

SYNTHESIS AND STUDY OF SOME BENZIMIDAZOLE AS
POSSIBLE ANTITUBERCULAR AGENTS

THESIS SUBMITTED
UNIVERSITY OF BOMBAY

FOR THE DEGREE OF
MASTER OF PHARMACY
IN
PHARMACEUTICAL CHEMISTRY

SUBMITTED BY
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UNDER THE GUIDANCE OF
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BOMBAY

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SYNTHESES AND STUDY OF
SOME BENZIMIDAZOLE DERIVATIVES AS POSSIBLE
ANTITUBERCULAR AGENTS

A
THESIS

Submitted to
THE UNIVERSITY OF BOMBAY
For
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By

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354

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..... VILAS LOKHANDE

STATEMENT UNDER UNIVERSITY RULES

As required by the University Rules 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 along with the source of the information in the " REFERENCES".

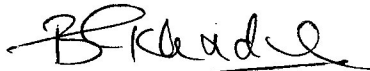
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Signature of the Candidate

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(DR. B. G. KHADSE)

Signature of the Research Guide

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PART I

INTRODUCTION

INTRODUCTION

Such has been the progress made in the epidemiology, the prevention and especially, the treatment of tuberculosis during the past three decades that this age-old killer of man has at last become a preventable and curable disease.

Through systematic research, it has been possible to develop an effective and simple technology that is inexpensive and amenable to standardization. As a result, the control of tuberculosis has ceased to be a primarily technical problem, requiring rare and highly specialized skills for its solution. Instead of only the privileged few who could be served in the past by the small number of specialists available, anyone suffering from tuberculosis or exposed to it may now enjoy the benefits of this technology, provided that it has been adopted to the requirements of a country's health programme. However, even within such a frame work, the efficient operation of a tuberculosis programme may encounter many difficulties. There is no uniform solution to existing or future problems. Each country will have to find the one that will suit its own needs best.

Even in United States to-day, over 35 million people have been infected with tubercle bacillus. Each

year 50,000 new cases of active disease, are diagnosed and 8,000 to 9,000 Americans die of tuberculosis.

In most Asiatic countries, the prevalence of this disease ranges between 0.5 to 5 percent. In a survey conducted by N.T.C.P., it was observed that about 1.5 % of the total population of the country is affected and nearly 2.5 million new cases are reported every year.¹

Peculiarities of the Problem :

There exist many obstacles that confront the investigator in the chemotherapy of tuberculosis. These difficulties are concerned with -

- 1) the rugged viability of the tubercle bacillus by virtue of its unique physical and chemical make-up;
- 2) the nature of the tissue changes that follow infection by tubercle bacilli;
- 3) the tendency of the disease to assume a chronic course with granulomatous lesions that are likely to persist regardless of the fate of the bacteria that induced them.

Tuberculosis, either acquired or produced experimentally, differs from most infections that have been found to be amenable to chemotherapeutic agents. In tuberculosis the

problem is not that of a simple septicemia or an acute inflammatory process but is instead that of an infection caused by an agent of considerable tenacity. The organism is harboured within the protection of a morbid anatomic structure that is frequently extensive and of long standing.

Critical Requirements for Effective Drug Therapy :

For effective and safe application, an antitubercular drug should have the following qualifications :

- 1) Very low order of chronic toxicity in virtue of the prolonged treatment required in this disease.
- 2) Capacity to penetrate all of the infectious lesions of the disease, and
- 3) Ease of administration, whether by mouth or by parenteral methods.

Chemotherapy of Tuberculosis :

It was found that no purpose was served by isolation and hospitalization in so far as spread of the disease to contacts is concerned, also climate has no role to play in the treatment. Dry climate or mountain air is not necessary for cure. Only chemotherapy is the keystone of management of all forms of tuberculosis in man.

After the identification of the cause of T. B. in 1882 another attempt was followed in 1885 with the discovery of X-rays by Roentgen. Even in spite of the above advances of the 19th century in a time log of 45 years no specific cure for the disease was obtained, with the advent of enlightened scientific atmosphere in 20th century. Streptomycin was discovered by Walksman. Then in rapid succession new drugs were added, namely, PAS (1949), INH (1952), Thiacetazone, Ethambutol, Rifampicin (1970) amongst others.

These available drugs can be divided into two broad categories - bactericidal and bacteriostatic.

Streptomycin and Viomycin	Partly bactericidal.
Rifampicin and Kanamycin	Fully bactericidal.
Isoniazid and Capreomycin	Fully bactericidal.
Pyrazinamide	Partly bacterial.
Ethambutol	Bacteriostatic.
Ethiacetazine	Bacteriostatic.
Cycloserin	Bacteriostatic.
PAS	Bacteriostatic.

DOSAGE AND TOXICITY

Drug	Dosage	Route of Administration	Toxicity
1. Rifampicin	450-600mg daily	Oral	Fever GI usually well tolerated. Flulike syndrome. Hepatic renal.
2. INH	5-8mg/kg	Oral and parenterally	Peripheral neuropathy, psychosis Euphoria, Dreams Hypersensitivity. Hepatitis well tolerated.
3. Streptomycin	30mg/kg 1gm/day .75gm for over 40 yrs. old.	I.M.	Eighth nerve. Vertigo, Ataxia Circumoral Paraesthesia Renal. Allergy-Drug Rash, Fever, contact dermatitis.
4. Pyrazinamide	1 to 1.5g/ daily	Oral	GI-Liver joint pains. Increased uric acid.
5. Ethambutol	25mg/kg for 2 months, then 15mg/ kg.	Oral	Retrobulbar neuritis.
6. Thiacetazone	3.5mg/kg. 150mg/daily for adult	Oral	GI Allergic-Rash, Fever. Steven Johnson Syndrome Exfoliative dermatitis, Hepatotoxic.
7. PAS Na or Ca salt	200mg/kg.	Oral, can be given parenterally	Gynaecomastia, GI-Nausea, Vomiting, Anorexia, Hepatic hypersensitivity, Goitre.
8. Ethionamide	500mg/ daily	Oral	GI-Liver.
9. Cycloserin	500mg/ daily	Oral	CNS-Epileptic fits Psychotic-Symptoms, Renal.
10. Kanamycin	1gm twice a week	I.M.	Renal, Eighth nerve.

Cycloserine, Ethionamide and Kanamycin are used for re-treatment of cases where bacilli are resistant to the standard drugs.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Mycobacteria are Gram-positive acid fast bacilli. There are several species of mycobacteria, but the most important clinically are those responsible for tuberculosis and leprosy. Chemotherapy does not cure these diseases in the strict sense of the word. Mycobacterial bacilli are very difficult to kill and are eliminated from the body extremely slowly after chemotherapeutic treatment of the infections. The success of chemotherapy depends upon the duration of treatment, the more prolonged, the more effective. Since it is so long (6 months to 4 years), 15 to 20 % of patients abandon it. Furthermore, although several useful agents are presently available, the chemotherapy of mycobacterial infections is still inadequate.

Antituberculous agents can be divided into the following classes :

1) Aminosalicylates and derivatives : Aminosalicylic acid, aminosalicylate calcium, amino salicylate potassium, amino salicylate sodium, PAS resin (Rezipas), Fenamisal (Tebamin), calcium benzamidosalicylate (Benzapas).

2) Hydrazides and derivatives : Isoniazid, Ftivazide, Salinazid (Acozide), sulfoniazid (Isorilone), Verazide

(Isoverazide), Streptoniazide (Streptoidrazide, Strazide), Glucazid, Menazone, Pasdrazide.

3) Thiosemicarbazone : Thioacetazone (Amithiozone, Conteben, Tilblone).

4) Thioamide : Ethionamide, Protionamide (Trevintix).

5) Thioureas : Thiocarbanidin (Thioban), Thiocarlide (Isoxyl).

6) Nicotinamides : Pyrazinamide, Morfozinamide.

7) Aliphatic diamines : Ethambutol.

8) Thiols : Ditophal (Etisul).

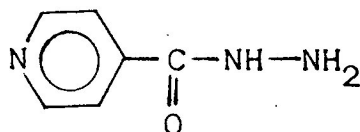
9) Surfactants : Macrocydon.

10) Antibiotics : Streptomycin, Kanamycin, Viomycin, Capreomycin, Cycloserine, Rifampin, Terizidone.

Isonicotinic Acid Hydrazide - INH (Isoniazide) :

In 1951, Fox² synthesized some pyridine analogues of amthiozone and found that β and γ isomers were active but that the α -isomer was not. An intermediate in the synthesis of isomer was isonicotinic acid hydrazide, which was tested against tuberculosis in mice and found to be more effective than any other agent. It has been called

isoniazide (Rimifon) and its isopropyl derivative Ipro-niazid (Morsilid).

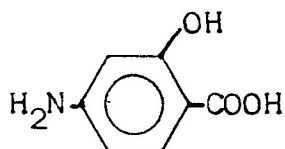


INH is known to be effective against tubercle bacillus. It is bacteriostatic and bactericidal in vitro. It is bactericidal even at its MIC for growing bacilli but do not affect resting cells.³ The 'resting' micro-organisms resume normal multiplication when removed from contact with the drug.

Several different modes of action of INH have been proposed, the primary one being the inhibition of mycolic acid synthesis. Second suggestion is that the drug chelates divalent metals and the copper, iron and cobalt chelates may be more effective in vitro than the parent drug. As the drug is a hydrazide, it can react with aldehydes such as pyridoxal phosphate, the coenzyme for decarboxylase and transaminases. It is unlikely that inhibition of these enzymes in the tubercle bacillus could do more than contribute to the bactericidal effect.

p-Amino Salicylic Acid (PAS) :

Bernheim⁴ shown in 1941 that benzoic acid and salicylic acids increase in oxygen uptake of virulent tubercle bacilli. Further, in 1946, Lehmann⁵ proposed p-amino salicylic acid as a chemotherapeutic agent for tuberculosis. This drug is useful only in tuberculosis and not in other infections.⁶ This led Lehmann⁵ to test a large series of related compounds for antitubercular activity. The most effective was PAS.



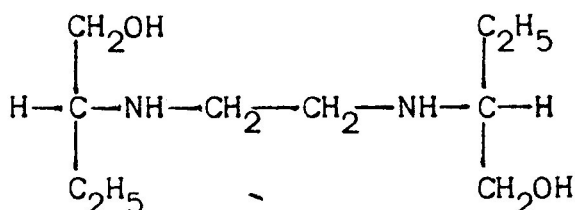
PAS was found to be highly bacteriostatic in vitro and also active orally against experimental infection in animals.^{7,8} It is effective against streptomycin resistant strain⁸, from 1 to 10 µg/ml PAS inhibit the growth of virulent tubercle bacilli and certain strains of the BCG organism, but the drug has little or no effect on the growth of other bacteria, including saprophytic mycobacteria. It is thus highly specific.

PAS acting presumably by interference with the salicylate and benzoate utilization by virulent mycobacteria. Para-amino benzoic acid, however, is a better antagonist⁹, and it is probable that PAS acts by interferring

with utilization of this by tubercle bacillus.

Ethambutol :

Ethambutol, d-(2,2'-(ethylene diamino)-di-1-butanol) was synthesized by Wilkinson et al.¹⁰ in 1961. The 1-isomer and meso form are inactive.

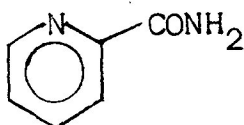


It is, effective against drug resistant strain of Mycobacterium tuberculosis and some other bacteria, e.g., M. kansasii, but it is not effective against microbes or fungi. Bacterial resistance to the drug develops in vitro when it is given alone. It is primarily bacteriostatic or weakly bactericidal.

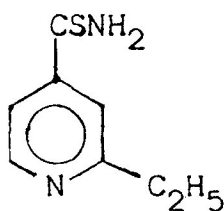
The structural requirement suggest that chelation of divalent metals may be important for some of the therapeutic and toxic effects of drug. Magnesium and also spermidine antagonize its action on strains of tubercle bacilli in vitro and its inhibition of RNA synthesis may be the result of magnesium chelation. DNA and protein synthesis are not directly affected.

Pyrazinamide :

Pyrazinamide was usually given in combination with other drugs. Such as Ethionamide and Cycloserine. It hampered bacteriostatic activity in vitro only at a slightly acidic pH presumably affecting the nicotinamide or nicotinic acid metabolism as a cofactor in dehydrogenase.

Ethionamide :

Ethionamide is approximately twice as active as Streptomycin and one-tenth as active as INH. It has got limited scope because of rapid development of resistance.^{11,12}

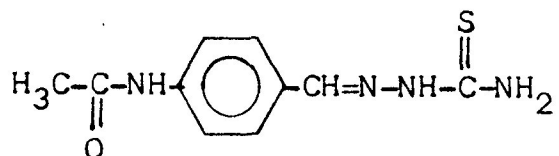


It is bactericidal and causes loss of acid fastness also by inhibition of mycolic acid synthesis.

Thiacetazone :

Among the large number of thiosemicarbazones tested,

the compound 4-acetyl amino benzaldehyde thiosemicarbazone shoed to be most efficacious.¹³



Thiacetazone suppresses the growth of M. tuberculosis by an unknown action. Its therapeutical usefulness is questionable.

ANTIBIOTICS

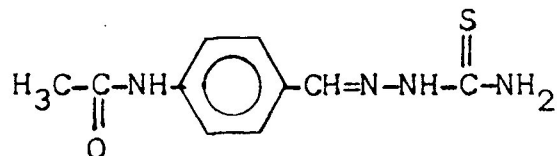
The presently available antibiotics effective against Mycobacterium tuberculosis make it possible to . virtually total success in the treatment of tuberculosis.

Streptomycin :

Streptomycin was first isolated from culture of Streptomyces griseus by Schatz, Bugic and Waksman¹⁴ in 1944. The discovery of other tuberculostatic compound that, given concurrently with antibiotic reduces the rate at which the microorganisms became drug resistant, in spite prolong exposure reached its full potential in the therapy of tuberculosis.

The activity of Streptomycin is bactericidal and bacteriostatic for the tubercle bacillus in vitro.

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The activity of Streptomycin is bactericidal and
bacteriostatic for the tubercle bacillus in vitro.

It may be also given in combination with penicillin in the treatment of resistant strain. It is chiefly effective against Gram-negative organisms.

Fitzgerald et al.¹⁵ showed that streptomycin inhibits enzyme induction in non-dividing cells of a mycobacterium. This suggest inhibition of protein synthesis. Streptomycin penetrates into the cell body, combines with 30s ribosomal particles but does not interfere with the attachment of messenger RNA to the ribosomes, and thus must alter the function of the ribosome after the mRNA is attached.¹⁶ These effects probably contribute to, but are not essential to the bactericidal action.

Viomycin, Kanamycin, Capreomycin :

Viomycin is a cyclic peptide. It was isolated from Streptomyces puniceus in 1951 by Mayers et al.¹⁷ and Bartz et al.¹⁸ It inhibits protein synthesis by binding to ribosomes as to aminoglycosides. It shows cross resistance with neomycin.

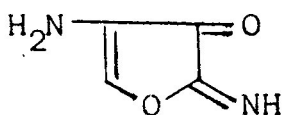
Kanamycin was isolated by Umezawa et al.¹⁹ in 1952 from a soil organism named Streptomyces kanamycetis. Its structural formula shows that it contains two amino sugars in glucosidic linkage with deoxystreptamine, which is also a component of neomycin. It inhibits enzyme

induction in mycobacteria and reacts like Streptomycin with nucleic acids.

Capreomycin was isolated by Herr et al.²⁰ from Streptomyces capreolus. It is a mixture of four peptides, molecular weights of approximately 900. This antibiotic is almost exclusively antimycobacterial. It is not active orally. Cross resistance between the three drugs has often been reported and seems to be rather complex.

Cycloserine :

Cycloserine is D-4-amino iso-oxazolidine-3-one means structurally resemblance to D-alanine. It is an inhibitor of enzyme reactions involving D-alanine. It inhibits the enzyme responsible for the synthesis of



dipeptide. As a result, this unit of the cell wall becomes defective and the cell lyse.

Rifampicin :

Rifampin is a characteristic group of individual members such as Rifampicin AMP (Rifampin or Rifampicin), Rifamycin, Rifamycin-O, Rifamycin-S, Rifamycin-SV,

Rifamycin-X and Rifamycin-AG, shown below related 2-acylamino-4,4'-naphthohydroquinone produced by Streptomyces mediterranei, are active against Gram-positive and Gram-negative bacteria.

It is a semisynthetic antibiotic. It is active against tubercle bacilli whether or not they are resistant to other drugs.

It is now considered as primary drug in the treatment of tuberculosis, Rifampicin-B has the unusual property that in oxygenated aqueous solution it tends to change spontaneously into other products with greater antibacterial activity. The structure of Rifamycin-B out of the related compounds involved in the activation process have been elucidated by chemical and X-ray crystallographic methods. Rifampicin exerts both bactericidal and bacteriostatic action. It inactivates the DNA-dependent RNA polymerase and thus, inhibits the RNA synthesis.

The most widely used antituberculostatics along with their structure are tabulated in Table 1.

Table I Antituberculous Agents

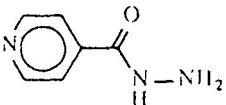
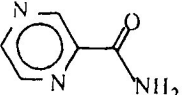
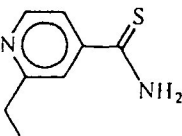
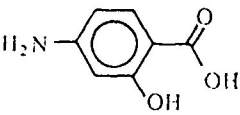
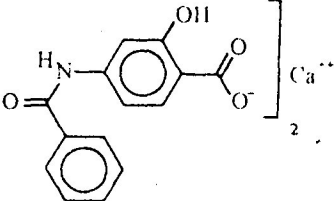
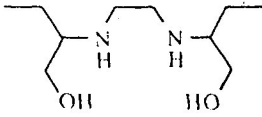
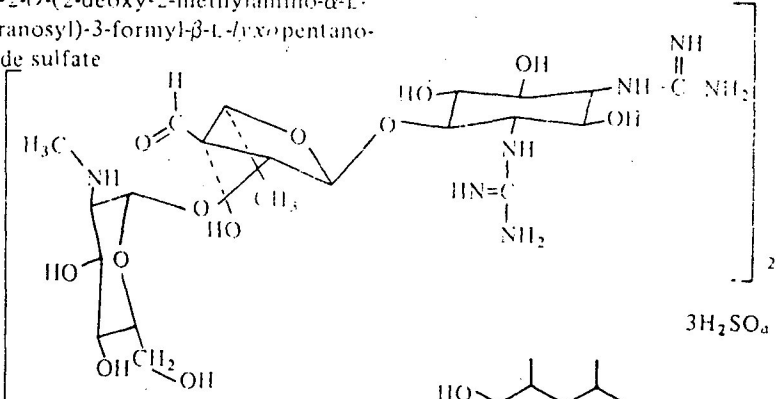
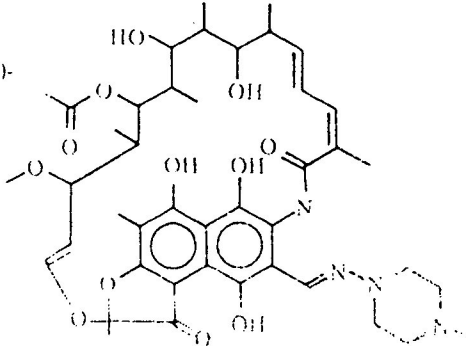
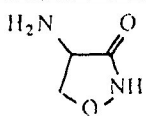
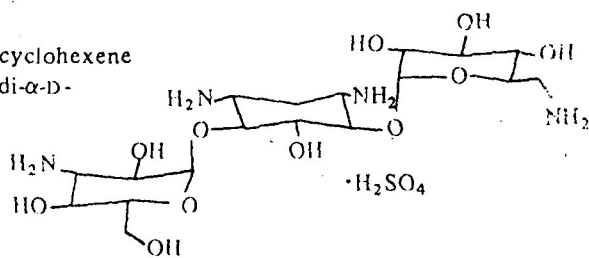
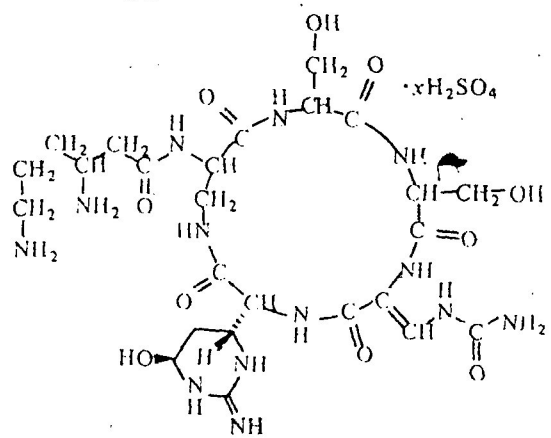
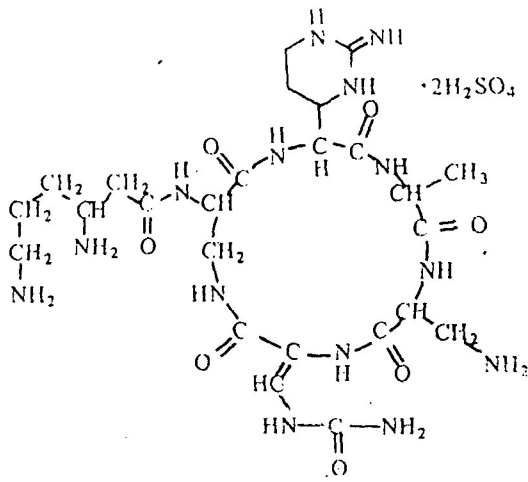
Official Name	Proprietary Name	Chemical Name	Structure
isoniazid*	Hyzyd Niconyl Nydrazid	isonicotinic acid hydrazide	
pyrazinamide*		pyrazinecarboxamide	
ethionamide*	Trecator-SC	2-ethylthioisonicotinamide	
aminosalicylic acid* (PAS)	Pamisyl Parasal	4-aminosalicylic acid	
benzoylpas calcium* (calcium benzamido-salicylate)	Benzapas	calcium 4-benzamidosalicylate	
ethambutol*	Myambutol	(+)-2,2'-(ethylenediimino)-di-1-butanol	
streptomycin sulfate*		2,4-diguanidino-3,5,6-trihydroxycyclohexyl-5-deoxy-2-O-(2-deoxy-2-methylamino-α-L-glucopyranosyl)-3-formyl-β-L-lyxopentano-furanoside sulfate	
rifampin* (rifampicin)	Rifadin Rimactane	3-[(4-methyl-1-piperazinyl)imino]methyl-rifamycin	

Table Antituberculous Agents (continued)

Official Name	Proprietary Name	Chemical Name	Structure
cycloserine*	Seromycin	<i>R</i> (+)-4-amino-3-isoxazolidinone	
kanamycin sulfate*	Kantrex	4,6-diamino-2-hydroxy-1,3-cyclohexene 3,6'-diamino-3,6'-dideoxydi- α -D-glucoside sulfate	
viomycin sulfate*	Viocin sulfate		
capreomycin sulfate*	Capastat sulfate		

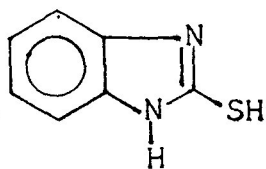
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PLAN OF WORK

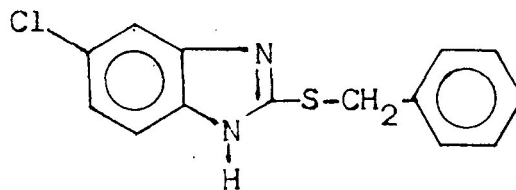
Tuberculosis is an infectious disease, caused by several species of mycobacteria, collectively termed the tubercle bacilli. The human pathogens of this class are M. tuberculosis and M. bovis. This is one of the deadliest disease which takes a heavy toll of human lives every year and constitutes a major health problem in this country.

Number of effective drugs like INH, sodium PAS, thiacetazone, streptomycin, ethambutol, pyrazinamide and rifamycin are available for long treatment of this disease. However, the problem of resistance shown by the organisms to these drugs individually are in combination pose a great problem. Hence, the development of new chemotherapeutic agent constitute a important step. With this understanding efforts are planned to synthesise and study new organic compounds.

2-Mercapto benzimidazole (I) and its derivatives (II) are known for their antibacterial and antifungal properties.^{21,22}

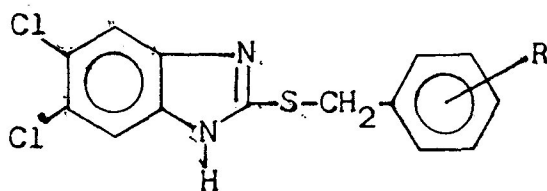


(I)



(II)

The following types (III) of benzimidazoles are reported from this laboratory for antitubercular and antifungal properties.²³



(III)

Taking into account the above evidences and Mayer's hypothesis which states that "a morphological relationship between mycobacteria and fungi may be paralleled by chemical relationship" i.e., substances showing antifungal activity are likely to show antitubercular activity also, the present synthetic work was planned.

Thus, the synthesis and biological study of various types of benzimidazoles was planned.

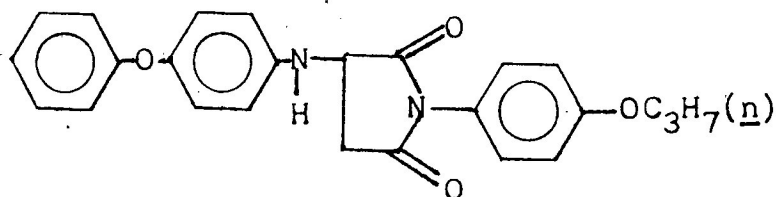
PART - II

Section - A

6-Chloro-5-phenoxy-2-(substituted-benzyl thio, hetero-aryl thio) benzimidazoles :

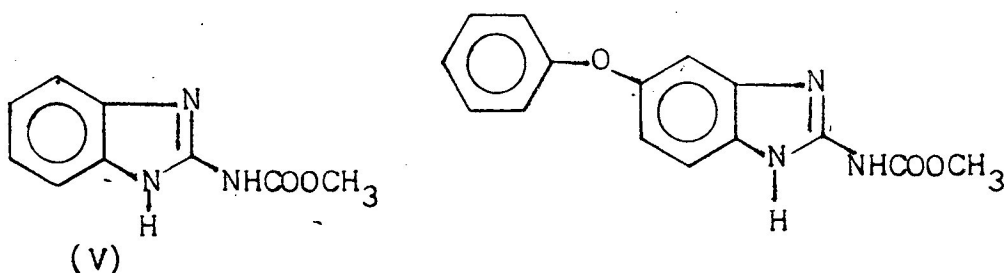
The compound having ether linkage, was synthesized in our laboratory, namely, 4-(o-phenoxy anilino)-N-(o,n -

propoxy phenyl) succinimide (IV) which inhibited the growth of M. tuberculosis at a concentration of $0.06 \mu\text{g/ml}^{24}$ in in vitro testing.



(IV)

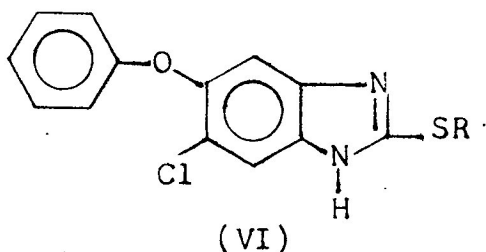
The efficacy of carbendazine (V) was found even more than expected²⁵ by substituting phenoxy group at the 5-position of the benzimidazole.



(V)

Carbendazine

On the basis of the information given earlier, it was proposed to prepare and test 6-chloro-5-phenoxy-2-(substituted benzyl thio) benzimidazoles (VI) as shown below :

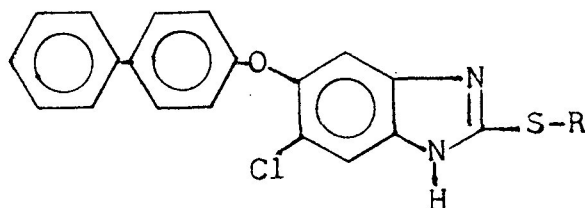


(VI)

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

Section - B6-Chloro-5-biphenyloxy-2-(substituted benzylthio) benzimidazoles :

Biphenyl derivatives are known in the literature for their antitubercular²⁶, antimicrobial²⁷, antifungal²⁸ and anthelmintic²⁹ properties. The incorporation of phenoxy group at 5-position of the benzimidazole molecule gave encouraging results. Hence, the synthesis of the following type (VII) of compounds having biphenyloxy linkage was planned. The various substituents at 2-position of benzimidazole could be shown as below :



(VII)

where, R = Substituted benzyl, hetero aryl.

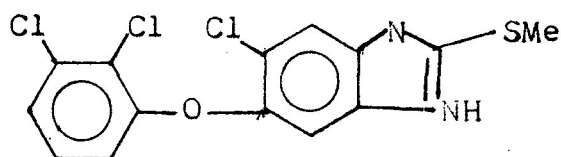
PART - III

Synthesis of 6-chloro-5-(substituted phenoxy)-2-
(substituted benzylthio/heteroaryl thio)-
benzimidazoles :

Halogens play an important role for the biological activity. Due to their electrochemical nature halogens

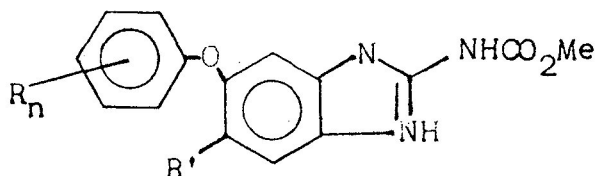
exert a pronounced influence on the biological behaviour of organic compounds. Halogen substitution in non-conjugated positions (negative halogen) usually increases both useful and toxic properties of active compounds, but not at the same rate.³⁰ The increase in toxicity is often negligible and many medicinal chemists look on aromatic halogen substitution, especially chlorine as a reasonable means of stepping up activity and widening the margin of safety in a given series.

The drug triclabendazole (VIII) is well documented in literature for its anthelmintic activity³¹ having the structural formula as below :



(VIII)

The following types of compounds (IX) are found to be active against helminths.³²

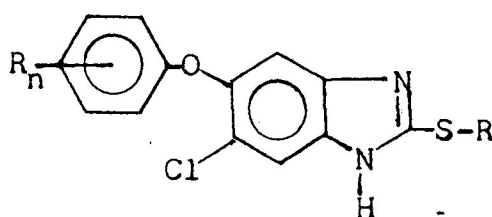


(IX)

where, R = H or Cl; R_n = H, 2,3 or 4-Cl; 2,5 or 3,5-Cl₂, etc.

In the chemistry of benzimidazoles it was observed that the biological activity is highly dependent on the substituents at 2 and 5 position of the benzimidazole moiety.

Thus, the synthesis of series of compounds (X) type were planned and it was decided to screen them for their antitubercular and antibacterial activities.



(X)

where, R = Various substituted benzyl, 7-chloro, 4-quinolinyl;

R_n = p-Chloro; 2,4-Cl₂; 2,5-Cl₂; 2,3-Cl₂.

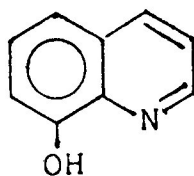
PART - IV

In an attempt to extend the biological profile of benzimidazoles, the synthesis of various 5-(substituted quinoloxo/napththoloxo)-6-chloro-2-(substituted benzyl thio)-benzimidazoles were planned as described below :

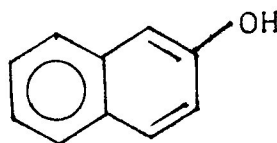
Section - A

Synthesis and study of 6-chloro-5-quinoloxo-2- (substituted benzylthio/heteroaryl thio)- benzimidazoles :

8-Hydroxy quinoline (XI) and β -naphthol (XII) are the true phenols, in the series of quinolinols and naphthols respectively. They show all the corresponding reactions with each other.



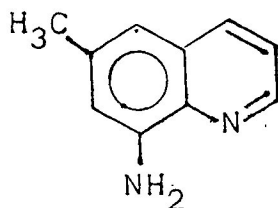
(XI)



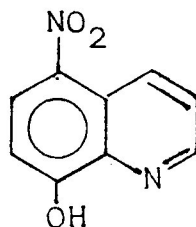
(XII)

In Germany, 8-hydroxy quinoline (XI) was first introduced in 1885 as an antiseptic and disinfectant. It is also used as bactericidal and fungicidal agent in medicinal preparation.

8-Amino-6-methyl quinoline (XIII) was claimed to possess antitubercular activity.³³ Nitroxolines (XIV) and its derivative with di-isopropyl amino as an amino component exhibited very good antimicrobial activity.³⁴

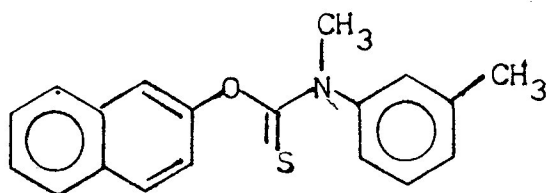


(XIII)



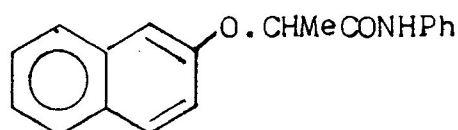
(XIV)

biological effects such as the drug 'tolnaftate', introduced as an antifungal drug³⁶ having structural formula as shown below (XVII).



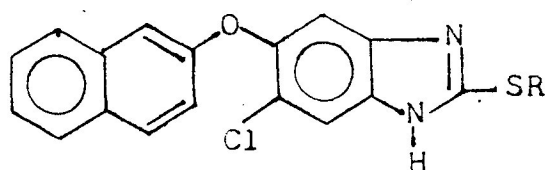
(XVII)

(β -Naphthoxy)-propionalide (XVIII) is a wide spectrum herbicide for the paddies.³⁷



(XVIII)

This finding gave impetus to incorporate this molecule in the benzimidazole moiety at five position. Thus, the synthesis and biological studies of these 5-naphtholoxo-6-chloro-2-(substituted benzylthio) benzimidazole types of compounds was proposed.



(XIX)

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

P A R T I I

C H E M I S T R Y

S e c t i o n - A

6-CHLORO-5-PHENOXY-2-(SUB-
STITUTED BENZYL THIO/HETERO-
ARYL THIO)BENZIMIDAZOLES.

C H E M I S T R Y

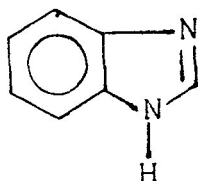
a) BENZIMIDAZOLE DERIVATIVES :

Biological active benzimidazoles :

The pharmacological history of several thousands of imidazole derivatives has been established over 30 years, after the discovery of the antibacterial and antifungal activity of benzimidazole by Wolley (1944)³⁸ which later led to the synthesis of benzimidazole derivatives with strong antiprotozoal and anthelmintic properties. The discovery of a new antibacterial (Azomycin), a trichomonacide (Metronidazole) and anthelmintic agents (Thiabendazole and Cambendazole) which contain prominently imidazole nucleus, has added impetus to investigations in these areas with particular emphasis on the synthesis of newer benzimidazole derivatives for pharmacological screening.

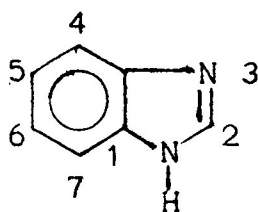
Chemistry of Benzimidazoles :

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



(I)

Since compounds of this type were formed by the loss of water, they are called " anhydro-bases " in the very early literature. These compounds were formed only by compounds in which the nitrogen containing groups were ortho to each other. They were expressed as derivatives of o-phenylene diamines. The numbering system for benzimidazole (II) is as follows :



(II)

Benzimidazole which contains a hydrogen atom attached to nitrogen in the 1-position readily tautamerise.³⁹



Synthesis of benzimidazoles :

The last systematic reviews on benzimidazoles were published in 1951⁴⁰ and 1953⁴¹, although subsequent surveys have appeared in articles⁴²⁻⁴⁴ covering the chemistry of both imidazoles and benzimidazoles. In the

latest review⁴⁵, a compilation of the synthesis, reactions and spectroscopic properties of benzimidazoles is presented.

General Methods :

Synthesis of benzimidazoles starts practically with o-phenylene diamines. In the literature survey, we have come across the following methods used for the synthesis of benzimidazoles :

- a) by reacting o-phenylene diamines with carboxylic acids.^{46,47}
- b) by reacting o-phenylene diamines with acid chlorides,^{48,49} ester⁵⁰ or acid anhydride.⁵¹
- c) by reacting o-phenylene diamine with amide⁵² or nitrile.⁵³
- d) by reacting o-phenylene diamine with aldehyde⁵⁴ or ketone⁵⁵,
- e) by reacting o-phenylene diamine with urea⁵⁶ or thiourea,⁵⁷ and
- f) by reacting o-phenylene diamine with isothiocyanate.⁵⁸

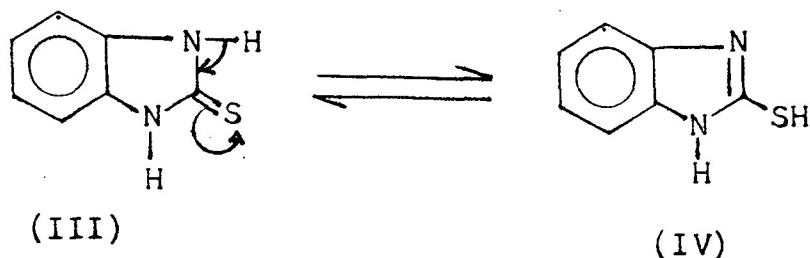
Properties of benzimidazoles :

The benzimidazole nucleus is very stable in character. It does not get easily oxidised by reduction.

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

2-Mercapto benzimidazole :

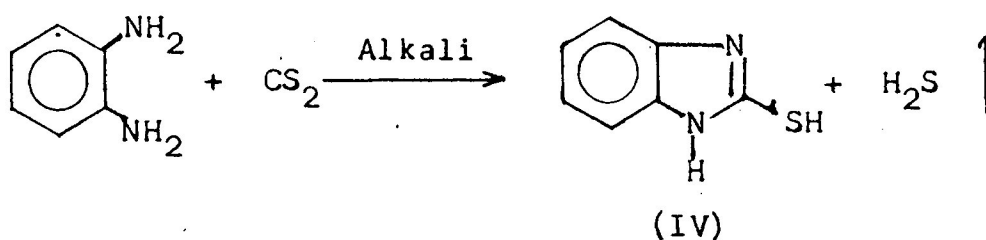
2-(3H) benzimidazole thione (III) and 2-mercapto benzimidazole (IV) are tautomeric substances analogous to 2-(3H)-benzimidazolone and 2-hydroxy benzimidazole.



Different methods of preparation of
2-mercapto benzimidazole :

a) Synthesis from o-phenylene diamine and
carbon disulfide :

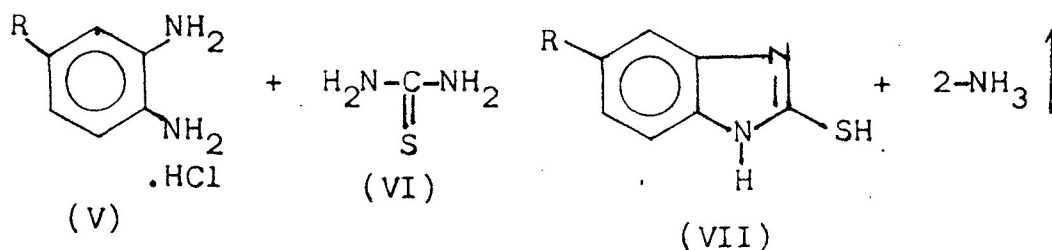
2-Mercapto benzimidazole, in general, may be prepared very conveniently by this method. The reaction is carried out usually by heating the reactants in alcoholic solution with or without the addition of alkali to the reaction mixture. 2-Mercapto benzimidazole (IV), itself, has been prepared by this method.^{59,60}



o-Phenylene diamines containing substituents in the phenyl ring have been used, including those containing alkyl,⁶¹ halogen,⁶² phenyl,⁶³ aniline⁶⁴ and sulfonamido⁶⁵ groups.

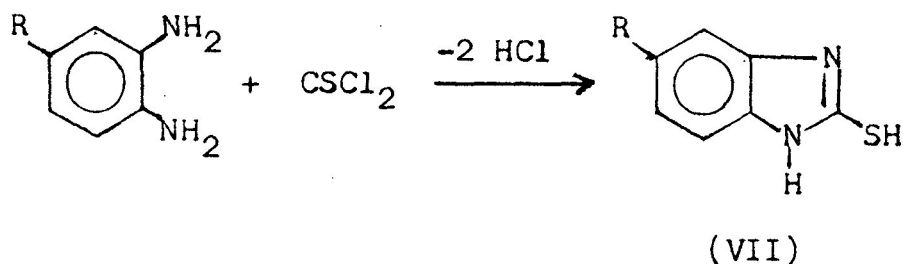
b) From o-phenylene diamine and thiourea :

This reaction is analogous to the preparation of 2-hydroxy benzimidazole from o-phenylene diamine and urea. Substituted-2-mercapto benzimidazoles (VII) may be prepared by this method by heating substituted o-phenylene diamine dihydrochloride (V) and thiourea (VI) to 170-180°C.⁶⁶ Excellent yields have been obtained by carrying out the reaction in amyl alcohol and heating under reflux until the evolution of ammonia becomes negligible.



c) From *o*-phenylene diamine and thiophosgene :

Billeter and Steiner⁶⁷ obtained 2-mercapto benzimidazole and 5-methyl-2-mercapto benzimidazole by action of thiophosgene on *o*-phenylene diamine and 3,4-diamino toluene, respectively. 3,4-Diamino benzene arsenic acid and thiophosgene gave 78 % yield of 2-mercapto-*s*-arsenic acid benzimidazole.⁶⁸

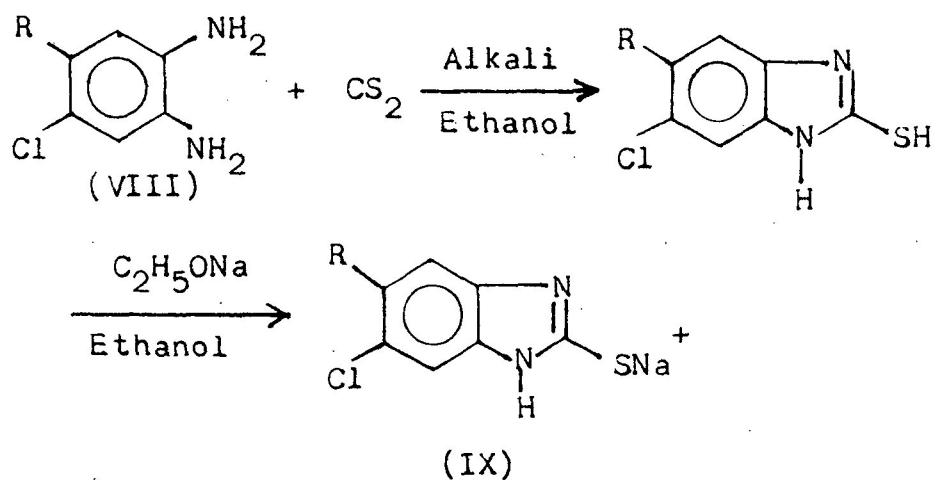


d) Miscellaneous methods :

2-Mercaptobenzimidazole can be prepared in 84-86.5% yield by the action of potassium ethyl xanthate on *o*-phenylene diamine.⁶⁹ 2-Mercapto benzimidazoles 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 benzimidazole⁷⁰ and 5-chloro⁷¹, 4-methyl⁷² and 5-methyl derivatives of 2-mercapto benzimidazole have been prepared.

Synthesis of 2-mercapto benzimidazoles
and its Na salt :

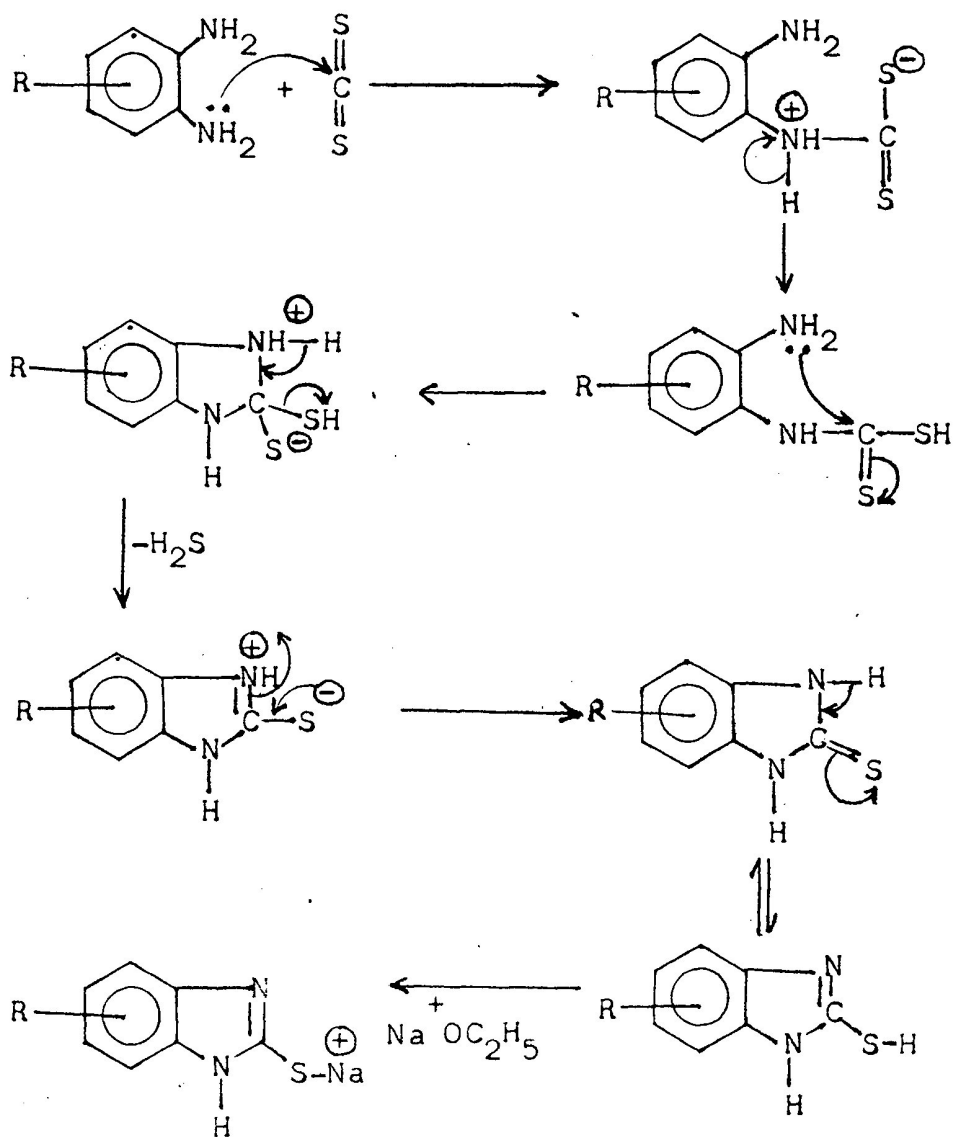
5-Substituted-6-chloro-2-mercapto benzimidazoles were prepared by the general and convenient method, such as refluxing 4,5-disubstituted-o-phenylene diamine (VIII) with CS_2 in the presence of alkali (KOH) for 3-4 hours in ethanol and neutralizing with aqueous AcOH. Then sodium salt of 2-mercapto benzimidazole (IX) was prepared by sodium ethoxide in ethanol.



Where, R = Phenoxy, biphenoxy, halogenated phenoxy, naphtholoxo, etc.

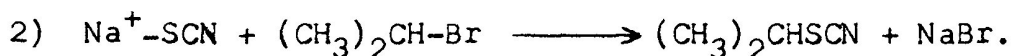
Probable reaction mechanism :

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



Reactions of 2-mercapto benzimidazoles :

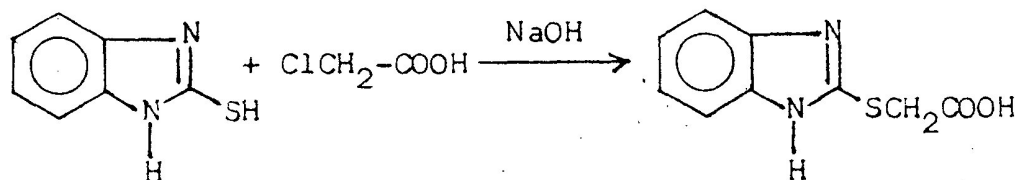
In general, sulphur compounds show greater nucleophilic reactivity than their oxygen analogs and substitutions by sulphur containing nucleophiles often occur under very mild conditions, and give high yields. The common leaving groups include halide, sulphonate ions, as usual and water (from conjugate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



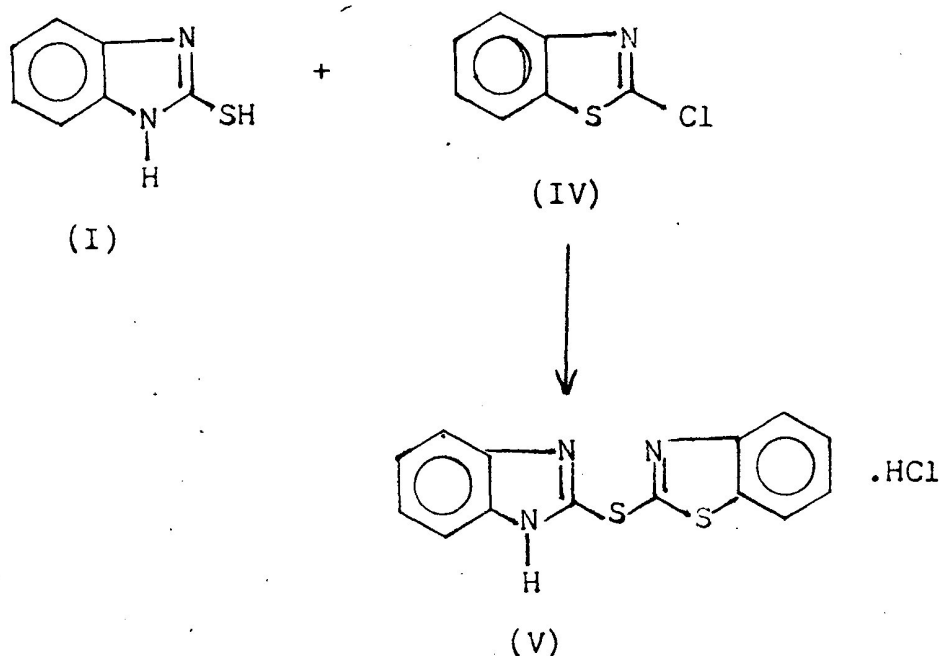
2-Mercapto benzimidazoles are generally stable substances and soluble in dilute alkali.

Alkylation occurs readily with replacement of the 2-mercapto hydrogen to yield s-alkylated derivatives.^{72,73}

2-Mercaptobenzimidazole may be treated with chloroacetic acid by refluxing in 2N sodium hydroxide solution.⁷⁴



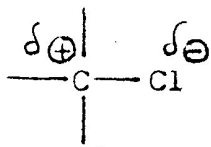
Similarly, 2-chlorobenzothiazole (IV) reacted with 2-mercapto benzimidazole yields 2-(benzothiazole-2'-mercapto)-benzimidazole hydrochloride (V) in 86 % yield.⁷⁵



b) CHEMISTRY OF BENZYL HALIDES :

Halogenation :

Halogenation is one of the most useful method for introduction of substituents in an aromatic system. Reactive substrates are substituted very rapidly. The carbon-halogen bond is a polar bond because of the high electronegativity to halogen. In an alkyl chlorides, for example, there is a slight positive charge on the carbon and a slight negative charge on halogen.



The carbon of an alkyl halide is, therefore, a good target for attack by a nucleophile.

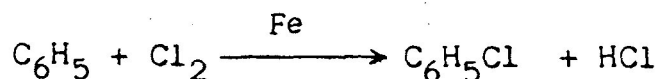
Aromatic halogen compounds :

There are two types of halogen compounds - i) the nuclear substitution products and ii) the side chain substitution products.

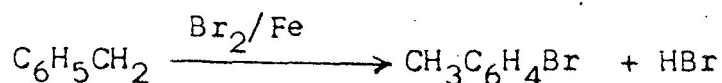
i) Nuclear substitution products (aryl halides) :

These compounds may be prepared by the following methods.

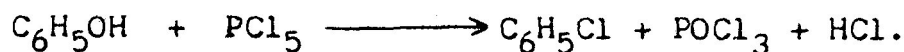
1) Direct halogenation : Low temperature and the presence of a halogen carrier favour nuclear substitution. Chlorination and bromination may be carried out at ordinary temperature in the presence of an iron, e.g., chlorobenzene is formed when benzene is treated with chlorine (1 mole) in the presence of iron.



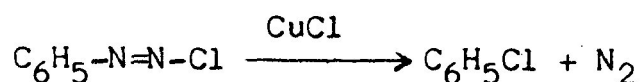
When toluene is brominated in the presence of iron (using 1 mole Br_2), a mixture of o and p-bromotoluenes is obtained.



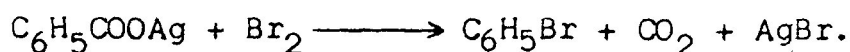
2) Treatment of nuclear hydroxy compounds with phosphorus pentachloride results in the formation of nuclear chlorinated compounds.



3) Decomposition of diazonium salts under suitable conditions is generally the most satisfactory method for preparing nuclear derivatives in the presence of cuprous chloride.

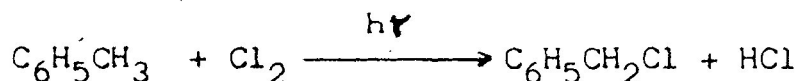


4) The silver salts of many aromatic acid react with bromine to form aryl bromides.

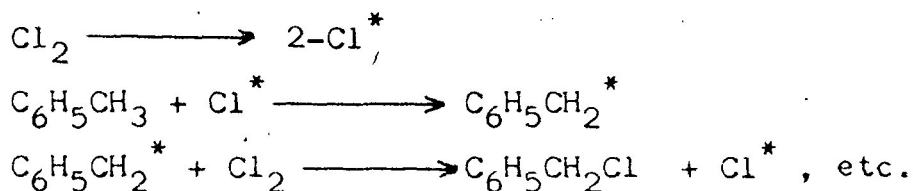


ii) Side chain substituted compounds :

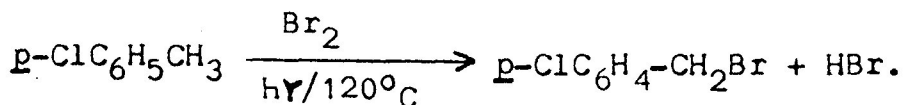
Side chain substitution is favoured by high temperature and light and the absence of halogen carriers e.g., when chlorinated at its boiling point in the presence of light, toluene is converted into benzyl chlorides.



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

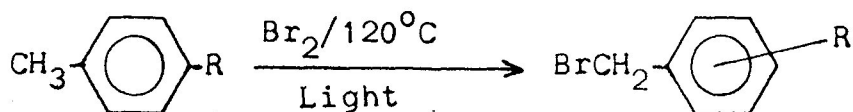


Similarly, bromination of *p*-chloro toluene at 120°C in the presence of light gives *p*-chlorobenzyl bromides.



p-Bromo, chloro, fluoro benzyl bromide :

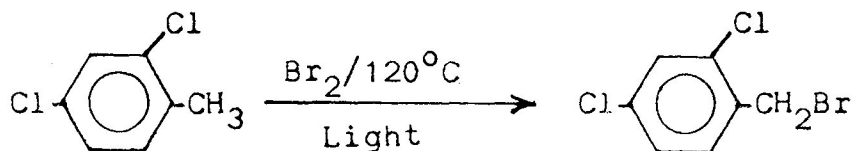
These were prepared by bromination of *p*-bromo toluene, *p*-chloro, and *p*-fluoro toluene as a side chain substitution at 120°C in the presence of light to get *p*-bromo⁷⁶, *p*-fluoro, *p*-chloro benzyl bromides.



where, R = Cl, F, Br.

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

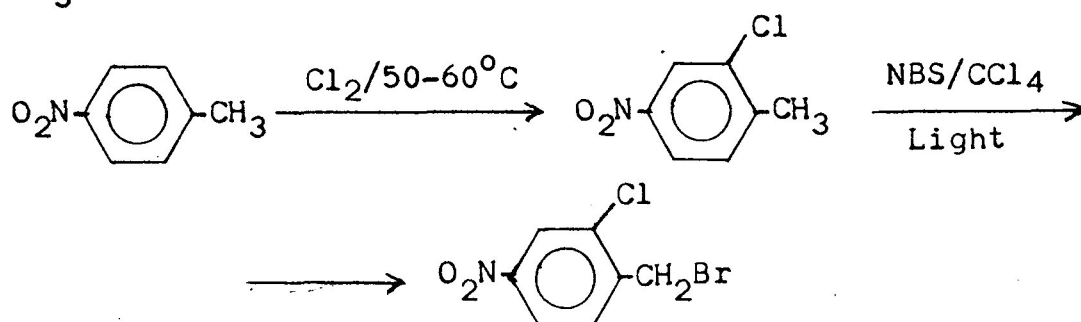
Bromination of 2,4-dichloro toluene at 120°C in the presence of light gives side chain substitution product, i.e., 2,4-dichloro benzyl bromide.⁷⁷



Similarly, 3,4-dichloro benzyl bromide⁷⁸ was obtained from 3,4-dichloro toluene.

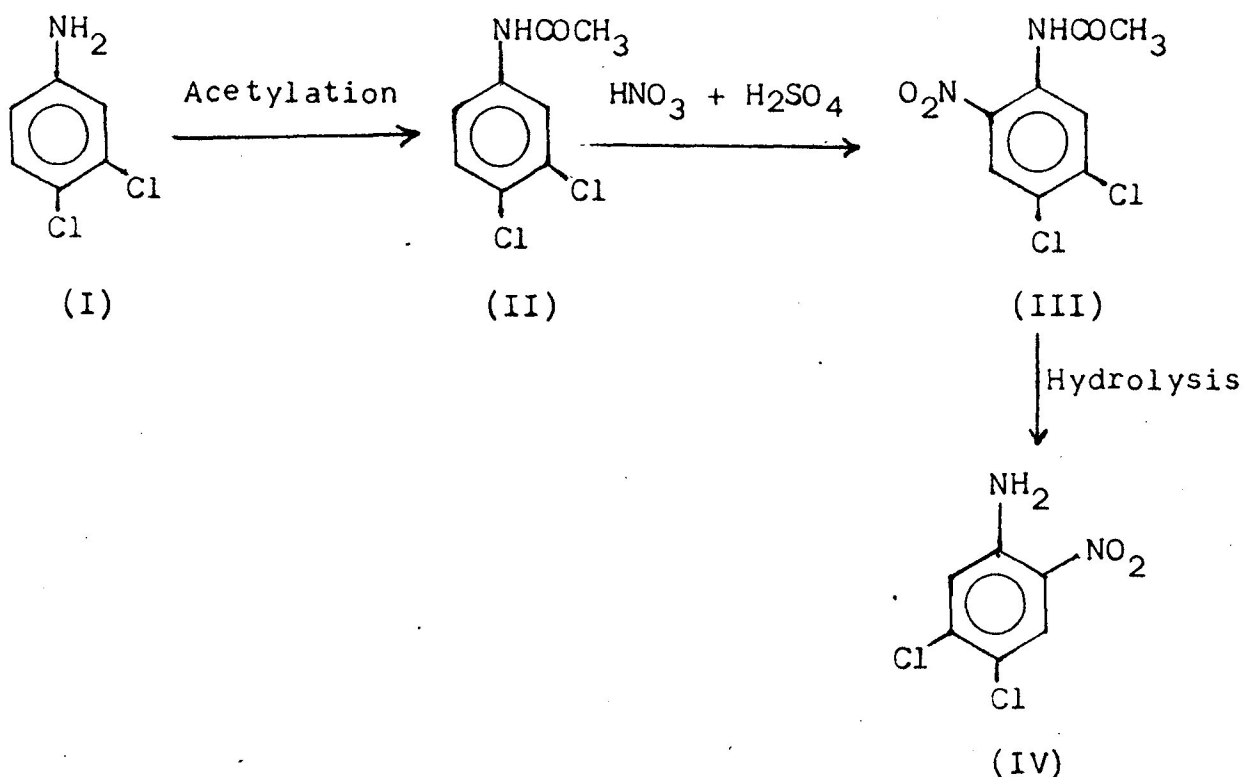
2-Chloro-4-nitrobenzyl bromide :

It was prepared by bromination of 2-chloro-4-nitro toluene with N-bromo succinamide by refluxing in carbon tetrachloride in the presence of benzoyl peroxide under illumination.⁷⁹ Whereas, 2-chloro-4-nitro toluene was obtained by chlorination of *p*-nitro toluene by passing chlorine gas at 50-60°C in the presence of SbCl₃ and FeCl₃.⁸⁰

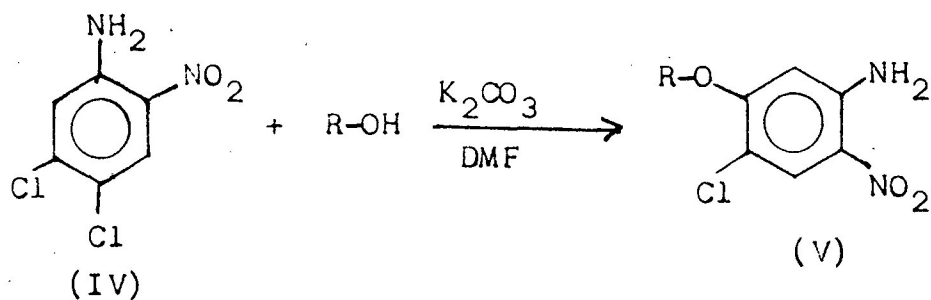


c) CHEMISTRY OF INTERMEDIATES :

4-Chloro-3-substituted-*o*-phenylene diamine is the major intermediate required for the synthesis of 5-phenoxy-6-chloro-2-substituted benzyl or aryl thio benzimidazoles in this section. The most convenient route adopted here is that from 3,4-dichloroaniline (I). It was acetylated and the acetyl derivative (II) was nitrated with concentrated H₂SO₄ and concentrated HNO₃ at 0-5°C, exclusively 2-nitro-4,5-dichloroacetanilide (III) is obtained. It was hydrolysed with 10% HCl to 2-nitro-4,5-dichloro aniline (IV) as shown below :



The purified 2-nitro-4,5-dichloro aniline (IV) was further reacted in the presence of anhydrous potassium carbonate with phenol, halogenated phenols, β -naphthol and 8-hydroxy quinoline by using DMF as solvent to obtain the corresponding phenoxy derivatives (V). The sequence of reaction could be explained as below :

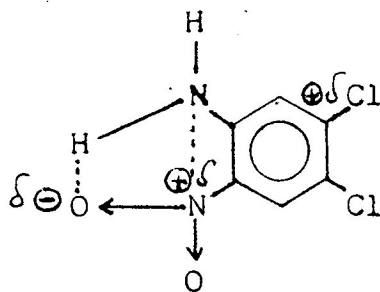


Where, R = Phenol, halogenated phenols, β -naphthol, 8-hydroxy quinoline.

The above (V) 2-nitro-4-chloro-5-phenoxy derivatives were further converted to the corresponding o-phenylene diamines by reduction with Raney nickel in presence of hydrogen gas or with anhydrous sodium sulphide.

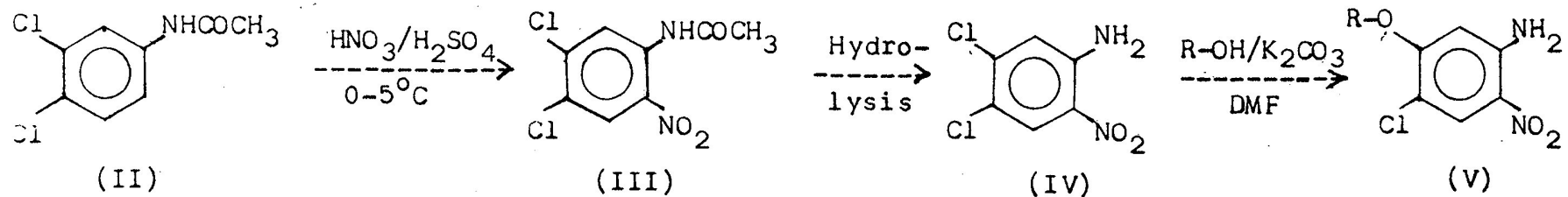
In the above set of reaction it could be noted that, in spite of using 2-nitro-4,5-dichloro acetanilide, its hydrolysed product i.e., 2-nitro-4,5-dichloro aniline reacts very smoothly and with high yield in the phenolic compounds in the presence of potassium carbonate and thus, there is no need of protecting the amino function in this molecule. On the contrary, because of the nitro and amino groups are in vicinity to each other probably there comes the phenomenon of hydrogen bonding of the vicinal amino and nitro groups and the electrowithdrawing nature of nitro group is more pronounced and to that is reflected in giving good yield of the phenoxy compound.

The phenomenon of hydrogen bonding could be shown as below :



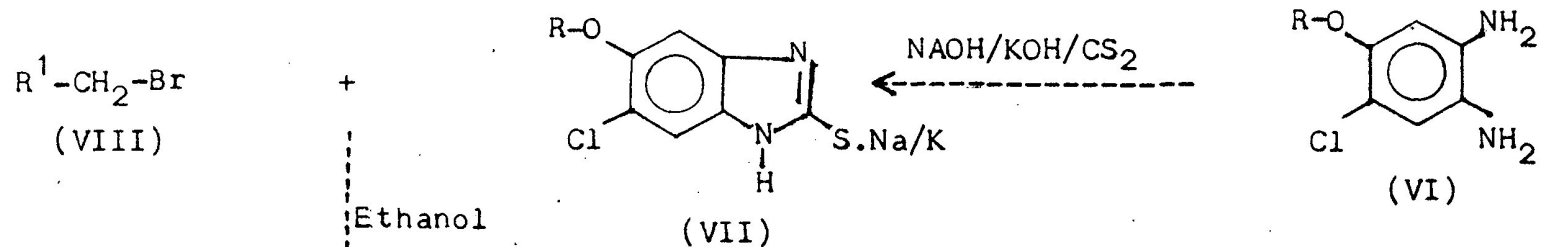
The final compounds 6-chloro-5-phenoxy-2-(substituted benzyl thio) benzimidazoles were obtained, which are shown in Scheme I.

SCHEME-I



R= Phenyl,
biphenyl.

Reduction by
Raney Ni/H₂



R¹ = Various substituted aryl
7-chloro, 4-quinolinyl.

P A R T I I

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

EXPERIMENTAL

PREPARATION OF SUBSTITUTED BENZYL HALIDES :

2,4-Dichlorobenzyl bromide :

2,4-Dichloro toluene 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 hours 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-dichloro benzyl bromide was vacuum distilled.

Yield : 20.0 g (83.3 %); b.p. 125-32°C/8 mm.
(Lit.⁸¹ b.p. 126-133°C/8 mm).

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

Yield : 19.2 g (80.0%); b.p. 115-120°C

Pyridinium salt m.p. 210°C.

(Lit.⁸² b.p., m.p. 210-211°C).

p-Bromotoluene :

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 hours until the colour became 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. 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 was 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 hours. 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 conc. H_2SO_4 , then with water. It was dried over a little calcium chloride, filtered and distilled.

Yield : 55.58 g (65.0 %); b.p. $183-185^\circ\text{C}$; m.p. $24-25^\circ\text{C}$.
(Lit.⁸³ b.p. $183-185^\circ\text{C}$; m.p. $25-26^\circ\text{C}$).

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 minutes. 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.⁷⁶ m.p. 61°C).

2-Chloro-4-nitrotoluene :

A mixture of p-nitrotoluene 50.0 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 or till the weight increased by 22 gms of chlorine. 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 (93.6 %); m.p. 65-66°C.

(lit.⁸⁰ 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 g 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-nitro benzyl bromide was obtained from the filtrate by removal of solvent and cooling. It was crystallized from methanol.

Yield : 15.0 g (60.0 %); m.p. 45°C.

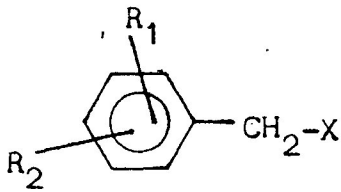
(Lit.⁷⁹ m.p. 46°C).

p-Nitrobenzyl bromide :

In a 1 litre three-necked flask was placed 300 g (22 moles) of technical p-nitrotoluene (m.p. 51-52°C). The flask was fitted with a liquid sealed stirrer, reflux condenser and a separatory 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 g (188 cc; 2.3 moles) of bromine was added dropwise over a period of 2 hours 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 light petroleum.

Yield : 315 g (66.0 %); m.p. 99°C.

(Lit.⁸⁴ m.p. 98-99°C).

TABLE-II. Substituted-benzyl halides

No.	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.	2-Chloro	4-Bromo	Bromo	125-32/8mm	-	126-33/8mm	-
3.	3-Chloro	4-Chloro	Bromo	115-20/6mm	210*	-	210-11
4.	2-Chloro	4-Nitro	Bromo	-	45	-	46
5.	H	4-Nitro	Bromo	-	99	-	99-100
6.	H	4-Fluoro	Chloro	85-87/30mm	-	87/30 mm	-

* Characterised as Pyridium salt.

3,4-Dichloro acetanilide :

In a 500 ml round bottomed flask, equipped with a reflux condenser, was placed 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 (12.7 ml; 0.22 mole) of glacial acetic acid and 0.1 g of zinc dust. The mixture was boiled gently for 30 minutes and then the hot liquid was poured in a thin stream into a one-litre beaker containing 500 ml of cold water whilst stirring was continued. It was cooled by using ice and the crude product was filtered at the pump and washed with a little cold water. It was dried on filter paper in the air. It was recrystallised and air-dried. •

Yield : 35.99 g (80.0 %); m.p. 120°C.

(Lit.⁸⁵ 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 into 50 ml three-necked round bottomed flask, equipped with a mechanical stirrer, a thermometer and a dropping funnel. It was stirred at 0 to 10°C. Nitrating mixture (conc. H₂SO₄ 10 ml, d 1.84 and nitric acid 2.2 ml, d 1.42) was added dropwise at 0°C to 10°C. The reaction mixture was stirred for further 2 hours at this temperature. Then

reaction mixture i.e., nitrating product was precipitated by pouring the acid mixture on crushed ice with vigorous stirring, the temperature being maintained at 0°C . It was neutralised by liquor ammonia, the crude 4,5-dichloro-2-nitro acetanilide was filtered, washed with ice-cold water, until neutral pH. The product was recrystallized from ethanol.

Yield : 9.5 g (76.5 %); m.p. 123°C .

(Lit.⁸⁶ m.p. $122-124^{\circ}\text{C}$).

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 added a solution of 5.6 g (0.1 mole) of KOH in 10 ml of water. It was refluxed for 40 minutes. It was diluted with 120 ml of water and distilled until 75 ml of distillate (alcohol and water) was collected. The residue was poured into 150 ml of cold water. The 4,5-dichloro-2-nitro aniline was separated out. It was filtered at the pump and washed with cold water. The crude material was purified from ethanol.

Yield : 15.69 g (75.80 %); m.p. 176°C .

(Lit.⁸⁷ m.p. $178.5-179^{\circ}\text{C}$).

4-Chloro-2-nitro-5-phenoxy aniline :

A mixture of 2.07 g (0.01 mole) of 4,5-dichloro-2-nitro aniline and 0.94 g (1 ml; 0.01 mole) of phenol with 0.99 g (0.01 mole) of potassium carbonate was heated at 115-120°C for three and half hours in DMF. The reaction mixture was ground in a mortar with 300 ml of warm water. The solid was removed by filtration, washed with water and the product recrystallized twice from ethanol.

Yield : 1.88 g (71.5 %); m.p. 134°C.

Analysis for $C_{12}H_9ClN_2O_2$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	54.44	3.40	10.58
Found	54.71	3.28	10.39

Preparation of 4-phenoxy-5-chloro-o-phenylene diamine :

In a hydrogenation bottle was taken 4-phenoxy-5-chloro-2-nitro aniline (3.174 g; 0.012 mole) in alcohol (40 ml). The reaction mixture was heated on water-bath to dissolve the nitro compound. Raney nickel (1.0 g) added to reaction mixture. This reaction mixture was hydrogenated in a Parr hydrogenator. After complete reduction, the content of the bottle was filtered through fluted filter paper. The Raney nickel was decomposed with

dilute HCl (9 %). The filtrate was concentrated under reduced pressure. The residue was recrystallized from hot benzene-petroleum ether.

Yield : 1.82 g (65.0 %); m.p. 84-85°C).

Analysis for $C_{12}H_{11}ClN_2O$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	61.40	4.69	11.94
Found	61.00	4.48	11.78

2-Mercapto-6-chloro-5-phenoxy-
benzimidazole :

Potassium hydroxide (9.6 g; 0.17 mole) was dissolved in the mixture of 150 ml ethanol (95 %) and 30 ml water. To this, 13.5 g CS_2 (10.71 ml; 0.17 mole) was added with stirring. This solution, at boiling temperature was added dropwise to a solution of 39.74 g (0.16 mole) of 3-phenoxy-5-chloro-o-phenylene diamine in 300 ml of ethanol, after 6 hrs, the EtOH was evaporated, the white residue was dissolved in H_2O and the product precipitated by addition of 25 ml of EtOH to 76 % 5-phenoxy-6-chloro-2-mercapto benzimidazole, m.p. 230°C (EtOH).

Yield : 32.29 g (73.0 %).

Analysis for $C_{13}H_9ClN_2OS$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	56.52	3.26	10.14
Found	56.40	3.08	9.91

6-Chloro-5-phenoxy-(3,4-dichlorobenzyl)-
thiobenzimidazole :

A solution of sodium salt of 6-chloro-5-phenoxy-2-mercapto benzimidazole 2.97 g (0.01 mole) and 3,4-dichloro benzyl bromide 2.39 g (0.01 mole) in 30 ml of ethanol was refluxed on water-bath for 3 hours. Then the solvent was removed under reduced pressure and some water added to it. The 6-chloro-5-phenoxy (3,4-dichlorobenzyl) thiobenzimidazole precipitated out and filtered. Recrystallized from methanol.

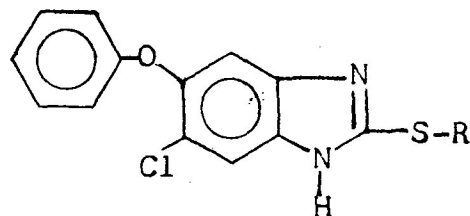
Yield : 3.04 g (70.0 %); m.p. 182°C.

Analysis for $C_{20}H_{13}Cl_3N_2SO$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	55.10	2.98	6.42
Found	55.54	2.51	6.66

Similarly, other substituted benzyl derivatives of 6-chloro-5-phenoxy-2-mercapto benzimidazole were prepared and their physical data is summarised in Table III.

TABLE III. 6-Chloro-5-phenoxy-2-(substituted benzyl or heteroaryl thio)-benzimidazoles.



No.	R	Yield %	M.p. °C*	Mol. formula	Elemental Analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	4-Chlorobenzyl	59.52	275	$C_{20}H_{14}Cl_2N_2OS$	59.85	3.49	6.98	59.72	3.39	7.02
2.	4-Bromobenzyl	62.00	225	$C_{20}H_{14}ClBrN_2OS$	53.87	3.14	6.28	54.01	3.25	6.37
3.	4-Fluorobenzyl	65.00	238	$C_{20}H_{14}FN_2OS$	62.41	3.64	7.28	62.37	3.52	7.19
4.	4-Nitrobenzyl	58.00	110	$C_{20}H_{14}ClN_3O_3S$	58.32	3.40	10.20	58.43	3.38	10.35
5.	3,4-Dichlorobenzyl	70.00	182	$C_{20}H_{13}Cl_3N_2OS$	55.10	2.98	6.42	55.54	2.51	6.66
6.	2,4-Dichlorobenzyl	76.00	207	$C_{20}H_{13}Cl_3N_2OS$	55.10	2.98	6.42	55.37	2.85	6.39
7.	2-Chloro-4-nitro- benzyl	79.00	115	$C_{20}H_{13}Cl_2N_3O_3S$	53.81	2.91	9.41	53.62	2.79	9.52
8.	7-Chloro-4-quino- linyl	68.10	210	$C_{22}H_{14}Cl_2N_3OS$	60.13	3.18	9.56	60.34	3.32	9.69

* Melting points are capillary melting points and are uncorrected.

P A R T I I

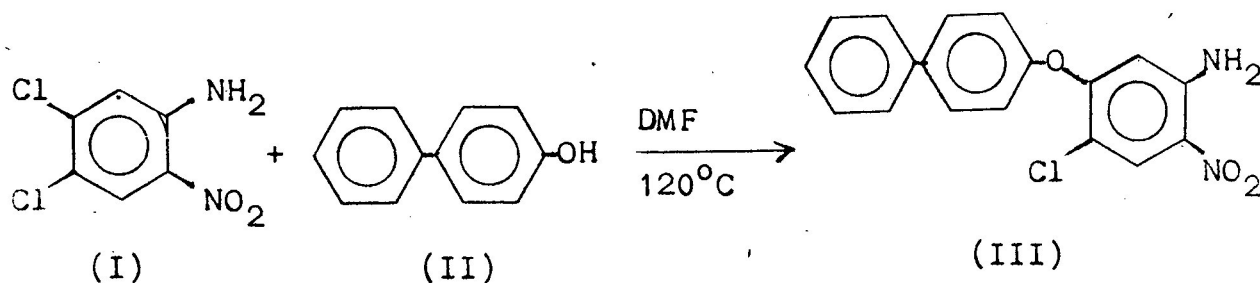
C H E M I S T R Y

S e c t i o n - B

6-CHLORO-5-BIPHENYLOXY-2-(SUB-
STITUTED BENZYLTHIO/HETEROARYL
THIO)BENZIMIDAZOLES.

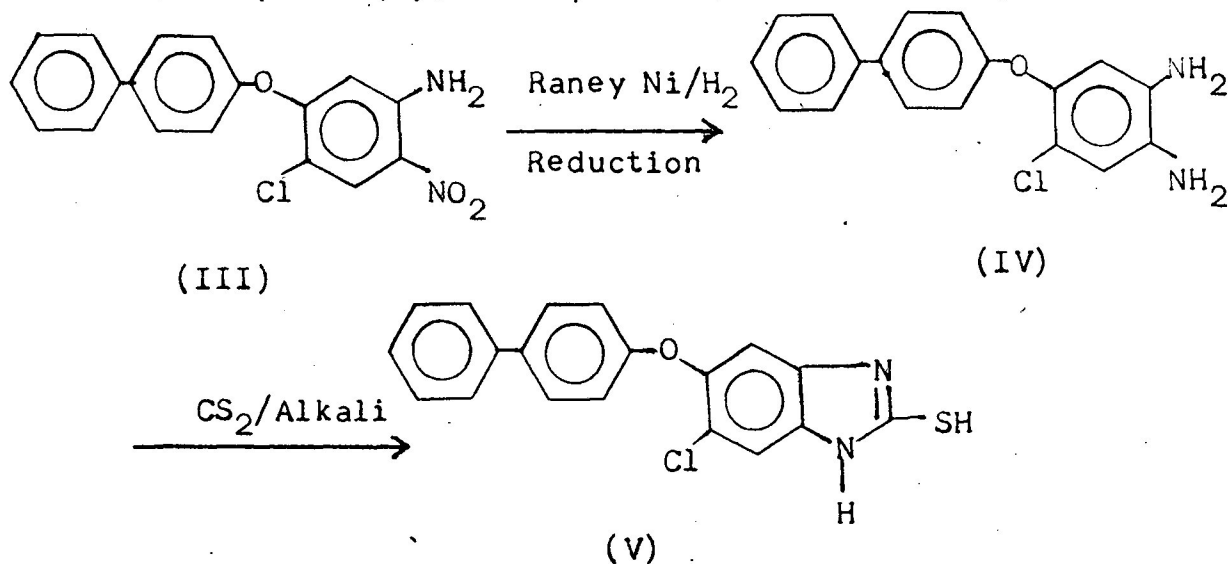
CHEMISTRY6-CHLORO-5-BIPHENYLOXY-2-(SUBSTITUTED BENZYLTHIO/
HETEROARYLTHIO) BENZIMIDAZOLES :a) 2-Nitro-4-chloro-5-biphenyloxy aniline :

4-Hydroxy biphenyl was reacted with 2-nitro-4,5-dichloro aniline to get 2-nitro-4-chloro-5-biphenyloxy aniline (III). Thus, equimolar quantities of 2-nitro-4,5-dichloro aniline (I) and 4-hydroxy biphenyl (II) in dimethyl formamide were treated at 120°C in presence of K_2CO_3 . Title compound was isolated and crystallized from ethanol.

b) 6-Chloro-5-biphenyloxy-2-mercapto-
benzimidazole :

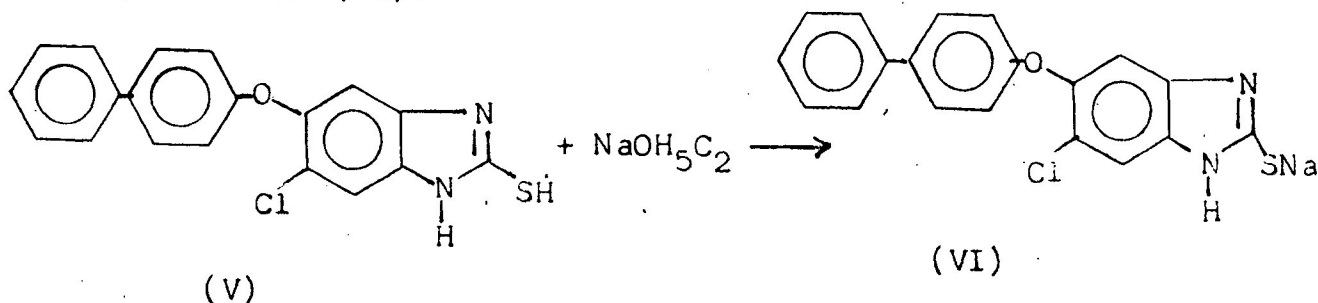
The compound 2-nitro-4-chloro-5-biphenyloxy aniline (III) was reduced over activated Raney Ni/ H_2 in Parr hydrogenation apparatus to yield 4-chloro-5-biphenyloxy-O-phenylene diamine (IV). This was then treated with carbon disulfide in presence of alkali in ethanol. The compound

thus obtained was neutralized with acetic acid to yield the title compound (V). Recrystallized from ethanol.



Sodium salt of 5-(biphenyloxy)-6-chloro-2-mercapto benzimidazole :

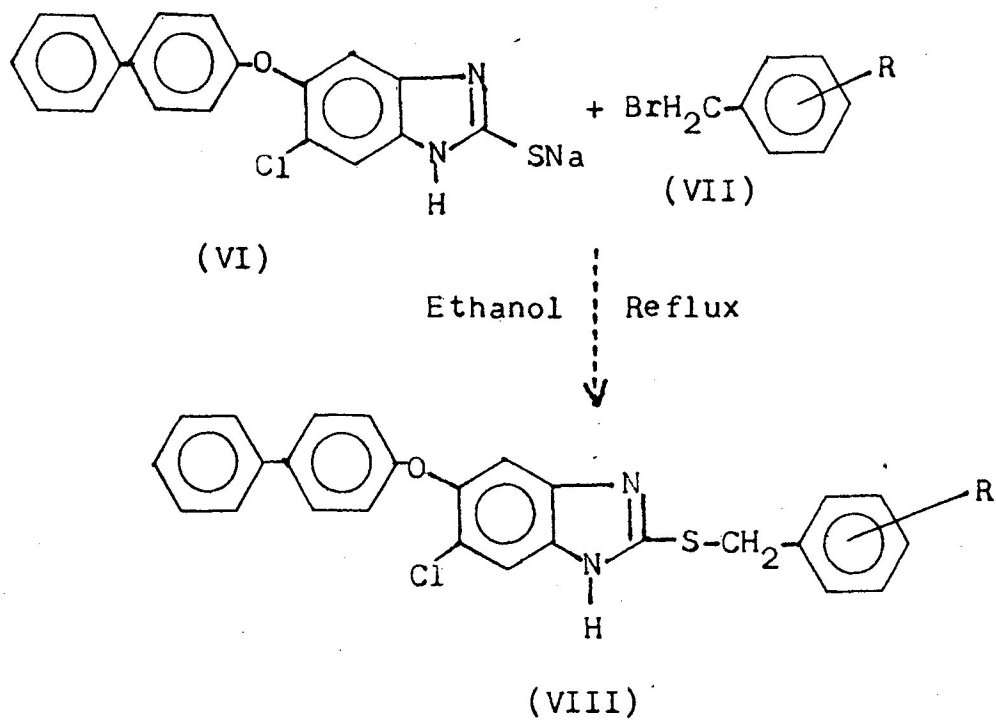
Equimolar quantities of 5-(biphenyloxy)-6-chloro-2-mercapto benzimidazole (V) and sodium ethoxide were refluxed in dry ethanol in anhydrous condition yielding the sodium salt (VI).



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

Sodium salt of 5-biphenyloxy-6-chloro-2-mercapto benzimidazole (VI) was refluxed with various substituted

benzyl bromide (VII) in equimolar quantities in ethanol yielding titled compounds (VIII).



PART II

EXPERIMENTAL

EXPERIMENTAL4-Chloro-2-nitro-5-biphenyloxy aniline :

In a 50 ml round bottomed flask a mixture of 4,5-dichloro-2-nitro aniline 2.07 g (0.01 mole), 4-hydroxy biphenoxy 1.7 g (0.01 mole) and potassium carbonate 0.99 g (0.01 mole) was refluxed in DMF for 6-8 hours. The hot reaction mixture was poured on crushed ice. 5-Chloro-2-nitro-4-biphenyloxy aniline was separated out. It was filtered and purified from ethanol.

Yield : 2.40 g (71.0 %); m.p. 120°C.

Analysis for $C_{18}H_{11}ClN_2O_3$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	63.81	3.24	8.27
Found	64.01	3.31	8.38

Preparation of 4-biphenyloxy-5-chloro-o-phenylene diamine :

Procedure as described in Part II, Section (A), page No. 52.

Yield : 2.097 g (68.0%); m.p. 115°C.

Analysis for $C_{18}H_{13}ClN_2O$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	70.01	4.21	9.07
Found	70.00	4.32	8.97

2-Mercapto-6-chloro-5-biphenyloxy benzimidazole :

Procedure as described in Part II, Section (A)
page No.53 .

Yield : 2.29 g (65.0 %); m.p. 255°C.

Analysis for $C_{19}H_{13}ClN_2S$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	67.73	3.86	8.31
Found	67.51	3.42	8.57

6-Chloro-5-biphenyloxy-(2',4'-dichlorobenzyl)thio-benzimidazole :

A solution of sodium salt of 5-biphenyloxy-6-chloro-2-mercapto benzimidazole 3.74 g (0.01 mole) and 2,4-dichlorobenzyl bromide 2.39 g (0.01 mole) in 30 ml of ethanol was refluxed on water-bath for 3 hours. Then the solvent was removed under reduced pressure and some water added to it. The 6-chloro-5-biphenyloxy-(2,4-dichlorobenzyl)-thiobenzimidazole precipitated out and filtered. Recrystallized from chloroform and hexane.

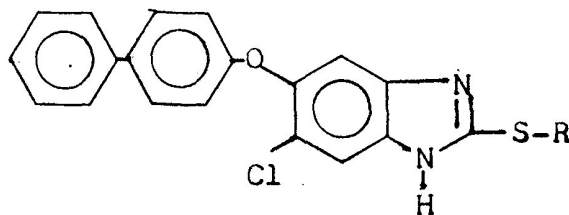
Yield : 3.57 g (70.0 %); m.p. 130°C.

Analysis for $C_{26}H_{17}Cl_3N_2OS$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	60.99	3.32	5.47
Found	60.83	3.03	5.39

Similarly, other substituted benzyl derivatives of 6-chloro-5-biphenyloxy,2-mercapto benzimidazole were prepared and their physical data is summarised in Table IV.

TABLE IV. 6-Chloro-5-biphenyloxy-2-(substituted benzyl or heteroaryl thio)benzimidazoles.



No.	R	Yield, %	M.p. °C ⁺	Mol. formula	Elemental Analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	4-Chlorobenzyl	62.0	210-11	C ₂₆ H ₁₈ Cl ₂ N ₂ OS	65.40	3.77	5.87	65.39	3.78	5.69
2.	4-Bromobenzyl	66.0	208	C ₂₆ H ₁₈ BrClN ₂ OS	59.82	3.45	5.36	59.79	3.39	5.48
3.	4-Fluorobenzyl	60.0	240	C ₂₆ H ₁₈ ClFN ₂ OS	67.75	3.90	6.08	67.69	3.79	6.27
4.	4-Nitrobenzyl	55.0	138	C ₂₆ H ₁₈ ClN ₃ O ₃ S	64.00	3.69	8.61	64.31	3.57	8.58
5.	3,4-Dichlorobenzyl	65.0	257	C ₂₆ H ₁₇ Cl ₃ N ₂ OS	60.99	3.32	5.47	60.69	3.51	5.39
6.	2,4-Dichlorobenzyl	70.0	130	C ₂₆ H ₁₇ Cl ₃ N ₂ OS	60.99	3.32	5.47	60.83	3.03	5.39
7.	2-Chloro-4-nitrobenzyl	71.0	188	C ₂₆ H ₁₇ Cl ₂ N ₂ O ₃ S	61.41	3.34	5.51	61.39	3.09	5.60
8.	7-Chloro-4-quinolinyl	73.0	205	C ₂₈ H ₁₈ Cl ₂ N ₃ OS	65.24	3.49	8.15	65.39	3.38	8.25

⁺ Melting points are capillary melting points and are uncorrected.

P A R T I I I

C H E M I S T R Y

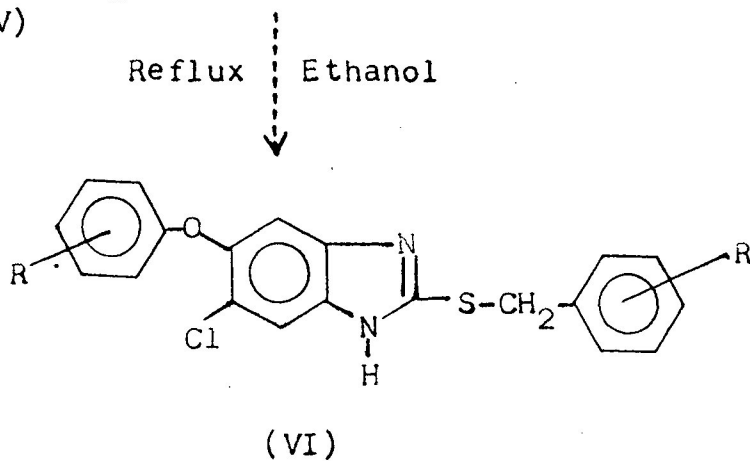
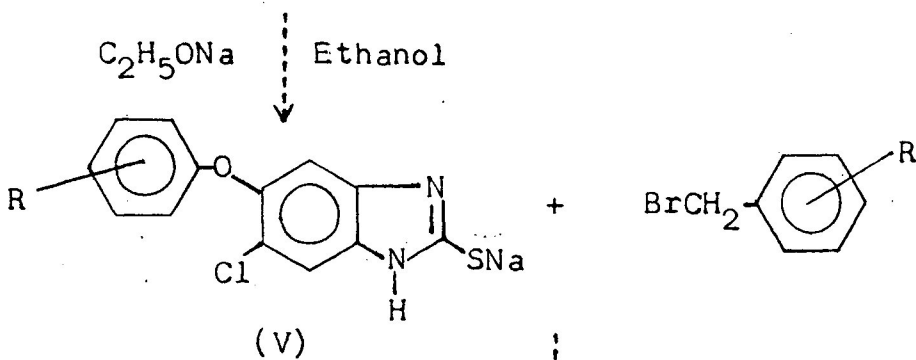
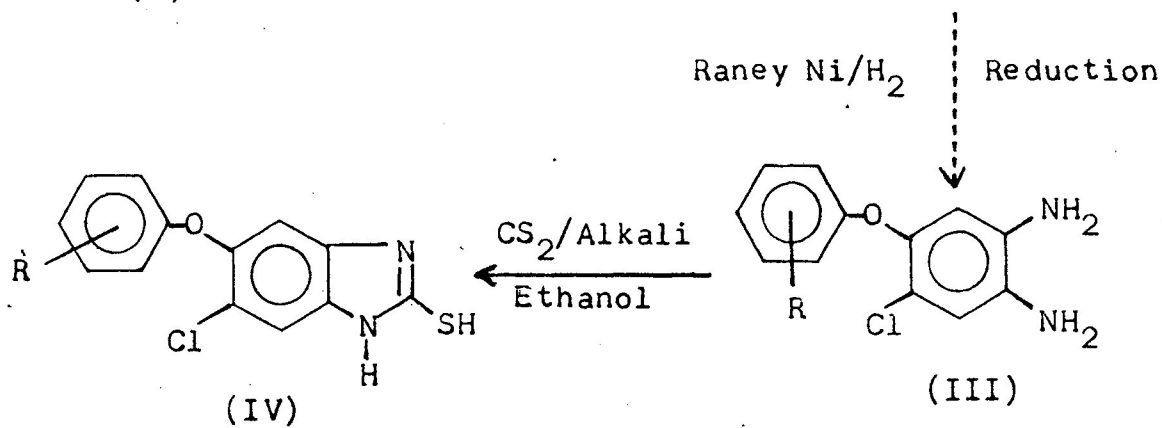
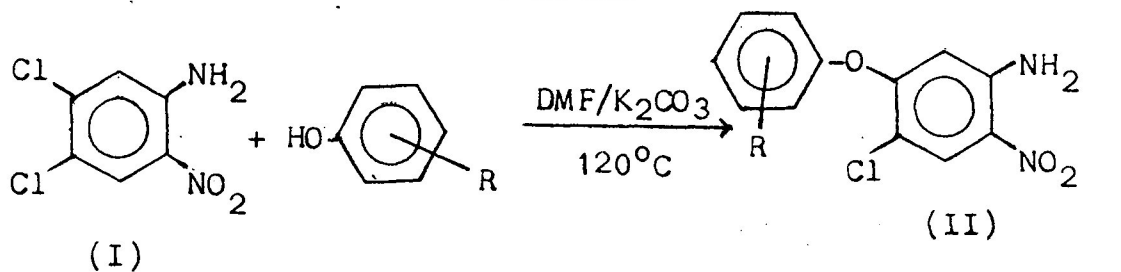
6-CHLORO-5-(SUBSTITUTED-
PHENOXY)-2-(SUBSTITUTED-
BENZYL THIO/HETEROARYL THIO)-
BENZIMIDAZOLES.

CHEMISTRY6-CHLORO-5-(SUBSTITUTED PHENOXY)-2-(SUBSTITUTED-BENZYL THIO/HETEROARYL THIO)BENZIMIDAZOLES :

This section deals with the preparation of 2-nitro-4-chloro-5-(substituted phenoxy) aniline (II). The active nature of chlorine at position 5 takes part in the substitution of phenoxy group in presence of anhydrous K_2CO_3 in DMF at $120^\circ C$. The desired product is obtained in quantitative yield.

2-Nitro-4-chloro-5-(substituted phenoxy) aniline (II) is further reduced by using Raney Ni/ H_2 . The reaction is very clean and gives good yield. This reduced compound (III) was further reacted with CS_2 in presence of NaOH to obtain sodium salt of 2-mercapto-6-chloro-5-substituted phenoxy)benzimidazole. It was further neutralized by using aqueous acetic acid. This thio compound (IV) was recrystallized from ethanol. It was further converted into sodium salt with sodium ethoxide. The corresponding Na salt derivative (V) was condensed with substituted benzyl halides in ethanol at reflux temperature. The final compound (VI) was recrystallised in ethanol. The sequence of reactions involved, are described as below in Scheme - II.

SCHEME - II



R = 4-Chloro, 2,3-dichloro, 2,5-dichloro, 2,4-dichloro.

P A R T I I I

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

EXPERIMENTAL

Synthesis of 4-chloro-2-nitro-5-(2',3'-dichloro-phenoxy)aniline :

A mixture of 4,5-dichloro-2-nitro aniline 2.07 g (0.01 mole), 2,3-dichlorophenol 1.63 g (0.01 mole) and potassium carbonate 0.99 g (0.01 mole) was refluxed in DMF for 6-8 hours. The hot reaction mixture was poured on crushed ice. 5-Chloro-2-nitro-4-(2',3'-dichloro phenoxy) aniline was separated out. It was filtered and recrystallized from ethanol.

Yield : 2.29 g (69.0 %) m.p. 122°C.

Analysis for $C_{12}H_7Cl_3N_2O_3$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	45.07	2.19	7.43
Found	45.00	2.15	7.31

Preparation of 4-(2',3'-dichloro phenoxy)-5-chloro-o-phenylene diamine :

Method as described in Part II, Section - A, page No. 52.

Yield : 1.96 g (65.0 %); m.p. 83-84°C.

Analysis for $C_{12}H_9Cl_3N_2O$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	47.44	2.96	9.22
Found	47.09	2.82	9.43

2-Mercapto-6-chloro-5-(2',3'-dichlorophenoxy)-benzimidazole :

Method as described in Part II, Section (A),
page No.53.

Yield : 2.34 g (68.0 %); m.p. 214-15°C.

Analysis for $C_{13}H_7Cl_3N_2S$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	47.33	2.12	8.49
Found	47.58	2.37	8.62

6-Chloro-5-(2',3'-dichlorophenoxy)-2-(3,4-dichlorobenzyl thio) benzimidazole :

Sodium salt of 5-(2',3'-dichloro phenoxy)-6-chloro-2-mercapto benzimidazole 3.67 g (0.01 mole) and 2,4-dichloro benzyl bromide 2.40 g (0.01 mole) were refluxed in ethanol for 3-4 hours. The solvent was removed under reduced pressure and some water added to it. The 6-chloro-5-(2',3'-dichloro phenoxy)-2-(3,4-dichlorobenzyl) thiobenzimidazole precipitated out and filtered. Recrystallised from chloroform.

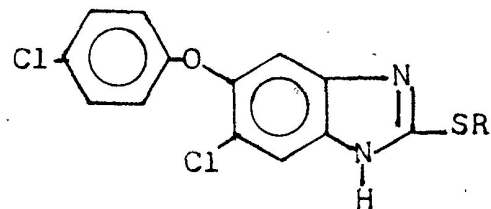
Yield : 3.52 g (70.0 %); m.p. 110°C.

Analysis for $C_{20}H_{11}Cl_5N_2OS$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	47.57	2.18	5.55
Found	47.53	2.09	5.48

Similarly, other substituted benzyl derivatives of 6-chloro-5-(substituted phenoxy)-2-mercapto benzimidazoles and 6-chloro-5-(4'-chlorophenoxy)-2-mercapto benzimidazoles were synthesized and their physical data is summarised in Tables V, VI, VII and VIII.

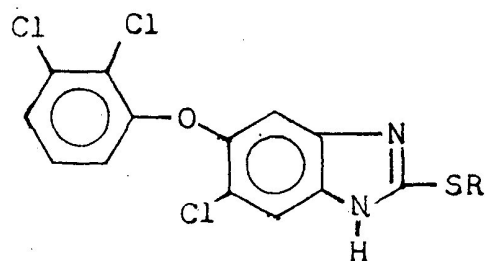
TABLE V. 6-Chloro-5-(4'-chloro-substituted phenoxy)-2-(substituted benzyl or heteroaryl thio)benzimidazoles.



No.	R	Yield %	M.p. °C*	Mol. formula	Elemental analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	4-Chlorobenzyl	60.0	224	C ₂₀ H ₁₃ Cl ₃ N ₂ OS	55.10	2.98	9.42	55.21	2.62	9.79
2.	4-Bromobenzyl	65.0	185	C ₂₀ H ₁₃ BrCl ₂ N ₂ OS	50.00	2.70	5.83	50.21	2.52	5.83
3.	4-Fluorobenzyl	70.0	273	C ₂₀ H ₁₃ Cl ₂ FN ₂ OS	57.27	3.10	6.68	57.39	3.29	6.27
4.	4-Nitrobenzyl	65.0	260	C ₂₀ H ₁₃ Cl ₂ N ₃ O ₃ S	53.81	2.91	9.41	53.69	2.79	9.69
5.	3,4-Dichlorobenzyl	72.0	111	C ₂₀ H ₁₂ ClN ₂ OS	51.06	2.55	5.95	51.37	2.69	5.89
6.	2,4-Dichlorobenzyl	60.0	122	C ₂₀ H ₁₂ ClN ₂ OS	51.06	2.55	5.95	51.12	2.67	5.79
7.	7-Chloro-4-quinolinyl	58.5	200	C ₂₂ H ₁₃ Cl ₃ N ₃ OS	55.75	2.74	8.87	55.69	2.63	8.65

* Melting points are capillary melting points and are uncorrected.

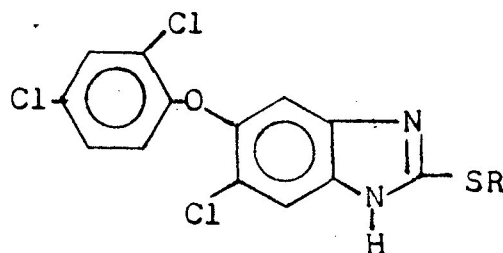
TABLE VI. 6-Chloro-5-(2',3'-dichloro substituted phenoxy)-2-(substituted-benzyl or heteroaryl thio)benzimidazoles.



No.	R	Yield %	M.p. °C*	Mol. formula	Elemental Analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	4-Chlorobenzyl	69.0	120	C ₂₀ H ₁₂ Cl ₄ N ₂ OS	51.06	2.55	5.95	51.29	2.60	6.01
2.	4-Bromobenzyl	67.2	262	C ₂₀ H ₁₂ BrCl ₃ N ₂ OS	46.64	2.33	5.44	46.39	2.49	5.39
3.	4-Fluorobenzyl	68.0	109-10	C ₂₀ H ₁₂ Cl ₃ FN ₂ OS	52.92	2.64	6.17	53.04	2.39	6.09
4.	4-Nitrobenzyl	63.0	180	C ₂₀ H ₁₂ Cl ₃ N ₃ O ₃ S	49.94	2.49	9.98	49.69	2.38	9.69
5.	3,4-Dichlorobenzyl	70.0	110	C ₂₀ H ₁₁ Cl ₅ N ₂ OS	47.57	2.18	5.55	47.53	2.09	5.48
6.	2,4-Dichlorobenzyl	73.0	130	C ₂₀ H ₁₁ Cl ₅ N ₂ OS	47.57	2.18	5.55	47.68	2.39	5.29
7.	7-Chloro-4-quinolinyl	72.0	145-46	C ₂₂ H ₁₂ Cl ₄ N ₃ OS	51.96	2.36	8.26	51.87	2.52	8.37

* Melting points are capillary melting points and are uncorrected.

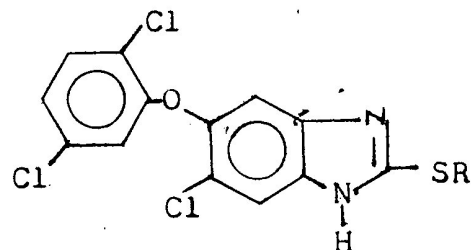
TABLE VII. 6-Chloro-5-(2',4'-dichloro substituted phenoxy)-2-(substituted benzyl or hetero aryl thio)benzimidazoles.



No.	R	Yield %	M.p. °C*	Mol. formula	Elemental Analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	4-Chlorobenzyl	68.0	220	C ₂₀ H ₁₂ Cl ₄ N ₂ OS	51.06	2.55	5.95	51.07	2.59	5.79
2.	4-Bromobenzyl	60.0	275	C ₂₀ H ₁₂ BrCl ₃ N ₂ OS	46.64	2.33	5.44	46.37	2.60	5.40
3.	4-Fluorobenzyl	62.0	230	C ₂₀ H ₁₂ Cl ₃ FN ₂ OS	52.92	2.64	6.17	51.81	2.59	6.23
4.	4-Nitrobenzyl	55.0	200	C ₂₀ H ₁₂ Cl ₃ N ₃ O ₃ S	49.94	2.49	9.98	49.87	2.37	9.79
5.	7-Chloro-4-quinolinyl	53.0	130	C ₂₂ H ₁₂ Cl ₄ N ₃ OS	51.96	2.36	8.26	51.82	2.51	8.31

* Melting points are capillary melting points and are uncorrected.

TABLE VIII. 6-Chloro-5-(2',5'-dichloro substituted phenoxy)-2-substituted-benzyl or hetero aryl thio)benzimidazoles.



No.	R	Yield %	M.p. °C*	Mol. formula	Elemental Analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	4-Chlorobenzyl	65.0	235	C ₂₀ H ₁₂ Cl ₄ N ₂ OS	51.06	2.55	3.95	51.02	2.49	3.72
2.	4-Bromobenzyl	66.0	195	C ₂₀ H ₁₂ BrCl ₃ N ₂ OS	46.64	2.33	5.44	46.37	2.42	5.72
3.	4-Fluorobenzyl	68.0	240	C ₂₀ H ₁₂ Cl ₃ FN ₂ OS	52.92	2.64	6.17	52.78	2.37	6.18
4.	4-Nitrobenzyl	70.0	145	C ₂₀ H ₁₂ Cl ₃ N ₃ O ₃ S	49.94	2.49	9.98	49.87	2.39	9.79
5.	2,4-Dichlorobenzyl	71.0	Oily	C ₂₀ H ₁₁ Cl ₅ N ₂ OS	47.57	2.18	5.55	47.42	2.10	5.47
6.	3,4-Dichlorobenzyl	69.0	205	C ₂₀ H ₁₁ Cl ₅ N ₂ OS	47.57	2.18	5.55	47.41	2.17	5.37
7.	2-Chloro-4-nitrobenzyl	71.0	140	C ₂₀ H ₁₁ Cl ₄ N ₃ O ₃ S	46.60	2.13	8.15	46.39	2.09	8.09
8.	7-Chloro-4-quinoliny	75.0	120	C ₂₂ H ₁₂ Cl ₄ N ₃ OS	51.96	2.96	8.26	51.87	2.79	8.19

* Melting points are capillary melting points and are uncorrected.

P A R T I V

C H E M I S T R Y

S e c t i o n - A

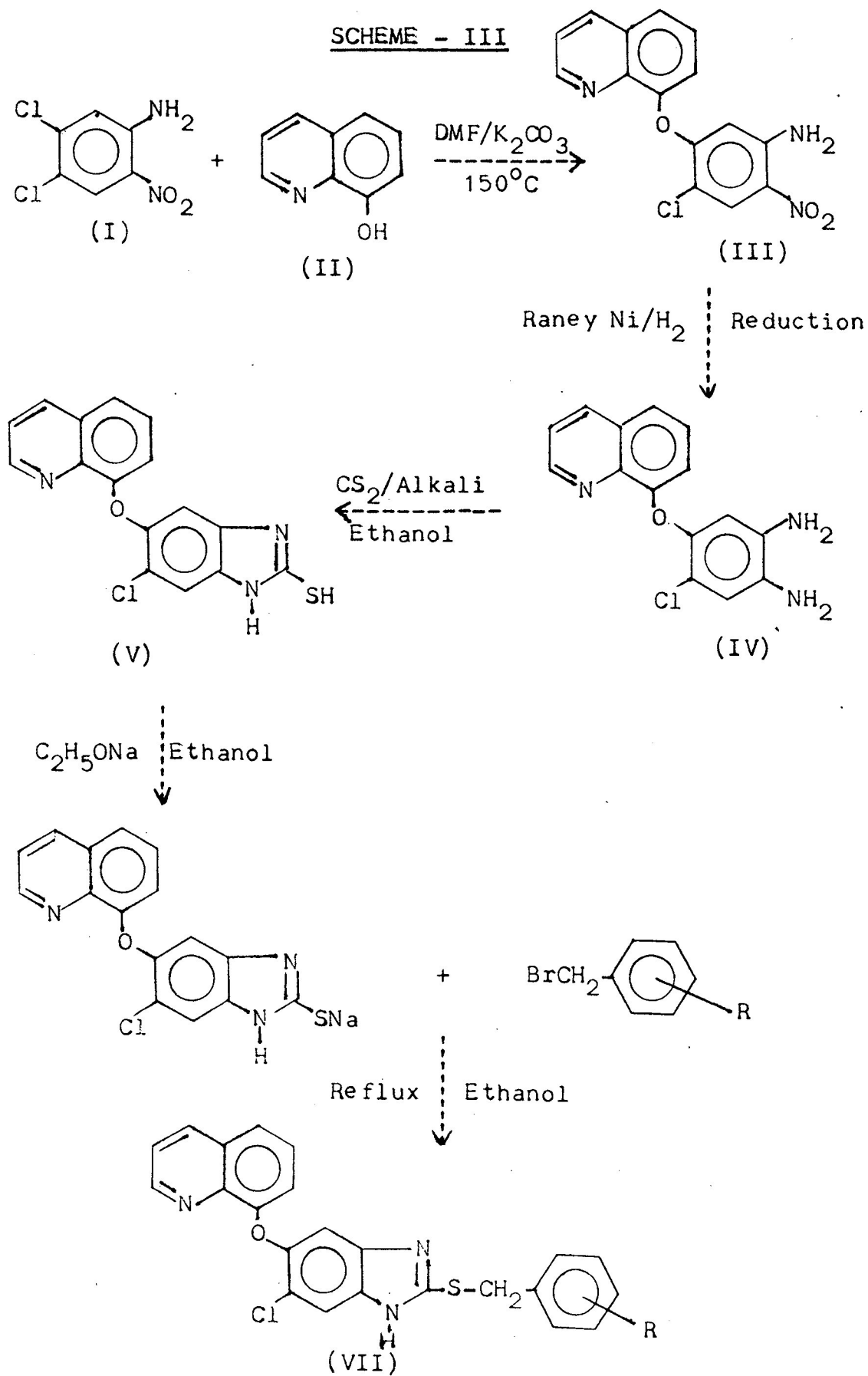
6-CHLORO-5-(8'-QUINOLOXY)-
2-(SUBSTITUTED-BENZYL THIO-
OR HETERO ARYL THIO)BENZIMI-
DAZOLES.

CHEMISTRY6-CHLORO-5-(8'-QUINOLOXY)-2-(SUBSTITUTED BENZYL THIO
OR HETEROARYL THIO)BENZIMIDAZOLES :

6-Chloro-5-(8'-quinoloxyl)-2-(substituted benzyl thio)benzimidazole (VII) was synthesized by using usual methods that consist of heating equimolar quantity of 4,5-dichloro-2-nitro aniline (I) and 8-hydroxy quinoline (II), in presence of K_2CO_3 and Cu powder, in DMF at $150^\circ C$ for 6-8 hours. Excess of DMF was removed under reduced pressure and poured on ice-cold water. Solid nitro compound (III) precipitated out, filtered and recrystallized from aqueous ethanol. This compound was further reduced in Parr hydrogenation apparatus. The obtained *o*-phenylene diamine (IV) was further reacted with CS_2 in presence of NaOH to obtain Na salt of 2-mercapto-6-chloro-5-(8'-quinoloxyl)-benzimidazole. The compound was neutralized with acetic acid, and purified 2-mercapto benzimidazole (V) again converted into Na salt (VI) by using sodium ethoxide. It was condensed with substituted benzyl halides in ethanol. The final compound (VII) was recrystallised from ethanol.

The sequence of chemical reactions involved could be schematically represented as below :

SCHEME - III



P A R T I V

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

EXPERIMENTALSynthesis of 4-chloro-2-nitro-5-(8'-quinoloxo)-aniline :

A mixture of 4,5-dichloro-2-nitro aniline 2.07 g (0.01 mole), 8-hydroxy quinoline 1.45 g (0.01 mole) and potassium carbonate 0.99 g (0.01 mole) was refluxed in DMF for 6-8 hours. After cooling the reaction mixture was poured on crushed ice. 5-Chloro-2-nitro-5-(8-quinoloxo)-aniline was separated out. It was filtered and recrystallized from aqueous ethanol.

Yield : 2.07 g (66.0 %); m.p. 240°C.

Analysis for $C_{15}H_{10}ClN_3O_3$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	57.05	3.16	13.31
Found	57.25	3.02	13.52

Preparation of 4-(8'-quinoloxo)-5-chloro-o-phenylene-diamine :

Same method as described in Part II, Section (A), page No. 52.

Yield : 1.81 g (~~64.5~~ (61.5 %)) : m.p. 145°C.

Analysis for $C_{15}H_{12}ClN_3O$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	60.91	4.06	14.2
Found	60.67	3.94	14.01

2-Mercapto-6-chloro-5-(8'-quinoloxo)benzimidazole :

Method as described in Part II, Section (A),
page No. 53.

Yield : 2.19 g (67.0 %); m.p. 118°C.

Analysis for $C_{16}H_{10}ClN_3OS$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	58.60	3.05	12.82
Found	58.23	3.37	12.48

6-Chloro-5-(8'-quinoloxo)-2-(4'-fluorobenzyl-
thio)benzimidazole :

Sodium salt of 5-(8'-quinoloxo)-6-chloro-2-mercapto
benzimidazole 3.49 g (0.01 mole) and 4-fluorobenzyl chloride
1.44 g (0.01 mole) were refluxed in ethanol for 7-8 hours.
The solvent was removed under reduced pressure and some
water added to it. The 6-chloro-5-(8'-quinoloxo)-4'-fluoro-
benzyl thiobenzimidazole precipitated out and filtered.
Recrystallized from chloroform.

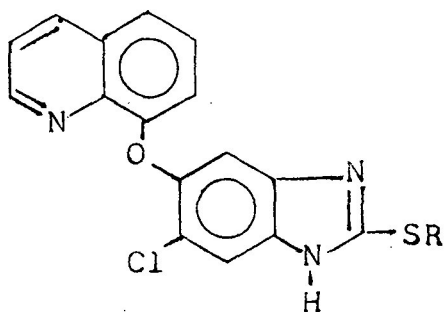
Yield : 3.07 g (70.7 %); m.p. 250°C.

Analysis for $C_{23}H_{15}ClFN_3OS$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	63.37	3.44	9.64
Found	63.43	3.19.	9.80

Other substituted benzyl derivatives of 6-chloro-5-
(8'-quinoloxo)-2-mercapto benzimidazole were synthesized in
the same manner and their physical data is summarised in
Table IX.

TABLE IX. 6-Chloro-5-(8'-quinoloxyl)-2-substituted benzyl or heteroaryl
Thio benzimidazoles.



No.	R	Yield %	M.p. °C*	Mol. formula	Elemental Analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	p-Chlorobenzyl	63.0	160	C ₂₃ H ₁₅ ClN ₃ OS	61.06	3.31	9.29	61.02	3.29	9.35
2.	p-Bromobenzyl	65.0	110	C ₂₃ H ₁₅ BrClN ₃ OS	55.58	3.02	8.45	55.31	3.15	8.35
3.	p-Fluorobenzyl	70.7	250	C ₂₃ H ₁₅ ClFN ₃ OS	63.37	3.44	9.64	63.43	3.19	9.80
4.	p-Nitrobenzyl	67.0	95	C ₂₃ H ₁₅ ClN ₄ O ₃ S	60.46	3.28	12.26	60.61	3.32	12.19
5.	2,4-Dichlorobenzyl	71.0	250	C ₂₃ H ₁₄ Cl ₃ N ₃ OS	56.73	2.87	8.63	56.79	2.62	8.42
6.	3,4-Dichlorobenzyl	73.0	155	C ₂₃ H ₁₄ Cl ₃ N ₃ OS	56.73	2.87	8.63	56.70	2.62	8.81
7.	2-Chloro amino	72.0	150	C ₂₃ H ₁₄ Cl ₂ N ₄ O ₃ S	56.21	2.85	11.40	56.32	2.69	11.29
8.	7-Chloro-4-quinolinyl	69.0	185	C ₂₅ H ₁₄ Cl ₂ N ₄ OS	61.34	2.86	11.45	61.09	2.62	11.32

* Melting points are capillary melting points and are uncorrected.

P A R T IV

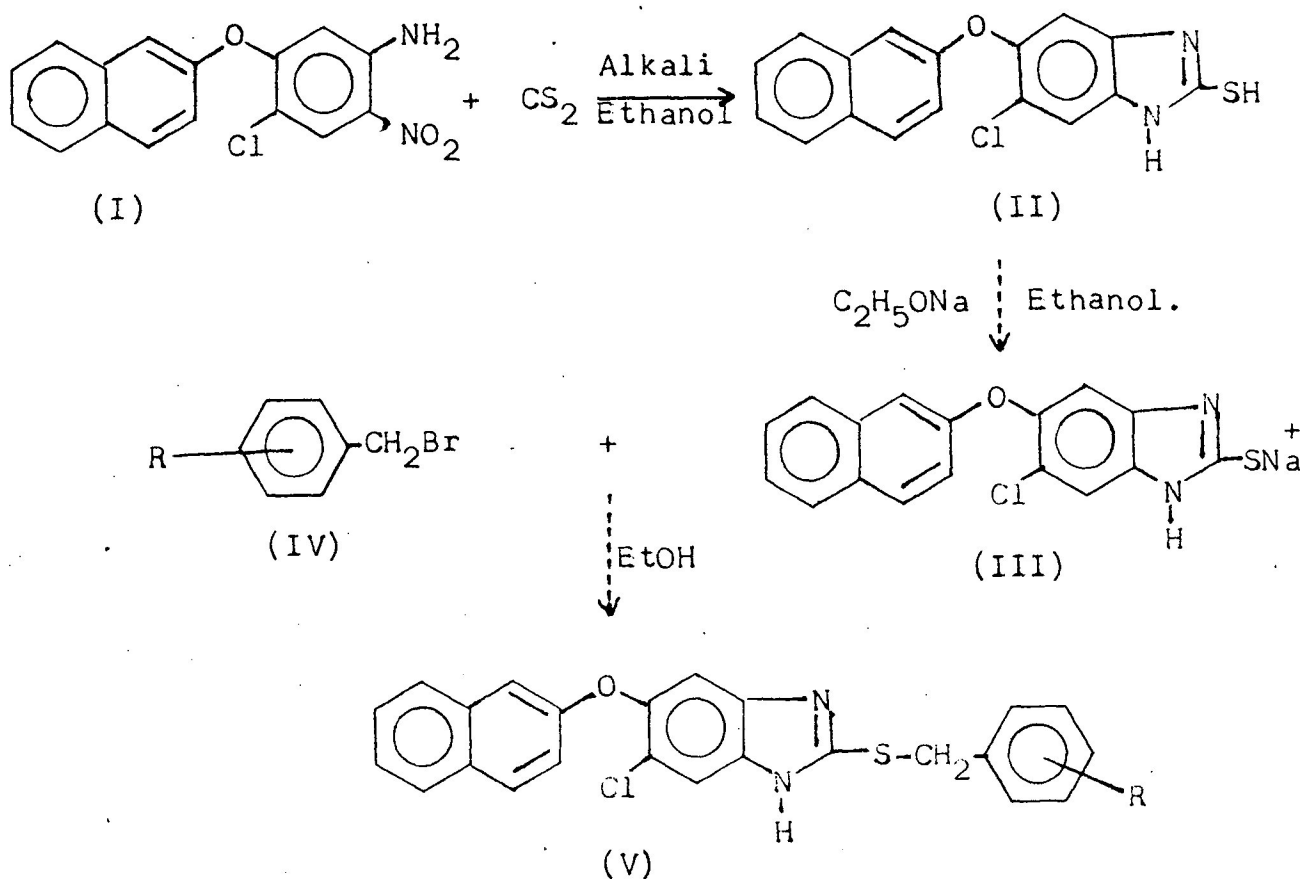
CHEMISTRY

S e c t i o n - B

6-CHLORO-5-NAPHTHOLOXY-2-
(SUBSTITUTED BENZYL THIO
OR HETEROARYL THIO)-
BENZIMIDAZOLES.

CHEMISTRY6-CHLORO-5-NAPHTHOLOXY-2-(SUBSTITUTED BENZYL THIO OR
HETERO ARYL THIO)BENZIMIDAZOLES :

5-Naphtholoxy-6-chloro-2-mercapto benzimidazole (V) was prepared by a general usual method which is already mentioned in Part II, Section (A), page No. 53 and it is most convenient method. This mercapto compound (III) was converted into its sodium salt (III), by sodium ethoxide in ethanol. Further it was reacted with different benzyl halides (IV) in ethanol at reflux temperature.



EXPERIMENTAL

EXPERIMENTAL5-Chloro-2-nitro-4-naphthoxy aniline :

In a 50 ml round bottomed flask, a mixture of 4,5-Dichloro-2-nitro aniline 2.07 g (0.01 mole), β -naphthol 1.44 g (0.01 mole) and potassium carbonate 0.99 g (0.01 mole) was refluxed in DMF for 6-8 hours. The hot reaction mixture was poured on crushed ice. 5-chloro-2-nitro-4-naphthoxy aniline was separated out. It was filtered and purified from aqueous methanol.

Yield : 2.07 g (69.0 %); m.p. 165°C.

Analysis for $C_{16}H_{11}ClN_2O_3$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	63.89	3.66	4.65
Found	63.49	3.42	4.82

Preparation of 4-naphthoxy-5-chloro-o-phenylene diamine :

Procedure as described in Part II, Section (A), page No.52.

Yield : 1.75 g (65.0%); m.p. 145°C.

Analysis for $C_{16}H_{13}ClN_2O$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	70.97	4.80	5.17
Found	70.76	4.65	5.35

2-Mercapto-6-chloro-5-naphtholoxo benzimidazole :

Procedure as described in Part II, Section (A),
page No. 53.

Yield : 2.29 g (70.5 %); m.p. 230°C.

Analysis for $C_{17}H_{11}ClN_2OS$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	62.67	3.07	8.60
Found	62.42	3.32	8.47

6-Chloro-5-naphtholoxo-2-(4'-bromobenzyl thio)-benzimidazole :

Sodium salt of 5-naphtholoxo-6-chloro-2-mercapto benzimidazole 3.48 g (0.01 mole) and 4-bromobenzyl bromide 2.5 g (0.01 mole) were refluxed in ethanol for 3-5 hours. After completion of the reaction, the solvent was removed under vacuum and some water added to it. The 6-chloro-5-naphtholoxo-(4'-bromobenzyl thio)benzimidazole precipitated out and filtered. Recrystallized from chloroform and hexane.

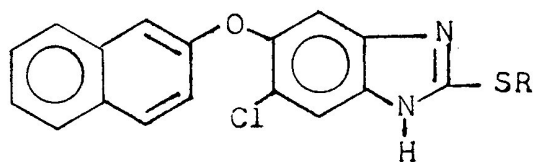
Yield : 3.41 g (69.0 %); m.p. 90°C.

Analysis for $C_{24}H_{16}BrClN_2OS$:

	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	58.12	3.22	5.15
Found	58.38	3.43	4.98

In the same way, other substituted benzyl derivatives of 6-chloro-5-naphtholoxo-2-mercapto benzimidazoles were synthesized and their physical data is summarised in Table X.

TABLE X. 6-Chloro-5-naphthoxy-2-(substituted benzyl or heteroaryl-thio)benzimidazoles.



No.	R	Yield %	M.p. °C*	Mol. formula	Elemental Analysis					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	p-Chlorobenzyl	62.0	99-100	C ₂₄ H ₁₆ Cl ₂ N ₂ OS	58.12	3.54	6.20	58.29	3.29	6.32
2.	p-Bromobenzyl	69.0	90	C ₂₄ H ₁₆ BrClN ₂ OS	58.12	3.22	5.15	58.38	3.43	4.98
3.	p-Fluorobenzyl	58.0	190	C ₂₄ H ₁₆ ClFN ₂ OS	66.28	3.68	6.44	66.19	3.60	6.30
4.	p-Nitrobenzyl	57.0		C ₂₄ H ₁₆ ClN ₃ O ₃ S	62.40	3.46	9.10	62.35	3.39	9.31
5.	2,4-Dichlorobenzyl	64.0	225	C ₂₄ H ₁₅ Cl ₃ N ₂ OS	59.32	3.08	5.76	59.19	3.10	5.62
6.	3,4-Dichlorobenzyl	63.0		C ₂₄ H ₁₅ Cl ₃ N ₂ OS	59.32	3.08	5.76	59.40	3.21	5.82
7.	7-Chloro-4-quinolinyl	68.5	170	C ₂₆ H ₁₅ Cl ₂ N ₃ OS	63.93	3.07	8.60	63.82	3.16	8.49

* Melting points are capillary melting points and are uncorrected.

P A R T V

BIOLOGICAL RESULTS AND DISCUSSION

BIOLOGICAL RESULTS AND DISCUSSION

It was well established that the gradual changes in chemical moiety could lead to a change in biological activity of drug. The actions of a drug are correlated to its chemical structure. The relatively minor modification in the drug molecule may result in major changes in pharmacological properties.

Taking into consideration the above fact, in our present study, various 2,5-disubstituted benzimidazoles derived from different biologically important moieties, were synthesized and screened for their in vitro antimicrobial activities.⁸⁸

Among the 5-phenoxy-6-chloro-2-(substituted benzylthio or heteroaryl thio) benzimidazoles from Part II, Section (A) (Table XI), page 84 substitution of 2,4-dichlorobenzyl and p-bromobenzyl at 2 position of the thio-benzimidazole inhibited the growth of M. tuberculosis at the concentration of 0.39 µg/ml in vitro but, on the other side, they are not much effective against Gram-positive and Gram-negative bacteria (S. aureus and E. coli). 3,4-Dichlorobenzyl substitution at 2 position of thiobenzimidazole moiety shows inhibition at 3.12 µg/ml against S. aureus microorganisms. In all other substituted group no satisfactory inhibition was observed against Gram-positive and M. tuberculosis bacteria.

Replacement of phenoxy group linkage by biphenyloxy at 5 position does not enhance in vitro antimicrobial activity of the parent moiety. Thus, the benzimidazole derivatives (Part II) , Section (B), namely, 6-chloro-5-biphenyloxy-2-(substituted benzylthio) benzimidazoles (Table XII) inhibit the growth of M. tuberculosis at the concentration ranging from 25 to 0.78 µg/ml. In case of antibacterial results the activity ranging from 100 to 25 µg/ml for both the strains, E. coli and S. aureus.

From this Part III, different 5-(chloro substituted phenoxy)-6-chloro-2-(substituted benzylthio) benzimidazoles (Table XIII) were screened for their antibacterial and antituberculous activity. The compounds have not shown much more significant anti T.B. activity.

When the 2,3-dichloro phenoxy substitution at 5-position and 3,4-dichlorobenzyl substituted at 2 position has shown anti T.B. activity at 0.78 µg/ml. At the same time it has inhibited the growth of S. aureus at 6.25 µg/ml and that of E. coli at 50 µg/ml, respectively. p-Bromo and p-chloro benzylthio at 2-position of the benzimidazole have shown good inhibition of growth of Gram-positive bacteria (S. aureus 6.25 µg/ml).

When the substitution at 5 position of the benzimidazole

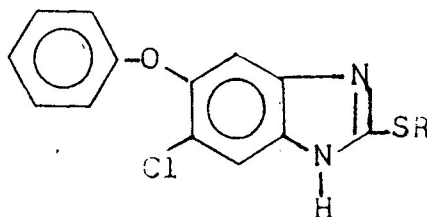
was 2,5-dichloro phenoxy and p-fluorobenzyl thio, at 2 position the activity was increased upto 0.78 µg/ml for anti T.B. and 100 and 12.5 µg/ml for E. coli and S. aureus, respectively. From the 4-halogen substituted phenyl derivatives at 2 position of the benzimidazole has shown good response against M. tuberculosis and Gram-positive bacteria. 2,4-Dichloro phenoxy and 4-chloro phenoxy substitution at 4 position have not shown any significant improvement in biological properties.

Among the various 6-chloro-5-(8'-quinoloxo)-2-(substituted benzylthio) benzimidazoles from Part IV, Section (A) (Table XIV) p-chlorobenzyl thio, 2,4-dichlorobenzyl thio group at 2 position in benzimidazole moiety imparted some activity to the lead moiety, inhibiting the growth of M. tuberculosis at concentration of 0.78 µg/ml, respectively. While p-bromobenzyl thio and 3,4-dichloro inhibited the growth of M. tuberculosis at 1.56 and 3.12 µg/ml, respectively. At the same time these compounds have not shown significant activity against Gram-positive and Gram-negative bacteria (S. aureus and E. coli).

When in some above benzimidazoles, position 5 was replaced with naphtholoxo group as in Part IV, Section (B), inhibition in the growth was found to be enhanced (Table XV) at lower concentration, but when these compounds were tested against S. aureus and E. coli, did not exhibited

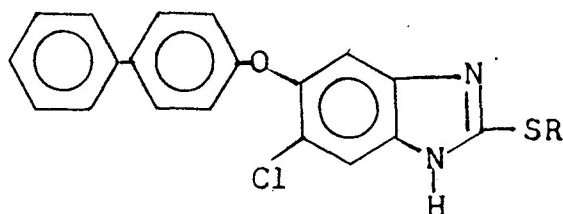
remarkable activity. The activity was ranging from 100 to 50 $\mu\text{g/ml}$ (Gram-positive and Gram-negative).

TABLE XI. 6-Chloro-5-phenoxy-2-(substituted benzyl thio or heteroaryl thio)benzimidazoles.



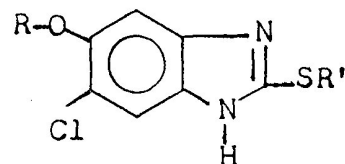
No.	R	MIC for H ₃₇ Rv strain of <u>M. tuber-</u> <u>culosis</u> μg/ml	MIC for <u>S. aureus</u> μg/ml	MIC for <u>E. coli</u> μg/ml
1.	p-Bromobenzyl	0.39	25	100
2.	p-Chlorobenzyl	1.56	12.5	-
3.	p-Fluorobenzyl	0.78	50	50
4.	p-Nitrobenzyl	3.12	25	50
5.	2,4-Dichlorobenzyl	0.39	50	-
6.	3,4-Dichlorobenzyl	6.25	3.12	50
7.	2-Chloro-4-nitro- benzyl	12.5	-	-
8.	7-Chloro-4-quinolinyl	25	12.5	50

TABLE XII. 6-Chloro-5-biphenyloxy-2-(substituted benzyl-
thio or heteroaryl thio)benzimidazoles.



No.	R	MIC for H ₃₇ Rv strain of <u>M. tuberculosis</u>	MIC for <u>S. aureus</u>	MIC for <u>E. Coli</u>
		µg/ml	µg/ml	µg/ml
1.	pBromobenzyl	1.56	50	100
2.	p-Chlorobenzyl	0.78	50	100
3.	p-Fluorobenzyl	1.56	25	50
4.	p-Nitrobenzyl	0.78	100	100
5.	2,4-Dichlorobenzyl	1.56	50	100
6.	3,4-Dichlorobenzyl	12.5	50	100
7.	2-Chloro-4-nitro- benzyl	25	-	-
8.	7-Chloro-4-quinol- inyl	12.5	50	50

TABLE XIII. 6-Chloro-5-(chloro substituted phenoxy)-2-(substituted benzyl
thio or heteroaryl thio) benzimidazoles.



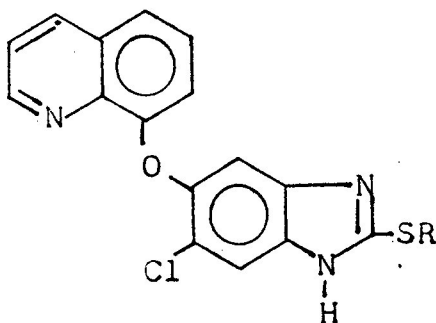
No.	R	R'	MIC for H ₃₇ Rv strain of <u>M. tuberculosis</u> μg/ml	MIC for <u>S. aureus</u> μg/ml	MIC for <u>E. coli</u> μg/ml
1.	4-Chlorophenyl	p-Bromobenzyl	12.5	50	50
2.	4-Chlorophenyl	p-Chlorobenzyl	6.25	50	50
3.	4-Chlorophenyl	p-Fluorobenzyl	25	25	50
4.	4-Chlorophenyl	p-Nitrobenzyl	50	50	50
5.	4-Chlorophenyl	2,4-Dichlorobenzyl	25	50	50
6.	4-Chlorophenyl	3,4-Dichlorobenzyl	12.5	50	100
7.	4-Chlorophenyl	7-Chloro-4-quinolinyl	50	50	50
8.	2,3-Dichlorophenyl	p-Bromobenzyl	3.12	6.25	50
9.	2,3-Dichlorophenyl	p-Chlorobenzyl	6.25	6.25	-
10.	2,3-Dichlorophenyl	p-Fluorobenzyl	1.56	50	100
11.	2,3-Dichlorophenyl	p-Nitrobenzyl	1.56	25	100
12.	2,3-Dichlorophenyl	2,4-Dichlorobenzyl	0.78	12.5	100

Contd--

TABLE -XIII (contd..)

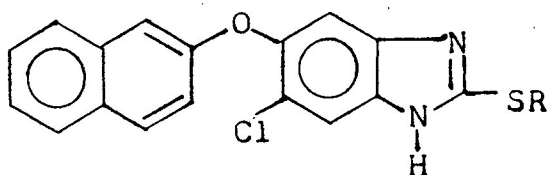
No.	R	R'	MIC for H ₃₇ Rv strain of <u>M. tuberculosis</u> µg/ml	MIC for <u>S. aureus</u> µg/ml	MIC for <u>E. coli</u> µg/ml
13.	2,3-Dichlorophenyl	3,4-Dichlorobenzyl	0.78	6.25	100
14.	2,3-Dichlorophenyl	2-Chloro-4-nitrobenzyl	25	-	-
15.	2,3-Dichlorophenyl	7-Chloro-4-quinolinyl	12.5	25	50
16.	2,4-Dichlorophenyl	p-Bromobenzyl	25	100	50
17.	2,4-Dichlorophenyl	p-Chlorobenzyl	12.5	-	-
18.	2,4-Dichlorophenyl	p-Fluorobenzyl	50	50	50
19.	2,4-Dichlorophenyl	p-Nitrobenzyl	-	-	-
20.	2,4-Dichlorophenyl	7-Chloro-4-quinonilyl	-	-	-
21.	2,5-Dichlorobenzyl	p-Bromobenzyl	1.56	6.25	100
22.	2,5-Dichlorobenzyl	p-Chlorobenzyl	12.5	25	100
23.	2,5-Dichlorophenyl	p-Fluorobenzyl	0.78	12.5	100
24.	2,5-Dichlorophenyl	p-Nitrobenzyl	6.25	25	50
25.	2,5-Dichlorophenyl	2,4-Dichlorobenzyl	12.5	25	100
26.	2,5-Dichlorophenyl	3,4-Dichlorobenzyl	6.25	6.25	100
27.	2,5-Dichlorophenyl	2-Chloro-4-nitrobenzyl	50	6.25	100
28.	2,5-Dichlorophenyl	7-Chloro-4-quinolinyl	12.5	50	50

TABLE XIV. 6-Chloro-5-(8'-quinoloxyl)-2-(substituted-benzylthio or heteroaryl thio)benzimidazoles.



No.	R	MIC for H ₃₇ Rv strain of <u>M. tuberculosis</u>	MIC for <u>S. aureus</u>	MIC for <u>E. coli</u>
		μg/ml	μg/ml	μg/ml
1.	p-Bromobenzyl	1.56	-	-
2.	p-Chlorobenzyl	0.78	100	100
3.	p-Fluorobenzyl	12.5	-	-
4.	p-Nitrobenzyl	25	100	50
5.	2,4-Dichlorobenzyl	0.78	100	50
6.	3,4-Dichlorobenzyl	3.12	50	50
7.	2-Chloro-4-nitrobenzyl	25	-	-
8.	7-Chloro-4-quinolinyl	12.5	100	100

TABLE XV. 6-Chloro-5-(naphtholoxy)-2-(substituted benzylthio- or heteroaryl thio)benzimidazoles.



No.	R	MIC for H ₃₇ Rv strain of <u>M. tuberculosis</u>	MIC for <u>S. aureus</u>	MIC for <u>E. coli</u>
		μg/ml	μg/ml	μg/ml
1.	p-Bromobenzyl	6.25	-	-
2.	p-Chlorobenzyl	1.56	100	100
3.	p-Fluorobenzyl	6.25	50	-
4.	2,4-Dichlorobenzyl	3.12	50	100
5.	3,4-Dichlorobenzyl	1.56	50	50
6.	7-Chloro-4-quinoliny	12.5	-	-

P A R T V

SPECTRAL STUDY AND IDENTIFICATION

SPECTROSCOPIC ANALYSIS OF NEW COMPOUNDS

Infra-red Spectroscopy :

Infra-red spectroscopy is one of the most powerful analytical techniques used by the modern chemist. Its most important use has been for the identification of organic compounds, because their spectra are generally complex and provide numerous maxima and minima that can be employed for comparison purposes. The infra-red technique has several advantages over the other usual methods of structural analysis (X-Ray diffraction, electron spin resonance, etc.). It provides useful information about the structure of a molecule quickly, without involving lengthy evaluation methods.

Perhaps, the most powerful function of infra-red spectroscopy is of establishing conclusively the identity of two samples that have identical spectra when determined in the same medium. The region between $1430\text{--}910\text{ cm}^{-1}$ in an infra-red spectrum is called the finger print region. No two different molecules have the same set of absorption bands in this region. Although similar molecules may show very similar spectra in the region between $4000\text{--}1430\text{ cm}^{-1}$, there will almost always be discernible differences in the finger print region.

The compounds prepared in this present investigation have been characterized by their infra-red spectrum.

The fundamental groups present in this class of compounds are listed below :

- i) 5-Substituted benzimidazole ring.
- ii) Aromatic ether.
- iii) C-S (sulphide) linkage.
- iv) Imidazole ring.
- v) Halogen linkage, C-X (X = halogen atom).

5-Substituted benzimidazole ring :

This ring structure⁸⁹ shows three absorption bands in the region between $900-800\text{ cm}^{-1}$. The bands are normally differentiated into 3 regions of absorption : $900-870\text{ cm}^{-1}$, $830-812\text{ cm}^{-1}$ and $820-800\text{ cm}^{-1}$.

Aromatic ether :

The aromatic ethers⁹⁰ are characterized by a strong absorption band in the region between $1300-1175\text{ cm}^{-1}$. A secondary absorption band of medium intensity appears in the region between $1070-1000\text{ cm}^{-1}$.

C-S (sulphide linkage) :

All the compounds prepared, have been identified by the absorption band which represents the sulphide linkage. These are characterized⁹¹ by an absorption band in the region between $1440-1415\text{ cm}^{-1}$.

A stretching vibration⁹¹ is assigned to the C-S linkage which occur in the region $700-610\text{ cm}^{-1}$. But this band is usually weak and sometimes may be absent.

Imidazole ring :

The ring stretching⁹² vibration of the imidazole ring is obtained at 1550 cm^{-1} . This is assigned to the C = N stretching vibration.

Halogen compounds (C - X) :

Where X = chlorine atom.

The C-Cl stretching vibrations⁹³ are characterized by absorption peaks in the region between $760-600\text{ cm}^{-1}$.

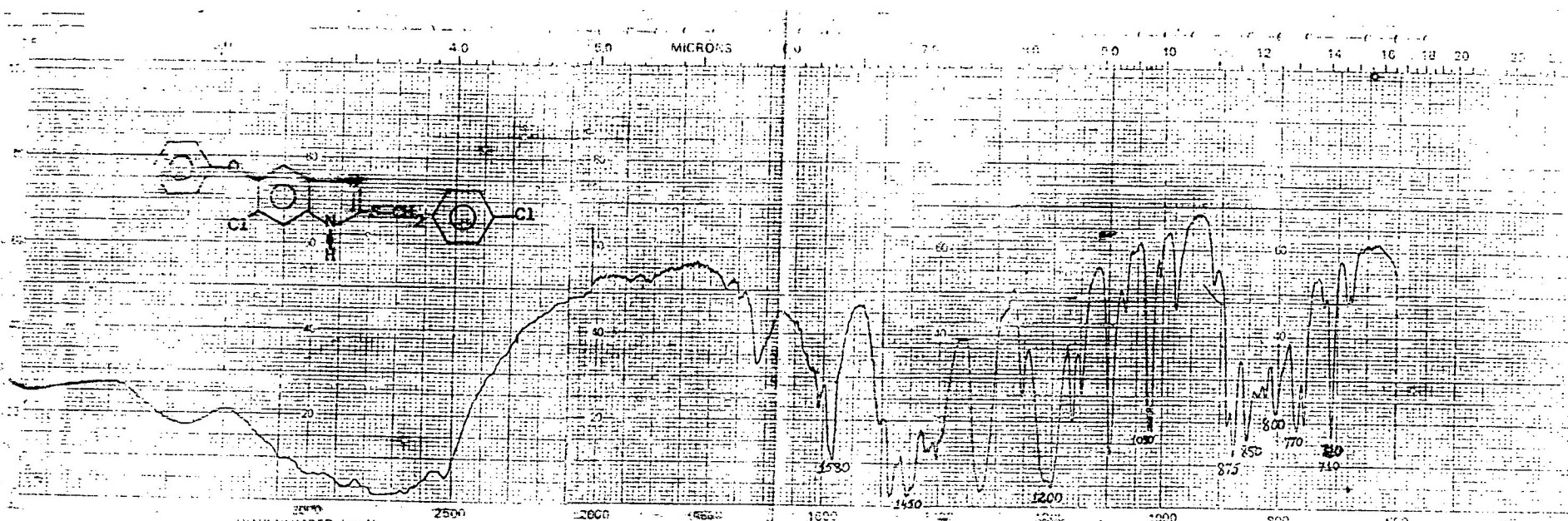
In addition to the data given above, zone of the compounds are characterized by other functional groups.

Compound No.3 contains a -NO_2 group. This is characterized by a strong band⁹⁴ in the $1661-1499\text{ cm}^{-1}$ region. Another band appears in the region between $1389-1259\text{ cm}^{-1}$. The exact position of the bands are dependent upon substitution and unsaturation in the vicinity of the NO_2 group. In the compound under discussion, these bands appear at 1510 and 1340 cm^{-1} , respectively

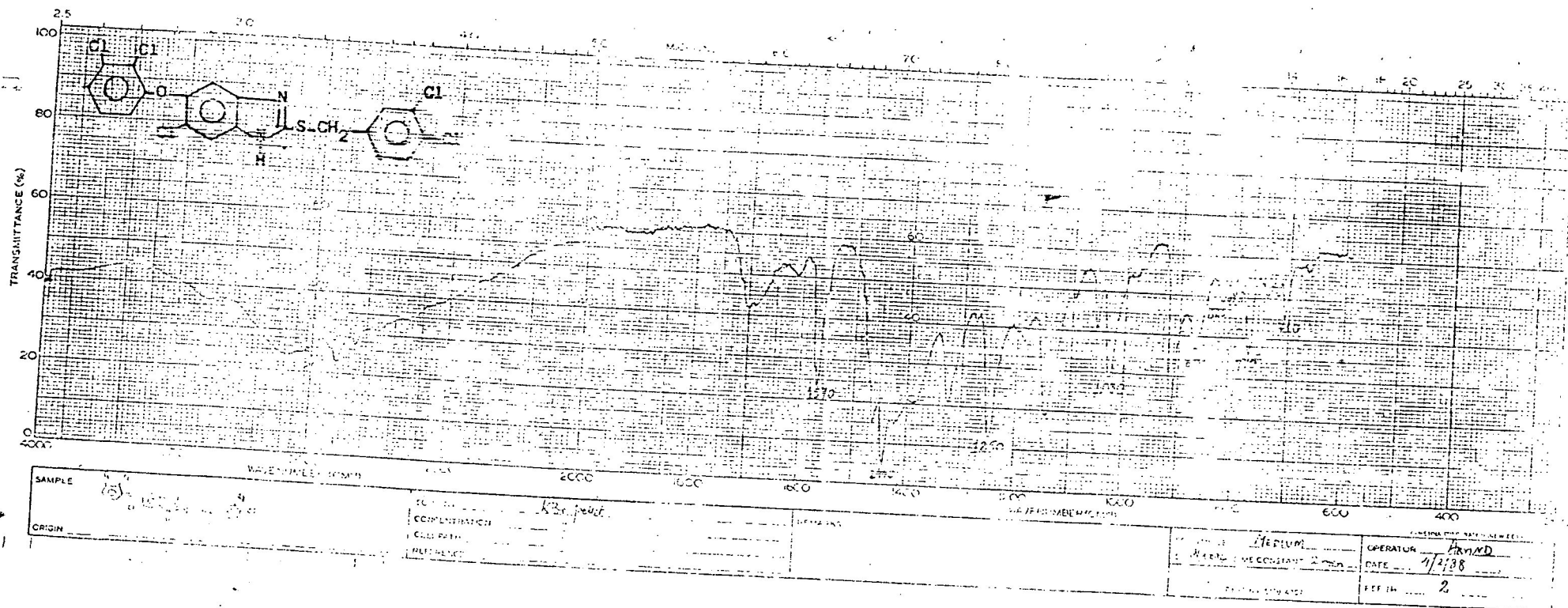
Experimental Data :

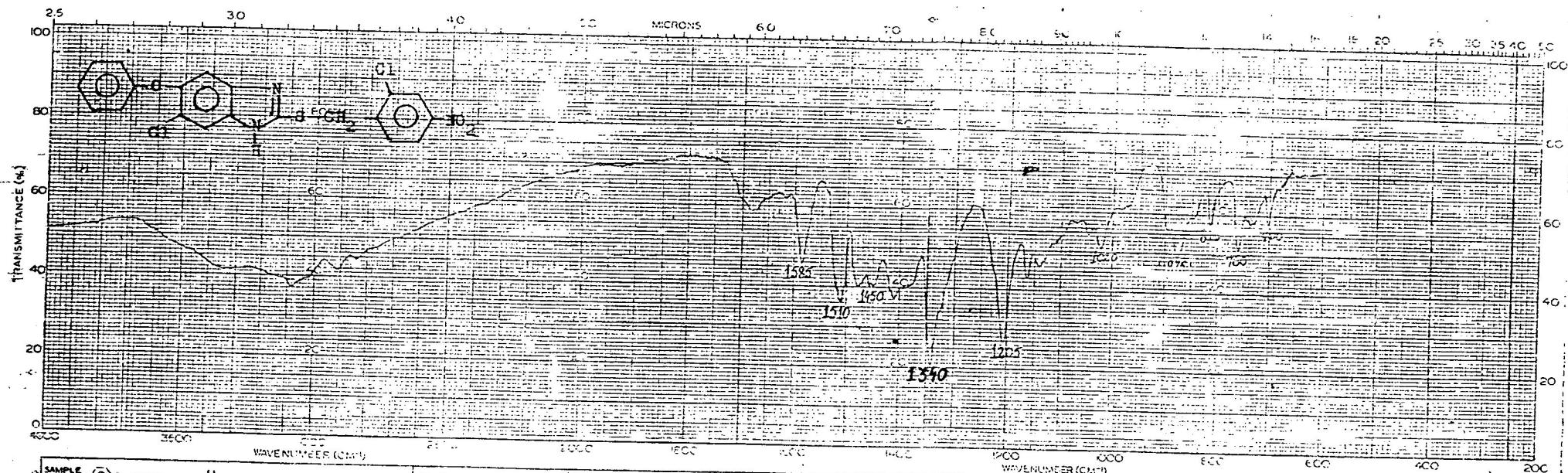
The compounds synthesized in the present work have been analysed by the KBr-pellet technique. Spectral grade potassium bromide was used for this purpose. All infra-red spectra were recorded on a Perkin Elmer 257 grating Infra-red Spectrophotometer.

Compd. No.	5-Substituted benzami- dazole			Aromatic ether		C-S (sulphide linkage)		Imidazole C=N, C-N	R-Cl linka- ge	
	Reqd. cm ⁻¹	900-870	830-812	820-800	1300-1175	1070-1000	1440- 1415	700-600	1550	800-600
1		875	850	800	1200	1030	1450	710	1580	770
2		870	825	800	1250	1030	1440	710	1570	770
3		875	815	-	1205	1020	1450	700	1585	760
4		870	840	-	1220	1010	1465	710	1600	770
5		870	840	-	1215	1030	1470	710	1590	760
6		870	830	810	1225	1015	1460	720	1570	760
7		870	840	-	1210	1030	1460	710	1580	760
8		875	830	800	1245	1015	1450	-	1590	760
9		875	830	-	1210	1025	1465	690	1550	-
10		870	830	-	1210	1030	1460	710	1550	770
11		880	820	-	1250	1025	1440	710	1570	780

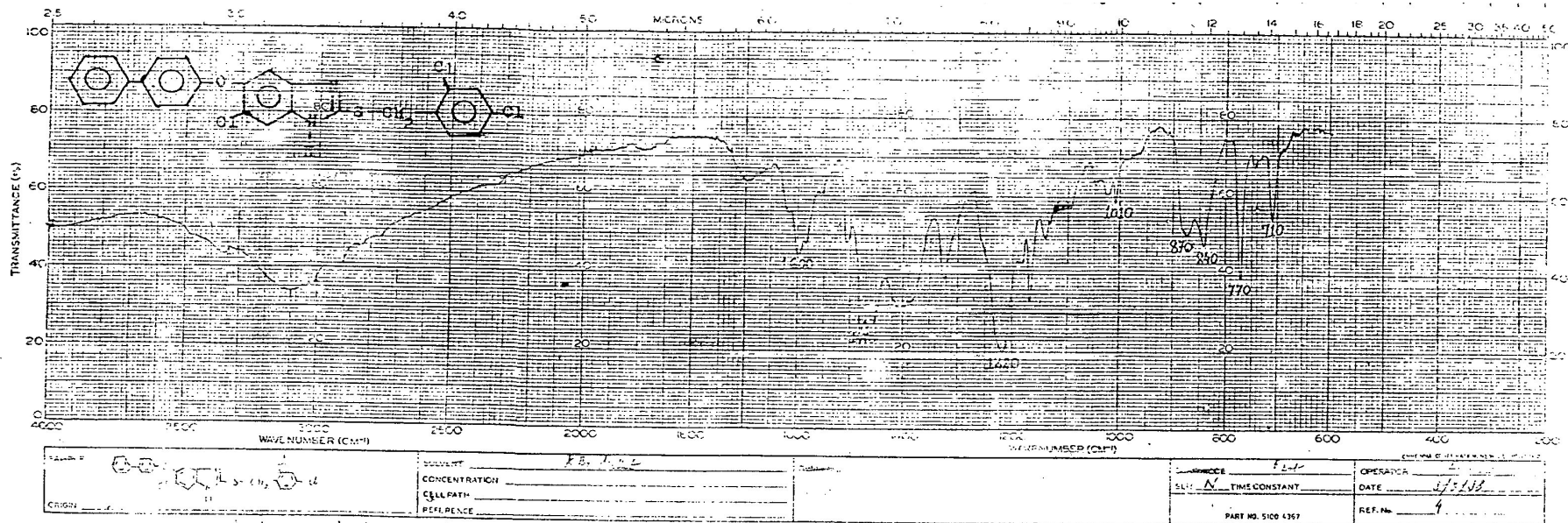


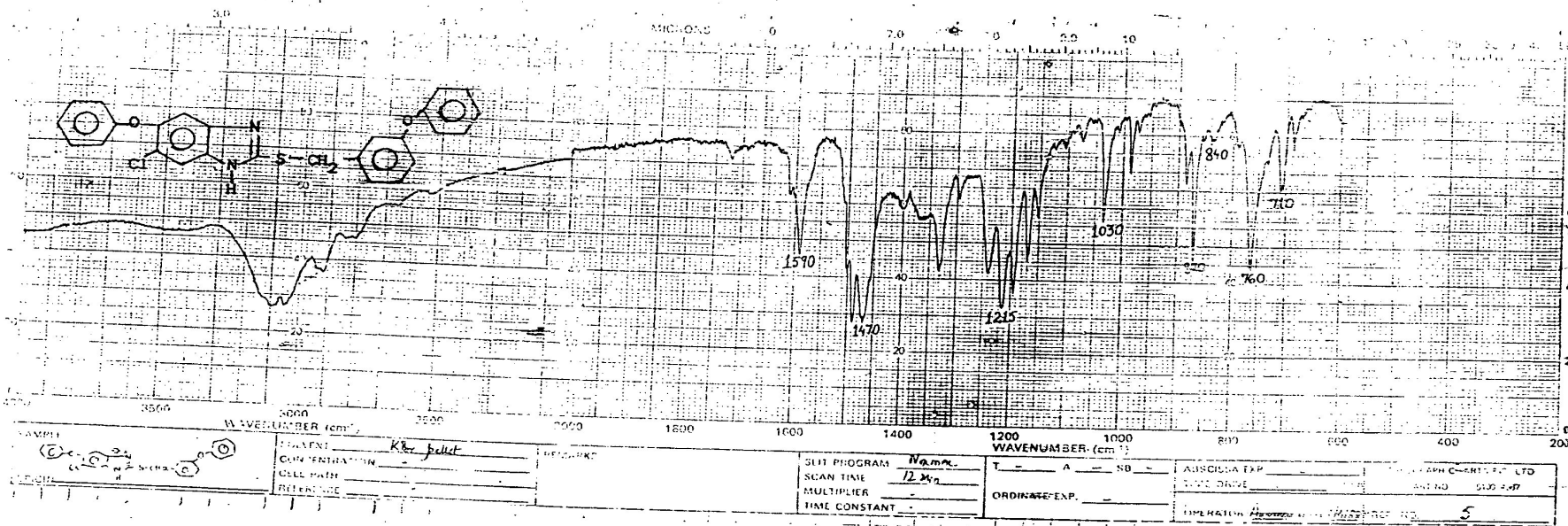
SAMPLE <chem>Clc1ccc(cc1)SCCSCc2ccc(Cl)cc2</chem>	SOLVENT	5B pellet	REMARKS	SIL. TEMPERATURE	NORMAL	I. A. 59	ADDITIONAL EXP.			
	CONCENTRATION			SCANNING TIME	12 min		BASELINE		BASE PLATE	
	CELL PATH			WAVELENGTH			GLASS PLATE			
	REFERENCE									
						OPERATOR: WIND 2/5/88				

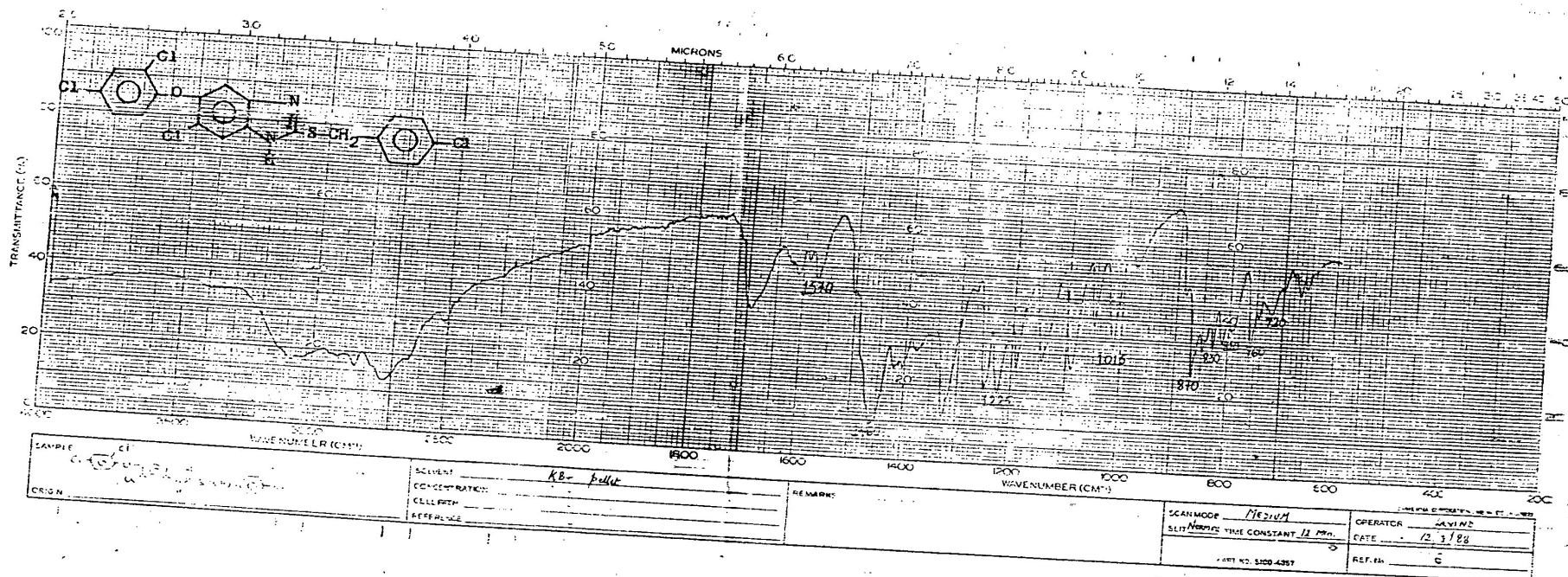


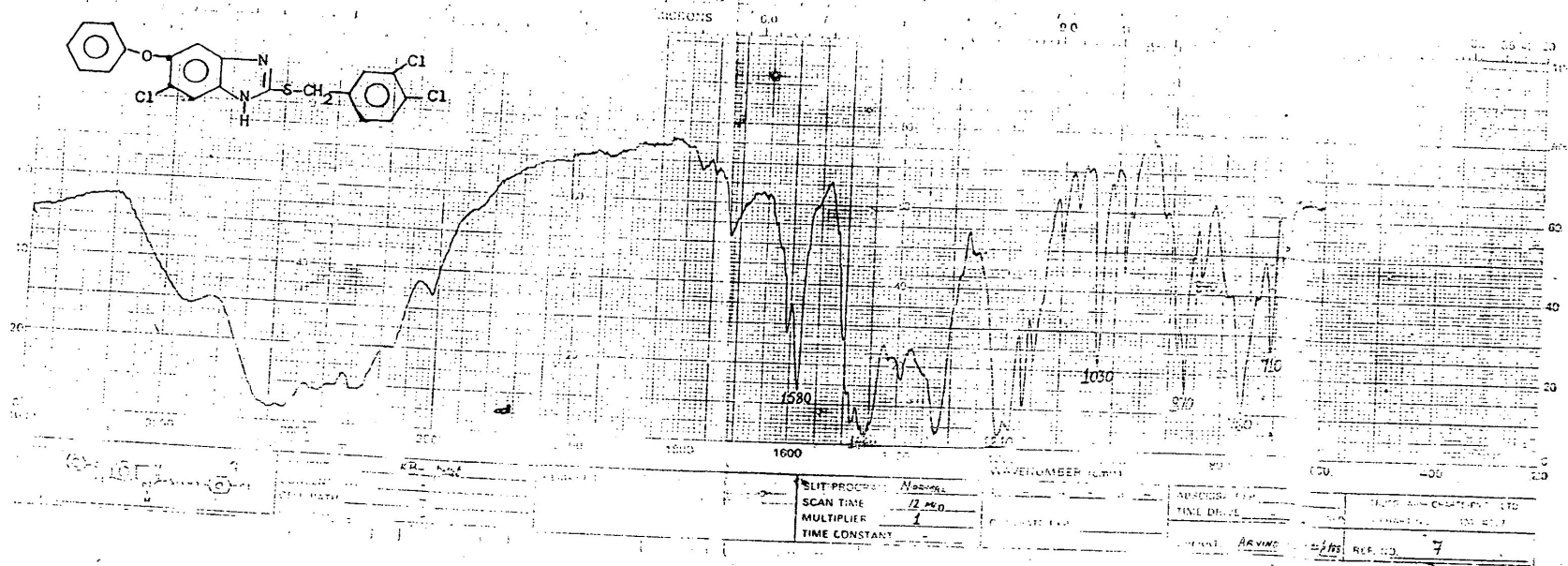


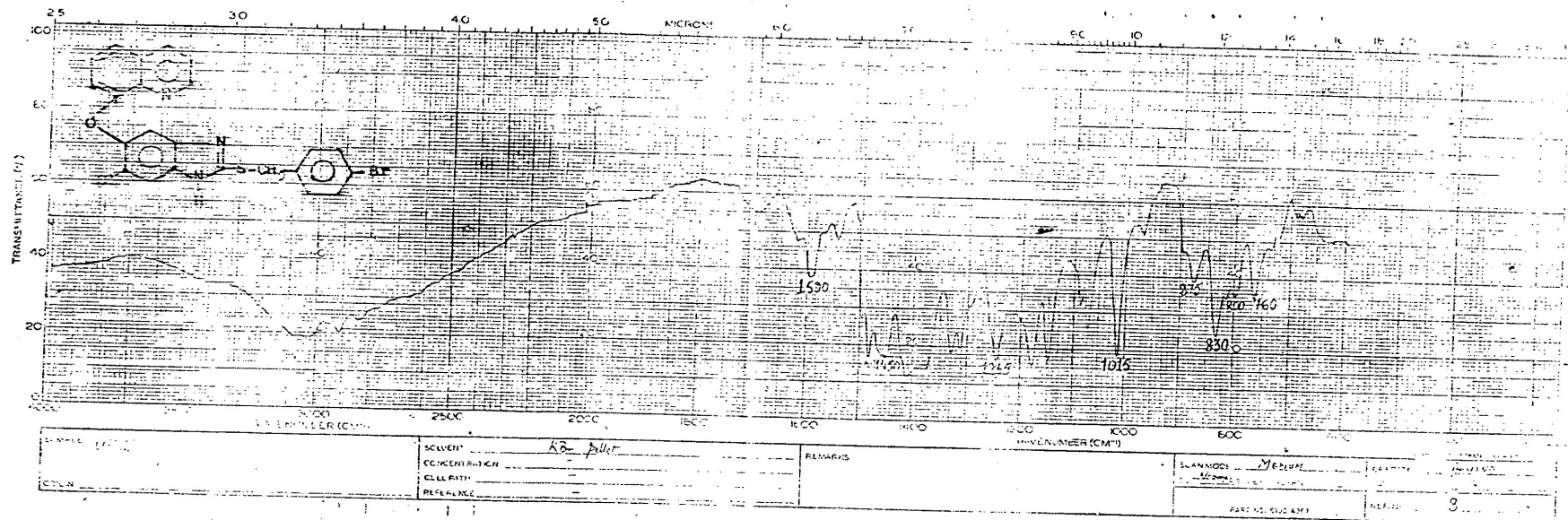
SAMPLE ORIGIN	<chem>c1ccc(cc1)OC(=O)c2cnc3ccccc3n2</chem> C1 C2	SOLVENT <u>CHLOR. FORM.</u> CONCENTRATION _____ CELL _____ REFERENCE _____	REMARKS _____ _____ _____	EXAMINER <u>MEDVON</u> CL. <u>16/5/88</u>	OPERATOR <u>16/5/88</u> DATE <u>16/5/88</u> REF. NO. <u>3</u>
		PART NO. 1357			

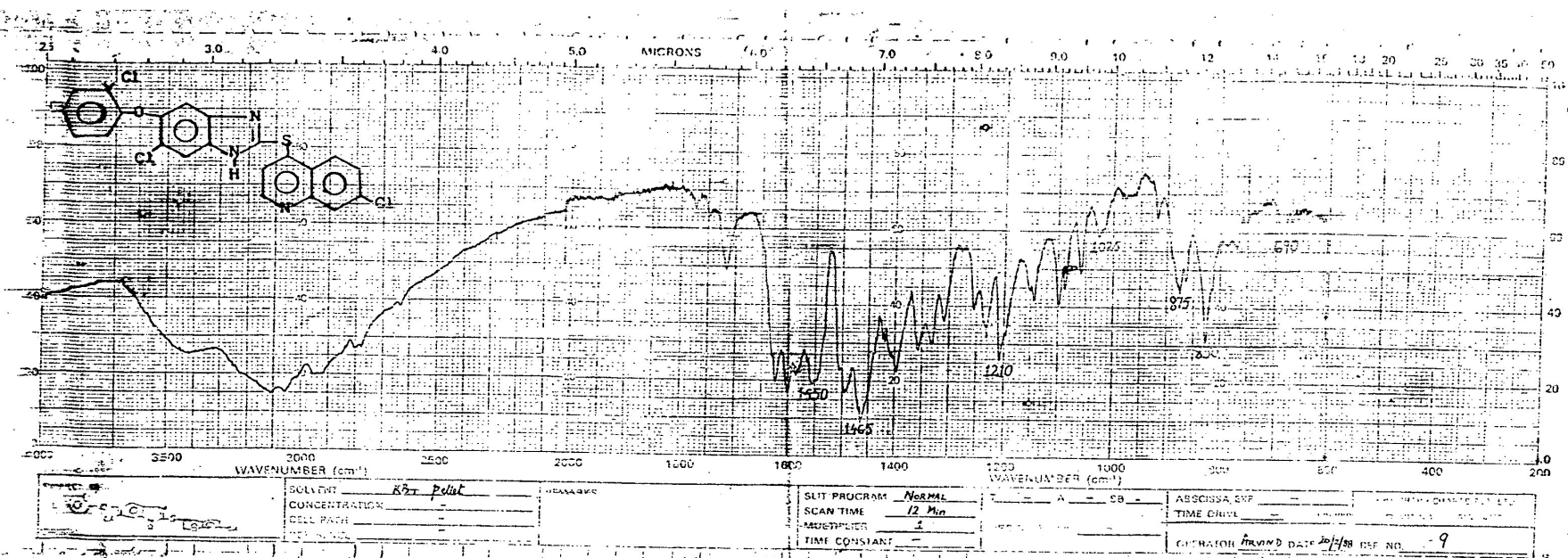


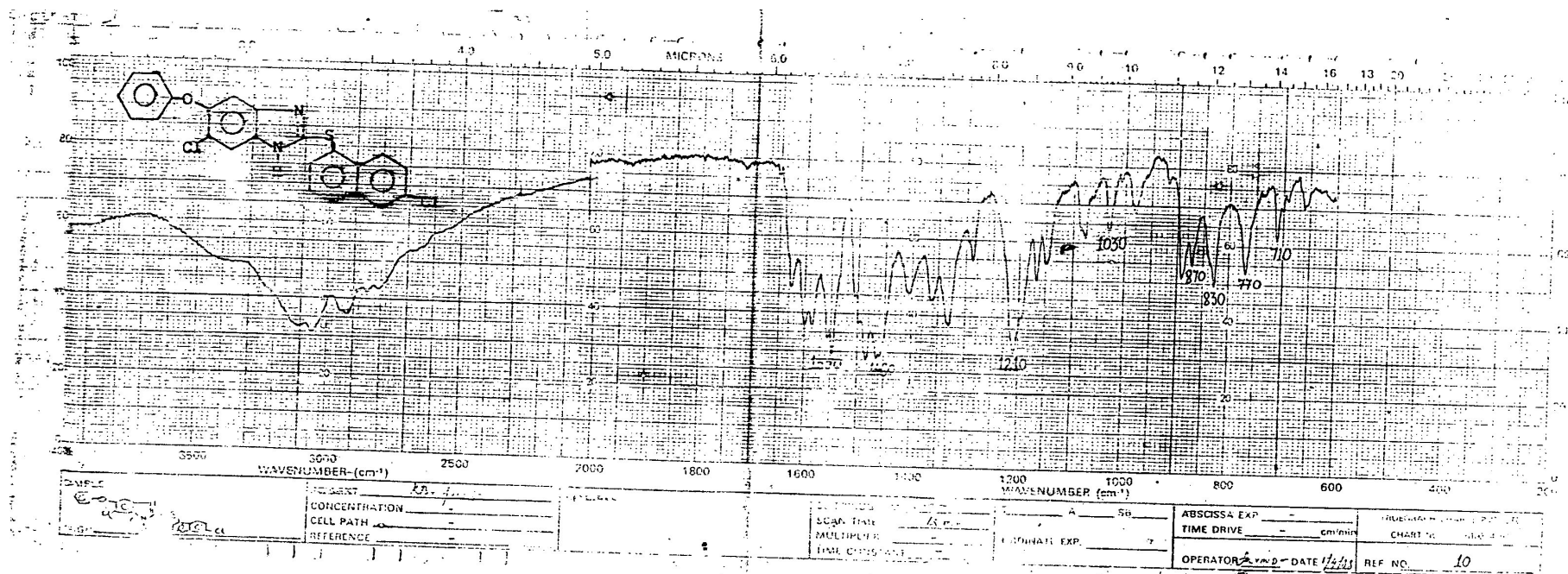




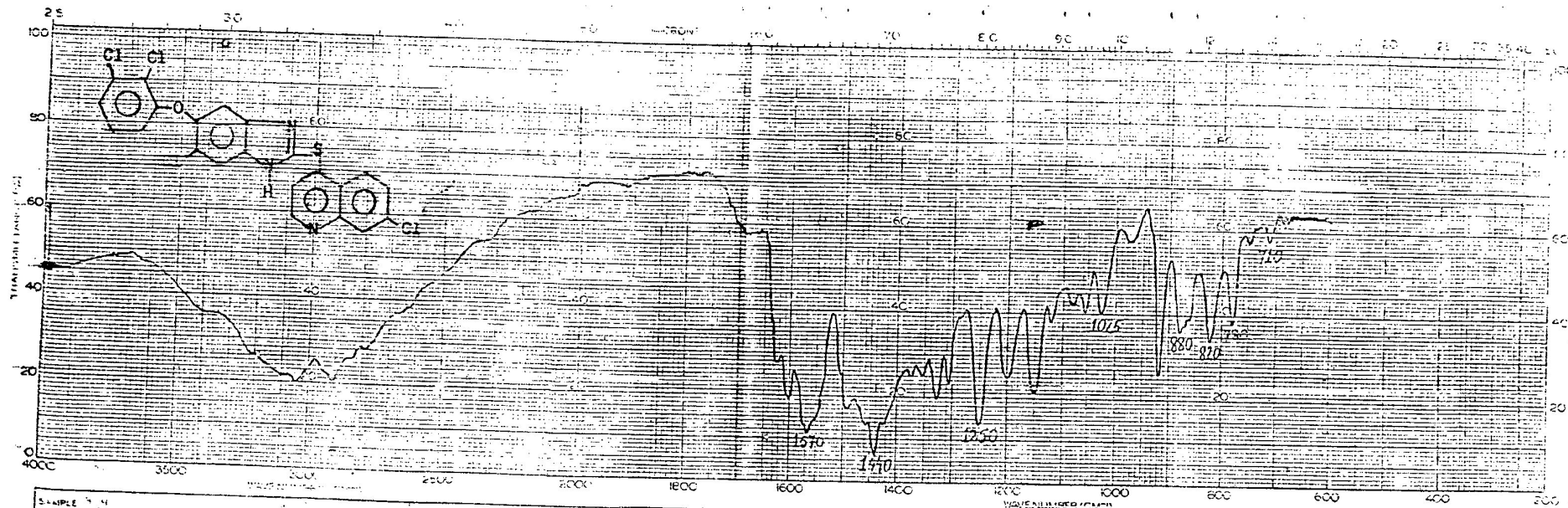








10/15/11



SAMPLE NO. 10115 CATION	SOLVENT <u>NO- pellet</u> CONCENTRATION <u>-</u> CARRIER <u>-</u> REFERENCE <u>-</u>	REMARKS 	TECHNIQUE <u>MEDIA</u> CLIP-IR TIME CONSTANT <u>-</u>	OPERATOR <u>ARVIND</u> DATE <u>24/2/88</u>
	PART NO. 5100 4367		REF. NO. <u>112</u>	

P A R T V

S U M M A R Y

S U M M A R Y

Tuberculosis is by far the most frequently encountered mycobacterial disease in the world and although its incidence has diminished significantly in the industrially more developed countries, it remains a major public health problem in most developing nations. Great progress has been made in the development of tuberculosis drugs. At present two potent substances are in common use (Rifampicin and Streptomycin). Streptomycin and/or Isonicotinic acid hydrazide combined with *p*-aminosalicylic acid are the drugs of first choice because they are most effective and least toxic. Following therapeutic failure with these, cycloserine, viomycin, kanamycin, pyrazinamide, ethionamide, capreomycin and ethambutol in a variety of combinations are used.

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

Part I deals with the introductory aspect with special references to the ways and means which are used at present in combination to eliminate the tuberculosis from society. This is followed by "Review of Literature" incorporating the historical background of chemotherapy as well as the brief account of current drugs utilization and their characteristics as antituberculosis agents. This part concludes with different bosting guide-lines behind the proposed synthetic work.

Part II covers the synthetic aspects of chemistry and various experimental procedures in the field of 5-substituted-6-chloro-2-mercapto benzimidazoles and substituted benzyl bromides.

In Section A, all the 6-chloro,5-phenoxy-2-(mercapto)benzimidazoles were synthesized by known literature method. Substituted benzyl bromides were also prepared by known literature method. These reactants were condensed in alcohol and isolated the final 6-chloro-5-phenoxy-2-(substituted-benzylthio/heteroaryl thio)-benzimidazoles.

In Part II, Section B, 6-chloro-5-biphenoloxo-2-(substituted-benzyl thio) benzimidazoles were synthesized by adopting the same synthetic route that was in Part II Section A.

Part III describes the replacement of chloro group with different substituted chlorophenols. Further, this part describes the condensation of 6-chloro-5-(chloro substituted phenoxy)-2-mercapto benzimidazoles with various substituted benzyl bromides and 4,7-dichloro quinolines. They were synthesized in the same manner as in Part II, Section A and characterized by their elemental analysis, TLC and IR spectral studies.

Part IV divided into two sections (Section A and Section B). In Section A, a series of heterocyclic derivatives of 6-chloro-5-quinoloxo-2-(substituted benzyl thio/heteroaryl thio) benzimidazoles were synthesized adopting the known literature method.

In Section A, 6-chloro-5-naphtholoxo-2-(substituted benzyl thio/heteroaryl thio)benzimidazoles were prepared in the same manner and studied for their biological activities.

Part V describes the method adopted in vitro antituberculous screening against M. tuberculosis. INH and sodium PAS were used as a standard drugs to compare our screening results. Screening data, while summarizing it revealed that 6-chloro-5-phenoxy-2-(p-bromobenzyl thio)-benzimidazole and 6-chloro-5-phenoxy-2-(p-chlorobenzyl thio)-benzimidazole have shown activity at 0.3 µg/ml and 1.25 µg/ml, respectively. In the case of biphenyloxy

substitution, 6-chloro-5-biphenyloxy-2-(p-fluorobenzyl thio) benzimidazole has shown the activity at 0.31 µg/ml. In Part III two compounds from 2,3-dichloro and 2,5-dichloro-substitution at five position of the benzimidazole moiety have inhibited the growth of M. tuberculosis at the concentration of 0.6 µg/ml and 1.25 µg/ml respectively.

While, in part IV the compounds by substitution of 8-hydroxy quinoline and β -naphthols at 5 position of the benzimidazole did not show any significant biological activity. This part ends with bibliography.

PART V

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S Y N O P S I S

S Y N O P S I S

Human awareness to tuberculosis (known as T.B.), the deadly disease, is as ancient as its discovery. Since the discovery of Tuberculosis Bacillus by Robert Koch in 1882 there have been various attempts by scientists of repute from all over the world to eradicate this disease. Also various national and international health organizations are engaged in health programmes for a fight against this disease.

This disease is found to be prevalent in Asiatic conditions. In a survey conducted by N.T.C.P. it was observed that about 1.5 % of the total population of the country is affected and nearly 2.5 million new cases are reported every year.¹ Though this disease is found to be less in percentage in the developed countries, tuberculosis nevertheless still remains one of the most prevalent diseases in developing countries.

After the identification of the cause of T.B. in 1882 another attempt was followed in 1895 with the discovery of X-rays by Roentgen. Even in spite of the above advances of the 19th century in a time lag of 45 years no specific cure for the disease was obtained, with the advent of enlightened scientific atmosphere in the 20th century.

Streptomycin was discovered by Waksman. Then in rapid succession new drugs were added, namely, PAS (1949), INH (1952), Thiacetazone, Ethambutol, Rifampicin (1970) amongst others.

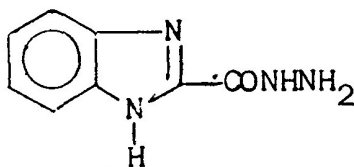
None of the above mentioned compounds used singly or in a combination have produced complete satisfactory therapeutic results.

Pulmonary tuberculosis still remains the commonest form of the disease, but extrapulmonary disease is also frequently reported. Of the latter nodal, gastrointestinal, bone and central nervous system tuberculosis are the dominant forms.

The main objective of the present study was to synthesize newer antitubercular chemotherapeutic agents, so as to prevent the recurrence of sufferings, morbidity and mortality.

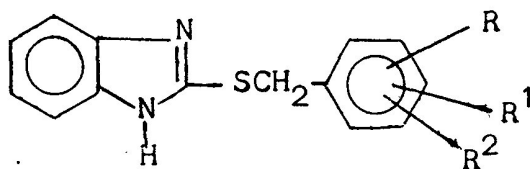
One of the most significant advances made in the various fields of Medicinal Chemistry is the evaluation of a series of benzimidazoles², especially a wide class of 2,5-disubstituted benzimidazoles³ for their marked biological activity.

Benzimidazole, 2-carboxylic acid hydrazide (I) was reported to have activity against BCG in vitro at the minimum inhibitory concentration of 15 µg/ml.⁴



(I)

A very interesting development occurred in the field of benzimidazoles with the emergence of broad spectrum antimicrobial compounds (II), for their potential antimicrobial activity.⁵



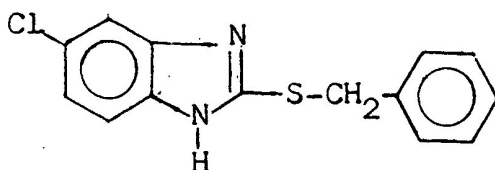
(II)

where, R, R¹, R² = Cl.

The primary aim of our study was to synthesize antitubercular and antibacterial compounds of higher efficacy. Mayer's hypothesis⁶ suggests that " a morphological relationship between mycobacteria and fungi may be paralleled by a biochemical relationship " i.e., substances acting as anti-fungal agents are likely to exhibit antitubercular action also.

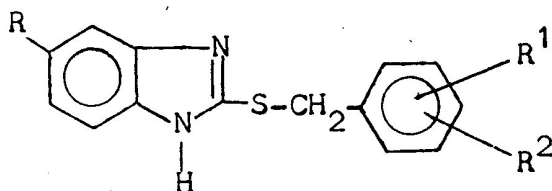
The antifungal activity⁷ of 2-mercapto benzimidazole derivatives, namely, 5(6)-chloro, 2-(benzylthio) benzimida-

zole (III) against Trichophyton interdigitate at a dilution 1:291, 900 or 3.4 $\mu\text{g/ml}$ has been reported.



(III)

Taking the initiative from Mayer's hypothesis a series of different 5(6)-substituted-2-(benzylthio) benzimidazole⁸ (IV) compounds were synthesized for antitubercular activity in our laboratory.

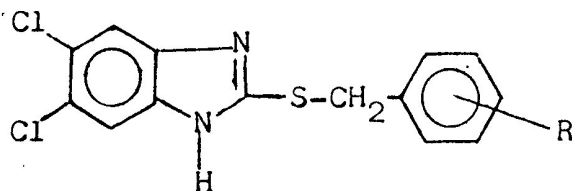


(IV)

where, $R = \text{H, Cl, CH}_3, \text{NO}_2$;

R^1 and $R^2 = 3\text{-Cl, 2-4-Cl}_2, \text{p-Br, p-Cl, p-NO}_2, 2\text{-Cl, 4-NO}_2, \text{etc.}$

A further study was undertaken by substituting one more chloro group at 6-position of the benzimidazole. Thus, different, 5,6-dichloro-2-(benzylthio)benzimidazoles (V) were synthesized and tested for in vitro antitubercular activity.⁹



(V)

where, R = 3,4; 2,3-Cl₂; p-NO₂; p-Br, etc.

Some of the above compounds were found to be active.

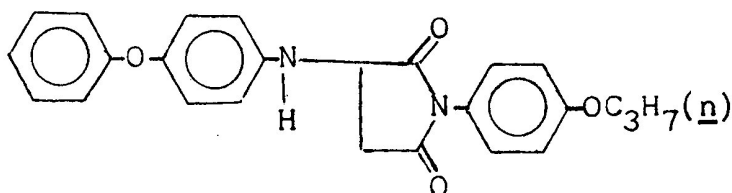
However, to obtain compounds of marked activity, more compounds of the series, 2,5-disubstituted-6-chloro benzimidazole were synthesized and screened for antitubercular activity.

PART I

Section - A :

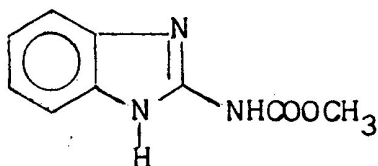
6-CHLORO-5-PHENOXY-2-(SUBSTITUTED BENZYLTHIO)- BENZIMIDAZOLES :

Studies in our laboratory revealed that 4-(p-phenoxy anilino)-N-(o,n-propoxy phenyl) succinimide (VI) inhibited the growth of M. tuberculosis, at a concentration of 0.06 µg/ml.¹⁰ as observed in in vitro testing.



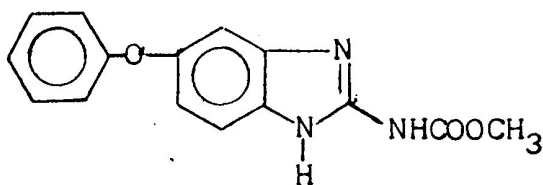
(VI)

The modification of compound (VII) by substituting phenoxy group at position 5 has resulted in a new compound (VIII) of a high efficacy value.¹¹



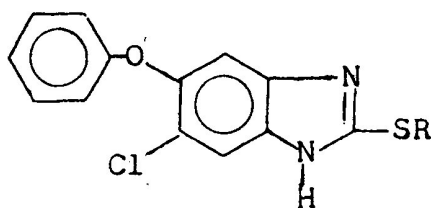
(VII)

CARBENDAZINE



(VIII)

Enhancement of biological activity of the benzimidazole nucleus by substitution of phenoxy linkage at 5-position and the usefulness of chloro group in benzimidazole group for biological activity, prompted us to synthesize 6-chloro-5-phenoxy-2-(substituted benzylthio)-benzimidazole derivatives (IX) of the following type.



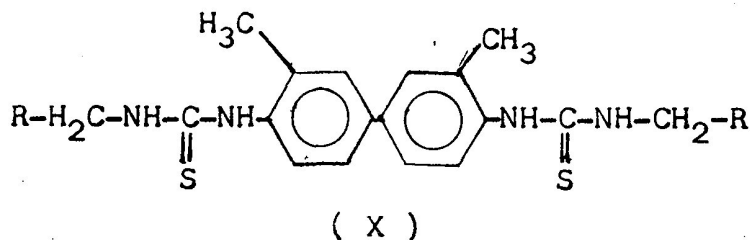
(IX)

where, R = various substituted benzyl and 7-chloro, 4-quinolinyl.

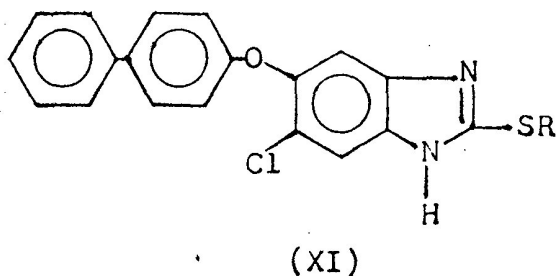
Section - B :6-CHLORO-5-BIPHENYLOXY-2-(SUBSTITUTED BENZYLTHIO)-
BENZIMIDAZOLES :

From our laboratory some of *p*-substituted biphenyl derivatives showed marked antitubercular activity.¹²

4,4'-Di-(substituted benzyldehde-3-thiosemicarbazone)3,3'-dimethyl biphenyl (X) was reported as tuberculostatic as well as antibacterial agent.¹³



It has been reported that biphenyl compounds exhibit antitubercular¹³, antimicrobial¹⁴, anthelmintic¹⁵, antifungal¹⁶, antiinflammatory¹⁷ and antiarthritic activity. This account emphasized the importance of *p*-substituted biphenyl derivatives. With this idea, series of compounds having the benzimidazole nucleus along with biphenyloxy linkage at 5 position were synthesized (XI).

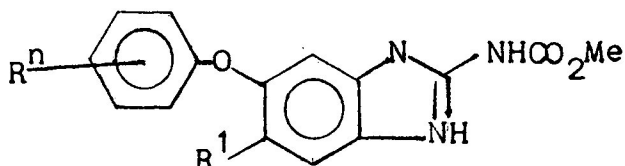


R = Substituted-benzyl, 7-chloro-4-quinolinyl.

PART IISYNTHESIS OF 6-CHLORO-5-(CHLORO-SUBSTITUTED PHENOXY)-
-2-(SUBSTITUTED BENZYL THIO) BENZIMIDAZOLES :

In consideration with the promising antitubercular activity of the compounds synthesised so far in Part-I (Section-A), with the relation of halogen substitution to biological activity, it was proposed to incorporate the chloro substituted phenols at the 5-position of benzimidazole.

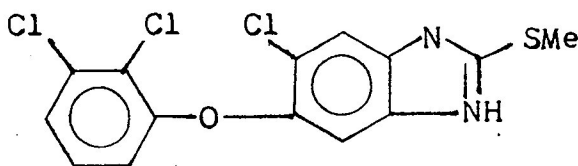
The compounds of the type (XII) were found to be biologically active against helminths.¹⁸



(XII)

where, $R^1 = \text{H or Cl}$; $R^n = \text{H, 2,3 or 4-Cl, 2,5 or 3,5-Cl}_2, \text{ etc.}$

The drug Triclabendazole (XIII) is well documented for its anthelmintic activity¹⁹ in veterinary medicine.

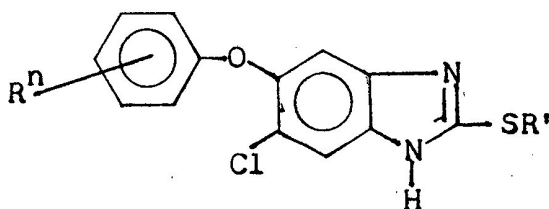


(XIII)

Considering the importance of chloro substituted phenoxy linkage at 5(6)-position of the benzimidazole moiety (which is shown in the structures XII and XIII) initiated to synthesize the following type of compounds (XIV).

Procedure for synthesis :

The compounds were synthesised by the known chemical routes and characterised by their analytical data for carbon, hydrogen and nitrogen. The various substitutions taken are shown below (XIV).



(XIV)

where, Rⁿ = 4-Cl; 2,3; 2,4; 2,5-Cl₂.

R' = Various substituted benzyl, 7-chloro-4-quinolinyl.

PART III

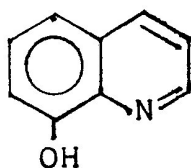
Section - A :

SYNTHESIS AND STUDY OF 6-CHLORO-5-QUINOLOXY-2-(SUBSTITUTED BENZYLTHIO) BENZIMIDAZOLE :

Quinoline derivatives are well known for their anti-malarial²⁰, antifungal²¹, and antibacterial²² effects.

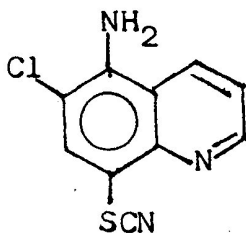
Chloroquine and Pamaquine are well known quinoline derivatives employed for the successful treatment of malaria.

The antibacterial and antifungal properties of the 8-quinolinol (XV) have been attributed to the unique ability of the isomeric quinolinols to chelate biochemically important metals.^{23,24} The quinolines were also found to be active against Escherichia coli.²⁵

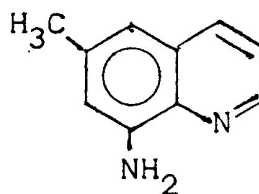


(XV)

Other derivatives, 5-amino-6-chloro,8-thiocyanato quinoline (a) were found to be active against Candida albicans²¹ while 8-amino-6-methyl quinoline (b) was claimed to possess antitubercular activity.²²

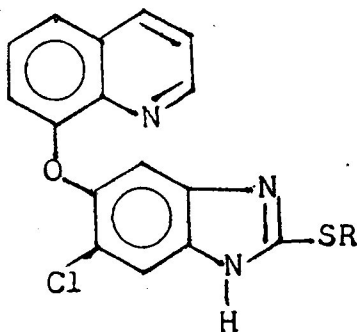


(a)



(b)

Hence, it was thought worthwhile to synthesize newer benzimidazole derivatives (XVI) by substituting 8-hydroxy quinoline at 5-position and screen them for their biological activity.



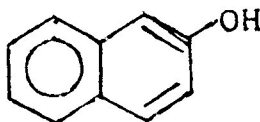
(XVI)

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

Section - B :

SYNTHESIS AND STUDY OF 6-CHLORO-5-NAPHTHOLOXY-2-(SUBSTITUTED BENZYLTHIO)BENZIMIDAZOLES :

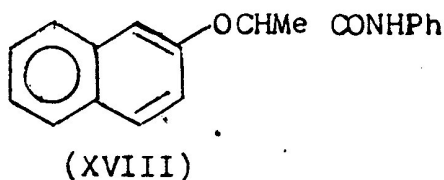
-Naphthol (XVII) has been used as antiseptic and anthelmintic agent.²⁶



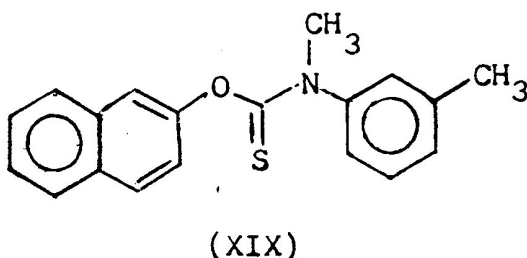
(XVII)

The derivatives of -naphthol are well known for their biological effects. -Naphthoxy propionanilide (XVIII)

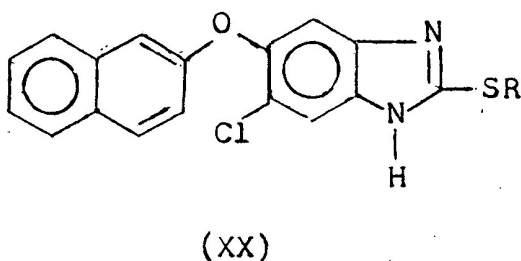
is a wide spectrum herbicide for rice paddies.²⁷



Drug Tolnaftate (XIX) is known to possess moderate antifungal activity.²⁸



Hence, it was proposed to synthesise entirely new naphtholoxo derivatives of benzimidazole nucleus having the general formula as below :



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

MICROBIAL TESTING/SCREENING :

Approximately, fifty new compounds have been synthesized and analysed correctly during the course of the

present work. The compounds described in the different sections have been screened for their in vitro antimicrobial activity against Mycobacterium tuberculosis strain of H₃₇Rv by using Rake's method.²⁹

Most of the compounds have inhibited the growth of M. tuberculosis at dilutions ranging from 50 µg/ml to 0.31 µg/ml.

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Signature of the Guide.

