyridine (XVIII). The case is different with 4-methylthiazole (VII). Assuming an ethylenic, non-aromatic (that is permanent, non-oscillating) double bond between C_4 and C_5, no corresponding tautomeric forms can be written.


(V)


(XVIII)

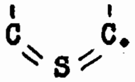

(VII)

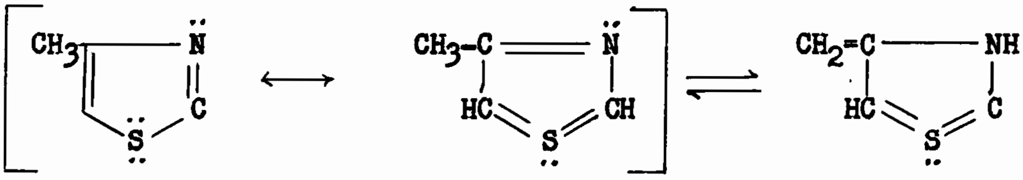
Erlenmeyer and Weber (24) found, using the deuterium exchange method, that the exchange of hydrogen atoms of 4-methylthiazole-5-carboxylic acid (IX) proceeded in accordance with a tautomeric equilibrium. They stated therefore that there is no justification for assuming the presence of an ethylenic double bond and that there is an aromatic double bond between C_4 and C_5. On this ground Erlenmeyer and Weber suggested the following formulation of the 4-methylthiazole-5-carboxylic acid (XIX). The question of the possible existence of this proposed structure will be discussed later.



(XIX)

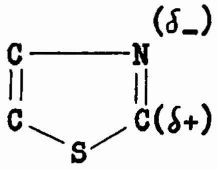
According to Erlenmeyer and Weber the exchange reaction of a 4-methylthiazole derivative with deuterium oxide leads to the result that thiazole cannot be represented by the classical structural formula. It was demonstrated that four hydrogen atoms were exchanged by dissolving 4-methylthiazole-5-carboxylic acid (XIX) in deuterium oxide. This means that besides the carboxylic hydrogen, the hydrogen atoms of the methyl group are also exchangeable. Under the same experimental conditions, methyl hydrogens, as in 2-methylbenzoic acid (o-toluic acid) are exchangeable. The occurrence of an exchange reaction is a good indication of the existence of tautomerism. One may therefore assume that a tautomeric structure, comparable to the known tautomerism of 2-methylthiazole, exists in the case of 4-methylthiazole. Such tautomerism, however, appears to be possible only for 2-methylthiazole (V) according to the distribution of bonds in the classical structural formula, but not for 4-methylthiazole (VII).

Their experimental results, concerning the interchangeability of hydrogen atoms of the 4-methyl group, led Erlenmeyer and Weber to the concept that resonance between several formulae, and tautomerism, can be assumed for 4-methylthiazole (XX). Such a formulation could explain the aromatic character of the thiazole ring. Modern concepts of the spatial distribution of valence bonds, however, preclude consideration of a structure containing two cumulated bonds . Such a system containing tetracovalent sulphur must be linear, and the thiazole nucleus would be unable to accommodate this group without prohibitive strain. The known stability of thiazole is inconsistent with a strained structure.

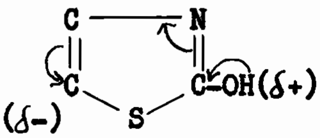


(XX)

In 1939, exploring the problem of the chemical behaviour of thiazole, Ochiai and Nagasawa (26) concluded that the carbon atom in 2-position is active towards nucleophilic reagents but inactive towards electrophilic reagents. Furthermore it was also found that when C_2 is substituted, either by an amino group or by a hydroxyl group, the reactivity in position 5 is highly increased towards electrophilic reagents. The following structures (XXI), (XXII) illustrate these properties.

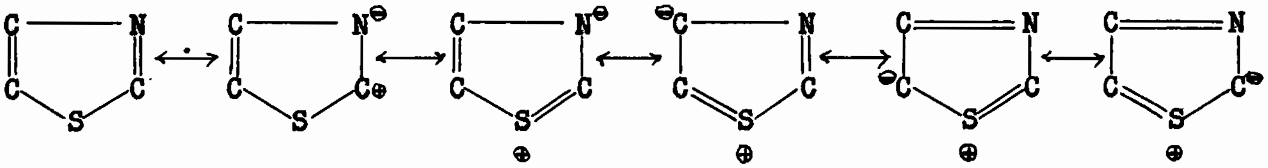


(XXI)



(XXII)

As a result of their investigation, a few years later, in 1941, the same authors (26) proposed the resonating structures of thiazole. It is significant that in these structures the use of tetravalent sulphur was entirely omitted. Among the given structures, (XXIII), (XXIV) and (XXV) can be regarded as more important than the structures (XXVI), (XXVII) and (XXVIII).



(XXIII) (XXIV) (XXV) (XXVI) (XXVII) (XXVIII)

Finally, the structure and aromatic nature of thiazole can be explained by the molecular orbital theory. The nitrogen atom and each carbon atom contributes one π electron and the sulphur atom two π electrons to the aromatic sextet. The two electrons of sulphur appear to resemble very closely the π electrons in a -CH=CH- group of an aromatic molecule. The p-orbitals of the nitrogen and sulphur atoms overlap with the p-orbital of the carbon atoms to form a molecular orbital of the thiazole molecule.

Theoretical considerations

Pullman and coworkers investigated the structure of thiazole and benzothiazole from a theoretical point of view. The structures of thiazole (XXIX) and benzothiazole (XXX), represented by the molecular diagram shown below, were given by Pullman and Metzger (27,28,29). The molecular diagrams show such parameters as

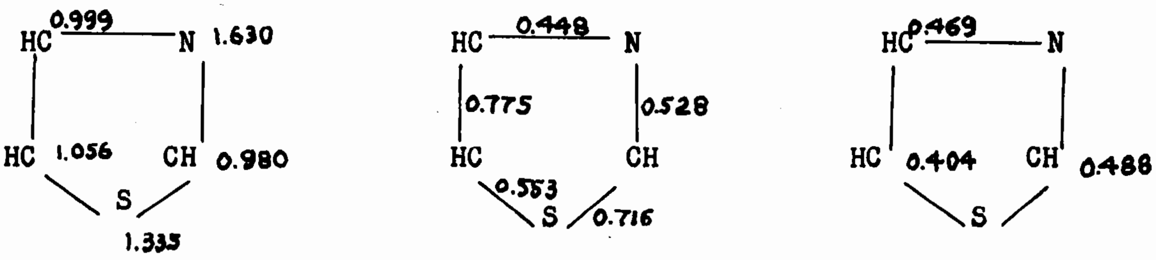
(a) electric charges,

(b) bond order,

and

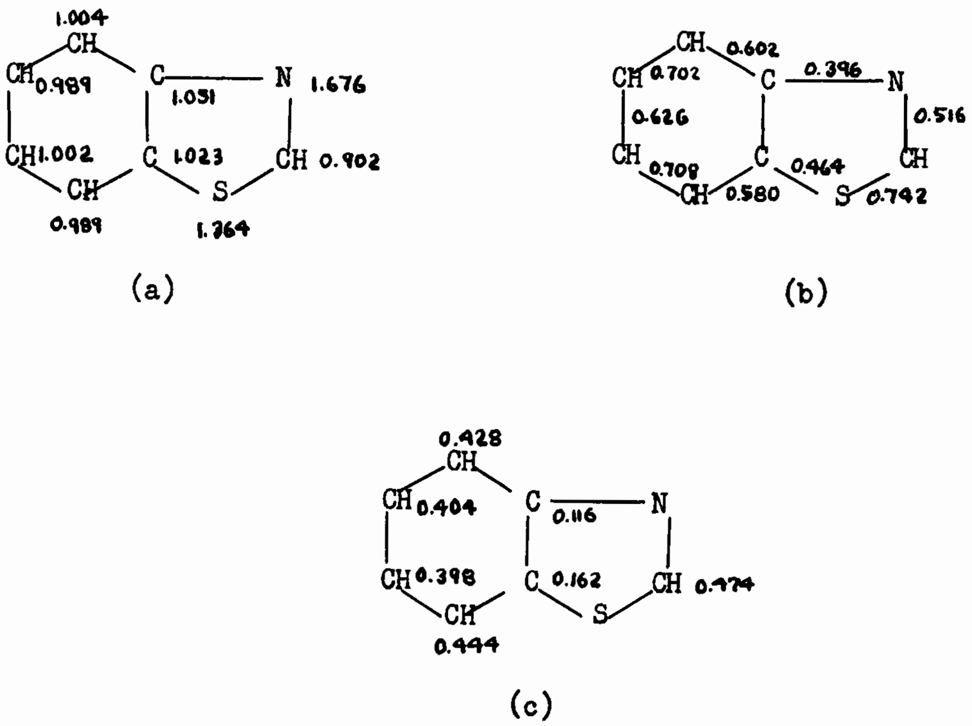
(c) free valences

which are necessarily approximative. The absolute values of the charges and bond orders are subject to modification, with an eventual improvement of the calculations. It is however fairly probable that the relative values would be only slightly changed.



(a) (b) (c)

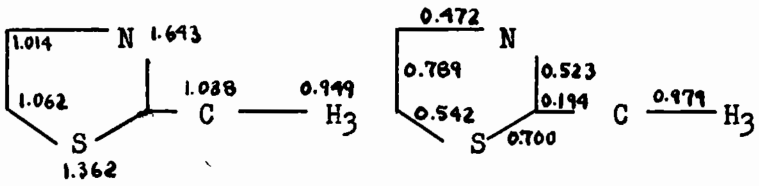
The molecular diagram of thiazole (XXIX)



The molecular diagram of benzothiazole (XXX)

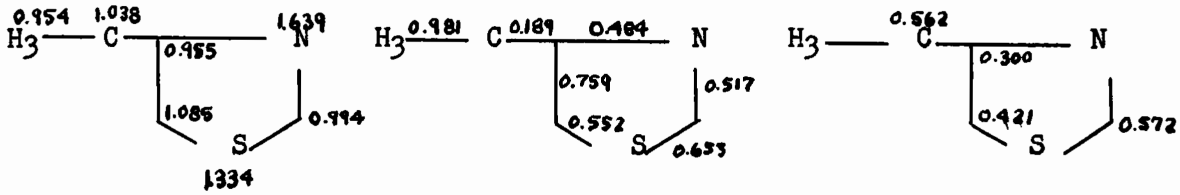
The diagrams (XXIX and XXX) previously given, show that the largest free valence index is - in both molecules - on carbon 2. Moreover, this is the only carbon atom which underwent an appreciable electrical discharge. A qualitative reasoning suggested that only the methyl group occupying this position should be activated. It also seems natural - according to Pullman's work - that this activation should be stronger in the case of 2-methylbenzothiazole than in the case of 2-methylthiazole. The explanation of this phenomenon is that, although the C_2 of the benzothiazole has a slightly smaller free valence index than the same carbon atom of the thiazole, its net positive charge is much larger.

The diagrams of the methylthiazoles (XXXI, XXXII, XXXIII) and of 2-methylbenzothiazole (XXXIV) give quantitative confirmation of these conclusions. The percentage of conjugation of the methyl group with the whole of the molecular periphery - of which the magnitude determines the activation of this group - can be deducted from one of the three following quantities: (i) the charge carried by the H_3 group; the difference between this charge and unity shows the number of electrons transferred towards the ring; (ii) the mobile index of the $C_{arom.}-C_{aliph.}$; in the absence of any conjugation this bond would be the single bond and its mobile index would be 0; (iii) the bond order of the $C\equiv H_3$ bond assimilated to a pseudo-triple bond; the greater the hyperconjugation of the alkyl group, the smaller is this order.



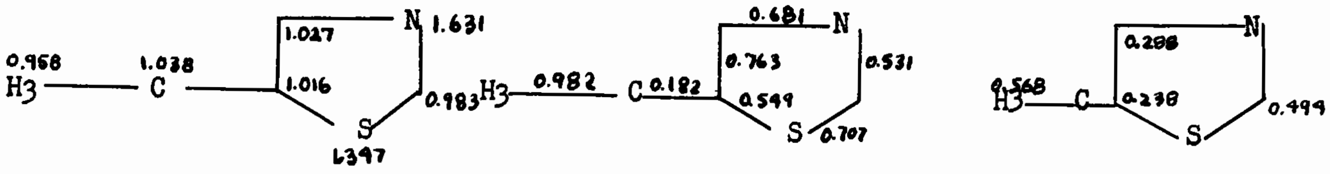
(a) (b) (c)

2-Methylthiazole (XXXI)



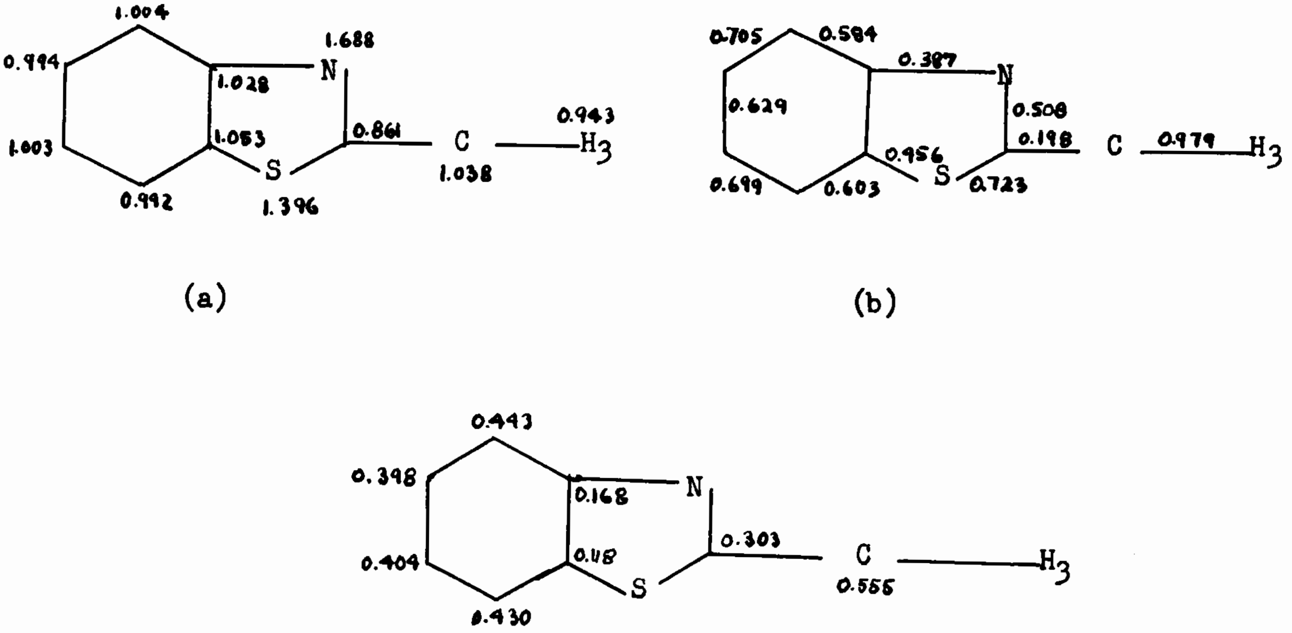
(a) (b) (c)

4-Methylthiazole (XXXII)



(a) (b) (c)

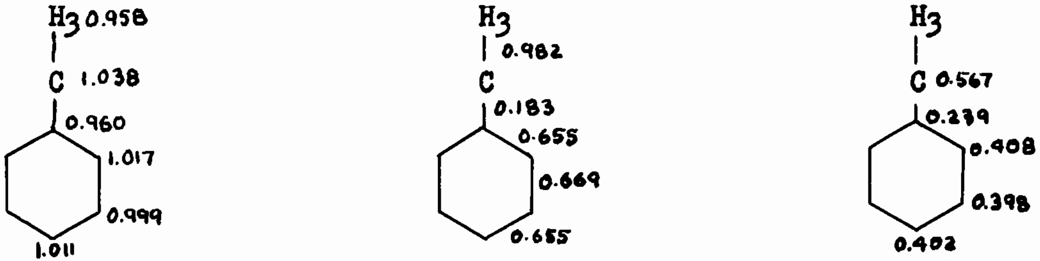
5-Methylthiazole (XXXIII)



(a) (b) (c)

2-Methylbenzothiazole (XXXIV)

The examination of these three quantities in the molecules mentioned above indicates that actually the activation of the methyl group increases in the order 4-methylthiazole < 5-methylthiazole < 2-methylthiazole < 2-methylbenzothiazole. Pullman and Metzger (27) found that the activation of the methyl group on an aromatic ring as, for example, in toluene (XXXV) is not as pronounced as in the heterocycles. The phenomenon is due in major part to the inductive effect of the nitrogen, which attracts the electrons of the alkyl group.

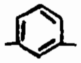


(a) (b) (c)

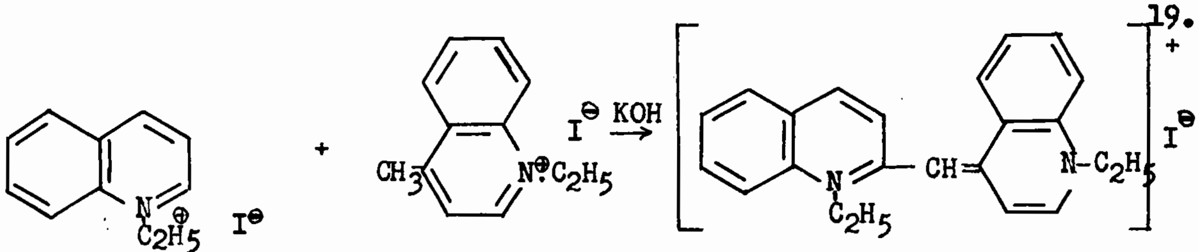
Toluene (XXXV)

It was also found by using purely theoretical approaches - particularly the methods of molecular orbitals and molecular diagrams - that the differences between the reactivities of methyl groups attached to the 2 and 5 positions depended on the degree of conjugation of those two substituents. The degree of conjugation is influenced by the deficiency of charges of aromatic carbon. The methyl group is characterized, in general, by its tendency to give electrons to an aromatic ring. This tendency should be augmented when a strong positive charge is present on the carbon atom to which this substituent is attached.

There is a considerable difference between the 2 and 5 carbon atoms of the thiazole regarding their electrical charges and their free valences. As calculated by the molecular orbital method, naturally the methyl groups attached to these two carbon atoms will differ considerably in their reactivity. The molecular diagram of thiazole clearly indicates a stronger discharge and a greater free valence for carbon 2 than for carbon 5. One can therefore state that a methyl group attached in position 2 will be more reactive than a methyl group in position 5. The same differences can be observed by comparing C_2 and C_4, and the methyl groups attached to these carbon atoms. Both the carbon atom in position 4, and the methyl group attached to it, are inert. These facts, found by Pullman and Metzger using theoretical methods, were also proved by other workers.

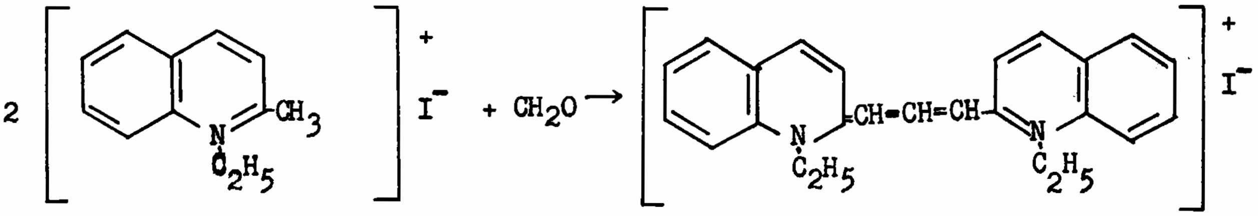
The similarity between the reactivity of methyl groups attached to thiazole and to pyridine was first observed by Mills and Smith (30) in 1922. Until that time, the reactivity of methyl groups attached to the pyridine nucleus had already been studied in numerous cases. The interaction between 2-methylpyridine and phthalic anhydride was reported first by Jacobsen and Reimer (31). Traub reported the condensation of 2-methylquinoline with phthalic anhydride (32). In both cases yellow-coloured substances, phthalones, were obtained. Schuster (33) carried out a reaction between benzaldehyde and 2,6-dimethylpyridine in the presence of zinc chloride, obtaining the dibenzylidene derivative (Ph·CH:CH  CH:CH·Ph). By reacting 2-methylpyridine with benzaldehyde, H. Baurath (34) synthesized α-stilbazole.

A review of cyanine dyes by Doja (35) and later by Hamer (36) describes the ability of quarternary quinolinium and lepidinium salts to form cyanine dyes. Any heterocyclic compound having a reactive methyl group can be used for the preparation of cyanine dyes (37, 38, 39, 40). The true cyanines, of which ethyl red (XXXVIII) is a typical example, are obtained by the action of alkali on a mixture of quinoline alkiodide (XXXVI) and lepidine alkiodide (XXXVII) (41). When the condensation of two heterocyclic compounds, both of which contain active methyl groups, is carried out in the presence of formaldehyde, ethyl orthoformate or chloroform, carbocyanine is formed. In the simplestof these reactions quinaldine ethiodide (XXXIX) is condensed with formaldehyde to yield 1,1'-diethyl-2,2'-carbocyanine iodide (XL) (42). Similarly, derivatives of 2-methylthiazoles (43) have yielded



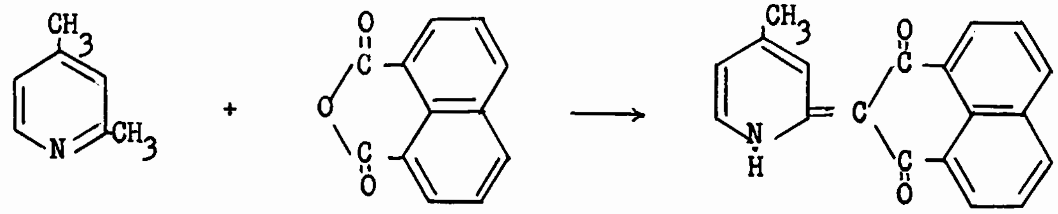
(XXXVI) (XXXVII) (XXXVIII)

the so-called thiocarbocyanines, used as valuable photosensitizers.

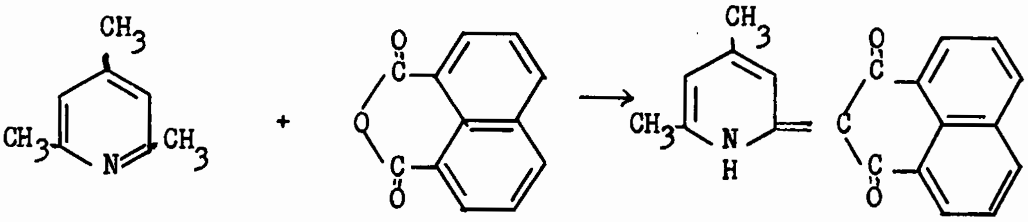


(XXXIX) (XL)

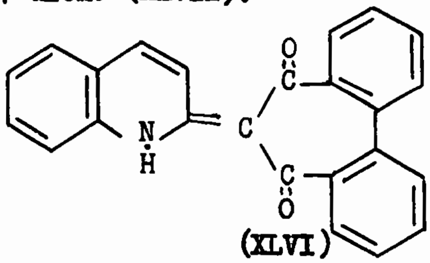
In 1939, Taurins (44) studied the condensation of naphthalic anhydride with 2-methylpyridine, 2,4-dimethylpyridine, 2,6-dimethylpyridine and 2,4,6-trimethylpyridine. The products obtained were named naphthalones. It was found that only one methyl group entered into condensation reaction with naphthalic anhydride and neither the second methyl group in the dimethylpyridines, nor the third methyl group in trimethylpyridine reacted. Thus the condensation of 2,4-dimethylpyridine (XLI) with naphthalic anhydride (XLII) yielded 2-[4-methyl-2(1H)pyridylidene]-1,3-perinaphthindandione (XLIII). 2,6-Dimethylpyridine behaved similarly. The condensation of 2,4,6-trimethylpyridine (XLIV) with naphthalic anhydride yielded 2-[4,6-dimethyl-2(1H)pyridylidene]-1,3-perinaphthindandione (XLV).

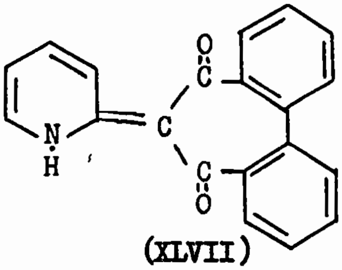


(XLI) (XLII) (XLIII)

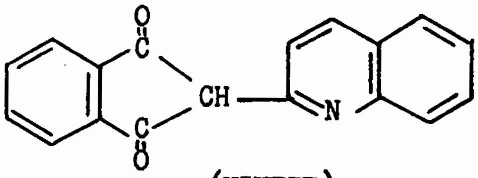

(XLIV) (XLII) (XLV)

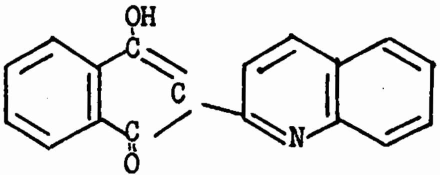
In the same year, the condensation of diphenic anhydride with methylpyridines was described by Taurins (45). Here again only one methyl group took part in the condensation reaction yielding the so-called diphenones. These compounds contain a seven membered ring and their colour is less intense than that of phthalones or naphthalones. As example, the structures of quinodiphenone (XLVI) and pyridodiphenone (XLVII) are given below. The condensation of 2-methylquinoline with diphenic anhydride resulted in the formation of 6-[2(IH)-quinolylidene]-dibenz(a,c)cycloheptadiene-5,7-dione (XLVI) and the condensation of 2-methylpyridine with the same acid anhydride led to the formation of 6-[2(1H)pyridylidene]-dibenz a,c cycloheptadiene-5, 7-dione (XLVII).


(XLVI)

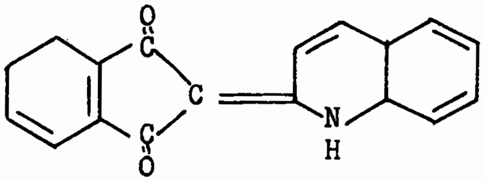

(XLVII)

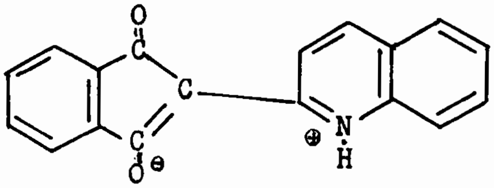
The structure of phthalones was studied by Eibner and coworkers (46, 47, 48, 49) and also by Kuhn and Bär (50). They examined the structure (XLVIII) of quinophthalone, as suggested by Eibner on an arbitrary basis and indicated that there is a lack of conjugation between the benzene ring and the quinoline nucleus. This structural formula does not explain the bright yellow colour of the compound.

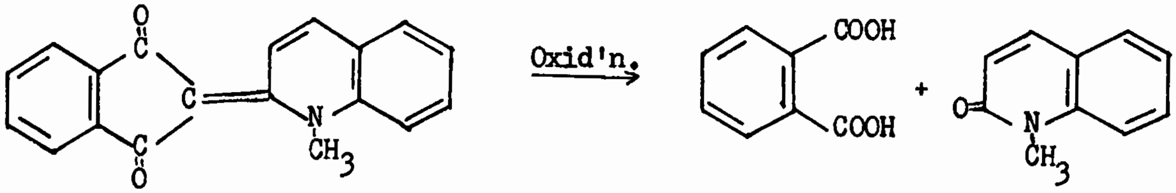

(XLVIII)


(XLIX)

The possibility of an enolic form (XLIX) was rejected, because the methylation of the compound gave an N-methyl derivative, the structure of which was established by oxidative degradation. Kuhn and Bär suggested that phthalones possess either the "indigoid" structure (L) or they exist as Zwitterions (LI) (51). The N-methyl quinophthalone (LII) gave, on oxidation, one molecule of phthalic acid and N-methyl-2 quinolone (LIII). Similarly, the oxidation of N-methyl-pyridophthalone yielded phthalic acid and N-methyl-2 pyridone. These results were in agreement with the similarity of the absorption spectra of N-methyl-pyridophthalone and pyridophthalone. Thus the indigoid structure accounts for the colour of the phthalones.


(L)


(LI)

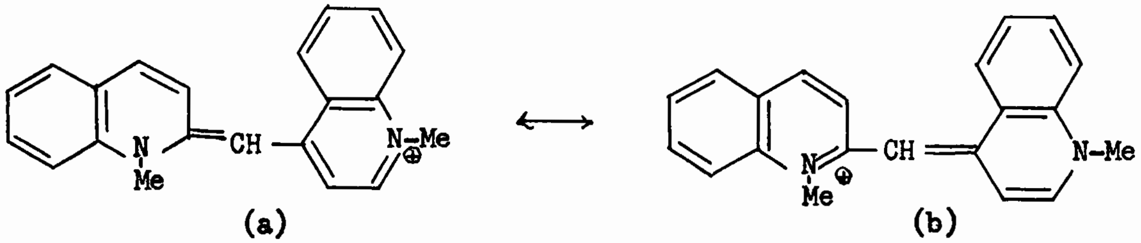


(LII) (LIII)

Colour and constitution

The colour of an organic compound, according to the classical theory postulated by Lewis and Calvin (52) is due to the oscillation of electrons in the molecule. Bury (53) stated that "the intense absorption of light that characterizes dyes is due to an intimate association of chromophore and resonance in the molecule". As observed by Willstätter and Picard (54), certain compounds containing the quinonoid structure were colourless, but the introduction of a chromophore group to certain positions of the molecule results in the possibility of resonance and consequently the development of colour.

In a series of studies Brooker (55) and coworkers investigated and explained the colour of certain cyanine dyes on the basis of the resonance theory, according to which the molecule of a cyanine dye, such as (LIV), is considered to be a resonance hybrid of two extreme states, the intense colours of the cyanines being attributed to such resonance. Thus in the case of (LIV), which is highly coloured, there is the resonance hybrid a b. The ionic charge can be on one of the ring carbon atoms or on the atom between the two rings. It was assumed that resonance of this type is very closely related to the occurrence of colour in many organic compounds and resonance structures have been assigned to practically all the principal dye types. Brooker and coworkers also stated that in the cyanine series, resonance states



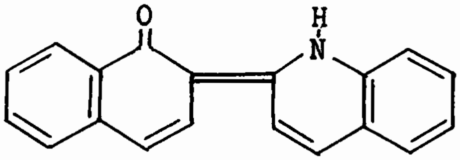
(LIV)

have almost the same internal energy and therefore the mobility of the linkages in the conjugated chain is very great. The relationship between the light absorption and the energy difference of the ground and excited states is expressed by the following equation

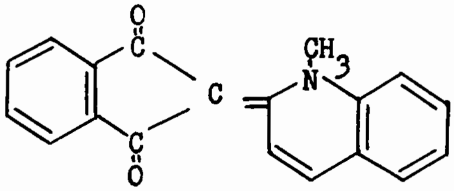
$$\lambda = \frac{h\ c}{E_1 - E_0}$$

where h is the Plank's constant, c is the velocity of light, E_1-E_0 is the difference in energy of the ground and excited state. This equation shows that the wavelengths of light that are absorbed by a substance depend upon $E_1—E_0$. The smaller the difference between the two energy states the longer the wavelength of light absorption. In the resonating structures, where separation of charges is present, the molecule is easily transferred to a higher energy level.

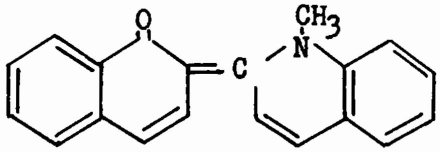
Phthalones are considered to be the simplest of the cyanine dyes. W. Jenny (56) published an article concerning the relationship between the structure and light absorption of a simple merocyanine of the structure (LV) 2-[2-(IH)-quinolylidene]-1(2H)-naphthalenone. He noted the similarity between the structures of N-methylquinophthalone (LII) and 2-[1-methyl-2(IH)-quinolylidene]-1(2H)-naphthalenone (LVI). The $\rangle$C=O group of quinophthalone is replaced by a -CH=CH- group in (LV). The absorption maximum of (LVI) is in the region of longer wavelength because the number of the resonating structures is considerably higher than in the N-methyl-quinophthalone. Also the longest possible distance for a mesomeric electron displacement between the auxochrome $\rangle N-CH_3$ group and the chromophore $\rangle$C=O group goes through five conjugated double bonds in the N-methyl-quinophthalone. The number of conjugated double bonds is nine in (LVI).



(LV)



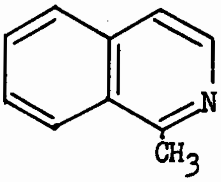
(LII)



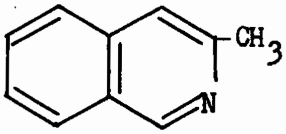
(LVI)

The reactivity of methyl groups attached to thiazole ring has been studied by several workers. Investigating the reactivity of methyl groups in heterocyclic bases, Mills and Smith (30) found that in its characteristic reactivity, the 2-methyl group in quinaldine, 2-picoline and in 2-methylthiazole resembles in many ways the methyl group in such compounds as the methyl ketones and nitromethane. Heinrich (57) and Vorländer (58) suggested that the 2-methyl group in "the pyridine and quinoline series owes its reactivity to its being associated with a -C=N- group, the effect of the -C:N- on the methyl group in the grouping CH_3-C:N- corresponding with that of the carbonyl group in the grouping $CH_3-\overset{|}{C}=O$ of the methyl ketones". In accordance with this suggestion Mills and Smith (30) have shown that the properties of a methyl group adjacent to the cyclic nitrogen atom in assymetric heterocycles, differ greatly according to the side of the nitrogen atom on which the group is situated.

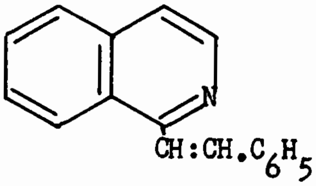
At first they investigated the two isomeric 1-, (LVII) and 3-methylisoquinolines (LVIII). The reactivity of the methyl groups towards benzaldehyde was compared and it was found that they are of a different reactivity. It was found that 1-methylisoquinoline (LVII) yielded 1-styrylisoquinoline



(LVII)



(LVIII)

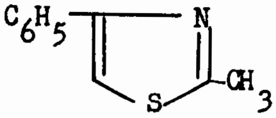


(LIX)

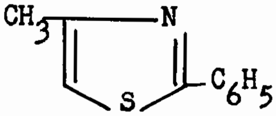
(LIX) when heated with benzaldehyde at 100° in the presence of a small quantity of zinc chloride. When, however, 3-methylisoquinoline (LVIII) was heated with benzaldehyde and zinc chloride, no condensation product was obtained even after prolonged heating.

In a similar manner, Mills and Smith (30) examined the reactivity of the methyl groups on the thiazole nucleus.

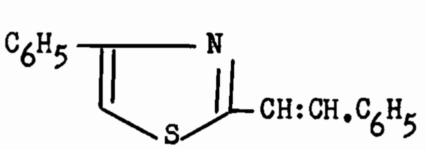
The great difficulties encountered in the preparation of simple methylthiazoles forced Mills and Smith to use the readily obtainable 4-phenyl-2-methylthiazole (LX) and 4-methyl-2-phenylthiazole (LXI) in their investigations. They brought (LX) and (LXI) in reaction with benzaldehyde and phthalic anhydride. It was found that the reaction between (LX) and benzaldehyde and also between (LX) and phthalic anhydride occurred very easily. In both cases the methyl group in position 2 entered into a condensation reaction yielding, with benzaldehyde, 4 phenyl-2-styrylthiazole (LXII) and 2-[4-phenylthiazolyl-(2)]-1,3-indandione (LXIII) with phthalic anhydride.



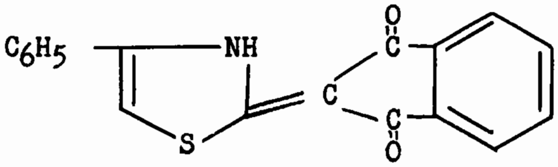
(LX)



(LXI)



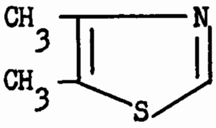
(LXII)



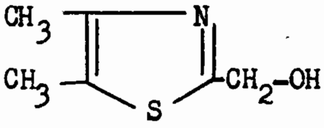
(LXIII)

On the other hand the methyl group in position 4 of (LXI) was found to be completely inert. No condensation reaction occurred with either of the reactants.

Erne and Erlenmeyer (59) studied the reactivity of methyl groups in positions 4 and 5 of the thiazole nucleus, and found that they did not react in condensation reactions. They reacted 4,5-dimethylthiazole (LXIV) with formaldehyde and observed that the condensation had occurred at position 2 resulting in the formation of 2-hydroxymethyl-4,5-dimethylthiazole (LXV).



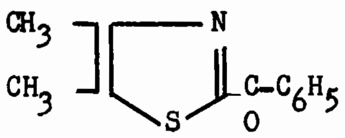
(LXIV)



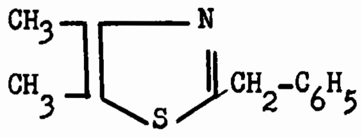
(LXV)

The structure of (LXV) was proved by reacting (LXIV) with phenyllithium. The resulting product 4,5-dimethylthiazolyl-2-lithium was brought into reaction with formaldehyde and the final product was 2-hydroxymethyl-4,5-dimethylthiazole (LXV).

4,5-Dimethylthiazole was also condensed with benzaldehyde (59). The reaction occurred at position 2, yielding a crystalline substance which was identified as 2-benzoyl-4,5-dimethylthiazole (LXVI) and an oil, 2-benzyl-4,5-dimethylthiazole (LXVII).

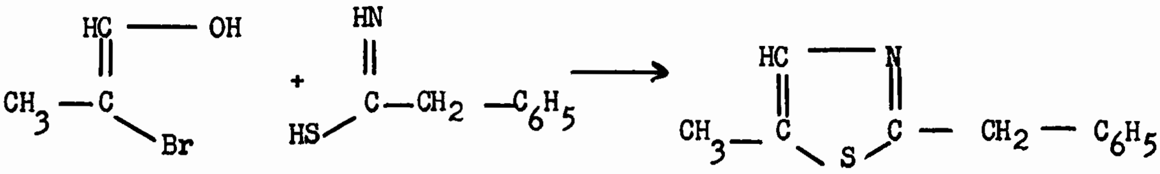


(LXVI)

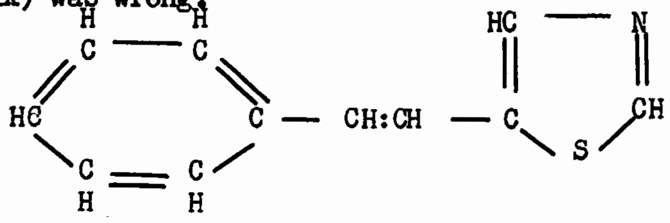


(LXVII)

The behaviour of the methyl group in position 5 towards formaldehyde and benzaldehyde was also studied by Erne and Erlenmeyer (59). In these experiments, 5-methylthiazole was used. Here, as in the case of 4,5-dimethylthiazole (LXIV), the methyl group proved to be completely inert. The condensation took place at position 2, yielding 2-benzyl-5-methylthiazole (LXVIII). The structure of this compound was proved by reacting α-bromo propionaldehyde (IX) with phenylthioacetamide (LXIX). By reacting 5-methylthiazole with benzaldehyde, Erne and Erlenmeyer demonstrated that the interpretation of Erlenmeyer and Smith (60), concerning the formation of 5-styrylthiazole (LXX) was wrong.



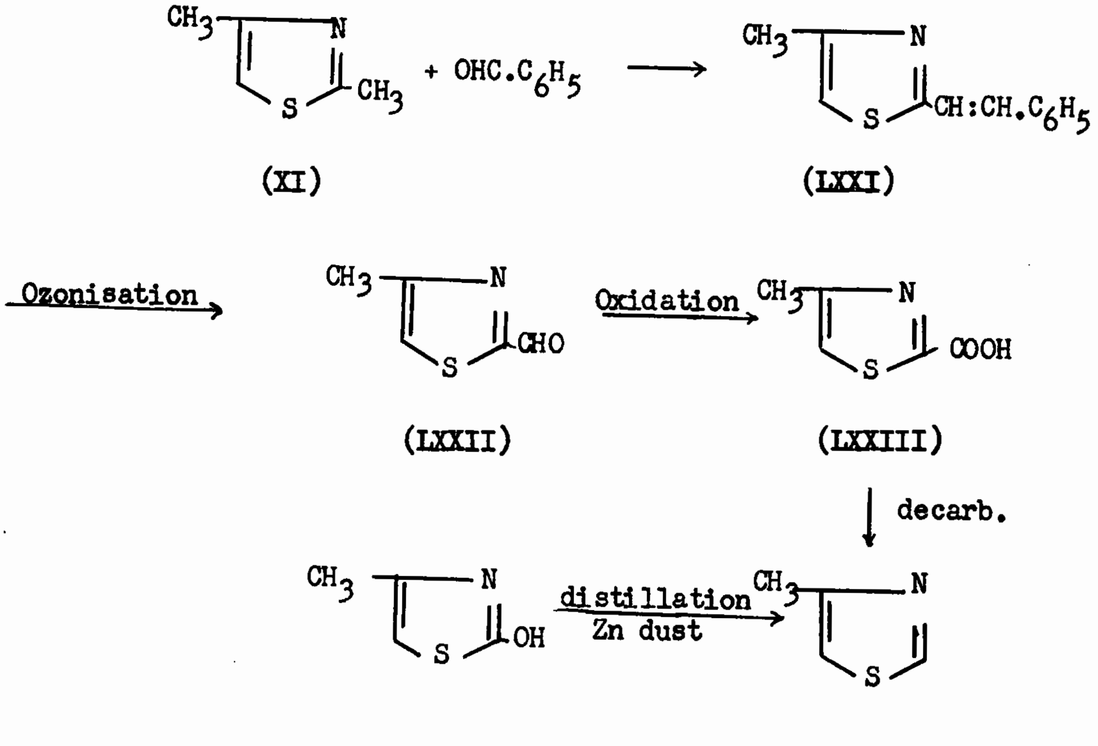
(IX) (LXIX) (LXVIII)



(LXX)

Finally, Kondo and Nagasawa (61) showed that in the case of 2,4-dimethylthiazole the methyl group in position 2 was able to enter into a condensation reaction with benzaldehyde, while the methyl group in position 4 was inert and remained unchanged. By condensing 2,4-dimethylthiazole (XI) with benzaldehyde, Kondo and Nagasawa obtained 2-styryl-4-methylthiazole

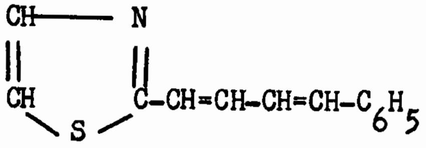
(LXXI). The structure of this compound was proved by first ozonising (LXXI) to an aldehyde (LXXII) which in the second step was oxidized to give 4-methylthiazole-2-carboxylic acid (LXXIII). On decarboxylation (LXXIII) yielded 4-methylthiazole (VII). This substance is identical with the compound prepared



(LXXIV) (VII)

by Hantzsch and Arapides (62) and later by Hantzsch (63) by zinc dust distillation of 2-hydroxy-4-methylthiazole (LXXIV).

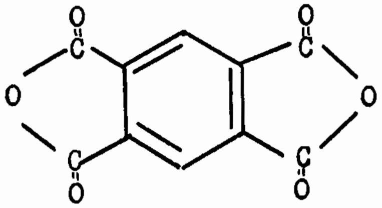
The reactivity of the 2-methyl group, using 2-methylthiazole was studied by Erlenmeyer, Weber et al. (64). 2-Methylthiazole was condensed with cinnamic aldehyde to obtain 1-phenyl-4-(thiazolyl-2)-butadiene (LXI).



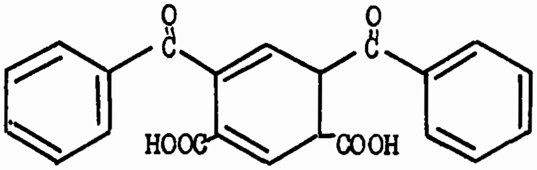
(LXXV)

Reactions of pyromellitic dianhydride

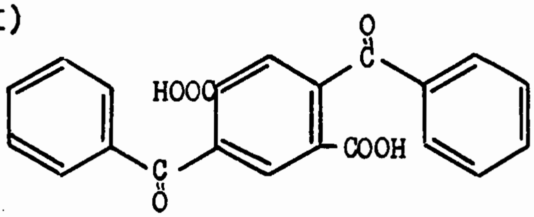
Pyromellitic dianhydride (LXXVI) can be condensed with various aromatic hydrocarbons such as benzene, toluene, etc. Philippi (65, 66, 67) described the condensation of benzene with pyromellitic dianhydride, during which process he obtained 4,6-dibenzoyl-1,3-isophthalic acid (LXXVII) and 3,6-dibenzoyl-1,4-terephthalic acid (LXXVIII) and with toluene the condensation gave 4,6-di-p-toluyl-1,3-isophthalic acid (LXXIX) and 3,6-di-p-toluyl-1,4-terephthalic acid (LXXX).



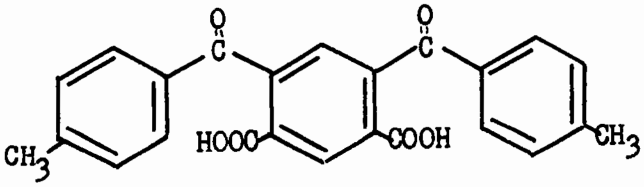
(LXXVI)



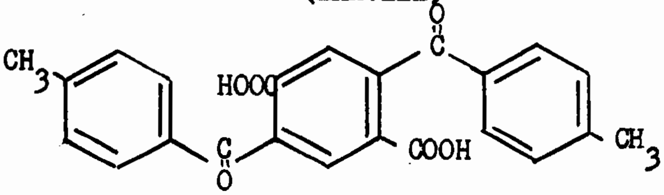
(LXXVII)



(LXXVIII)



(LXXIX)

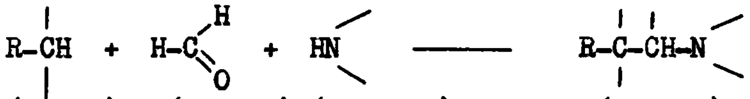


(LXXX)

Seka and coworkers (68,69) and Silberrad (70,71,72) gave further evidence concerning the ability of pyromellitic dianhydride to enter into condensation reaction.

The Mannich Condensation

Study of the behaviour of methyl groups, attached to the thiazole ring, in Mannich condensation reaction was the second part of this investigation. The Mannich reaction consists in the condensation of a primary or secondary amine with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. The reaction was named after Carl Mannich, who first recognized the significance and general applicability of this condensation. The Mannich condensation may be represented in generalized form:



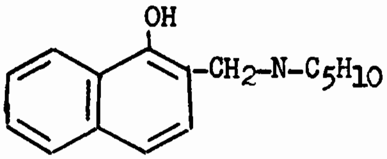
(LXXXI) (LXXXII) (LXXXIII) (LXXXIV)

where (LXXXI) is a compound containing active hydrogen, (LXXXII) is formaldehyde and (LXXXIII) is a primary or secondary amine. LXXXIV is the Mannich product. A thorough review of the literature has been presented by Blicke (73).

Mechanism of the Mannich Condensation

The mechanism of the Mannich reaction has been studied by several workers. Mannich and Krösche (74) and later Mannich and Kather (75) found that by mixing formaldehyde with certain amines, an addition compound, namely an alcohol, is formed. It was suggested that this product is also formed as an intermediate compound by the interaction of the amine and formaldehyde during the Mannich reaction. Bodendorf and Koralewsky (76), however, disproved this suggestion on the basis of their experimental findings. They found that the condensation of antipyrine with dimethylaminomethanol gave much poorer yield than when antipyrine was condensed with either formaldehyde and the amine or formaldehyde and the amine hydrochloride. It was also found that the alcohol formed by the condensation of antipyrine and formaldehyde did not react with dimethylamine at all. Bodendorf and Koralewsky therefore concluded that neither hydroxymethyl compound satisfies the requirement of an intermediate.

Formation of methylene-bis-amine ($R_2N\text{-}CH_2\text{-}NH_2$) was suggested by Feldman and Wagner (77) as a plausible intermediate step. The preparation of several Mannich bases was realized by the interaction of methylene-bis-amines with phenols. Thus, condensing methylene-bis-piperidine with 1-naphthol, they obtained 2-piperidino-methyl-1-naphthol (LXXXV) and similarly 1-piperidinomethyl-2-naphthol, by using 2-naphthol.

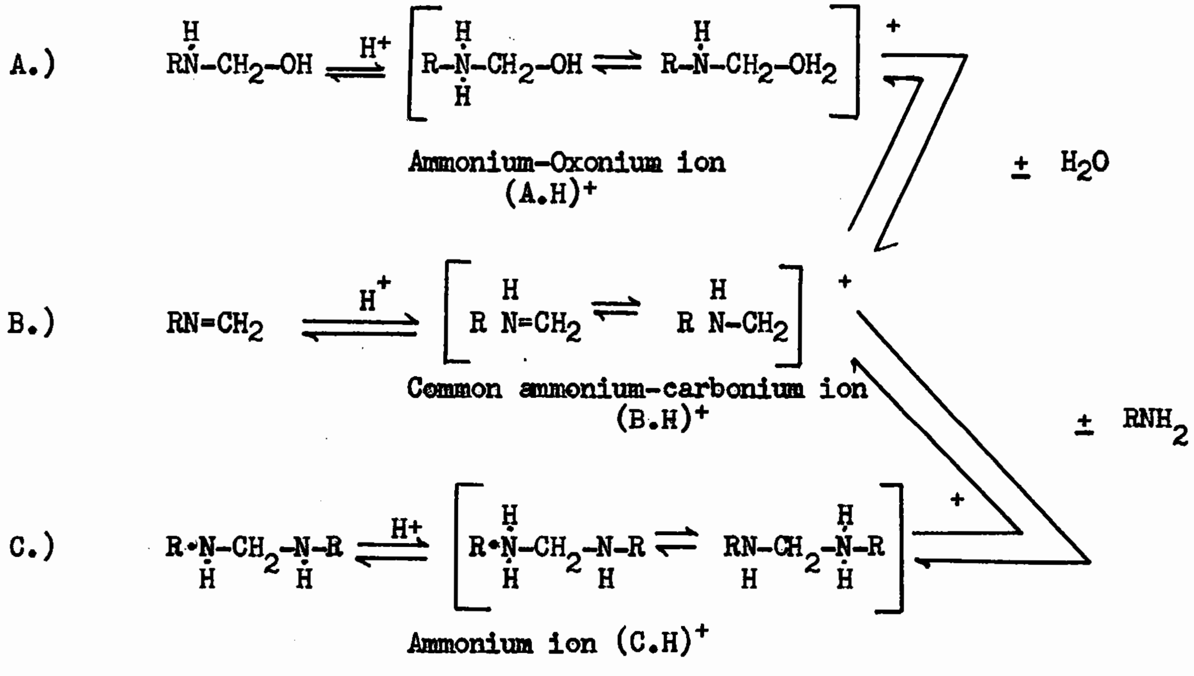


(LXXXV)

A few years later Lieberman and Wagner (78) presented another approach to a possible mechanism. A cation, $R_2N\text{-}\overset{|}{\underset{|}{C}}^{\oplus}$ is formed from the condensation products of the formaldehyde and amine which combines with the anion of the reactive hydrogen compound. Acidity of the reactive hydrogen compound and/or added acid induces the formation of the cation, while the presence of bases (for example the amine present, or added alkali) helps the formation of the anion. It has been experimentally shown that excess of acid interferes with the primary condensation of the amine and formaldehyde and also depresses the ionization tendency of the compound containing the mobile hydrogen. On the other hand excess of alkali may decrease or even prevent the formation of the cation

R_2N-$C^{\oplus}$, thus obstructing or preventing the reaction. It has been suggested that the cation originates in the alkylidene-bis-amine, which is the condensation product of the aldehyde and amine. This view was strengthened by experimental evidence when Mannich condensation products were obtained in normal yields using methylene-bis-amines instead of amines and formaldehyde.

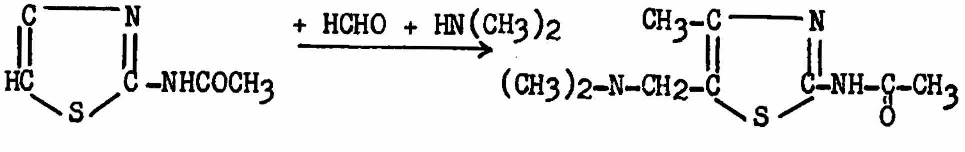
Wagner (79) outlines the way in which the different results of acid-induced reactions of formaldehyde with amines and of the condensation products of formaldehyde and amines, i.e., methylene amines or Schiff bases, methylene-bis-amines, etc., may be correlated by the assumption that these condensation products, by accession of a proton, are convertible to a common cation. This is shown in the table below.



By taking up one proton, the methylolamine (A) forms an ammonium-oxonium ion $(A.H)^+$ and similarly the methylene-bis-amine (C) forms an ammonium ion $(C.H)^+$. It can be seen in the table that while the oxonium ion contains the element of water properly combined as such, the ammonium ion contains a molecule of amine as such. Loss of water or amine respectively results in the common cation $(B.H)^+$, the ammonium-carbonium ion, which in the case of a secondary amine can be represented as follows $(R_2NCH_2)^+$. Briefly, it is possible to state that A, B and C by accession of a proton can yield a common cation.

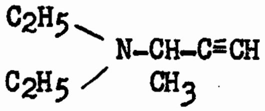
The postulation of a common cation $(R_2NCH_2)^+$, which can be derived from A, B and C by action of an acid, and also during the reaction of formaldehyde and a primary or secondary amine in the presence of acid, provides an explanation of the fact that, in certain reactions promoted by acid, there may be used either the formaldehyde and primary or secondary amine, or preformed methylene-bis-amine or Schiff's base. The existence of these ions was conceived by Stewart and Bradley (80) on grounds partly speculative or inferential.

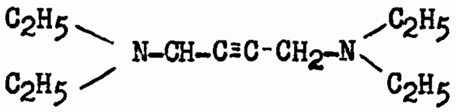
A thorough search of the literature revealed that only one thiazole derivative has been studied in Mannich condensation reaction. Albertson (81) reported a successful reaction, when 2-acetamido-4-methylthiazole (LXXXVI) was treated with dimethylamine and formaldehyde in acetic acid solution. The product obtained was 2-acetamido-4-methyl-5-(dimethylaminomethyl)-thiazole (LXXXVII). The reactivity of the hydrogen atom in position 5 of the thiazole is surprising. It was shown, however, that elimination of the 2-acetamido group greatly diminished the reactivity of the thiazole nucleus towards this type of reaction. Albertson attempted the Mannich condensation of 2,4-dimethylthiazole (XI), but only a very minute yield of an unidentified product was obtained.



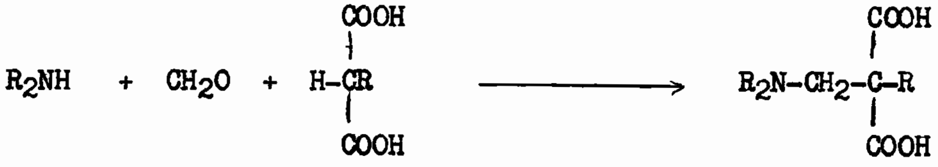
(LXXXVI) (LXXXVII)

Mannich-type condensations of some monosubstituted acetylenes with formaldehyde and secondary amines have been described by Mannich and Chang (82) and later by Jones, Marszak and Bader (83). The interaction of arylacetylene, formaldehyde and a secondary amine yielded an unsaturated base containing one triple bond. Rose and Weedon (84) reported that 3-diethylaminobut-1-yne (LXXXVIII) reacted readily with paraformaldehyde and diethylamine, or piperidine, giving the acetylenic diamines (LXXXIX).


(LXXXVIII)


(LXXXIX)

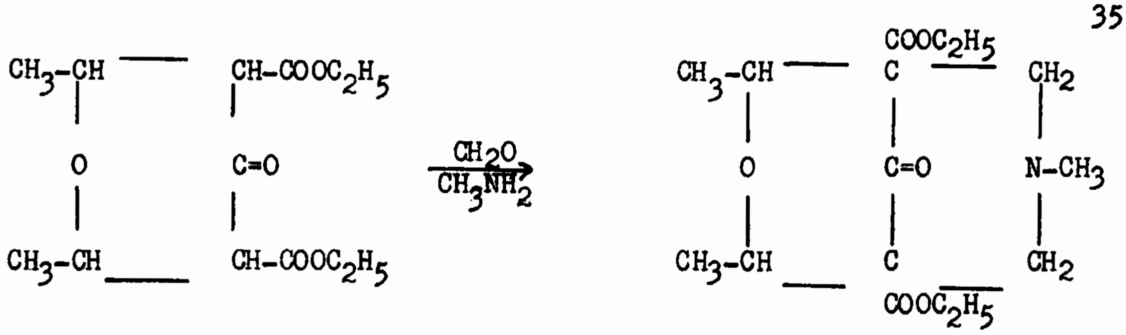
Acids and esters were also known to possess active hydrogen. In 1920 Mannich and Kather (75) observed that the action of formaldehyde and a secondary amine on malonic acid (XC) results in the formation of a β-amino acid (XCI). A few years later Mannich and Ganz (85) described the preparation of several β-amino dicarboxylic acids by utilization of Mannich condensation. The best results were obtained when a monoalkylated malonic acid was used. The dibasic amino acid formed has the tendency to lose one mole of carbon dioxide.



$$R_2NH \quad + \quad CH_2O \quad + \quad \text{H-}\overset{\displaystyle COOH}{\underset{\displaystyle COOH}{\text{C}}}\text{R} \longrightarrow R_2N\text{-}CH_2\text{-}\overset{\displaystyle COOH}{\underset{\displaystyle COOH}{\text{C}}}\text{-R}$$

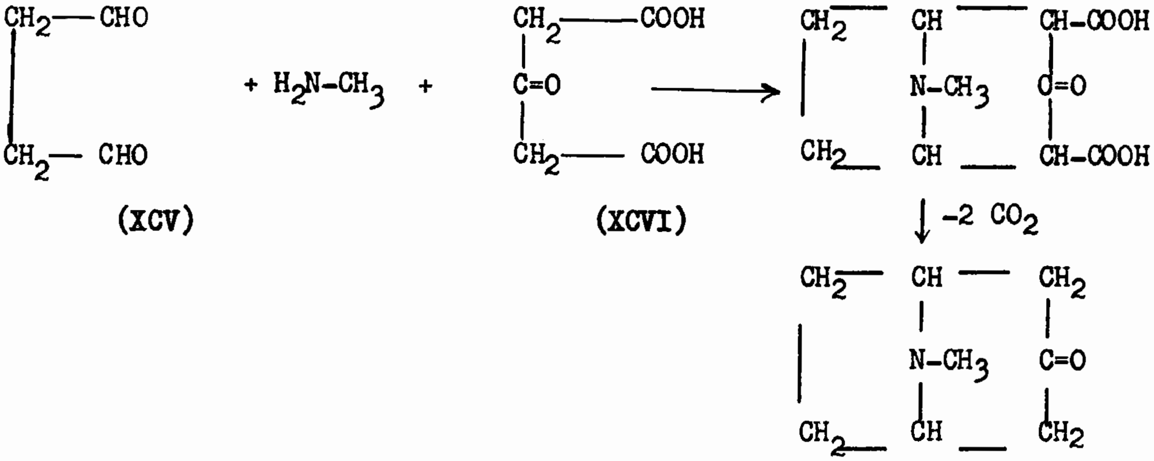
(XC) (XCI)

Mannich and Mück (86) synthesized a bicyclic compound, a derivative of pydin (XCIII) by the condensation of 3,5-dicarbethoxy-2,4-dimethyl-tetrahydropyron (XCII) with formaldehyde and methylamine.



(XCII) (XCIII)

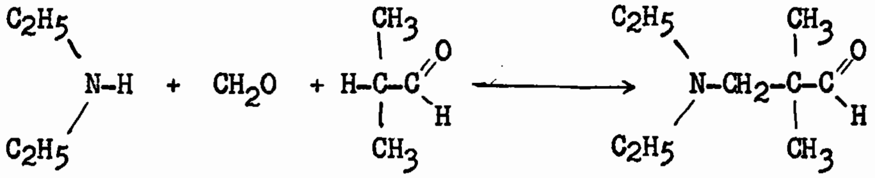
Mannich condensation was utilized in the synthesis of tropinone (XCIV) - a bicyclic alkaloid - by Robinson (87). He condensed succinaldehyde (XCV) with methylamine and acetonedicarboxylic acid (XCVI).



(XCV) (XCVI)

(XCIV)

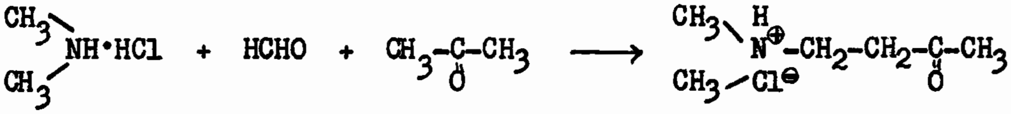
Aldehydes react with formaldehyde and primary or secondary amine in such a way that the α-hydrogen atom of the aldehyde is substituted by a dialkylamino methyl group. Certain types of local anaesthetics are prepared from N-substituted-β-aminoaldehydes. A cumbersome way of preparing these compounds was reported by Wohl (88) as early as 1901. Mannich and coworkers (89,90) synthesized α,α'-dimethyl-β-diethylaminopropionaldehyde (XCVII) by the action of diethylamine and formaldehyde on isobutyraldehyde (XCVIII). The success of the reaction depends on the number of reactive hydrogen atoms adjacent to the aldehyde group. The course of reaction is unambiguous when only one hydrogen atom is present, while the presence of a methylene group adjacent to the carbonyl group leads to a complicated result.



(XCVIII) (XCVII)

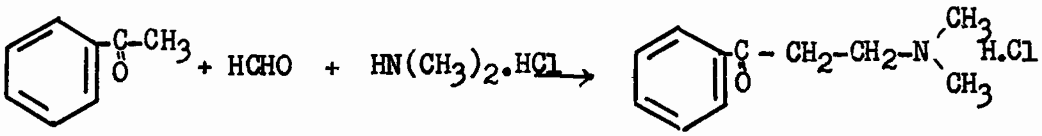
The Mannich condensation of ketones has been more extensively studied than that of aldehydes. Saturated and α,β-unsaturated ketones, cycloalkanones, mixed aliphatic aromatic ketones, cyclic ketones and, finally, heterocyclic ketones are all able to undergo Mannich reaction with both primary and secondary amines. When primary amine is used the first product is a secondary amine, which often reacts further to give a tertiary amine.

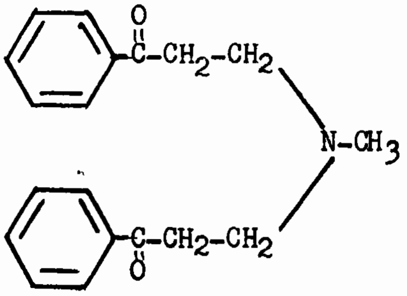
In one of his first works Mannich (91) synthesized ketobases by treating acetone with a secondary amine, namely dimethylamine, in the presence of formaldehyde. (equation a)

a) 

$$(CH_3)_2NH\cdot HCl + HCHO + CH_3-\underset{\underset{O}{\|}}{C}-CH_3 \longrightarrow (CH_3)_2\overset{H}{N}^{\oplus}(Cl^{\ominus})-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

Mannich and Heilner (92) described the synthesis of a β-aminoketone from acetophenone, formaldehyde and dimethylamine hydrochloride. (equation b). The use of two moles each of acetophenone and formaldehyde and one mole of methylamine hydrochloride yielded β,β'bis(benzoylethyl)methylamine (XCIX).

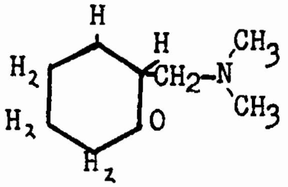
b) 



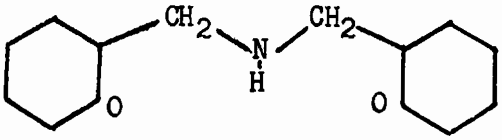
(XCIX)

Later Mannich and Lammering (93) investigated the reaction between mixed aromatic-aliphatic ketones, formaldehyde and salts of secondary amines. Nitro and amino-acetophenones have been reported by Mannich and Dannehl (94) as compounds able to participate in Mannich condensation reaction. Wheatley and Fitzgibbon (95) described the reaction of p-nitroacetophenone. They used various amines and obtained the expected β-(di)-alkylamino-p-nitroacetophenone in fair yields.

Mannich and Brown (96) showed that cyclic ketones too, can be used for the synthesis of Mannich bases. The reaction was unambiguous when secondary amine was used, but a mixture of compounds was produced with primary amines when the molecular ratio of the reactants was one to one. Cyclohexanone was treated with formaldehyde and dimethylamine in equimolecular quantities. The isolated product was identified as 1-(dimethylaminomethyl)-cyclohexanone (C). The condensation of two moles each of cyclohexanone and formaldehyde with one mole of methylamine resulted in the formation of bis-[(cyclohexanone-(2)-yl)]-methylamine (CI). Later Mannich and Schaller (97) carried out similar studies on cyclopentanone.

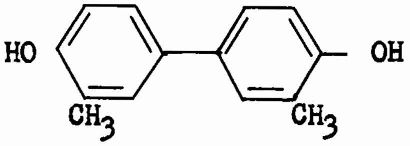


(C)



(CI)

Phenols are able to undergo Mannich condensation. Meadow and Reid (98) utilized Mannich reaction for the introduction of amino groups such as $-CH_2NR_2$, into the nucleus of various types of phenolic compounds. Two dimethylaminomethyl groups were introduced in position ortho to each of the hydroxyl groups in 4,4'-di-o-cresol (CII). The structure of 4,4'-dihydroxybiphenol would permit the introduction of four dimethylaminomethyl groups. Marc Julia (99) reported that the reaction always takes place in position ortho to the phenolic group.

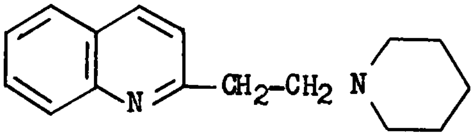


(CII)

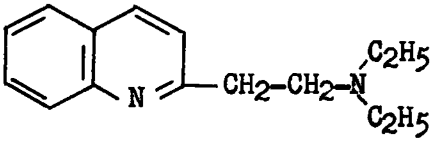
The scope of the Mannich condensation has been extended to heterocyclic compounds. In heterocyclic compounds, three types of active hydrogen atoms may be involved; (1) those directly attached to the nucleus as in antipyrine and indole, (2) those attached to the α-carbon of an alkyl group attached to the ring as for example in α-picoline and quinaldine; and finally (3) those attached to side chains where the activation is provided by some group other than the ring as in 2-acetothienone or 2-acetylfurane, etc.

The Mannich reaction of pyrrole, using aliphatic amines as well as piperidine and morpholine, was reported by Bachman and Heisey (100). A mixture of mono- and disubstituted products was obtained. Later Herz, Dittmer and Cristol (101) described the preparation of some monosubstituted derivatives of pyrrole by the Mannich condensation.

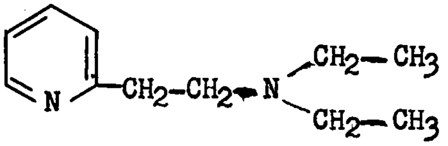
Condensation of 2-methylquinoline with formaldehyde and piperidine was first reported by Kermack and Muir (102). The ratio of 2-methylquinoline, formaldehyde and piperidine was 1:2:2. The product of this reaction was identified as 2-(piperidinoethyl)quinoline (CIII). Similarly, using 2-methylquinoline hydrochloride, formaldehyde and diethylamine, they obtained a viscous yellow oil, 2-(β-diethylaminoethyl)-quinoline (CIV). Unsuccessful attempts were made to substitute acetaldehyde for formaldehyde in these reactions. In the same year, after completion of the above-mentioned work, Heou-Feo and Delépine (103) reported the preparation of 2-(β-diethylaminoethyl)-quinoline (CIV) by a method essentially the same as described by Kermack and Muir. The three compounds were used in equimolecular quantities. The yield was very poor. This work also dealt with the condensation of 2-methylpyridine with formaldehyde and diethylamine. The resulting product was characterized as 2-(β-diethylaminoethyl)-pyridine (CV).



(CIII)

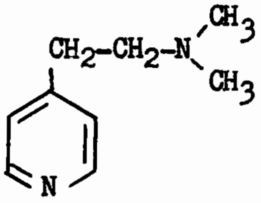


(CIV)

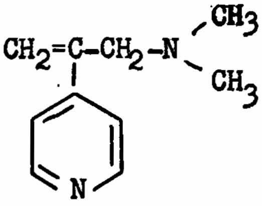


(CV)

Matuszko and Taurins (104) investigated Mannich condensation of 4-methylpyridine. They found that the main product of the condensation of 4-methylpyridine with formaldehyde and dimethylamine hydrochloride was not the expected 4-(β-dimethylaminoethyl)-pyridine (CVI), but an unsaturated base, namely 4-(methylene-β-dimethylaminoethyl)-pyridine (CVII). Similarly the unsaturated base characterized as 4-(α-methylene-β-piperidylethyl)-pyridine was obtained in the condensation of 4-methylpyridine, formaldehyde and piperidine. The unsaturated bases turned reddish-brown on standing even in a closed container. 4-Methylpyridine reacted normally with formaldehyde and diethyl-, di-isopropyl-, and di-n-butylamine, to give the corresponding 4-dialkylaminoethylpyridines. 4-(β-Pyrrolidylaminoethyl)-pyridine was obtained when pyrrolidine was used as the amine, and the use of morpholine resulted in the formation of 4-(β-morpholylaminoethyl)-pyridine.

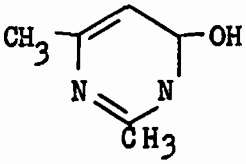


(CVI)

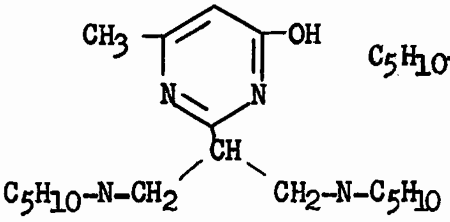


(CVII)

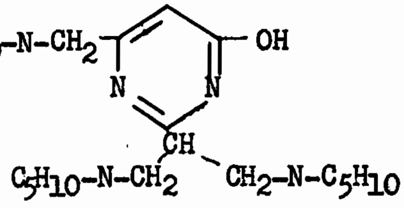
Snyder and Foster (105) investigated the Mannich condensation of pyrimidines. It was found that 2,6-dimethyl-4-hydroxypyrimidine (CVIII) is able to react with both of its methyl groups. The condensation of (CVIII) with formaldehyde and piperidine yielded in 2-[bis-(piperidinomethyl)-methyl]-4-methyl-6-hydroxypyrimidine (CIX) and 2-[bis-(piperidinomethyl)-methyl]-4-(piperidinomethyl)-6-hydroxypyrimidine (CX). When morpholine was used instead of piperidine, a condensation of a similar kind was observed.



(CVIII)

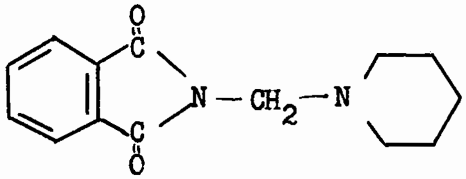


(CIX)



(CX)

The aminomethylation through the use of Mannich reaction is not limited only to C-H acid groups. Certain Mannich bases of substances possessing active hydrogen on nitrogen were already prepared before the idea of Mannich reaction became known. N-Piperidinomethylphthalimide (CXI) can be regarded as the first N-Mannich base.



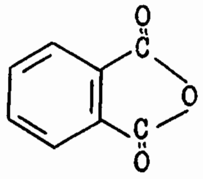
(CXI)

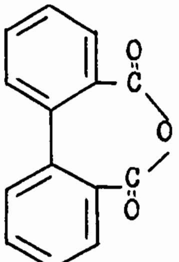
This compound was first prepared by Sachs (106) around the end of the nineteenth century, by gentle heating of an alcoholic suspension of phthalimide with formaldehyde and piperidine. Twenty years later Einhorn (107) described the preparation of N-diethylaminomethylisatine. The preparation of N-piperidinomethylcarbazole was reported by Feldman and Wagner (77) in 1942. Hellmann and Löschmann (108) dealt with the problem of the synthesis of several N-dialkylaminomethyl derivatives of phthalimide, succinimide, isatin and carbazole. Piperidine, morpholine, diethyl and dimethyl amines were used during these investigations. Bombardieri and Taurins (109) studied the Mannich condensation of 2-pyrrolidone, hydantoin, uracil, 2,4-thiazolidinedione and aliphatic nitramines. They accomplished the synthesis of a series of new Mannich bases.

DISCUSSION

I. Condensation reactions of methylthiazoles and aromatic anhydrides

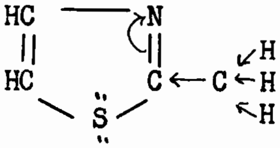
The group of merocyanines includes three types of compounds which possess some common structural features, namely, the aromatic system with a 1,3-diketo grouping linked to a nitrogen heterocyclic ring, like pyridine and quinoline. These are phthalones, naphthalones and diphenones. The names of these substances are derived from those of phthalic, naphthalic and diphenic anhydrides, which undergo condensation reactions when heated with methylpyridines and methylquinolines. The objective of this work was, partly, to extend the group of merocyanines by including the derivatives of unsubstituted or methyl-substituted thiazoles. That could be accomplished by the condensation of mono- and dimethylthiazoles with anhydrides of di- and poly-carboxylic acids of the aromatic series as phthalic (CXII), naphthalic (XLII), diphenic (CXIII) and pyromellitic dianhydride (LXXVI). At the same time another goal was pursued, namely, the examination of the reactivity of methyl groups attached in various positions of the thiazole ring.


(CXII)

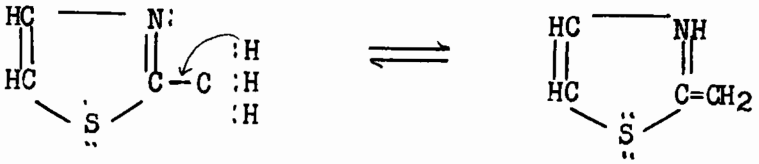

(CXIII)

The relative reactivity of the methyl groups of methylthiazoles has not as yet been investigated and for this reason the present study appeared promising in order to reveal the qualitative and if possible the quantitative differences under which condensation could take place.

The condensation reactions of methylpyridines with aromatic anhydrides allowed the prediction that similar reactions would take place in the thiazole series. The methyl group attached in 2 position of the thiazole ring is of a similar nature to the methyl group in 2 position of the pyridine nucleus. This similarity arises from the electron withdrawing force of the annular nitrogen atom in both cases. It can also be predicted that the 2-position of the thiazole is activated to a certain extent by the annular sulphur. As a result of the electron withdrawing by N and S there is electron deficiency of the carbon atom in 2 position. This electron deficiency combined with the electron-repelling character of the methyl group reveals that the hydrogen atoms of this particular methyl group are activated and consequently mobile as can be illustrated by the following scheme:



There is also an alternative possibility of a tautomeric shift of a proton towards the annular nitrogen atom.

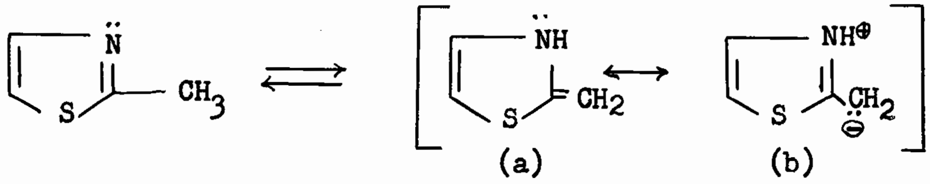


The mobile hydrogens of a methyl group in the 2 position of thiazole are unique. They differ markedly from the unreactive hydrogens of methyl groups at the 4 and 5 positions, because the activating effect of the annular nitrogen and sulphur atoms does not appear to influence such methyl groups. All these considerations indicated that condensation of methyl groups in 4 and 5 positions should require more drastic conditions than in the case of 2-methylthiazole.

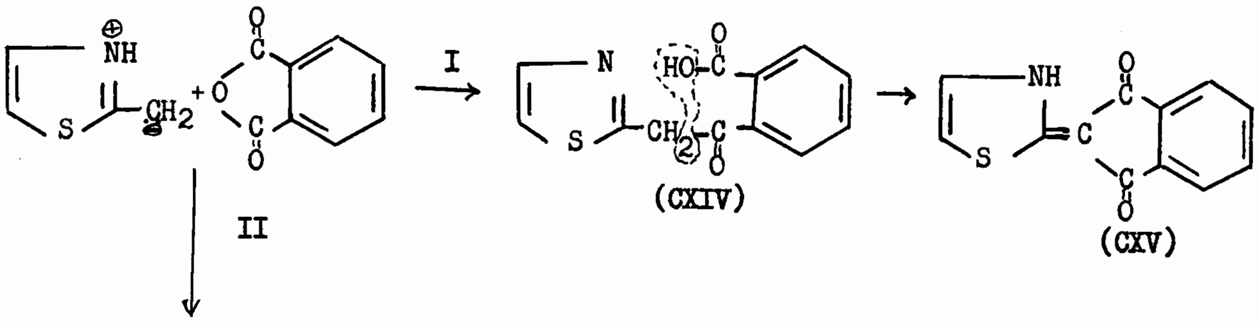
Each condensation reaction of methylthiazoles with aromatic anhydrides was carried out at different temperature and for different length of time in order to determine the optimum conditions of the process. To facilitate the reactions, anhydrous zinc chloride was used as a catalyst. The ratios of the catalyst as well as the ratios of the reagents were varied. These condensations were carried out both at atmospheric pressure and in sealed tubes. It was found that only phthalic and naphthalic anhydrides were reactive and that reactions occurred only with thiazoles containing the methyl group in C_2 position. Methyl groups in four and five positions on the thiazole ring did not show any reactivity towards the acid anhydrides. The reaction products were yellow crystalline substances possessing the structure of 2-substituted derivatives of 1,3-indandione and 1,3-perinaphthindandione respectively.

Mechanism of the condensation reactions

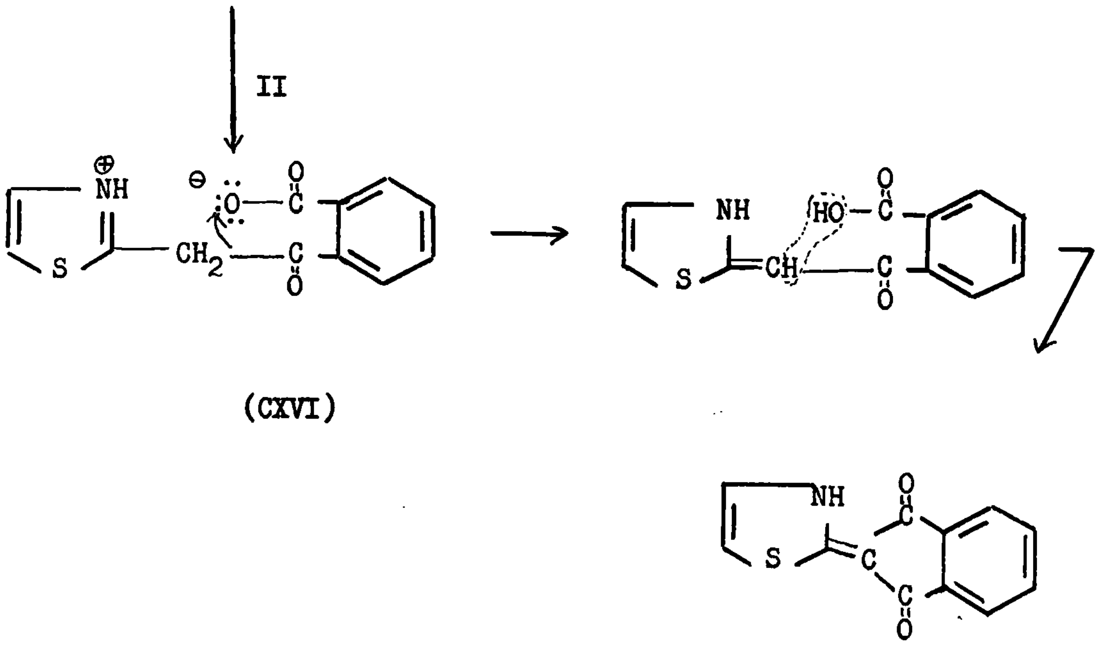
The mechanism of the condensation of 2-methylthiazole with anhydrides of aromatic dicarboxylic acids can be satisfactorily explained by assuming that the 2-methylthiazole reacts in one of its tautomeric forms B. The resonance form B of the methylene-tautomer is a typical carbanion. In the first step the anhydride ring is opened and an unstable intermediate compound (CXIV) is formed. In this addition compound the hydrogen atoms of the methylene group are activated because, in addition to the electron withdrawing forces of the annular nitrogen and sulphur, there is an activating effect of the α-carbonyl group. The latter group exerts a strong activating effect on the hydrogens of the methylene group because of the vicinity of the aromatic ring. Such a strong activating effect is in agreement with analogous cases observed; for example, 2-halo acetophenone. Thus the activated hydrogen atoms, together with an oxygen atom, will be eliminated in the form of water in two subsequent steps. The following scheme expresses the mechanism of this condensation reaction.



A B



(CXIV) (CXV)

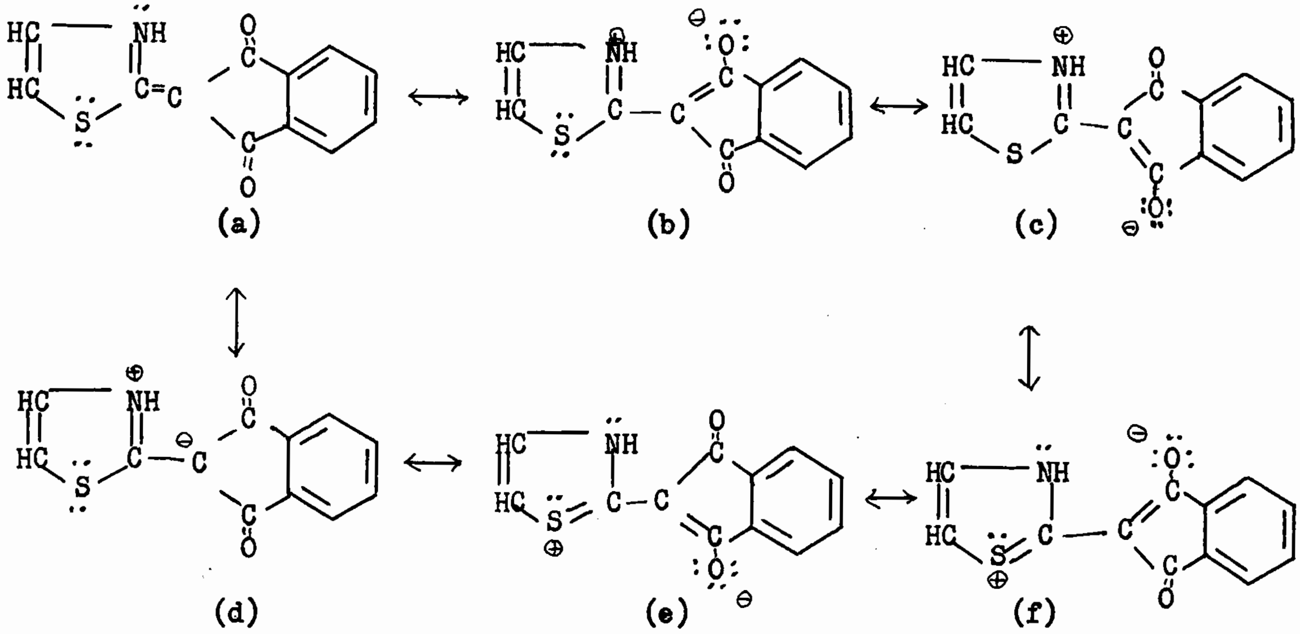


(CXVI)

(CXV)

The elimination of water can occur in two slightly different ways as indicated by paths I and II. In path I, the initial step is the formation of an acid (CXIV) which loses a molecule of water with a simultaneous migration of a hydrogen atom to the annular nitrogen and a shift of the double bond. In path II a polar compound (CXV) is formed as the first intermediate possessing a positive charge on nitrogen and a negative charge on oxygen. The second step consists of the migration of an activated hydrogen atom of the methylene group to the negatively-charged oxygen accompanied by a simultaneous shift of the double bond. The final step is the elimination of a molecule of water and the closure of the indane ring.

The prototropic shift gives rise to an extended conjugation system which must be considered as a resonance hybrid of many resonating structures. In some of the resonance structures there is a separation of electrical charges which is responsible for the shift of the light absorption towards longer wavelengths and consequently the appearance of a yellow colour (110). The structure of the 2-[2-(4-thiazoline)]-1,3-indandione corresponds to the following resonance hybrid: (CXV a-f).

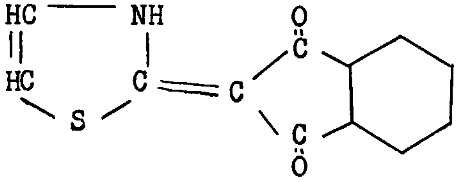


(CXV)

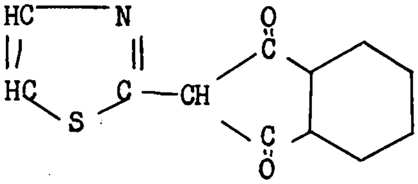
This resonance hybrid of the thiazolophthalone involves several dipolar forms and contains an extended system of conjugated double bonds. Such structure explains its high melting point and the intense light absorption.

Condensation of 2-methylthiazole with phthalic anhydride

The condensation of 2-methylthiazole (V) with phthalic anhydride (CXII) took place with great ease. A mixture of equimolecular quantities of 2-methylthiazole and phthalic anhydride was heated at 180-190° for several hours. At the end of the reaction, the mixture was treated with hot dilute acid to remove the basic unreacted 2-methylthiazole. The principal product isolated from the mixture is a dark yellow crystalline substance, 2-[2-(4-thiazoline)]-1,3-indandione (CXV); m.p. 310-312°.



(CXV)



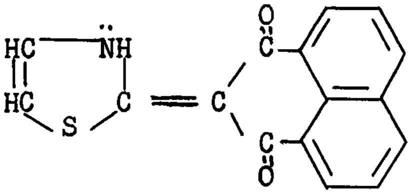
(CXVII)

The classical formula (CXVII) of the condensation product cannot explain its deep colour. Apparently there is a possibility of resonance in the indandione and thiazole parts of the molecule but the -CH group might act as a kind of barrier and inhibit a free shift of π electrons throughout the whole molecule. For this reason a prototropic shift of the hydrogen to give the structure (CXV) might be necessary to explain the appearance of the colour. A similar prototropic shift has been postulated by methylation and oxidation studies of pyridophthalone (50).

The thiazolophthalone (CXV) is insoluble in water, dilute acetic acid and carbon tetrachloride; soluble in methyl alcohol, ethyl alcohol, benzene and dioxane; easily soluble in chloroform and glacial acetic acid and very soluble in acetone and ether. The yield of the compound was 20 per cent. Neither addition of zinc chloride catalyst nor elevation of the temperature nor prolongation of the reaction time influenced the yield. When the compound was treated with sodium alkoxide or with hot 2N sodium hydroxide, a deep red-coloured crystalline sodium salt was obtained. From the reaction mixture another crystalline compound was also isolated. After subjecting it to solubility and classification tests the compound was found to be phthalic acid.

Condensation of 2-methylthiazole with naphthalic anhydride

Naphthalic anhydride (XLII) gave a condensation product with 2-methylthiazole (V), but the reaction did not take place as readily as with phthalic anhydride. Presence of zinc chloride catalyst, higher temperature and considerably longer time was necessary to bring about this condensation. The ratios of 2-methylthiazole:naphthalic anhydride and zinc chloride were as follows: 1:1:0.75 and 1:1:0.5. Somewhat higher yield was obtained when the ratio of zinc chloride was 0.75 to 1:1 of the other two components. On completion of the reaction and after removal of the excess 2-methylthiazole present, the reaction mixture was dissolved in 25 per cent hot hydrochloric acid and filtered. The filtrate was treated with very dilute sodium hydroxide and the precipitate thus formed was recrystallized from hot glacial acetic acid. The dark yellow, crystalline substance which was obtained in a low yield (11 per cent) melted at 241-242° and was found to be 2-[2-(4-thiazoline)]-1,3-perinaphthindandione (CXVIII). Thiazolonaphthalone (CXVIII) can be formulated in a similar way as a resonance hybrid and thus the structure explains both the high melting point (241-242°) and the colour.



(CXVIII)

In contrast to the reactivity of the 2-methyl group, the inertness of the 4-methyl group could be predicted on the basis of Pullman and Metzger's calculations. Concerning the electrical charges and free valences, there is a considerable difference between carbon atoms in the 2 and 4 positions. It can be seen from the molecular diagrams of 2- and 4-methylthiazole (XXII, XXIII), that the carbon atom in position 4 possesses smaller free valence and weeker electrical charge than carbon 2. Obviously the methyl group in C_4 should be less reactive than the one in C_2.

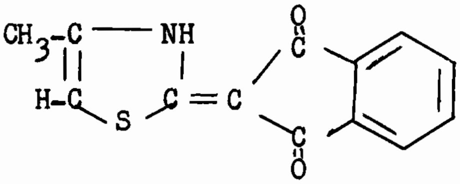
The condensation of 4-methylthiazole (VII) with phthalic anhydride (CXII) was attempted by heating of equimolecular quantities of the reactants in a wax bath at 180-190° for several hours. A yellowish crystalline substance appeared on cooling the reaction mixture which, after purification, melting point determination and classification tests was identified as phthalic acid. A large portion of the 4-methylthiazole was recovered. Another attempt was made, this time using zinc chloride catalyst. Again 4-methylthiazole was recovered and phthalic acid was isolated. The reaction was repeated in a sealed tube, once using zinc chloride and another time without the catalyst. No condensation product was obtained under any conditions.

Several experiments under different conditions were carried out to condense 4-methylthiazole with naphthalic anhydride. The reaction failed in all attempts to produce any condensation products. Both starting materials could be recovered.

5-Methylthiazole behaved in a similar way to 4-methylthiazole. No condensation products were obtained under any conditions with either phthalic or naphthalic anhydride. These negative results gave further support concerning the inertness of 4-, and 5-methylthiazole.

These experiments demonstrated the reactivity of a methyl group at C_2 and the inertness of methyl groups in the four and five positions on the thiazole ring towards aromatic acid anhydrides. On the basis of these observations it was expected that 2,4-dimethylthiazole (IX) would react only with its 2-methyl group yielding 2-[4-methyl-2-(4-thiazoline)]-1,3 indandione (CXIX). In the first experiment, equimolecular quantities of 2,4-dimethylthiazole and phthalic anhydride were heated together at 180-190° for four hours. After the elimination of the unreacted 2,4-dimethylthiazole, the crude product was recrystallized from alcohol. The molecular weight determination and elementary analysis of the purified, crystalline substance indicated that only one methyl group had taken part in the condensation reaction. The product was characterized as 2-[4-methyl-2-(4-thiazoline)]-1,3-indandione (CXIX); m.p. 255.5-256°. The yield was 27 per cent of the theoretical.

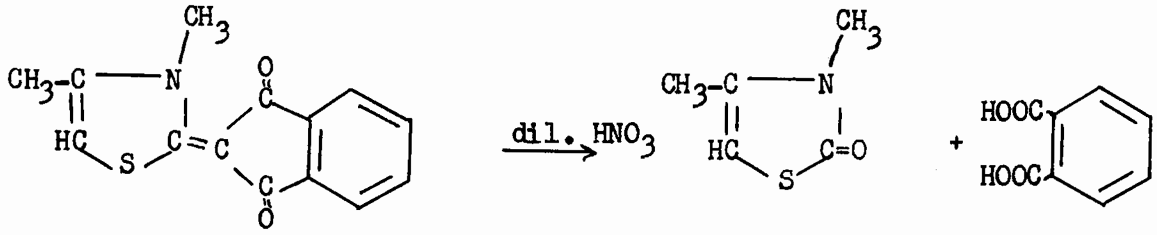
It is possible to postulate the structure of this compound on the basis of previous experimental results. Since 2-methylthiazole condensed with phthalic and naphthalic anhydrides and the methyl group of 4-methylthiazole was inert it is therefore justifiable to conclude that 2,4-dimethylthiazole reacted with its 2-methyl group and not with the one at C_4. However, it seemed to be necessary to attempt to find ways to force the 4-methyl group into reaction. In a second attempt the ratio of phthalic anhydride and 2,4-dimethylthiazole was 2:1. The reaction mixture was heated at 180-190° for four hours as in the previous experiment. The melting point and mixed melting point determinations indicated that the product is identical to (CXIX). The yield was unchanged. When the condensation was carried out in a sealed tube the yield was almost doubled (46.5 per cent of the theoretical) but the second methyl group still remained unaffected. Neither the presence of zinc chloride catalyst nor the prolongation of the reaction time could force the second methyl group into condensation reaction. On treatment with sodium ethoxide or with hot sodium hydroxide, it gave a glittering, deep red crystalline sodium salt.



(CXIX)

Methylation and subsequent oxidation studies analogous to those carried out by Kuhn and Bär (50) were undertaken in order to establish the structure of (CXIX). The compound was methylated by simply adding it to ethereal diazomethane and the mixture was allowed to stand at room temperature for 40 hours. The 2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione (CXX) was recrystallized from water and was oxidized with dilute nitric acid. Two degradation products, namely phthalic acid and N-methyl-2-thiazolone (CXXI) should be obtained.

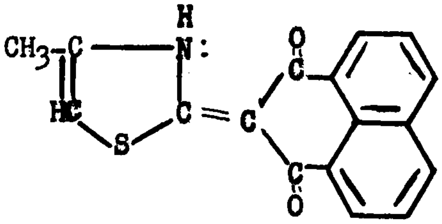
No difficulty was encountered in isolating the phthalic acid, and the phthalein test was used for its identification. After the phthalic acid was extracted the solution was neutralized and saturated with solid sodium hydroxide. A strong pungent odour, characteristic of 4-methylthiazole developed instantly with simultaneous appearance of a semi-solid material. Separation of the N-methyl-2-thiazolone, using ether as extracting medium, was attempted several times without success. It was impossible to isolate any definite product from the thiazole part of the molecule. This probably is due to sensitivity of the thiazole ring to the drastic conditions of oxidation.



(CXX) (CXXI)

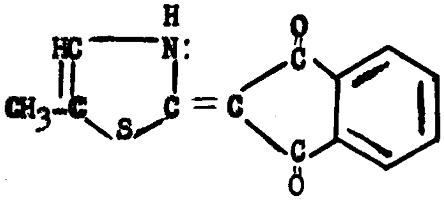
The ultra-violet and infrared absorption spectra of (CXIX) and (CXX) were measured. The ultra-violet spectra were measured in the laboratory while the infrared was carried out by A. Taurins on the Perkin-Elmer double beam spectrophotometer Model 21 in the laboratories of the National Research Council, Ottawa.

The reaction between 2,4-dimethylthiazole (IX) and naphthalic anhydride resulted in 2-[4-methyl-2-(4-thiazoline)]-1,3-perinaphthindandione (CXXII). The anhydride (0.05 mole) and the dimethylthiazole (0.05 mole) were melted together in the presence of zinc chloride (0.037 mole) at 220-240° for ten hours. Several recrystallizations from a dioxane-water mixture (each requiring several days) resulted in large dark-brown crystals. The product (CXXII) which was obtained in 17.2 per cent yield, melted at 216-217° and the carbon, hydrogen, nitrogen analysis was in excellent agreement with the calculated values for the compound. The molecular weight determination gave a value which was very close to the calculated molecular weight (molecular weight; theoretical: 293.326, found 289.4). When the reaction was repeated in a sealed tube, by using a smaller amount of the zinc chloride, the yield was slightly higher, 22.15 per cent. Shortening of the reaction time resulted in the recovery of the starting materials, and no product was obtained.



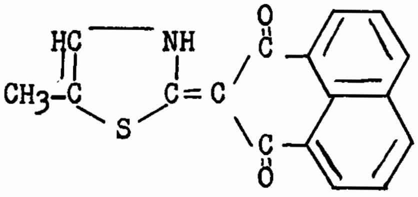
(CXXII)

Comparing the results of all the previously described experiments, it could easily be concluded that the only reactive methyl group on the thiazole ring was attached to position 2, since the attempted condensations with 4-methylthiazole (VII) and 5-methylthiazole (X) with phthalic and naphthalic anhydrides failed. It was therefore assumed that in the condensation of 2,5-dimethylthiazole with phthalic anhydride, 2-[5-methyl-2-(4-thiazoline)]-1,3-indandione (CXXIII) would be formed. This presumption was confirmed by experiments. Two condensations were carried out simultaneously. In one case the reaction mixture contained 1:1 molar quantities of the reactants and in the second case phthalic anhydride and 2,5-dimethylthiazole were mixed in a 2:1 molar ratio. These mixtures were heated at 180-190° for four hours. The products isolated from both reaction mixtures were found to be identical. Both substances melted at the same temperature and no depression of the mixed melting point occurred. The deep colour of the compound suggests a long conjugated system and a structure similar to the one given for (CXV). The deep red sodium salt of the product was also prepared.



(CXXIII)

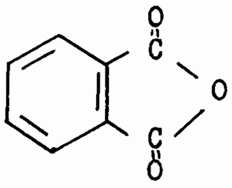
The use of zinc chloride was necessary again to help the condensation of naphthalic anhydride with 2,5-dimethylthiazole (XIII). The amount of zinc chloride used influenced the yield. It was found that the highest yield was obtained when the ratio of 2,5-dimethylthiazole:naphthalic anhydride and zinc chloride was 1:1:0.5 and the molar ratio of 1:1:1 resulted in the lowest yield. A mixture of the reactants was heated at 220-240° for ten hours and after purification by recrystallization from glacial acetic acid a dark brown crystalline product was isolated and characterized as 2-[5-methyl-2-(4-thiazoline)]-1,3-perinaphthindandione (CXXIV); m.p. 302-303°. Similarly to the previous cases, the sodium salt of (CXXIV) is a deep red colour.



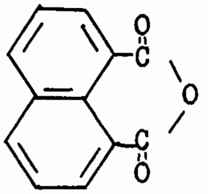
(CXXIV)

Several attempts were made to condense 2-methylthiazole (V) and 2,4-dimethylthiazole (XI) with diphenic anhydride (CXIII). The reaction was attempted once by simply heating a mixture of the components; (XI) and (CXIII) - without a catalyst - for twelve hours in a wax bath. The temperature was gradually raised from 180-250°. In other reactions zinc chloride catalyst was used, and its ratio to the other two components was changed. The temperature and time were also varied. In one instance hydroquinone inhibitor was added to the mixture in an attempt to prevent polymerization. Reactions were also carried out in a sealed tube, but without success. In each case a dark brown, soft amorphous compound was obtained and attempts to isolate a crystalline condensation product failed.

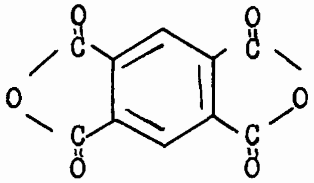
The negative results were surprising since diphenic anhydride was reported by Taurins (45) to condense with quinaldine and 2-methylpyridine (XVIII). To explain the negative result in this condensation the structures of phthalic (CXII) and naphthalic (XLII) anhydrides and that of the pyromellitic dianhydride (LXXVII) were compared with the structure of diphenic anhydride (CXIII). It is obvious that in the case of diphenic anhydride, after opening the anhydride ring, free rotation is possible. What course the reaction takes after the opening of the anhydride ring is not known.



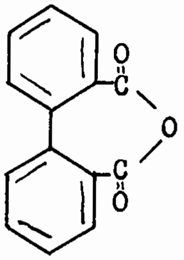
(CXII)



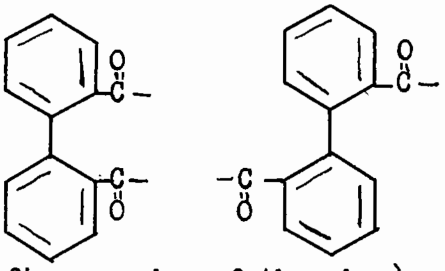
(XLII)



(LXXVI)



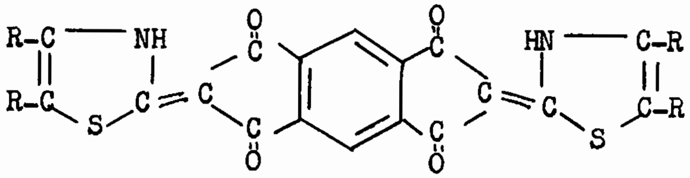
(CXIII)



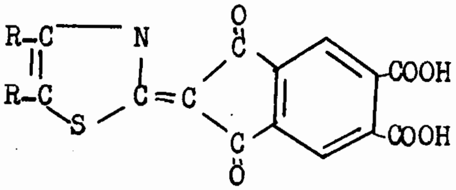
(after opening of the ring)

Attempted condensation with pyromellitic dianhydride

The pyromellitic dianhydride (LXXVI) is structurally similar to phthalic anhydride and it was expected that condensation reaction will readily occur with thiazoles containing a methyl group in position two. It was presumed that the condensation may give one of the two following compounds; one in which two moles of the methylthiazole is condensed with the pyromellitic dianhydride (CXXV) and another in which only one mole of the methylthiazole is condensed to one of the anhydride rings while the water thus liberated would react with the other anhydride ring giving a dibasic acid (CXXVI)



(CXXV)



(CXXVI)

A mixture of pyromellitic dianhydride and 2,4-dimethylthiazole was heated at 180-190° for several hours and purification of the resulting brown mass was attempted. After washing the powdered mixture with one per cent hydrochloric acid, several solvents were tried in an attempt to find an appropriate medium for recrystallization however without any success. In the next attempt 2 moles of 2,4-dimethylthiazole was heated with one mole of pyromellitic dianhydride at 180-190° for several hours. In other attempts zinc chloride catalyst was used in different ratios. All these experiments gave negative results. No condensation product could be isolated from the reaction mixtures.

II. Mannich condensation of methylthiazoles

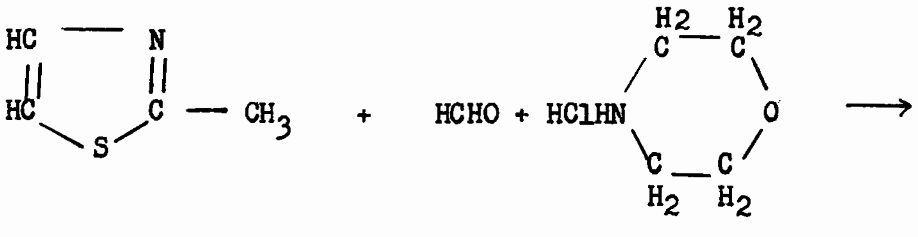
The second part of this investigation consisted of the Mannich condensation of methylthiazoles. It was shown again that while the methyl group on C_2 of the thiazole ring was able to react with formaldehyde and secondary amines (morpholine and piperidine) the methyl groups on C_4 and C_5 did not show any reactivity. The Mannich bases prepared from 2-methyl-, 2,4-dimethyl-, and 2,5-dimethylthiazole are colourless liquids. They were characterized as dipicrates.

The Mannich condensation of 2-methylthiazole was first attempted by dropwise addition of formaldehyde to a mixture of equimolecular amounts of 2-methylthiazole and morpholine. The mixture was stirred at room temperature for six hours, and then divided into two equal parts. The first part was extracted with ether and dried over anhydrous sodium sulphate while the second half was extracted with chloroform and dried over anhydrous potassium carbonate and distilled under reduced pressure. After evaporating the solvents used for extraction, the unchanged 2-methylthiazole was almost entirely recovered. The reaction was repeated at higher temperatures and it was observed that the amount of the recovered 2-methylthiazole decreased as the temperature was raised. The 2-methylthiazole could not be recovered from the dark-brown mixture which was kept above 90°. The reaction time was 6 hours in all cases. No condensation product could be obtained.

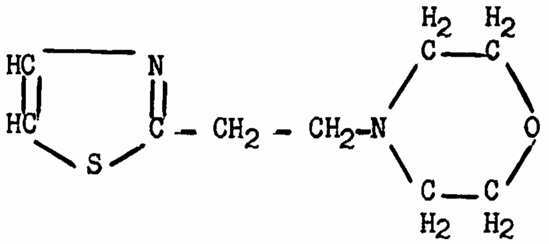
The mixtures mentioned above were slightly basic because of the presence of the free morpholine. Lieberman and Wagner (78) showed that even a slight excess of a base can hinder the initial condensation of the amine and formaldehyde, thus preventing or obstructing the formation of the cation $R_2N\overset{|}{\underset{|}{C}}{}^{+}$ which would combine with the anion of the active hydrogen-containing compound. It was therefore attempted to neutralize the mixture of the 2-methylthiazole and morpholine by dropwise addition of acetic acid. Several reactions were tried but no product was obtained. The use of the amine hydrochloride was finally decided upon and the reaction was a success, although the yield was poor.

Morpholine hydrochloride (CXXVII) was dissolved in a small amount of water and was mixed with an equimolecular quantity of 2-methylthiazole. Formaldehyde was added in the form of 37 per cent aqueous solution over a period of forty-five minutes while the mixture was agitated and heated at 85-90°. On completion of the reaction, the mixture was neutralized with aqueous potassium carbonate and extracted with ether. By distilling the extract under reduced pressure a colourless, viscous liquid was produced; b.p. 79-81° at 3 mm. The yield was 7.1 per cent. The reaction was repeated once by changing the ratio of the starting materials used and another time by extending the reaction time from two hours and forty-five minutes to five hours. No product could be isolated from the dark brown mixture and somewhat lower yield (6.5 per cent of the theoretical) was obtained when the ratio of formaldehyde, morpholine hydrochloride and 2-methylthiazole was 2:2:1 instead of 1:1:1 as in the first successful experiment.

After standing for thirty minutes at room temperature, the compound showed signs of decomposition. Its dipicrate derivative was stable and was used for analysis and characterization of the compound. The nitrogen analysis of the picric acid derivative was in excellent agreement with the calculated values for the dipicrate of 2-(morpholinoethyl)-thiazole (CXXVIII).

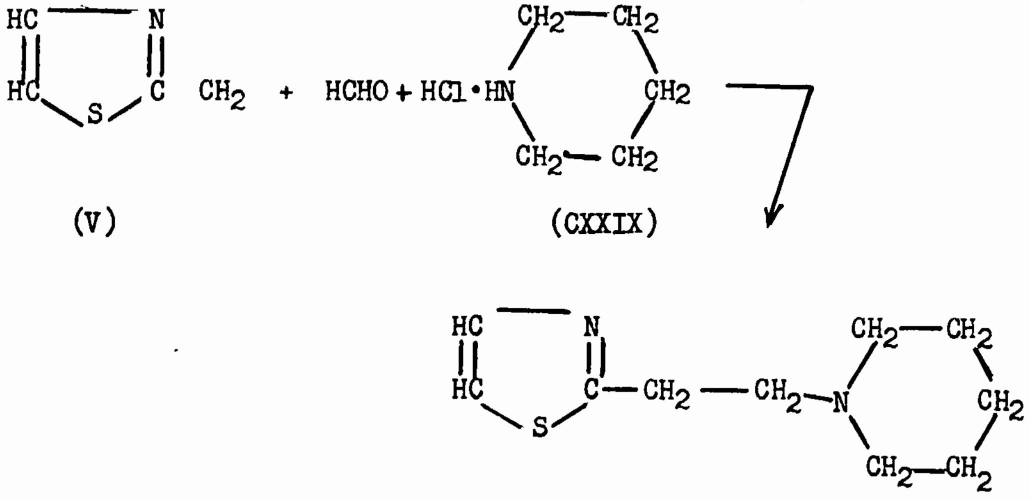


(V) (CXXVII)



(CXXVIII)

The condensation of 2-methylthiazole with formaldehyde and piperidine hydrochloride (CXXIX) yielded 2-(piperidinoethyl)-thiazole (CXXX).



(V) (CXXIX)

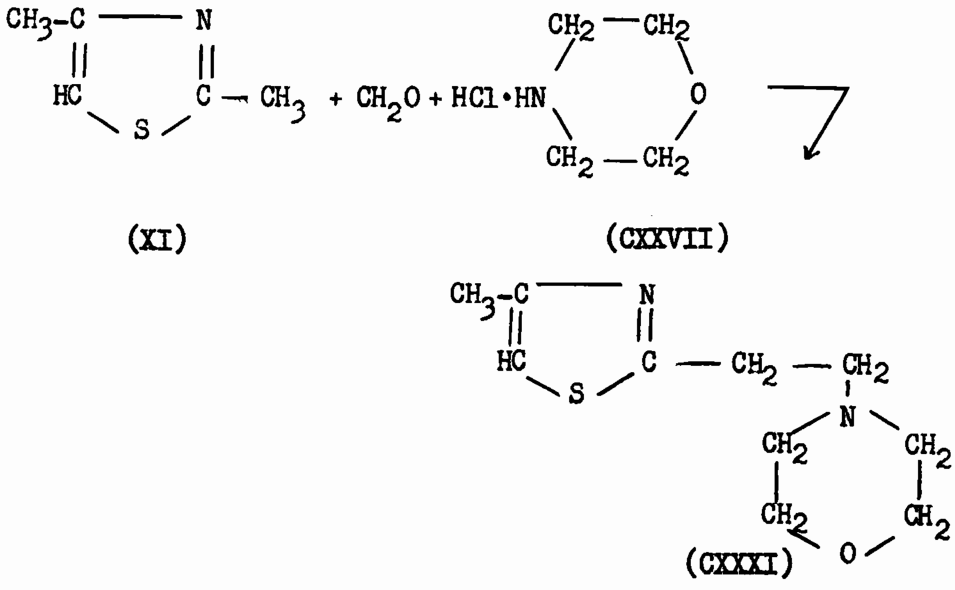
(CXXX)

The product isolated from the reddish-brown reaction mixture was a colourless, viscous liquid. The maximum yield, 19.9 per cent, was obtained when the reaction was carried out at higher temperature (80-85°) during a shorter period of time. The compound decomposed rapidly at room temperature but its dipicrate, which formed easily as yellow needles, was stable.

Since Mannich condensation was successfully attempted with 2-methylthiazole, it was almost certain that 2,4-dimethylthiazole and 2,5-dimethylthiazole too would lead to a positive result. It was anticipated that the product in each case would result from reaction of the 2-methyl group.

whether the methyl groups in C_4 and C_5 positions are reactive or inert in the Mannich-type condensation, had to be studied. In some of the reactions equimolecular quantities of the reactants have been used and in others the ratio of the amine hydrochloride, formaldehyde and methylthiazole was 2:2:1.

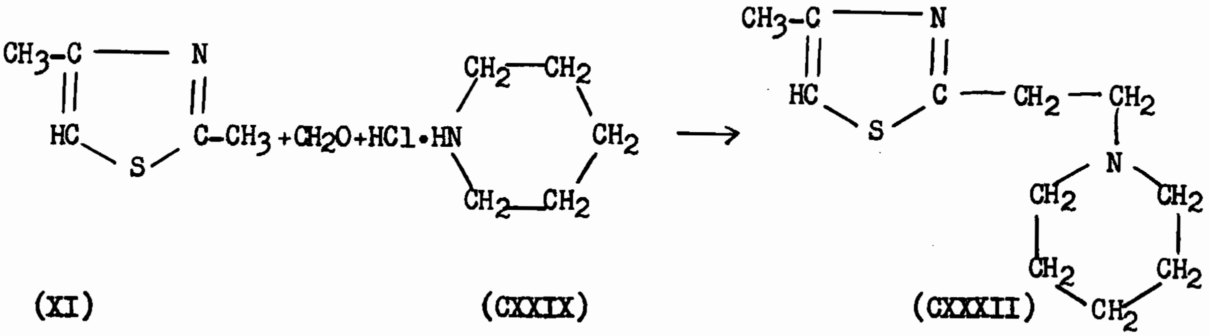
To an agitated mixture of 2,4-dimethylthiazole (XI) and morpholine hydrochloride (CXXVII) aqueous formaldehyde was added dropwise. The highest yield, 16.97 per cent, was obtained when the ratio of the reactants was 1:1:1, the temperature 90-95° and the reaction time six hours. When the temperature was lower, the reaction time shorter and the ratio of morpholine hydrochloride, formaldehyde and 2,4-dimethylthiazole was 2:2:1, the yield was considerably diminished. On completion of the reaction, the mixture was neutralized with 20 per cent potassium carbonate solution and extracted with ether. By subsequent distillation at reduced pressure, an unstable, colourless, viscous liquid was isolated. Its dipicrate was prepared and analyzed. The corresponding Mannich base was characterized as 4-methyl-2-(morpholinoethyl)-thiazole (CXXXI).


(XI)

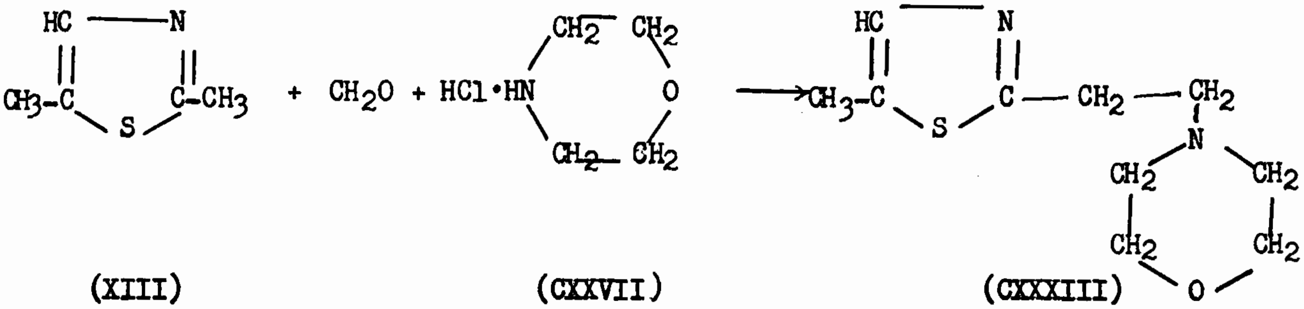
(CXXVII)

(CXXXI)

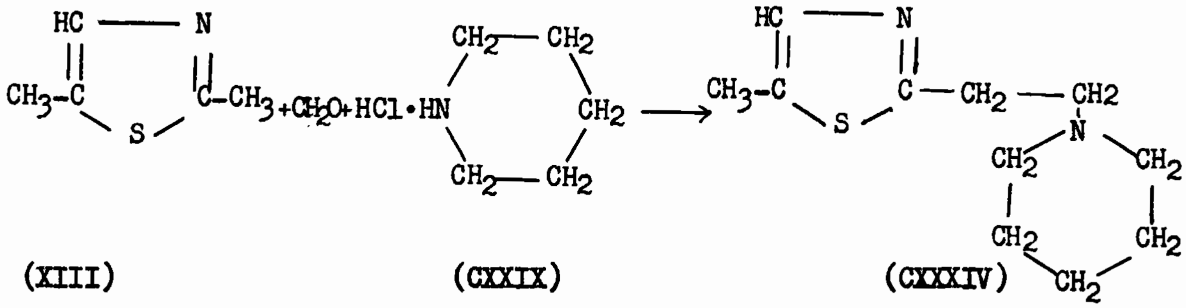
The reaction of piperidine hydrochloride (CXXIX) and formaldehyde with 2,4-dimethylthiazole (XI) resulted in the formation of 4-methyl-2-(piperidinoethyl)-thiazole (CXXXII). The optimum yield was obtained when the ratio of the amine hydrochloride, formaldehyde and dimethylthiazole was 2:2:1 and the mixture was heated at 80-90° for two hours. The yield was considerably smaller at lower temperature even though the reaction time had been extended. When the reaction mixture was heated above 95°, no product could be isolated at all.


(XI) (CXXIX) (CXXXII)

The behaviour of 2,5-dimethylthiazole (XIII) in Mannich condensation was similar to that of 2,4-dimethylthiazole. One product was isolated in each case in which the 2-methyl group alone had reacted, while 4-, and 5-methyl groups remained unchanged. On distillation of the reaction mixture, containing 2,5-dimethylthiazole, morpholine hydrochloride and formaldehyde, a colourless viscous liquid was collected at 135-136° and 7 mm. pressure. Its dipicrate derivative was prepared and analyzed. The free base was characterized as 5-methyl-2-(morpholinoethyl)-thiazole (CXXXIII).


(XIII) (CXXVII) (CXXXIII)

The Mannich product of 2,5-dimethylthiazole (XIII), formaldehyde and piperidine hydrochloride (CXXXIX) is 5-methyl-2-(piperidinoethyl)-thiazole (CXXXIV), a high boiling, colourless, viscous and unstable liquid. The yield of the product depended mainly on the temperature at which the reaction had been carried out and to a lesser extent on the reaction time and the ratio of the starting materials.



(XIII) (CXXXIX) (CXXXIV)

Several attempts were made to obtain the Mannich bases of 4- and 5-methylthiazole. These efforts were without exception unsuccessful. A mixture of 4-methylthiazole, formaldehyde and morpholine hydrochloride was heated at 85-90° for six hours. After termination of the reaction the mixture was neutralized and subsequently extracted. Distillation of the ethereal extract yielded 1 g. of bis-morpholinomethylene; m.p. 150-151°, a known compound which could be identified by mixed melting point determination. The 4-methylthiazole could be recovered from the mixture of the attempted condensation with formaldehyde and piperidine hydrochloride. The Mannich condensation of 5-methylthiazole was only attempted once due to the difficulty of the preparation of this thiazole derivative. This attempt with formaldehyde and morpholine hydrochloride gave a negative result.

The condensation of 2,4-dimethylthiazole with formaldehyde and dimethylamine hydrochloride was carried out by using equimolecular quantities of starting materials. The reaction temperature was 50-60° in one case and 80-90° in the second case. At the higher temperature a compound was formed which was extracted with ether, dried over anhydrous sodium sulphate and distilled. 1.2 g. of a viscous, colourless liquid was obtained which decomposed within a few minutes on standing at room temperature. With picric acid, a yellow oil was formed rather than a crystalline product. The compound could not be analyzed and thus identification was impossible.

EXPERIMENTAL

General Procedure

Starting materials

2-Methylthiazole, 4-methylthiazole, 5-methylthiazole, 2,4-dimethylthiazole, 2,5-dimethylthiazole, diphenic anhydride and naphthalic anhydride were prepared and purified in the laboratory. Phthalic anhydride and a part of the naphthalic anhydride were obtained from the Fisher Scientific Co., while the pyromellitic acid, from which the dianhydride was prepared in this laboratory, was supplied by E.I. Du Pont de Nemours and Co. Inc. The hydrochlorides of morpholine, piperidine and dimethylamine were prepared by the neutralization of amines with hydrochloric acid in an evaporating dish, which was cooled in ice water. The dilute acid was added gradually with stirring until the solution became faintly acidic to litmus. The solution was evaporated slowly over a low flame nearly to dryness. The solid amine hydrochloride was recrystallized from absolute methanol and dried in a vacuum dessicator over anhydrous calcium chloride.

Purification of Reaction Products

The products of condensation reactions of the various methylthiazoles and aromatic acid anhydrides were purified as follows. In order to eliminate the unchanged thiazole derivative, the reaction mixture was washed either with dilute acetic acid or with one per cent hydrochloric acid. Then the mixture was filtered, washed thoroughly with tepid water and recrystallized several times from an appropriate solvent. The crystalline product was dried in vacuo over phosphorus pentoxide prior to analysis.

The substances resulting from the Mannich condensation reactions were liquids. After completing the condensations the reaction mixtures had to be made alkaline in order to convert the amine salt to the free base. To accomplish this, an excess of 20% aqueous solution of potassium carbonate was used. The alkaline solution was extracted with several portions of ether and the combined extracts were dried over anhydrous sodium sulphate overnight. The solvent, along with the low boiling unreacted starting materials, was evaporated under reduced pressure. The residue was transferred to a 25 ml. pear-shaped Claisen flask equipped with a short but effective column. For repeated distillations a small specially-constructed distilling apparatus was used. All distillations were carried out under reduced pressure with the aid of a Cenco High Vac pump.

The weights and melting points of the crystalline products were determined only after drying the samples at suitable temperatures - unless otherwise indicated - using chemical drying agents. Molecular weights were determined by the Rast camphor method. Carbon, hydrogen and nitrogen analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, New York.

It is necessary to mention the physiological activity which was observed during the preparation of methylthiazoles. The majority are skin-irritating, 2-methylthiazole having the strongest effect. A few hours after performing the distillation of the 2-methylthiazole, reddening of the hands, where contact had occurred, was observed. This reddening was followed by blistering and later by peeling of the affected areas. These red spots on the skin, similar to deep burns, were very painful and remained for several weeks before disappearing.

Preparation of Thiazole (III)

Thiazole was prepared in a pure state, for determination of infrared absorption spectrum, by diazotizing 2-aminothiazole and by boiling the product with alcohol. The method described by Popp (7) was modified as follows. A cold mixture of 50 g. of 2-aminothiazole, 250 g. of concentrated sulphuric acid and 50 ml. of water was saturated with dinitrogen trioxide (N_2O_3). The excess dinitrogen trioxide was expelled by bubbling air through the mixture. Alcohol was added and the solution boiled for an hour. After evaporating the alcohol and destroying ethylsulphuric acid, formed during the reaction, the mixture was filtered, the dark brown filtrate was made slightly alkaline with sodium carbonate and distilled. The distillate was made alkaline with solid sodium hydroxide and the thiazole which separated was extracted with ether. The ethereal extract was dried over solid potassium hydroxide and distilled. Sixteen g. of thiazole, boiling at 116.8° was collected. The yield was 38 per cent of theoretical.

Preparation of 2-Methylthiazole (V)

A mixture of 20 g. of thioacetamide and 26 g. of chloroacetaldehyde-hydrate was added to a mixture of 40 ml. of glacial acetic acid and 20 ml. of benzene. This mixture was heated on a water bath for 30 minutes. When the reaction started it was necessary to cool the mixture in a water bath. The solvents and unreacted chloroacetaldehyde were distilled off under reduced pressure. The residue, a brown viscous liquid was diluted with 80 ml. of water and neutralized with solid sodium carbonate. The 2-methylthiazole was steam distilled. The distillate was saturated with potassium carbonate and extracted with ether several times. The fraction boiling between 120-130° was collected; 13.2 g. of 2-methylthiazole was obtained corresponding to 50 per cent yield. Because further purification was necessary, the compound was redistilled and the fraction boiling between 127-128° collected. 7.9 g. (29.9 per cent) of pure 2-methylthiazole resulted.

Preparation of 4-Methylthiazole (VII)

A mixture of 13.5 g. of formamide, 13.2 g. of phosphorus pentasulphide and 21.5 g. of chloroacetone was cooled in an ice-water bath for 2-3 hours and then allowed to stand at room temperature for an additional 2-3 hours. A violent reaction ensued and the mixture turned black. After refluxing on a water bath for about an hour, 100 ml. of water was added to the mixture, which was then made distinctly acidic. This acidified mixture was extracted with ether and the ethereal extract discarded.

Subsequently, the acidic solution was made alkaline and steam-distilled. The distillate was extracted with ether and redistilled. The fraction consisting of 4-methylthiazole, and boiling at 130-134° was collected. The yield was 11.2 g. (48.6 per cent).

Preparation of 5-Methylthiazole (X)

To 200 ml. of absolute ether, 51.4 g. of thioformamide and 51.4 g. of α-bromopropionaldehyde was added. The ether was distilled off slowly and the residue neutralized with 200 ml. of 2N sodium hydroxide. This neutralized mixture was extracted with ether. Only 5.8 g. of 5-methylthiazole

(6.95 per cent) was obtained. The boiling temperature was 70-71° under 41 mm. pressure.

Preparation of 2,4-Dimethylthiazole (XI)

Into a 500 ml. round-bottomed flask, provided with a reflux condenser, was placed 200 ml. of dry benzene. A mixture of 75 g. (1.27 mole) of acetamide and 50 g. of finely powdered phosphorus pentasulphide was prepared and transferred immediately to the flask. Then 5 ml. of a mixture of 100 ml. (1.24 mole) of chloroacetone and 37.5 ml. of benzene was added. The reaction mixture was heated carefully on a water bath and the chloroacetone-benzene mixture was gradually introduced through the reflux condenser. The progress of the reaction was controlled by the amounts of chloroacetone added. As soon as the reaction had begun, the mixture became a black oily liquid. After all the chloroacetone had been added and reaction was no longer apparent, the mixture was refluxed on the water bath for a half hour.

To the dark mixture 187-190 ml. of water was added with shaking. After 30 minutes the mixture was poured into a separatory funnel, and the reddish upper layer containing the benzene and other impurities was discarded. The lower layer was made alkaline by the addition of 5N sodium hydroxide and the crude 2,4-dimethylthiazole, which separated as a black upper layer was removed with ether. The aqueous lower layer was extracted several times with 30-40 ml. portions of ether.

The combined ethereal extracts were dried over anhydrous sodium sulphate and filtered. The ether was removed by distillation over a water bath and the residual oil fractionated at atmospheric pressure. The fraction boiling at 140-150° was collected and redistilled. The yield of 2,4-dimethylthiazole boiling at 142-145° was 33.86 per cent based on acetamide.

Preparation of 2,5-Dimethylthiazole (XIII)

This preparation differs from that given by Hubacher (21) in that α-bromopropionaldehyde was used instead of the less reactive α-chloropropionaldehyde. A mixture of 26.3 g. of α-bromopropionaldehyde (0.192 mole) and 20 g. thioacetamide (excess, 0.316 mole) was refluxed on a water bath for 15 minutes. The reaction was extremely violent, therefore the reaction mixture was cooled in a water bath prior to the refluxing. After 15 minutes, about 50 ml. of 2N HCl was added to destroy the unreacted thioacetamide. After cooling, the mixture was made alkaline with about 100-150 ml. 2N sodium hydroxide and then steam-distilled. The thiazole derivative separated as a yellow oil. The compound was then extracted with ether, dried over solid potassium hydroxide and distilled. The fraction between 148-152° was collected. Yield 8.7 g. (28.89 per cent of the theoretical) .

Preparation of 2-[-2-(4 Thiazoline)]-1,3-indandione (CXV)

In a 100 ml. round-bottomed flask was placed 4.95 g. of 2-methylthiazole (0.05 mole) and 7.4 g. of phthalic anhydride (0.05 mole). This mixture was heated at 180-190° for about four hours. After cooling it gave a yellowish-brown cake, which had the characteristic odour of 2-methylthiazole. After washing the mixture twice with 20 ml. of hot 1% hydrochloric acid the product weighed 2.3 g. which corresponded to a 20.01 per cent yield. A part of the crude product was recrystallized from alcohol, and another part from dioxane. M.p. 310-312°.

Anal. Calcd. for $C_{12}H_7O_2NS$: C, 62.87; H, 3.08; N, 6.11%

Found: C, 62.67; H, 3.12; N, 6.05%

Preparation of 2-[2-(4-Thiazoline)]-1,3-perinaphthindandione (CXVIII)

A mixture of 9.9 g. of naphthalic anhydride (0.05 mole), 4.95 g. of 2-methylthiazole (0.05 mole) and 5.1 g. of freshly fused and pulverized zinc chloride (0.0375 mole) was heated at 240-250°. After ten hours a dark brown brittle cake was obtained. This product was washed with 1 per cent, hot hydrochloric acid, filtered, washed with water, dissolved in 25 per cent hot hydrochloric acid and filtered through a sintered glass funnel. To the filtrate was added dilute sodium hydroxide solution to neutralize hydrochloric acid. The condensation product was filtered off and recrystallized from a mixture of glacial acetic acid and water. The compound was dissolved in hot glacial acetic acid and while the mixture was kept boiling water was added dropwise until turbidity appeared. On standing for a few hours, a dark yellow compound crystallized. The yield was 1.5 g. (10.75 per cent of the theoretical). M.p. 241-242°.

Anal. Calcd. for $C_{16}H_9O_2NS$: N, 5.01%.

Found: N, 5.24%.

Preparation of 2[4-Methyl-2(4-thiazoline)]-1,3 indandione (CXIX)

Into a 100 ml. round-bottomed flask, equipped with a reflux condenser was placed 5.65 g. (0.05 mole) of 2.4-dimethylthiazole and 7.4 g. (0.05 mole) of phthalic anhydride. The mixture was heated at 181-188° for

for four hours. A dark yellow cake was obtained on cooling. After washing with 1% HCl, the product was recrystallized from ethyl alcohol. Bright yellow crystals were obtained, which under the microscope appeared to be cubic. The yield was 3.3 g. (27.16 per cent of theoretical); m.p. 255.5-256°. Molecular weight: theoretical 243.27, found 255.6. Molecular weight determination showed that only one methyl group had reacted with the anhydride.

The reaction described above was repeated using two moles of phthalic anhydride to one mole of 2,4-dimethylthiazole. A mixture of 5.65 g. of 2,4-dimethylthiazole and 14.8 g. of phthalic anhydride was heated at 181-188° for four hours. The product obtained was found to be identical with the product described above.

The reaction was carried out in a sealed tube. Again only one methyl group reacted with the anhydride. The yield was considerably higher than previously: 46.59 per cent of the theoretical.

The reaction was repeated in the presence of zinc chloride catalyst both in a sealed tube and at atmospheric pressure. In both cases the reaction product described above was isolated.

Anal. Calcd. for $C_{13}H_9O_2NS$: C, 64.19; H, 3.73; N, 5.76%

Found C, 64.36; H, 3.56; N, 5.71%

Preparation of 2-[4-methyl-2-(4-thiazoline)]-1,3-perinaphthindandione (CXXII)

a). A mixture of 5.65 g. of 2,4-dimethylthiazole (0.05 mole), 9.9 g. of naphthalic anhydride (0.05 mole) and 5.1 g. of zinc chloride (0.037 mole) was heated to 220-240° in a molar ratio 1:1:0.75. The mixture was kept at this temperature for ten hours. A dark brown cake was obtained, which was powdered and washed with 1% HCl, filtered and washed again with water. The crude product so obtained was dissolved in 75 ml. of 25% hot hydrochloric acid filtered and the filtrate diluted with 200 ml. of water. The hydrochloride was thereby hydrolyzed to the free compound. Then the yellowish-brown precipitate was filtered, dried and recrystallized from a dioxane-water mixture. Two and a half grams of the product was obtained (17.2 per cent of the theoretical). M.p. 216-217°. Molecular weight, theoretical: 293.32; found 289.4.

Anal. Calcd. for $C_{17}H_{11}O_2NS$: C, 69.59; H, 3.78; N, 4.77%
Found: C, 69.59; H, 3.77; N, 4.60%.

b). A mixture of 5.6 g. of 2,4-dimethylthiazole (0.05 mole), 9.9 g. of naphthalic anhydride (0.05 mole) and 3.4 g. of zinc chloride (0.025 mole) was heated in a sealed tube at 220-240° for ten hours. The solidified brittle black mixture was powdered, washed with one per cent hydrochloric acid, filtered and washed again with water. The crude product was then dissolved in 25 per cent hot hydrochloric acid and filtered. To the filtrate was added 190 ml. of water. The precipitate was collected on a Buchner funnel and recrystallized from a dioxane-water mixture. The substance melted at 216-217°. The yield of (CXXII) was 3.2 g.; 22.15 per cent of the theoretical.

The yield was lowered when the amount of zinc chloride was less than in the previous experiment. When the ratio of 2-methylthiazole: naphthalic anhydride:zinc chloride was 1:1:0.5, the yield obtained was 7 per cent of the theoretical.

Preparation of 2-[5-methyl-2-(4-thiazoline)]-1,3-indandione (CXXIII)

A mixture of 2.8 g. of 2,5-dimethylthiazole (0.025 mole) and 3.7 g. of phthalic anhydride (0.025 mole) was heated in a wax bath to 180-190°. After four hours heating a crystalline mass was obtained. The product was washed with 20 ml. of one per cent hydrochloric acid, filtered and washed several times with hot distilled water, dried and weighed. The yield of the crude product was 1.83 g., 30.58 per cent of the theoretical. The compound can be recrystallized either from alcohol, yielding bright yellow needles, or from acetic acid, yielding bright yellow palettes. M.p. 288-289°.

The reaction was repeated by using two moles of phthalic anhydride to one mole of 2,5-methylthiazole. The product obtained was found to be identical (by melting point and mixed melting point determination) with the product described above. The yield was unchanged. Treatment of the product with sodium ethoxide results in a deep red crystalline sodium salt.

Anal. Calcd. for $C_{13}H_9O_2NS$: N, 5.76%;

Found: N, 5.85%.

Preparation of 2-[5-methyl-2-(4-thiazoline)]-1,3-perinaphthindandione (CXXIV)

a). The naphthalic anhydride supplied by Fisher Scientific Co. was recrystallized from concentrated nitric acid (sp. gr. 1.4) prior to carrying out the reaction. In a 100 ml. round-bottomed flask was placed 11.3 g. of freshly-distilled 2,5-dimethylthiazole (0.1 mole), 19.8 g. of naphthalic anhydride and 10.2 g. (0.075 mole) of freshly-fused and finely pulverized zinc chloride. The mixture was kept at 220-240° for ten hours. After cooling the dark brown brittle cake was powdered, washed with dilute (one per cent) hot hydrochloric acid, filtered, washed with distilled water and dried. The crude product was recrystallized several times from a glacial acetic acid and water mixture and 8.7 g. of (CXXIV) was obtained which corresponds to 29.69 per cent of the theoretical. Melting point 302-303°.

Anal. Calcd. for $C_{17}H_{11}O_2NS$: N, 4.77%

Found: N, 4.65%.

b). The reaction was repeated using two moles of naphthalic anhydride to one mole of 2,5-dimethylthiazole and 0.75 mole of zinc chloride. The isolated substance had the same melting point as the product described above. A mixed melting point of the two was not depressed. The yield was the same.

c). To 2.8 g. of 2,5-dimethylthiazole, 4.95 g. of naphthalic anhydride and 1.7 g. of zinc chloride was added. The ratio of the reagents was 1:1:0.5 respectively. The mixture was heated in a wax bath at 220-240° for ten hours and was subjected to the purification process as described above. Recrystallization yielded 2.4 g. of (CXXIV) (32.7 per cent of the theoretical).

d). In another attempt, the ratio of the reactants was 1:1:1. The reaction time and temperature were not changed. Starting with 2.8 g. of

2,5-dimethylthiazole, 4.95 g. of naphthalic anhydride and 3.4 g. of zinc chloride, the mixture yielded 2.1 g. of crude (CXXIV) corresponding to 28.67 per cent of the theoretical.

Preparation of 2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione (CXX)

To a solution of diazomethane in ether prepared from 20.6 g. of nitrosomethylurea, was added 4.3086 g. of 2- 4-methyl-2-(4-thiazoline) -1.3-indandione (CXIX). Gas evolution started instantly. The reaction was allowed to proceed at room temperature for 40 hours with occasional shaking. The methylated yellow insoluble product after filtration and drying weighed 2.888 g. (63.22 per cent of the theoretical) and melted at 168-170°. After two recrystallizations from water the melting point was raised to 170-171°.

Anal. Calcd. for $C_{14}H_{11}O_2NS$: N, 5.44%,
Found: N, 5.25%.

Attempted oxidative degradation of 2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione (CXX)

In a 100 ml. round-bottomed flask was placed 0.5408 g. of (CXX) and 70 ml. of dilute nitric acid (1 part of concentrated nitric acid to two parts of water). The mixture was heated on a steam bath until the compound dissolved. Extracting with ether, a pale yellow crystalline substance was obtained which was purified and identified as phthalic acid. The acidic solution was made alkaline with solid sodium hydroxide and was then extracted with ether. The ether was evaporated and an amorphous greasy compound was obtained. Attempts to purify this substance, or to prepare its 2,4-dinitrophenylhydrazone derivative failed. Recrystallization was attempted from ether, water, alcohol, chloroform and benzene.

Attempt to condense 2,4-dimethylthiazole with diphenic anhydride

In the first attempt, 5.65 g. of 2,4-dimethylthiazole (0.05 mole) and 11.21 g. of diphenic anhydride (0.05 mole) were melted together and kept at 204-208° for four hours. A dark brown, viscous semisolid mixture was obtained from which no crystalline product could be isolated. In the second attempt 0.7 g. of 2,4-dimethylthiazole (0.00625 mole), 1.4 g. of diphenic anhydride (0.00625 mole) and 0.2125 g. of freshly fused and finely pulverized zinc chloride (0.00156 mole) were heated at 215-222° for four hours. (Molar ratio; 1:1:0.25). In a series of reactions which were carried out, the molar ratios were as follows, 2,4-dimethylthiazole:diphenic anhydride: zinc chloride = 1:1:0.5, 1:1:0.75, 1:1:0.1, 1:1:0.3. The reaction time was varied between four and twelve hours. Reactions were also attempted in a sealed tube. In one instance a few mg. of hydroquinone was added to the reaction mixture to prevent polymerization. No product was isolated in these attempts.

Attempted condensation of 2-methylthiazole with diphenic anhydride

Attempts failed to form a reaction product when a mixture, which contained 0.1 equimolecular amounts of 2-methylthiazole and diphenic anhydride and various amounts of zinc chloride, was heated at 200-210° for several hours.

Attempt to condense 4-methylthiazole with phthalic anhydride

A mixture of 2.5 g. of 4-methylthiazole (0.025 mole) and 3.7 g. of phthalic anhydride (0.025 mole) was heated at 180-190° for four hours. All attempts to isolate a reaction product from the cooled mixture proved unsuccessful. Quantitative amounts of 4-methylthiazole were recovered.

The experiment was modified by adding zinc chloride catalyst to the mixture but no condensation product could be isolated.

Attempted reaction of 4-methylthiazole with naphthalic anhydride

No reaction took place when a mixture of 2.5 g. of 4-methylthiazole (0.025 mole), 4.95 g. of naphthalic anhydride (0.025 mole) and 1.7 g. of anhydrous zinc chloride was heated to 195-215° for 10 hours. Both the 4-methylthiazole and the naphthalic anhydride were recovered entirely.

Attempted condensation of 5-methylthiazole with phthalic anhydride

Similarly to the attempt with 4-methylthiazole, an experiment was performed with 5-methylthiazole and phthalic anhydride but it also failed to yield any reaction product.

The experiment was repeated at higher temperatures and with the reaction time extended from four to six and eight hours but both attempts were unsuccessful.

Attempted condensation of 5-methylthiazole with naphthalic anhydride

Similar attempts were made with 5-methylthiazole and naphthalic anhydride. Zinc chloride catalyst was used but these experiments also failed to yield any reaction product. 5-Methylthiazole could not be recovered.

Attempted condensation of 2,4-dimethylthiazole and pyromellitic dianhydride

No apparent reaction took place when 2,4-dimethylthiazole and pyromellitic dianhydride were mixed in 2:1 ratio and were heated at 180-190° for several hours. The experiment was repeated with the application of higher temperature and the extension of reaction time to six and eight hours, and also in the presence of zinc chloride catalyst. All attempts to form a crystalline condensation product were unsuccessful.

II. The Mannich Condensations

Preparation of 2-(Morpholinoethyl)-thiazole (CXXVIII)

a). To a solution of 12.3 g. of morpholine hydrochloride in 10 ml. of water, 9.9 g. of 2-methylthiazole was added. The mixture was stirred at 85-90° for forty-five minutes while 8.5 g. of 37 per cent formaldehyde was introduced dropwise. Heating and stirring were continued for 2 additional hours. The reaction mixture turned light brown; it was cooled, the hydrochloric acid neutralized with 20 per cent potassium carbonate solution and extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate and the ether evaporated at reduced pressure. The product, 1.6 g. of a colourless viscous liquid, was collected at 79-81° and 3 mm. pressure. The yield was 7.1 per cent of the theoretical. The compound decomposed in a few hours on standing at room temperature. For the purpose of characterization the substance was converted to its dipicrate in ethanol. The dipicrate was obtained as yellow needles after two recrystallizations from ethanol; m.p. 151-152.5°.

Anal. Calcd. for $C_{21}H_{20}O_{15}N_8S$: N, 17.14%

Found: N, 17.04%.

The free compound was characterized as 2-(morpholinoethyl)-thiazole (CXXVIII).

b). A mixture of 24.6 g. of morpholine hydrochloride dissolved in 20 ml. of water and 9.9 g. of 2-methylthiazole was stirred at 85-90°. To this mixture 17 g. of 37 per cent formaldehyde was added dropwise over a period of 45 minutes. The heating and stirring were continued for two and a half additional hours. After cooling, the mixture was neutralized with a 20 per cent solution of potassium carbonate and extracted with several portions of ether. The collected ethereal extracts were dried over anhydrous sodium sulphate and the ether evaporated at reduced pressure. The residue yielded 1.5 g. (6.5 per cent of the theoretical) of 2-(morpholinoethyl)-thiazole (CXXVIII).

c). In a 100 ml. round-bottomed flask equipped with a mechanical stirrer, reflux condenser, dropping funnel and a thermometer, was placed a mixture of 12.3 g. of morpholine hydrochloride in 10 ml. water and 9.9 g. of 2-methylthiazole. The mixture was heated and stirred at 85-90° for 45 minutes while 8.5 g. of 37 per cent formaldehyde was added dropwise. Heating and stirring were continued for four and a quarter additional hours. The reaction mixture turned very dark brown and a tar-like material settled to the bottom of the flask. After neutralization, extraction with ether and evaporation of the ether, the residue did not yield any product. This shows that prolonged heating causes decomposition of the product.

Preparation of 2-(piperidinoethyl)-thiazole (CXXX)

a). Nine and nine-tenths grams of 2-methylthiazole and 12.1 g. of piperidine hydrochloride dissolved in 20 ml. of water, contained in a 100 ml. three-necked flask provided with a thermometer, mechanical stirrer and dropping funnel were heated to 50-60° on a water bath. Eight and five tenths grams of 37 per cent formaldehyde was added dropwise to the mixture during the first thirty minutes. The mixture was stirred at the same temperature for five and a half additional hours. Then the mixture was cooled, made alkaline with 20 per cent potassium carbonate, extracted with several portions of ether and dried over anhydrous sodium sulphate. After evaporating the ether at reduced pressure, the residue yielded 3.4 g. (17.35 per cent of the theoretical) of a viscous, colourless liquid boiling at 115-119° and 4 mm. pressure. The liquid decomposed rapidly on standing at room temperature. The dipicrate formed readily in ethanol solution and recrystallization from ethanol yielded bright yellow needles; m.p. 152-153°. On the basis of the analytical data obtained for the dipicrate the product was identified as 2-(piperidinoethyl)-thiazole.

Anal. Calcd. for $C_{22}H_{22}O_{14}N_8S$: N, 17.11%

Found: N, 17.18% and 17.25%.

A white crystalline derivative was prepared with mercuric chloride. This substance decomposed readily and the melting point could not be determined.

b). A mixture of 9.9 g. of 2-methylthiazole and 12.1 g. of piperidine hydrochloride was stirred at 80-86°. To the mixture, 8.5 g. of aqueous formaldehyde (37 per cent) was added dropwise within 30 minutes. The reaction was continued for two additional hours. At the completion of the reaction time, the reddish-brown reaction mixture was cooled, made alkaline with 20 per cent potassium carbonate solution, extracted with ether and the ethereal extract dried over anhydrous sodium sulphate. The ether was evaporated at reduced pressure and the residue yielded 3.9 g. of a colourless viscous liquid; b.p. 114-121° at 4 mm. pressure. The yield was 19.9 per cent of the theoretical.

Preparation of 4-methyl-2-(morpholinoethyl)-thiazole (CXXXI)

a). In a 100 ml. flask was placed a mixture of 11.3 g. (0.1 mole) of 2,4-dimethylthiazole and 12.4 g. of morpholine hydrochloride (0.1 mole) dissolved in 20 ml. of water. The mixture was heated on a water bath to 90-95° with vigorous stirring while 8.3 g. of 37 per cent formaldehyde (0.1 mole) was added from the dropping funnel over a period of one and a half to two hours. After the addition of formaldehyde, heating and stirring were continued for four additional hours. The reaction mixture was then cooled, the hydrochloride neutralized with 20 per cent potassium carbonate and the solution extracted with several portions of ether. The collected ethereal extracts were dried over anhydrous sodium sulphate and the ether evaporated at reduced pressure. Distillation of the residue yielded 3.6 g. (16.97 per cent of the theoretical) of a viscous colourless liquid; b.p. 134-137° at 4 mm. pressure. The dipicrate was prepared in ethanol solution and recrystallization from ethanol yielded dark-yellow needles; m.p. 137-139°. The dipicrate was analyzed and the condensation product characterized as 4-methyl-2-(morpholinoethyl)-thiazole.

Anal. Calcd. for $C_{22}H_{22}O_{15}N_8S$: N, 16.78%

Found: N, 17.04%.

b). A mixture of 11.3 g. of 2,4-dimethylthiazole (0.1 mole) and 24.7 g. of morpholine hydrochloride (0.2 mole) was heated to 85-90°. Sixteen and six tenths g. of 37 per cent formaldehyde was added dropwise while stirring vigorously. After two hours heating and stirring the reddish-brown reaction mixture was cooled, made alkaline with 20 per cent aqueous potassium carbonate and extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate and the ether evaporated at reduced pressure. 2,4-Dimethylthiazole distilled over at 26-29° and 4 mm. pressure and 6.5 g. of it was collected. This amount corresponds to 57.52 per cent of the starting quantity. The residue yielded 2.3 g. of 4-methyl-2-(morpholinoethyl)-thiazole, 10.84 per cent of the theoretical.

Preparation of 4-methyl-2-(piperidinoethyl)-thiazole (CXXXII)

a). The reaction was carried out by introducing 16.6 g. of 37 per cent formaldehyde into a mixture of 11.3 g. of 2,4-dimethylthiazole and 24.6 g. of piperidine hydrochloride dissolved in 20 ml. of water. The ratio of 2,4-dimethylthiazole:piperidine hydrochloride:formaldehyde was 1:2:2. The mixture was kept at 50-60° and stirred. After 6 hours the mixture was cooled, neutralized with 20 per cent potassium carbonate, extracted with ether and the extract dried over anhydrous sodium sulphate. The ether was evaporated and the residue yielded 1.6 g. of a viscous water-clear liquid; b.p. 96-98° at 5 mm. pressure. The yield was 7.6 per cent of the theoretical. The compound showed signs of decomposition on standing at room temperature for about an hour. The dipicrate, m.p. 150-152°, was prepared and analyzed. On the basis of the analytical data, the free base was characterized as 4-methyl-2-(piperidinoethyl)-thiazole

Anal. Calcd. for $C_{23}H_{24}O_{14}N_8S$: N, 16.83%

Found: N, 16.91%.

b). In a 100 ml. round-bottomed flask equipped with a mechanical stirrer, reflux condenser and thermometer, was placed 24.6 g. of piperidine hydrochloride dissolved in 20 ml. of water, 11.3 g. of 2,4-dimethylthiazole and 16.6 g. of 37 per cent formaldehyde. The reaction mixture was stirred well at 80-90° for 2 hours and then cooled, made alkaline with 20 per cent potassium carbonate solution and extracted with five 20 ml. portions of ether. The combined ethereal extracts were dried over anhydrous sodium sulphate. After evaporating the ether at reduced pressure, the residue yielded 4.2 g. of 4-methyl-2-(piperidinoethyl)-thiazole, 20 per cent of the theoretical.

c). The reaction was repeated by using the same amounts of reactants as in the previous two experiments. The reaction mixture was stirred at 95-100° for two hours. The resulting dark-brown colour indicated that polymerization had occurred. After neutralization, extraction of the solution and evaporation of the ether extract, distillation of the residue did not yield any condensation product.

d). Piperidine hydrochloride (12.2 g., 0.1 mole), 2,4-dimethylthiazole (11.3 g., 0.1 mole) and 8.3 g. of 37 per cent formaldehyde were mixed together in a 100 ml. flask. The mixture was stirred at reflux temperature for forty-five minutes and became very dark. Polymerization occurred. No condensation product was obtained.

Preparation of 5-methyl-2-(morpholinoethyl)-thiazole (CXXXIII)

a). A mixture of 11.3 g. of 2,5-dimethylthiazole and 12.3 g. of morpholine hydrochloride dissolved in 15 ml. of water was stirred at 50-60° for six hours. To this mixture, 8.5 g. of 37 per cent formaldehyde was added dropwise during the first hour. (The ratio of the reactants; 1:1:1). At the end of the reaction time allowed, the reddish-brown coloured mixture was cooled and made slightly alkaline with 20 per cent potassium carbonate solution. Extraction with ether was followed by drying over anhydrous sodium sulphate and evaporation of the ether under reduced pressure. A viscous, water-clear liquid was obtained by distilling the residue at 135-136° and 7 mm. pressure. The yield was 2.2 g., 10.37 per cent of the theoretical. The compound showed signs of decomposition (reddish-brown colour) on standing at room temperature for 30 minutes. The dipicrate derivative was prepared from ethanol and recrystallized from ethanol; m.p. 147-149°. The free Mannich base was characterized as 5-methyl-2-(morpholinoethyl)-thiazole on the basis of the analytical data obtained for its dipicrate.

Anal. Calcd. for $C_{22}H_{22}O_{15}N_8S$:	N, 16.7 %
Found:	N, 16.55%.

b). Into a 100 ml. three-necked, round-bottomed flask was introduced 11.3 g. of 2,5-dimethylthiazole (0.1 mole) and 12.3 g. of morpholine hydrochloride (0.1 mole) dissolved in 15 ml. of water. The mixture was stirred at 80-90° while 8.5 g. of 37 per cent formaldehyde (0.1 mole) was added dropwise over a period of one hour. The heating and stirring were continued for an additional two and a half hours. The cooled reaction mixture was made alkaline with 20 per cent potassium carbonate and extracted with ether. The ether solution was dried over anhydrous sodium sulphate and distilled under reduced pressure. 1.6 g. of 5-methyl-2-(morpholinoethyl)-thiazole was collected at 135-136° and 7 mm. pressure. The yield was 7.54 per cent of the theoretical.

c). The reaction was repeated as follows. A mixture of 9.4 g. of 2,5-dimethylthiazole and 10.2 g. of morpholine hydrochloride (no water) was stirred at 80-90° and 7.1 g. of 37 per cent formaldehyde was added dropwise over a period of 15 minutes. The reaction was continued for an additional 30 minutes. The resulting reddish-brown mixture was treated as described in the previous experiments. Distillation yielded 1.6 g. of 5-methyl-2-(morpholinoethyl)-thiazole, corresponding to 9.06 per cent of the theoretical.

Preparation of 5-methyl-2-(piperidinoethyl)-thiazole (CXXXIV)

a). A mixture of 11.3 g. of 2,5-dimethylthiazole (0.1 mole) and 12.1 g. of piperidine hydrochloride (0.1 mole) dissolved in 20 ml. of water was heated and stirred at 50-60° and 8.5 g. of 37 per cent formaldehyde was added dropwise over a period of one hour. Heating and stirring were continued for an additional 5 hours. The ensuing procedure was similar to that described previously. After evaporating the ether under reduced pressure, the residue yielded 3.2 g. (15.2 per cent) of an oily colourless liquid; b.p. 128-131° at 4 mm. pressure. Signs of decomposition appeared on standing at room temperature for 30 minutes. The dipicrate formed in ethanol. Recrystallization from ethanol yielded bright yellow needles; m.p. 138-139°. The base was characterized as 5-methyl-2-(piperidinoethyl)-thiazole.

Anal. Calcd. for $C_{23}H_{24}O_{14}N_8S$:	N, 16.75%
Found:	N, 16.63%.

b). To a vigorously-stirred mixture of 2.9 g. of 2,5-dimethylthiazole and 3.2 g. of piperidine hydrochloride dissolved in 5.3 ml. of water, 2.1 g. of 37 per cent formaldehyde was added dropwise over a period of 15 minutes. The ratio of the reactants was 1:1:1. During the addition of formaldehyde, and for an additional 15 minutes, the mixture was stirred and the temperature kept at 80-90°. One gram of 5-methyl-2-(piperidinoethyl)-thiazole was obtained. The yield was 18.55 per cent.

c). In a 100 ml. three-necked flask was placed 11.3 g. of 2,5-dimethylthiazole (0.1 mole) and 24.2 g. of piperidine hydrochloride (0.2 mole). The mixture was kept at 80-90° while 17.0 g. of 37 per cent formaldehyde (0.2 mole) was introduced over a period of 30 minutes. The heating and stirring were maintained for an additional hour. The mixture was subjected to the neutralization, extraction and drying procedures already described; distillation yielded 2.7 g. of 5-methyl-2-(piperidinoethyl)-thiazole (CXXXIV) corresponding to 15.46 per cent yield.

Attempted condensation of 2-methylthiazole with formaldehyde and morpholine

a). To a stirred mixture of 9.9 g. of 2-methylthiazole (0.1 mole) and 8.7 g. of morpholine (0.1 mole), 8.5 g. of formaldehyde was added dropwise over a period of 30 minutes. The stirring was continued at room temperature for an additional five and a half hours. The mixture was then divided into two equal parts and the first half was extracted with ether and dried over anhydrous sodium sulphate. The second half was extracted with chloroform and dried over anhydrous potassium carbonate. The ether and chloroform extracts were evaporated at reduced pressure. A clear liquid boiling at 35-36° and 12 mm. pressure was collected in both cases and was found to be the unchanged 2-methylthiazole.

b). The reaction was repeated using the same amounts of the reactants but the temperatures in the consecutive reactions were as follows: 50-60°, 70-80°, 90-95° and reflux temperature. No Mannich base was obtained any case.

Attempted Mannich condensation of 4-methylthiazole with formaldehyde and morpholine hydrochloride

A mixture containing 9.9 g. of 4-methylthiazole (0.1 mole) and 12.3 g. of morpholine hydrochloride (0.1 mole) dissolved in 12 ml. of water was stirred at 85-90° while 8.5 g. of 37 per cent formaldehyde was added dropwise over a period of one hour. The stirring and heating were continued for an additional 5 hours. The distillation of the residue yielded 7.6 g. of 4-methylthiazole at 25-28° and 7 mm. pressure. Also 1 g. of a water-clear viscous liquid distilled over at 96-100° and 6-7 mm. pressure. The latter did not contain sulphur and was identified by the melting point of its dipicrate (and also by mixed melting point) as bis-morpholinomethylene; m.p. 150-151°.

Attempted Mannich condensation of 4-methylthiazole with formaldehyde and piperidine hydrochloride

An equimolecular mixture of 4-methylthiazole, piperidine hydrochloride dissolved in a few ml. of water and formaldehyde was heated and stirred at 80-90° for 6 hours. On distillation the 4-methylthiazole was recovered almost quantitatively.

Attempted condensation of 5-methylthiazole with formaldehyde and morpholine hydrochloride

Similarly to the reactions described previously, 5-methylthiazole was allowed to react with formaldehyde and morpholine hydrochloride dissolved in water. The reaction time was 6 hours and the temperature was maintained at 80-90°. No reaction product was isolated on distillation.

Attempted reaction of 2,4-dimethylthiazole with formaldehyde and dimethylamine hydrochloride

a). A mixture of 11.3 g. of 2,4-dimethylthiazole (0.1 mole) and 8.2 g. of dimethylamine hydrochloride (0.1 mole) dissolved in 10 ml. of water was heated at 50-60° for 6 hours. Eight and a half grams (0.1 mole) of 37 per cent formaldehyde was added to the well-stirred mixture over a period of 45 minutes. No product was obtained after evaporation of the ether.

b). The reaction was repeated using the same amounts of reactants. The mixture was kept at 80-90° for 6 hours while vigorous stirring was applied. Distillation of the residue yielded 1.2 g. of a viscous, water-clear liquid; b.p. 100-104° at 5 mm. pressure. The reaction product decomposed readily. Darkening of the product could be observed after a few minutes standing at room temperature. A derivative with picric acid was formed in ethanol, but turned to a sticky yellow oil on standing for a short while or when recrystallization was attempted. Neither the original product nor its derivative was stable enough for analysis.

Attempt to condense 2,4-dimethylthiazole with morpholinomethanol

A mixture of 11.3 g. of 2,4-dimethylthiazole and 11.7 g. of morpholinomethanol was stirred at 90-95° for one and a half hours. Extraction with ether and distillation of the extract did not yield any condensation products.

Infrared spectra of methylthiazoles

Randall, Fowler, Fuson and Dangl (111) have measured the infrared spectra of 2-mercapto-4,5-dimethylthiazole (I), 2-aminothiazole (II), 2-mercapto-4-phenylthiazole (III) and 2-amino-4-(p-biphenyl)thiazole (IV) in the range 3510-1200 cm^{-1}. They found that for each compound there are two bands arising by the absorption of infrared radiation by the thiazole ring:

compound I . . . . 6.16μ (1623 cm^{-1}) and 6.76μ (1479 cm^{-1}),
compound II . . . 6.15μ (1626 cm^{-1}) and 6.60μ (1515 cm^{-1}),
compound III . . . 6.37μ (1570 cm^{-1}) and 6.70μ (1493 cm^{-1}),
compound IV . . . 6.12μ (1634 cm^{-1}) and 6.50μ (1538 cm^{-1}).

The infrared spectra of several N-acetylderivatives of 2-aminoalkylthiazoles and sulphonic acid of 2-amino-4-methylthiazole has been studied by Bogomolov, Sheǐnker and I.Ya. Postokovskŭ (112).

We studied the infrared absorption spectra of thiazole, 2-methyl-, 4-methyl-, 5-methyl-, 2,4-dimethyl-, and 2,5-dimethylthiazole of liquid samples and solutions in carbon disulphide. In the latter case, bands between 1400 and 1650 cm^{-1} were eliminated. The absorption bands of these compounds can be classified as follows.

a) <u>The region 3110-3050 cm^{-1}</u>

Thiazoles and methylthiazoles, like aromatic hydrocarbons, show C-H stretching vibrations in the infrared spectra between 3110 and 3050 cm^{-1}. Liquid samples show bands of high intensity, but solutions in carbon disulphide produce relatively weaker bands.

b) <u>The region 2980-2860 cm^{-1}</u>

These bands are given by methyl groups in asymmetric and symmetric vibrations.

c) The region 2450-1775 cm^{-1} shows a few bands in the spectrum of thiazole and methylthiazole. They are weak, but probably they could be studied better in 1.0 cm. cell. It is possible, that bands in this region arise from overtone and combination tone vibrations.

d) The region 1630-1480 cm^{-1}

These bands can be assigned to skeletal vibrations of the thiazole ring. They are similar to the infrared bands observed in the spectrum of aromatic hydrocarbons.

e) The region 1445-1375 cm^{-1}

The bands of this spectral region occur not only in the spectra of methylthiazoles, but in the spectrum of thiazole as well. Usually, they arise by antisymmetric and symmetric deformation vibrations of the methyl group $C-CH_3$. However, since thiazole also shows a very strong band at 1385 cm^{-1}, we must assign this band to skeletal vibrations of the thiazole ring itself.

f) The region 1320-1175 cm^{-1}

Since the bands of this region are present in the spectra of all thiazoles, they must be assigned to the vibrations of C=C and C=N bonds of the thiazole ring.

g) The region 1160-940 cm^{-1}

The bands of this region are characteristic thiazole ring vibrations.

h) The low frequency (900-640 cm^{-1}) region

The spectral bands of this region are produced by out of plane bending vibrations of the C-H groups of the thiazole ring.

List of the infrared spectra

No. 1 Thiazole, liquid.

No. 2 Thiazole, in CS_2 solution.

No. 3 2-Methylthiazole (3800-1400 cm^{-1}), liquid.

No. 4 2-Methylthiazole (1400-600 cm^{-1}), in CS_2 solution.

No. 5 4-Methylthiazole, liquid.

No. 6 4-Methylthiazole, in CS_2 solution.

No. 7 5-Methylthiazole, liquid.

No. 8 2,4-Dimethylthiazole, liquid.

No. 9 2,5-Dimethylthiazole, liquid.

TABLE I

Abbreviations: vs = very strong,

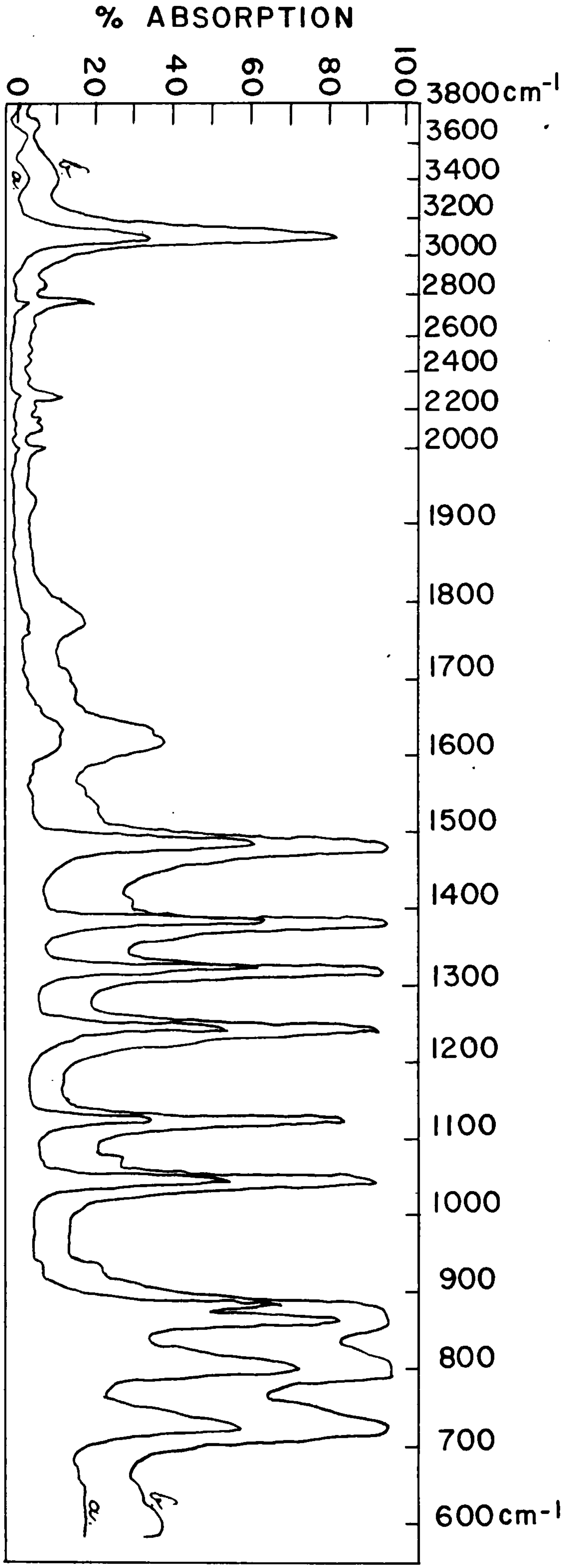
s = strong,

m = medium,

w = weak,

vw = very weak.

These symbols indicate the relative intensities of the spectral bands.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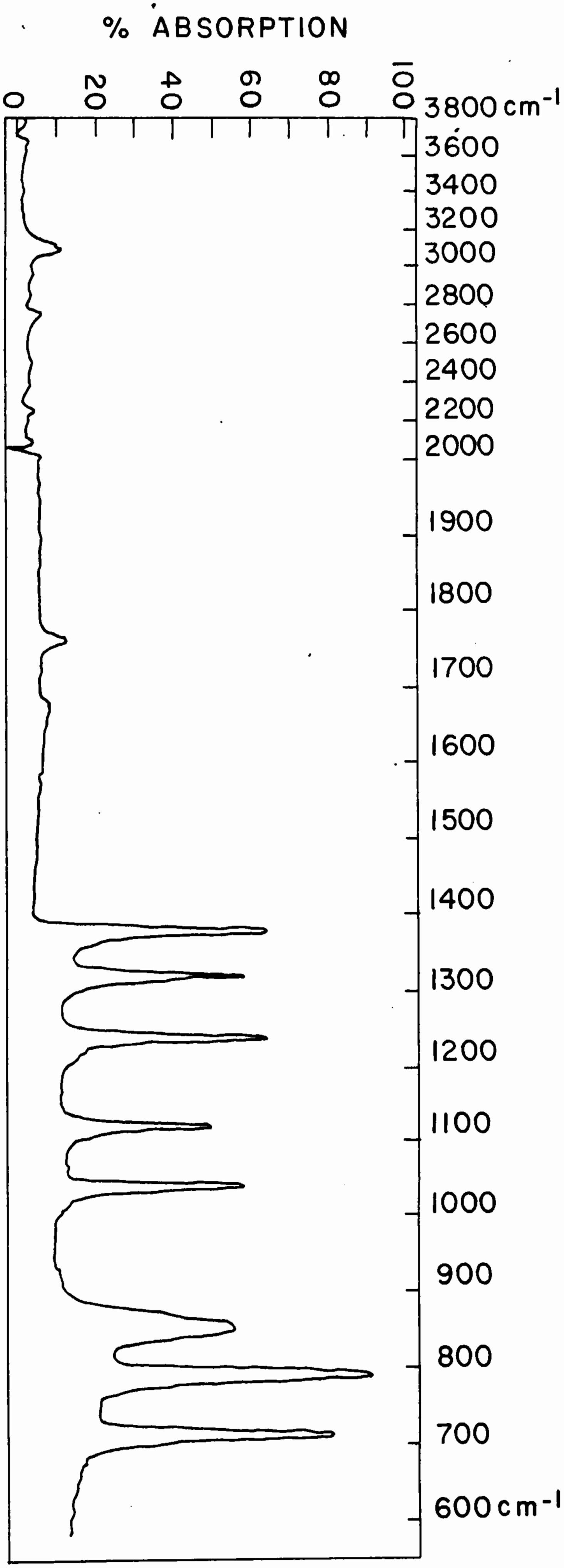
0
20
40
60
80
100
3800 cm⁻¹
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600 cm⁻¹
a
b
a.
b.

No. 1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100
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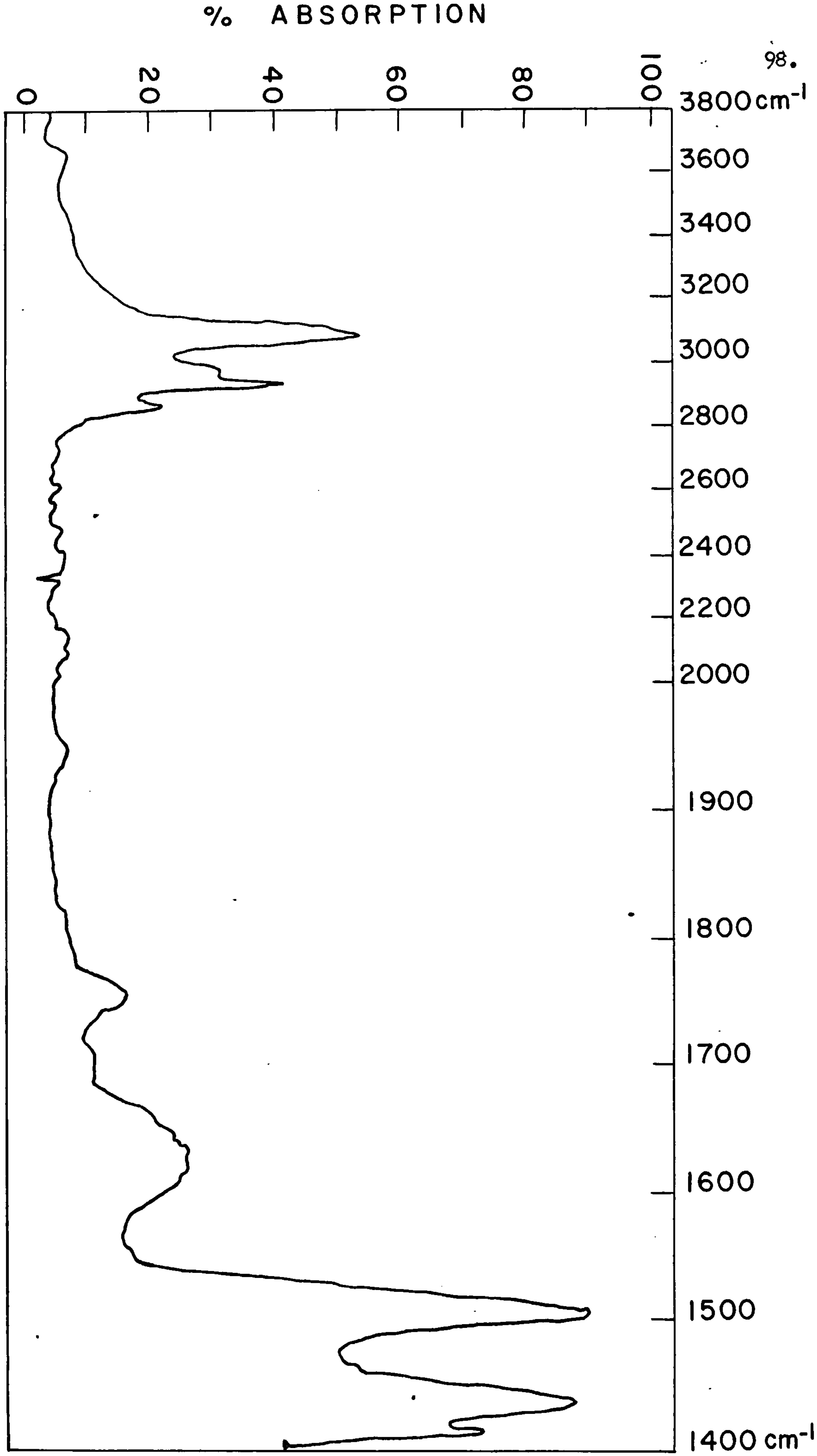
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600 cm-1

No. 2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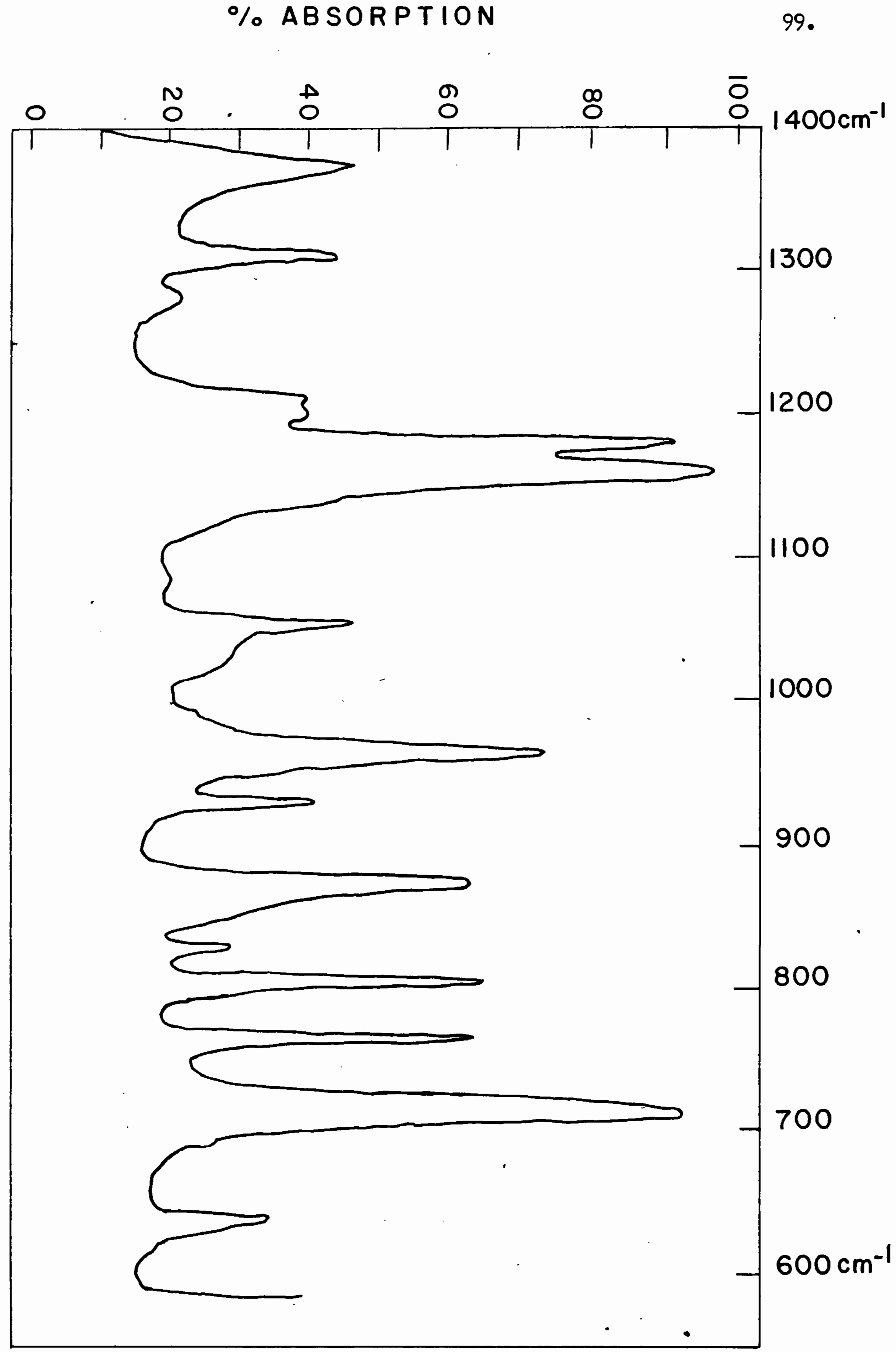
80
100
3800 cm⁻¹
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400 cm⁻¹

No. 3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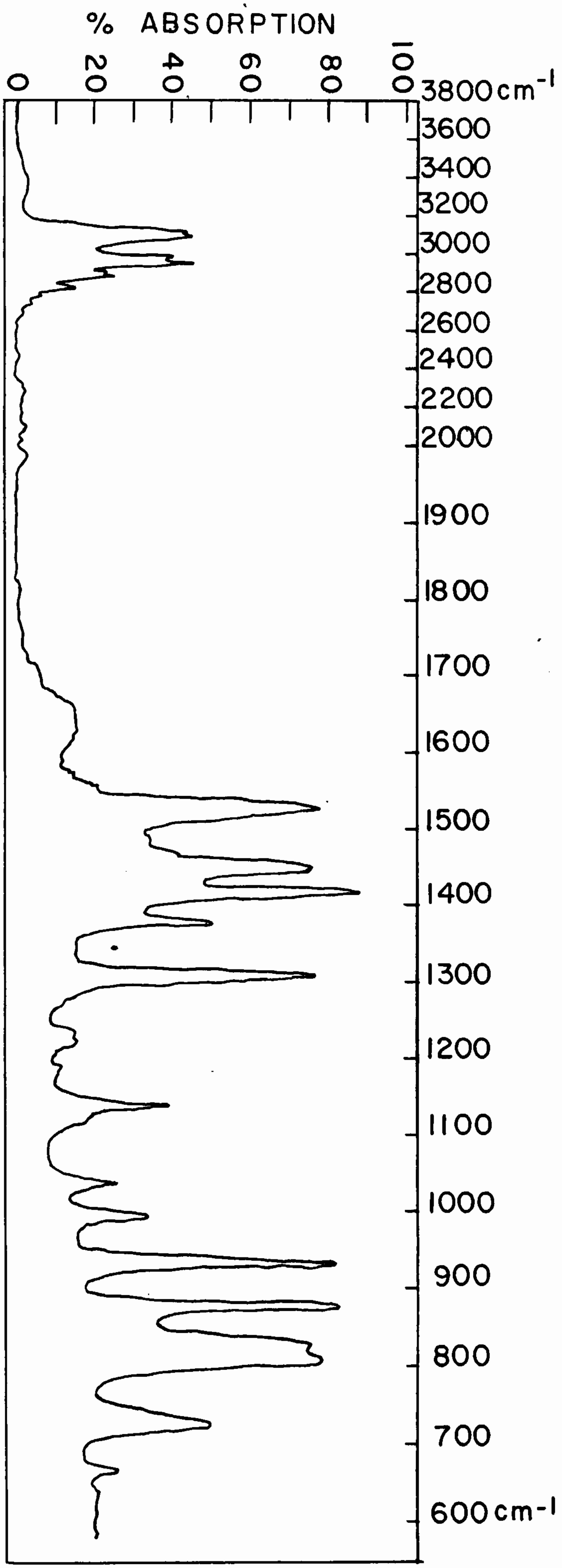
20
40
60
80
100
1400cm^{-1}
1300
1200
1100
1000
900
800
700
600 cm^{-1}

No. 4

No. 5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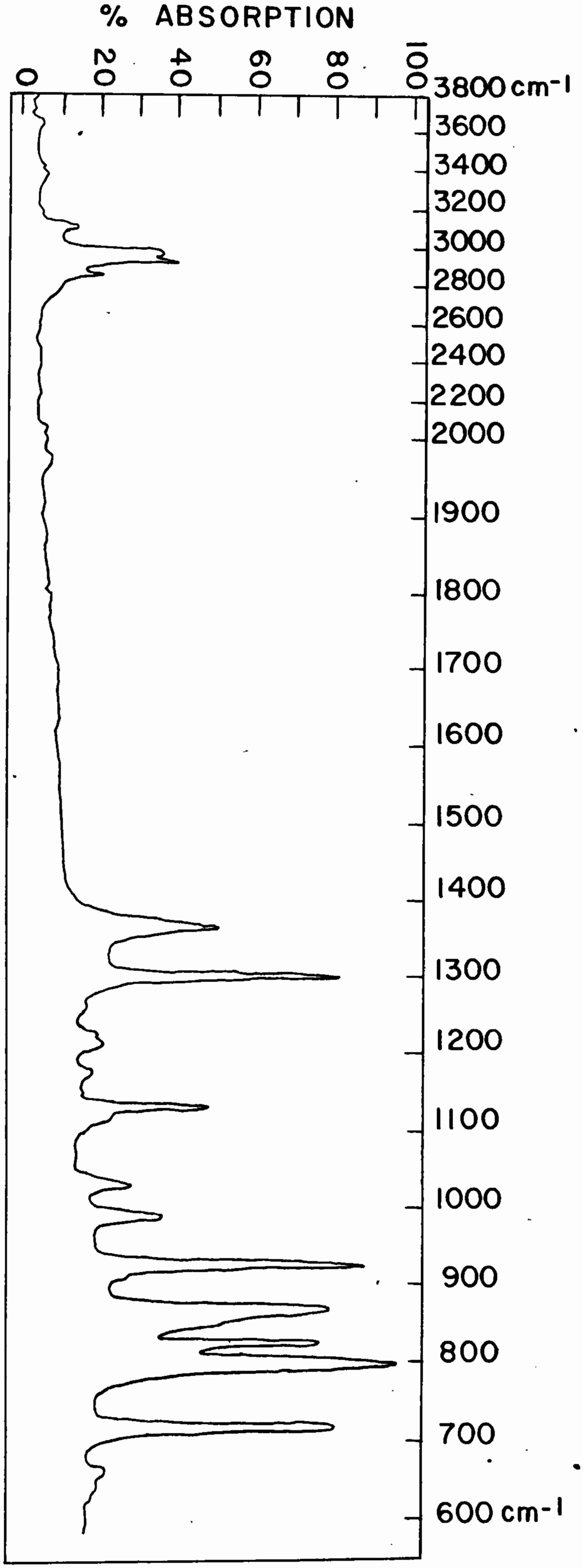
60
80
100
3800 cm-1
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600 cm-1

No. 6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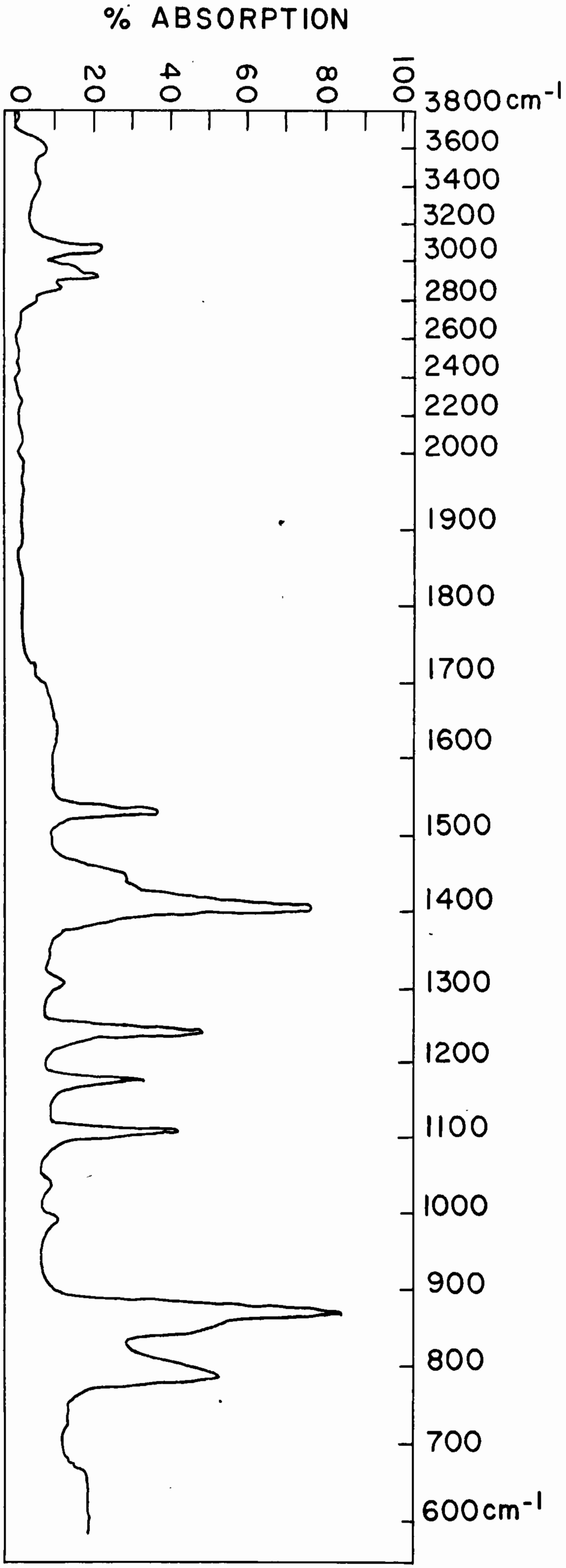
40
60
80
100
3800 cm-1
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600 cm-1

No. 7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20
40
60
80
100
3800 cm^{-1}
3600
3400
3200
3000
2800
2600
2400
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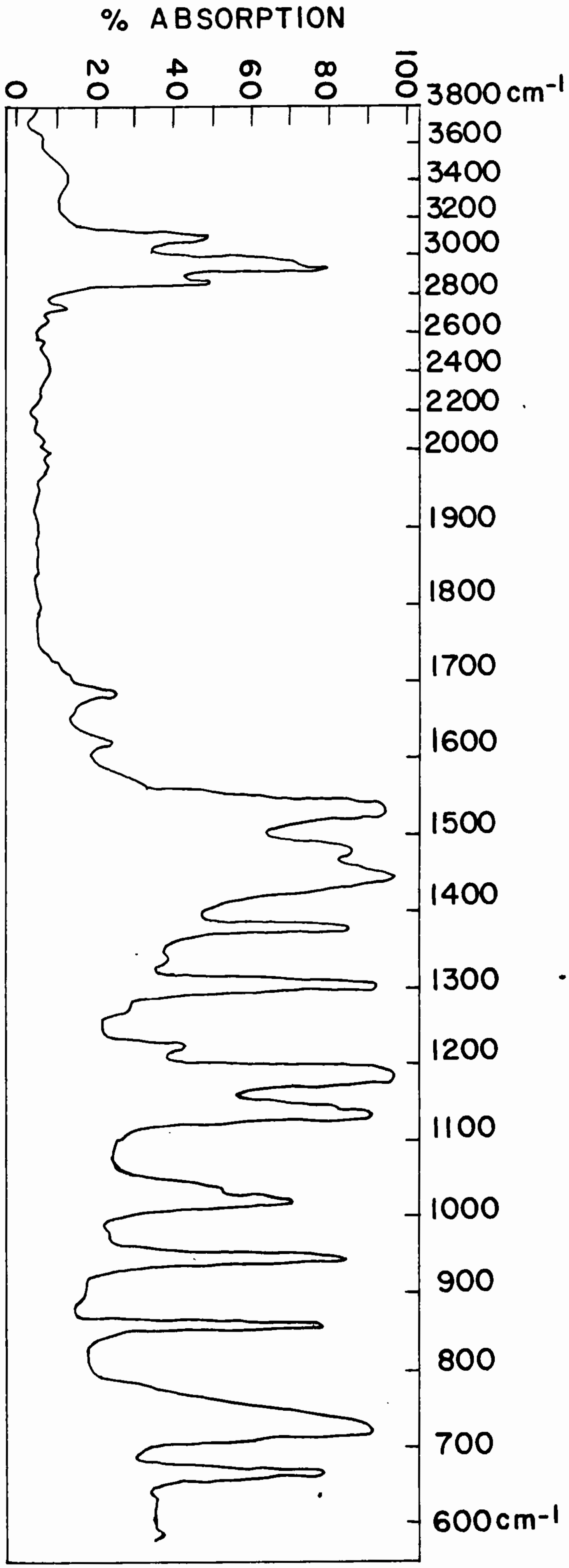
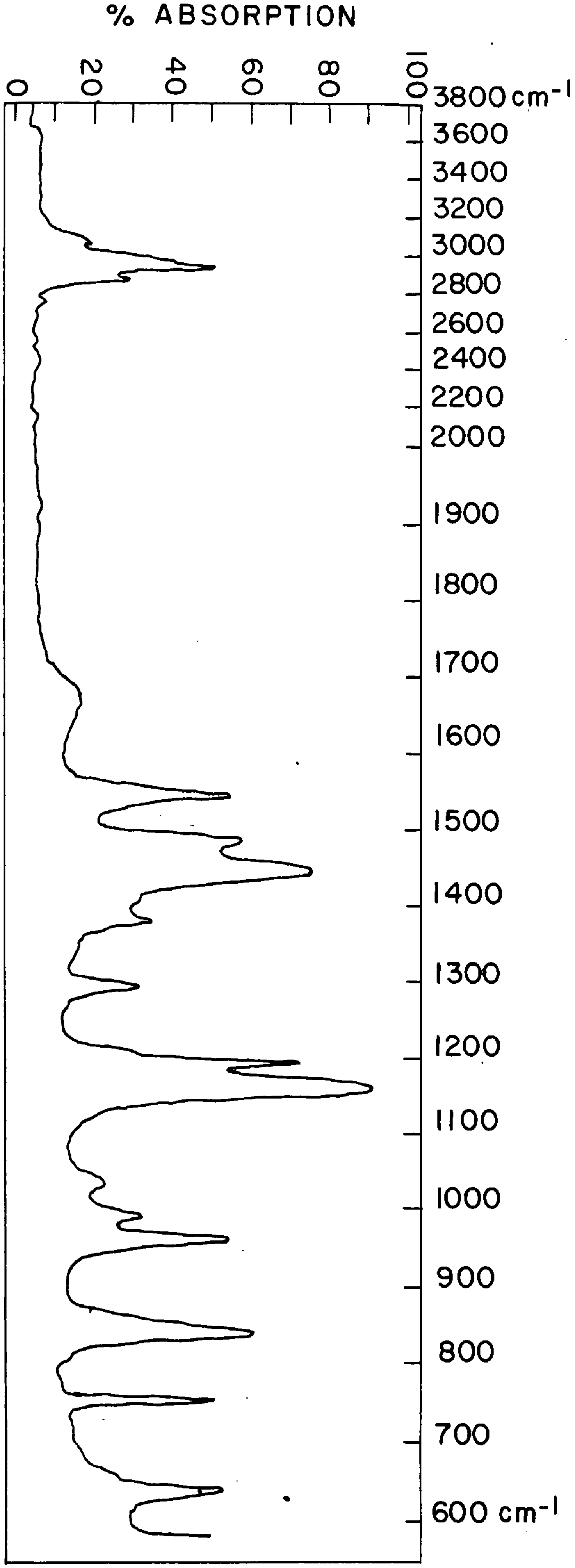
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600 cm^{-1}


% ABSORPTION
0
20
40
60
80
100
3800 cm-1
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600 cm-1

No. 8


% ABSORPTION
0
20
40
60
80
100
3800 cm-1
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600 cm-1

No. 9

TABLE I

Infrared spectra of methylthiazoles

	Thiazole		2-Methylthiazole		4-Methylthiazole		5-Methylthiazole		2,4-Dimethylthiazole		2,5-Dimethylthiazole	
	Liquid	In CS_2	Liquid	In CS_2	Liquid	In CS_2	Liquid	In CS_2	Liquid	In CS_2	Liquid	In CS_2
a	3090 vs	3090 vs	3090 vs		3090 s	3110 w	3090 m	3090 m	3100 m	3110 vw	3050 m	3050 m
			2980 s		2980 s	2970	2960 w	2960 s	2960 s	2970 m	2960 m	2960 m
b			2940 vs		2875	2935	2935 m	2935 s	2937 vs	2937 m	2935 s	2935 s
					2820	2860	2860 w	2860 m	2865 s	2860 w	2870 w	2860 m
	2750 w	2750 w										
c	2260 w	2260 vw										
	1775 w	1765 vw	1775 w					1690 w	1690 w	1690 vw	1680 vw	1680 w
	1615 m		1625		1630 w				1620 w			
d			1510 vs		1525 vs		1530 s		1530 vs		1540 s	
	1485 vs								1480 vs		1485 s	
			1435 vs		1445 vs		1445 m		1445		1445 vs	
e			1415 s		1415 vs		1405					
	1385 vs	1380 vs		1375 m	1380 vs	1375 m		1385 s	1380 vs	1375 s	1375 w	1375 s
	1320 vs	1320 vs		1310 m	1310 vs	1310 vs	1305 vw	1305 vw	1305 vs	1305 vs		
				1280 vw							1280 w	1290 m
f	1240 vs	1240 vs			1225 vw	1220 vw	1240 s	1235 vs	1220 vw			
				1210 m								
				1180 vs			1175 s	1175 s	1185 vs	1185 vs	1190 vs	1192 vs
				1160 vs	1140 s	1140 m			1140 vs	1137 vs	1160 vs	1160 vs
	1120 vs	1120 s					1107 s	1110 vs				
	1040 vs	1040 s		1055 m	1035 m	1035 w		1030 vw	1035 m	1037 vw	1035 w	1035 w
g									1015 s	1015 w		
					995 m	995 vs	990 w				990 w	990 w
				965 s							960 s	960 s
				930 m	930 vs				940 vs	940 m		
	880 vs	875(sh)		875 s	875 vs	875 vs						
	860 vs	855 s					870 vs	860 s				
				830 w	830 vs	830 s	847 s	845 s	833 vs		840 s	840 vs
	800 vs	780		805 s	805 vs	802 vs	785 s	780 vs				
				765 vs							755 s	755 vs
h	720 vs	715 vs		710 vs	725 s	720 vs			720 vs	720 vs		
				640 s	665 w				665 s	665 s	640 s	640

2-[3,4-Dimethyl-2-(4-thiazoline)]-1,3-indandione

$C=10^{-4}$

Wavelength (λ) mμ	Optical density (A)	Molar Extinction Coefficient (ε)
242	1.61	16,166
246	1.44	14,434
250	1.275	12,752
254	1.12	11,155
260	0.77	8,908
264	0.55	5,555
270	0.26	2,642
274	0.19	1,981
276	0.18	1,871
280	0.19	1,971
284	0.21	2,112
290	0.33	3,343
294	0.41	4,114
298	0.47	4,734
300	0.57	5,785
302	0.70	7,077
304	0.72	7,297
306	0.56	5,655
308	0.38	3,828
310	0.27	2,712
314	0.16	1,661
320	0.16	1,591
324	0.18	1,861
326	0.20	2,060
330	0.27	2,727
334	0.37	3,773
336	0.44	4,454
338	0.52	5,215
340	0.61	6,126
342	0.70	7,097
344	0.81	8,188
346	0.93	9,399
348	1.07	10,880
350	1.22	12,242

2-[4-Methyl-2-(4-thiazoline)]-1,3-indandione

Wavelength (λ) mμ	Optical density (A)	Molar Extinction Coefficient (ε)
242	1.44	14,405
246	1.32	13,333
250	1.19	11,991
254	1.07	10,710
256	.99	9,909
260	.77	7,757
264	.51	5,155
268	.26	2,522
270	.19	1,981
274	.15	1,426
280	.19	1,931
282	.22	2,227
286	.31	3,163
290	.51	5,105
294	.61	6,176
300	.99	9,989
302	1,09	10,910
304	1.03	10,031
306	.82	8,258
308	.62	6,226
310	.39	3,933
314	.17	1,776
316	.16	1,631
318	.17	1,711
320	.19	1,926
324	.26	2,622
330	.44	4,554
334	.62	6,296
338	.88	8,858
340	1.03	10,360
346	1.52	15,215
350	1.95	19,519

2-[4-Methyl-2-(4-thiazoline)]-1,3-indandione

Wavelength (λ) mμ	Optical density (A)	Molar Extinction Coefficient (ε)
350	1,98	19,819
354	2.49	24,924
360	2.98	29,829
364	3.18	31,831
370	3.62	36,236
372	3.82	38,238
374	3.78	37,837
376	3.48	34,834
380	2.46	24,624
384	1.53	15,315
390	0.84	7,937
394	0.61	5,685
400	0.44	3,928
410	0.26	2,672
420	0.18	1,891
430	0.13	1,381
440	0.099	990
450	0.067	680
460	0.047	475
470	0.037	380
476	0.035	360
480	0.037	370
484	0.039	390
490	0.042	420

2-[3,4-Dimethyl-2-(4-thiazoline)]-1,3-indandione

Wavelength (λ) mμ	Optical density (A)	Molar Extinction Coefficient (ε)
350	1.25	12,512
354	1.60	16,116
360	2.12	21,271
364	2.44	24,424
370	2.76	27,727
374	3.02	30.230
378	3.10	31,031
380	3.06	30,630
384	2.66	26,726
390	1.87	18,818
394	1.35	13,538
400	.810	8,108
410	.398	3,983
420	.249	2,492
430	.161	1,621
440	.104	1,041
450	.071	710
460	.050	510
470	.029	290
474	.027	280
476	.029	290
480	.029	290
484	.031	320
490	.035	350

List of the ultraviolet spectra

Fig. 1. 2-[4-methyl-2-(4-thiazoline)]-1,3-indandione

(240-350 mμ) (I)

and

2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione

(240-350 mμ) (II)

Fig. 2. 2-[4-methyl-2-(4-thiazoline)]-1,3-indandione

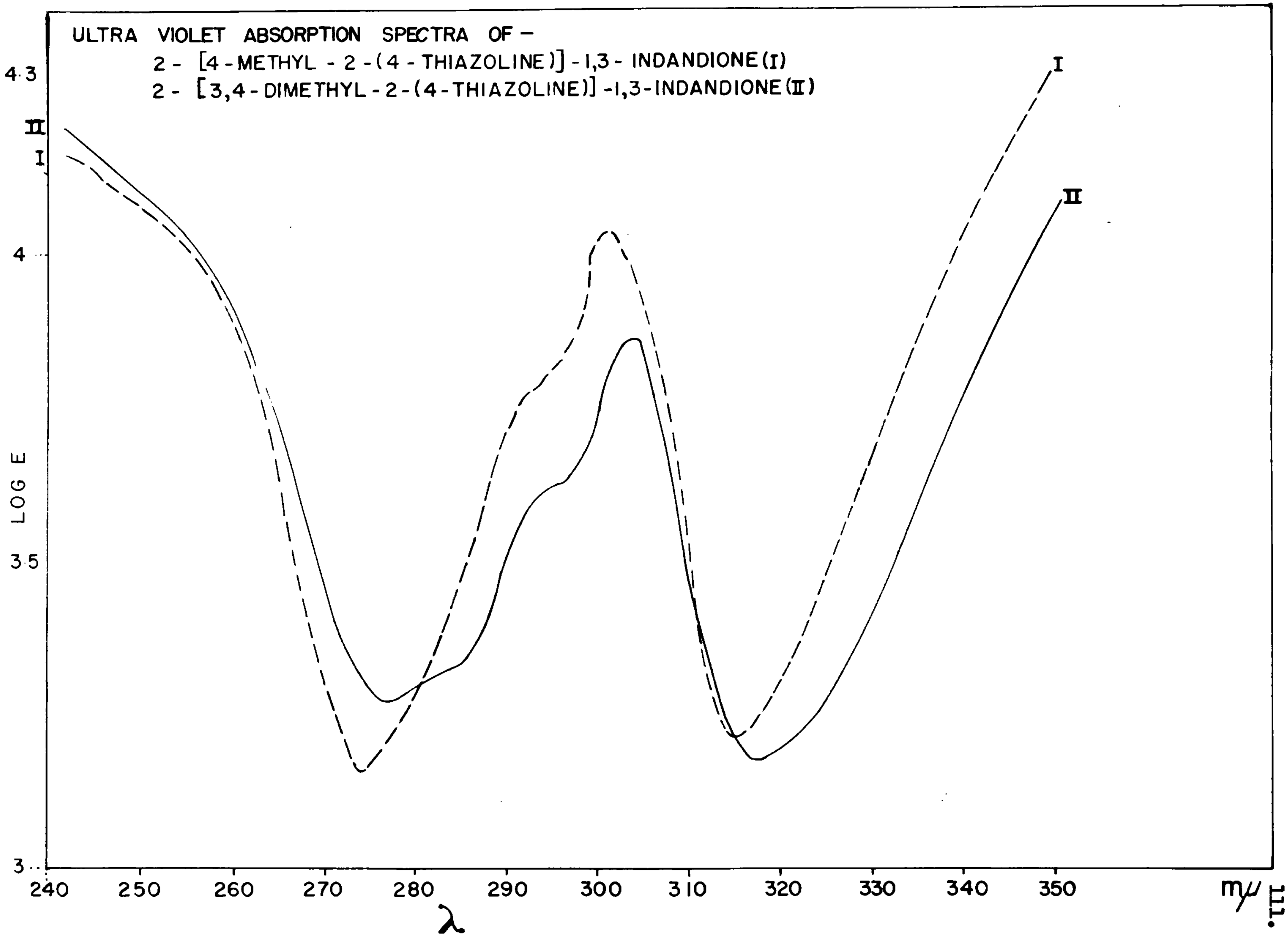
(350-490 mμ) (I)

and

2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione

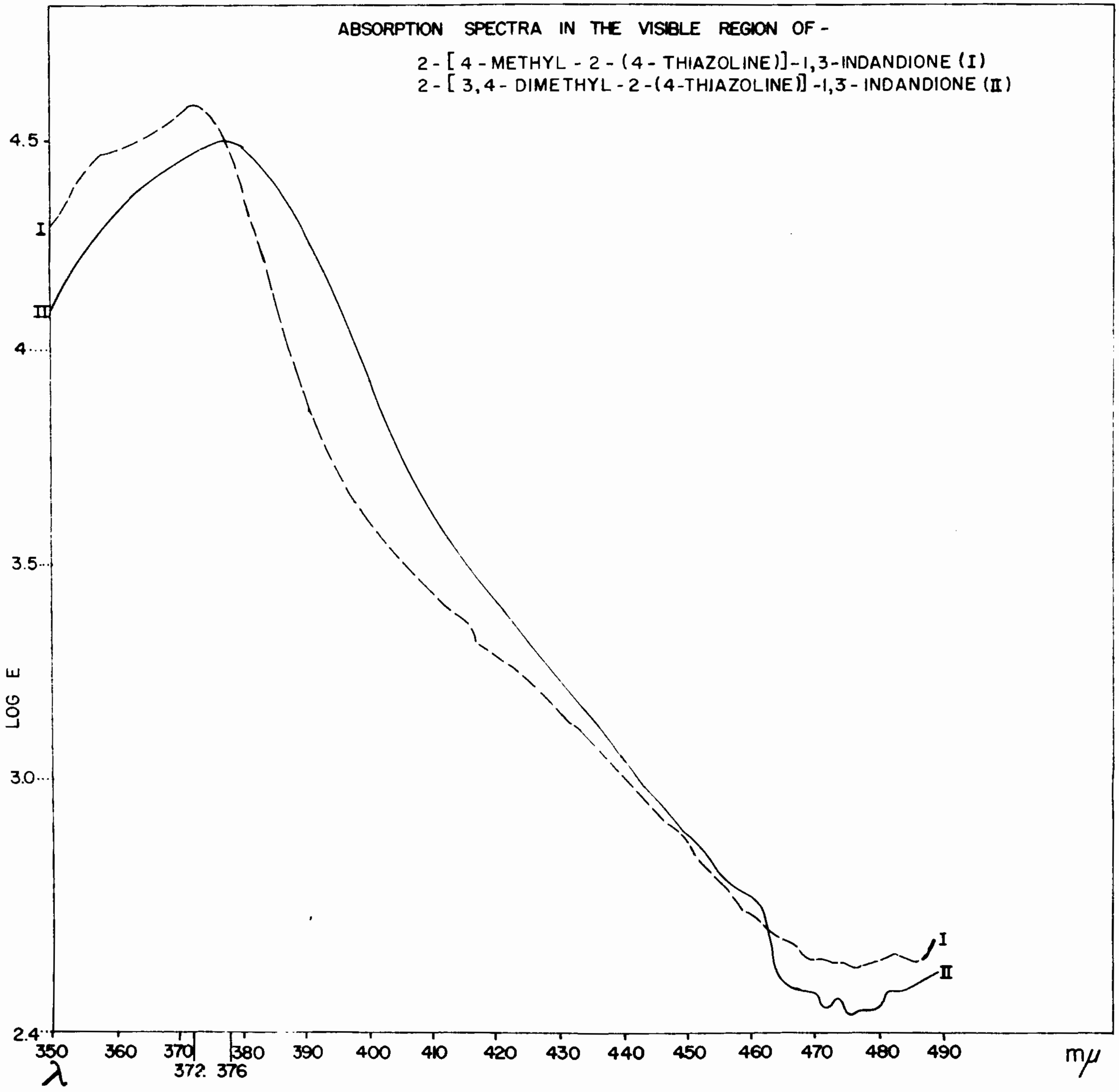
(350-490 mμ) (II)

FIG. 1



ULTRA VIOLET ABSORPTION SPECTRA OF —
2 - [4 - METHYL - 2 - (4 - THIAZOLINE)] - 1,3 - INDANDIONE (I)
2 - [3,4 - DIMETHYL - 2 - (4 - THIAZOLINE)] - 1,3 - INDANDIONE (II)
LOG E
4.3
4
3.5
3
II
I
I
II
240
250
260
270
280
290
300
310
320
330
340
350
mμ
λ

FIG. 2



ABSORPTION SPECTRA IN THE VISIBLE REGION OF -

2 - [4 - METHYL - 2 - (4 - THIAZOLINE)] - 1,3 - INDANDIONE (I)

2 - [3,4 - DIMETHYL - 2 - (4-THIAZOLINE)] - 1,3 - INDANDIONE (II)

SUMMARY AND CONTRIBUTIONS TO KNOWLEDGE

The present investigation demonstrated the reactivity of methyl groups in the 2 position of the thiazole nucleus. In this work the reactivity of methyl groups in positions 2, 4 and 5 was tested by condensing methylthiazoles with anhydrides of aromatic dicarboxylic acids. During the investigation the following results were obtained:

1) Methyl groups in position 4 and 5 on the thiazole ring were inert. No condensation occurred under any conditions by reacting 4-methylthiazole and 5-methylthiazole with anhydrides.

2) The following products, which can be regarded as merocyanines, have been prepared for the first time by condensing 2-methylthiazole, 2,4-dimethylthiazole and 2,5-dimethylthiazole with phthalic and naphthalic anhydride:

a) 2-[2-(4-thiazoline)]-1,3-indandione, m.p. 310-312°
b) 2-[4-methyl-2-(4-thiazoline)]-1,3-indandione, m.p. 255-256°
c) 2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione, m.p. 170-171°
d) 2-[5-methyl-2-(4-thiazoline)]-1,3-indandione, m.p. 287-288°
e) 2-[2-(4-thiazoline)]-1,3-perinaphthindandione, m.p. 241-242°
f) 2-[4-methyl-2-(4-thiazoline)]-1,3-perinaphthindandione, m.p. 216-217°
g) 2-[5-methyl-2-(4-thiazoline)]-1,3-perinaphthindandione, m.p. 302-303°

3) Sodium salts of all these merocyanines have been prepared.

4) The ultraviolet absorption spectra of 2-[4-methyl-2-(4-thiazoline)]-1,3-indandione and 2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione have been investigated between 242 and 490 m . The following absorption maxima were found:

a) 2-[4-methyl-2-(4-thiazoline)]-1,3-indandione

λ max. 302 and 372 mμ

b) 2-[3,4-dimethyl-2-(4-thiazoline)]-1,3-indandione

λ max. 304 and 378 mμ

5) Molecular weight determinations and elementary analyses indicated that only one methyl group reacted.

6) No products were obtained with diphenic anhydride and pyromellitic dianhydride.

7) For the first time Mannich condensation of the methylthiazoles has been successfully carried out, thus extending the scope of this type of reaction to the thiazole derivatives. In the Mannich condensation too, only the 2-methyl group on the thiazole ring showed reactivity while the 4- and 5-methyl groups were proved to be inert.

8) The following Mannich bases have been prepared for the first time by condensing 2-methylthiazole, 2,4-dimethylthiazole and 2,5-dimethylthiazole with formaldehyde and either morpholine hydrochloride or piperidine hydrochloride.

a) 2-(Morpholinoethyl)-thiazole, b.p. 79-81°/3 mm.

b) 2-(Piperidinoethyl)-thiazole, b.p. 115-119°/4 mm.

c) 4-Methyl-2-(morpholinoethyl)-thiazole, b.p. 134-137°/4 mm.

d) 4-Methyl-2-(piperidinoethyl)-thiazole, b.p. 96-98°/5 mm.

e) 5-Methyl-2-(morpholinoethyl)-thiazole, b.p. 135-136°/7 mm.

f) 5-Methyl-2-(piperidinoethyl)-thiazole, b.p. 128-131°/4 mm.

9) Dipicrates of all the Mannich bases have been prepared and analyzed.

10) The condensation products of dimethylamine hydrochloride, formaldehyde and methylthiazoles were very unstable.

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