SYNTHESIS AND STUDY OF HETEROCYCLIC COMPOUNDS AS POSSIBLE ANTITUBERCULAR AGENTS

THESIS SUBMITTED FOR THE DEGREE OF
MASTER OF PHARMACY
IN
PHARMACEUTICAL CHEMISTRY

SUBMITTED BY
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UNDER THE GUIDANCE OF
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359

1988

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A

THESIS

Submitted to

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For

The Degree of

MASTER OF PHARMACY

In

The Faculty of Technology

(PHARMACEUTICAL CHEMISTRY)

By

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(1988)

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..... SUBHASH PATIL

Statement under University Rule

As required by the University Rule No. 0.412 and 0.413, I state that the work presented in this thesis is original in nature and so far to the best of my knowledge has not been submitted for any degree to this or any other University.

Wherever reference has been made to the work of others, it has been clearly indicated alongwith the source of the information in the "References".

(S.M. PATIL)

Signature of the Candidate

Forwarded through the Research Guide.

(DR. B.G. KHADSE)

Signature of the Research Guide

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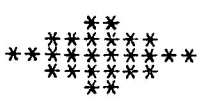


Part..... I

I N T R O D U C T I O N

INTRODUCTION

Tuberculosis is a systemic disease, the commonest form in man, being the chronic pulmonary variety, It can also involve other organs. In our country where the percentage of educated and economically well-to-do people is so low, tuberculosis is going to be a major problem.

Recent estimate by WHO indicates that about 8-10 million cases of tuberculosis are prevalent, of which 70 to 80 per cent are in developing countries. WHO estimates that about 2 to 3 million new cases occur every year and 3 million cases die every year.[1] Recent survey in India has detected 10 million active cases of tuberculosis, of which 2.5 million were infectious.[2]

Worldwide there are millions of new cases with deaths also in the millions per year. With the vast reservoir of infected individuals and the development of active disease among this group, tuberculosis will continue to be a major problem.

Approach to chemotherapy is satisfying but has no notable success in developing antimycobacterial agents. There are many effective chemotherapeutic drugs to treat the tuberculosis patients. The desired effect of streptomycin was quickly recognized and rapidly utilised.

The widespread effectiveness of Isoniazid led to its rapid use in the therapy. Inspite of good progress, the problem remains today because of the complex nature of tuberculosis infection. Combination drug therapy is of proven value in the treatment of tuberculosis but what and how to combine for optimum effect is not resolved.

Antibiotics like penicillin, auromycin, terramycin and chloramphenicol as well as the most active 'sulpha' drugs have not shown any significant activity against tuberculosis. From a detailed tuberculosis review, it is found that, tuberculosis is almost unique among bacterial diseases.

None of the present antitubercular drugs have shown satisfactory therapeutic results because of limitations such as -

1) Weak activity;
2) Development of resistance;
3) Mode of drug action;
4) Persistance of Tubercle bacilli in tissues in lesions for long period of time.[3]

Hence, there is constant need for newer and better eradicative drugs which will be more effective and less toxic than those available at present.

CLASSIFICATION OF PARASITES :

Mycobacterium tuberculosis was isolated by Robert Koch in 1882 as the principle cause of tuberculosis in human beings. It is a member of the family *Mycobacteriaceae*, order *Actinomycetales*. The genus Mycobacterium includes both saprophytic and pathogenic species. The saprophytic mycobacteria are widely distributed in nature, in soil, in water, on grain and grass, in butter and upon the skin of man and other animals. The pathogenic species may produce disease in a variety of mammals, birds, reptiles, fish and other cold blooded animals.

M. bovis, is the principle cause of tuberculosis in cattle and *M. avium*, is the cause of tuberculosis of fowl, which rarely cause clinical disease in man.

MORPHOLOGY AND STAINING :

M. tuberculosis is a slender rod type organism which may vary from 0.2 to 0.5 μ in width and from 2 to 6 μ in length. It may be straight but more frequently appears slightly curved. The rods are non-motile, non-sporogenous and non-encapsulated.

All the members of the family Mycobacteriaceae after staining resist decolorization with mineral acids and, therefore, are referred as "acid-fast". Acid fastness apparently depends upon the integrity of the cell wall and/or the cytoplasmic membrane rather than upon the staining of a specific substance within the cell.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Tuberculosis is an infectious disease, caused by several species of mycobacteria, collectively termed as tubercle bacilli. The important human pathogens of this class are *M. tuberculosis* and *M. bovis*. Drug therapy has now revolutionized the treatment of tuberculosis and forms the most important aspect of its management. Chemotherapy is the keystone of the management of all forms of tuberculosis in man.

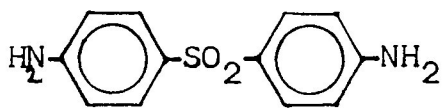
Available antitubercular drugs have been divided into synthetic products, and antibiotics and within these two categories they are listed with products having structural similarities grouped with the representative first introduced into the therapy.

SYNTHETIC PRODUCTS :

(1) Sulfones :

The sulfones were synthesized because of their analogy with the sulfonamides. The discovery of these agents marked the beginning of the chemotherapeutic era by making possible a direct attack on microbial infections. The first sulfone derivative synthesised was

4,4'-diamino diphenyl sulfone (I) (dapsone) and its glucose bisulfite derivative, glucosulfone sodium showed activity in suppressing experimental tuberculosis infections.[4,5]

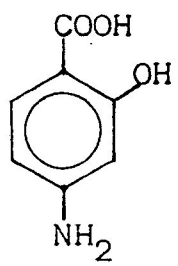


(I)

Though slightly more active than sulfonamides in experimental tuberculosis, sulfones have proved ineffective in clinical tuberculosis even when used in combination with isoniazid or PAS.

(2) <u>p-Amino salicylic acid</u> :

It was observed that, benzoates and salicylates stimulated the respiration of virulent but not avirulent mycobacteria.[6] It was suggested that, these compounds might be involved in the oxidative metabolism of the bacilli. Then Lehmann[7] tested a large series of compounds structurally similar to benzoic acid for their antituberculous activity. The most effective among these was p-aminosalicylic acid (II).



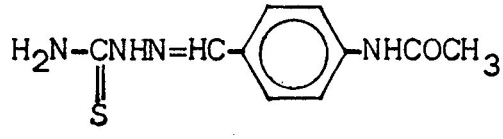
(II)

Activity :- PAS has shown *in vitro* bacteriostatic activity and also active orally in animals in experimental infections.[8,9] PAS is specifically active against mycobacteria and against only certain species in this genus.[10] It is equally effective against streptomycin-resistant strains.

Mechanism of Action :- It was demonstrated that *p*-aminobenzoic acid antagonizes the antibacterial activity of PAS *in vitro* and *in vivo*. This property can probably be explained by the finding that PAS is taken up into cells by an active process, possibly by the route used for assimilation of PABA. The formation of mycobactin, an ionophore for iron transport, is strongly inhibited by PAS and the bacteriostatic activity of PAS might be due to the inhibition of iron uptake.[11-13]

(3) Thioacetazone :

The synthesis of a series of thiosemicarbazones as intermediates in the preparation of sulfathiadiazoles[14,15] which has weak antitubercular activity, led to the discovery of the thiosemicarbazone of *p*-acetamido benzaldehyde (thioacetazone, amithiozone) (III) the most active compound of the series.[16-18]



(III)

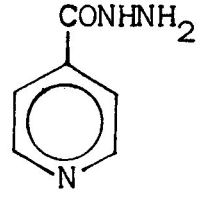
Thioacetazone

The mechanism of action of thioacetazone is unknown. It is counteracted by p-aminobenzoic acid.[19]

(4) Isonicotinic acid hydrazide (INH) :

In 1945, Chorine [20] reported that nicotinamide possesses tuberculostatic action. Examination of the compounds related to nicotinamide revealed that many pyridine derivatives possess tuberculostatic activity; among these are congeners of isonicotinic acid. Because the thiosemicarbazones were known to inhibit M.tuberculosis, the thiosemicarbazone of isonicotinaldehyde was synthesized and studied. The starting material for this synthesis was the methyl ester of isonicotinic acid and the first intermediate was isonicotinylhydrazide (INH) (IV).

This isoniazid was tested and proved to be a very potent antitubercular agent in vitro and in vivo.[21,22]



(IV)

It acts on growing cells and not on resting cells and is effective against intracellular bacilli also. Its effect on the atypical mycobacteria is marginal or non-existant.

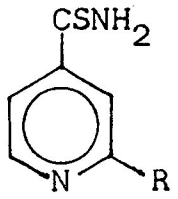
Isoniazide is one of the most effective anti-tuberculous drugs but, when it is administered alone, resistance is developed. Therefore, it is administered with other antituberculous drugs, which delay the emergence of resistant tubercle bacilli.

While the mechanism of action of isoniazide is unknown there are several hypotheses. These include effect on lipids, nucleic acid biosynthesis and glycolysis.[23] Takayama and associates[24] have suggested a primary action of isoniazide to inhibit the biosynthesis of mycolic acid, important constituent of the mycobacterial cell wall. This drug can also act by chelating heavy metal ions, especially, copper which are essential for *M. tuberculosis*.

(5) Ethionamide :

Thioisonicotinamide[25-27] had a good antitubercular activity *in vivo*. Since then, it was thought that some metabolic product of the drug was responsible for the activity *in vivo* and this led to the synthesis and testing

of a series of potential thioisonicotinamide metabolites and various other derivatives. Among these, 2-ethylthio-isonicotinamide or ethionamide (V) was selected for clinical use.



(V)

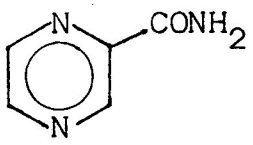
Where, R = H = Thioisonicotinamide

R = $-C_2H_5$ = Ethionamide.

Ethionamide is very effective in the treatment of experimental tuberculosis in animals. It is bactericidal and causes loss of acid fastness by inhibition of mycolic acid synthesis.

(6) <u>Pyrazinamide</u> :

Pyrazinamide (VI) is the synthetic pyrazine analog of nicotinamide.

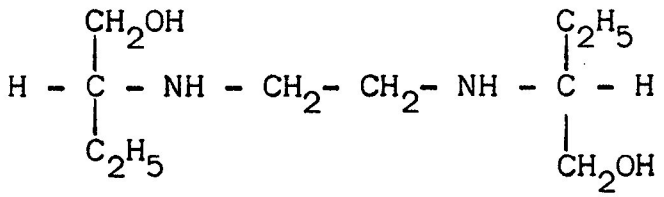


(VI)

Pyrazinamide exhibits bactericidal activity *in vitro* only at a slightly acidic pH. Tubercle bacilli within monocytes *in vitro* are killed by the drug at a concentration of 12.5 µg/ml. Resistance develops rapidly if pyrazinamide is used alone.

(7) Ethambutol :

Thomas and co-workers[28] found that N,N'-diisopropylethylene diamine was effective in the treatment of experimental tuberculosis in mice. A number of congeners of this compound were examined. Out of this (+) N,N'-bis-(1-hydroxy-2-butyl) ethylenediamine dihydrochloride (Ethambutol) (VII) proved to be the most tuberculostatic.



(VII)

Activity :- It is effective against mycobacteria resistant to INH, PAS, streptomycin and ethionamide as well as against many atypical mycobacteria. Ethambutol is a bacteriostatic drug and its main use is as a substitute for PAS in combination with the bacterial drugs.

Mechanism of Action :- It is suggested that, ethambutol interferes with a function of cellular polyamines and divalent cations involved in the synthesis or stabilization of RNA possibly forming a chelate.

ANTIBIOTICS :

1) Streptomycin :

A potent antimicrobial substance, streptomycin was first isolated from the culture of *Streptomyces griseus* by Schatz, Bugie and Waksman early in 1944, and it was soon shown to inhibit the growth of the tubercle bacillus and a number of gram-positive and gram-negative micro-organisms *in vitro* and *in vivo*.[29] The chemical structure of streptomycin is N-Methyl-1-glucosanimide streptosidostreptidine.

Streptomycin specifically inhibits initiation of protein synthesis.[30] Streptomycin penetrates into the cell body, combines with 30-S ribosomal particles and thus alters the function of the ribosome after the m-RNA is attached. These effects probably contribute to the bactericidal action.

2) Viomycin, Kanamycin and Capreomycin :

Viomycin is a basic peptide antibiotic. It was discovered independently by two groups of investigators[31,32]

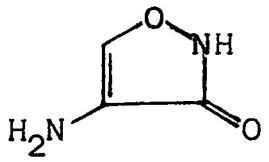
from actinomycete named Streptomyces griseus by one group and Streptomyces floridae by the other. It is effective against streptomycin resistant strains and shows cross resistance with neomycin.

Kanamycin, an antibiotic produced by Streptomyces kanamyceticus was first produced by Umezawa and co-workers in 1957.[33] The molecule contains deoxystreptamine and two amino sugars, kanosamine and 6-glucosamine. Its activity against M. tuberculosis is weaker than that of streptomycin.[34]

Capreomycin is an antimicrobacterial cyclic peptide isolated from Streptomyces capreolus. It contains four peptide components. Bacterial resistance develops when it is given alone.

3) Cycloserine :

Cycloserine (VIII) is produced by Streptomyces orchidaceus. It is D-4-amino-3-isoxazolidone.

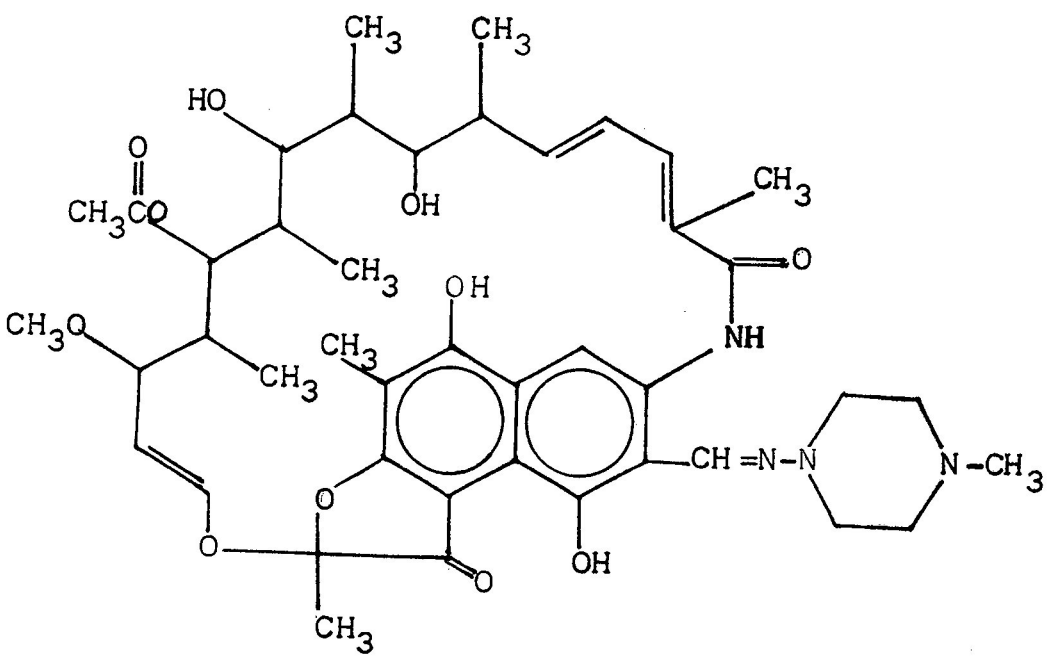


(VIII)

The drug is stable in alkaline solution but is rapidly destroyed when exposed to neutral or acidic pH. It inhibits the enzyme which is responsible for the synthesis of dipeptide. As a result of this, the cell wall becomes defective and the cell lyse.

4) Rifampicin :

The rifamycins are a group of structurally similar, complex macrocyclic antibiotics produced by *Streptomyces mediterranei*. Rifampin (IX) is a semisynthetic derivative of one of these rifamycin B.



(IX)

Mechanism of Action :- Rifampin inhibits DNA dependant RNA polymerase of mycobacteria and other micro-organisms leading to suppression of initiation of chain formation in RNA synthesis. Rifampin is bactericidal for both intracellular and extracellular microorganisms.[35]

Rifampin is now largely used for the treatment of human tuberculosis both for the newly diagnosised patients and for patients whose primary chemotherapy has failed. It is administered in combination with other antitubercular drugs mainly isoniazide.

TABLE-1 : Summary of antitubercular drugs.

Drug	Administration	Toxic effects	Resistance, cross resistance
1) Isoniazide (INH)	Oral : well absorbed	Liver dysfunction, peripheral neuritis	Resistance develops slowly cross resistance to amino salicylates and streptomycin.
2) Ethambutol (EMB)	Oral : well absorbed	Retrobulbar neuritis with visual disturbances; allergic rashes, gastrointestinal tract disturbances.	Resistance develops slowly, but no cross resistance reported
3) Rifampin (REM)	Oral : well absorbed	Hepatic dysfunction; thrombocytopenia	No cross resistance
4) Streptomycin(STM)	Intramuscular : well absorbed	Vestibular auditory dysfunction of 8th nerve; renal dysfunction; skin rashes, neuromuscular blockade.	Resistance develops slowly.
5) Kanamycin (KM)	Intramuscular	Auditory dysfunction primarily; vestibular auditory dysfunction of 8th nerve; skin rashes, renal dysfunction, neuromuscular blockade.	--

(Table-1.....Contd.)

Drug	Administration	Toxic effects	Resistance, cross resistance
6) Viomycin (VM)	Intramuscular	Cranial nerve (VIII), renal damage.	--
7) Capreomycin (CPM)	Intramuscular	Cranial nerve (VIII) renal dysfunction.	--
8) p-Amino salicylic Acid (PAS)	Oral : well absorbed	Nausea, vomitting, diarrhoea, gastro-intestinal tract disturbances.	Resistance develops slowly; cross resistance to rifampicin
9) Cycloserine (CS)	Oral	CNS toxicity (psychosis and convulsions), headache, fever skin rashes.	--
10) Pyrazinamide (PZA)	Oral : peak serum concentration in 2 hr.	Hepatotoxicity; anorexia, nausea; fever and skin rashes.	Resistance develops in 6-7 weeks.
11) Ethionamide (ETA)	Oral : well absorbed	Gastrointestinal disturbances; allergic reactions; hypoglycaemia, psychoses in alcoholics.	Resistance develops; cross resistance to prothionamide and thiacetazone.
12) Thiacetazone	Oral : slow	Gastrointestinal disturbances; visual disturbances; blood dyscrasias, anaemia, hepatic dysfunctions.	Resistance develops; cross resistance to ethionamide and prothionamide.

PLAN OF WORK

PLAN OF WORK

Tuberculosis is one of the major communicable disease responsible for morbidity and mortality especially in developing countries.

It is described in the literature that tuberculosis is as "one of the most wide spread of human ills, the most chronic and persistant of infections, with largest period of infectivity of any disease".[36]

Organic molecules like PAS, INH, ethambutol and streptomycin are the drugs so far in the hands of physician. Because of limitations such as weak activity, development of resistance, mode of action and also due to the persistance of tubercle bacilli in the tissue in lesions for long period of time none of these above drugs has shown complete satisfactory therapeutic results.

Hence, there is constant need for newer and better eradicative drugs which will be more effective and less toxic than those available at present.

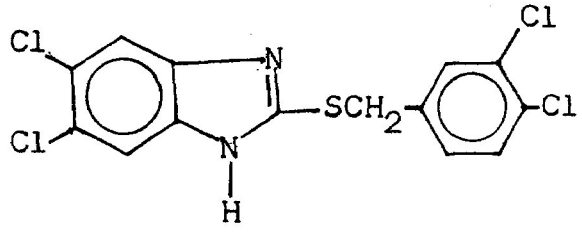
With the above view, it was planned to synthesize different types of organic compounds as explained in the different parts included in plan of work.

PART - II

5-(N-Methylpiperazino/morpholino)-6-chloro-2-substituted benzyl/heteroaryl thiobenzimidazoles :

A number of 2-thiobenzimidazole derivatives have demonstrated a broad spectrum of significant biological activity, i.e. plant growth inhibition,[37,38] bactericidal,[39] fungicidal,[39] and virucidal,[39] activities.

Also our laboratory reported number of benzimidazole derivatives of good antitubercular activities. Out of these 5,6-dichloro-2-(3,4-dichlorobenzyl) thiobenzimidazole (I) showed antitubercular activity at the concentration of 3.12 μg/ml.[40]



(I)

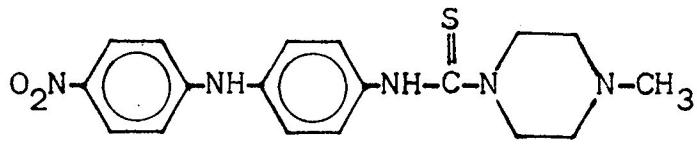
Hence, it was proposed to prepare substituted benzimidazole derivatives with the view of getting more active compounds against $H_{37}Rv$ strain of *M. tuberculosis*.

The compounds prepared in this Part are described under Section A and B.

SECTION-A

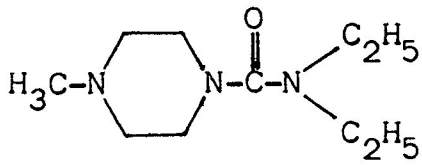
Synthesis of 5-(N-methyl piperazino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

Substituted N-methyl piperazine of the following type compound (II) is an experimental antifilarial drug currently being evaluated in man.[41]



(II)

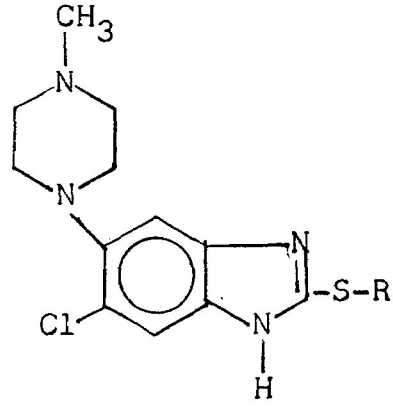
Diethyl carbamazine (III), a derivative of N-methyl piperazine is the drug of choice in the treatment of micro-filarial infection.[42]



(III)

Also literature survey revealed that substitution of N-methyl piperazine enhances the antimicrobial activity of the parent moiety.[43]

It was therefore decided to combine these two unique moieties of thiobenzimidazole and N-methyl piperazine to form the following (IV) type of compounds.



(IV)

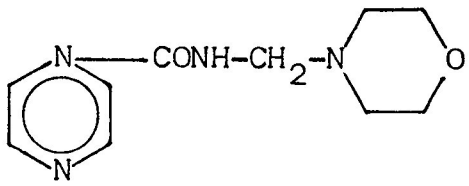
Where, R = Substituted benzyl, 7-chloro-4-quinolinyl.

These could be prepared by condensing sodium salt of 2-mercapto-5-N-methyl-piperazino-6-chloro benzimidazole with different benzyl bromides in ethanol at reflux temperature.

SECTION-B

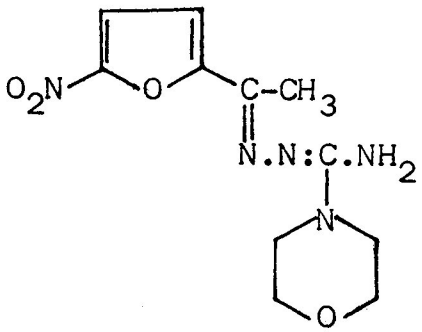
Synthesis of 5-(morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

Felder and his co-workers[44] reported an antitubercular agent, Morphozinamide (V) which was found less toxic but equally effective as compared with pyrazinamide.



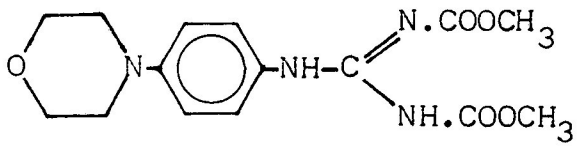
(V)

Morpholine substituted semicarbazone (VI) from our laboratory showed activity at the concentration of 0.4 µg/ml which is comparable with Na.PAS presently available standard drug.



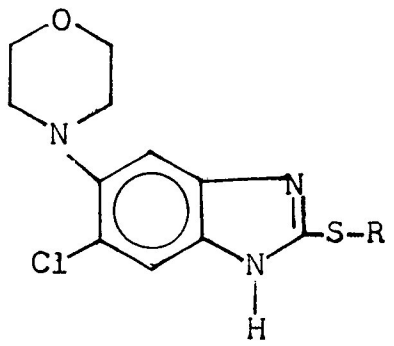
(VI)

The compound (VII) noted below from our laboratory exhibited excellent antitubercular activity at the concentration of 0.02 µg/ml *in vitro* against $H_{37}Rv$ strain of *M. tuberculosis*.



(VII)

Taking into account the antitubercular activities shown by morpholino substituted derivatives, the synthesis and study of new type (VIII) of morpholino substituted thiobenzimidazoles was planned.



(VIII)

Where, R = substituted benzyl, 7-chloro-4-quinolinyl.

PART - III

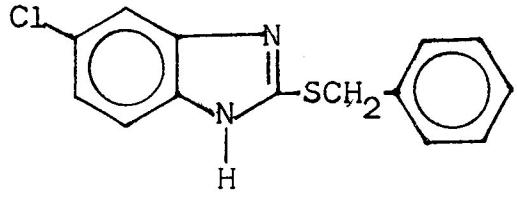
Synthesis of 5-(propylthio/benzylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

In literature, different thio substituted benzimidazole derivatives have demonstrated significant biological activities.[45,46] So in this part it was proposed to undertake the synthesis and biological study of benzimidazole derivatives having propyl and benzylthio linkages at 5-position of the benzimidazole moiety.

SECTION-A

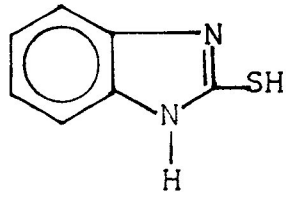
Synthesis of 5-(n-propylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

During the literature survey it was found that, 2-mercapto benzimidazole derivative, namely, 5(6)-chloro-2-(benzylthio) benzimidazole (IX) possesses antifungal activity against *Trichophyton interdigitate*, at a dilution 1:290, 900 or 3.4 µg/ml.[47]



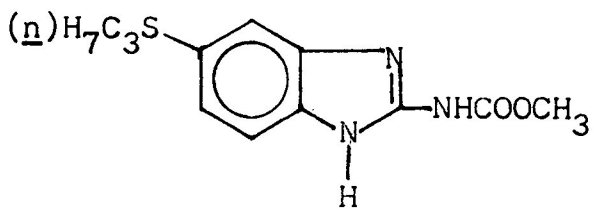
(XI)

Similarly, bacteriostatic activity was also reported for 2-mercapto-benzimidazole (X) against *S. aureus*.[48]



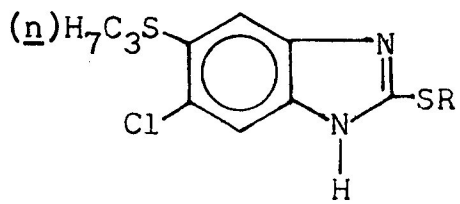
(X)

Encouraging results were presented by a research group of S.K. and F. Laboratories, who demonstrated that substitution of the benzimidazole nucleus in the 5-position by propylthio group as in Albendazole (XI)[49] resulted in the formation of very good anthelmentic drug.



(XI)

All these stresses the importance of the sulfide linkage attached to the benzimidazole nucleus. Hence, synthesis of a series of compounds of the following (XII) type was planned.



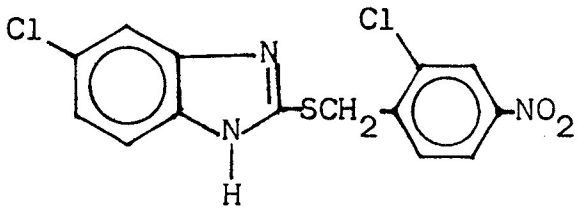
(XII)

Where, R = Substituted benzyl, 7-chloro-4-quinolinyl.

SECTION-B

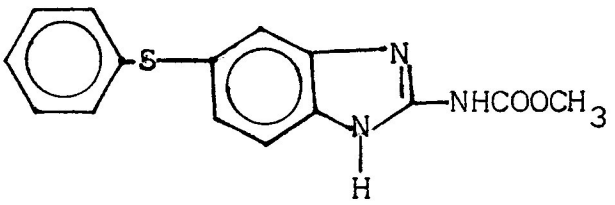
Synthesis of 5-(benzylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

Khairnar *et al.*[50] reported 5(6)-chloro-2-(2-chloro-4-nitrobenzyl) thiobenzimidazole (XIII) which showed anti-tuberculosis activity at 1.56 μg/ml concentration *in vitro* against $H_{37}Rv$ strain of *M. tuberculosis*.



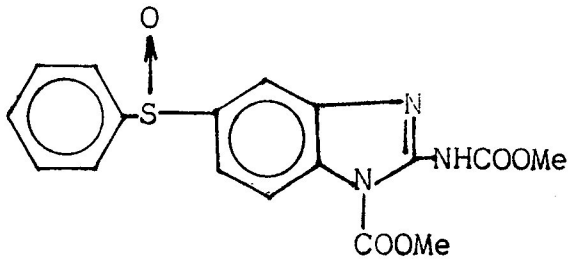
(XIII)

Fenbendazole (XIV)[51] is reported as a potent anthelmintic drug.



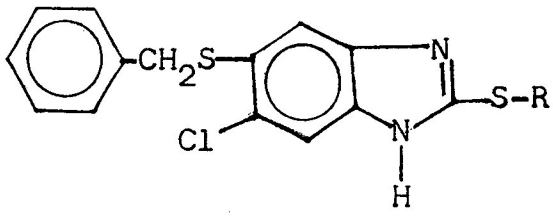
(XIV)

N. Vishwanathan and A.R. Sidhye[52] reported the compound (XV) which is highly active against the hookworm *Necator americans* in hamster.



(XV)

All these facts tempted us to incorporate the benzylthio linkage at 5-position of the 2-substituted thiobenzimidazoles and thus the preparation and study of the following type (XVI) of compounds was planned.



(XVI)

Where, R = Substituted benzyl, 7-chloro-4-quinolinyl.

PART - IV

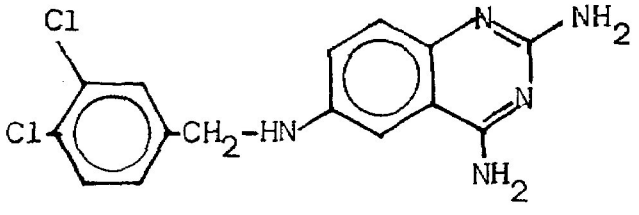
Synthesis of thioureas-N-(substituted aryl)-N'-[6-(2,4-diamino) quinazolyl] :

A large number of N-N'-diaryl-thioureas were synthesized by Buu-Hoi *et al*. and were reported to show tuberculostatic activity and inhibitory properties against influenza virus.[53] They also found that all the diaryl

thioureas described presented chelating properties towards heavy metals, and a link between this property and biological activity have been suggested.[54] A number of thiourea derivatives have reported to exhibit marked antituberculous,[55] antibacterial[56] and fungicidal activities.[57]

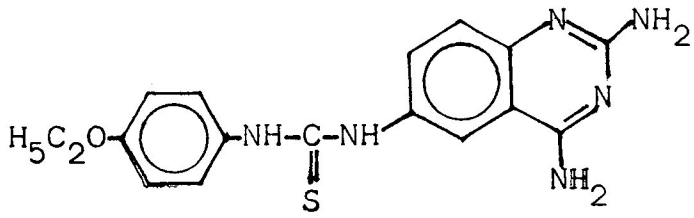
It was observed that the 2,4-diamino configuration afforded optimum inhibitory activity and that small hydrophobic groups located in position 5 and/or 6, caused substantial increase in inhibitory potency.[58]

One of the early non-classical prototype, namely 2,4-diamino-6-[(3,4-dichlorobenzyl) amino]-quinazoline (XVII) displayed strong antimalarial activity against *P. berghei* in mice and *P. gallanaceum* in chicks.[59]

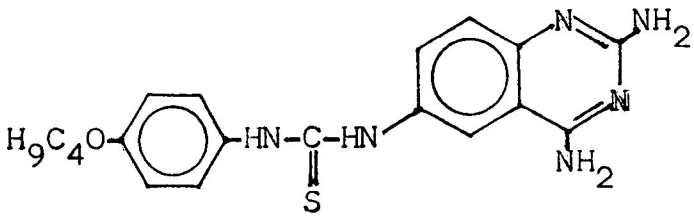


(XVII)

Khairnar *et al.*[60] reported the following types of quinazoline thioureas (XVIII, XIX) which exhibited very good *in vitro* antitubercular activities at the concentration of 1.56 μg/ml each against $H_{37}Rv$ strain of *M. tuberculosis*

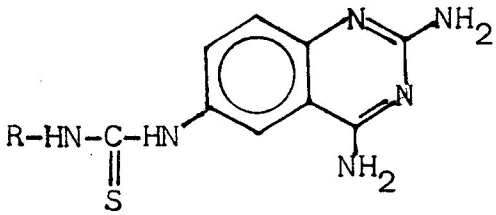


(XVIII)



(XIX)

All these facts tempted us to synthesize and study the following types (XX) of quinazoline thioureas.



(XX)

Where, R = Substituted aryl.

These could be prepared by condensing different aryl substituted isothiocyanates with 2,4,6-triamino quinazoline in ethanol.

Part.....II

C H E M I S T R Y

SECTION-A

5-(N-methyl piperazino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles

5-(N-methyl piperazino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

Benzimidazoles :

Many benzimidazole derivatives possess antiparasitic,[61] antibacterial,[62] and antiviral[63] activities. These are relatively non-toxic and have less side effects.

General methods of benzimidazole synthesis :

In general, all synthetic routes for the benzimidazole derivatives starts from o-phenylenediamines. Following are the various methods reported in the literature for the synthesis of benzimidazoles.

a) By reacting o-phenylene diamines with carboxylic acids.[64,65]

b) By reacting o-phenylene diamines with acid chlorides,[66,67] esters[68] or acid anhydride.[69]

c) By reacting o-phenylene diamines with aldehyde[70] or ketone.[71]

d) By reacting o-phenylene diamines with urea[72] or thiourea.[73]

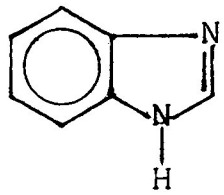
e) By reacting o-phenylene diamines with isothiocyanate.[74]

The benzimidazole nucleus is very stable in character. It does not get easily oxidised or reduced.

Benzimidazoles are weakly basic, but somewhat less than imidazoles They are, in general, soluble in dilute acids. Benzimidazoles are sufficiently acidic to be soluble in aqueous alkali and form N-metallic compounds.

The acidic properties of benzimidazole like those of imidazoles[75] seem to be due to stabilisation of the ion by resonance. The solubility of benzimidazoles in alkaline solutions depends on the particular compounds in reaction. The more acidic benzimidazoles may be soluble in less basic solutions, such as K_2CO_3 solution. Benzimidazoles form salts with acids readily.

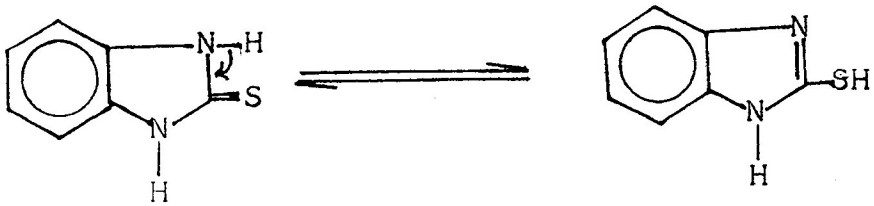
The benzimidazole contain a phenyl ring fused to an imidazole ring as indicated in the structure (I).



(I)

<u>2-Mercaptobenzimidazole</u> :

2-(3H)-Benzimidazole thione (II) and 2-mercapto-benzimidazole (III) are tautomeric forms, analogous to 2-(3H)-benzimidazolone and 2-hydroxybenzimidazole.

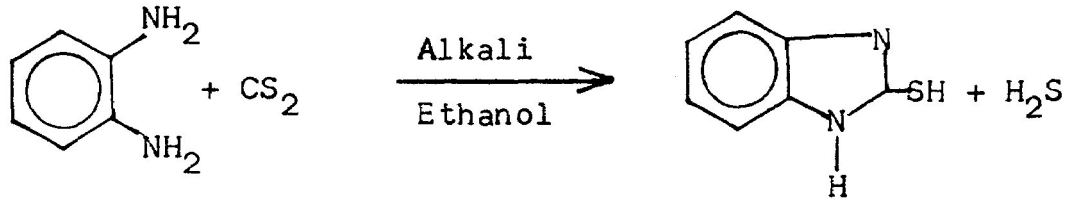


(II) (III)

Methods of preparation of 2-mercapto benzimidazoles :

a) Synthesis from o-phenylenediamine and carbon disulfide :

2-Mercaptobenzimidazole, in general, may be prepared very conveniently by this method. The reaction is carried out usually by heating the reactants in alcoholic solution with or without the addition of alkali to the reaction mixture. 2-Mercaptobenzimidazole (III), itself, has been prepared by this method.[76,77]



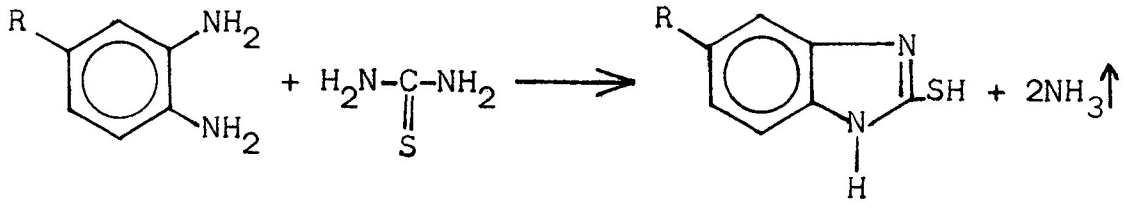
(III)

o-Phenylenediamines having substituents in the phenyl ring have been used, including those with alkyl,[78] halogen,[79] phenyl,[80] aniline[81] and sulfonamido[82] groups.

b) From o-phenylenediamine and thiourea :

The reaction is analogous to the preparation of 2-hydroxy benzimidazole from o-phenylenediamine and urea. 2-Mercapto benzimidazoles may be prepared by this method by heating o-phenylenediamine dihydrochloride and thiourea

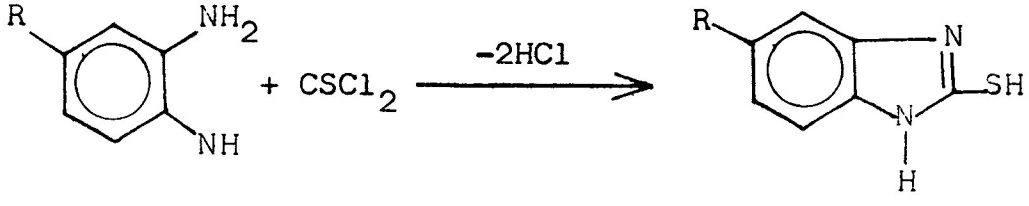
to 170-180°C.[83] Excellent yields have been obtained by carrying out the reaction in amyl alcohol and heating under reflux until the solution of ammonia becomes negligible.



(IV)

c) <u>From o-phenylene diamine and thiophosgene</u> :

Billeter and Steiner[84] obtained 2-mercapto benzimidazole and 5-methyl-2-mercaptobenzimidazole by action of thiophosgene on o-phenylene diamine and 3,4-diamino toluene respectively, 3,4-Diaminobenzene arsenic acid and thiophosgene gave 70 per cent of 2-mercapto-5-arsenic acid benzimidazole.[85]



(IV)

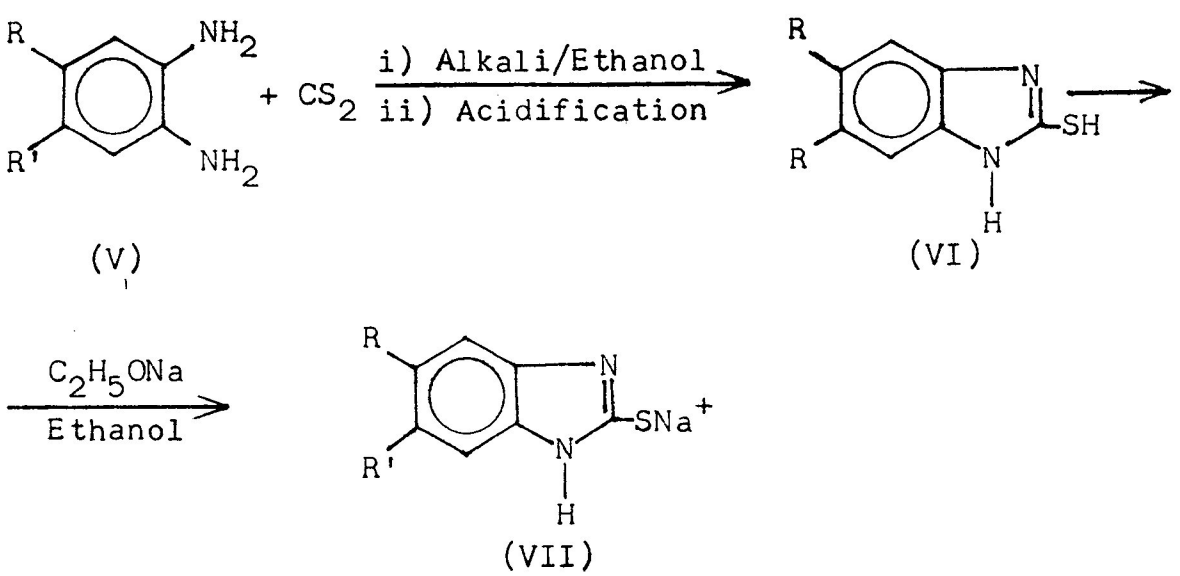
d) <u>Miscellaneous methods</u> :

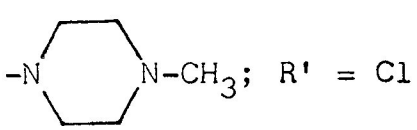
2-Mercaptobenzimidazole can be prepared in 84-86.5 per cent yield by the action of potassium ethyl xanthate on o-phenylene diamine.[86]

2-Mercaptobenzimidazoles have also been prepared from o-phenylene diamine dihydrochloride and ammonium thiocyanate. A solution of the two substances is usually evaporated to dryness on a steam bath and then heated for short time. By this method, 2-mercapto benzimidazole and 5-chloro,[79] 4-methyl[87] and 5-methyl derivatives of 2-mercapto benzimidazole have been prepared.

Synthesis of 2-mercaptobenzimidazoles :

5,6-Disubstituted-2-mercapto benzimidazoles (VI) were prepared by the general and convenient method, such as refluxing 4,5-disubstituted-o-phenylene diamine (V) with carbondisulfide in the presence of alkali (KOH) in ethanol and neutralising with aqueous ACOH. Then sodium salt of 2-mercaptobenzimidazole (VII) were prepared by sodium ethoxide in dry ethanol, as shown below.

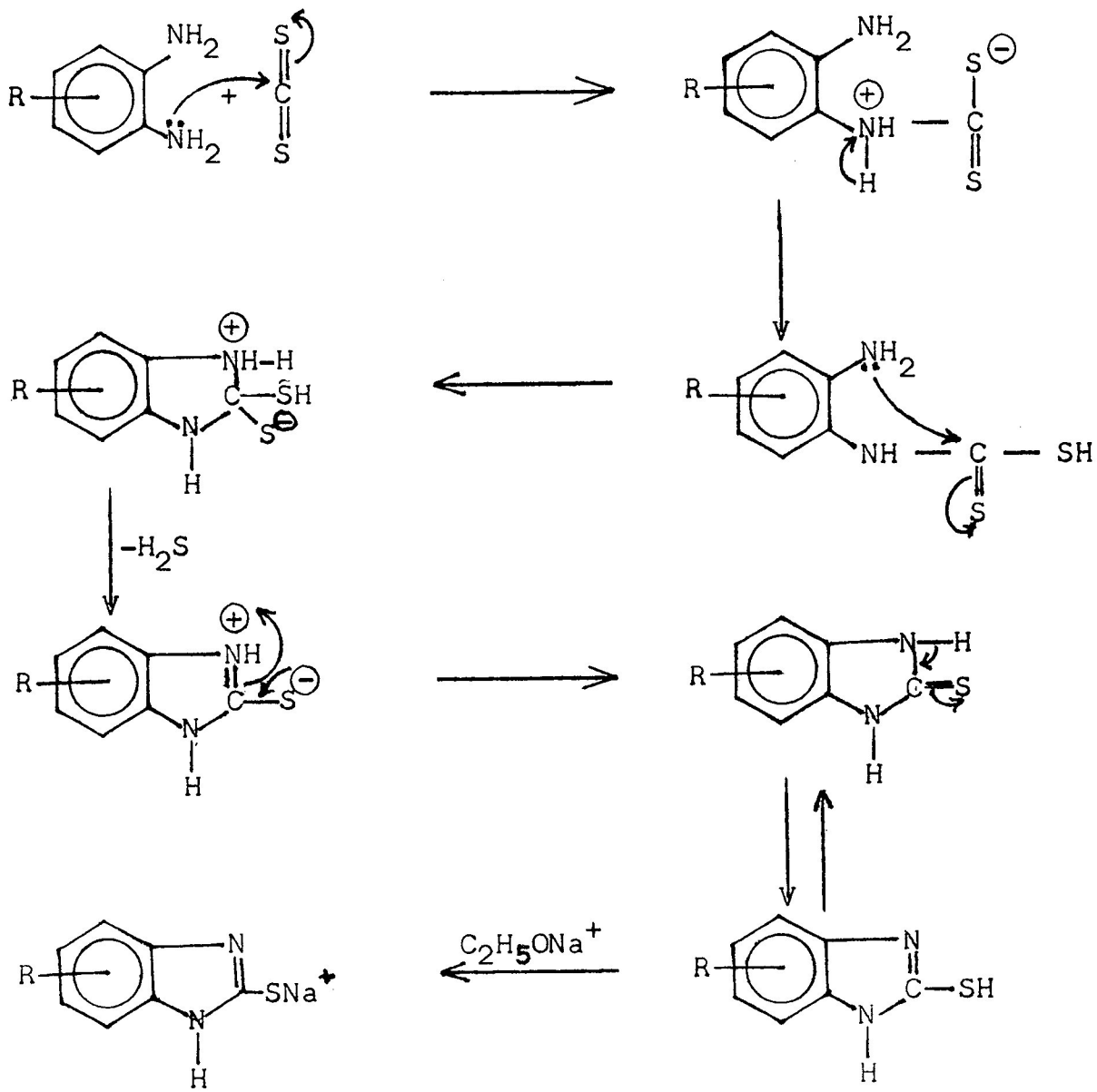


Where, R = 

; R' = Cl

Probable reaction mechanism :

Simple nucleophilic addition to the carbon atom of reactive carbon disulfide.



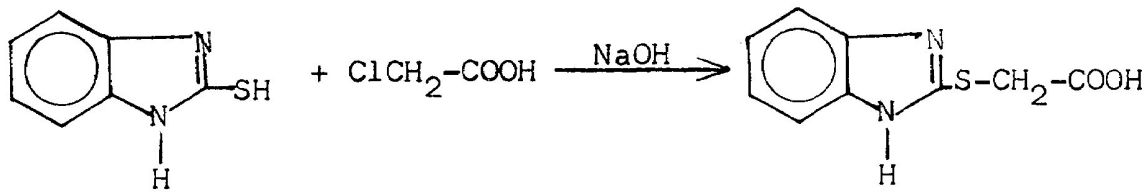
Reactions of 2-mercaptobenzimidazoles :

In general, sulfur compounds show greater nucleophilic reactivity than their oxygen analogs and substitutions by sulfur containing nucleophiles often occur under very mild conditions and give high yields. The common leaving groups include halide, sulfonate ions and water (from conjugate acids of alcohols), e.g.

i) $CH_3SH + (CH_3)_2\text{-}CH\text{-}CH_2\text{-}Br \longrightarrow CH_3\text{-}S\text{-}CH_2\text{-}CH(CH_3)_2 + HBr$

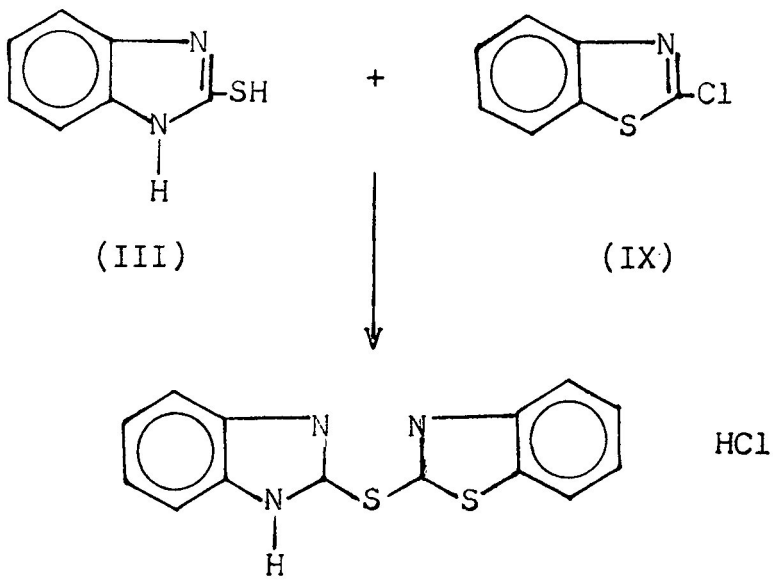
ii) $Na^+\text{-}SCN + (CH_3)_2\text{-}CH\text{-}Br \longrightarrow (CH_3)_2CHSCN + NaBr$

Alkylation occurs readily with replacement of the 2-mercaptohydrogen to yield s-alkylated derivatives.[88,89] 2-Mercaptobenzimidazole (III) may be alkylated with chloroacetic acid by refluxing in 2N sodium hydroxide solution.[90]



(III) (VIII)

2-Chlorobenzothiazole (IX) reacted with 2-mercaptobenzimidazole to yield 2-(benzothiazole-2'-mercapto) benzimidazole hydrochloride (X) in 86 per cent yield.[91]



(III) (IX)

(X)

Benzyl halides :

The substituted benzylhalides required for the synthetic work were prepared by the methods described in the literature. The general procedures are discussed as below.

Side chain substitution is favoured by high temperature and light, and the absence of halogen carriers,e.g., when chlorinated at its boiling point in the presence of light, toluene is converted into benzyl chloride.

$$C_6H_5CH_3 + Cl_2 \xrightarrow{hr} C_6H_5CH_2Cl + HCl$$

It is generally believed that side chain substitution proceeds by a chain reaction.

$$Cl_2 \longrightarrow 2\ Cl\ :$$

$$C_6H_5CH_3 + Cl^{\bullet} \longrightarrow C_6H_5CH_2^{\bullet} + HCl$$

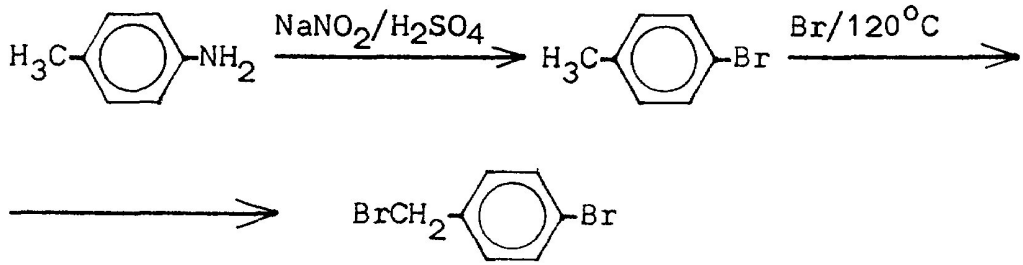
$$C_6H_5CH_2^{\bullet} + Cl_2 \longrightarrow C_6H_5CH_2Cl + Cl^{\bullet},\ \text{etc.}$$

Similarly, bromination of p-chlorotoluene at 120°C in the presence of light gives p-chlorobenzylbromide.

$$p\text{-}ClC_6H_4CH_3 \xrightarrow[hr/120^{o}C]{Br_2} p\text{-}ClC_6H_4CH_2Br + HBr$$

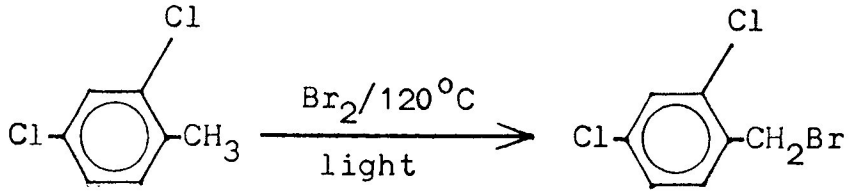
p-Bromobenzyl bromide :

It was prepared by bromination of p-bromo toluene as a side chain substitution at 120°C in the presence of light.[92] p-Bromo toluene was obtained by diazotization of p-toluidine and decomposition of the diazonium salt in the presence of cuprous bromide.[93]



2,4-Dichloro and 3,4-Dichloro benzyl bromides :

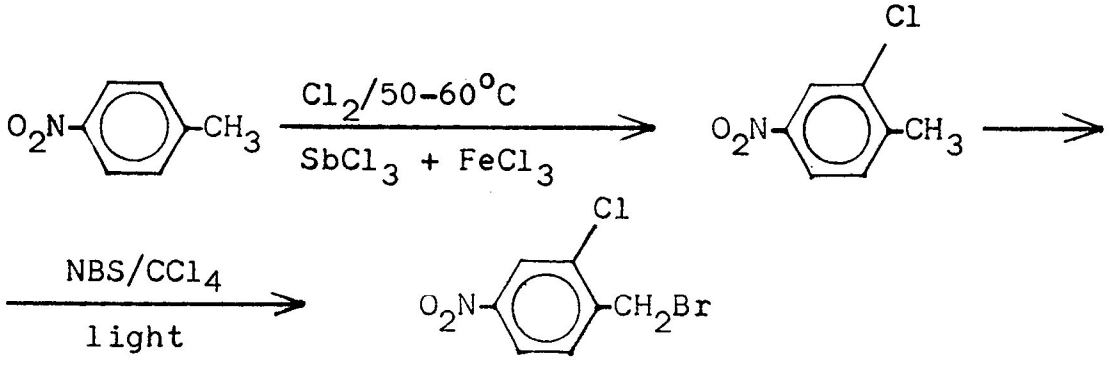
Bromination of 2,4-dichlorotoluene at 120°C in the presence of light, gives side chain substitution product, i.e. 2,4-dichloro benzyl bromide.[94]



Similarly, 3,4-dichlorobenzyl bromide[95] was prepared from 3,4-dichloro toluene.

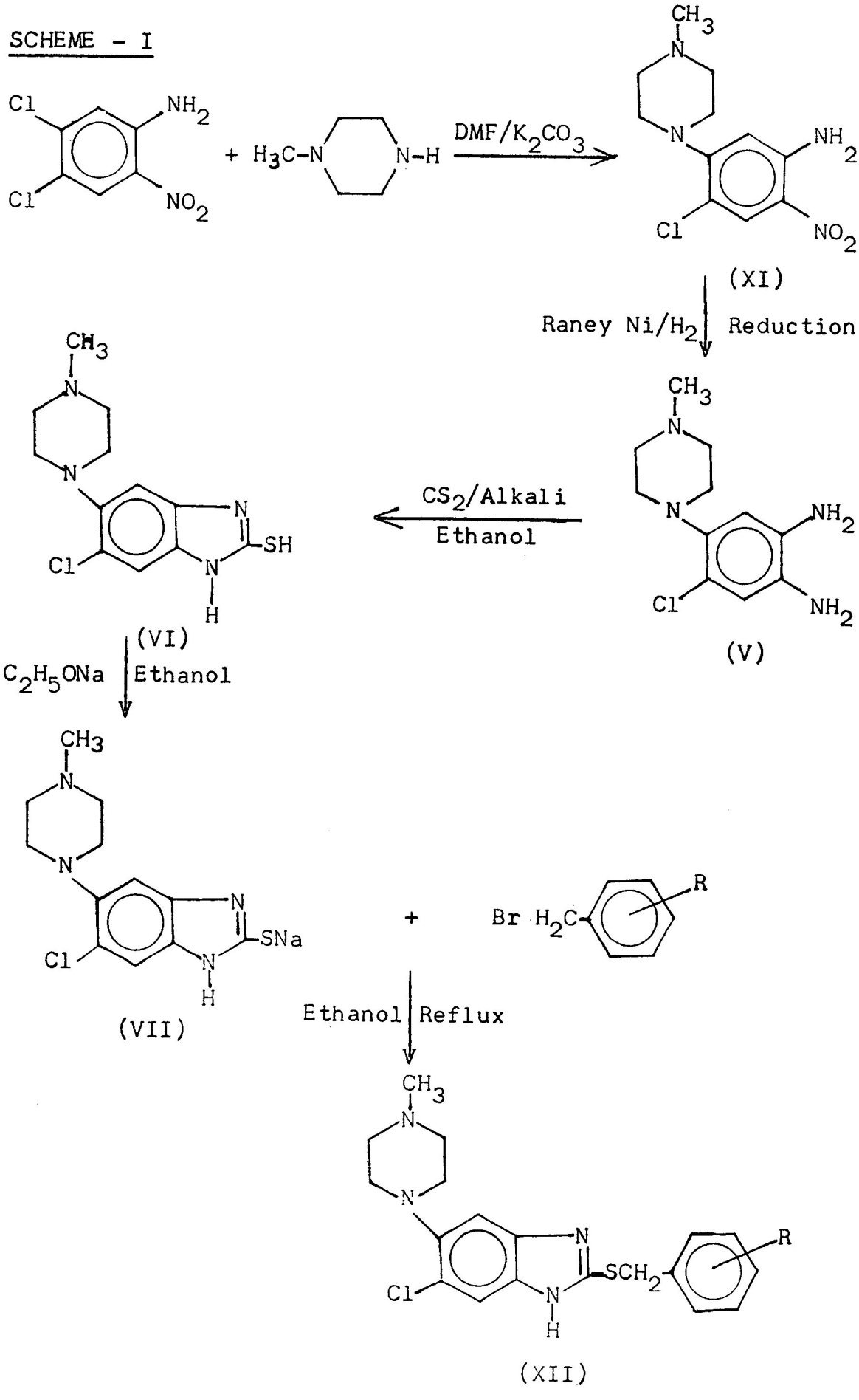
<u>2-Chloro-4-nitro benzyl bromide</u> :

It was prepared by bromination of 2-chloro-4-nitro toluene with N-bromo succinimide by refluxing in carbon tetra chloride in the presence of benzyl peroxide under illumination,[96] whereas, 2-chloro-4-nitro toluene was obtained by chlorination of <u>p</u>-nitro toluene by passing chlorine gas at 50-60°C in the presence of $SbCl_3$ and $FeCl_3$.[97]



The final compounds i.e. 5-N-methyl piperazino-6-chloro-2-substituted thiobenzimidazoles were obtained as shown in Scheme-I.

SCHEME - I


Cl
NH2
Cl
NO2
+ H3C-N
N-H
DMF/K2CO3
CH3
N
N
NH2
Cl
NO2
(XI)
Raney Ni/H2
Reduction
CH3
N
N
NH2
Cl
NH2
(V)
CS2/Alkali
Ethanol
CH3
N
N
N
SH
Cl
N
H
(VI)
C2H5ONa
Ethanol
CH3
N
N
N
SNa
Cl
N
H
(VII)
+
Br H2C
R
Ethanol
Reflux
CH3
N
N
N
SCH2
R
Cl
N
H
(XII)

Part.....II

C H E M I S T R Y

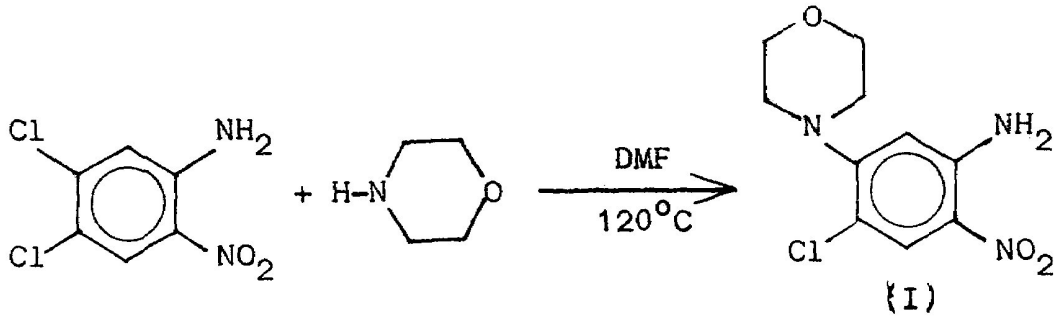
SECTION-B

5-(Morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

5-(Morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

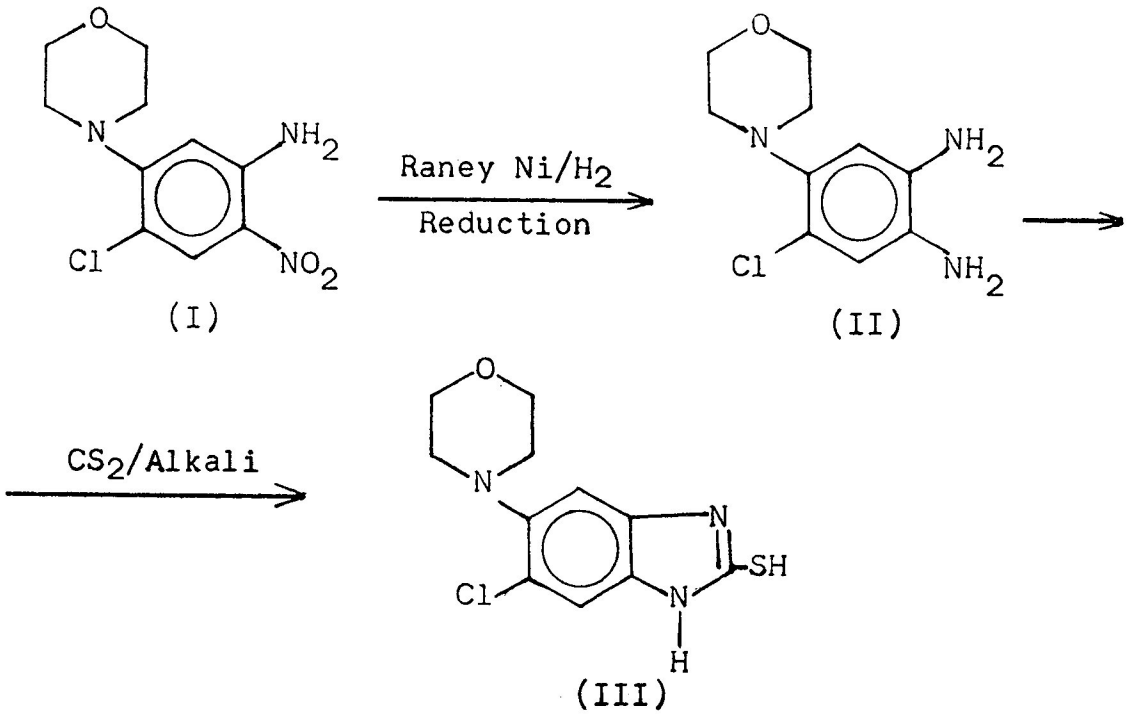
a) 2-Nitro-4-chloro-5-morpholino aniline (I) :

Cyclic secondary amines like morpholine, N-methyl piperazine were reacted with 2-Nitro-4,5-dichloro aniline to get 2-Nitro-4-chloro-5-substituted anilines. Thus, equimolar quantities of 2-nitro-4,5-dichloroaniline and morpholine were treated in Dimethyl formamide in the presence of K_2CO_3 at 120°C to yield the titled compound. It was then recrystallised from ethanol.



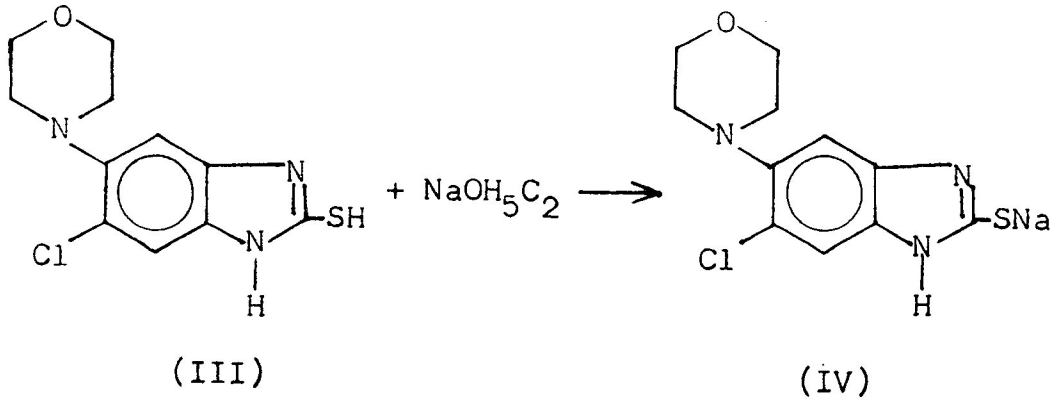
b) 5-(Morpholino)-6-chloro-2-mercapto benzimidazole (III) :

The compound 2-nitro-4-chloro-5-morpholino aniline was reduced over activated Raney Ni/H_2 in Paar hydrogenation apparatus to yield 4-chloro-5-morpholino-o-phenylene diamine. This was then treated with carbon disulfide in the presence of alkali in ethanol. The compound thus obtained was neutralised with aqueous ACOH to yield the titled compound. Recrystallised from ethanol.



c) <u>Sodium salt of 5-(morpholino)-6-chloro-2-mercapto benzimidazole</u> (IV) :

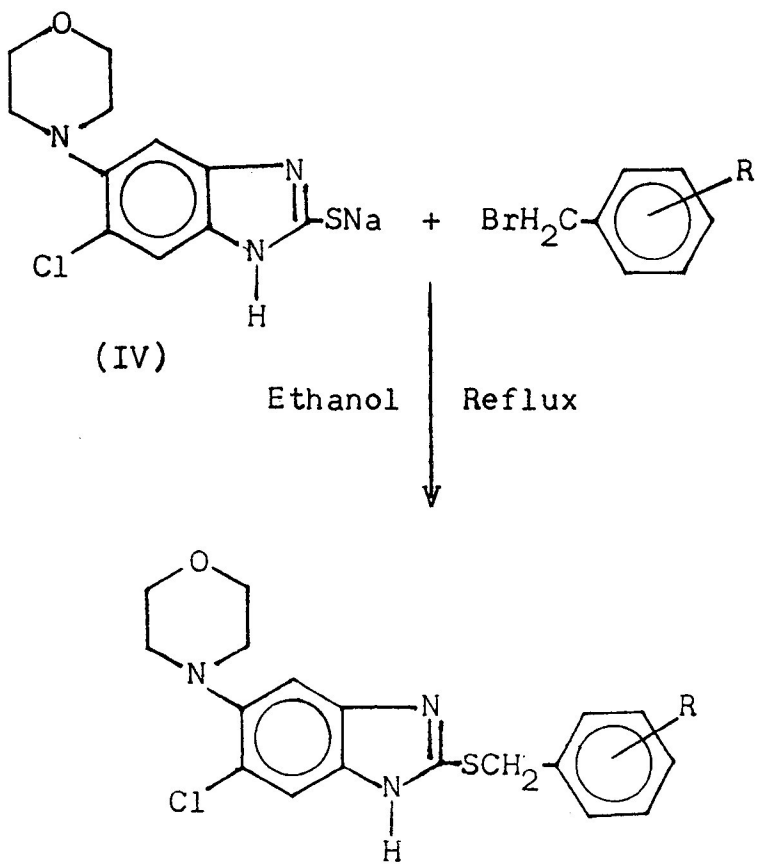
Equimolar quantities of 5-morpholino-6-chloro 2-mercapto benzimidazole and sodium ethoxide were refluxed in dry ethanol in anhydrous condition yielding the sodium salt.



(III) (IV)

d) <u>5-(Morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles</u> (V) :

Sodium salt of 5-morpholino-6-chloro-2-mercapto benzimidazole was refluxed with various substituted benzyl bromides in equimolar quantities in ethanol yielding the titled compounds.



(IV)

(V)

Part.....II

E X P E R I M E N T A L

PREPARATION OF SUBSTITUTED BENZYL HALIDES :

2,4-Dichlorobenzyl bromide :

2,4-Dichlorotoluene 16.1 g (0.1 mole) was taken in 250 ml 3-necked round bottomed flask provided with mercury sealed stirrer, a dropping funnel and reflux condenser with a guard tube. The flask was placed in a gas chamber in an oil-bath at 120°C (bath temperature) and exposed to light of a 100 watt lamp with constant agitation. Then bromine 22.4 g (0.14 mole) was added during 2 hrs and the stirring was continued for another 30 minutes, By this time the evolution of hydrogen bromide was ceased. The resulting oil as 2,4-dichlorobenzyl bromide was vacuum distilled.

Yield : 20.0 g (83.3 %), b.p. 125-132°C/8 mm.
(Lit.[94] b.p. 126-133°C/8 mm).

Similarly, 3,4-dichlorobenzyl bromide was prepared from 3,4-dichlorotoluene by taking the same quantities and the resultant oil was vacuum distilled.

Yield : 192 g (80.0 %), b.p. 115-120°C,
Pyridinium salt, m.p. 210°C.
(Lit.[95] m.p. 210-211°C).

p-Bromo toluene :

At first the hydrobromic acid-cuprous bromide solution was prepared by taking a mixture of crystalline copper sulphate 31.5 g, (0.125 mole), copper turnings 10.0 g (0.15 mole), sodium bromide dihydrate 77.0 g (0.55 mole), conc. sulphuric acid 15.0 g (8.2 ml; 0.14 mole) and water (500 ml) in 2 litre round bottomed flask and refluxing over a flame for 3-4 hrs until the colour become yellowish.

Then the diazonium solution of p-toluidine was prepared as follows : A solution of p-toluidine 53.5 g (0.5 mole) and conc. sulphuric acid 98.0 g (53.5 ml; 0.95 mole) in a 500 ml of water was cooled below 20°C and diazotized with a solution of sodium nitrite 35.0 g (0.5 mole) in 60 ml of water. This required 20-30 minutes and the temperature was maintained between 15 and 20°C by means of ice-bath.

A three litre round bottomed flask containing hydrobromic acid cuprous bromide solution were arranged for steam distillation. After this was heated, the diazonium solution was gradually added from a separatory funnel and a current of steam was passed through the reaction mixture at the same time. This process required

two hrs. The aqueous steam distillate was made alkaline with sodium hydroxide solution and the crude product p-bromo toluene was separated from the water layer. This product was purified by washing once with concentrated sulphuric acid, then with water. It was dried over a little calcium chloride, filtered and distilled.

Yield : 55.58 g (65.0 %), b.p. 183-185°C, m.p. 24-25°C. Lit.[98] b.p. 183-185°C, m.p. 25-26°C).

p-Bromobenzyl bromide :

p-Bromotoluene 20.4 g (0.12 mole) was taken in 250 ml 3-necked round bottomed flask equipped with mercury sealed stirrer, a dropping funnel and a reflux condenser with guard tube. It was then heated in an oil-bath at 120°C (bath temperature) and illuminated with the light of a 100 watt lamp. Then bromine 20.4 g (0.128 mole) was added dropwise during the period of 2 hrs and stirring was continued for further 30 min. By this time the evolution of hydrogen bromide had ceased. The product, p-bromobenzyl bromide solidified upon standing and was filtered and washed three times with 10 ml of alcohol.

Yield : 19.38 g (65.0 %), m.p. 60°C. (Lit.[99] m.p. 61°C).

2-Chloro-4-nitrotoluene :

A mixture of p-nitrotoluene 50 g (0.36 mole) antimony trichloride 5.0 g (0.02 mole) and ferric chloride 5.0 g (0.03 mole) was taken in a 500 ml two necked round bottomed flask with guard tube and gas passing tube. The mixture was melted on water-bath at 50-60°C, then dry chlorine gas was passed through the mixture at 50-60°C for 1.5 hrs. Then the mixture was quenched with water and steam distilled. The product 2-chloro-4-nitrotoluene was obtained by the filtration of distillate and crystallized from ethanol.

Yield : 58.6 g (93.61 %), m.p. 65-66°C.
(Lit.[97] m.p. 65-67°C).

2-Chloro-4-nitrobenzyl bromide :

2-Chloro-4-nitrotoluene 17.15 g (0.1 mole) and N-bromo succinamide 16.4 g (0.1 mole) were taken in 250 ml round bottomed flask with 1 gm of benzoyl peroxide in 100 ml carbon tetrachloride. This mixture was refluxed on water-bath under illumination of light of 100 watt lamp for 2 hrs. Then the mixture was filtered to remove succinamide and product, 2-chloro-4-nitrobenzyl bromide was obtained from the filtrate and crystallised from methanol.

Yield : 15.0 g (60.0 %), m.p. 45°C.
(Lit.[96] m.p. 46°C).

p-Nitrobenzyl bromide :

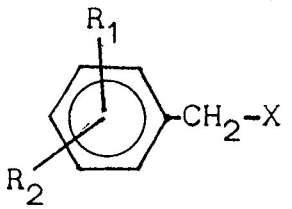
In a 1 lit three necked flask was placed 300 gm (2.2moles) of technical p-nitrotoluene (m.p. 51-52°C). The flask was fitted with a liquid sealed stirrer, reflux condenser and a seperatory funnel arranged so that the steam reaches nearly to the bottom of the flask. The condenser was attached to a glass trap. The flask was heated in an oil-bath at 145-50°C and 365 gm (188 cc; 2.3 mole) of bromine was added dropwise over a period of 2 hrs and heating and stirring was continued for further 30 minutes. By this time the evolution of hydrogen bromide had ceased. After cooling at 20°C the crystals were filtered and washed three times with cold light petroleum ether.

Yield : 315 gm (66 %), m.p. 99°C.

(Lit.[100] m.p. 98°C-99°C).

Similarly, other substituted benzyl halides were prepared and their physical data is summarised in Table(2).

TABLE-2 : Substituted benzyl halides



	R_1	R_2	X	B.p. °C.	M.P. °C	Reported B.P. °C	Reported M.P. °C
1.	H	4-Bromo	Bromo	-	60	-	61
2.	H	4-Chloro	Bromo	-	50	-	51
3.	H	4-Fluro	Chloro	85-87/30 mm	--	87/30 mm	--
4.	2-Chloro	4-Chloro	Bromo	125-132/8 mm	--	126-33/8 mm	--
5.	3-Chloro	4-Chloro	Bromo	115-120/6 mm	210[a]	-	210-11
6.	2-Chloro	4-Nitro	Bromo	-	45	-	46
7.	H	4-Nitro	Bromo	-	99	-	99-100
8.*	H	3-Hydroxy	Bromo	-	--	-	--
9.*	H	3-Phenoxy	Bromo	-	--	-	--

a- Characterised as pyridinium salt.

* Available from the laboratory.

3,4-Dichloro acetanilide :

35.64 g (0.22 mole) of 3,4-dichloro aniline, 22.45 g (20.78 ml; 0.22 mole) of acetic anhydride, 13.21 g (12.70 ml; 0.22 mole) of glacial acid and 0.1 g of zinc dust were taken in a 500 ml round bottomed flask equipped with a reflux condenser. The mixture was refluxed for 30 minutes and the hot liquid was poured in a thin stream into a one litre beaker containing 500 ml of cold water, whilst the stirring was continued. The crude product was separated out. It was filtered at the suction and washed with a little cold water. It was recrystallised in ethanol and air dried.

Yield : 35.90 g (80.0 %), m.p. 120°C.
(Lit.[101] m.p. 121°C).

4,5-Dichloro-2-nitro acetanilide :

A solution of 3,4-dichloro acetanilide 10.2 g (0.05 mole) in 10 ml concentrated sulphuric acid was taken in a 50 ml three necked flask, equipped with mechanical stirrer, a thermometer and a dropping funnel and cooled to 0 to 10°C in an ice bath. Nitrating mixture (concentrated sulphuric acid 10 ml; d 1.84 and nitric acid 2.2 ml; d 1.42) was added dropwise at 0 to 10°C. Stirring was continued for further 2 hrs at this temperature. Then

this reaction mixture was poured on crushed ice with vigorous stirring at 0°C. The product was neutralised by liquor ammonia. The crude 4,5-dichloro-2-nitro-acetanilide was filtered alongwith the washing the ice-cold water, until the neutral pH. The product was recrystallised from ethanol.

Yield : 9.5 g (76.50 %), m.p. 123°C.
(Lit.[102] m.p. 122-124°C).

4,5-Dichloro-2-nitro aniline :

To a solution of 24.9 g (0.1 mole) of 4,5-dichloro-2-nitro acetanilide in 30 ml of boiling ethyl alcohol was added a solution of 5.6 g (0.1 mole) of KOH in 10 ml of water. It was refluxed for 40 minutes. Further it was diluted with 120 ml of water and distilled until 75 ml of distilate (alcohol and water) was collected. The residue was poured into 150 ml of cold water. The product 4,5-dichloro-2-nitro aniline was separated out. It was filtered at the pump and washed with cold water. The product was recrystallised from ethanol.

Yield : 15.69 g (75.80 %), m.p. 176°C.
(Lit.[103] m.p. 178.5-179°C).

4-Chloro-5-(n-methyl piperazino)-2-nitro aniline :

A mixture of 2.07 g (0.01 mole) of 4,5-dichloro 2-nitro aniline and 1.0 g (1.119 ml; 0.01 mole) of N-methyl piperazine with 1.38 g (0.01 mole) of potassium carbonate was heated in DMF at 115-120°C for three and half hrs in an oil bath. The reaction mixture was ground in a mortor with 300 ml of warm water. The solid product was separated out, washed with water and filtered. The product was recrystallised twice from ethanol.

Yield : 1.89 g (70.0 %), m.p. 200°C.

4-Chloro-5-(N-methyl piperazino)-o-phenylenediamine:

In a hydrogenation bottle, 4-chloro-5-(N-methyl piperazino)-2-nitro aniline 3.24 g (0.012 mole) was taken in 40 ml of alcohol. The reaction mixture was heated on water-bath to dissolve the nitro compound. Raney nickel (1.0 g) was added to the reaction mixture. This bottle was fixed on Paar hydrogenator. After complete reduction, the content of the bottle was filtered through fluted filter paper. The Raney nickel was decomposed with dilute HCl (10 %). The filtrate was concentrated under reduced pressure. The residue was recrystallised from hot benzene petroleum ether.

Yield : 1.72 g (60 %), m.p. 130°C.

5-N-Methyl piperazino-6-chloro-2-mercapto benzimidazole :

Potassium hydroxide 0.56 g (0.01 mole) was dissolved in the mixture of 25 ml ethanol (95 %) and 5 ml water. To this 0.76 g (0.60 ml; 0.01 mole) carbon disulfide was added with stirring. This solution was added dropwise at boiling temperature to a solution of 2.4 g (0.01 mole) 4-chloro-5-(N-methyl piperazino)-o-phenylene diamine in 15 ml ethanol. After 6 hrs, the ethanol was evaporated. The brownish residue was dissolved in H_2O and the product precipitated by addition of 4 ml AcOH. It was filtered and recrystallised from ethanol.

Yield : 1.9 g (69.0 %), m.p. 190°C.

Analysis for : $C_{12}H_{15}ClN_4S$

	% C	% H	% N
Calcd.	50.95	5.30	19.81
Found	50.67	5.55	19.62

5-(N-Methyl piperazino)-6-chloro-2-(p-chlorobenzyl) thiobenzimidazole :

A solution of sodium salt of 5-N-methyl-piperazino-6-chloro-2-mercapto benzimidazole 3.04 g (0.01 mole) and p-chloro benzyl bromide 2.05 g (0.01 mole) in 30 ml of ethanol was refluxed on water-bath for three hrs. Then the solvent was removed under reduced pressure and it was

diluted with water. The 5-N-methyl piperazino-6-chloro-2-(p-chlorobenzyl) thiobenzimidazole precipitated out and filtered. Recrystallised from methanol.

Yield : 2.53 g (67.0 %), m.p. 200°C.

Analysis for : $C_{19}H_{20}Cl_2N_4S$

	% C	% H	% N
Calcd.	56.00	4.91	13.75
Found	56.32	4.72	14.15

Similarly, other substituted thiobenzimidazole derivatives of 5-(N-methyl piperazino)-6-chloro-2-mercapto-benzimidazole were prepared and their physical data is summarised in Table (3).

5-(Morpholino)-6-chloro-2-mercapto benzimidazole :

5-Morpholino-6-chloro-2-mercapto benzimidazole was prepared by employing the same procedure as explained for the preparation of 5-(N-methyl piperazino)-6-chloro-2-mercapto benzimidazole.

m.p. 171°C.

Analysis for : $C_{11}H_{12}ClN_3OS$

	% C	% H	% N
Calcd.	48.96	4.45	15.57
Found	48.69	4.32	15.66

5-(Morpholino)-6-chloro-2-(2,4-dichloro-benzyl) thiobenzimidazole :

A solution of sodium salt of 5-morpholino-6-chloro-2-mercapto benzimidazole 2.91 g (0.01 mole) and 2,4-dichloro benzyl bromide 2.04 g (0.01 mole) in 30 ml of ethanol was refluxed on water-bath for three hrs. Then the solvent was removed under reduced pressure and some water added to it. The final compound 5-(morpholino)-6-chloro-2-(2,4-dichlorobenzyl)-thiobenzimidazole was precipitated out and filtered, recrystallised from methanol.

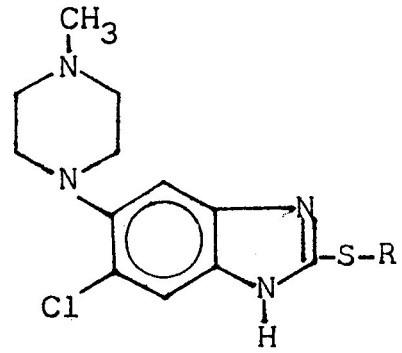
Yield : 2.44 g (74.44 %), m.p. 225°C.

Analysis for : $C_{18}H_{16}Cl_3N_3OS$

	% C	% H	% N
Calcd.	65.73	4.86	12.78
Found	66.12	4.45	13.02

Similarly, other substituted thiobenzimidazole derivatives of 5-morpholino-6-chloro-2-mercapto-benzimidazole were prepared and their physical data is summarised in Table (4).

TABLE-3 : 5-(N-Methyl piperazino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles

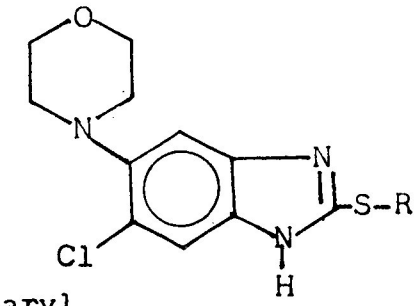


Where, R = Substituted benzyl and heteroaryl

No.	R.	M.P.* °C	Mol. Formula	% Yield	ANALYSIS Calculated % C	% H	% N	Found % C	% H	% N
1.	p-Bromo benzyl	239	$C_{19}H_{20}BrClN_4S$	63.0	50.38	4.41	12.37	50.20	4.30	12.12
2.	p-Chloro benzyl	200	$C_{19}H_{20}Cl_2N_4S$	67.0	56.00	4.91	13.75	56.32	4.72	14.15
3.	p-Fluro benzyl	307	$C_{19}H_{20}ClFN_4S$	61.5	58.37	5.12	14.33	58.49	5.27	14.55
4.	m-Hydroxy benzyl	311	$C_{19}H_{21}ClN_4OS$	57.2	58.67	5.40	14.41	58.39	5.09	14.61
5.	p-Nitro benzyl	Oily	$C_{19}H_{20}ClN_5O_2S$	60.5	54.59	4.78	16.76	54.63	4.55	16.81
6.	m-Phenoxy benzyl	290	$C_{25}H_{25}ClN_4OS$	52.0	64.57	5.38	12.05	64.39	5.43	12.37
7.	2-Chloro-4-nitro benzyl	120	$C_{19}H_{19}Cl_2N_5O_2S$	66.0	50.43	4.20	15.48	50.79	4.35	15.19
8.	2,4-Dichloro benzyl	175	$C_{19}H_{19}Cl_3N_4S$	65.0	51.63	4.30	12.68	51.80	4.45	12.39
9.	3,4-Dichloro benzyl	115	$C_{19}H_{19}Cl_3N_4S$	65.7	51.63	4.30	12.68	51.35	4.25	12.92
10.	7-Chloro-4-quinolinyl	121	$C_{21}H_{19}Cl_2N_5S$	59.5	56.75	4.27	15.76	56.49	4.39	15.49

*Melting points are capillary melting points and are uncorrected.

TABLE-4 : 5-(Morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles.



Where, R = Substituted benzyl, heteroaryl

No.	R	M.P.* °C	Mol. Formula	% Yield	ANALYSIS Calculated % C	% H	% N	Found % C	% H	% N
1.	p-Chloro benzyl	228	$C_{18}H_{17}Cl_2N_3OS$	64.0	54.80	4.31	10.65	55.01	4.60	11.01
2.	p-Fluro benzyl	307	$C_{18}H_{17}ClFN_3OS$	60.4	57.21	4.50	11.12	57.02	4.59	10.98
3.	p-Nitro benzyl	208	$C_{18}H_{17}ClN_4O_3S$	59.5	53.38	4.20	13.84	53.58	4.35	13.49
4.	m-Phenoxy benzyl	270	$C_{24}H_{22}ClN_3O_2S$	53.0	63.77	4.87	9.30	63.39	4.93	8.99
5.	2,4-Dichloro benzyl	225	$C_{18}H_{16}Cl_3N_3OS$	74.44	65.73	4.86	12.78	66.12	4.45	13.02
6.	3,4-Dichloro benzyl	233	$C_{18}H_{16}Cl_3N_3OS$	72.5	65.73	4.86	12.78	65.34	4.91	12.37
7.	2-Chloro-4-nitro benzyl	205	$C_{18}H_{16}Cl_2N_4O_3S$	70.0	49.19	3.64	12.75	49.25	3.35	12.64
8.	7-Chloroquinolinyl	265	$C_{20}H_{16}Cl_2N_4OS$	61.0	55.67	3.71	12.99	55.35	3.52	13.02

* Melting points are capillary melting points and are uncorrected.

Part.....III

C H E M I S T R Y

SECTION-A

5-(*n*-Propylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles.

5-(n-Propylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

This section deals with the preparation of 2-nitro-4-chloro-5-n-propylthio aniline (II). Because of the activated nature of chlorine substituent in 2-nitro-4,5-dichloroaniline (I), it could be easily reacted with n-propyl thiol in the presence of anhydrous potassium carbonate in DMF at about 120°C. The desired product is obtained in about 90 % yield.

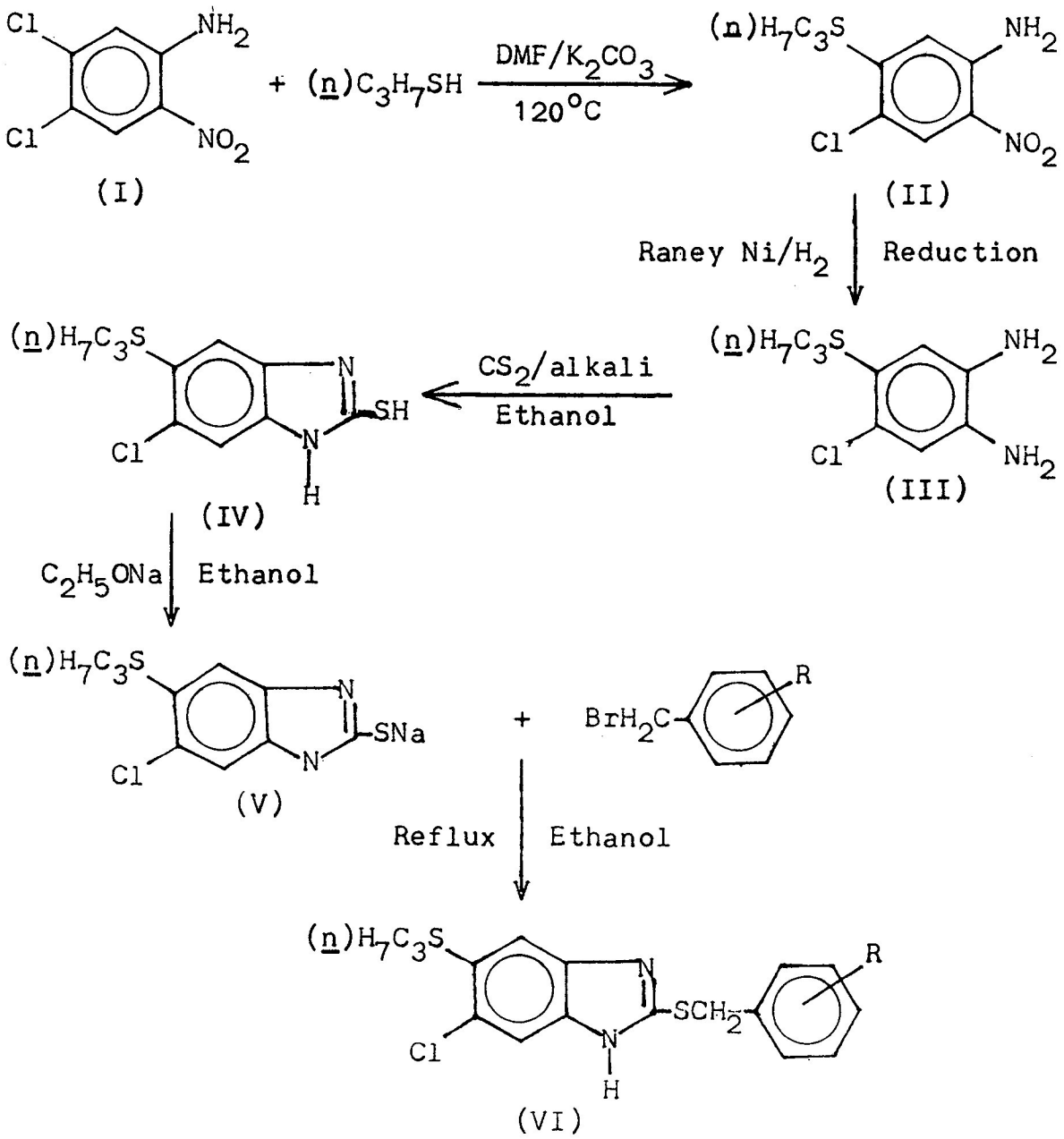
2-Nitro-4-chloro-5-(n-propylthio)-aniline (II) thus obtained is further reduced with Raney Nickel in Paar hydrogenator, as the reaction is very clean and yields are very good. This was the preferred laboratory method used throughout this work for reduction of n-alkylthio (II) or n-phenylthio compounds (Section-B; II).

Thus, the 4-chloro-5-n-alkylthio-1,2-diamino benzene (III) was further reacted with carbon disulfide in the presence of sodium hydroxide to obtain sodium salt of 2-mercapto-4-chloro-5-n-alkylthio benzimidazole. The crude sodium salt thus obtained was neutralised with aqueous acetic acid. The thio compound (IV)liberated was crystalised from ethanol. This purified compound was converted to its sodium salt with sodium ethoxide. The corresponding sodium salt derivative (V) was condensed

with substituted benzyl halides in refluxing ethanol to obtain 5-(n-propylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles (VI).

The sequence of chemical reactions involved could be schematically represented as below Scheme-II .

SCHEME - II



Part.....III

C H E M I S T R Y

SECTION-B

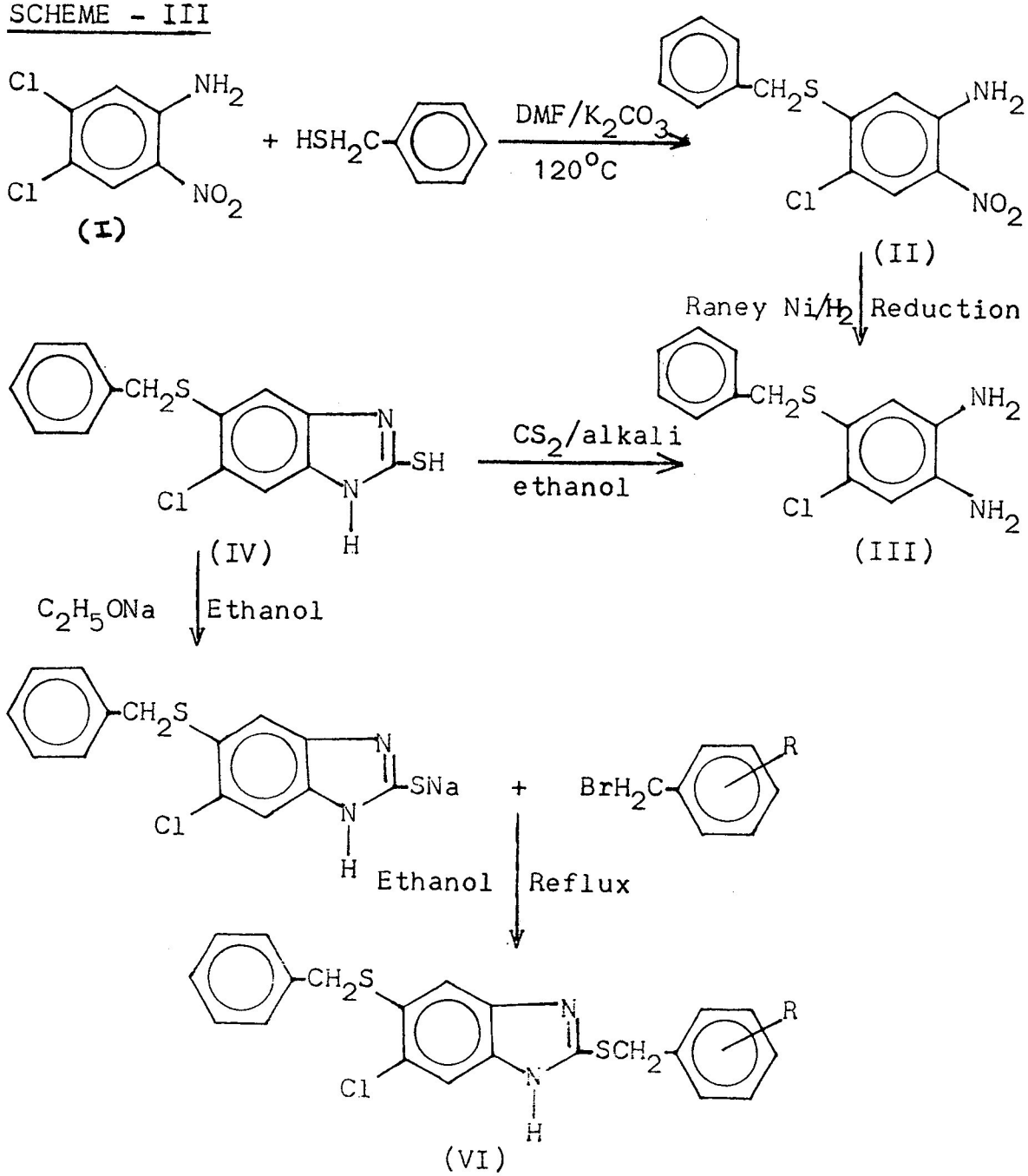
5-(Benzylthio)-6-chloro-2-substituted benzyl or hetero-aryl thiobenzimidazoles.

5-(Benzylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

Similar sequence of reactions as described in the previous section was followed to prepare the titled compound(VI)

The reactions involved are represented sequentially as below.

SCHEME - III



Part.....III

E X P E R I M E N T A L

5-(n-Propylthio)-6-chloro-2-mercapto benzimidazole :

Potassium hydroxide 0.56 g (0.01 mole) was dissolved in the mixture of 150 ml ethanol (95 %) and 30 ml water. Then 0.76 g (0.60 ml, 0.01 mole) of carbon disulfide was added to the above solution. This solution was added dropwise at boiling temperature to 2.16 g (0.01 mole) of 4-chloro-5-n-propylthio-o-phenylene diamine in 15 ml ethanol. The reaction was continued for three hrs. Then ethanol was distilled out. The off white residue was dissolved in water. The product was precipitated by the addition of 5 ml AcOH. It was filtered and recrystallised from ethanol.

Yield : 1.83 g (71.20 %), m.p. 179°C.

Analysis for : $C_{10}H_{11}ClN_2S_2$

	% C	% H	% N
Calcd.	46.38	4.25	10.82
Found	46.19	3.98	10.48

5-(n-Propylthio)-6-chloro-2-(p-nitrobenzyl)-thiobenzimidazole :

A solution of sodium salt of 5-n-propylthio-6-chloro-2-mercapto-benzimidazole 2.80 g (0.01 mole) and p-nitro benzyl bromide 2.16 g (0.01 mole) in 30 ml ethanol was refluxed on water-bath for three hrs. Then the solvent was removed under reduced pressure and some water

was added to it. The 5-n-propylthio-6-chloro-2-(p-nitrobenzyl) thiobenzimidazole precipitated out and filtered. Recrystallised from methanol.

Yield : 2.84 g (72.30 %), m.p. 155°C.

Analysis for : $C_{17}H_{16}ClN_3O_2S_2$

	% C	% H	% N
Calcd.	51.81	4.06	10.66
Found	52.11	3.82	10.97

Similarly, other substituted thiobenzimidazole derivatives of 5-(n-propylthio)-6-chloro-2-mercapto benzimidazole were prepared and their physical data is summarised in Table (5).

5-(Benzylthio)-6-chloro-2-mercapto benzimidazole :

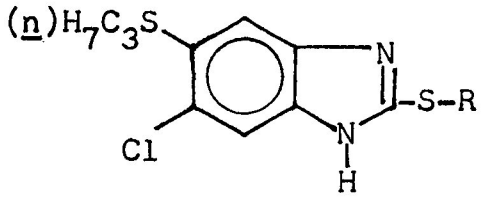
5-Benzylthio-6-chloro-2-mercapto benzimidazole was prepared by using the same procedure as explained for the preparation of 5-(n-propylthio)-6-chloro-2-mercapto benzimidazole.

m.p. 245°C.

Analysis for : $C_{14}H_{11}ClN_2S_2$

	% C	% H	% N
Calcd.	54.77	3.58	9.12
Found	54.58	3.42	9.41

TABLE-5 : 5-(n-Propylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles



Where, R = Substituted aryl, heteroaryl

No.	R	M.P.* °C	Mol. Formula	% Yield	ANALYSIS Calculated % C	% H	% N	Found % C	% H	% N
1.	p-Bromo benzyl	250	$C_{17}H_{16}BrClN_2S_2$	64.0	47.69	3.74	6.54	47.58	3.52	6.73
2.	p-Chloro benzyl	209	$C_{17}H_{16}Cl_2N_2S_2$	61.0	53.23	4.17	7.30	53.02	4.43	7.49
3.	p-Fluro benzyl	255	$C_{17}H_{16}ClFN_2S_2$	59.8	55.63	4.36	7.63	55.29	4.48	7.89
4.	m-Hydroxy benzyl	275	$C_{17}H_{17}ClN_2OS_2$	53.5	55.93	4.66	7.67	56.02	4.49	7.59
5.	p-Nitro benzyl	155	$C_{17}H_{16}ClN_3O_2S_2$	72.3	51.81	4.06	10.66	52.11	3.82	10.97
6.	2,4-Dichloro benzyl	235	$C_{17}H_{15}Cl_3N_2S_2$	70.5	48.83	3.59	6.70	48.59	3.42	6.52
7.	3,4-Dichloro benzyl	225	$C_{17}H_{15}Cl_3N_2S_2$	65.5	48.83	3.59	6.70	48.68	3.32	6.59
8.	2-Chloro-4-nitro benzyl	125	$C_{17}H_{15}Cl_2N_3O_2S_2$	63.0	47.64	3.50	9.80	47.90	3.39	10.02
9.	7-Chloro-4-quinolinyl	270	$C_{19}H_{15}Cl_2N_3S_2$	59.5	54.25	3.56	9.99	54.09	3.52	10.14

* Melting points are capillary melting points and are uncorrected.

5-(Benzylthio)-6-chloro-2-(p-bromobenzyl) thiobenzimidazole :

A solution of sodium salt of 5-benzylthio-6-chloro-2-mercapto benzimidazole 3.28 g (0.01 mole) and p-bromo benzyl bromide 2.50 g (0.01 mole) in 30 ml of ethanol was refluxed on water-bath for three hrs. Then the solvent was removed under reduced pressure and diluted with 50 ml of water. The final compound 5-benzylthio-6-chloro-2-(p-bromo benzyl)-thiobenzimidazole was precipitated out and filtered. Recrystallised from methanol.

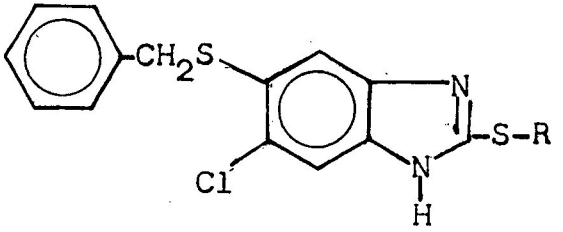
Yield : 3.33 g (70.09 %), m.p. 270°C.

Analysis for : $C_{21}H_{16}BrClN_2S_2$

	% C	% H	% N
Calcd.	52.97	3.36	5.88
Found	53.13	3.73	6.15

Similarly, the other substituted thiobenzimidazole derivatives of 5-benzylthio-6-chloro-2-mercaptobenzimidazole were prepared and their physical data is summarised in Table (6).

TABLE-6 : 5-(Benzylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles.



Where, R = Substituted benzyl, heteroaryl

No.	R	M.P.* °C	Mol. Formula	% Yield	ANALYSIS Calculated % C	% H	% N	Found % C	% H	% N
1.	p-Bromo benzyl	270	$C_{21}H_{16}BrClN_2S_2$	70.09	52.97	3.36	5.88	53.13	3.73	6.15
2.	p-Chloro benzyl	165	$C_{21}H_{16}Cl_2N_2S_2$	65.5	58.44	3.71	6.49	58.58	3.59	6.52
3.	p-Fluro benzyl	300	$C_{21}H_{16}ClFN_2S_2$	63.0	60.76	3.85	6.75	60.49	3.62	6.43
4.	m-Hydroxy benzyl	Oily	$C_{21}H_{17}ClN_2OS_2$	55.0	61.06	4.11	6.78	61.47	4.32	6.82
5.	p-Nitro benzyl	222	$C_{21}H_{16}ClN_3O_2S_2$	69.5	57.05	3.62	9.50	57.29	3.53	9.89
6.	2,4-Dichloro benzyl	68	$C_{21}H_{15}Cl_3N_2S_2$	70.0	54.11	3.22	6.01	54.32	3.43	6.33
7.	3,4-Dichloro benzyl	60	$C_{21}H_{15}Cl_3N_2S_2$	66.5	54.11	3.22	6.01	54.42	3.51	5.98
8.	2-Chloro-4-nitro benzyl	Oily	$C_{21}H_{15}Cl_2N_3O_2S_2$	64.0	52.91	3.14	8.81	53.01	3.29	8.79
9.	7-Chloro-4-quinolinyl	210	$C_{23}H_{15}Cl_2N_3S_2$	58.0	58.94	3.20	8.97	59.11	3.32	8.59

* Melting points are capillary melting points and are uncorrected.

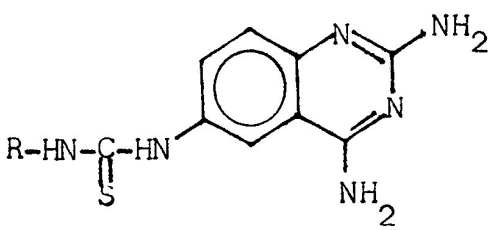
Part.....IV

C H E M I S T R Y

Thioureas-N-(substituted aryl)-N'-[6-(2,4-diamino) quinazolyl]

Thioureas-N-(substituted aryl)-N'-[6-(2,4-diamino) quinazolyl] :

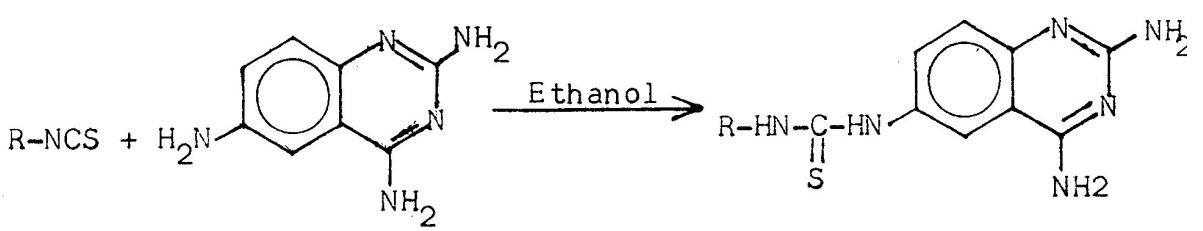
Various substituted thioureas are known to exhibit various types of biological activities such as antitubercular[104] and antimalarial.[105] Hence, extensive synthetic efforts were directed towards the introduction of -NH-C(=S)-NH- linkage into the 2,4-diamino quinazoline nucleus at 6-position to obtain thiourea derivatives of the type (I).



(I)

Where, R = Substituted aryl.

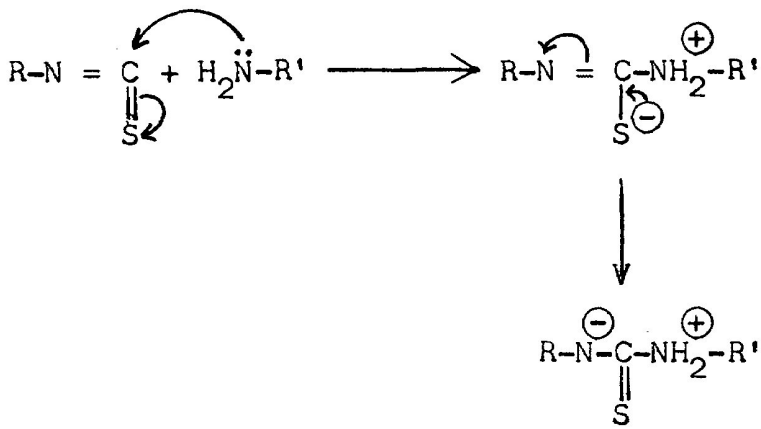
These thiourea derivatives were prepared by the condensation of 2,4,6-triamino quinazoline, where only 6-amino group reacts with isothiocyanates in ethanol at reflux temperature.



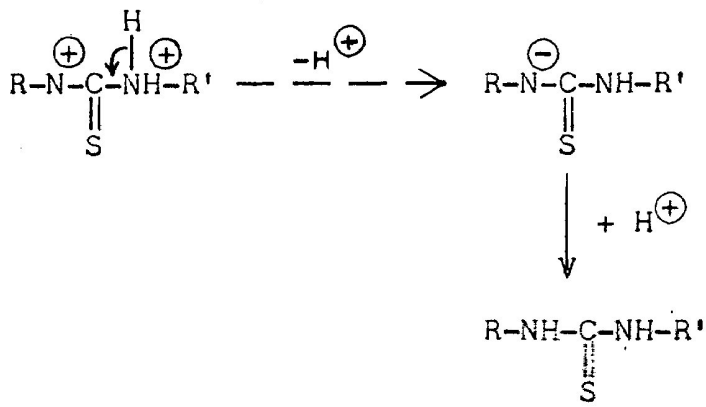
Reaction mechanism :

Simple addition of the nucleophile ($R'-NH_2$) to the carbon atom of the isothiocyanate groups ($R-N=C=S$) give thiourea derivatives as the addition product as shown below :

i) Attack of nucleophile to the carbon atom of isothiocyanate group :



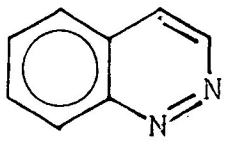
ii) Transfer of hydrogen ion :



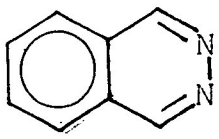
The reaction products are very stable and formed very rapidly.

Chemistry of quinazoline :

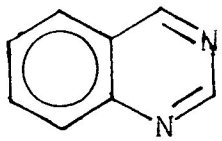
The following benzodiazines are theoretically possible, and are known; the first two are derived from pyridazine, the third from pyrimidine and the fourth from pyrazine.



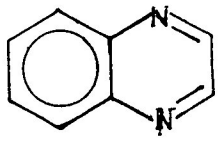
Cinnoline



Phthalazine



Quinazoline

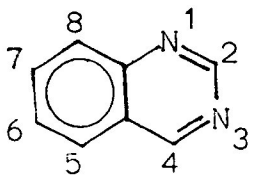


Quinoxaline

Due to electron withdrawing effect of the second heteroatom, quinazoline shows more basicity than rest of the above possible structures. It forms N-oxides and quarternary salts.

Quinazoline is also known in literature by the names phenmiazine, benzyleneamidine, benzo-1,3-diazine, 5,6-benzopyrimidine and 1,3-diazanapthalene.

Weddige[106] first time observed that his compounds were isomeric with cinnoline and quinoxaline, thats why he has adapted the name quinazoline (II). Now, it is universaly recognized by scientists.



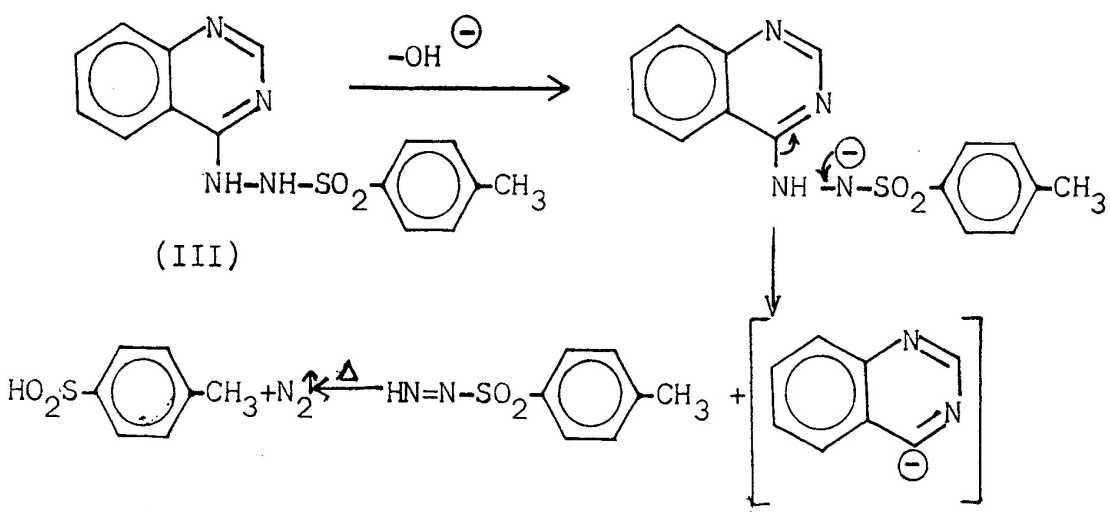
(II)

The numbering for this structure is suggested by Paul and Busch[107] which is now presently being used in the literature.

Synthesis of quinazoline :

In 1895, quinazoline was prepared by heating 2-carboxyquinazoline with calcium oxide.[108] Gabriel[109] prepared same compound with quantitative yield by the oxidation of 3,4-dihydroxy quinazoline with potassium ferrocyanate in alkaline condition. It can be prepared by reductive cyclization of bisformamido-o-nitro benzaldehyde with zinc in acetic acid.[110]

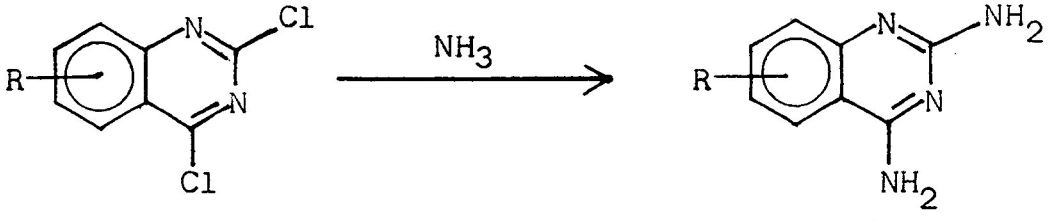
In alkaline condition, 4-N'-toluene-p-sulfonyl hydrazino quinazoline (III) hydrochloride was decomposed to quinazoline.[111] The reaction is very useful for the preparation of quinazoline. Nitrogen gas and p-toluene sulfonic acid are formed as by products.



Quinazolines may be prepared by the action of ammonia on acylated o-aminobenzaldehyde or aminoacetophenone.[112]

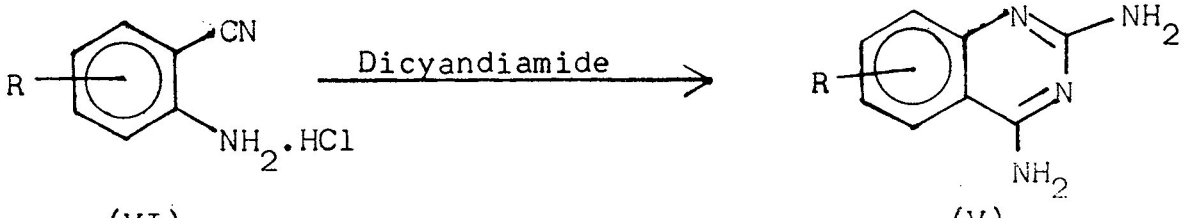
Preparation of 2,4-diamino quinazolines :

2,4-Diamino quinazoline (V) can be prepared by the replacement of 2 and 4-chlorine atoms by amines in 2,4-dichloro quinazoline.[113] (IV). 2,4-Diamino-6-methyl quinazoline was prepared by bubbling ammonia through a hot solution of 2,4-dichloro-6-methyl quinazoline in hot phenol.



(IV) (V)

Various alkyl substituted[114,115] 2,4-diamino quinazolines were synthesized by heating the o-aminobenzonitrole hydrochloride (VI) with dicyandiamide at 150-160°C for a short period.



(VI) (V)

Where, R = 6-butyl, 5-methyl, 5-ethyl, 6-propyl.

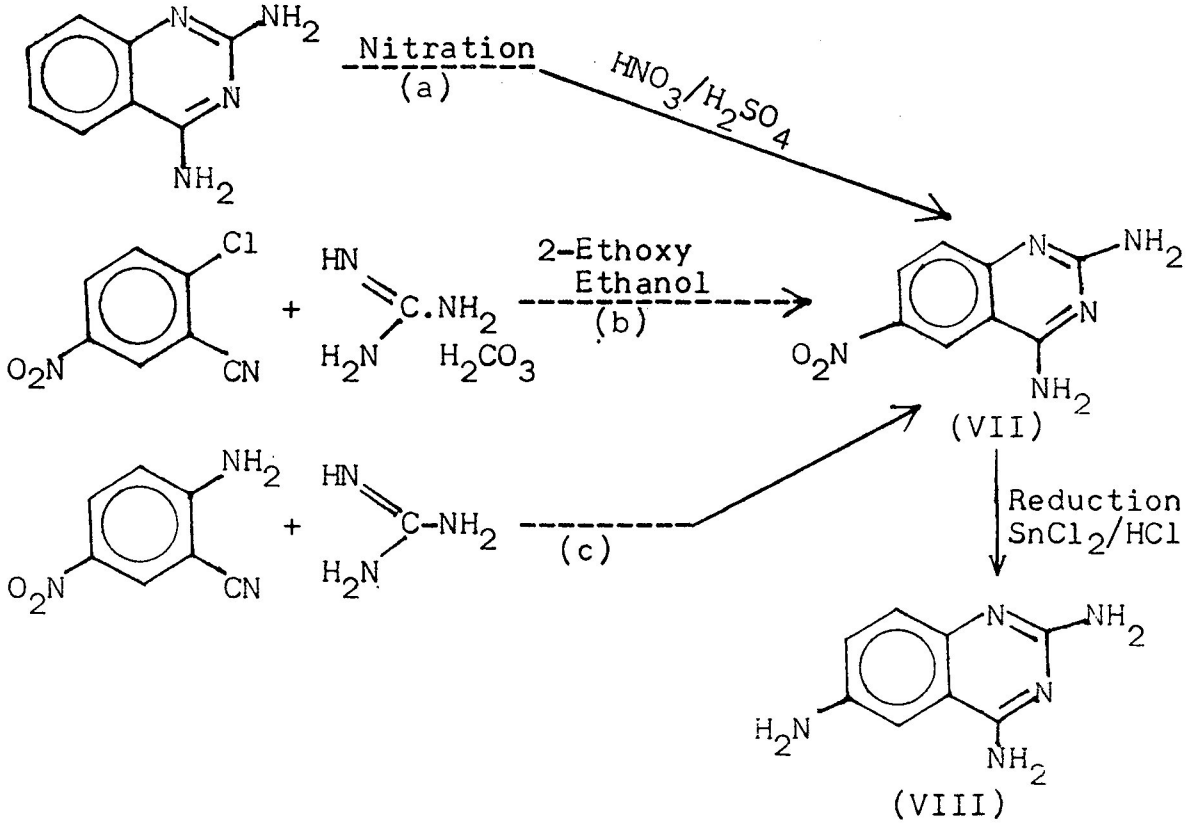
Synthesis of 2,4,6-triaminoquinazoline :

2,4,6-Triaminoquinazoline (VIII) can be prepared by using 2,4-diamino-6-nitro quinazoline (VII) as a basic raw material. It can be obtained in high yields by using the following three methods.[116]

a) Nitration of 2,4-diamino quinazoline.

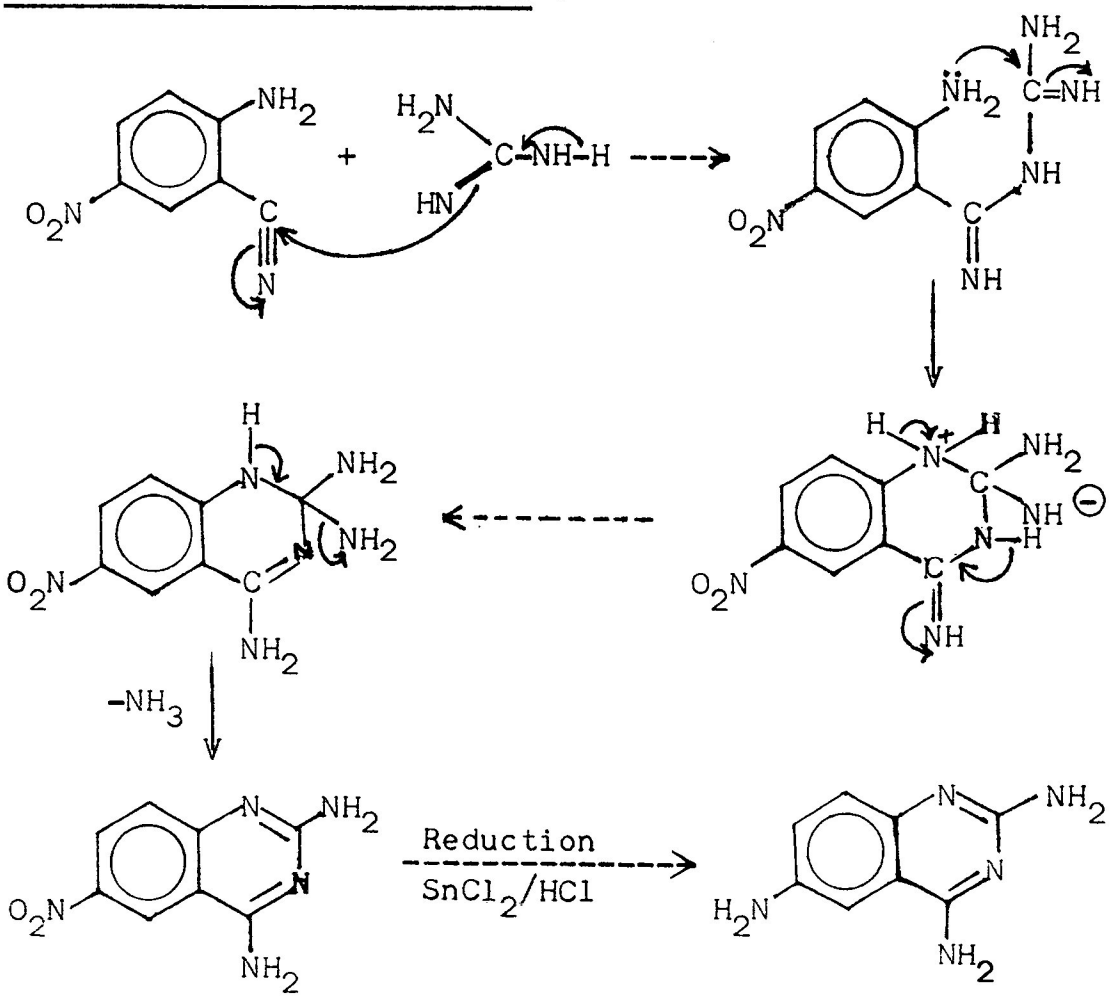
b) Reaction of 2-chloro-5-nitro benzonitrile with guanidine carbonate, where 2-chloro-5-nitro benzonitrile was prepared by heating 2-chloro-5-nitro benzoic acid with $MeSO_2NH_2$ (methyl-sulfonamide) and excess of PCl_5 at 180°C for ½ hr.[117]

c) Reaction of 5-nitro anthranilonitrile with guanidine.



Thus, requisite 2,4,6-triamino quinazoline was prepared by a selective and convenient method (C) i.e. by the reaction of 5-nitro anthranilonitrile with guanidine in ethanol at reflux temperature for 4-5 hrs and evolution of ammonia was detected during the reaction, to obtain 2,4-diamino-6-nitro quinazoline (VII). Further reduction of this with tin chloride in HCl gives the 2,4,6-triamino quinazoline (VIII).[116]

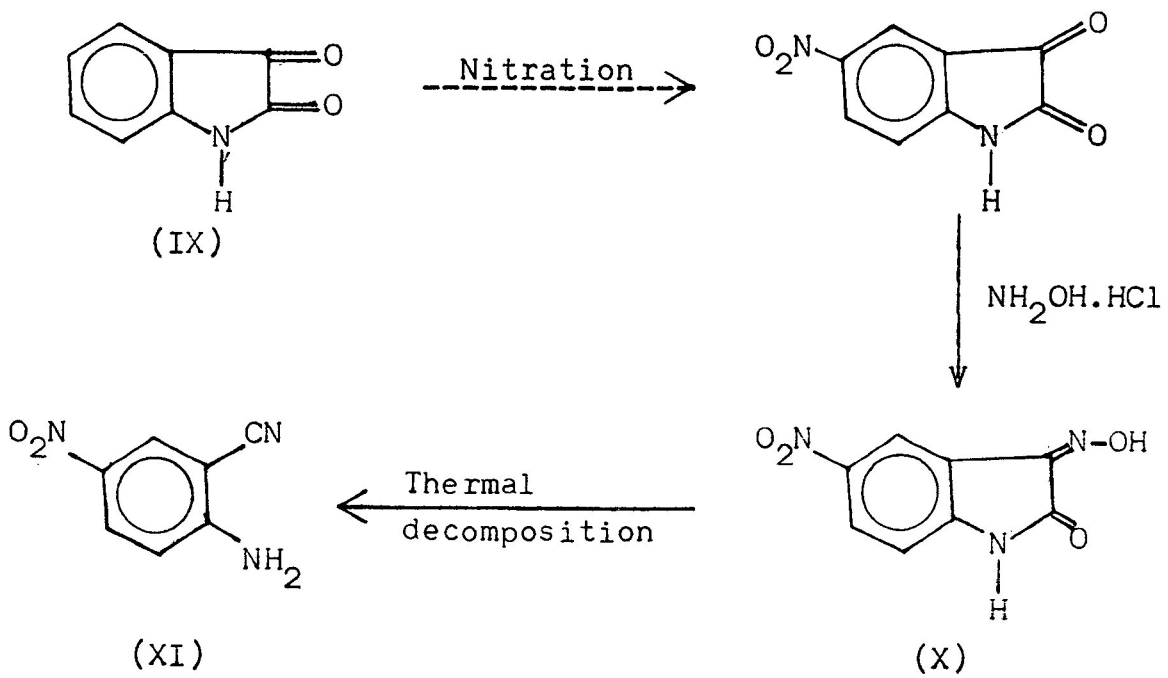
Probable reaction mechanism :



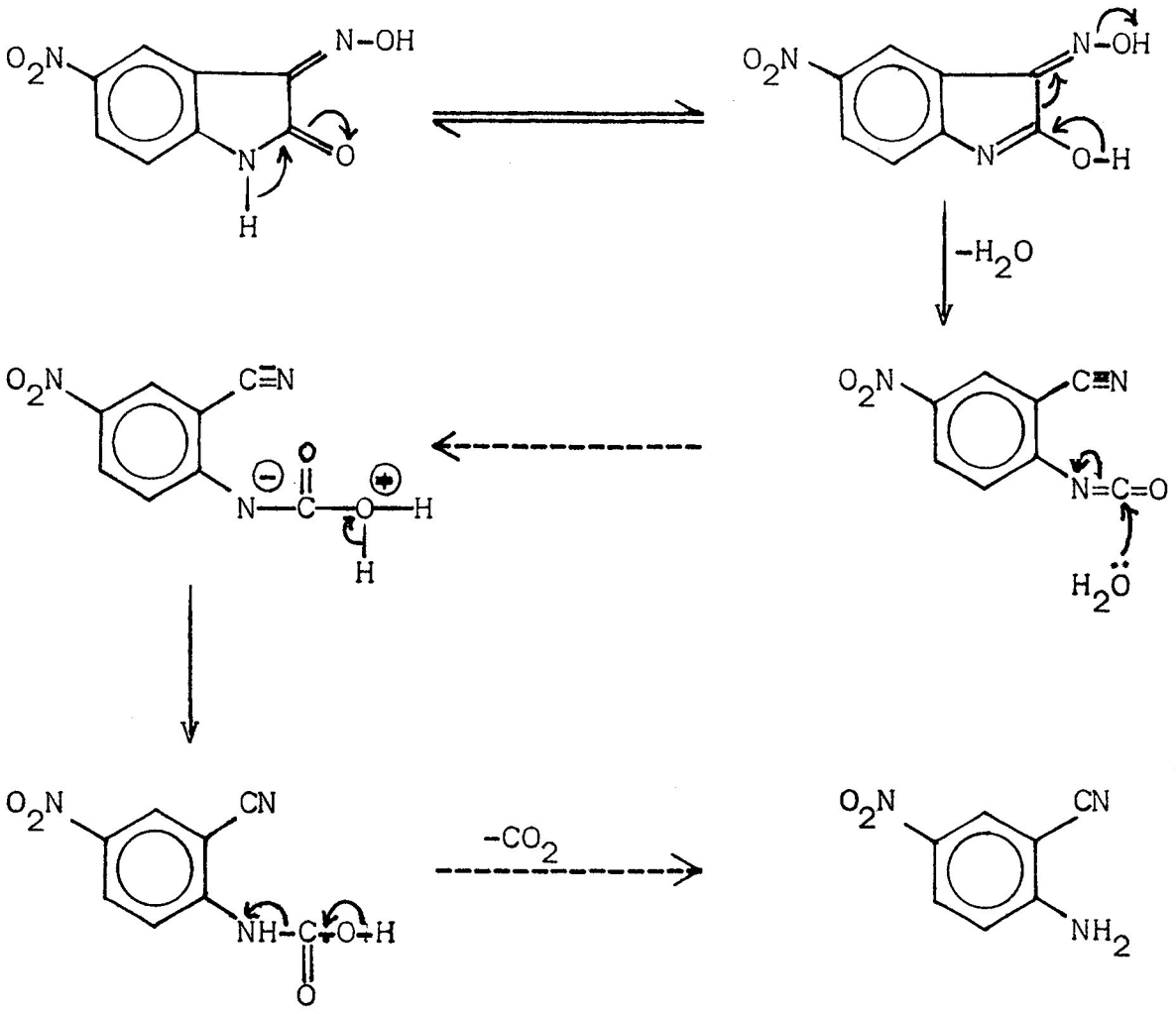
Preparation of 5-nitroanthranilonitrile (XI) :

This compound was prepared either by reaction of 5-nitro anthranilamide with $POCl_3$.[118] But it was obtained in 66 % yield, by the selective method, i.e. by the thermal decomposition of 5-nitro-isatin-3-oxime (X) in nitrobenzene.[119] The two carbonyl groups of isatin have widely differing properties. The one at position-3 is ketonic and undergoes typical reactions of ketones. For instance, with hydroxy amine, it gives oxime. The carbonyl group at position-2- of isatin is similar to that of amide in properties.

5-Nitro-isatin-3-oxime was prepared by the nitration of isatin (IX)[120] and then converted to its oxime with hydroxyl amine hydrochloride in an alkaline medium.



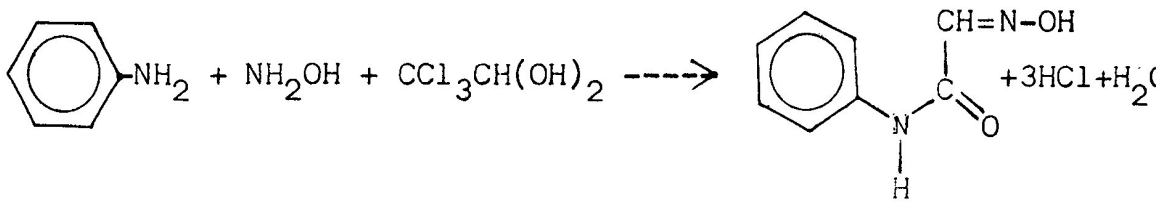
Probable reaction mechanism :



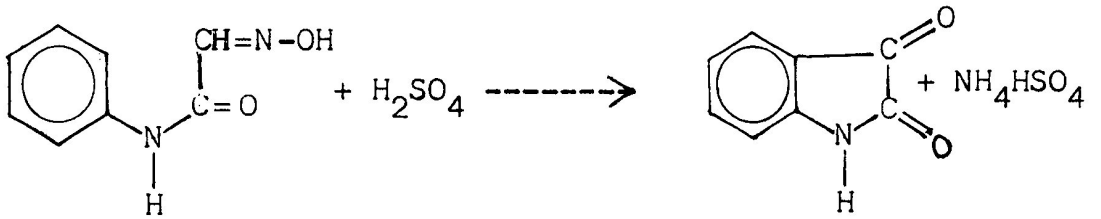
Hydroxamic acid (unstable)

Preparation of isatin :

The most frequently used synthesis of isatins in the sandmeyer procedure,[121] which involves the formation of an isonitroso acetanilide (XIII) from an aniline (XII), chloral hydrate and hydroxylamine. The isonitroso acetanilid (XIII) is cyclised into the isatin (XIV) on treatment with sulphuric acid.



(XII) (XIII)



(XIII) (XIV)

Chemistry of aryl isothiocyanates :

The methods of preparation of aryl isothiocyanates are divided into different sections, which summarizes number of reagents used for synthesis of isothiocyanates.

(1) Reactions of amines with sulfur compounds :

Thiophosgene (Fig 1A) : This method is based on the direct treatment of primary amine (XV)(chart on page 78) with thiophosgene (Fig 1A). The first product of the reaction is an unstable thiocarbamoyl chloride (XVI) which splits off HCl easily yielding (XX).[122] In case of aromatic amines (XV) especially with electron accepting reagents (XVII) may be formed as by-products[123] (Fig 1B).

The formation of (XVII) can be prevented by the use of small excess of thiophosgene.

Generally, a solution of arylamine in neutral organic solvents e.g., $CHCl_3$, dichloroethane, is added to the water emulsion of thiophosgene. The rate of reaction is retarded by the side reaction of HCl with the free amine and, therefore, use of bases such as $CaCO_3$, Na_2CO_3, $NaHCO_3$ is recommended for binding HCl.

Aryl amines which are highly susceptible for atmospheric oxidation, may be used in the form of hydrochloride salt. But in this case, the use of $CaCO_3$ or alkali carbonates keeps the reaction mixture neutral and assists in the slight hydrolysis of the salt.

Thiocarbamoyl derivatives :- N,N-Diethylthiocarbamoyl chloride is a new reagent which could replace the use of toxic thiophosgene reagent. It is a one step method and consists in the heating of (XV) with N,N-diethylthiocarbamoyl chloride (Fig 1C), in a inert solvent.[12]

(2) Decomposition of dithiocarbamic acid and its salts or esters :

Decomposition of dithiocarbamic acid salt (XVIII) :

(XIV) Prepared by the action of CS_2 and NaOH may be decomposed by heavy metal salts such as $Pb(NO_3)_2$,[125]

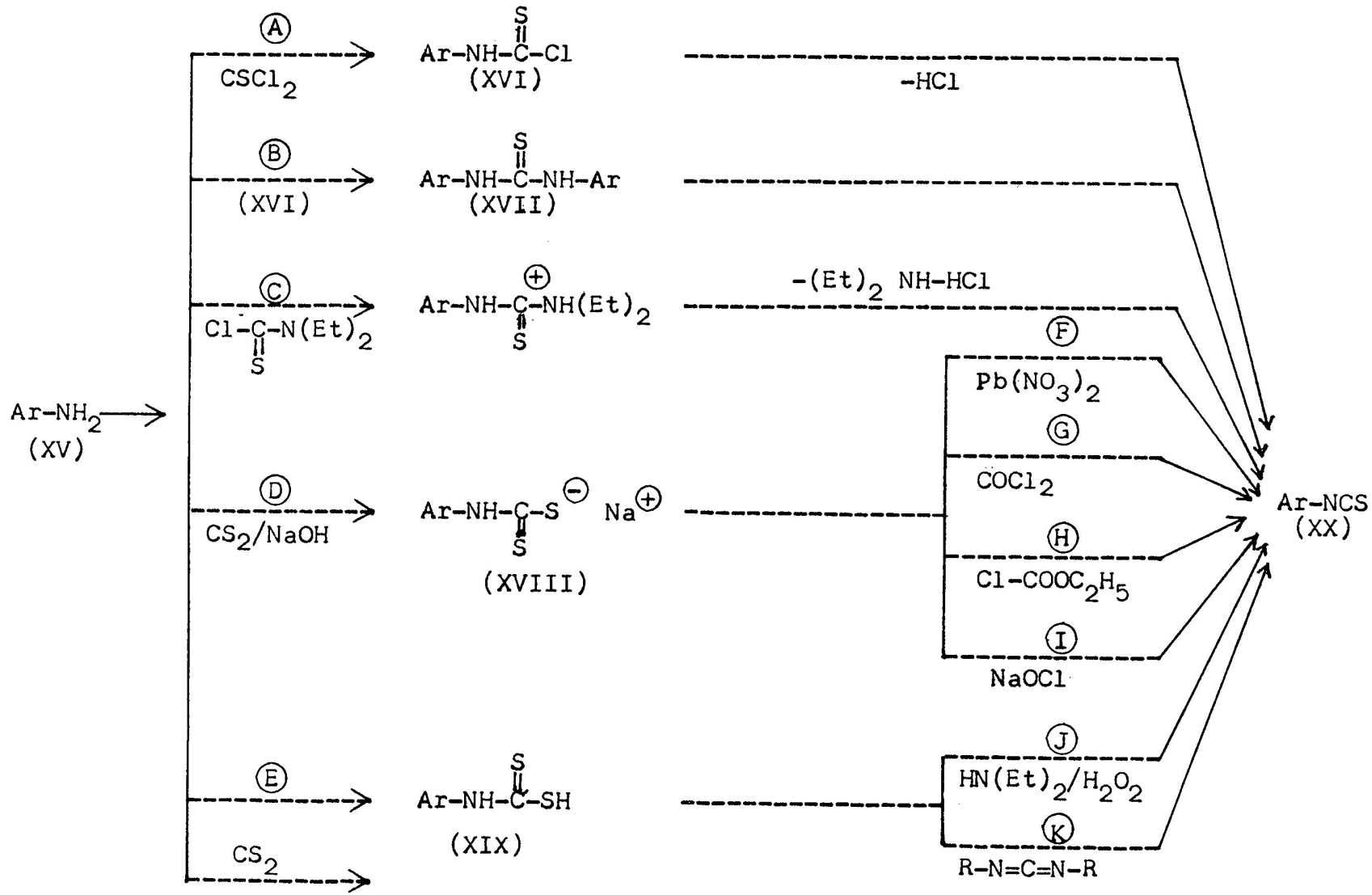
cupric sulfate, $FeCl_3$, etc (Fig. 1F) by phosgene solution[126] (Fig 1G), by ethyl chloroformate[127-129] (Fig 1H), and by NaOCl in NaOH solution[130] to yield (XX) (Fig 1I).

Decomposition of dithiocarbamic acid (XIX) :

Primary amines (XV) react with CS_2 in suitable organic solvent to yield (XIX), which can be directly decomposed with dicyclohexyl carbodimide in the presence of pyridine or triethylamine (Fig 1K) to yield corresponding isothiocyanate (XX).[131]

(XIX) Prepared *in situ* can be treated with H_2O_2 in the presence of diethylamine to produce (XX)[132] (Fig 1J). This one step method is suitable only for the preparation of aliphatic isothiocyanates.

Fig 1 : SCHEME SHOWING THE METHODS USED FOR SYNTHESIS OF ARYL ISOTHIOCYANATES.



Part.....IV

E X P E R I M E N T A L

(2) Isatin :

In a 1 litre three necked flask with a stirrer, thermometer and air-condenser, conc. sulfuric acid (326 ml; sp. gr. 1.84) was placed and warmed to 50°C. To this, dry isonitroso acetanilide 75.0 g (0.46 mole) was added at such a rate, as to keep the temperature between 60°C and 70°C but not higher. External cooling should be applied at this stage, so that, the reaction could be carried out more rapidly. After complete addition of the isonitroso acetanilide, the solution was heated to 80°C and kept at this temperature for 10 minutes to complete the reaction. Then the reaction mixture was cooled to room temperature and poured on 10-12 times its volume of cracked ice. After standing for about an half-hour, the isatin was filtered with suction, washed several times with cold water to remove the sulfuric acid and then dried in air. The product was pure enough for further reaction.

Yield : 50.0 g (75.0 %), m.p. 191-192°C.
(Lit.[133] m.p. 192°C).

5-Nitro isatin :

A solution of isatin 29.4 g (0.2 mole) in concentrated sulfuric acid 132 g (92 ml) was taken in a 250 ml three necked flask, equipped with a mechanical stirrer, a thermometer and a dropping funnel, and cooled to 0°C in

an ice-bath. To this, added slowly dropwise fumming nitric acid 12.6 g (8.4 ml, d 1.50) and the temperature was kept near to 0°C. After complete addition, the reaction mixture was allowed to stand for 30 minutes and then poured over 1 kg of cracked ice. A yellow precipitate of 5-nitro isatin was separated immediately, and filtered witn suction. Recrystallised from 50 % methyl alcohol.

Yield : 30.0 g (85.0 %), m.p. 254-255°C.
(Lit.[120] m.p. 254-255°C).

5-Nitro isatin-3-oxime :

In a 500 ml round bottom flask a mixture of 5-nitro isatin 19.2 g (0.1 mole), hydroxylamine-hydrochloride (7.0 g, 0.1 mole) and sodium formate 6.8 g (0.1 mole) were taken in H_2O (150 ml). The above mixture was refluxed on burner for 45 minutes and the brownish oxime was separated. The solution was cooled, and the precipitated oxime filtered and dried at 50°C. Recrystallised from ethanol.

Yield : 17.60 g (85.0 %), m.p. 234-235°C.
(Lit.[134] m.p. 235°C).

5-Nitro anthranilo nitrile :

5-Nitro isatin-3-oxime (20 g) was heated to reflux in nitrobenzene (70 ml) using 250 ml round bottomed flask on burner for 45 minutes. Then the solution was cooled

to room temperature and nitrobenzene was removed by steam distillation. The residue was cooled and precipitated. The brownish 5-nitro anthranilonitrile was filtered with suction. Recrystallised from aqueous acetone.

Yield : 10.4 g (66.0 %), m.p. 205-206°C.
(Lit.[119] m.p. 205-206°C).

2,4-Diamino-6-nitro quinazoline :

In a 250 ml three necked flask equipped with mechanical stirrer, a reflux condenser with a guard tube and a dropping funnel was taken a filtered solution of guanidine hydrochloride 2.88 g (0.03 mole) and sodium metal 0.75 g (0.033 mole) in absolute alcohol (50 ml).

This system was arranged on steam bath. A solution of 5-nitroanthranilonitrile 4.89 g (0.03 mole) in ethanol (10 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred under reflux for 5 hrs. Then it was cooled & the precipitated 2,4-diamino-6-nitro quinazoline was filtered and washed with ethanol.

Yield : 4.6 g (75.3 %), m.p. 360°C.
(Lit.[116] m.p. 360°C).

2,4,6-Triamino quinazoline :

In a hydrogenation bottle, was taken 2,4-diamino-6-nitro-quinazoline 4.10 g (0.02 mole) in dimethyl formamide (10 ml). The reaction mixture was heated in an heating mentle to dissolve the nitro compound. Raney nickel (1 g) was added to reaction mixture. This bottle was fixed on Parr hydrogenator. After complete reduction, the content of the bottle was filtered through buchner funnel. The Raney nickel was decomposed with dilute hydrochloric acid (10 %). The filtrate was concentrated under reduced pressure. The residue was recrystallised from water.

Yield : 2.21 g (63.72 %), m.p. 258-260°C.
(Lit.[116] m.p. 257-258°C).

3,5-Dichloro-4-hydroxyphenyl isothiocyanate :

In a three necked round bottomed flask (500 ml) fitted with mechanical stirrer, air condenser and dropping funnel was taken thiophosgene 1.6 g (1.08 ml; 0.144 mole) and 100 ml solution of aqueous acetic acid and dilute HCl (20 ml). The mixture was stirred in ice-cold condition for 20 minutes. 3,5-Dichloro-4-hydroxyaniline 2.3 g (0.0129 mole) in chloroform (100 ml) was added dropwise

to it maintaining the temperature at $0^{o}C$. The reaction mixture was further stirred at this temperature for 4 hrs. The chloroform layer was separated, washed with water till it showed neutral pH, dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The solid thus obtained was recrystallised from hot hexane.

Yield : 1.34 g (33.0 %), m.p. $98^{o}C$.

Analysis for : $C_7H_3Cl_2NOS$

	% C	% H	% N
Calcd.	38.17	1.36	6.36
Found	38.43	1.21	6.65

2,4,5-Trichlorophenyl isothiocyanate :

In a 250 ml three-necked flask equipped with a mercury sealed mechanical stirrer, water condenser, and a dropping funnel, was taken thiophosgene 1.3 g (0.88 ml; 0.0115 mole) in 50 ml of ice cold water and 50 ml of aqueous acetic acid. To it was added a solution of 2,4,5-trichloroaniline 1.96 g (0.01 mole) in chloroform (100 ml) dropwise maintaining the temperature at $0^{o}C$. The reaction mixture was stirred further at this temperature for 4 hrs. The chloroform layer was separated and washed with water,

till it became neutral. The chloroform layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. The solid obtained was recrystallised from hot hexane.

Yield : 1.65 g (70.0 %), m.p. 49°C.

Analysis for : $C_7H_2Cl_3NS$

	% C	% H	% N
Calcd.	35.22	0.83	5.87
Found	35.60	1.22	5.65

All the other substituted phenyl isothiocyanates were similarly prepared and are listed in Table (7).

Preparation of Thiourea, N-(p-isopropyl phenyl)-N'-[6-(2,4-diamino) quinazolinyl] :

A mixture of 2,4,6-triamino quinazoline 0.875 g (0.005 mole) and p-isopropyl phenyl isothiocyanate 0.885 g (0.005 mole) in ethanol was refluxed for 4 hrs on steam-bath. The solvent was removed under vacuum and the residue was taken in hexane, triturated well and filtered. The resultant thiourea derivative was recrystallised from aqueous ethanol.

Yield : 1.22 g (70.0 %), m.p. 187°C.

Analysis for : $C_{18}H_{20}N_6S$

	% C	% H	% N
Calcd.	61.36	5.68	23.86
Found	61.58	5.97	23.78

All the other thiourea derivatives were prepared by similar procedure during the course of this work. Their physical data is summarised in Table (8).

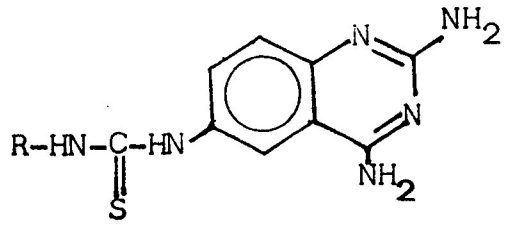
TABLE-7 : Substituted aryl/hetero aryl isothiocyanates.

R — NCS

No.	R	M.P. °C	Mol. Formula	ANALYSIS Calculated % C	% H	% N	Found % C	% H	% N
1.	2-Chloro-5-nitro phenyl	74	$C_7H_3ClN_2O_2S$	39.16	1.39	13.05	38.82	1.20	12.90
2.	3,5-Dibromo-4-hydroxy phenyl	123	$C_7H_3Br_2NOS$	27.17	0.97	4.53	27.64	1.02	4.78
3.	3,5-Dibromo-4-ethoxy phenyl	66	$C_9H_7Br_2NOS$	32.03	2.07	4.15	32.29	2.15	4.37
4.	3,5-Dichloro-4-hydroxy phenyl	98	$C_7H_3Cl_2NOS$	38.17	1.36	6.36	38.43	1.21	6.65
5.	3,5-Dichloro-4-ethoxy phenyl	110	$C_9H_7Cl_2NOS$	43.53	2.82	5.64	43.74	2.63	5.47
6.	2,5-Dichloro-4-nitro phenyl	150	$C_7H_2Cl_2N_2O_2S$	33.73	0.80	17.24	33.48	1.24	11.53
*7.	p-Isopropyl phenyl	-	-	-	-	-	-	-	-
8.	8-Quinolinyl	117-20	$C_{10}H_6N_2S$	64.51	3.22	15.05	64.39	3.47	15.47
9.	2,4,5-Trichloro phenyl	49	$C_7H_2Cl_3NS$	35.22	0.83	5.87	35.60	1.22	5.65
10.	3,4,5-Trimethoxy phenyl	63-65	$C_{10}H_{11}NO_3S$	53.33	4.88	6.22	53.12	4.69	6.56

* Available from the laboratory

TABLE-8 : Thioureas-N-(Substituted aryl)-N'-[6-(2,4-diamino)-quinazolyl]



No.	R	M.P.* °C	Mol. Formula	% Yield	ANALYSIS Calculated % C	% H	% N	Found % C	% H	% N
1.	2-Chloro-5-Nitro phenyl	251	$C_{15}H_{12}ClN_7O_2S$	65.5	46.20	3.08	25.15	46.58	2.85	24.84
2.	3,5-Dibromo-4-hydroxy phenyl	153	$C_{15}H_{12}Br_2N_6OS$	69.8	37.19	2.47	17.35	36.92	2.78	16.98
3.	3,5-Dibromo-4-ethoxy phenyl	150	$C_{17}H_{16}Br_2N_6OS$	70.4	39.85	3.12	16.40	40.03	2.94	16.04
4.	3,5-Dichloro-4-hydroxyphenyl	145	$C_{15}H_{12}Cl_2N_6OS$	69.0	45.55	3.03	21.26	45.12	2.89	20.84
5.	3,5-Dichloro-4-ethoxy phenyl	156	$C_{17}H_{16}Cl_2N_6OS$	70.2	48.21	3.78	19.85	48.63	3.42	19.88
6.	2,5-Dichloro-4-nitro phenyl	245	$C_{15}H_{11}Cl_2N_7O_2S$	68.0	42.44	2.59	23.19	41.97	2.19	22.87
7.	p-Isopropyl phenyl	187	$C_{18}H_{20}N_6S$	70.0	61.36	5.68	23.86	61.58	5.97	23.78
8.	8-Quinolinyl	240	$C_{18}H_{15}N_7S$	60.0	59.81	4.15	27.13	59.87	3.85	27.46
9.	2,4,5-Trichloro phenyl	290	$C_{15}H_{11}Cl_3N_6S$	59.5	43.52	2.65	20.30	43.13	2.92	19.96
10.	3,4,5-Trimethoxy phenyl	205	$C_{18}H_{20}N_6O_3S$	61.0	53.98	4.99	20.99	53.68	4.84	20.87

* Melting points are capillary melting points and are uncorrected.

Part..... V

BIOLOGICAL RESULTS, DISCUSSION & CONCLUSION

BIOLOGICAL RESULTS, DISCUSSION & CONCLUSION

The progress in chemotherapy is intimately associated with the development of adequate screening methods which guide the research workers in the selection of agents for clinical studies and set the pattern for future drug design. The primary evaluation of drugs involves *in vitro* testing of their activity against a particular organism which they are meant to inhibit.

Screening procedure :

In vitro antituberculosis testing was carried out against the human virulent strain of *Mycobacterium* tuberculosis ($H_{37}Rv$) by the method of disperse culture technique using Kirchner's medium containing Tween-80 as described by Rake *et al*.[135] Sterile normal bovine serum (0.5 ml) was added to sterile Kirchner disperse medium (4.5 ml) dispersed in borosilicate test tube (150 x 20 mm). It was inactivated by heating at 56°C for thirty minutes.

The compounds (25 mg) under test were dissolved in (10 ml) solvent such as dimethyl formamide, dilute-HCl, ethanol etc. as the case may be. The serial drug dilutions were made in such a way as to give final concentrations of

of 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.19 μg/ml. The inoculum consisted of 0.1 ml of standard suspension of M. tuberculosis ($H_{37}Rv$) containing 10^6 bacilli/ml was added to each test tube. The tubes were incubated at 37°C for seven to eight days and then examined for the presence or absence of the growth of the test organisms. The lowest concentration which showed no visible growth was taken as an end point.

Control tubes with INH and ethambutol as standard drugs and tubes without any drugs were kept for comparison. Also the solvents used for dissolving the substances under study were similarly tested to see that, they did not affect the growth at the concentrations used under these experimental conditions. INH inhibited the growth upto 0.04 μg/ml and ethambutol upto 0.15 μg/ml.

Results and Discussion :

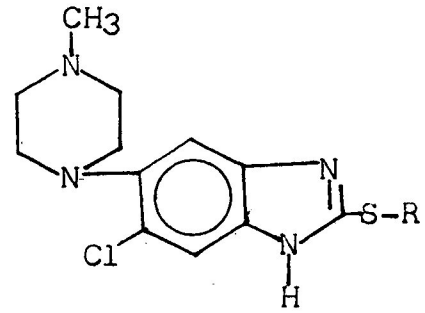
A total of fourty six compounds were synthesized and subjected for their in vitro antibacterial and anti-tubercular screening. Most of the compounds have shown antitubercular activity at MIC values ranging from 25 to 0.312 μg/ml. The MIC of fifteen compounds is 1.25 μg/ml. Rest of the compounds have shown satisfactory results.

From the various 5-(N-methyl piperazino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles (Part-II, Section-A) almost all the compounds exhibited good *in vitro* antitubercular activities (Table 9, Page 91). The most active of them were 5-(N-methyl piperazino)-6-chloro-2-(*p*-chlorobenzyl) thiobenzimidazole (0.625 µg/ml) (Compound No.2) and 5-(N-methyl piperazino)-6-chloro-2-(*p*-bromo benzyl) thiobenzimidazole (0.78 µg/ml) (Compound No. The activity of this series against *S. aureus* and *E. coli* ranges from 12.5 to 100 µg/ml. For antitubercular activity, halogen substitution at para position of benzyl nucleus was observed to be favourable.

The compounds from 5-(morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazole series (Part-II, Section-B) did not show any marked antitubercular and antibacterial activities (Table-10, Page No. 92). The most active compound from this series was 5-(morpholino)-6-chloro-2-(*p*-fluro-benzyl) thiobenzimidazole (0.625 µg/ml) (Compound No.2) for antitubercular activity. This indicates that the presence of morpholine did not play any significant role.

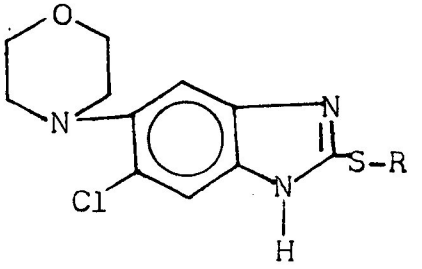
Table (11, Page No. 94) represents the activities of 5-(*n*-propylthio)-6-chloro-2-substituted benzyl or hetero-aryl thiobenzimidazoles (Part-III, Section-A). All the

TABLE-9 : 5-(N-Methyl piperazino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles.



No.	R	In vitro testing results against		
		$H_{37}Rv$ strain of *M. tuberculosis* in µg/ml	*S. aureus* in µg/ml	*E. coli* in µg/ml
1.	*p*-Bromo benzyl	0.78	100	100
2.	*p*-Chloro benzyl	0.625	12.5	50
3.	*p*-Fluro benzyl	2.5	50	100
4.	*m*-Hydroxy benzyl	1.25	50	50
5.	*p*-Nitro benzyl	1.25	50	50
6.	*m*-Phenoxy benzyl	0.625	50	50
7.	2-Chloro-4-nitro benzyl	1.25	50	100
8.	2,4-Dichloro benzyl	1.25	12.5	100
9.	3,4-Dichloro benzyl	1.25	12.5	100
10.	7-Chloro-4-quinolinyl	1.25	50	50

TABLE-10 : 5-(Morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles.



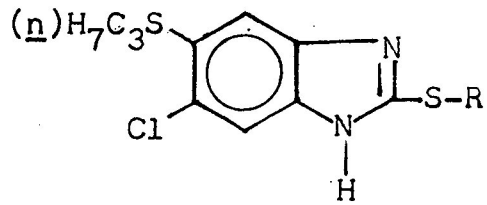
No.	R	In vitro testing results against		
		$H_{37}Rv$ strain of *M. tuberculosis* in µg/ml	*S. aureus* in µg/ml	*E. coli* in µg/ml
1.	*p*-Chloro benzyl	2.5	--	100
2.	*p*-Fluro benzyl	0.6	50	25
3.	*p*-Nitro benzyl	25	--	100
4.	*m*-Phenoxy benzyl	12.5	--	50
5.	2,4-Dichloro benzyl	2.5	--	50
6.	3,4-Dichloro benzyl	5.0	--	50
7.	2-Chloro-4-Nitro benzyl	12.5	--	100
8.	7-Chloro-4-quinolinyl	1.25	--	100

compounds of this series were found active with the inhibitory concentration ranging from 0.312 to 5 μg/ml for M. tuberculosis and for gram +ve and gram -ve micro-organisms it ranges from 3.12 to 100 μg/ml. Notable among these for anti-tubercular activity were 5-(n-propylthio)-6-chloro-2-(p-bromo benzyl) thiobenzimidazole (0.312 μg/ml), (Compound No.1), 5-(n-propylthio)-6-chloro-2-(m-hydroxy-benzyl) thiobenzimidazole (0.312 μg/ml) (Compound No.4), 5-(n-propylthio)-6-chloro-2-(2-chloro-4-nitrobenzyl) thiobenzimidazole (0.312 μg/ml) (Compound No.8) and 5-(n-propylthio)-6-chloro-2-(7-chloro-4-quinolinyl) thio-benzimidazole (0.312 μg/ml) (Compound No.9). When these compounds were screened for gram +ve and gram -ve bacteria, compound namely 5-(n-propylthio)-6-chloro-2-(2,4-dichloro-benzyl) thio-benzimidazole has shown activity at 3.12 μg/ml against S. aureus and rest of the compounds did not show any marginal activity.

In this series also halogen substitution in the benzyl nucleus on the thiobenzimidazole moiety imparted good antituberculous and antibacterial activities to the corresponding compounds.

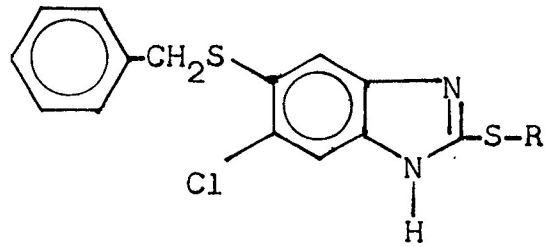
All the nine compounds from 5-(benzylthio)-6-chloro-2-substituted thiobenzimidazole series (Part-III, Section-B) were screened for antitubercular and antibacterial activities. Almost all compounds exhibited good antitubercular and average antibacterial activities (Table-12, Page No. 95).

TABLE-11 : 5-(n-Propylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles:



No.	R	In vitro testing results against		
		$H_{37}Rv$ strain of *M. tuberculosis* in µg/ml	*S. aureus* in µg/ml	*E. coli* in µg/ml
1.	p-Bromo benzyl	0.312	50	100
2.	p-Chloro benzyl	2.5	12.5	100
3.	p-Fluro benzyl	5.0	50	100
4.	m-Hydroxy benzyl	0.312	50	100
5.	p-Nitro benzyl	1.25	100	100
6.	2,4-Dichloro benzyl	2.5	3.12	100
7.	3,4-Dichloro benzyl	5.0	6.25	100
8.	2-Chloro-4-nitro benzyl	0.312	6.25	100
9.	7-Chloro-4-quinolinyl	0.312	50	100

TABLE-12 : 5-(Benzylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles.



No.	R	In vitro testing results against		
		$H_{37}Rv$ strain of *M. tuberculosis* in µg/ml	*S. aureus* in µg/ml	*E. coli* in µg/ml
1.	*p*-Bromo benzyl	0.625	50	50
2.	*p*-Chloro benzyl	0.625	100	---
3.	*p*-Fluro benzyl	1.25	50	100
4.	*m*-Hydroxy benzyl	25	50	50
5.	*p*-Nitro benzyl	1.25	25	100
6.	2,4-Dichloro benzyl	1.25	12.5	100
7.	3,4-Dichloro benzyl	0.312	3.125	50
8.	2-Chloro-4-nitro benzyl	5.0	25	100
9.	7-Chloro-4-quinolinyl	1.25	100	100

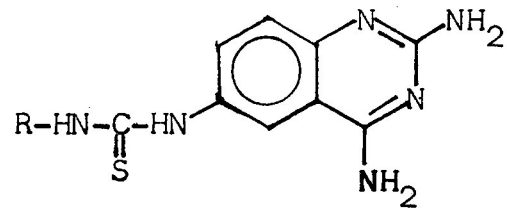
Among these, 5-(benzylthio)-6-chloro-2-(p-bromo benzyl) thiobenzimidazole (0.625 µg/ml) (Compound No.1), 5-(benzylthio)-6-chloro-2-(p-chlorobenzyl) thiobenzimidazole (0.625 µg/ml)(Compound No.2) and 5-(benzylthio)-6-chloro-2-(3,4-dichloro benzyl) thio-benzimidazole (0.312 µg/ml) (Compound No.7) seems to be promising. The same compound, i.e. 5-(benzylthio)-6-chloro-2-(3,4-dichlorobenzyl) thiobenzimidazole (Compound No.7) exhibited the antibacterial activity at 3.125 µg/ml against S. aureus. This indicate that presence of halogen substitution is significant for antitubercular and antibacterial activities.

From various thioureas-N-(substituted aryl)-N'-[6-(2,4-diamino)-quinozolyl] (Part-IV) screened, for antitubercular and antibacterial activities. All these compounds exhibited good antitubercular activity which ranges from 10 go 3.12 µg/ml. (Table 13, Pate No. 97). Most of these compounds were inactive against S. aureus and E. coli. The most active for antitubercular activity from these were thiourea-N-(2,5-dichloro-4-nitrophenyl) N'-[6-(2,4-diamino) quinazolinyl] (0.312 µg/ml)(Compound No.6 and thiourea-N-(2,4,5-trichlorophenyl)-N'-[6-(2,4-diamino)-quinazolinyl] (0.312 µg/ml) (Compound No.9).

Conclusion :

The following important conclusions could be drawn on the basis of the findings of in vitro screening of the various thiobenzimidazoles and thioureas.

TABLE-13 : Thioureas-N-(substituted aryl)-N'-[6-(2,4-diamino) quinazolyl].



No.	R	In vitro testing results against $H_{37}Rv$ strain of *M. tuberculosis* in µg/ml	*S. aureus* in µg/ml	*E. coli* in µg/ml
1.	2-Chloro-5-nitro phenyl	1.25	25	--
2.	3,5-Dibromo-4-hydroxy phenyl	2.5	--	100
3.	3,5-Dibromo-4-ethoxy phenyl	0.625	--	Not active at 100
4.	3,5-Dichloro-4-hydroxy phenyl	5.00	--	100
5.	3,5-Dichloro-4-ethoxy phenyl	1.25	--	50
6.	2,5-Dichloro-4-nitro phenyl	0.312	50	--
7.	*p*-Isopropyl phenyl	10.0	--	50
8.	8-Quinolinyl	2.5	--	50
9.	2,4,5-Trichlorophenyl	0.312	25	50
10.	3,4,5-Trimethoxyphenyl	1.25	50	100

2-Substituted thiobenzimidazoles having heterocyclic N-methyl piperazine at 5-position were significantly more active than the corresponding morpholino substitution at the same position.

The presence of halogen in benzylthio at 2-position of the benzimidazole moiety greatly contributes to antitubercular activity.

In the case of n-propylthiol and benzylthiol at 5-position of the thiobenzimidazole, substitution of n-propylthiol is much more significant than the benzylthiol. In these two series also halogen substitution plays important role for antitubercular activity and antibacterial activity.

In substituted quinazoline thioureas also halogen substitution seems to be useful for imparting biological activity to the molecule.

SPECTROSCOPIC METHOD OF ANALYSIS

SPECTROSCOPIC METHOD OF ANALYSIS

Infrared spectroscopy :

Infrared spectroscopy is the most versatile, highly efficient and important technique for solving the problems relating to structural elucidation of organic molecules without the tiresome evaluative method.

A molecule is not a rigid assemblage of atoms, it can be considered to resemble a system of balls of varying masses, corresponding to the atoms of the molecule and springs of varying strengths, corresponding to the chemical bonds of a molecule. The various stretching and bending vibrations of a bond occur at certain quantized frequency. When the infrared light of the frequency, corresponding to the bond vibration is incident on the molecule, energy is absorbed and the amplitude of that vibration is increased. When the molecule reverts from the excited state, the absorbed energy is released as heat. This is recorded by the spectrophotometer in the form of absorption bands.

All the absorption bands cannot be characterised in infrared spectroscopy but those that can, however provide a wealth of structural information about a molecule. Hence, it is extremely useful in the identification of functional groups.

The region between 1430-910 cm^{-1} in infrared spectrum is particularly rich in absorption bands. Although similar molecules may show very similar spectra in the region 4000-1430 cm^{-1}, there will be discernible differences in the 1430-910 cm^{-1} region. For this reason, it is frequently called the finger pring region.

The compounds reported in Part II, Section A have been characterized by the following groups.

5-Substituted benzimidazole ring :

This ring structure[136] shows three absorption bands in the region between 900-800 cm^{-1}. The bands are normally differentiated into three regions of absorption. 900-870 cm^{-1} 830-812 cm^{-1}, and 820-800 cm^{-1}.

N-Methyl piperazine ring :

The CH_2 wagging vibration of the piperazine ring is observed at 1290 cm^{-1}. An absorption peak at 720 cm^{-1} represent the ring vibration of the piperazine molecule.

C-S-C (Sulphide) linkage :

The C-S-C linkage is characterized[137] by an absorption band in the region between 1440-1415 cm^{-1}. A stretching vibration[137] is also assigned to the sulphide linkage which occur in the region 700-600 cm^{-1}. But this band is usually weak and sometimes may be absent.

Imidazole ring :

The ring stretching vibration[138] of the imidazole ring is obtained at 1550 cm^{-1}. This is assigned to the C = N and C - N stretching vibration.

Halogen compounds (C-X) : Where X = Chlorine atom.

The C-Cl stretching vibrations[139] are characterized by absorption peaks in the region between 760-600 cm^{-1}.

Substituted benzene ring :

The 1,4-substituted on the benzene ring is identified by a strong band in the region between 1125-1050 cm^{-1}.

The compounds reported in Part II, Section B have been characterized by the presence of the morpholine ring, in addition to some of the group frequencies discussed earlier. The N-methyl piperazine ring is absent in this class of compounds.

The morpholine ring[140] is characterized by three strong bands in the region between 1300-1100 cm^{-1}. These normally appear at 1248, 1142 and 1107 cm^{-1}.

The compounds reported in Part III, Section A are further characterized by the following group frequencies.

n-Propyl :

This group gives rise to an absorption peak of medium intensity in the region between 2900-2800 cm^{-1}.

Halogen compound (C-X) : Where, X = Flourine.

This is characterized[141] by a strong band in the region between 1400-1000 cm^{-1}.

$-NO_2$ group :

The $-NO_2$ group exhibits absorption due to a symmetrical and asymmetrical stretching.[142] The asymmetrical absorption is observed as a strong band in the 1661-1499 cm^{-1} region. The symmetrical absorption occurs in the region between 1389-1259 cm^{-1}. The exact position of the bands is dependent on substitution and unsaturation in the vicinity of the $-NO_2$ group.

In addition to some of the group frequencies discussed earlier, the compounds reported in Part III, Section B have been characterized by the presence of the monosubstituted benzene ring. This gives rise to an absorption frequency in the region between 1525-1475 cm^{-1}.

The compounds listed in Part IV have been identified by the following group frequencies.

Primary amine :

The primary amines[143] give two absorption bands in the region between 3500-3300 cm^{-1}. The first of these which is due to the asymmetric stretching mode is usually found near 3500 cm^{-1}, and the second, which arises from the corresponding symmetrical mode, near 3400 cm^{-1}

A secondary absorption peak is observed in the region between 1340-1250 cm^{-1}.

Secondary amine :

This group gives rise to an absorption peak in the region 1360-1280 cm^{-1}.

Aromatic ether :

The aromatic ethers[144] are characterized by an absorption band of medium intensity in the region between 1070-1000 cm^{-1}

Thiocarbonyl group :

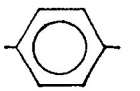
The thiocarbonyl group which is linked to nitrogen as in the class of compounds under discussion, exhibit two absorption bands[145] of medium intensity. The first band is found in the 1525-1425 cm^{-1} region while the second occurs in the 1300-1075 cm^{-1} region.

Experimental data :

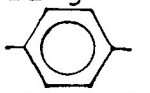
The compounds synthesized in the present investigation have been analysed by the KBr-pellet technique. Spectral grade potassium bromide was used for this purpose. All infrared spectra were recorded on a Perkin-Elmer 257 grating Infrared Spectrophotometer.

TABLE-13 : Infrared Data of the New Compounds.

PART II, Section-A

Compound No.		5-Substituted Benzimidazole			C-S-C(Sulphide) linkage		-N-Methyl piperazine		Imidazole C=N, C-N Str.	1,4-Subs. Benz. ring 	R-Cl linkage
	Reqd. Cm^{-1}	900-870	830-812	820-800	1440-1415	700-600	1290	720	1550	1125-1050	760-600
1		-	835	820	1445	650	1280	710	1590	1090	740

PART II, Section-B

Compound No.		5-Substituted Benzimidazole			C-S-C(Sulphide) linkage		Morpholine			Imidazole C=N, C-N Str.	1,4-Subs. Benz. ring 	R-Cl linkage
	Reqd. cm^{-1}	900-870	830-812	820 800	1440 1415	700-600	1248	1142	1107	1550	1125-1050	760-600
2.		875	855	840	1440	650	1250	1170	1110	1580	-	760
3.		865	855	840	1470	650	1255	1175	1115	1600	-	730
4.		875	850	840	1440	650	1260	1155	1100	1575	1090	750
5.		875	860	840	1470	650	1255	1175	1110	1550	-	765

(Table 13.....Contd.) PART III, Section-A

Compound No.		5-Substituted Benzimidazole			C-S-C(Sulphide)linkage		Imidazole C=N, C-N, Str.	1,4-Subs. Benz. ring	$n-C_3H_7$	$-NO_2$ group		Halogen compounds	
												C-F	C-Cl
	Reqd. cm^{-1}	900-870	830-812	820-800	1440 1415	700-600	1550	1125-1050	2900-2800	1661-1499	1389-1259	1400-1000	760-600
6.		-	835	-	1445	675	1590	1090	-	-	-	1230	770
7.		880	850	805	1440	680	1590	1090	2940	1510	1330	-	765
8.		-	850	840	1455	680	1600	-	2900	-	-	-	750
9.		-	850	840	1455	680	1600	1090	2900	-	-	-	750

Contd.....

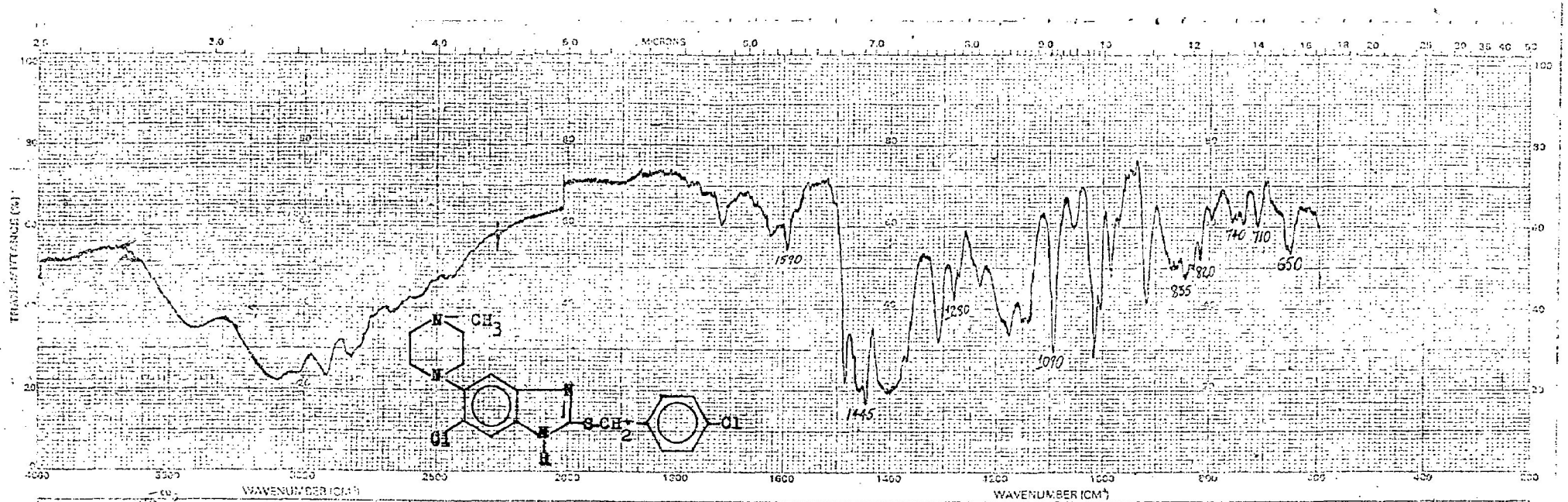
(Table 13.....Contd.).

PART III, Section-B.

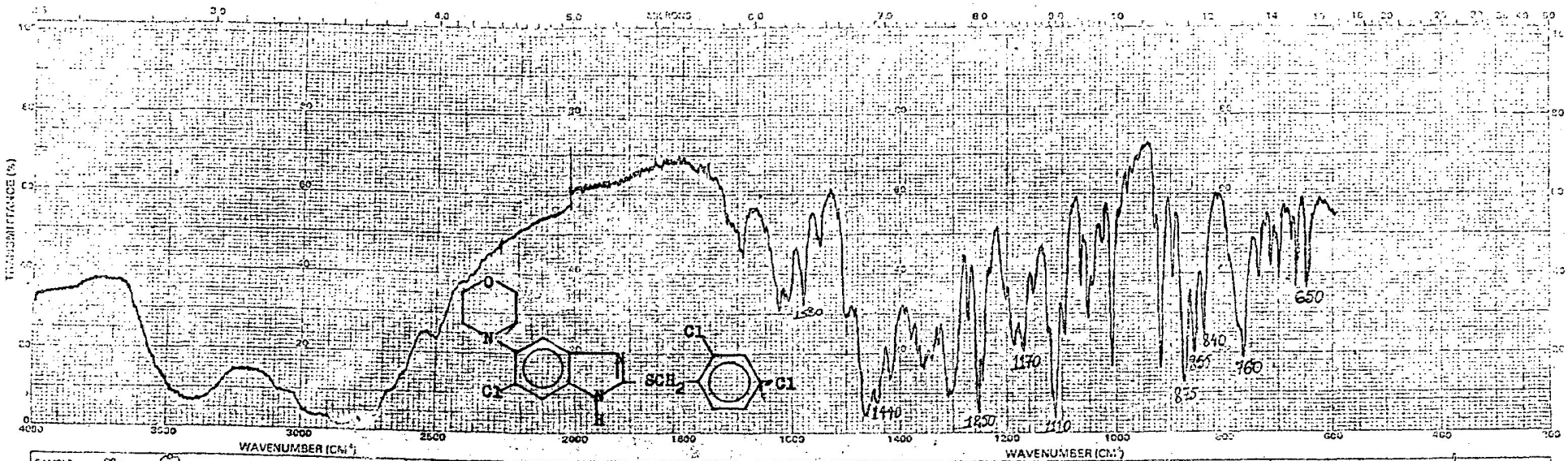
Compound No.	5-Substituted Benzimidazole			C-S-C(Sulphide) linkage		Imidazole C=N,C-N Str.	1,4-subs. Benz. ring	Mono-subs. Benz. ring	Halogen compounds C-Cl
Reqd. cm^{-1}	900-870	830-812	820-800	1440-1415	700-600	1550	1125-1050	1525-1475	760-600
10.	865	845	835	1445	-	1595	1095	1485	750
11.	-	850	835	1450	680	1600	1090	1490	725

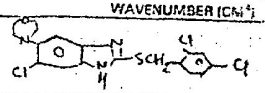
PART IV

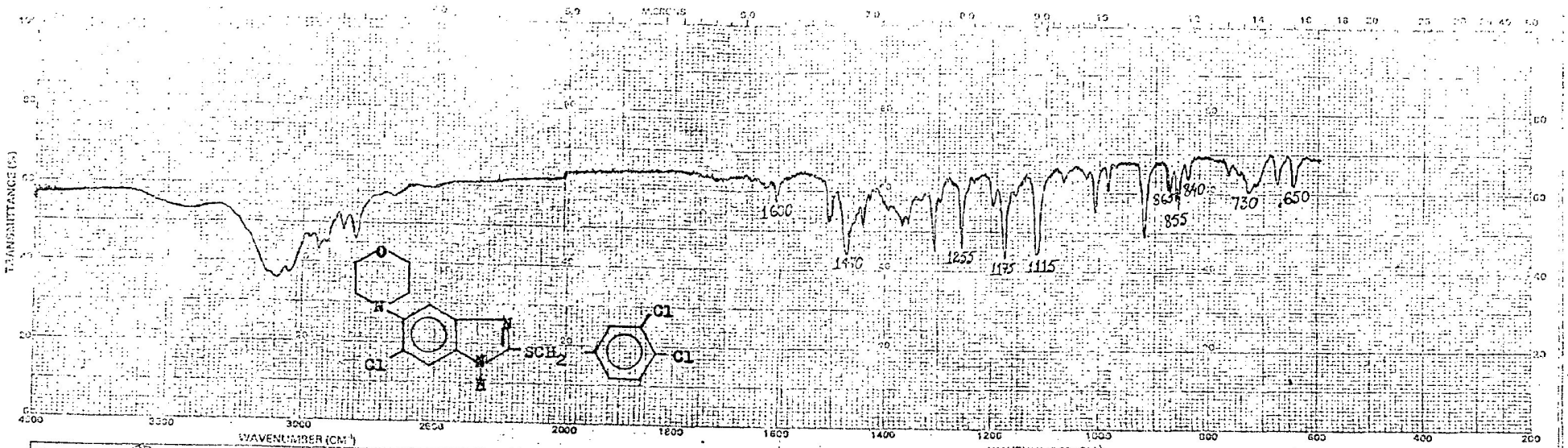
Compound No.	Primary Amine			Secondary Amine	Aromatic Ether	Thiocarbonyl N-C=S group		Halogen compounds C-Cl
Reqd. cm^{-1}	3500	3400	1340-1250	1360-1280	1070-1000	1525-1425	1300-1075	760-600
12.	3400	3300	1225	1380	1030	1460	1070	810

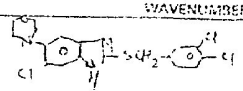


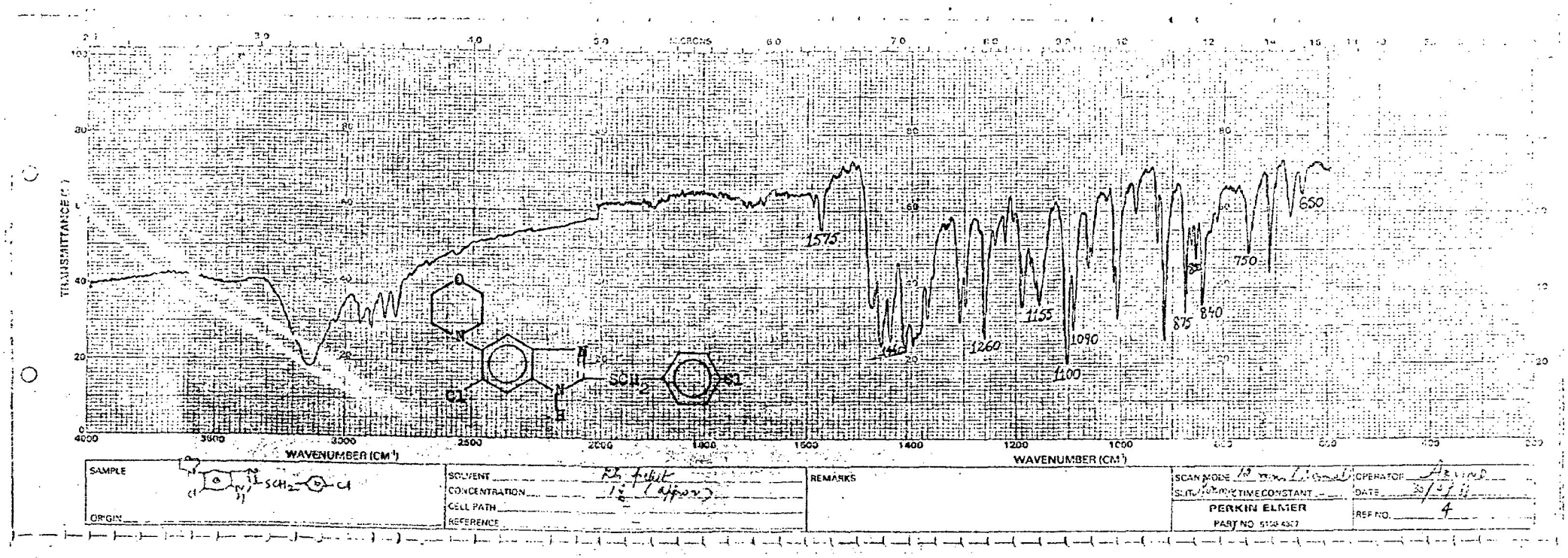
SAMPLE	SOLVENT KBr pellet	REMARKS	SCAN MODE ___ OPERATOR ___
	CONCENTRATION		SLIT ___ TIME CONSTANT ___ DATE ___
ORIGIN	CELL PATH		PERKIN ELMER
	REFERENCE		PART NO. 5100.4307 REF NO. 1



SAMPLE m_3 	SOLVENT KBr fillet	REMARKS	SCAN MODE MEDIUM / SLIT / TIME CONSTANT / TOTAL	OPERATOR ARVIND
ORIGIN	CONCENTRATION			DATE 25/4/88
	CELL PATH		PERKIN ELMER	REF NO. 2
	REFERENCE		PART NO. 5100-4257	



SAMPLE  ORIGIN	SOLVENT KBr pellet CONCENTRATION CELL PATH REFERENCE	REMARKS	SCAN MODE MEDIUM SLIT Normal TIME CONSTANT 12 min PERKIN ELMER PART NO. 5100-4357
OPERATOR Arvind DATE 25/4/88 REF NO. 3			



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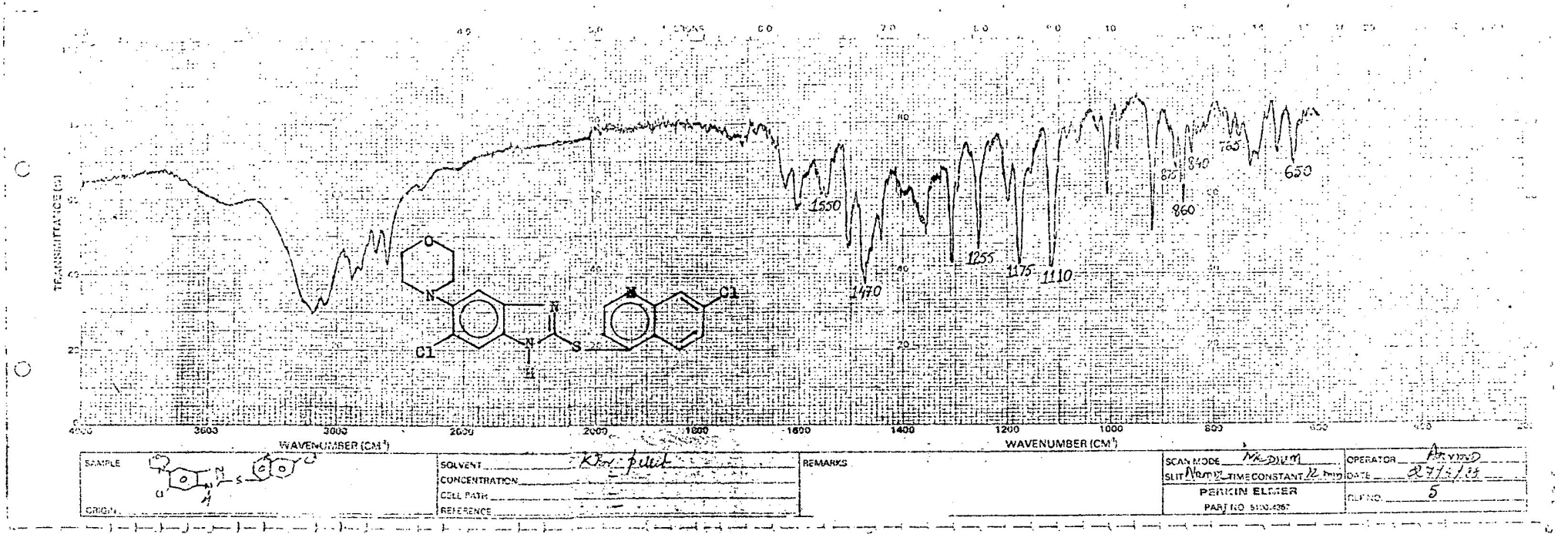
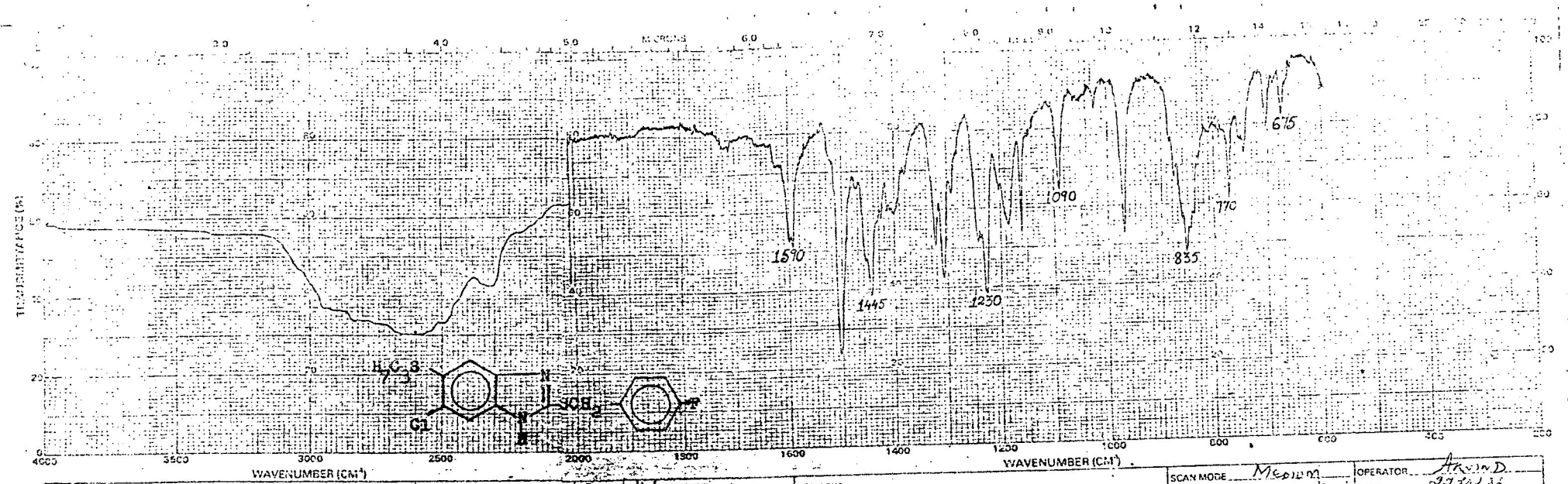
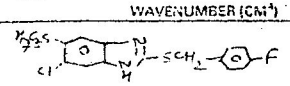
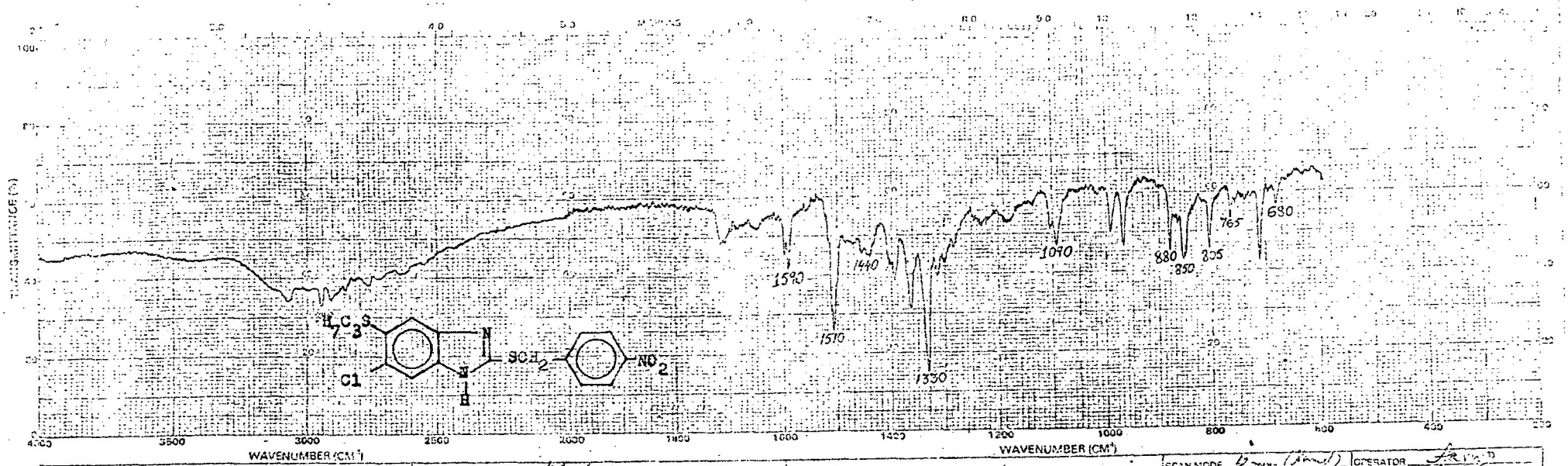


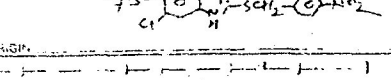
SAMPLE	SOLVENT KBr pellet	REMARKS	SCAN MODE Medium
	CONCENTRATION		SLIT Normal TIME CONSTANT 12 min
ORIGIN	CELL PATH		PERKIN ELMER
	REFERENCE		PART NO 5100-4267

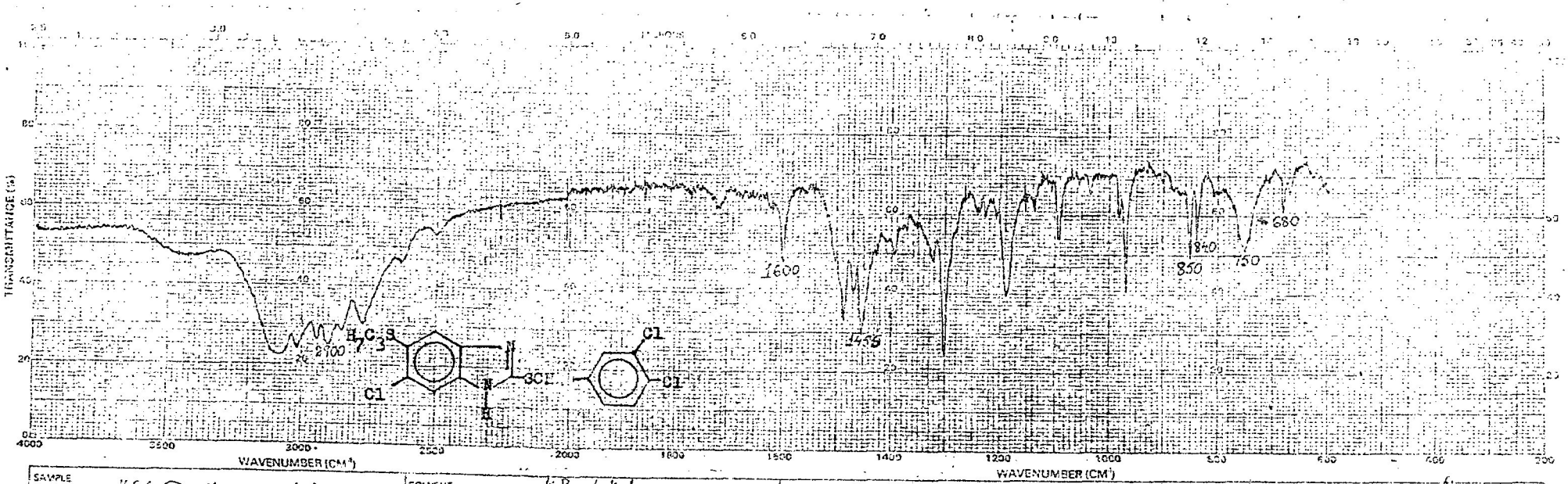
OPERATOR Arvind
DATE 27/5/93
SLIP NO. 5

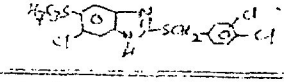


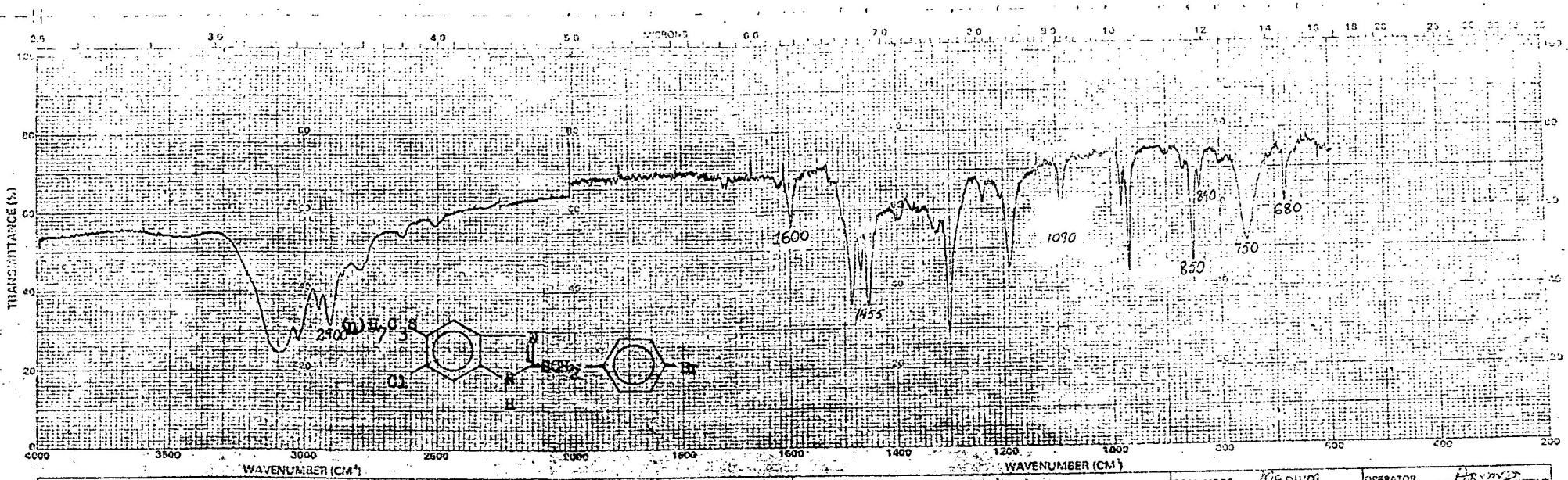
SAMPLE 	SOLVENT KBr pellet	REMARKS	SCAN MODE Medium
	CONCENTRATION		SLIT Normal TIME CONSTANT 12 min
	CELL PATH		PERKIN ELMER
	REFERENCE		PART NO. 5170-4367
			OPERATOR Arvind D.
			DATE 27/9/85
			REF NO. 6

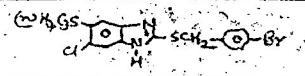


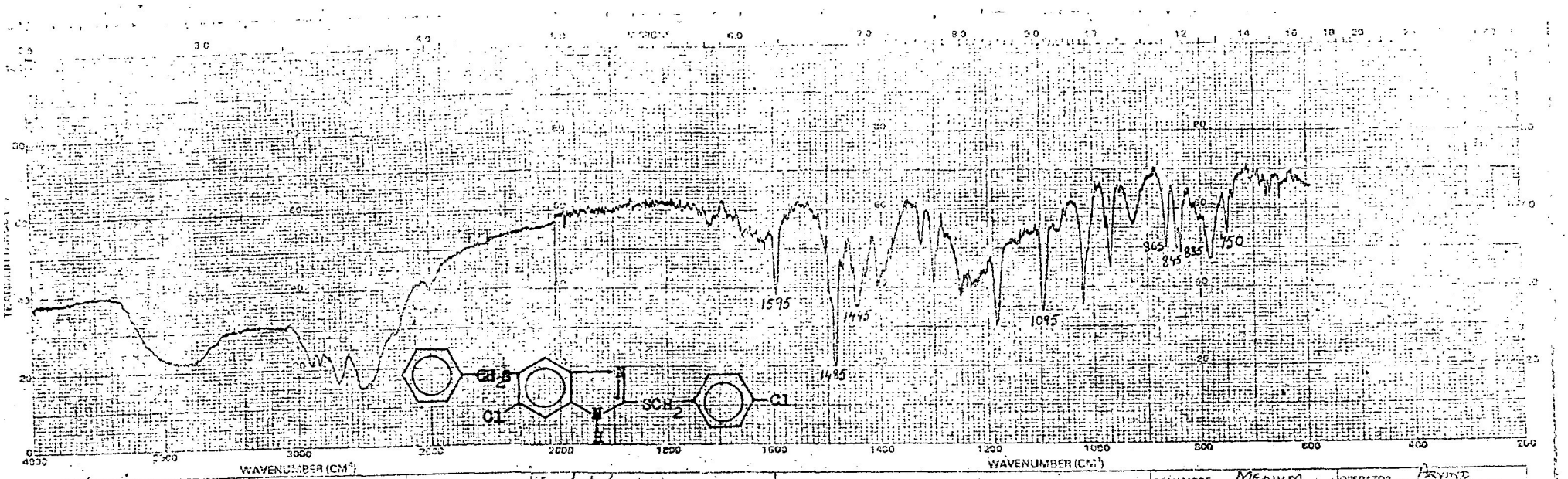
SAMPLE  ORIGIN	SOLVENT KBr pellet CONCENTRATION 1% (1/100) CELL PATH REFERENCE	REMARKS	SCAN MODE Wavenumber (Normal) SUT Normal TIME CONSTANT PERKIN ELMER PART NO. 5929-4007
OPERATOR [illegible] DATE 30/4/93 REF NO. 7			

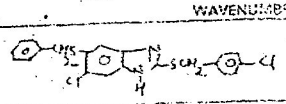


SAMPLE  ORIGIN	SOLVENT KBr pellet CONCENTRATION CELL PATH REFERENCE	REMARKS	SCAN MODE Medium SLIT/RESPONSE TIME CONSTANT 2 min PERKIN ELMER PART NO. 5100-0230
OPERATOR Pravin D DATE 29/4/98 REF NO. 8			

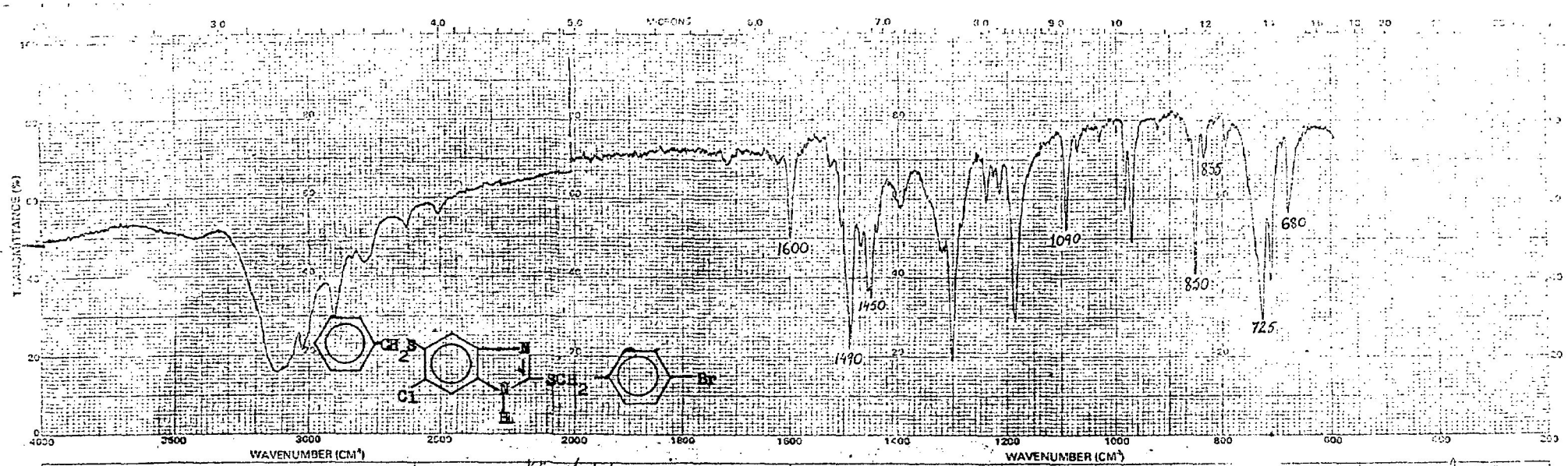


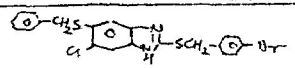
SAMPLE 	SOLVENT KBr pellet	REMARKS	SCAN MODE Medium / SLIT Normal / TIME CONSTANT 3 / OPERATOR [illegible] / DATE 3/14/88
ORIGIN	CONCENTRATION		PERKIN ELMER PART NO. 5100-4357 / REF NO. 9
	CELL PATH		
	REFERENCE		

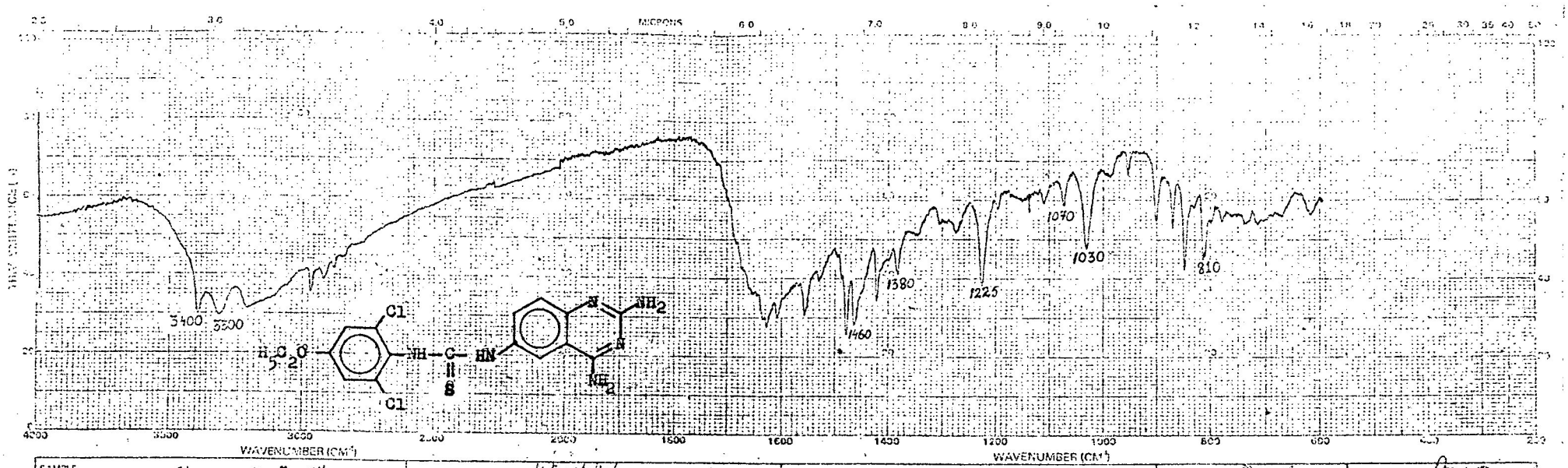


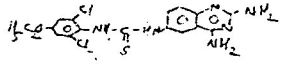
SAMPLE 	SOLVENT KBr pellet	REMARKS	SCAN MODE Medium
	CONCENTRATION —		SLIT Normal TIME CONSTANT 12
	CELL PATH —		PERKIN ELMER
	REFERENCE —		PART NO. 5100-3267
ORIGIN			

OPERATOR Devinder
DATE 09/5/02
REF NO. 10



SAMPLE  ORIGIN	SOLVENT KBr pellet CONCENTRATION CELL PATH REFERENCE	REMARKS	SCAN MODE MEDIUM SLIT AUTOMATIC TIME CONSTANT 1.0 PERKIN ELMER PART NO. 5110 4237
OPERATOR [illegible] DATE 02/7/05 REF. NO. 11			



SAMPLE  ORIGIN	SOLVENT KBr pellet CONCENTRATION CELL PATH REFERENCE	REMARKS	SCAN MODE Medium SLIT 2.0 mm TIME CONSTANT 2 min	OPERATOR Arvind DATE 9/5/88
			PERKIN ELMER PART NO. 5100-4097	REF NO. 12

S U M M A R Y

SUMMARY

In the present work, our ultimate goal was to establish the logical design of chemotherapeutic agents, which would selectively act against the mycobacteriae, that are infecting to the human beings. In the present study, it is the collection of different views regarding chemical, experimental and biological aspects. The entire work carried out during this course of study is divided into five parts.

Part-I, deals with the introductory aspects. This is followed by review of literature incorporating historical background of chemotherapy as well as the brief account of current drugs. This is concluded with plan of work consisti of different boosting guide lines behind the proposed synthetic work.

Part-II, covers the synthetic chemistry and various experimental aspects regarding the specific synthetic work carried out during the course of study. This part is divided into two sections A and B. The series under Section-A, deals in detail with the synthetic aspect of 5-(N-methyl-piperazino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles. These were obtained by reacting sodium salt of 2-mercapto-5-(N-methyl piperazino)-6-chloro benzimidazole with different substituted benzyl halides in ethanol.

2-Mercapto-5-(N-methyl piperazino)-6-chloro-benzimidazole was prepared by the general method such as reacting the corresponding substituted o-phenylene diamine with carbon disulfide in the presence of alkali.

Substituted benzyl halides were prepared by known literature method.[94,99,100]

The series under Section-B comprises the chemistry and synthetic aspects of 5-(morpholino)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles. These were prepared in the same manner as mentioned in Section-A.

Part-III is divided into Section A and B. 5-(n-propylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles (Section-A) were synthesized, considering the fact that the sulfide linkage at 5-position of benzimidazole moiety shows a variety of biological activities.[49] These were prepared by condensing sodium salt of 2-mercapto-5-(n-propylthio)-6-chloro benzimidazole with various substituted benzyl halides in ethanol at reflux temperature.

Section-B, covers the chemistry and synthetic aspects of 5-(benzylthio)-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles.

These were obtained by condensation of sodium salt of 2-mercapto-5-(benzylthio)-6-chloro-benzimidazole with substituted benzyl halides in ethanol.

In Part-IV we have studied the importance of substituted thioureas and prepared new type of quinazoline thioureas.

The introduction of side-chain such as $-NH-\overset{\overset{S}{\|}}{C}-NH-$ into the 2,4-diamino quinazoline nucleus at 6-position exhibited various types of biological activities such as antitubercular[104] and antimalarial.[105] This initiated the synthesis of thioureas N-(substituted aryl)-N'-[6(2,4-diamino)-quinazolinyl]. These were prepared by condensation of different aryl isothiocyanates prepared by the standard literature method,[122] with 2,4,6-triamino quinazoline in ethanol.

Part-V describes the method adopted for *in vitro* antitubercular screening against $H_{37}Rv$ strain of *M. tuberculosis*. INH and ethambutol were used as standard drugs for comparison. Structure activity relationship is discussed in detail and the conclusions are made regarding various thiobenzimidazoles and quinazoline thioureas. The structure assignment of the synthesised compounds is done in 'Spectroscopic Analysis' section. This part is concluded with the bibliography.

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S Y N O P S I S

S Y N O P S I S

Tuberculosis is one of the deadliest diseases which takes a heavy toll of human lives every year. It is a chronic bacterial disease still ranking high as a public health problem, even in the developing countries of the world. Tuberculosis can go on for several months or even a few years, if it is not treated at all or if it is not treated properly. It is estimated that, every year, 50-100 million people are infected by the tubercle bacilli and, of these, 10-20 million develop overt disease and 3 million die.[1]

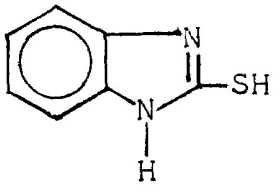
At present, INH, PAS, Ethambutol, Streptomycin and Rifampin, etc are the drugs of choice in different combinations in the treatment of tuberculosis. At times, however, the cases of toxic manifestation of antimicrobial agents are encountered. Also few strains of tubercle bacilli are resistant to these standard drugs. This evokes a formidable therapeutic problem and impart an essentiality to have a better drug having potent activity, lower toxicity and effective against resistant strains.

Thus, the work done in this direction is divided into different parts as briefly described here.

PART - II

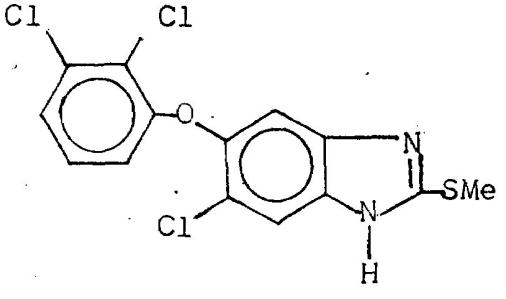
5-(N-METHYL PIPERAZINO/MORPHOLINO)-6-CHLORO-2-SUBSTITUTED BENZYL THIO OR HETERO ARYL THIOBENZIMIDAZOLES :

In literature, 2-mercapto-benzimidazole (I) derivatives are reported for their bacteriostatic and antifungal activities.[2,3]

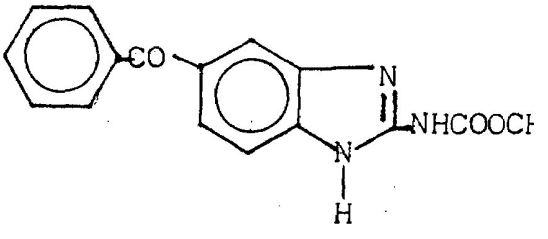


(I)

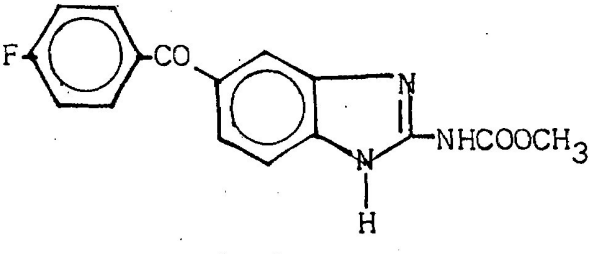
Also, long range of benzimidazole derivatives such as triclabendazole (II), mebendazole (III), flubendazole (IV etc, are available as established anthelmintic drugs.



(II)

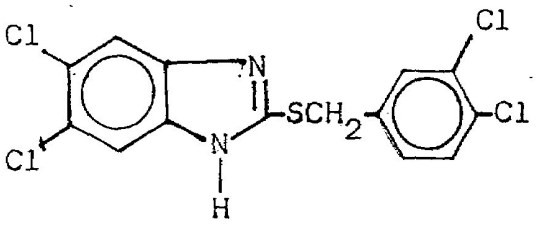


(III)



(IV)

Our laboratory reported number of benzimidazole derivatives of good antitubercular activity. Out of that 5,6-dichloro,2-(3,4-dichlorobenzyl) thiobenzimidazole (V) showed antitubercular activity at the concentration of 3.12 μg/ml.[4]



(V)

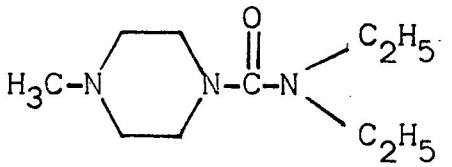
Thus, considering the biological and non-toxic properties of the benzimidazoles, the work in this line was continued. Various types of benzimidazoles with variety of aryl substitution at 2-position and hetero-aryl substituted at 5-position were synthesized. All these compounds were studied for their antitubercular activity *in vitro* against $H_{37}Rv$ strain of *M. tuberculosis*.

These compounds are described in Part-I under Section A and B.

Section - A :

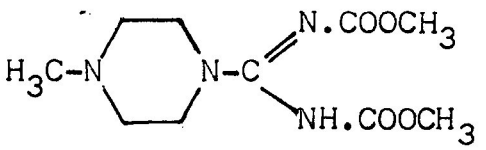
Synthesis and study of 5-N-methyl piperazino-6-chloro-2-substituted benzyl thio or heteroaryl thiobenzimidazoles :

Diethyl carbamazine (VI) is the drug of choice in the treatment of microfilarial infection.[5]



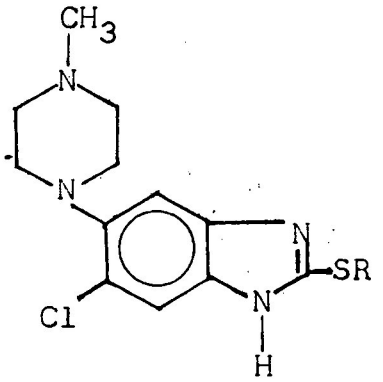
(VI)

In our laboratory also following type of substituted N-methyl piperazino compound (VII) has shown good *in vitro* antitubercular activity at the concentration of 12.5 μg/ml.



(VII)

Literature survey revealed that substitution of N-methyl piperazine enhances the antimicrobial activity of the parent moiety.[6] These findings gave impetus to incorporate N-methyl piperazine linkage at 5-position of the benzimidazole moiety. With this view following type of compounds (VIII) were synthesized and studied for their *in vitro* antitubercular activity.



(VIII)

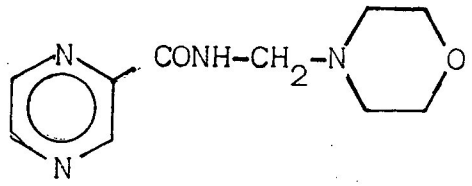
Where, R = Substituted benzyl, 7-chloro-4-quinolinyl, etc.

Section - B

Synthesis and study of 5-morpholino-6-chloro-2-substituted benzyl thio or hetero-aryl thiobenzimidazoles :

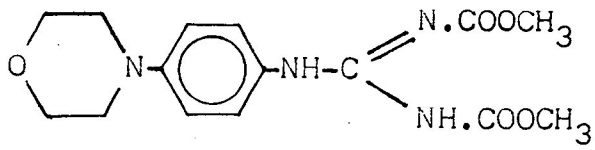
Literature survey shows that, morpholine itself is a active moiety against *Trichomonas vaginalis*.[7]

Felder *et al*.[8] reported morphozinamide (IX) as a antitubercular drug.



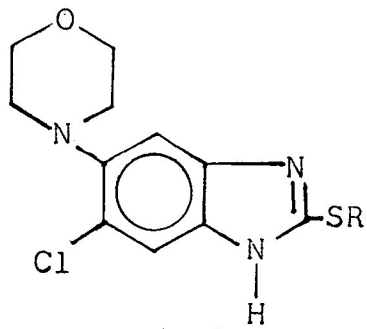
(IX)

Similarly following type of compound (X) from our laboratory showed *in vitro* antitubercular activity at the concentration of 0.2 μg/ml which is equivalent to standard antitubercular drug INH.



(X)

The above findings initiated us to synthesize new type of compounds (XI) having morpholino linkage at the 5-position of the basic benzimidazole moiety.



(XI)

Where, R = Substituted benzyl, 7-chloro-4-quinolinyl, etc.

These compounds were prepared by condensing sodium salt of 2-mercapto, 5-morpholino-6-chloro benzimidazole with different substituted benzyl bromides and 4,7-dichloro quinoline in ethanol and were studied for their in vitro antitubercular activity.

PART - III

5-(PROPYLTHIO/BENZYLTHIO)-6-CHLORO-2-SUBSTITUTED-BENZYLTHIO OR HETEROARYL THIOBENZIMIDAZOLES :

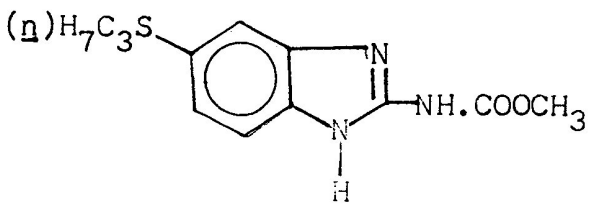
It is well known that different thio substituted benzimidazole derivatives have demonstrated significant biological activities.[9,10] Hence, it was proposed to undertake the studies of benzimidazole derivatives having propyl and benzyl thio linkages at 5-position of the benzimidazole moiety.

This part is divided into two sections.

Section - A

Synthesis and study of 5-propylthio-6-chloro-2-substituted benzyl or heteroaryl thiobenzimidazoles :

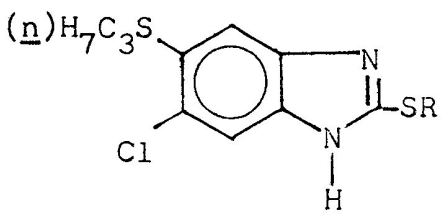
Encouraging results were presented recently by a research group of S.K. & F. Laboratories, who demonstrated that substitution of the benzimidazole nucleus in the 5-position by propyl thio group as in Albendazole (XII)[11] resulted in the formation of very good anthelmintic drug.



(XII)

Albendazole

Taking lead from this, it was thought worthwhile to synthesize following type of compounds (XIII).



(XIII)

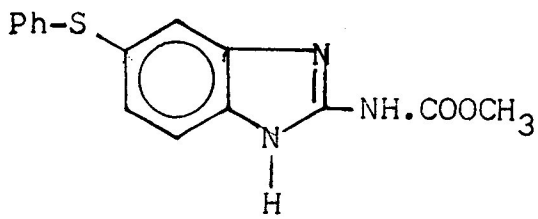
Where, R = Substituted-benzyl, 7-chloro-4-quinolinyl, etc.

All these compounds were screened for their *in vitro* antitubercular activity.

Section - B

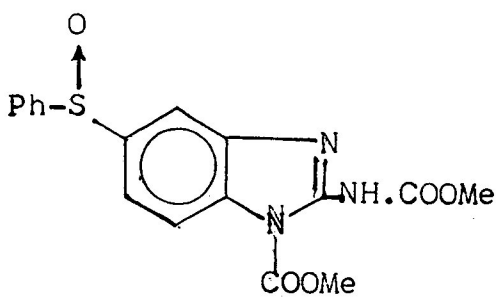
Synthesis and study of 5-benzyl thio, 6-chloro-2-substituted benzyl thio or heteroaryl thiobenzimidazoles :

Fenbendazole (XIV)[12] is reported as a potent anthelmintic drug.



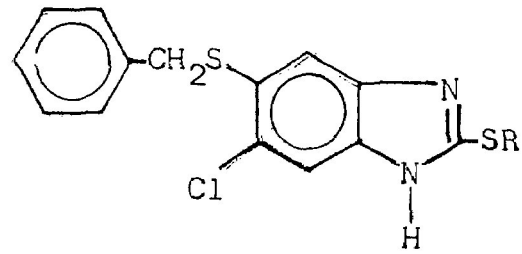
(XIV)

Recently, N. Vishwanathan and A.R. Sidhaye[13] reported the compound (XV) which is highly active against the hookworm Necator americanus in hamster.



(XV)

Thus, considering the biological usefulness of the sulfide linkage and sulfino group at 5-position of the benzimidazole nucleus, following type (XVI) of pompounds were synthesized.



(XVI)

Where, R = Substituted benzyl, 7-chloro-4-quinolinyl, etc.

All these compounds were prepared by condensing sodium salt of 2-mercapto-5-benzylthio-6-chloro benzimidazole with different benzyl bromides and 4,7-dichloro quinoline in ethanol.

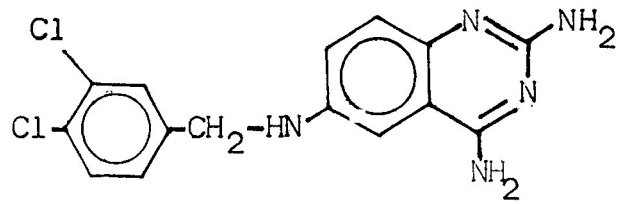
The compounds thus prepared were screened for their *in vitro* antituberculosis activity.

PART - IV

SYNTHESIS AND STUDY OF THIOUREAS-N-(SUBSTITUTED-ARYL)-N'-[6-(2,4-DIAMINO) QUINAZOLINYL] :

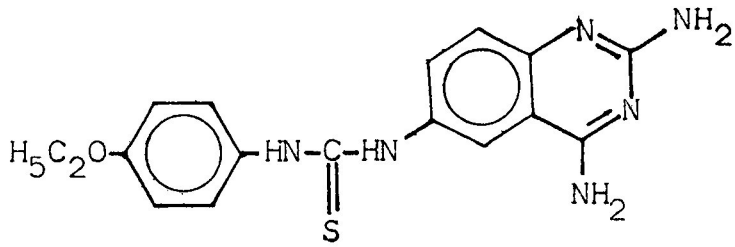
Substituted thiourea derivatives are known for antibacterial,[14] insecticidal,[15] and antileprotic[16] activities.

One of the early nonclassical prototype, namely 2,4-diamino-6-[(3,4-dichlorobenzyl) amino]-quinazoline (XVII) displayed strong antimalarial activity against *P. berghei* in mice and *P. gallinaceum* in chicks.[17]

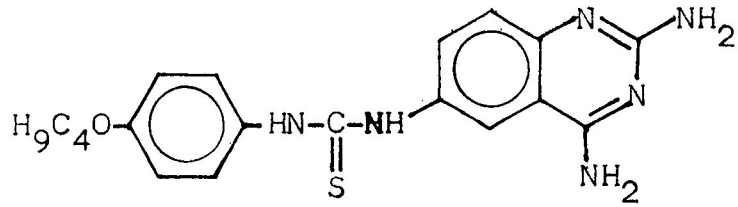


(XVII)

In our laboratory, following type of quinazoline thioureas (XVIII) and (XIX) also exhibited very good *in vitro* antitubercular activities each at the concentration of 1.56 μg/ml.[18]

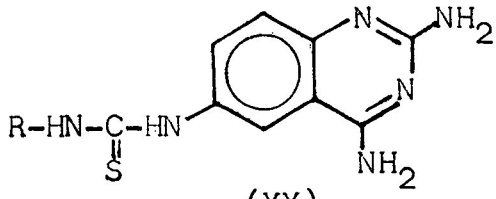


(XVIII)



(XIX)

All the above facts, gave impetus to synthesize thioureas-N-(substituted aryl)-N'-[6-(2,4-diamino)-quinazolinyl] (XX).



(XX)

Where, R = Substituted aryl.

These compounds were screened for their *in vitro* antitubercular activities against $H_{37}Rv$ strain of *M. tuberculosis*.

Quinazoline thioureas were prepared by condensing different aryl substituted isothiocyanates with 2,4,6-triamino quinazoline in ethanol.

PART - V

BIOLOGICAL RESULTS AND DISCUSSION :

About forty six compounds were synthesized during the course of the study. All these compounds were screened *in vitro* against $H_{37}Rv$ strain of *M. tuberculosis* by Rake's method.[19] The compounds were dissolved in suitable inert solvent, incorporated in different concentration into medium and tested against $H_{37}Rv$ strain by serial dilution method. After incubation at 37°C for 9 days absence or presence of growth indicated the activity of the compound under evaluation.

All the synthesized compounds have been screened for their antitubercular activity *in vitro* against *M. tuberculosis* strain of $H_{37}Rv$

On the basis of biological activity attempt will be made to correlate Structure Activity Relationship in the thesis.

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