CHEMISTRY OF THE THIAZOLES

Part V. Fine Structure and Orientation

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1. Introduction

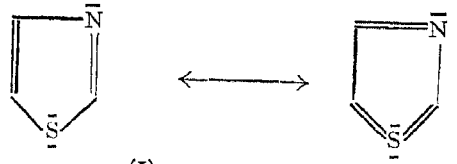
The thiazole ring system from the point of view of fine structure remains the least studied of the heterocyclic compounds. None of the customary physical or physico-chemical measurements which give us accurate ideas about the dispositions of the various atoms in the ring, the bond distances, the valency angles and the state of polarisation of the atoms, have been made with thiazole or any of its derivatives. So, to understand the fine structure of the thiazole derivatives, we have to rationalise *a posteriori* on the basis of the physical properties and the chemical reactivities of the various thiazole derivatives so far reported. This paper is an attempt in this direction.

2. Polarisation (Mesomerism) and Disposition of the Atoms in the Ring

There are some very characteristic properties of thiazole and its derivatives which should be reflected in their fine structure. Though thiazole is a five membered heterocyclic compound, in its properties such as the boiling point, basicity, solubility in water, odour, reactivity, isosterism and resistance to the attack of electrophilic reagents, it strikingly resembles the six-membered compound pyridine and also pyrimidine, and sharply differs from the five-membered heterocyclic compounds, thiophene, furan, oxazole, glyoxaline and pyrrole. There are some thiazole derivatives which, in their properties and behaviour, resemble the corresponding thiophene, furan, or glyoxaline derivatives rather than the pyridines. Next, the thiazole compounds fall into two groups: the first consists of thiazole and some derivatives which are stable and resist attack by electrophilic reagents, while the second group comprises of derivatives which show properties quite the reverse of this. Thirdly, in some substitution reactions, even with the reagents of the same category, there is a difference in the orientation of the incoming group; in the case of nitration and sulphonation, the position taken by the incoming group is different from that in halogenation. Lastly, the reactivities of the various groups or atoms present in thiazoles differ

markedly depending upon the position they occupy in the ring and also upon the substituents in the other positions.

To seek an explanation for these properties, one of the methods adopted is to rely on the resonant structures. Erlenmeyer *et al.*[1] studied the deuterium and hydrogen exchange in 4-methylthiazole-5-carboxylic acid and postulated that thiazole exists in the resonant forms represented by the formula (I) and express the view that this postulation provides an explanation for an aromatic linkage between the carbon atoms 4 and 5 and for an "aromatic sulphur", *i.e.*, a sulphur atom that does not behave as a thioether. On the basis of the general rules available for the postulation of the



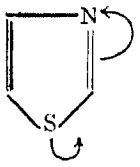
(I)

resonant structures and on analogy with the structures proposed for the other heterocyclic ring systems, we could write down a number of resonant formulæ for thiazole also. But this does not help us because we cannot assess the contributions of the various forms due to lack of data to calculate the resonance energies, bond distances, or the character of the various bonds. On the other hand, we can get far ahead by examining the mesomeric influences in the thiazole ring, the polarisation of the various atoms, the nature of the bonds, and the effects of the substituents in the ring as revealed by the experimental results, as is shown below:

The system N—C_2—S.—This system is taken together since these three atoms individually influence the properties of the other. Of the two heterocyclic atoms, nitrogen dominates in governing the properties of thiazole which is evidently because it has the lesser number of unshared electron pairs than sulphur.[2] Depending upon the nature of the substituents at C_2, the ring nitrogen can function in two diametrically opposed roles, *viz.*, (i) as an electron sink, when the substituent at C_2 is an electron acceptor (nitro, carboxy, carbonyl, sulphonic, or cyano groups) or cannot tautomerise with the nitrogen (hydrogen, halogens) and (ii) as an electron source or a relay of electrons when the substituent at C_2 (amino, substituted amino, hydroxy, substituted hydroxy, mercapto, substituted mercapto groups) is an electron donor or can tautomerise with nitrogen (hydroxy, mercapto and amino groups). These two possibilities as regards the function of nitrogen account for the two types of effects resulting in the segregation of the thiazoles into the abovementioned two classes as shown below:

(i) In the first case, due to the electron attraction (—T effect) of the ring nitrogen (II), there is a deactivation of the thiazole nucleus to the substitution by electrophilic reagents, just as in pyrimidine[3] or pyridine.[3] The carbon atom 2 which becomes kationoid in reactivity can however make up its electron defect to some extent from the sulphur atom, the system thus becoming a partially neutralised one.[4] As a result, C_2 is not attacked by electrophilic reagents but is capable of attack by nucleophilic reagents. In addition, the substituent at C_2 shows properties of one attached to a carbonyl or a carboxyl group[5]—*e.g.*, the 2-methyl group in 2-methyl-4-phenylthiazole, 2-methylthiazole, 2 : 4-dimethylthiazole react with formaldehyde, chloral or aromatic aldehyde[6, 7, 8] and is also easily oxidised[9]; the 2-halogenothiazoles are easily attacked by nucleophilic reagents[10, 11]; the 2-carboxylthiazoles are easily decarboxylated[12, 13, 14]; the 2-aminothiazoles do not form Schiff's bases, nor undergo diazotisation and Sandmeyer's reaction under ordinary conditions[15, 16] typical of the aromatic amines.

(ii) In the second group of thiazoles, the ring nitrogen acts as an electron donor (III or IV) or a relay of electrons (V) and leads to electron density (availability of π electrons) at C_5 which is thus attacked easily by electrophilic reagents. Such derivatives of thiazole stand as a contrast to those of the first group; they are very reactive and are not as stable as those of the former group; the 2-aminothiazoles gradually darken and decompose and the 2-hydroxythiazoles polymerise. In these derivatives, the atoms or groups at C_5 are activated so that they react with comparative ease with nucleophilic reagents.



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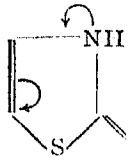

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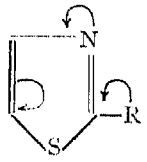

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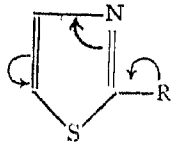

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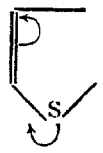
Carbon atom 4.—The carbon atom 4 is attached to nitrogen by a single bond and there is no reaction known in which we can postulate a double bond between C_4 and nitrogen. This fact casts doubt on the physical basis of the resonant structures wherein there is a double bond between C_4 and nitrogen. We find a distinct difference in properties of the atoms or groups attached to C_2 and C_4—*e.g.*, the methyl groups[6, 7, 8] and halogens[20, 21, 22] attached to C_4 are inert; the 4-carboxylthiazoles are the most resistant of the lot to undergo decarboxylation[12, 13, 17]; the 4-aminothiazoles are not at all stable,[18, 19] while the 2-aminothiazoles are comparatively the stablest of the lot.[18]

The double bond between C_4 and C_5.—The bond connecting C_4 and C_5 does not behave as an aliphatic double bond. It does not add on halogens or get easily hydrogenated. It undergoes substitution at C_4 or C_5 depending upon the activation mechanism. The chlorine or bromine atoms at C_4 and C_5 are comparatively inert[20, 21, 22] unless activated by other groups. The 5-aminothiazoles behave as typical aromatic amines[23, 24, 25] (while the 2-amino and 4-aminothiazoles do not), being diazotisable under normal conditions and capable of formation of Schiff's bases.

The double bond is attached to the two heterocyclic atoms nitrogen and sulphur, of which the sulphur functions always as the electron donor. On the other hand, nitrogen, as shown above, can function in two capacities depending upon the nature of the substituent at C_2; in either case, the effect due to sulphur is suppressed. In the isolated heteroenoid system (VI), the polarisation due to sulphur should lead to electron density at C_4. But this is counteracted by the attachment of C_4 to nitrogen. When the nitrogen functions as an electron sink, there is internal neutralisation as shown in (VII) and no substitution occurs at C_4. On the other hand, when nitrogen acts as an electron source or relay of electrons, polarisation as shown in (III), (IV) or (V) takes place leading to activation of C_5 and thus the effects due to sulphur and nitrogen cross. Since nitrogen is more anionoid than sulphur,[2] the effects due to nitrogen win out and substitution occurs at C_5 and not at C_4. We thus realise how thiazole differs from thiophene as regards substitution.



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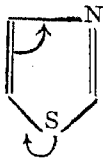

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The comparative effects at positions 2, 4 *and* 5.—Unlike the other heterocycles, the positions 2, 4 and 5 in thiazole are not alike and we should have some idea about the relative electron densities at these three positions. Calculations by quantum mechanical theories have been made in analogous cases,[25a] but we are not competent to pass remarks on these, except that these calculations have to take into account a number of factors that contribute to the electron densities in the heterocyclic system. The experimental evidence for this could be sought for in two directions: (*a*) by comparison of the physical and chemical properties of a series of isomeric thiazoles having the same substituent at the three positions, and (*b*) by substitution

reactions. The data available presented in the following table, does not furnish an unequivocal answer to this question.

The melting point of a compound is a result of a number of complex factors[28] and only in very straightforward cases could it be taken as an indication of the electron mobilities. We find that in the acetamidothiazole series, the order of increasing melting point is $2 > 4 > 5$. On the other hand, in the carboxylic acid series, it is reversed, namely, $5 > 4 > 2$ (it should be noted that the electronic effects of the acetamido and the carboxyl groups are of opposing nature). As regards the ease of decarboxylation of the thiazole carboxylic acids, the sequence is $2 > 5 > 4$ and it should be noted also that decarboxylation can take place by more than one mechanism.[29] The stability of the aminothiazoles and the reactivities of the halogenothiazoles to attack by nucleophilic reagents also point to the sequence $2 > 5 > 4$.

Comparison of the physical properties and reactivities of the isomeric thiazoles

Position of substituent	2	4	5	Order
Methylthiazole, b.p. ..	127·5–28°/ 729 mm.	133–4° 131–2°	141–2°	5>4>2
Phenylthiazole, b.p. ..	267–9°/ 732 mm.	273°	?	
m.p. ..	?	52°	45–6°	
picrate, m.p. ..	124–5°	164–5°	138–9°	4>5>2
Aminothiazole, m.p. ..	90°	?	83–4°	2>5
Acetamidothiazole, m.p. ..	203°	175–6°	159–60°	2>4>5
Thiazolecarboxylic acid, m.p. ..	102°	196–7°	218°	5>4>2
Ease of decarboxylation of the acids ..				2>5>4
Stability of the aminothiazoles ..				2>5>4
Reactivity of the halogenothiazoles ..				2>5>4
Reactivity of the Me groups ..				2>5/4
Ease of hydrolysis of acetamidothiazole ..				2>5
Substitution in nitration and sulphonation ..				5>4>2
Halogenation ..				2>5/4
Anionoid substitution (picrylchloride) ..				2>4>5

In the case of substitution reactions, the halogenation of thiazole could have given the clue. But this does not proceed on under normal conditions. Thiazole has been brominated only at high temperatures to 2-bromothiazole.[26] Since bromination at high temperature is a complex reaction,[27] unless we have information as to the nature of the radical that attacks thiazole, we cannot jump to the conclusion that the electron density is maximum at the position 2. Thiazole has been sulphonated to thiazole-5-sulphonic acid, but in this case, as would be shown later on, it is the thiazolium ion that undergoes substitution. As regards substitution by picrylchloride, it is also the ion that undergoes substitution.

On the whole, we recognise two sequences 2, 4, 5 as regards the melting points and substitution of the thiazolium ions, and 2, 5, 4 for the reactivities of the compounds. Unless more systematic work is done in this direction, we have to reserve judgment on this issue.

3. SUBSTITUTION IN THE THIAZOLES

The Japanese workers were the first to carry out systematic work on the problem of substitution in the thiazole derivatives and they have made some generalisations. But they have used only the disubstituted thiazoles, so that the entering group has no choice as regards the position of substitution. They rely on the ease of substitution for deciding the orienting influences. Schofield[30] who has dealt with substitution in the heterocyclic derivatives has not considered the thiazoles at all.

In the case of the benzene derivatives, the substitution is decided by two factors: (i) the nature of the substituent already present, whether it is electron attracting or electron releasing, and (ii) the nature of the reagent used for substitution, whether it is electrophilic (kationoid) or nucleophilic (anionoid). In the heterocyclic compounds, wherein all the atoms in the ring are not identical as in benzene, the problem becomes more complex. In addition to the influence of the substituents, the polarisation of the ring itself due to the hetero atoms has also to be taken into account and we have no quantitative method of gauging which of the effects would win out in case they are of opposing nature. Then there is the question of the part played by the reagent used for substitution. If the hetero atom of the ring is capable of quaternary salt formation with the reagent used, then the directive effect of this ion is to be taken into account, so that this necessitates the subclassification of the electrophilic or nucleophilic reagents depending whether they form salts or not with the compounds attacked.

3.1. Substitution by Electrophilic (Kationoid) Reagents

In the case of the thiazoles, the abovementioned complex situation prevails. Of the electrophilic reagents that are employed, namely, nitric acid, sulphuric acid, halogens, diazonium salts, nitrous acid, benzaldehyde, formaldehyde, etc., the first two are capable of formation of quaternary salts with the thiazole ring nitrogen (protonisation), while the others are not. This introduces an important difference in mechanism between nitration and sulphonation on the one hand from the other substitution reactions.

3.1.1. Substitution by Electrophilic Reagents—Nitration and Sulphonation

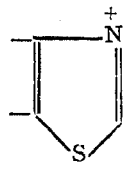
In these two cases, it is the thiazolium ion (VIII) that undergoes substitution and the one single factor that appears to govern the orientation is the positive pole, nitrogen. So, for the entering group, the first choice is that position farthest removed from nitrogen, namely C_5. Of the remaining two positions, C_4 should be more negative than C_2, since nitrogen is attached to C_2 by a double bond, which means that the position 4 would be preferred more than C_2. So, the orientation sequence for nitration and sulphonation should be $C_5 > C_4 > C_2$. This is what is observed. In the orientation of the incoming group, the influence of the positive pole dominates irrespective of the influence of the substituent in the ring and thus this resembles what is observed in the furan and thiophene compounds.[31] However, the effect of the substituent already present in the compound comes into play only as regards the speed of substitution. If the orienting effect of the group present and that of the pole lead to the same result, substitution takes place with great ease; but if they are of opposing nature, the substitution is either difficult or does not take place at all. The general principle in aromatic substitutions, that the groups that are electron acceptors slow down the substitution rate while the electron donors increase the speed, holds good here also. The above deductions are confirmed by the data available so far.

Thiazole is not nitrated even at temperature of the boiling water-bath.[20] If the nitration is carried out under more drastic conditions as in the case of pyridine,[32] we can predict the formation of 5-nitrothiazole. Thiazole has been sulphonated at 250° C. to thiazole-5-sulphonic acid. Thus thiazole resembles pyridine rather than thiophene or furan which undergo substitution very readily or are decomposed by acids[31] by violent reactions.

2-Methylthiazole (the methyl group showing a weak + I effect) undergoes nitration only with difficulty to furnish 2-methyl-5-nitrothiazole in about 4 per cent. yield.[11, 35] 2-Hydroxythiazole,[35] 2-aminothiazole,[20] and 2-acetamidothiazole[20] (wherein the substituents are strong electron donors)

undergo substitution with great ease to furnish the 5-nitro derivatives. In addition, 2-aminothiazole on sulphonation furnishes the 5-sulphonic acid derivative,[33] 2-hydroxy-4-methylthiazole,[36] 2-amino-4-methylthiazole,[20, 32] 2-acetamido-4-methylthiazole,[20] and 2:4-dimethylthiazole,[20] all undergo nitration to yield the corresponding 5-nitro derivatives and on sulphonation furnish the 5-sulphonic acid derivatives. On the other hand, 2-chlorothiazole,[20] and 2-nitrothiazole[37] do not undergo nitration or sulphonation. 2-Bromothiazole, which could not be nitrated,[20] has been sulphonated under drastic conditions to 2-bromothiazole-5-sulphonic acid.[33]

4-Methylthiazole furnishes 4-methylthiazole-5-nitrothiazole on nitration[38, 39] and 4-methylthiazole-5-sulphonic acid on sulphonation.[36] Thus it is clear that position 5 is preferred to position 2 by the entering group. 4-Phenylthiazole[40] gets substituted in the benzene ring rather than in the thiazole nucleus; this could be interpreted to mean that benzene undergoes substitution more easily than thiazole and the polarisation in this case being as shown in (IX). While 4:5-dimethylthiazole furnishes the 2-nitrothiazole derivative, 4-phenyl-5-methylthiazole also gets nitrated in the benzene nucleus.



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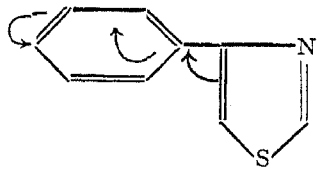


(IX)

5-Methylthiazole could be nitrated only with difficulty furnishing 4-nitro-5-methylthiazole.[11, 38] The nitration of 2-amino-5-methylthiazole has been reported a failure[38]; probably more drastic conditions are required. 2-Acetamido-5-methylthiazole, however, furnishes 2-acetamido-4-nitro-5-methylthiazole.[38] 2:5-Dimethylthiazole on nitration and sulphonation have been reported to furnish the 4-substituted product.[38] In the nitration of 2-acetamido-5-bromothiazole, instead of the nitro group entering the position 4, it replaces the bromine atom at C_5, furnishing 2-acetamido-5-nitrothiazole,[43] analogous to what happens in the thiophene series.[44] Garreau[41] has shown that bromine atom in these positions to be positive like hydrogen and hence we can anticipate the replacement by the nitro group. When a strong electron donating group (amino, acetamido, or methoxy) is present at C_5, it activates the position 4 and 2 and nitration in such cases is facile. 5-Acetamidothiazole undergoes nitration with ease to furnish 5-acetamido-4-nitrothiazole.[35, 57] 2-Benzyl-5-acetamidothiazole[24] and 2-methyl-5-ethoxythiazole get nitrated with ease to furnish the 4-nitrothiazoles.

In all the nitrations dealt with above, it should be noted that it takes place through the thiazolium ion as a result of the reagent forming a salt with the molecule attacked. On the other hand, if nitration would be effected with a reagent that does not form a salt,[44a] the mechanism should be different and we can expect differences in the orientation of the incoming group in some cases.

3.1.2. Substitution by Other Electrophilic Reagents

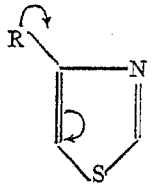
In the case of substitution by other electrophilic reagents that do not form salts with nitrogen, the orientation is decided by the influence of the substituent present, and also by the polarisation of the ring.

Thiazole, as shown before, is resistant to attack by electrophilic reagents. It cannot be halogenated at ordinary conditions. On bromination in the vapour phase, thiazole yields 2-bromothiazole and 2: 5-dibromothiazole.[26] Other reactions with thiazole have not been tried.

As far as the substitution at the position 2 is concerned, an electron donor always activates the position 5 as shown in (IV) or (V), while the electron acceptor reduces the speed of substitution or completely stops it. The halogens, while they create electron density at C_5, reduce the speed of substitution due to the inductive effect. 2-Methylthiazole undergoes bromination only with difficulty to yield 2-methyl-5-bromothiazole.[35] On the other hand, 2-aminothiazole,[33, 45, 46, 47] 2-acetamidothiazole,[48] 2-hydroxythiazole,[35] all undergo halogenations to furnish the 5-halogenothiazoles. 2-Nitrothiazole[37] and 2-chlorothiazole[15] could not be brominated. However, 2-bromothiazole, which could not be brominated under ordinary conditions, furnishes 2: 5-dibromothiazole in the vapour phase.[26] While 2-amino-5-methylthiazole[38] and 2: 5-dibromothiazole[38] do not get brominated, 2-aminothiazole, 2-amino-4-methylthiazole,[45, 50] 2: 4-dimethylthiazole[18] and 2-hydroxy-4-methylthiazole[50] all get brominated to yield the 5-bromo derivatives. This shows that the bromine atom is reluctant to enter the position 4. 2-Aminothiazole couples with diazonium salts.[16, 20, 49] Similarly, 2-hydroxythiazole[35] and 2-hydroxy-4-methylthiazole[20] couple with diazonium salts. But 2-amino-4-methylthiazole[18] and 2: 4-dimethylthiazole do not couple. 2-Hydroxythiazole[35] and 2-hydroxy-4-methylthiazole[52] react with acetic anhydride furnishing the corresponding 5-acetylthiazole derivatives. Mannich reaction (formaldehyde and dimethylamine) has been found to be successful with 2-acetamidothiazole and 2-acetamido-4-methylthiazole furnishing 5-dimethylaminomethyl derivatives[51]; on the other hand, 2: 4-dimethylthiazole gives only a trace of a product. Mercuration and thiocyanation have been reported with 2-acetamidothiazole and other derivatives to furnish

the 5-substituted products[43]; but these reactions are quite likely to be free radical substitution reactions rather than substitution by electrophilic reagents.

As regards the 4-substituted thiazoles, the data available is scanty, though compounds of this class are of great importance to decide some crucial issues. While we could expect the 4-carboxy, nitro (not known so far), and 4-bromo (not so far) thiazoles not to undergo substitution, as regards the others (acetamido-; ethoxy thiazoles), the orientation is difficult to predict, whether it would lead to the activation of the position 2 or 5, as shown in (X) and (XI). 4-Methylthiazole does not undergo bromination



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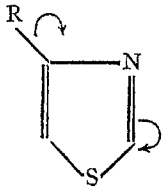
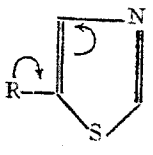


(XI)

under the usual conditions.[50] Treatment of 4-methylthiazole with benzaldehyde has been reported to lead to the 2-substituted product.[53]

Among the 5-substituted derivatives, not many cases have also been studied. It is in such derivatives that the orientation between nitration and sulphonation differ from the halogenations. Of the two positions 2 and 4 available for substitution, in nitration and sulphonation the position 4 is preferred. In the halogenations, the position 2 is chosen by the entering group. But if there is a strong electron donating group present at the position 5, there is activation of the position 4 also so that we get 2 : 4-disubstituted products, the mechanisms (XII) and (XIII) operating evidently. 5-Methylthiazole on bromination furnishes 2-bromo-5-methylthiazole.[35] On boiling 5-methylthiazole with benzaldehyde, 2-substituted product is obtained.[8, 54] 5-Acetamidothiazole on bromination furnishes, even with one molecular equivalent of bromine 2 : 4-dibromo-5-acetamidothiazole.[35, 57]



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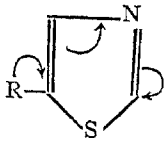

(XIII)

5-Amino-2-benzylthiazole undergoes easily diazo coupling.[24] 5-Ethoxy-2-methylthiazole gets easily brominated to furnish the 4-bromo derivative.[22]

3.2. Substitution by Nucleophilic (Anionoid) Reagents

The reagents that are in vogue as representatives of this class are: sodamide, active anions (NH^-, OH^-, CN^-, etc.). In the case of the thiazoles, picrylchloride and 2:4-dinitrochlorobenzene have been tried.

The reaction with sodamide has been reported in only one case 4-Methylthiazole yields with sodamide 2-amino-4-methyl-thiazole.[36] But it is known that sodamide adds on to the carbon nitrogen double bond as a preliminary to substitution.[55] If this be the case, the use of this reaction as a gauge of the electron density at the various positions is of limited applicability.

The reaction with picrylchloride has been well studied with a number of thiazoles.[56] In these cases, the initial product formed is reported to be a quaternary salt which subsequently undergoes substitution. So, here also, as in the case of nitration, it is the thiazolium ion that decides the orientation of the incoming group. Since the present case is a substitution by the nucleophilic reagent, the order preference for the various positions should be the reverse of that for the electrophilic reagents and hence should be $2 > 4 > 5$.

The results obtained are best interpreted on this basis. McLean and Muir[56] have treated thiazole, 2-methylthiazole, 5-methyl-thiazole, 2:4-dimethylthiazole and 2:5-dimethylthiazole with picrylchloride and have studied the products obtained. Though the actual orientations have not been studied experimentally, the results obtained could be interpreted convincingly. Thiazole gives easily a picryl derivative, as contrasted with the difficulty of nitrating and brominating thiazole. The substitution compound has been assigned the structure of 2-picryl thiazole, because all the thiazoles in which the position 2 is free undergo substitution easily. Thus, 5-methylthiazole also easily gives the picryl derivative while 2-methylthiazole gives no substitution product at all. While 2:4-dimethylthiazole did not give a substitution product, 2:5-dimethylthiazole does yield a substitution product though not as easily as thiazole or 5-methylthiazole. 4-Methylthiazole and 2:4-dimethylthiazole did not even form the quaternary salts. The above results could be explained convincingly if we assume the order $2 > 4 > 5$ for the reactivity of the nucleophilic reagents.

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