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Study of Synthesis and Biological Importance of Thiozole (Hetrocyclic Compound)

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ABSTRACT

Present study has been carried on synthesis and biological importance of hetrocyclic compounds containing thiozole have attracted world wide attention of a large number of chemists, pharmacologist & biologists on accounts of their significant therophetic and biological properties associated with them. Result of the study shown that they are used as antitubercular, amoebicidal agents, fungicides etc.

Key words: Hetrocyclic Compound, Thiozole, antimicrobial activity.

INTRODUCTION

Heterocyclic systems containing thiazole show wide range of activities. The versatility of these nuclei is demonstrated by the fact that some of these compounds exhibit antifungal, antibacterial, antihistaminic, antihyroid and antitubercular activities. The synthetic importance of thiazoles, thiadiazoles, thiadiazines and their condensed heterocyclic systems have been increased much by their recent uses as anthelmintics, antineoplastic, vulcanization accelerators and photographic sensitizers.

Broad – spectrum anthelmintic activity of dl-6-phynyl-2, 3, 5, 6-tetrahydroimidazo [2, 1-b] thiazole hydrochloride (tetramisole hydrochloride) against Ascaris lumbricoides and Enterobius vermicularis in man and against a variety of adult and immature gastro-intestinal and pulmonary nematodes in laboratory animals, poultry and livestock has been reported. Janssen and Coworkers found that the condensed thiazole systems possessed more biological activity than its cleavage products. Rudii[1] also made the similar observations. In the present investigations, the synthesis of heterocyclic systems, namely, Thiazolo[3, 2-b]-s-triazole, Thiazolo [2, 3-c]-s-triazole, s-Triazolo [3, 4-b][1, 3, 4] have been accomplished..

It was one of the primary aims of the author to study the orientation of cyclization in a situation where there was the possibility of the formation of two isomeric products during cyclization. The orientation of the cyclized product was secured by unequivocal synthesis of thiazolo [2,3-c]-s-triazole system.

Synthesis

General methods for the syntheses of Thiazoles

The synthesis of true thiazoles began with the work of Hofmann who prepared 2-chloro and 2-phenylbenzothiazoles. Hantzsch was, however, the first to report the synthesis of simple thiazole compounds in a series of papers, beginning from 1887.

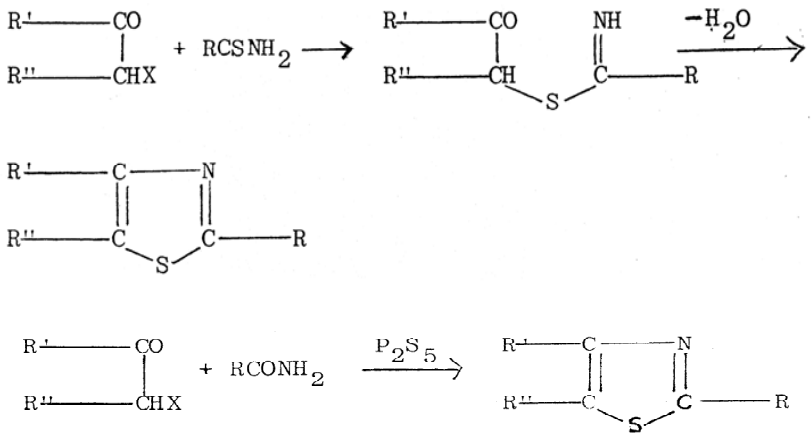
After the pioneer work of Hofmann and Hantzsch, the knowledge of thiazole chemistry developed steadily. Bogert and coworkers greatly expanded this field. Mills in 1922 realized the importance of cyanine dyes containing the thiazole ring as photographic sensitizers. Thus, the commercial importance of benzothiazoles gave impetus to the study of thiazole chemistry.

The general methods for the synthesis of thiazoles are classified on the basis of the fragments of the ring that is contributed by each reactant to build thiazole ring.

Type (i) Synthesis

In this type of synthesis, 1, 5-and 3, 4-bonds of the thiazole ring are formed.

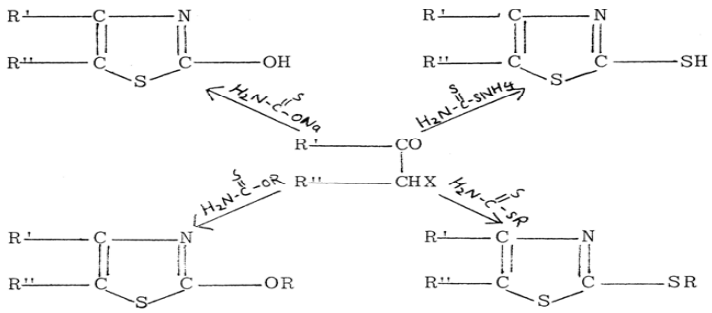
(a) The method first reported by Hantzsch and known as Hantzsch thiazole synthesis is the interaction between a-haloketones or a-halogenoaldehydes and thioamide. With proper choice of suitable reactants, thiazoles having alkyl, aryl or heterocyclic substituents attached to any of the three positions (C_2, C_4 or C_5) of the thiazole ring can be synthesised.



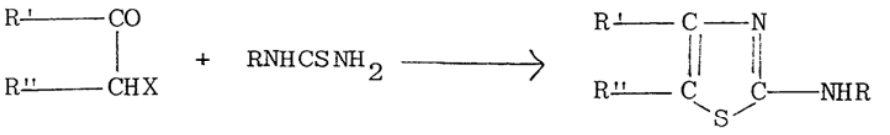
Thioamide can be substituted by amide and phosphorus pentasulphide in the synthesis of 2-alkyl-thiazoles.

Use of salts and esters of dithiocarbamic acid in place of thioamide results in the synthesis of 2-mercaptothiazole and 2-alkylmercapto thiazoles respectively, whereas the salt and o-esterof monothiocarbamic acid yield 2-hydroxythiazoles and 2-alkoxythiazoles respectively.

Another application of this method is

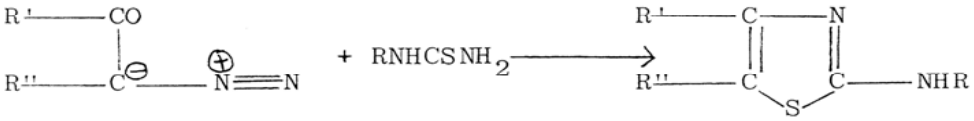


the synthesis of 2-aminothiazoles by substituting thioamides with thioureas. 2-Aminothiazoles are obtained in excellent yield even under strongly acidic medium in which many thioamides are unstable.

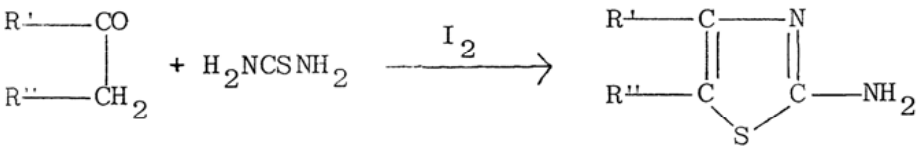


R = H, alkyl or aryl

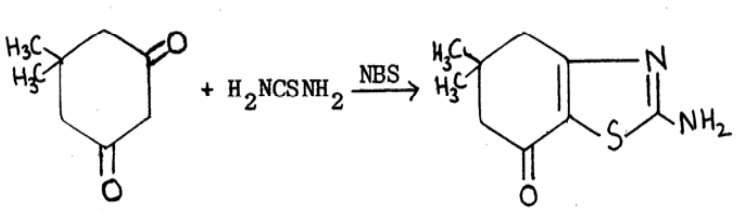
King and Miller obtained 2-substituted aminothiazoles by using diazoketones in place of α-haloketones in the above reaction.



King made an important modification in the synthesis of 2-aminothiazoles by treating a ketone (R' $COCH_2R$") with thiourea in presence of an oxidant, usually iodine. The halogen can be replaced bythionylchloride, sulphur trioxide, sulphuryl chloride, sulphuric acid, chlorosulphuric acid and nitric acids. a-Haloketone does not seem to be an intermediate since reagents such as SO_3, H_2SO_4 and HNO_3 also produce aminothiazoles although in low yield.



Pujari and Jag Mohan made further modification of this method by using N-bromosuccinimide in place of halogen in the synthesis of 2-aminobenzothiazole.

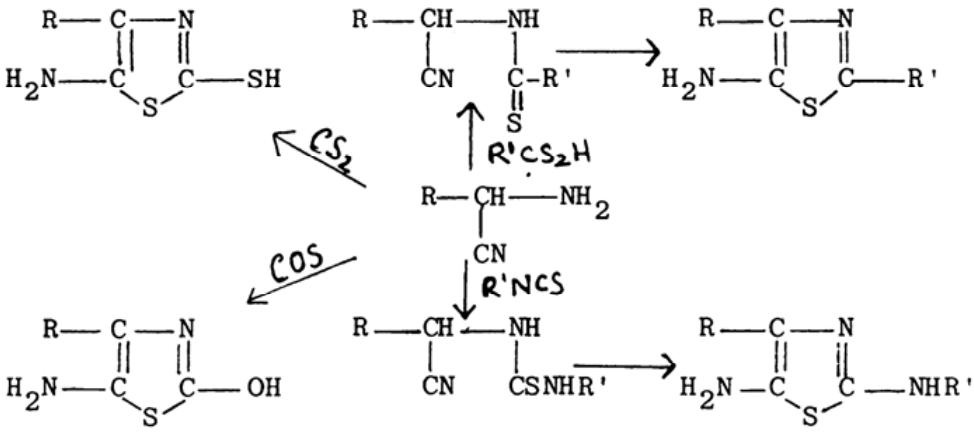


Type (ii) synthesis

This type of synthesis involves the formation of 1, 5-and 2,3-bonds of the thiazole ring and includes the preparation of (a) 5-Amino-thiazoles (b) 5-Hydroxythiazoles and (c) Thiazolines.

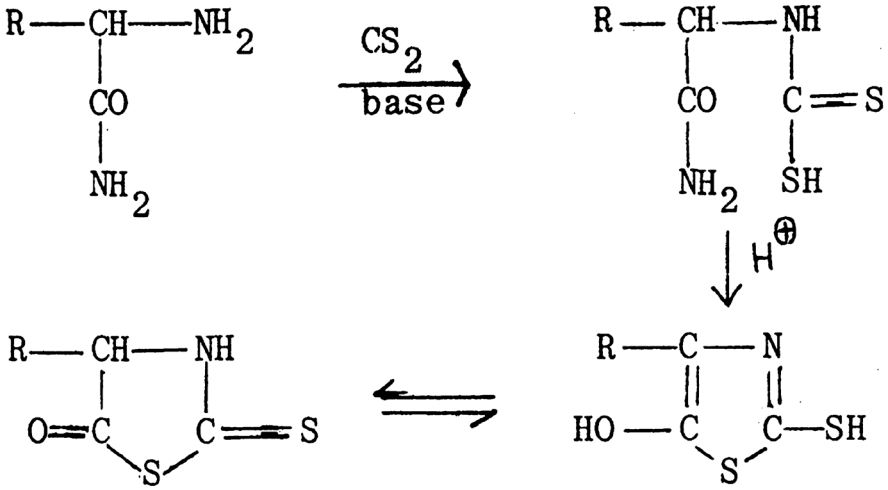
(a) The reaction of a-aminonitriles with dithioformic acid (salt or ester), carbon disulphide, carbon oxysulphide and isothiocyanates yields 2-alkyl-5- aminothiazoles, 2-mercapto-5-aminothiazoles, 2-hydroxy-5-aminothiazoles and 2-substituted amino-5-aminothiazoles respectively.

The reaction of α-aminoamides with carbon



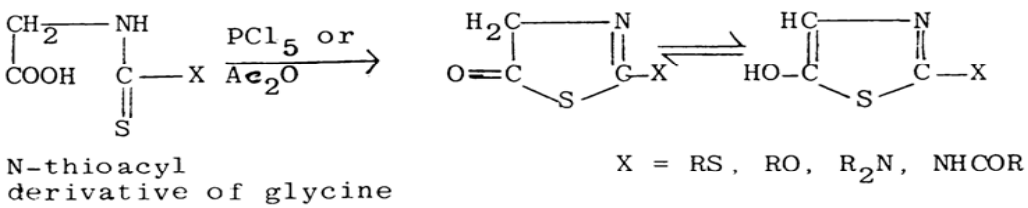
disulphide in presence of a base gives the salt of dithiocarbamic acid, which when treated with acid, undergoes cyclization to give 2-mercapto-5-hydroxy-thiazole (2-mercapto-5-thiazolidone).

5-Hydroxythiazoles are obtained by the cyclization of N-thioacyl derivatives of glycine with PCl_5 or Ac_2O.



EXPERIMENTAL

All melting points are uncorrected. Thin layer chromatography (tlc) was performed on BDH silica-gel (G) plates using acetone-benzene (1 : 3) as solvent system IR and PMR spectra were recorded on the Beckman IR-20 and Perikin-Elmer 90MHz instruments respectively. [n max in cm^{-1} and chemical



shifts in d (ppm) downfield from TMS].

3- a-Naphthyl-5-mercapto-s-triazole (II)

1- a-Naphthoyl-3-thiosemicarbazide (I, 8.2 g, 0.033 mole) in 8% sodium hydroxide solution (100 ml) was refluxed for about 3hr. The reaction mixture was cooled to the room temperature and acidified with dilute acetic acid. The product separated was filtered, washed with water and crystallised from ethanol as colourless shining needles, yield 4.3 g (57%), m.p. 264^0 [Found : N, 18.96; S, 14.58. $C_{12}Hm_9N_3S$ requires N, 18.50; S, 14.19%] ; IR : 755, 780, 1590, 1610, 2580, 3060.

3- a-Naphthyl-5-p-nitrobenzoylmethylmercapto-s-triazole (IIIa, R=p-O_2N-C_6H_4-)

A mixture of II (2.27 g, 0.01 mole) and p-nitrophenacyl bromide (2.44g, 0.01 mole) in anhydrous ethanol (200ml) and DMF (10 ml) was heated under reflux for 5 hr. Cooled to the room temperature and neutralised with aqueous potassium carbonate solution. The yellow solid separated was filtered, washed with water and crystallised from ethanol as light yellow needles, m.p.2120, yield =2.09 (52%) [Found : S, 8.62. $C_{20}H_{14}N_4O_3S$ requires S, 8.21%]; IR : 765, 790, 840, 1350, 1535, 1570, 1610, 1690, 3150, 3400.

Similarly, the following compounds were prepared IIIb (R=p-Cl-C_6H_4-) : m.p. 150^0, yield 63% [Found : S, 9.12. $C_{20}H_{14}N_3OSCl$ requires S, 8.43%] ; IR : 715, 770, 800, 830, 1575, 1620, 1695, 3450.
IIIc (R = p-Br-C_6H_4-) : m.p. 185^0, yield 66% [Found : S, 7.08. $C_{20}H_{14}N_3OSBr$ requires S, 7.55%]; IR : 720, 780, 800, 535, 1535, 1680, 3220.

2- a-Naphthyl-5-p-nitrophenylthiazolo [3,2-b]-s-triazole (IVa, R=p-O_2N-C_6H_4-)

A mixture of IIIa (1.0 g), P_2O_5 (4g) and H_3PO_4 (3 ml) was heated on an oil-bath at 150^0 for about 3hr. The reaction mixture was cooled, poured into water and neutralized with aqueous potassium carbonate solution. The solid thus obtained was filtered, washed with water and crystallized from DMF-ethanol mixture as greenish yellow granules, m.p. 198^0, yield 0.43 g (35%) [Found : C, 64.81; H, 3.44; s, 8.80. $C_{20}H_{12}N_4O_2S$ requires C, 64.52; H, 3.23; S,8.60%] ; IR : 765, 790, 840, 1500, 1540, 1590, 3100, 3125; PMR (TFA): 7.45 (1H, s, C6-H), 7.57 [1H, dd, C_2, –H, $J_{2',3'}$ = 7.2 Hz (ortho-coupling), $J_{2',4'}$ = 2.7 Hz (meta-coupling)], 7.80-8.02 [4H, m, $C_{3'}$–H, $C_{6'}$–H and $C_{7'}$–H], 8.17 [1H, dd, $C_{5'}$-H, $J_{5',6'}$ 7.2 Hz (ortho-coupling), $J_{5',7'}$ 2.7 Hz (meta-coupling)], 8.43 (4H, q, J=9 Hz, p- nitrophenyl protons), 8.98 [1H, dd, $C_{8'}$–H, $J_{7',8'}$=7.2.Hz (ortho-coupling), $J_{6',8'}$ = 2.7 Hz (meta-coupling)].

Other compounds prepared similarly were : IVb (R = p-C1-C_6H_4–) : Yield 63%, m.p. 150^0 [Found: c, 66.60; H, 3.46; N, 12.02; S, 9.10. $C_{20}H_{12}N_3SCl$ requires C, 66.39; H, 3.32; N, 11.62, S, 8.85%]; IR : 760, 780, 800, 825, 1640, 3100.

IVc (R = p-Br-C_6H_4-) : Yield 52%, m.p. 166^0 [Found : C, 58.85. H, 3.10; N, 9.86; S, 8.32. $C_{20}H_{12}N_3SBr$ requires C, 59.11; H, 2.96; N, 10.34; S, 7.88%]; IR : 730, 770, 800, 830, 1640, 3120.
3-a-Naphthyl-5-p-nitrophenylthiazolo [2, 3-c]-s-triazole (Via, R=p-O_2N–C_6H_4–)

A mixture of Va (1 g)and $POCl_3$ was heated on an oil-bath (120-130^0)for 3hr. The reaction mixture was cooled, poured into water and neutralized with aqueous potassium carbonate solution. The solid thus obtained was filtered, washed with water and crystallized from ethanol mixture as yellow crystals, m.p. 233^0, yield 0.43 g (42%) [Found : C, 64.24; H, 3.42; s, 7.89. $C_{20}H_{12}N_4O_2S$ requires C, 64.52; H, 3.23; S,8.60%] ; IR : 725, 780, 820, 1625; PMR (TFA): 7.76 (1H, s, C_6-H), 7.90 [1H, dd, C_2, –H), 8.02-8.52 [9H, m, $C_{3'}$ –H, $C_{4'}$–H, $C_{6'}$–H, $C_{7'}$–H, $C_{5'}$–H and p-nitrophenyl protons), 8.72 [1H, dd, $C_{8'}$–H)

Other compounds prepared similarly were : VIb (R = p-C1-C_6H_4–) : Yield 64%, m.p. 166^0 [Found: C, 66.72; H, 3.61; N, 12.00; S, 9.47. $C_{20}H_{12}N_3SCl$ requires C, 66.39; H, 3.32; N, 11.72, S, 8.85%]; IR : 735, 775, 810, 1625.

IVc (R = p-Br-C_6H_4-) : Yield 35%, m.p. 186^0 [Found : C, 58.85. H, 3.39; N, 9.87; S, 8.24. $C_{20}H_{12}N_3SBr$ requires C, 59.11; H, 2.96; N, 10.34; S, 7.88%]; IR : 725, 770, 840, 830, 1620.

Evaluation of useful biological importance
Relative merits of the compounds as anti-bacterials.

The compounds, (R = p-Br-C_6H_4–), (Ar = p-Br-C_6H_4–),and (R = p-Cl-C_6H_4–) pertaining to the following systems have been evaluated for their anti-

bacterial activity. The results of antibacterial screening and the conclusions derived from them regarding the relationship between anti-bacterial activity and the structural changes are summarized.

1. Thiazolo [3, 2-b]-s-triazole
2. Thiazolo [3, 2-c]-s-triazole

The most widely used method for determining the anti-bacterial activity of drugs consists of cultivating the bacteria in a test tube or nutrient agar plate to which the drug has been added. Factors which influence the results of any test method include (i) species of test organism (ii) composition and pH of the medium (iii) inoculum of organism (iv) diluting fluid (v) concentration and stability of the drug solution and (vi) temperature and duration of incubation.

For studying the anti-bacterial properties, many methods are available but Kirby-Barr disc diffusion and plate dilution methods as reported by Nakahara *et al.*, has been used in the present investigations.

The test organism was a two-hour culture of Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa incubated and grown in peptonewater medium at37^{0}.

Anti-bacterial testing

(Experimental results and conclusions derived therefrom)

Incubation period	-	18 hr.
Temperature	-	37^{0}C
M.I.C.	-	Minimum inhibitory concentration.
E.coli.		-
Escherichia coli		
S.aureus		- *Staphylococcus*
aureus (NCTC 6571)		
Ps. aeruginosa	-	*Pseudomonas aeruginosa* (NCTC 10662)

Relative merits of the compounds as antifungals

Method used

The compounds which were tested for anti-bacterial activity have also been studied for their antifungal action by bio-assay. Kirby-Barr disc diffusion and plate dilution methods as reported by Nakhara et al.[163] has been used by the author in the present investigations.

Bio-assay aims at determining the fungistatic or fungicidal efficiency of a compound to figures of performance that can be compared with similar data obtained from other fungistatics of fungicides. It is useful in the evaluation of fungicides since chemistry of the process by which the fungicides function is not yet thoroughly studied. Candida albicans is a most common human pathogen. Therefore, it was used as a fungus strain..

Table 1.

S. No.	Name	MIC (µg/ml)		
		E.coli	*S.aureus*	*Ps. aerugi*
1.	2-α-Naphthyl-5-p-bromophenylthizaolo [3,2-b]-s-triazole	-	neat	-
2.	3-α-Naphthyl-5-p-bromophenylthizaolo [2,3-c]-s-triazole	-	neat	-

Table 2:

S. No.	Name	MIC	(µg/ml)	
			Candida	albical
1.	2-α-Naphthyl-5-p-bromophenylthizaolo [3,2-b]-s-triazole	-	-	-
2.	3-α-Naphthyl-5-p-bromophenylthizaolo [2,3-c]-s-triazole	-	-	-

CONCLUSION

Comparison of the antibacterial and antifungal activity of the compounds reveals that the two isomeric systems namely thiazolo (3,2-b]-s-triazole and thiazolo [2, 3-c]-s-triazole posses the same activity. The compounds were found active against S.aureus / C.albicans., when tested as neat samples and may be used for local application in the form of powder of ointment provided further studies indicate absence of toxicity following local application. In the present investigation, the author has synthesised various types of heterocyclic compounds containing a thiazole, has been achieved.

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