

**SYNTHESIS AND STUDY OF BENZIMIDAZOLE,
BENZOTHIAZOLE AND SUBSTITUTED THIAZOLES AS
POSSIBLE ANTIFUNGAL AND ANTIBACTERIAL AGENTS**

**THESIS SUBMITTED
UNIVERSITY OF BOMBAY**

**FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
ORGANIC CHEMISTRY**

**SUBMITTED BY
SANJAY D. PALAV**

**UNDER THE GUIDANCE OF
DR. B.G. KHADSE**

**DEPARTMENT OF CHEMOTHERAPY
HAFFKINE INSTITUTE FOR TRAINING, RESEARCH & TESTING
BOMBAY**

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**Synthesis and Study of
Benzimidazole, Benzothiazole and
Substituted Thiazoles as Possible
Antifungal and Antibacterial Agents**

**A
Thesis**

**Submitted to
THE UNIVERSITY OF BOMBAY**

For

**The Degree of
DOCTOR OF PHILOSOPHY**

**in
The Faculty of Science
(Organic Chemistry)**

by

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SDPalav
Sanjay D. Palav

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STATEMENT

Statement submitted under Rule 0.770

For the thesis which I intend to submit, no degree or diploma or distinction has been conferred on me before, either in this or in any other university.

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Statement 1:

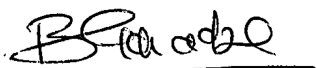
The work embodied in the thesis to be submitted is original, based on the discovery of new facts, viz the syntheses and characterisation of new and unknown compounds of possible chemotherapeutic value. Also included in the thesis are new relation of facts, observed on the basis of *in vitro* testing.

The assestment of the compounds has been made at the Department of Chemotherapy and Department of Microbiology, Haffkine Institute, Parel, Bombay-400 012.

Statement 2 :

During the study, all available information of related nature published in scientific journals by previous workers in allied fields has been used as a source of information as indicated in the "References".

The entire work has been planned and carried out by the candidate.



(Dr. B.G. Khadse)

Signature of the
Research Guide



(Sanjay D. Palav)

Signature of the
Student

PART - I

INTRODUCTION AND REVIEW OF LITERATURE



The developing countries have been experiencing an epidemiological transition, with rapid aging of the population together with an increasing incidence of non-communicable diseases linked to changes in life style. The growing prevalence of cancer, cardiovascular disease, diabetes and other chronic conditions in addition to the long-standing problems of communicable diseases such as cholera, malaria and tuberculosis impose a double burden on health care systems in these countries. In addition there is a pandemic of HIV infection and AIDS, which imposes a particularly heavy burden on developing countries.¹

All these realities must be taken into account in implementing public health action geared to achieving the goal of health for all by the year 2000 AD.

Each year about 50 million people die throughout the world. Of these, about 6.8 million deaths are registered in the developing market economies, 4.2 million in eastern Europe, 7 million in the group of least developed countries and 32 million elsewhere in the developing world. Reliable data on causes of death show that, the infectious and parasitic diseases continue to pose serious risk to adult health in developing countries. This catalogue of diseases account for about 17 million deaths or almost half of all deaths occurring in developing countries. TB claims around 3 million lives each year, 90 % of which are among the adult population. Pneumonia is the cause of about 2 million adult

deaths each year in developing countries. Other major health risks for adults includes malaria, schistosomiasis, hepatitis B and AIDS, each of which account for several hundred thousand adult deaths each year.²

Research in vaccines, pharmaceuticals and medical equipments are becoming even more expensive with the result that, end products are priced out of the reach of developing countries. Yet pressures from manufacturers and donors to adopt these costly new technologies and even from the general public, are intense. The trend seems to be towards more and more expensive treatments for diseases affecting less number of people. In general, it is hoped that R and D will develop new and improved preventive therapeutic and enabling technologies, giving attention to simplicity and adaptability to meet the needs of developing countries.

Hence, we must develop new approaches, mechanisms, partnerships and resources that can expedite this process. The problems now being faced may not be susceptible to approaches that have been applied in the past. We cannot continue doing what we have always done. Tomorrow cannot be just more of yesterday. We need flexibility and pragmatism as much as innovation but the stress must invariably be on action.

FUNGAL INFECTIONS

Fungal diseases have brought misery to millions of people in tropical and subtropical regions mainly due to the unhygienic conditions of their living.

Mycotic infections of humans are conveniently divided into three groups :

- (1) Dermatophytoses consisting of contagious superficial skin infections that are limited to the epidermal region
- (2) Candidiosis affecting the skin and mucous membranes
- (3) The subcutaneous, pulmonary, lymphatic and systemic mycoses which are not contagious.

They are caused by free living saprophytes that invade the skin, lungs, lymphatic tissue and various organs of susceptible hosts who have accidentally been in contact with the fungal environment.

CHEMOTHERAPEUTIC ASPECTS OF FUNGAL INFECTIONS :

There are very few agents available for the treatment of fungal infections mainly because the majority of fungal infections are rarely life threatening to man and are less common and also they are eukaryotic pathogens. It is difficult to develop drugs which are specific for fungi without being concomitantly toxic to the man.

The composition of the fungal cell wall, the material surrounding it and the cytoplasmic membranes within cell wall play important roles in the permeability of fungi to antifungal agents.

Principle antifungal agents can be divided on the basis of their origin as:

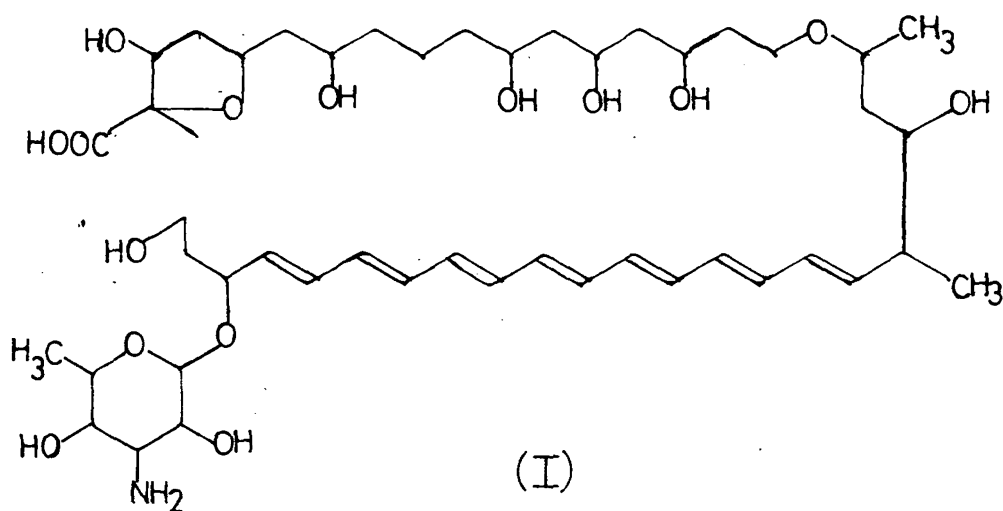
- (1) antibiotics produced by various micro-organisms
- (2) synthetic chemical compounds.

POLYENE ANTIFUNGAL ANTIBIOTICS :

Polyenes show broad antifungal activity against organisms ranging from yeasts to filamentous fungi and from saprophytic to pathogenic fungi.

NYSATATIN (I):

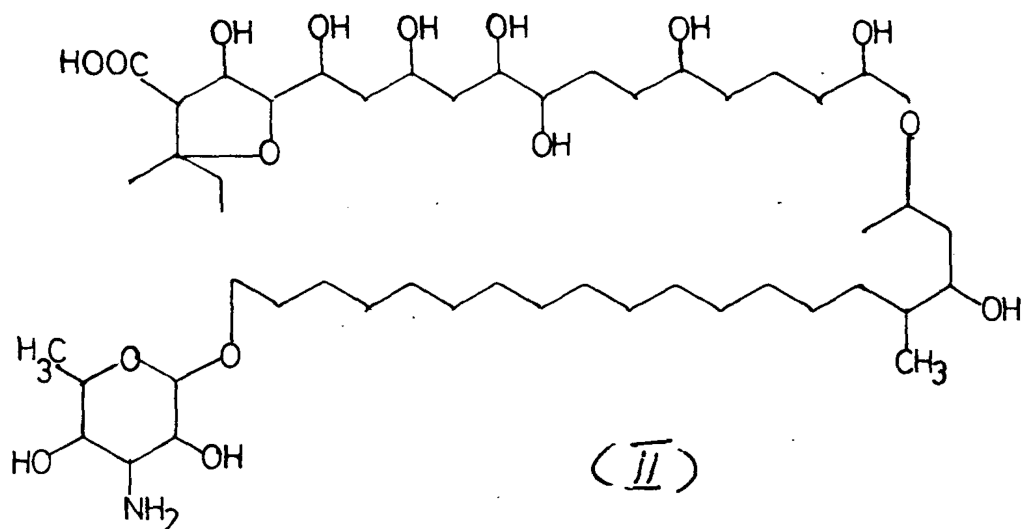
It is produced by *Streptomyces noursei* and was discovered by Hazen and Brown.



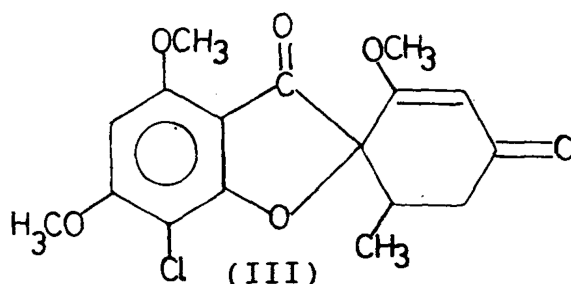
The minimal inhibitory concentration of tetraene antibiotics such as Nysatatin and Pimaricin for *Candida* species, *Cryptococcus neoformans* and the Dimorphic fungi causing systemic mycoses is of the order of micrograms (1.56-12.5 ug/ml).³

AMPHOTERICIN B (II):

It is produced by *Streptomyces nodosus* and was discovered by Gold *et al.* The drug is amphoteric and is very active against pathogenic yeasts.⁴

GRISEOFULVIN (III):

It was discovered by Oxford *et al* in 1939 from *Penicillium griseofulvin*. According to Brain, griseofulvin a cell wall



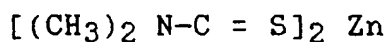
antibiotic particularly active in dermatophytes, interferes with biosyntheses of chitinous elements of the hyphal wall.⁵

SYNTHETIC ANTIFUNGALS:

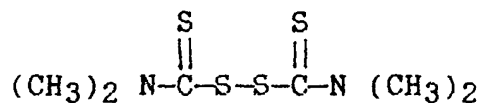
SULPHUR CONTAINING DRUGS :

A variety of organic compounds that contain divalent S-atom attached to C-atom have *in vitro* fungistatic action and many of these have been employed in tropical therapy of dermatophytoses.

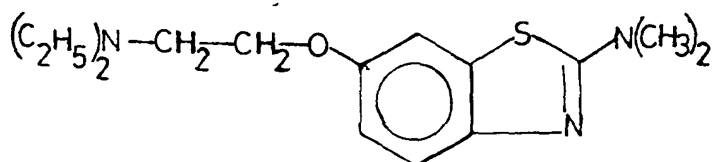
Dithiocarbamates such as dimethyl derivatives(IV), thioureas such as tetraethyl thiuram disulfide (V) and 6-(β -diethylaminoethoxy) -2-N,N-diethylamino benzothiazole (VI) are some of the examples.^{6,7}



(IV)

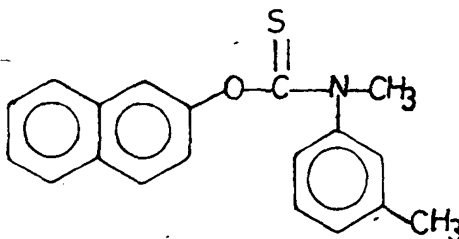


(V)



(VI)

A widely used compound with unusually high *in vitro* and *in vivo* activity against the dermatophytes is Tolnafate (VII). It is also effective against candidal lesions.⁸



(VII)

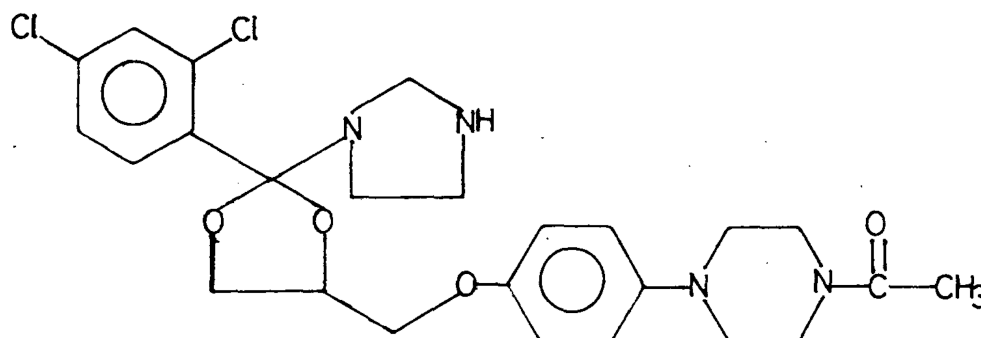
AZOLE DERIVATIVES:

The antifungal azoles are synthetic compounds with one or more 5-membered rings, where each ring contains either two (imidazole) or three (triazole) N- atoms.

IMIDAZOLES :

Imidazoles are one of the two major classes of antifungal azole derivatives, the other being triazoles.

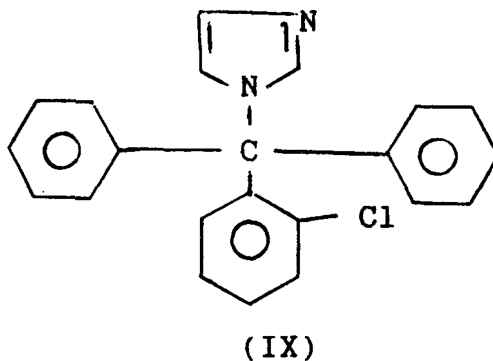
Ketoconazole (VIII) the first successful orally absorbable antifungal azole was introduced in 1979. It offered a number of significant advantages, including its broad spectrum antifungal activity.⁹



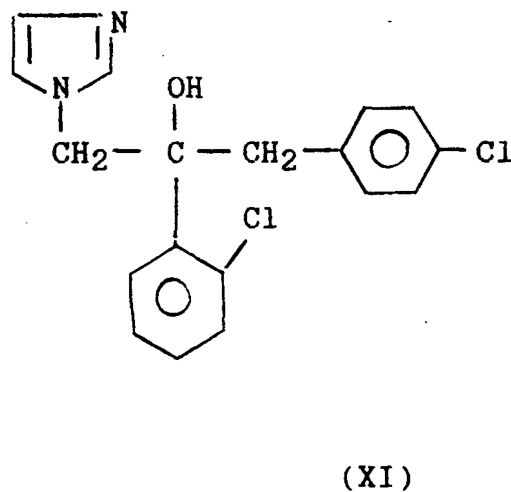
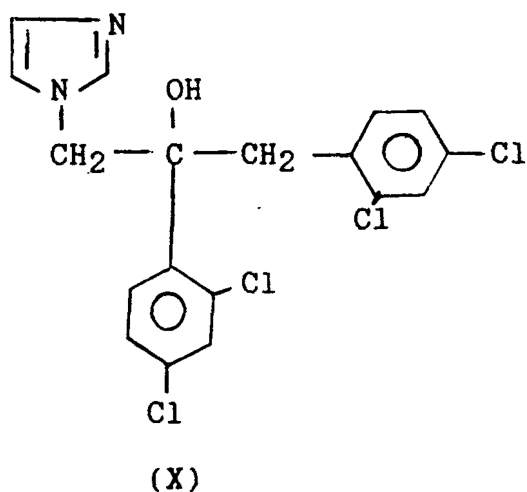
(VIII)

Successful treatment of these endemic mycosis is dependent on the daily dosage, which ranges from 400-800 ug/day and duration of the therapy.

Clotrimazole (IX) was developed in 1969 and is utilized topically in superficial mycosis or orally in clinical trials in deep mycosis .



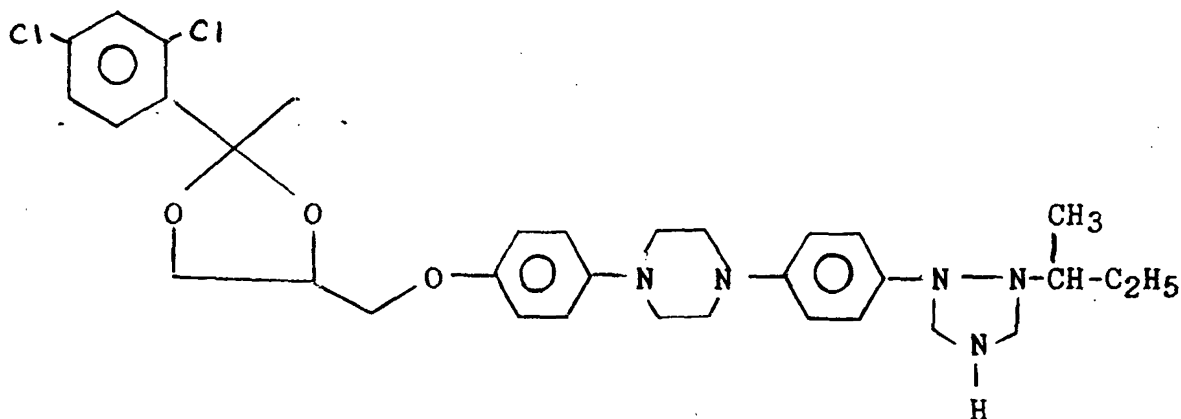
Miconazole (X) is a well known antifungal drug of 1969 used topically on superficial mycoses and by oral or intravenous routes in deep mycoses in clinical experimental trials.



Econazole (XI) was described by Godrepol and is used as topical agent in superficial mycoses and as asystemic antifungal drug by oral and intravenous routes in deep mycoses.

TRIAZOLES :

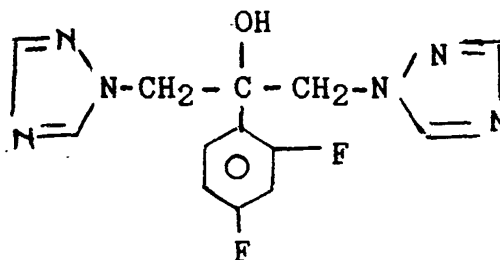
Among triazoles, Itraconazole (XII) exhibits excellent activity against most of human fungal pathogens. Its potential advantages includes a broader spectrum of activity, more desirable pharmacokinetic profile and less toxicity.¹⁰



(XII)

At doses ranging from 50-400 ug/day, itraconazole has been shown to be effective therapy most of the fungal diseases.¹¹

Fluconazole (XIII) is active in suppressive therapy and primary

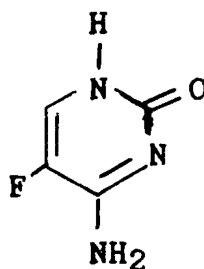


(XIII)

treatment of cryptococcal meningitis in patients with AIDS who are at low risk for treatment failure. It may also be useful in primary treatment of coccidioidal meningitis. It is active in the treatment of mucosal candidosis, including oropharyngeal and oesophageal candidosis.¹²

PYRIMIDINE DRUGS :

5-Fluorocytosine (XIV) is effective in systemic candidosis and



(XIV)

cryptococcosis. It has very marked selective antifungal activity *in vitro* and *in vivo* against pathogenic yeasts like *Candida albicans* and other species of *Candida cryptococcus neoformens*, *Torulopsis glabrata* and has moderate activity on fungi such as *aspergillus*.¹³

Considerable progress in treating systemic fungal infections has been achieved through better application of established antifungal agents and the development of promising new investigational agents. This ever expanding battery of antifungal agents exhibits a wide variety of pharmacokinetic properties, mechanism of action and toxicities. Understanding these parameters is critical for the appropriate use and continued development of these drugs.

The field of antifungal chemotherapy has finally reached the stage where many new agents from different classes of compounds with different mechanism of action are being synthesized and extensively studied.

Ideally a new antifungal should possess following characteristics :

- (1) Potent, broad spectrum antifungal activity
- (2) No toxicity

(3) Flexibility of oral or parental administration

(4) Favourable pharmacokinetics including complete bioavailability and effective tissue penetration.

Antifungal agents may be classified as to their chemical structure, mode of action and antifungal spectrum of activity. Table 1 lists the common antifungal agents with their adverse effects and drug interactions.



TABLE 1

TOLERABILITY OF DRUG INTERACTION PROFILE OF ANTIFUNGAL DRUGS.

DRUG	ADVERSE EFFECT	DRUG INTERACTION
AMPHOTERICIN B Deoxycholate	nephrotoxicity, fever, chills, phlebits, hypo kalaemia, anaemia, GI disturbance	Azotaemia, with amino glycosides, cyclosporin Pulmonary toxicity with granulocytes transfusion.
Lipid Formulation	Not known	-
FLOURINATED PYRIMIDINES		
Flucytosine	Bone marrow suppression hepatotoxicity, GI disturbances	Minimal
AZOLES		
<u>Imidazoles</u>		
Miconazole	Headache, pruritus, thrombo phlebits, hepatotoxicity autoinduction of hepatic degrading enzymes	-
Ketoconazole	GI disturbance, hepato- toxicity	Drugs that induce hepatic microsomal enzymes eg. Rifampicin, antacids
<u>Triazoles</u>		
Itraconazole	GI disturbance, rare hepatotoxicity	Not known
Fluconazole	GI disturbance, rare hepatotoxicity, rare Stevens-Johnsons syndrome	Not known
Saperconazole	GI disturbance, rare hepatotoxicity, rare Stevens-Johnsons syndrome	Not known
SCH 39304	Onco genic	UNKNOWN
ICI 195739	UNKNOWN	UNKNOWN
SOZ 89485	UNKNOWN	UNKNOWN

DEVELOPMENTAL STEPS IN ANTIBACTERIAL AGENTS :

The discoveries of antibacterial drugs was started by the introduction of the Dapsone known as promin in 1940.

In 1944, Streptomycin, as an antibiotic, was newly isolated by Worksman from the soil organisms *Streptomyces griseus* as a fermentation product.

Although, screening of antibacterial agents will continue to be a possible way to discover useful new drugs, the increasing knowledge of the biochemistry of bacteria makes possible a more rational approach to the biosynthesis of the bacterial cellwall. This indicates the targets for inhibitors of the biosynthetic pathway present specifically in the micro-organisms of the bacterium species.

Selective inhibitors could open up new horizons in the therapy of bacterial infections because they will be ineffective in the eukaryotic cells of the host, therefore, potentially will have less toxicity. Furthermore, since they will be ineffective also on other micro-organisms, they will not alter the normal microbial flora.

Another specific constituent of pathogenic bacteria is the cord factor and more extensive studies on its biosynthesis might indicate the possibilities of inhibiting its formation.

Inhibitors of either the formation or the function of mycobactim are also of potential practical interest in view of the stimulating role played by these factors in the growth of

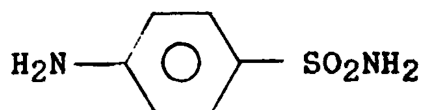
mycobacteria. The discovery of the competitive inhibition of mycobactin P by chronic mycobactin P does not antagonise the growth of other mycobacteria, because these micro-organisms overcome the inhibitory effect by making greater quantities of mycobactins on different ones.¹⁴

A better knowledge of the mechanism of mycobacterial resistance to drug could indicate the duration in which to search for new products specifically overcoming this mechanisms. Present knowledge of the genetic mechanisms and genotypical systems governing resistance in mycobacteria is limited because of the difficulty of using mycobacteria in classical genetic techniques. Therefore, at present, the delay or prevention of the evolution towards resistance of mycobacterial flora and the formation of atypical strains is accomplished only through combination therapy based on the complementary action of the constituents.

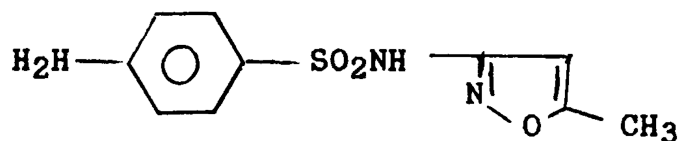
SYNTHETIC ANTIBACTERIAL COMPOUNDS :

SULPHONAMIDES :

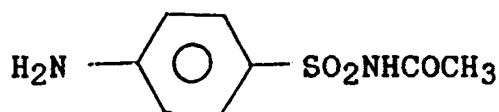
Derivatives of p-aminobenzene sulphonamides were first employed as antibacterial agents. Among these sulphanilamide (XV), sulphamethoxazole (XVI), sulfacetamide (XVII), sulfadiazine (XVIII) and sulfisoxazole (XIX) are the important ones.



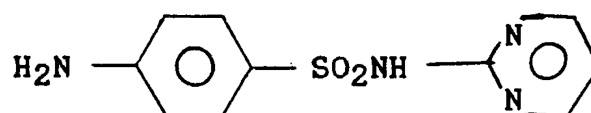
(XV)



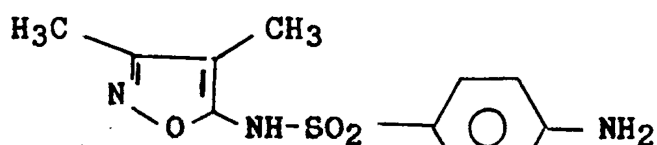
(XVI)



(XVII)



(XVIII)

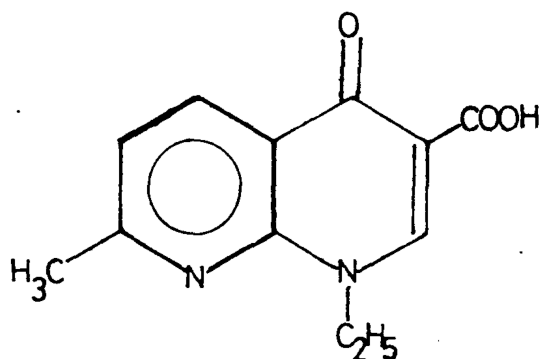


(XIX)

The sulphonamides have a wide range of activity against both Gram-positive and Gram-negative bacteria and are rapidly absorbed by the gastrointestinal tract. However, resistant strains of bacteria to the sulphonamides have become common and hence are used in combination with antibiotics.

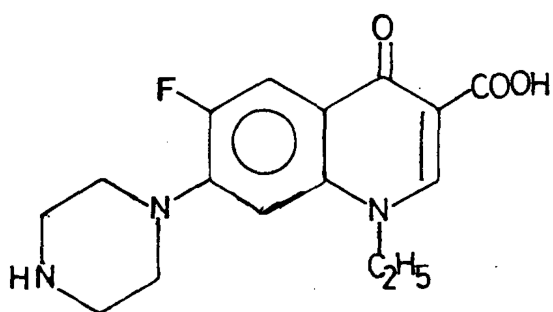
QUINOLONES :

In this class of antibacterial agents Nalidixic acid (XX) is an important compound used mainly for the treatment of urinary tract infections.

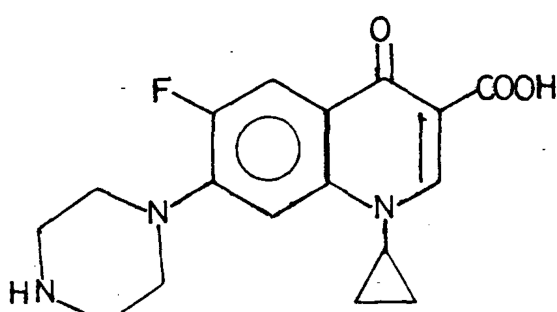


(XX)

Recently, Norfloxacin (XXI) and ciprofloxacin (XXII) are in use against *E. coli*, various species of *Salmonella*, *Enterobacter* and others.¹⁵



(XXI)



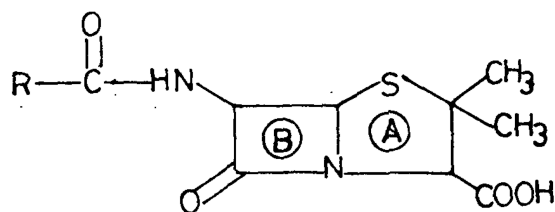
(XXII)

Ciprofloxacin is the most active antibacterial agent having bioavailability of about 60 %. The primary mechanism is inhibition of bacterial DNA- gyrase and is effective in oral and intravenous administrations.¹⁶

PENICILLINS (XXIII):

In 1928, Alexander Fleming discovered penicillin, the most important class of antibiotics. Despite the discovery of several other antibacterial agents, the penicillins are widely used with new derivatives being produced every year. Due to their unique

advantages , members of this group of antibiotics are presently the drugs of choice for large number of infectious diseases.



(XXIII)

The basic structure of penicillin consists of a thiazolidine ring (A) connected to a β -lactum ring (B) to which is attached a side chain (R) through C- NH linkage. The penicillin nucleus is an important requirement for biological activity, alteration of which causes loss of all significant activity. Many of the antibacterial and pharmacological characteristics of penicillins is determined by its side chain (R) which can also alter the susceptibility of the resultant compounds to inactivating enzymes (β -lactamases).

Penicillins are classified according to their spectrum of antibacterial activity. While the pharmacological properties of the individual drugs in the various classes would constitute a lengthy discussion, certain generalisations can however be made. Following absorption, penicillins are widely distributed throughout the body. Therapeutic concentrations of these agents are quite rapidly achieved in tissues but comparatively much lower levels are found in prostatic secretions, brain tissue and intraocular fluid.

The penicillins do not penetrate the living phagocytic cells to a great extent. This class of compounds are quite rapidly eliminated particularly by glomerular filtration and renal tubular filtration, as a result of which high concentration of the drug are found in the urine. Therefore, they exhibit short half-lives, approximately in the range of 30-60 minutes.

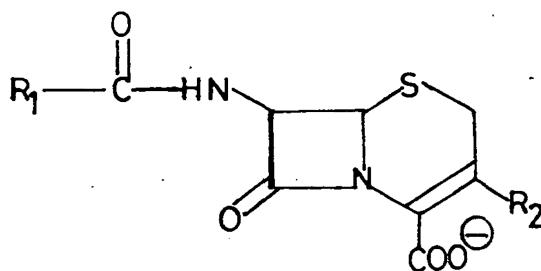
No sooner was the fact established that penicillins are capable of eradicating microorganisms, it was partially administered in every situation where there was a risk of bacterial infection. But after the investigation of prophylaxis under controlled conditions, it is now understood that penicillin is highly efficient in some situations, quite the contrary in others and of questionable value in still others.

The commonly cited adverse effects in the usage of penicillins, which are probably the most common cause of drug allergy, has been the hypersensitivity reactions. Such reactions could occur with any dosage form of penicillin, but as the drug is rapidly eliminated the allergic reactions usually subside. In some cases the symptoms may persist for one or two weeks after withdrawal of treatment while in other cases the reaction is mild and disappears during therapy with the drug. At the worst of circumstances an extreme allergic reaction may even result in death of the patient.

CEPHALOSPORINS (XXIV)

The cephalosporins (XXIV) were first introduced in the mid

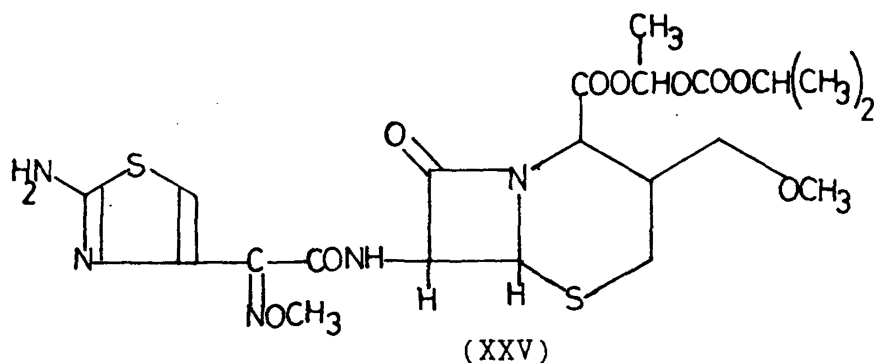
1960's and were the first β -lactam antibacterials to have broad antibacterial spectrum. Since then, research has produced more microbiologically active cephalosporins, especially against gram-negative organisms, and also some, that are particularly stable in the presence of β -lactamases. Unfortunately until recently, most of these potent cephalosporins such as



(XXIV)

cefotaxime and ceftazidime could only be administered by intravenous or intramuscular injection, thus necessitating hospitalization. However, third generation oral cephalosporins have recently been developed. Because of their broad antibacterial spectrum, the cephalosporins have proved valuable for the treatment of respiratory tract infections, particularly acute exacerbations of chronic bronchitic (AECB) and bronchopneumonia, which are frequently caused by more than one organism. The newer β -lactam-stable oral cephalosporins, such as *Cefpodoxime proxetil*, are of potential value for these indications.

Cefpodoxime proxetil is the orally administered prodrug of cefpodoxime, a broad spectrum third generation cephalosporin

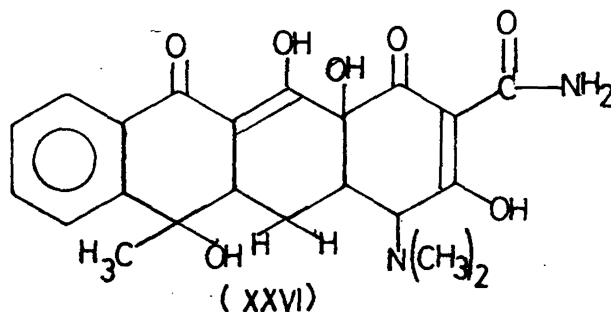


antibiotic possessing *in vitro* and *in vivo* bacterial activity comparable or superior to that of currently available oral and parenteral β -lactum antibiotics.

TETRACYCLINS (XXIV):

These exhibit a wide range of activity against gram-positive and gram-negative bacteria. In general gram-positive bacteria are affected by lower concentrations of tetracycline than the gram-negative species. However, they are rarely recommended for infections caused by gram-positive bacteria due to problems of resistance and availability of superior antibacterial agents.

Micro-organisms that have developed resistance to one tetracycline frequently exhibit resistance to the other members of the family.

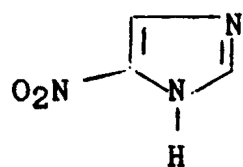


The bacterial species possibly exhibit resistance only after exposure to the drug. The tetracyclines were initially useful for treatment of infections with aerobic gram-negative bacteria but most species are now relatively resistant. Nevertheless, more than 90 % of strains of *Haemophilus influenzae* may still be sensitive to either tetracycline or doxycycline.

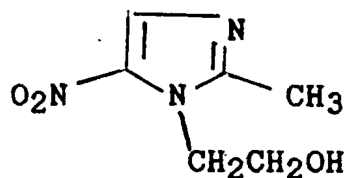
The tetracyclines produce gastrointestinal irritation to varying degrees in some individuals and are more common after oral administration. Diarrhoea may also be a side effect, which though frequent and fluid, do not contain blood or leukocytes. Doxycycline and to a lesser extent other derivatives may produce mild-to-severe reactions in the skin of treated individuals exposed to sunlight.

Biologically active benzimidazoles :

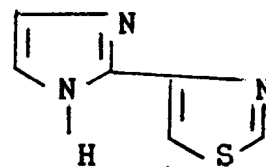
The pharmacological history of several thousands of imidazole derivatives has been established over 30 years, after the discovery of the antibacterial and antifungal activity of benzimidazole by Wolley (1944)¹⁷ which later led to the synthesis of benzimidazole derivatives with strong antiprotozoal and anthelmintic properties. The discovery of the antibacterial (Azomycin, XXVII), a trichomonacide (Metronidazole, XXVIII), anthelmintic agents (Thiabendazole, XXIX and Cambendazole, XXX) and recent drugs such as Omeprazole (XXXI) and Lansoprazole (XXXI) which contain prominently imidazole and benzimidazole



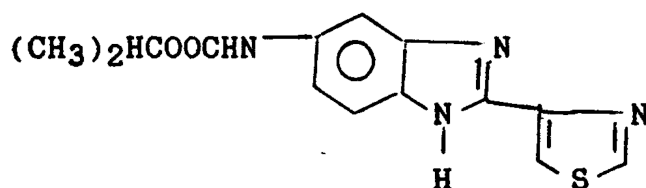
(XXVII)



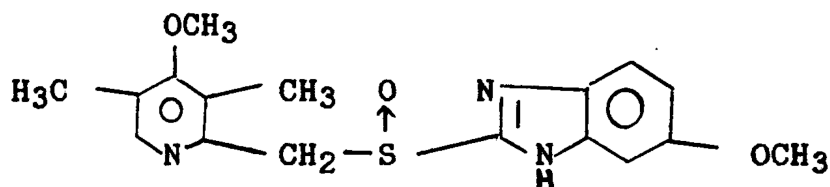
(XXVIII)



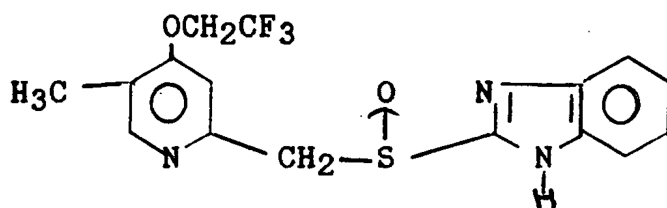
(XXIX)



(XXX)



(XXXI)



(XXXII)

nucleus, has added impetus to investigations in these areas with particular emphasis on the synthesis of newer benzimidazole derivatives for pharmacological screening.

PART - I

PLAN OF WORK

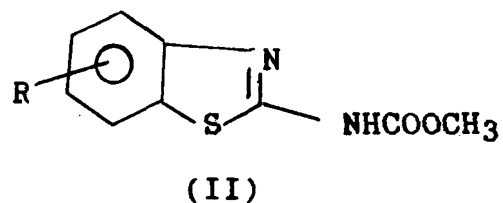
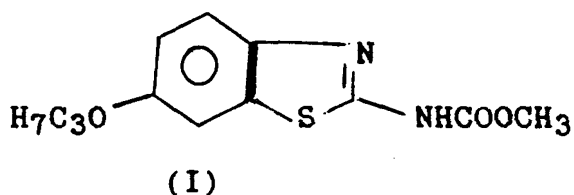
Considerable progress has been made in past 30 years in the chemotherapy of microbial diseases. Still the development of resistance to the drugs by microbials is an important problem facing the chemotherapist. The rapidity of development of resistance varies widely under different circumstances. Besides this, the potent drugs used in the clinical therapy over years are being reported to show newer side effects. Thus, there is a need for better eradivative drugs which will be more effective and less toxic than the current ones.

An attempt has been made to synthesize new derivatives of substituted benzimidazole, benzothiazole and thiazoles as parent moieties.

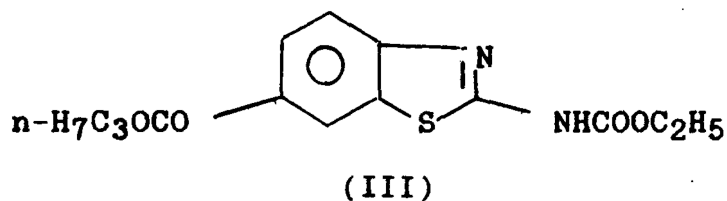
PART II: 5,6-DISUBSTITUTED-2-(N,N-DIALKYL THIOCARBAMIDO)
BENZOTHIAZOLES

Studies of benzothiazoles, have resulted in the development of tioxidazole (I), an anthelmintic compound for intestinal worms.¹⁸

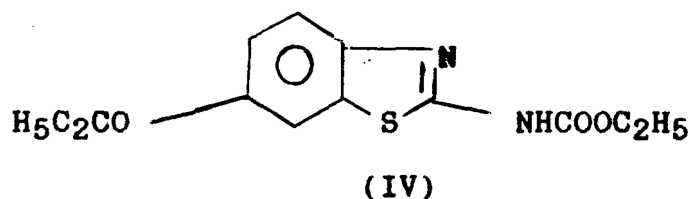
Nagarajan *et al* have also reported a series of 2,6 disubstituted benzothiazoles (II) which showed activity against *N. americanus* infection in neonatal hamsters.¹⁹



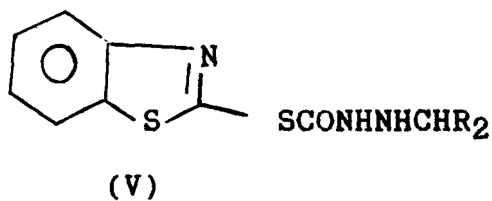
In recent papers, Naim *et al* have reported 2,6 acetamido 6n-propyloxy carbonyl benzothiazole (III) which eliminates 85 % of *A. ceylanicum* at a oral dose of 250 mg/kg in cotton rats.²⁰



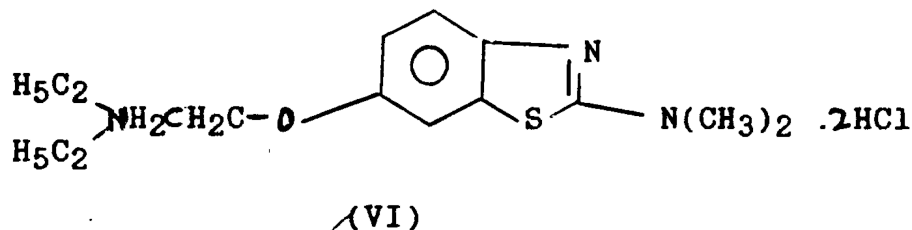
Also, 2-ethoxy carbonyl amino 6-ethoxy carbonyl benzothiazole (IV) eliminates 90 % of microfilaria in the blood at intraperitoneal dose of 30 mg/kg X 5 days.



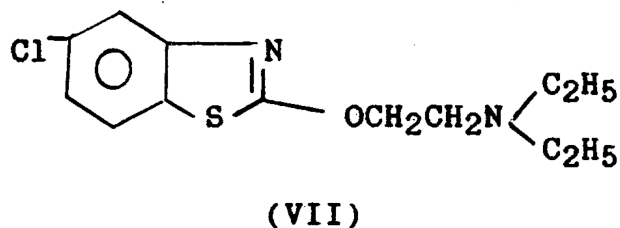
Asaad and Falmy, synthesized benzothiazoles of type (V) and were found to show inhibition zone of 9-18 mm on various bacteria at a concentration of 0.01g/ml.²¹



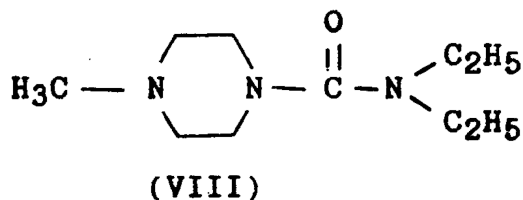
The literature survey reveals that Diamthazole dihydrochloride (VI) containing benzothiazole derivatives moiety shows antifungal activity²².



Halethazole (VII) is another benzothiazole derivative having chloro substitution at 5-position which shows antifungal activity²³.

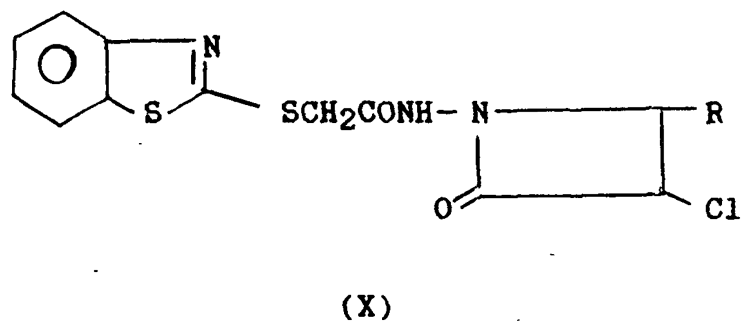
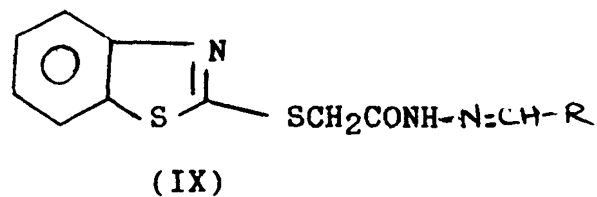


N,N-Diethyl carbamazine (Hetrazan) (VIII) having N,N-diethyl carbamoyl linkage is a well marked antifilarial agent²⁴.

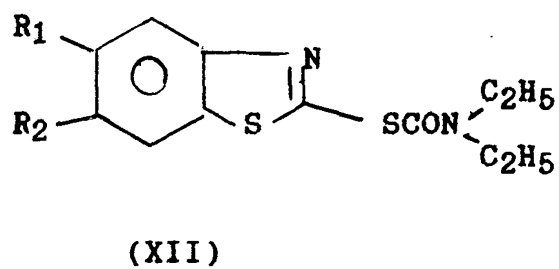
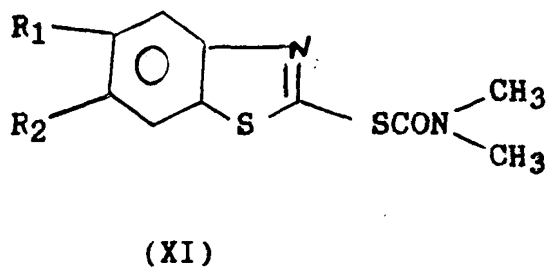


Besides Hetrazan (VIII), Diamthazole dihydrochloride (VI) and Halethazole (VII) also have N,N-dialkyl linkage as the side chain.

Further, benzothiazoles of type (IX) and (X) were found to exhibit moderate to good antibacterial and antifungal activity.²⁵



Thus, a combination of various 5,6-disubstituted-2-mercapto benzothiazoles with N,N-dialkyl carbamoyl linkage at their 2-position (XI) and (XII) have been effected so as to study their antibacterial and antifungal properties.



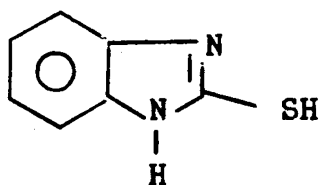
Where $R_1 = \text{H, Cl, NO}_2$

$R_2 = \text{H, Cl, F, OCH}_3$

PART III : 5,6-DISUBSTITUTED-2-(N,N-DIALKYL THIOCARBAMIDO)
BENZIMIDAZOLES

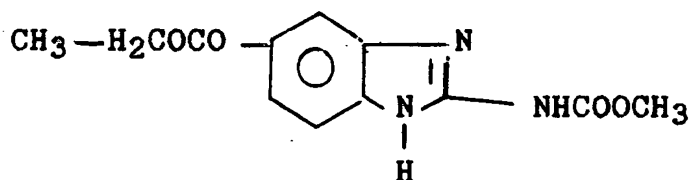
It has been observed from the literature survey that the benzimidazole derivatives shows broad spectrum activities e.g. mebendazole, flubendazole, albendazole etc.

2-Mercapto benzimidazole (XIII) itself is a bacteriostatic and antifungal agent.²⁶



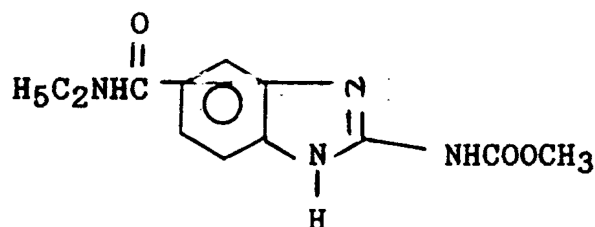
(XIII)

Recently, Ram *et al* synthesized 5-carboxy 1H benzimidazole 2-carbamates (XIV) which were found to be curative against adult *B. pahangi* microfilariae in jirds at the dose of 12.5 mg/kg when given for 5 days and 82 % effective at a dosage of 6.25 mg/kg when given for 5 days and also *A. vitae* in jirds at 25 mg/kg when given for 5 days.²⁷

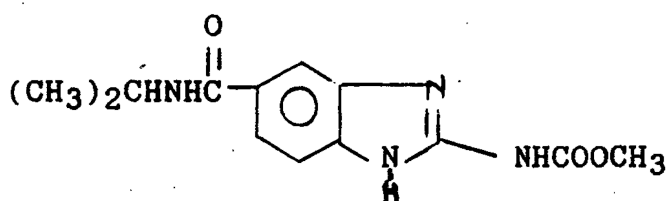


(XIV)

Also, (XV) and (XVI) were found to show activity against *B. pahangi* in jirds at 25 mg/kg X 5 days and 6.25 mg/kg X 5 days.²⁷

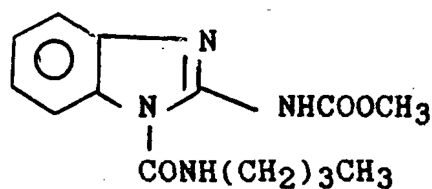


(XV)



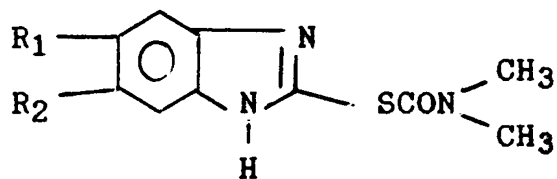
(XVI)

In addition to these, Banomyl (XVII) was found to show antifungal activity.²⁸

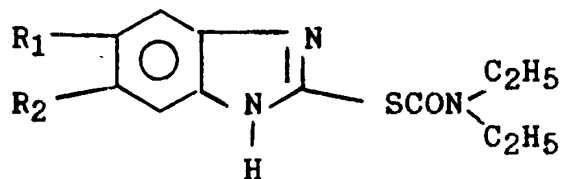


(XVII)

Thus, considering the importance of dialkyl carbamoyl linkage as effective synthons in preparing compounds of medicinal value, several 5,6-disubstituted-2-mercapto-benzimidazoles have been condensed with N,N-dialkyl carbamoyl chloride. The resultant compounds depicted as (XVIII) and (XIX) have been then screened for their antibacterial and antifungal properties.



(XVIII)



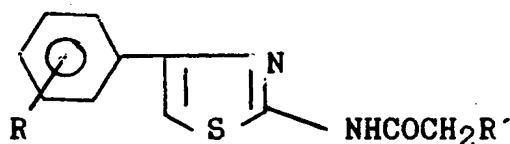
(XIX)

Where $R_1 = \text{H, Cl}$

$R_2 = \text{H, Cl, NO}_2, \text{CH}_3$

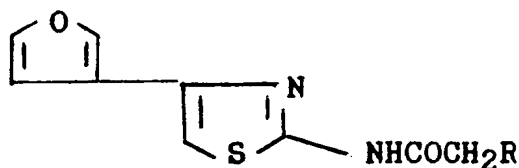
PART IV: 2-(SUBSTITUTED PHENYL/ANILINO)-4-[m-(N,N-DIALKYL UREIDO) PHENYL] THIAZOLES

The thiazole derivatives are reported to exhibit various biological properties. Bhargava et al have synthesized a series of 2-(N-substituted -glycylamino)-4-substituted -phenylthiazoles (XX) useful as local anesthetics.²⁹



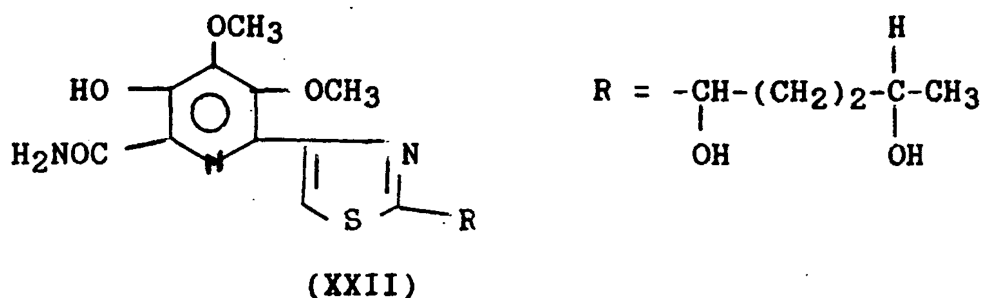
(XX)

Saldabols and Medne have reported thiazoles derivatives (XXI) exhibiting furan ring at the 4-position possessing bactericidal as well as virucidal activities.³⁰

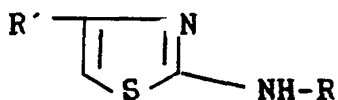


(XXI)

In a latest report published in the 'Drugs made in Germany', thiazole derivatives (XXII) having substituted pyridine ring at the 4-position have been found to possess antifungal activity.³¹

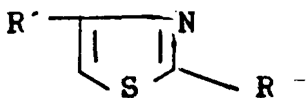


Very recently 2,4 disubstituted thiazole derivatives of type (XXIII) are reported to show antibacterial and antifungal properties.³²



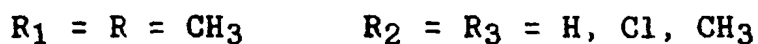
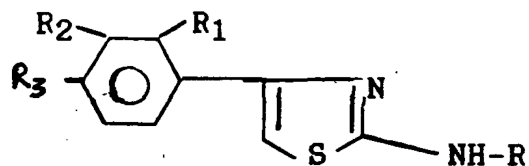
(XXIII)

Prabhu *et al.* have reported that 2,4-disubstituted thiazoles (XXIV) have shown good response against tubercule bacilli.³³



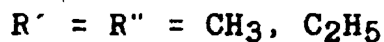
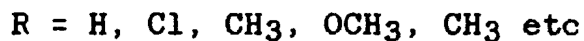
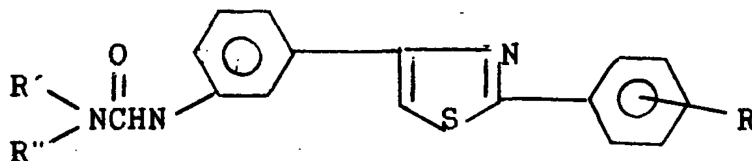
(XXIV)

Grafe *et al.* reported 4-substituted phenyl 2-substituted aminothiazoles (XXV) as antiviral agents .³⁴

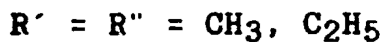
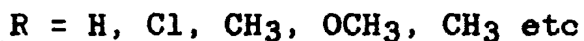
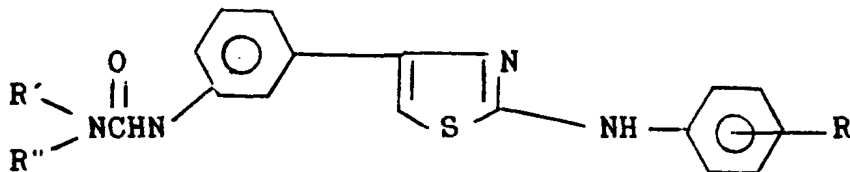


(XXV)

Thus, based on the above facts, a series of following types of compounds (XXVI) and (XXVII) were synthesized and their bactericidal and antifungal properties were studied.



(XXVI)



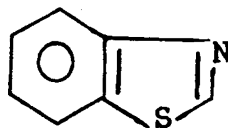
(XXVII)

PART - II

SECTION - A

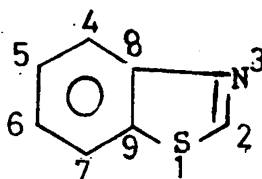
**CHEMISTRY
OF
BENZOTHAZOLES**

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



(I)

These compounds were formed only by compounds in which the nitrogen and sulphur atoms were ortho to each other. They were expressed as derivatives of o-amino thiophenols. The numbering systems for benzothiazole (II) is as follows :



(II)

SYNTHESIS OF 2-AMINO 6-SUBSTITUTED BENZOTHAZOLES

TYPE - A (THIOCYANATION REACTION) :

Thiocyanation is one of the many organic reactions useful to synthetic organic chemist. It is a simple electrophilic reaction showing close similarity with halogenation. Therefore, the reaction is often classified as pseudohalogenation and the reagent as pseudohalogen. As far as chemical reactivity is concerned the thiocyanogen behaves exactly similar as halogen.

The direct substitution of hydrogen atom by a thiocyano group (-SCN) through the use of thiocyanogen (SCN)₂ is commonly referred as thiocyanation.

Since the reagent is extremely unstable, certain precautions must be observed for its use in the reactions. Thiocyanogen is a liquid which on cooling forms a colourless crystalline solid melting between -3° to -2°C . At room temperature it polymerises rapidly to a reddish orange, amorphous mass of indefinite composition known as pseudothiocyanogen. Although, relatively stable in inert dry solvents, thiocyanogen may polymerise in solution, especially, under the catalytic effect, influence of heat, light and moisture.

Due to the extreme sensitivity of thiocyanogen towards hydrolysis and polymerisation, it is employed in solution and more commonly is produced *in situ*.

METHODS FOR THE USE OF THIOCYANOGEN IN SUBSTITUTION REACTIONS

Two general methods, which can be practically applicable have been described for the use of thiocyanogen in substitution reactions- i) free thiocyanogen in organic solvents; ii) thiocyanogen liberated gradually in organic solvents from a metal thiocyanate by various reagents.

• FREE THIOCYANOGEN

This method was the first to be employed and is still a useful procedure when the reaction involved is slow, as in addition reactions or when the product is difficult to purify. Usually the only contaminant of the product other than starting material is polythiocyanogen, which is entirely insoluble in water and in organic solvents.

The reagent is prepared by the action of an oxidising agent upon thiocyanic acid in an organic solvent and is accomplished by means of such reagents as lead tetra acetate, lead peroxide or manganese dioxide³⁵, but the yield is so low that the preparation of metal thiocyanate is much to be preferred. Lead thiocyanate reacts rapidly and quantitatively with bromine to form thiocyanogen and lead bromide, which is removed rapidly by filtration. Halogen carriers such as phenyliodo chlorides³⁶, sulfuryl chlorides³⁷ or certain N-chloroamides^{38,39,40} can also be used but do not appear to possess any advantages over bromine or chlorine.

Solvents that have been used with thiocyanogen include benzene, bromobenzene, carbon tetrachloride, chloroform, ether, ethylene bromide, carbon disulfide, petroleum ether, methyl acetate, nitromethane, anhydrous formic acid and acetic acid. At low temperature such solvents as saturated solution of alkali thiocyanates in methanol^{41,42} or acetone⁴³ can be used. The yield in the thiocyanation of amine is 20-30 % higher when the reaction is carried out in a neutral medium like methanol rather than in acetic acid. The formation of a thiazole is also inhibited in a neutral solvent. Ether is usually not satisfactory because the solvent is attacked and because some of the amine is precipitated as the thiocyanate^{44,45}.

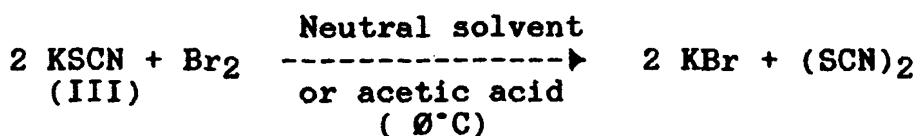
Moisture must be excluded from thiocyanation solution in order to prevent hydrolysis. Another troublesome side reaction, particularly in concentrated solutions is polymerisation, which

is induced by light, heat and the presence of hydrolysis products. Polymerisation is reported to be dependent upon the dielectric constants of the solvents^{44,46,47}. Stirring is said to retard polymerisation. For the usual synthetic reaction the preferred procedure is to generate thiocyanogen in a solution of the substance to be thiocyanated at a rate equal to the rate of the removal by reaction. The low concentration of reagent, maintained in this way minimises polymerisation. The reagent is generated from the thiocyanate salts by chemical reactions.

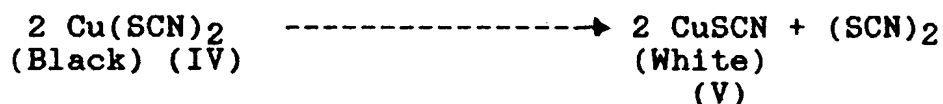
THIOCYANOGEN GENERATED FROM SALTS BY CHEMICAL REAGENTS

In this method the alkali metal thiocyanate (III) is dissolved in acetic acid or formic acid^{47,48}, or better in neutral solvent like methyl acetate, acetone or methanol^{41,49} and then the compound to be thiocyanated is introduced to the above solution. Bromine or chlorine is added to the cooled solution at such a rate that the thiocyanogen reacts as fast as it is liberated. The neutral solvent that is susceptible to attack by halogen is protected by saturating the solution with an appropriate alkali metal halide or by using a large excess of an alkali metal thiocyanate in the reaction mixture. Other reagent for producing thiocyanogen from potassium thiocyanate have been described .

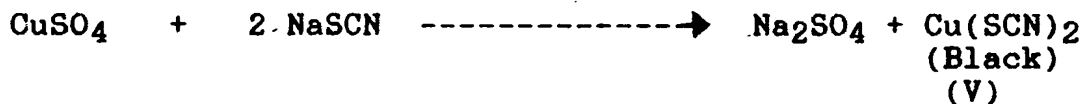
The chemical transformation can be written as below:-



Cupric thiocyanate ⁵⁰, the use of which may be considered as still another modification of this general procedure, shows promise of being very effective. It releases thiocyanogen merely by the dissociation of the cupric (IV) to cuprous salt (V).



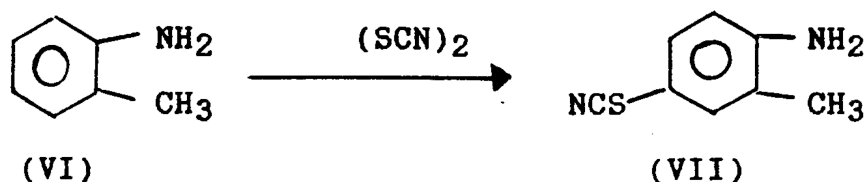
Cupric thiocyanate (IV), prepared in advance, or a paste of copper sulfate and sodium thiocyanate in equivalent proportions is added to a solution of the compound in methanol or acetic acid and the mixture is warmed to 35°-80°C, until the black cupric thiocyanate has changed completely to the white cuprous thiocyanate.



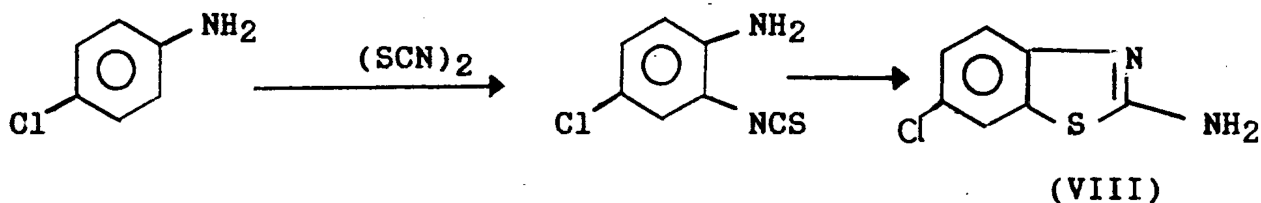
This procedure has the advantage over the others of permitting higher temperatures for thiocyanation.

THIOCYANATION OF AROMATIC AMINES

The thiocyanation group (-SCN) is introduced into aromatic amines with rapidity. It enters preferentially at a free *para* position if available, otherwise at *ortho* position. For example, *o*-toluidine (VI) is converted to 4-thiocyano-*o*-toluidine (VII) (80 % yield) ⁵¹.

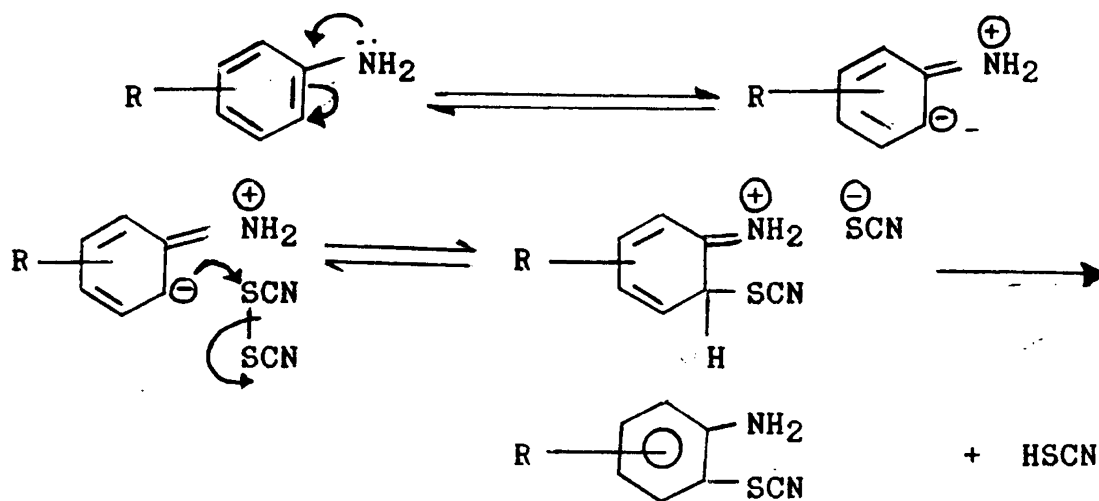


The thiocyanation takes place in the position ortho to the primary amine group. The final product in such cases is often an amino benzothiazole formed by the secondary reaction between the amino group and the adjacent thiocyno group. In this secondary reaction, since the amino group is having loan pair of electrons ion, it will be added to the C=N bond of the thiocyno group to give resultant 2-amino 6-substituted benzothiazole (VIII)



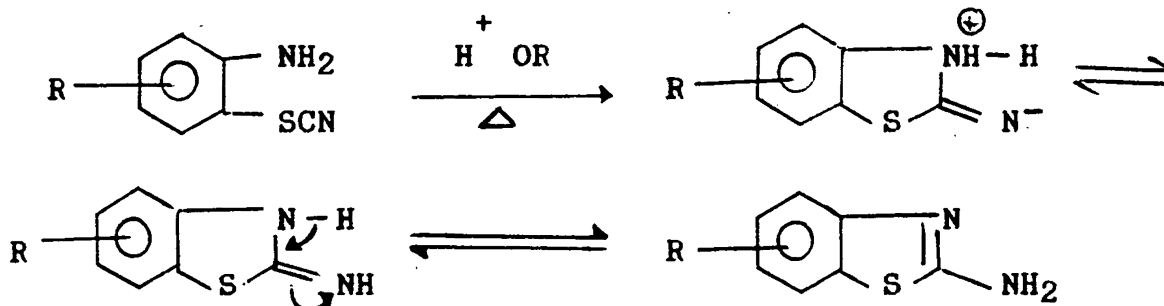
Mechanism:

The mechanism of thiocyanogen reaction probably consists of the initial attack of thiocyanogen to the activated site of 4-substituted aniline where due to the mesomeric effect of amino group the ortho position is having surplus of electrons which rendered the site to act as a good electron rich centre, to give an intermediate species as :-



The unstable intermediate species immediately loses a proton to retain the aromatic character of the molecule which gives higher stability.

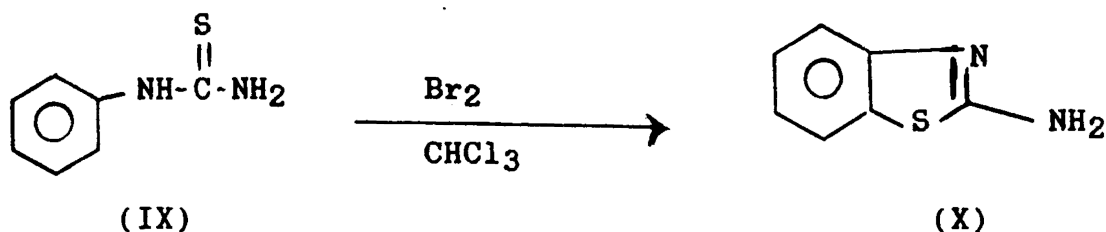
The intermediate, under the influence of acid and heating adds an amino function to the adjacent thiocarbonyl group as:



HUGERSCHOER SYNTHESSES :

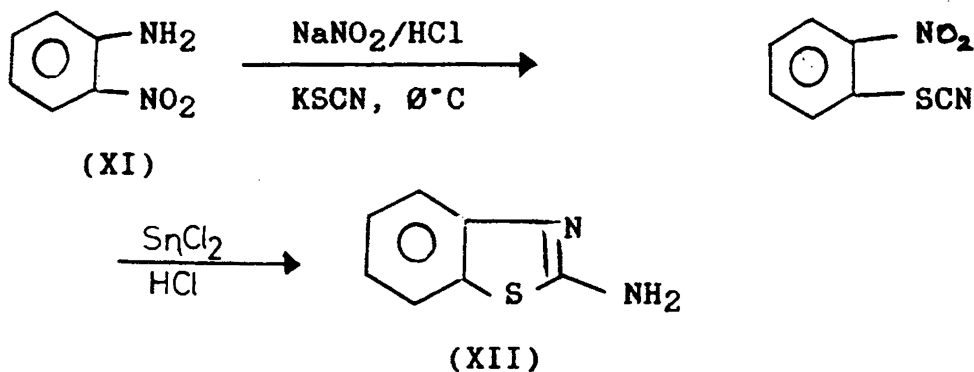
This synthesis is restricted to the preparation of 2-amino derivatives of the benzothiazoles (X) and employs the action of oxidising agent such as bromine, upon arylthioureas (IX) in an inert solvent such as chloroform, ethylene dichloride, chlorobenzene or acetic acid. Sulfuryl chloride can be

substituted for bromine.⁵²⁻⁵⁴ However, potassium ferrocyanide in alkaline media, the reagent for the Jacobson ring closure, gives no thiazole from the arylthiourea.^{55,56}



Generally, the yields in the Hegerschoff reaction are excellent and frequently nearly quantitative.

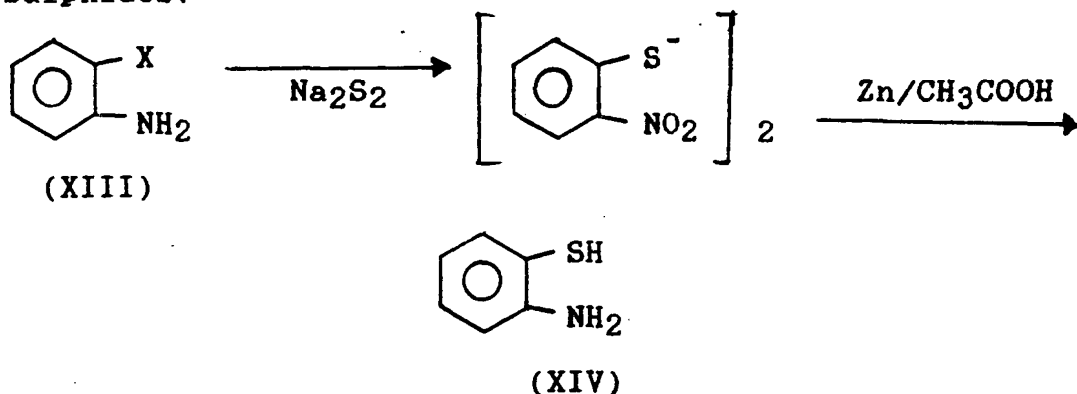
2-Amino benzothiazoles (XII) have been prepared from o-thiocyano-nitro compounds of the type (XI) by reduction using stannous chloride in HCl and FeSO₄ in ammonia.^{57,58}



In the present study, the raw materials viz. 2-amino 6-substituted benzothiazoles are synthesized by thiocyanating p-substituted anilines with KSCN and bromine in acetic acid at cold conditions, according to the literature methods.

METHODS FOR THE PREPARATION OF o-AMINO THIOPHENOLS :

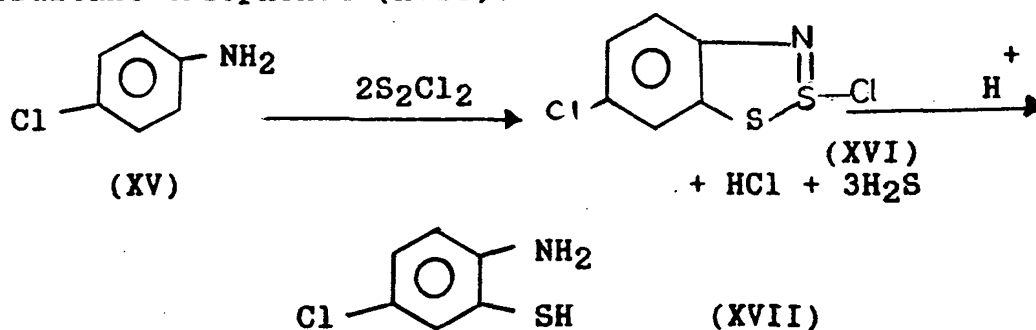
(i) Sodium salt of di(o-nitrophenyl) disulfide are obtained by reaction of o- amino thiophenols with an excess of sodium polysulphides.



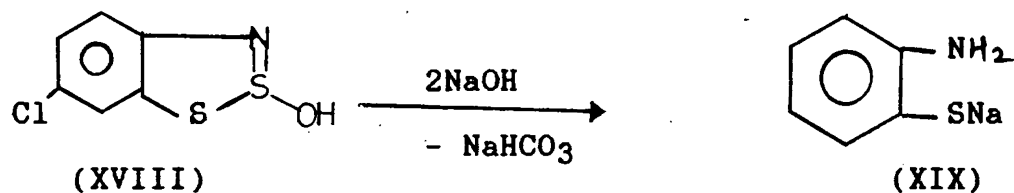
The disulphide salts thus obtained are further reduced with zinc in acetic acid to give o-amino thiophenols.⁵⁹⁻⁶⁸

(ii) Herz process :

The Herz process for the preparation of o-aminothiophenols from aromatic amines has been applied extensively to the synthesis of benzothiazole intermediates. The term Herz reaction is used to describe the overall reaction leading to the preparation of o-amino benzene thiols by the condensation of aromatic amines (XV) with sulphuryl chloride which yields the thiazoilium chloride (XVI), the hydrolysis of which gives the resultant thiophenol (XVII).⁶⁹⁻⁷³



Hydrolysis of thiazolium chloride proceeds through the replacement of chlorine by OH group to give a thiazolium hydroxide (XVIII). This replacement can usually be carried out in neutral solutions but the hydroxyl compounds is not always isolated. Aqueous or aqueous alcoholic alkali then opens the 5-membered ring to give the Na-salt of o-amino thiophenols (XIX) and sodium hydrogen sulphite.



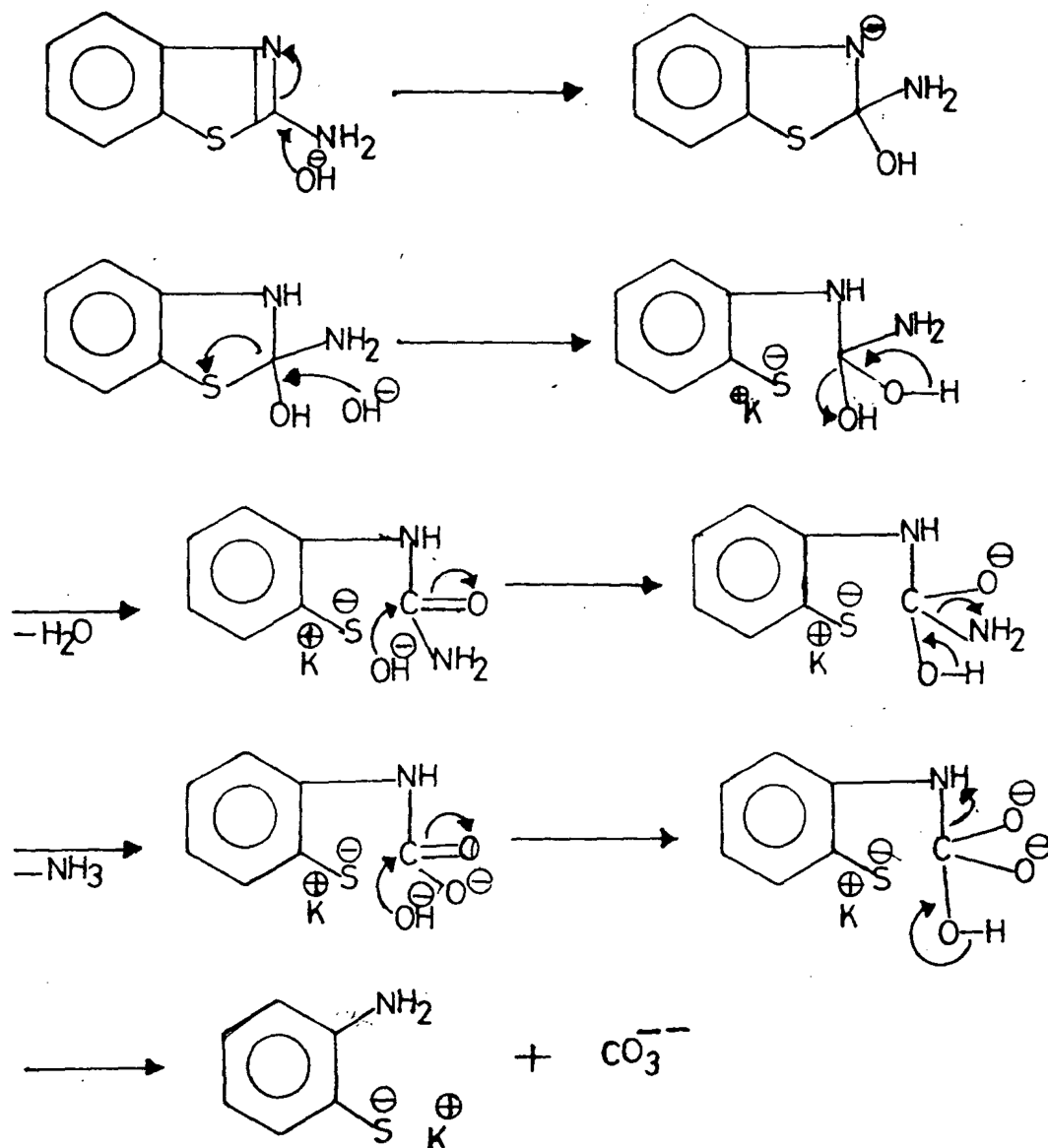
The reaction mixture containing the hydrolysis product can be used directly in many synthesis, but the thiol can be prepared and collected, if required as the free base or as zinc mercaptide.

The reaction is limited to the preparation of o-amino thiophenols containing as substituents in the 5-position Cl or a group which is not replaced by Cl (bromine, diethylamino, ethoxyl, methoxyl or methyl). Because nitro groups are replaced, it is not possible to protect 5-position with a nitro group and subsequently reduce and remove or alter the protecting group in the usual way. This is a severe limitation to the aromatic amines that are unsubstituted in the para position which undergoes chlorination by sulphur mono chloride.^{68-70,72}

The alkaline cleavage of benzothiazoles also constitutes a valuable source of o-amino thiophenols. In this manner many nuclear substituted amino thiophenols are obtainable from benzothiazoles.

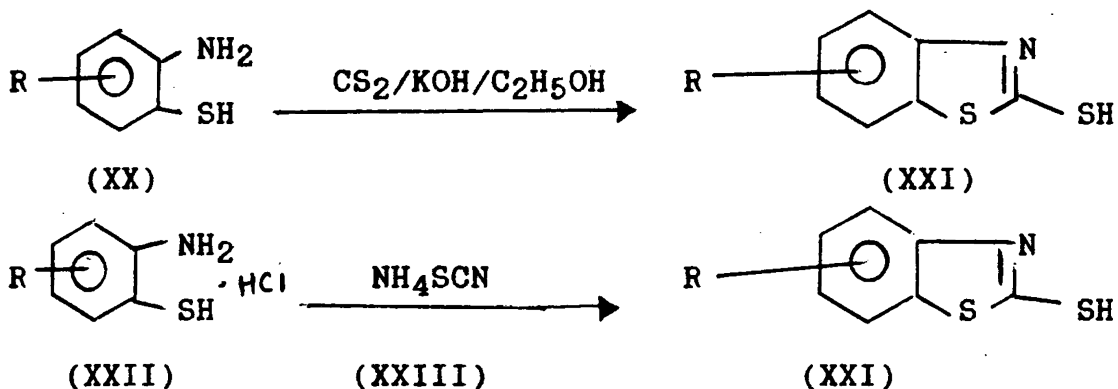
Mechanism :

It involves the initial attacks of OH ion to the imino N-atom of the 2-amino benzothiazoles to give the intermediate which instantaneously gets protonated by the action of water through elimination of OH⁻ ion. This intermediate being highly unstable results into opening of the thiazole nucleus which on further eliminating a molecule of water gives urea derivative. This urea derivative is finally hydrolysed.



SYNTHESIS OF 2-MERCAPTO BENZOTHAZOLES

Substituted 2-mercapto benzothiazoles (XXI) have been synthesized in 84-86 % yields by the action of potassium ethyl xanthate on o-amino thiophenols (XX). Similarly the same have been prepared by heating a solution of o-amino thiophenols dihydrochloride (XXII) and ammonium thiocyanate (XXIII). A solution of the two is usually evaporated to dryness on a steam bath and then heated for short time. By this method, 2-mercapto benzothiazole and 5-chloro, 4-methyl, and 5-methyl derivatives of 2-mercapto benzothiazoles have been prepared.



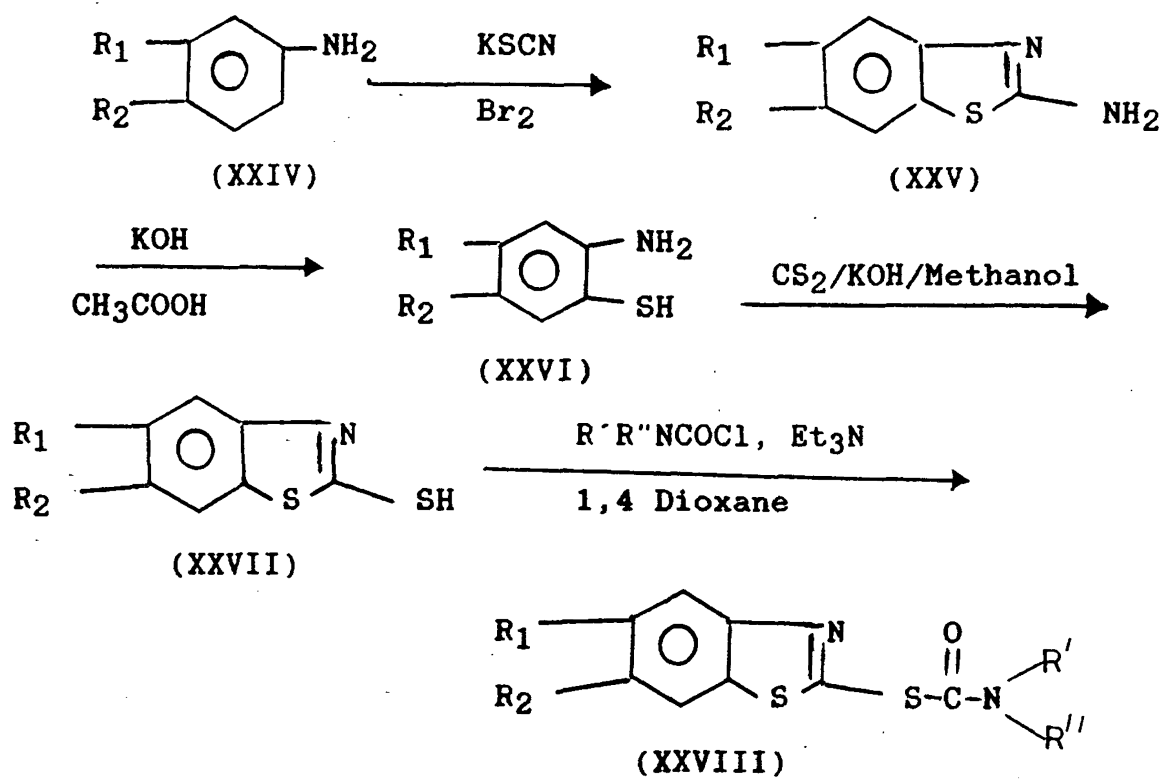
In the present investigation 5,6-disubstituted 2-mercapto N,N-dialkylthiocarbamido benzothiazoles were synthesized in the following manner:

p-Substituted anilines (XXIV) were treated with potassium thiocyanate in presence of bromine in acetic acid and the resultant o-thiocyano aryl amine on further intramolecular cyclization gave the 6-substituted-2-amino benzothiazoles (XXV). These were then cleaved with 50 % KOH at reflux temperature to give the o-amino substituted thiophenols (XXVI).

The o-amino substituted thiophenols were then cyclised with potassium xanthate in methanol to get the 2-mercapto substituted benzothiazoles (XXVII).

The 2-mercapto 5,6 disubstituted benzothiazoles obtained as per above procedures were condensed with N,N-dialkyl carbamoyl chlorides in presence of triethylamine as a catalyst and 1,4 dioxane as a solvent to give the desired compounds (XXVIII).

The schematic diagram leading to the formation of the title compounds summarising the various reactions discussed so far is given in the scheme I.

SCHEME -I
 $\text{R}_1 = \text{H}, \text{Cl}, \text{NO}_2$
 $\text{R}_2 = \text{H}, \text{Cl}, \text{F}$
 $\text{R}' = \text{R}'' = \text{CH}_3, \text{C}_2\text{H}_5$

PART - II

SECTION - B

EXPERIMENTAL

This section deals with the synthesis of 5,6 disubstituted-2-(N,N-dialkyl thiocarbamido) benzothiazoles which involves the following steps:

- (1) Preparation of 2-amino-5,6-disubstituted benzothiazoles
- (2) Preparation of 2-amino-5,6-disubstituted thiophenols
- (3) Preparation of 2-mercapto 5,6-disubstituted benzothiazoles
- (4) Preparation of 5,6-disubstituted-2-(N,N-dialkyl thiocarbamido) benzothiazole

Preparation of 2-amino 6- chloro benzothiazole :

In a 500 ml three necked round bottomed flask equipped with a mechanical stirrer, air condenser and a dropping funnel was placed a solution of p-chloro aniline (25 gm, 0.2 mole) in 150 ml acetic acid and a solution of potassium thiocyanate (25 gms, 0.257 mole) in 150 ml acetic acid. The mixture was stirred at 10°C-15°C for 10 minutes.

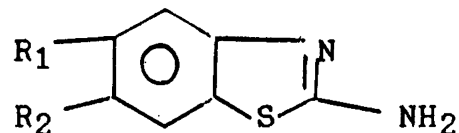
To this a mixture of bromine (40 gms, 13 ml, 0.25 mole) in 60 ml acetic acid was added dropwise maintaining the temperature between 5-10°C. The mixture was allowed to stand overnight at room temperature. It was then diluted with 400 ml hot water and filtered. The cooled solution was neutralised with ammonia. The solid separated was filtered, washed with water and dried. It was recrystallised from ethanol.

Yield : 19 gms (51 %)

m.p. : 197-198°C.

Lit. m.p.^{74,75} : 197°C.

TABLE 2

2 AMINO 5,6-DISUBSTITUTED BENZOTHAZOLES

SR.NO.	R ₁	R ₂	m.p. °c		YIELD %		REF
			OBSERVED	REPORTED	OBSERVED	REPORTED	
1	H	H	126-129	128-129	64-66	65	74,75
2	H	Cl	197-8	197	51	51	74,75
3	Cl	Cl	185-90	187	75	80	76
4	H	OCH ₃	163	164	84	86	77
5	H	F	182	183	68	70	77
6	H	OC ₄ H ₉	119	117	84	86	78

Preparation of 2-amino 5-chloro thiophenol :

A mixture of 2-amino 6-chloro benzothiazole (18 gms, 0.1 mole) and 50 % KOH solution (50 ml) was refluxed in 100 ml round bottomed flask equipped with a reflux condenser for one hour. It was allowed to cool at 10°C and diluted with water. The solution was acidified with acetic acid at 0-5°C. The solid separated was filtered, washed with water and dried. It was then recrystallised from chloroform.

Yield : 10 gm (63 %)

m.p. : 110-12°C.

Lit. m.p.⁷⁹ : 110°C.

Preparation of 6-chloro 2-mercapto benzothiazole :

In a 100 ml round bottomed flask equipped with two double walled condensers was placed a solution of 2-amino 5-chloro thiophenol (25.6 gm, 0.16 mole) in 100 ml of methanol. To this K-xanthate [CS_2 (13.8gm, 10.7 ml, 0.17 mole), KOH (9.6 gm, 0.17 mole), methanol 150 ml and water 30 ml)] was added. The reaction mixture was refluxed on a water bath for about 8 hours till the vapours of H_2S ceases. The excess of methanol was distilled out. The reaction mixture was cooled to 10°C . It was then acidified with acetic acid. The solid separated was filtered out immediately and washed with water. It was recrystallised from chloroform.

Yield : 25.8 gms (80 %)

m.p. : 198°C .

Lit. m.p.⁸⁰ : $198-200^\circ\text{C}$.

Preparation of 6-chloro-2-(N,N-diethyl thiocarbamido)
benzothiazole :

In a 100 ml three necked round bottomed flask equipped with a reflux condenser, dropping funnel, and a mechanical stirrer was placed a solution of 2-mercapto 6-chloro benzothiazole (0.201 gm, 0.001 mole) in 10 ml dry 1,4 dioxane and triethylamine (0.1 gm, 0.001 mole). The reaction mixture was stirred at 50-60°C for about half an hour. To this N,N-diethyl carbamoyl chloride (0.162 gm, 0.0012 mole) in 10 ml 1,4 dry dioxane was added dropwise at the same temperature. The mixture was allowed to stir for two more hours at the same temperature. It was then kept overnight at room temperature. The solution was poured on crushed ice. The solid separated was filtered, washed with water and dried. It was purified by column chromatography using 60-120 mesh size silica gel and chloroform as an eluant.

Yield : 0.141 gms (47 %)

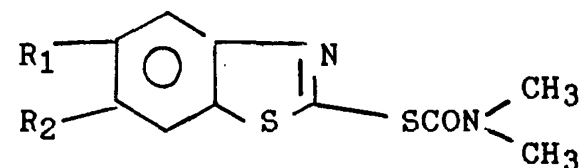
m.p. : 158-9 °C

ELEMENTAL ANALYSIS

	Required	Found
C % :	47.92	48.14
H % :	4.32	4.65
N % :	9.31	9.57

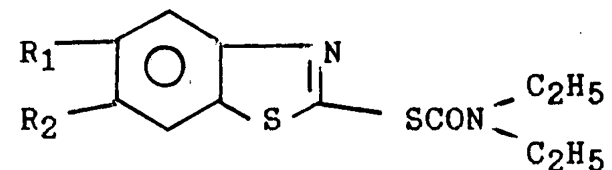
In a similar manner different 5,6 disubstituted 2-mercapto benzimidazoles were condensed with N,N- dialkyl carbamoyl chloride to obtain the respective final benzimidazoles compounds whose physical data are represented in Tables 3 and 4.

TABLE 3

5,6-DISUBSTITUTED -2-(N,N-DIMETHYL THIOCARBAMIDO) BENZOTHAZOLES

SR. NO.	R ₁	R ₂	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
							REQUIRED			FOUND		
							C	H	N	C	H	N
1	H	H	C ₁₀ H ₁₀ N ₂ OS ₂	238	183-5	46	50.42	4.20	11.76	50.88	4.83	12.37
2	H	Cl	C ₁₀ H ₉ ClN ₂ OS ₂	272.5	175-6	57	44.03	3.30	10.27	43.78	2.94	10.57
3	Cl	Cl	C ₁₀ H ₈ Cl ₂ N ₂ OS ₂	307	130-2	48	39.08	2.60	9.12	38.86	3.04	9.47
4	H	OCH ₃	C ₁₁ H ₁₂ N ₂ O ₂ S ₂	268	144-5	62	49.25	4.47	10.44	49.37	4.88	10.53
5	H	F	C ₁₀ H ₉ FN ₂ OS ₂	256	154-6	59	46.87	3.51	10.93	47.42	4.13	11.52
6	NO ₂	F	C ₁₀ H ₈ FN ₃ O ₃ S ₂	301	123-5	43	39.86	2.65	13.95	40.23	2.57	14.68
7	H	OC ₄ H ₉	C ₁₄ H ₁₈ N ₂ O ₂ S ₂	310	113-5	53	54.19	5.80	9.03	53.89	6.12	8.74
8	H	OC ₂ H ₅	C ₁₂ H ₁₄ N ₂ O ₂ S ₂	282	127-8	57	51.06	4.96	9.92	50.86	5.21	9.68

TABLE 4

5,6-DISUBSTITUTED -2-(N,N-DIETHYL THIOCARBAMIDO) BENZOTHAZOLES

SR. NO.	R ₁	R ₂	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
							REQUIRED			FOUND		
							C	H	N	C	H	N
1	H	H	C ₁₂ H ₁₄ N ₂ OS ₂	266	166-8	56	54.13	5.26	10.52	54.65	4.75	11.23
2	H	Cl	C ₁₂ H ₁₃ ClN ₂ OS ₂	300.5	158-9	47	47.92	4.32	9.31	48.14	4.65	9.57
3	Cl	Cl	C ₁₂ H ₁₂ Cl ₂ N ₂ OS ₂	335	135-7	53	42.98	3.58	8.35	43.23	3.33	8.47
4	H	OCH ₃	C ₁₃ H ₁₆ N ₂ O ₂ S ₂	296	106-7	62	52.70	5.40	9.45	52.37	5.88	9.53
5	H	F	C ₁₂ H ₁₃ FN ₂ OS ₂	284	148	59	50.70	4.57	9.86	50.12	5.23	9.22
6	NO ₂	F	C ₁₂ H ₁₂ FN ₃ O ₃ S ₂	329	133-5	58	43.76	3.64	12.76	44.03	3.57	12.68
7	H	OC ₄ H ₉	C ₁₆ H ₂₂ N ₂ O ₂ S ₂	338	103-5	58	56.80	6.50	8.28	56.89	6.12	8.04
8	H	OC ₂ H ₅	C ₁₄ H ₁₈ N ₂ O ₂ S ₂	310	117-8	66	54.19	5.80	9.03	53.86	6.11	8.88

SPECTRAL ANALYSIS OF 5.6 disubstituted- 2-N,N-(dialkyl-
thiocarbamido) benzothiazoles

6-FLUORO-2-N,N-(DIMETHYLTHIOCARBAMIDO) BENZOTHIAZOLE
(COMPOUND NO.5 , TABLE NO 3)

IR (KBr cm^{-1})

3800 (-CH₃), 1660 (C=O), 1600 (ARM),

1260 (-N-C=O), 1110 (N-C-S),

PMR (CdCl₃) -

3.04 - 3.30 (s, 6H, -CH₃), 7.15 - 8.0 (m, 3H, Ar-H)

MS

m/z : 256 (m^+)

6-FLUORO-2-N,N -(DIETHYLTHIOCARBAMIDO) BENZOTHIAZOLE
(COMPOUND NO.1 , TABLE NO 4)

IR (KBr cm^{-1})

3000 (-CH₂), 1670 (C=O), 1590 (ARM), 1260 (-N-C=O), 1100 (N-C-S),

6-FLUORO-2-N,N -(DIETHYLTHIOCARBAMIDO) BENZOTHIAZOLE
(COMPOUND NO. 5, TABLE NO. 6)

IR (KBr cm^{-1})

2980 (-CH₃), 1640 (C = O), 1590 (ARM), 1250 (-N-C=O),

1120 (N-C=S)

PMR (CdCl₃) :

1.282-1.358 (t, 6 H, -CH₃), 3.435 - 3.538 (q, 4H, -CH₂),

7.153-7.948 (m, 3 H, Ar-H)

6-CHLORO-2-N,N -(DIETHYLTHIOCARBAMIDO) BENZOTHIAZOLE
(COMPOUND NO. 2 , TABLE NO. 4)

IR (KBr cm^{-1})

3000 (-CH₂CH₃), 1670 (C=O), 1590 (ARM),

1240 (-N-C=O), 1100 (N-C-S),

PMR (CdCl₃) δ :

1.36-1.44 (t, 6H, -CH₂CH₃), 3.44-3.52 (q, 4H, -CH₂CH₃),

7.44-7.96 (m, 3H, Ar-H)

MS

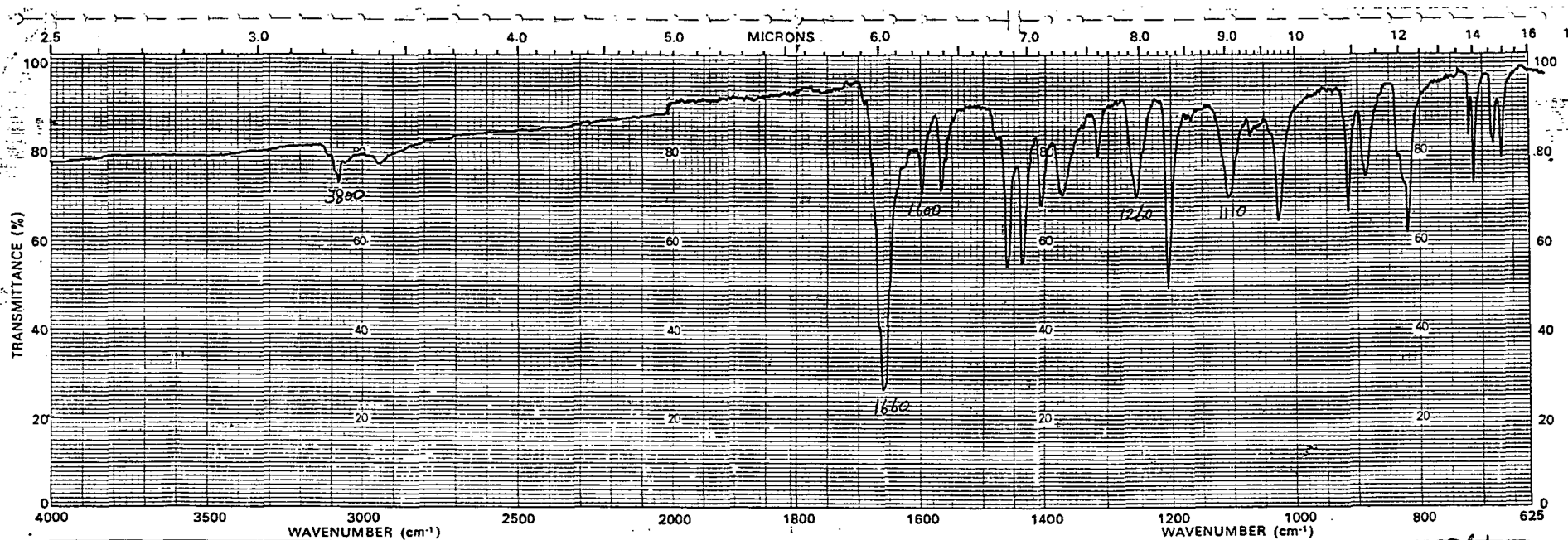
m/z : 300 (m^+)

6-ETHOXY 2-N,N -(DIETHYLTHIOCARBAMIDO) BENZOTHIAZOLE
(COMPOUND NO. 8 , TABLE NO. 4)

IR (KBr cm^{-1})

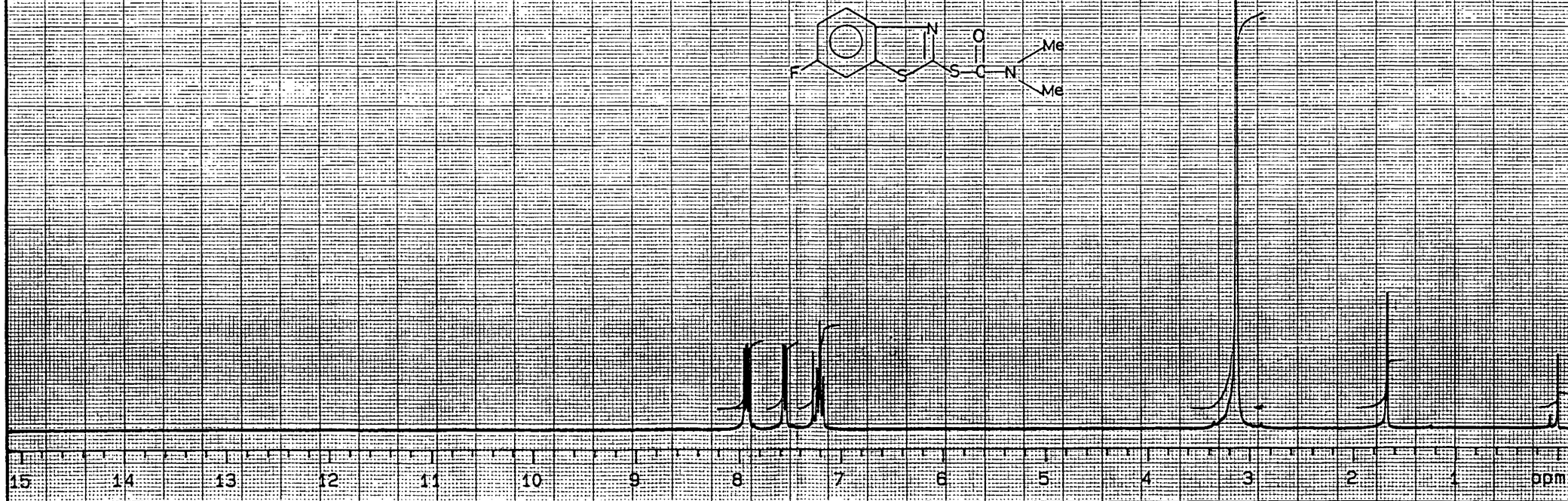
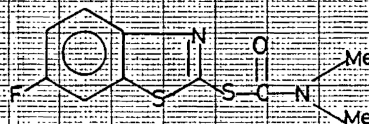
3000 (-C₂H₅), 1660 (C=O), 1600 (ARM),

1240 (-N-C=O), 1080 (N-C-S),



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	CONCENTRATION: <u>1%</u>		SLIT: <u>Normal</u>	DATE: <u>7/6/94</u>
	CELL PATH:	CHART NO. <u>472</u> 5089	TRUEGRAPH CHARTS PVT. LTD.	
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5	2272.3	7.58	4.5
6	2269.8	7.57	4.5
7	2264.3	7.55	4.4
8	2261.7	7.54	4.2
9	2180.4	7.27	4.1
10	2169.4	7.23	3.3
11	2166.9	7.22	3.0
12	2160.5	7.20	5.8
13	2157.9	7.19	5.0
14	2151.5	7.17	2.8
15	2148.9	7.16	2.4
16	936.8	3.12	42.3
17	501.3	1.67	7.2
18	0.0	0.00	3.9



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SP6

Number

File exp

Date Jul 22 93

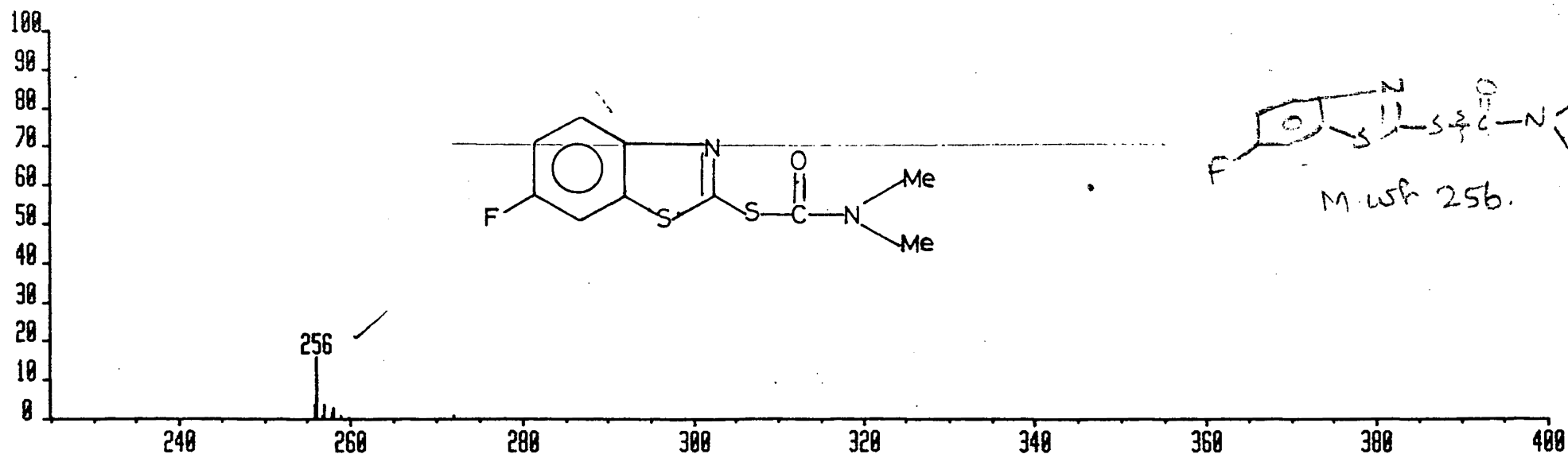
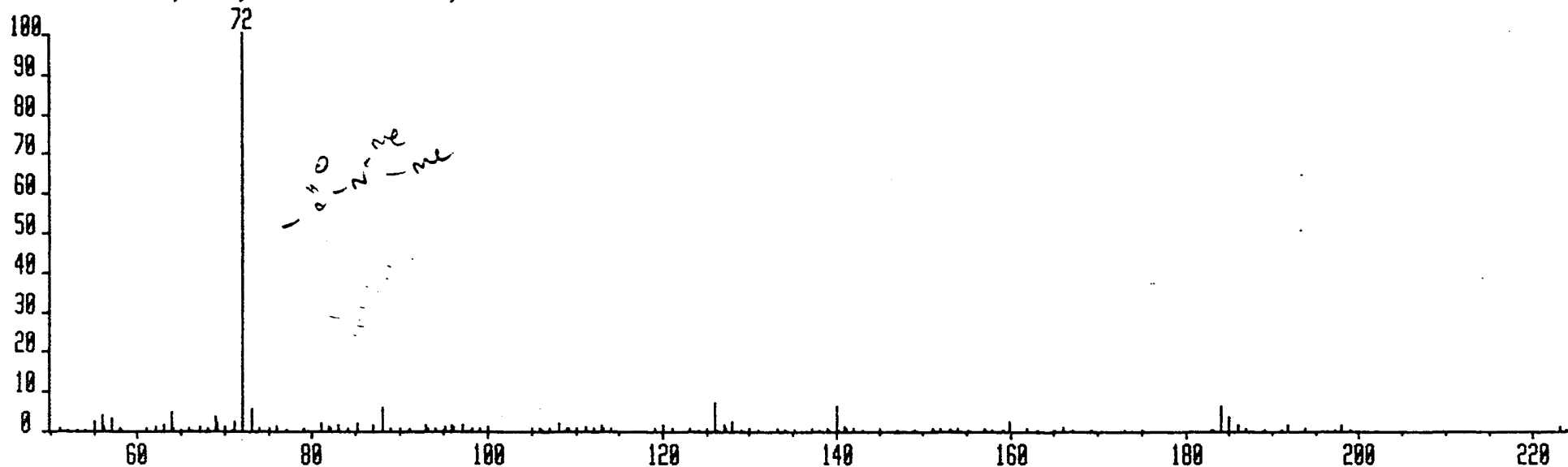
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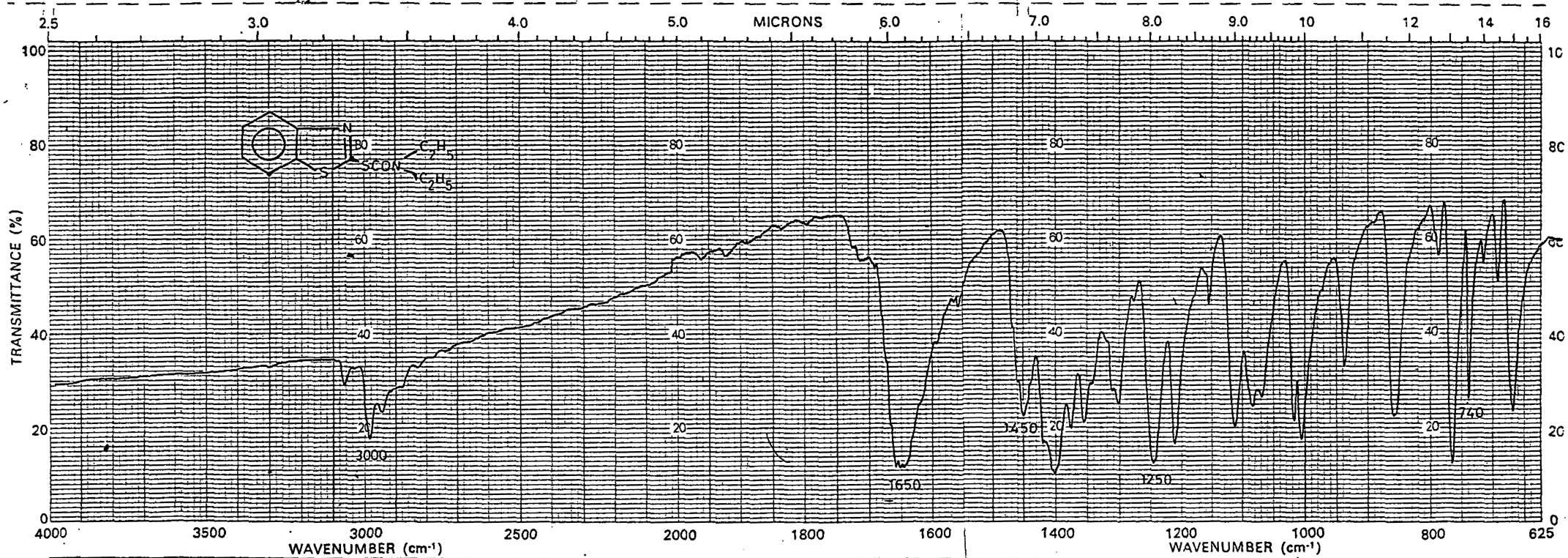


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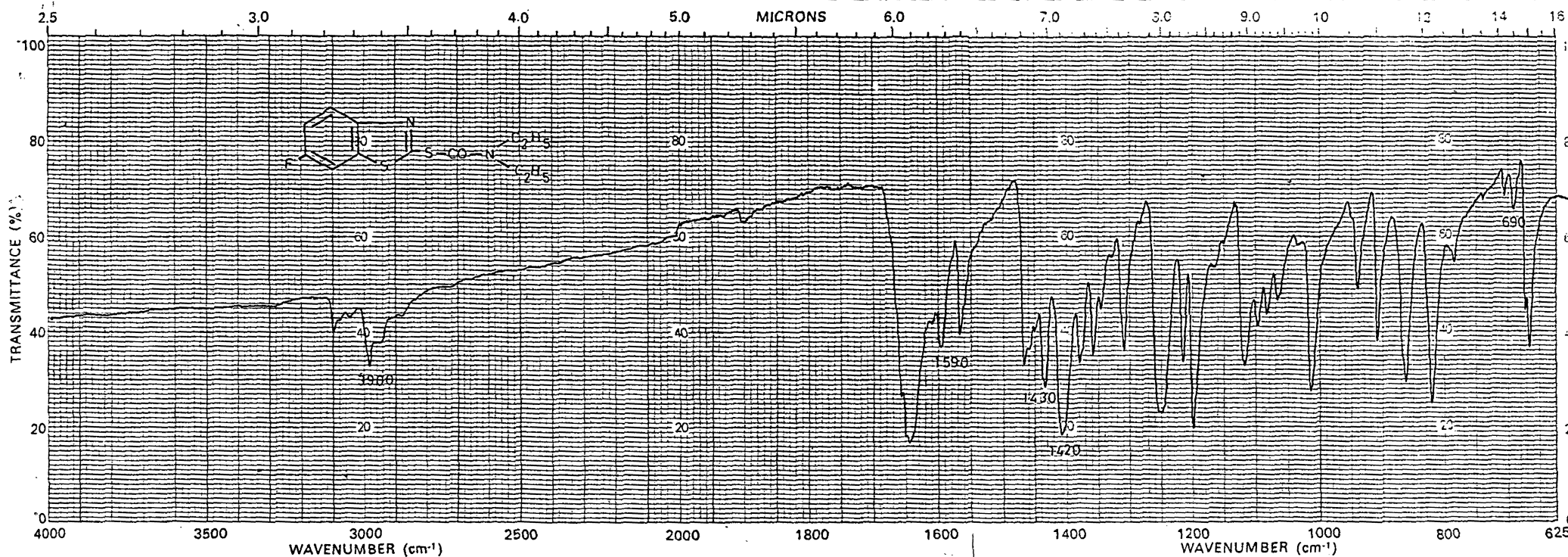
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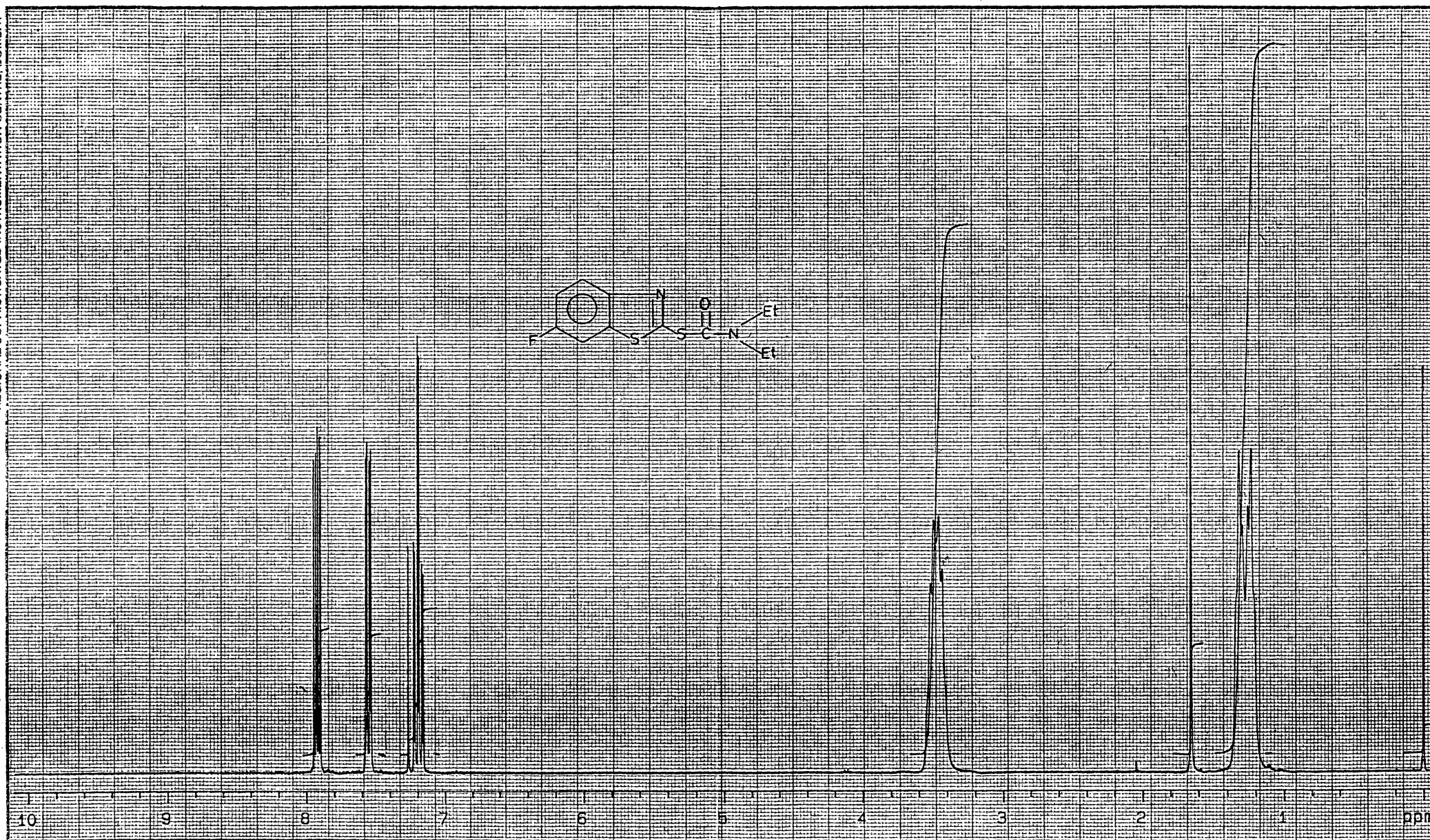




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		REFERENCE	TRUEGRAPH CHARTS PVT. LTD.		



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	CELL PATH			
	REFERENCE			



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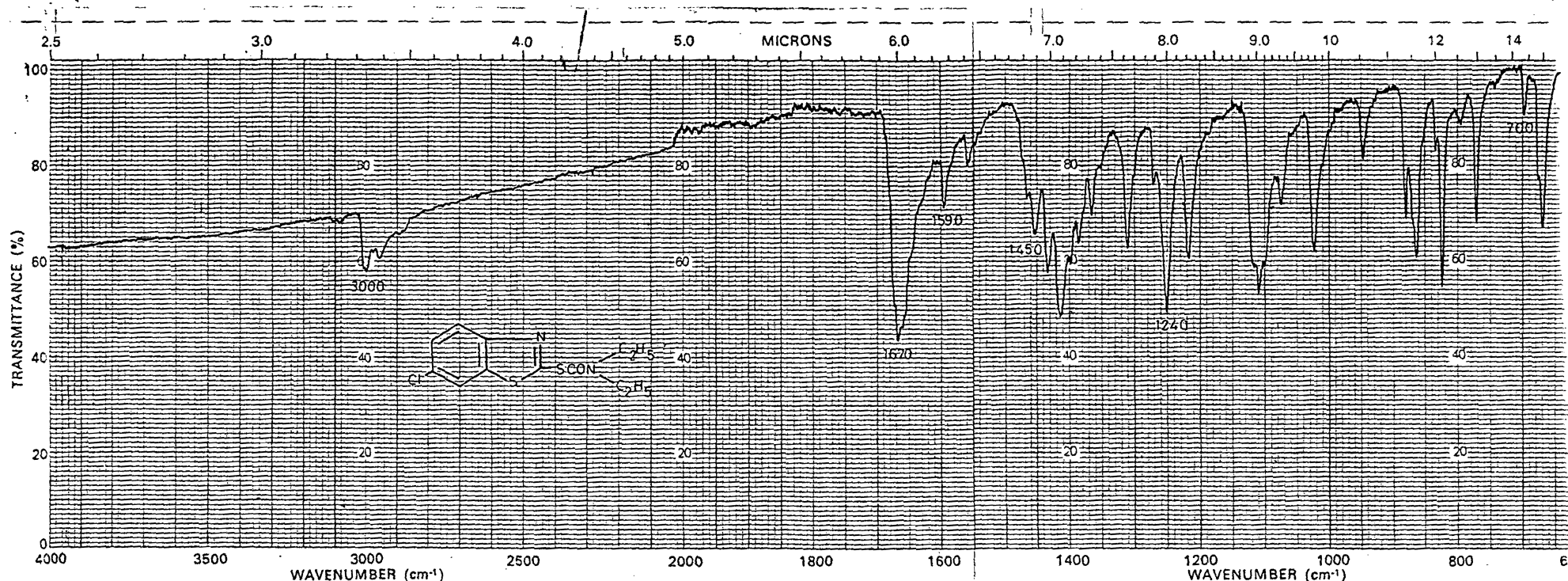
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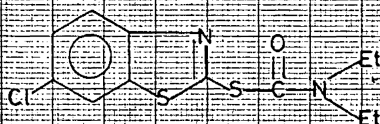
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7	2226.4	7.42	12.3
8	2219.8	7.40	11.3
9	2217.8	7.39	10.9
10	2180.1	7.27	9.6
11	1056.7	3.52	4.6
12	1050.5	3.50	5.7
13	1043.7	3.48	5.3
14	1037.5	3.46	5.6
15	1030.7	3.44	4.6
16	499.4	1.67	1.4
17	413.7	1.38	1.1
18	393.4	1.31	7.9
19	386.8	1.29	6.3
20	376.2	1.25	7.4
21	370.4	1.23	7.6
22	331.9	1.11	0.7
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OBSERVE
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Spec. Width 9998.8 Hz Offset 1293.1 Hz
Acq. Time 4.001 sec Delay 0 sec
Pulse Width 8.0 sec Transients 32

DECOUPLE
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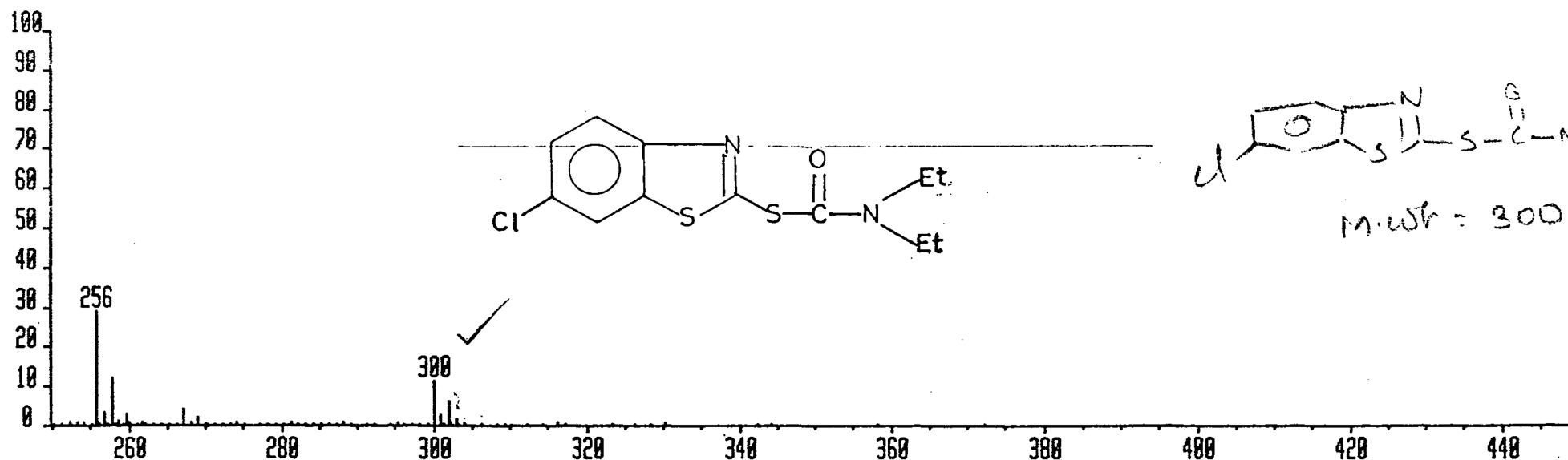
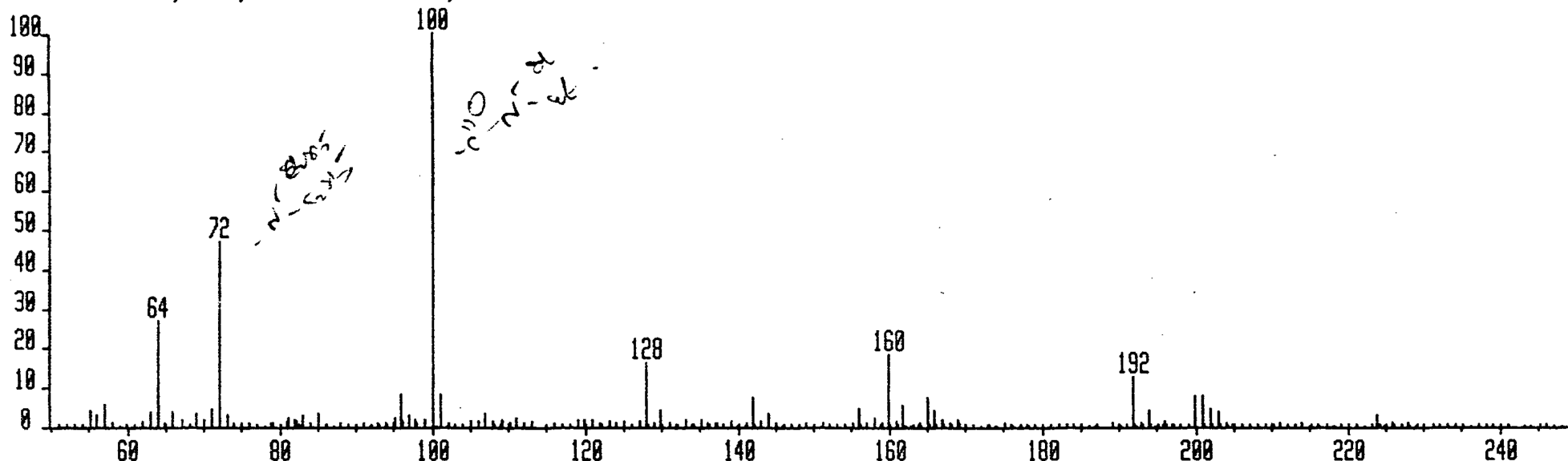
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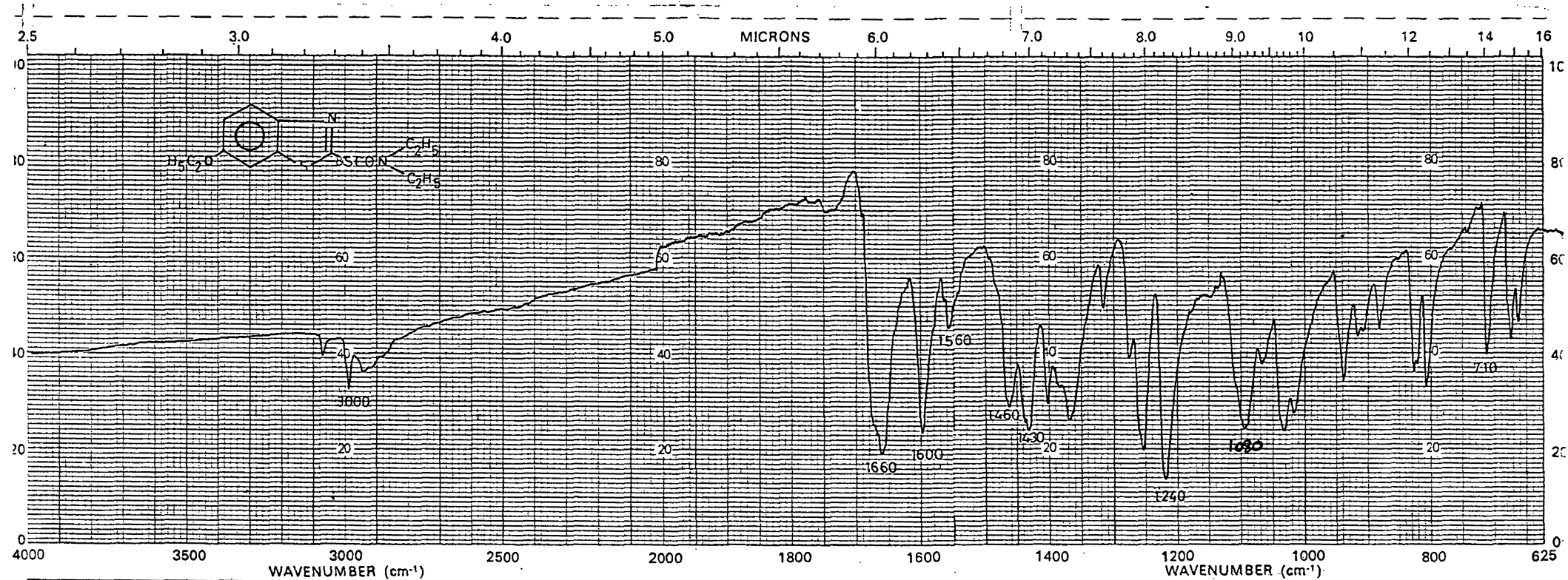
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 MS FACILITY, RSIC, PANJAB UNIVERSITY, CHANDIGARH-14 [INDIA] PT= 0°

EI+
 Sys: NOMASS
 Cal: SD009

HMR: 30300000
 MASS: 100



checked



SAMPLE <chem>COc1ccc2c(c1)sc(NC(=O)NCC)c2</chem> ORIGIN	SOLVENT <u>CHCl₃</u>	REMARKS CHART NO. 472-5099 TRUEGRAPH CHARTS PVT. LTD.	SCAN SPEED <u>Medium</u>	OPERATOR <u>Sargey</u>
	CONCENTRATION <u>1%</u>		SLIT <u>Normal</u>	DATE <u>28/10/02</u>
	CELL PATH			
	REFERENCE			REF. NO.

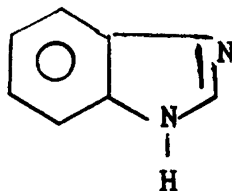


PART - III

SECTION - A

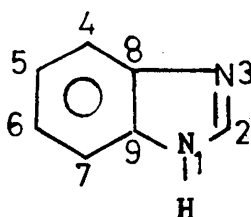
**CHEMISTRY
OF
BENZIMIDAZOLES**

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



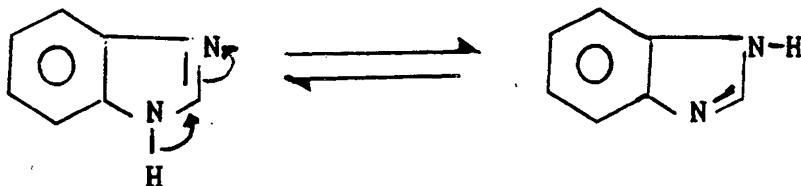
(I)

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 systems for benzimidazole (II) is as follows :



(II)

Benzimidazole which contains a hydrogen atom attached to nitrogen in the 1-position readily tautomerise ⁸¹.



Synthesis of benzimidazoles :

The last systematic reviews on benzimidazoles were published in 1951⁸², and 1953⁸³, although subsequent surveys have appeared in articles⁸⁴⁻⁸⁶ covering the chemistry of both imidazoles and benzimidazoles. In the latest reviews⁸⁷, 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 diamine with carboxylic acids.^{88,89}

b) by reacting o-phenylene diamines with acid chlorides^{90,91}, ester⁹² or acid anhydride⁹³

c) by reacting o-phenylene diamine with amide⁹⁴ or nitrile⁹⁵

d) by reacting o-phenylene diamine with aldehyde⁹⁶ or ketone⁹⁷

e) by reacting o-phenylene diamine with urea⁹⁸ or thiourea⁹⁹ and

f) by reacting o-phenylene diamine with isothiocyanate¹⁰⁰.

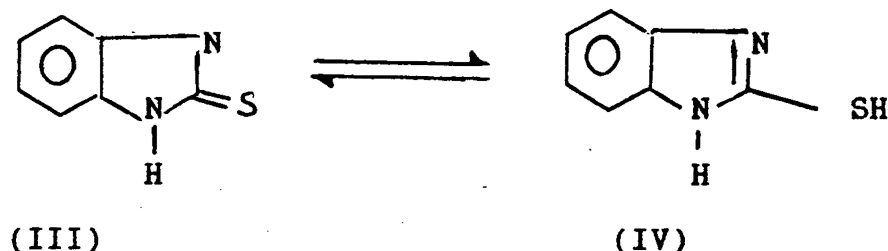
Properties of benzimidazoles :

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 :

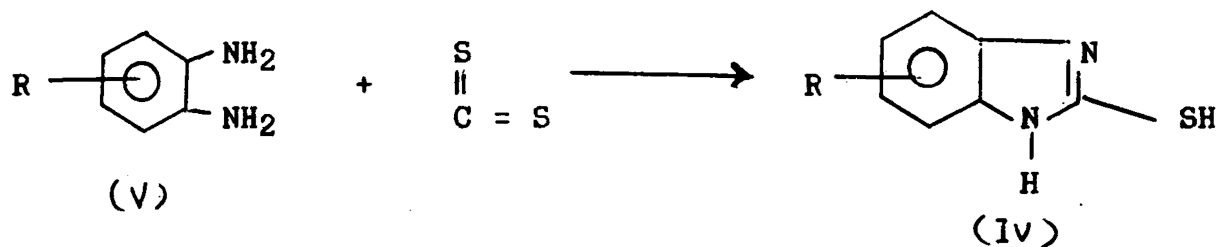
2-(3H) Benzimidazole thione (III) and 2-mercapto benzimidazole (IV) are tautomeric substances analogous to 2-(3H) benzimidazolone and 2-hydroxy benzimidazole.



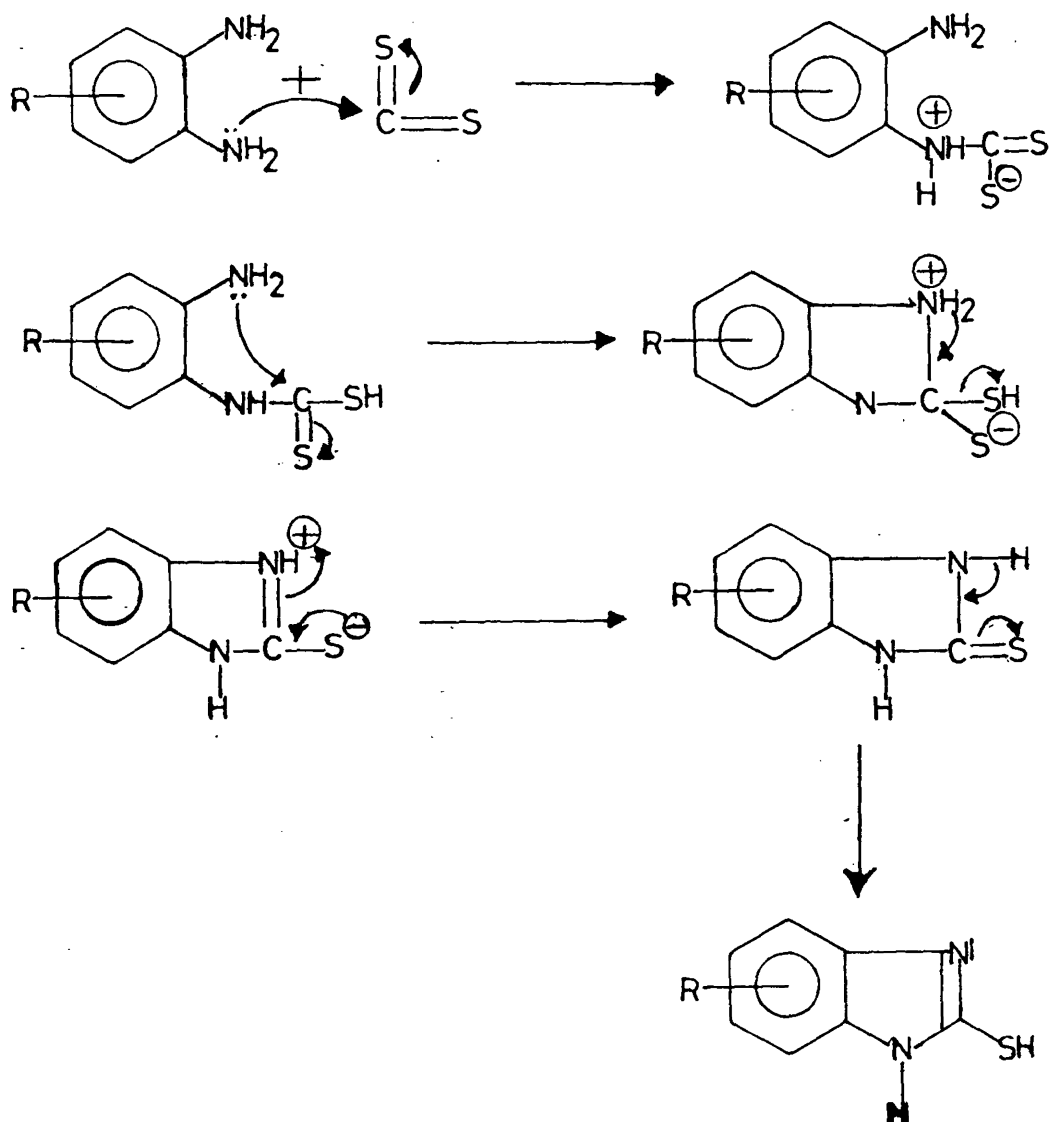
Different methods of preparation of 2-mercapto benzimidazole :

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

2- Mercapto benzimidazole (IV) in general may be very conveniently prepared by this method. The reactants, o-phenylene diamine (V) and carbon disulfide are condensed by heating in the alcoholic solution with or without addition of alkali. 2-Mercapto benzimidazole itself has been prepared by this method^{101,102}.



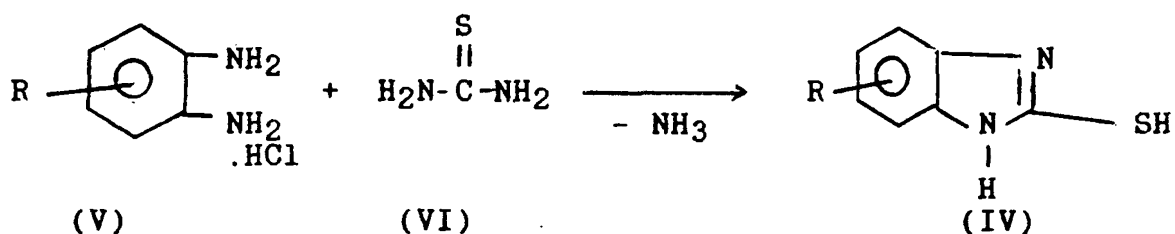
PROBABLE MECHANISM



o-Phenylene diamines containing substituents in the phenyl ring have been used, including those containing alkyl¹⁰³, halogen¹⁰⁴, phenyl¹⁰⁵, aniline¹⁰⁶ and sulphonamido¹⁰⁷ groups.

(b) From o-phenylene diamine and thiourea :

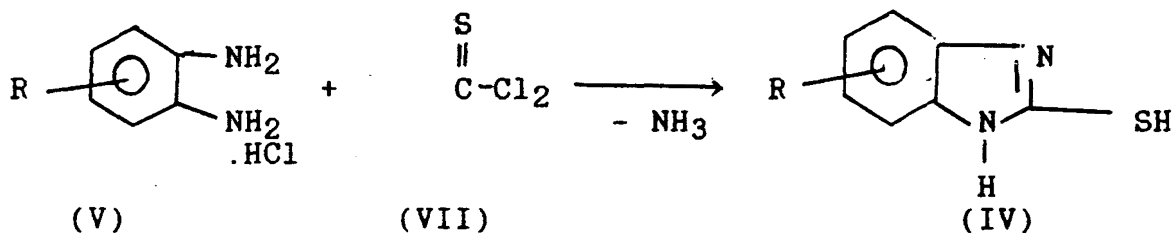
This reaction is analogous to the preparation of 2-hydroxy benzimidazole from o-phenylene diamine (V) and urea (VI). Substituted o-phenylene diamine and thiourea are heated at 170-80 °C⁹⁸.



The excellent yields of substituted 2-mercapto benzimidazoles (IV) can be obtained by using amyl alcohol at reflux temperature till evolution of ammonia gas ceases.

(c) From o-phenylene diamine and thiophosgene :

Bellester and Steiner obtained substituted 2-mercapto benzimidazoles (III) and 5-methyl-2-mercapto benzimidazole by the action of thiophosgene (VII) on o-phenylene diamine (V) and 3,4-diamino toluene, respectively.^{108,109}



(d) Miscellaneous methods :-

2-Mercapto benzimidazole can be prepared in 84-86 % yield by the action of potassium ethyl xanthate on o-phenylene diamine¹¹⁰. 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 a short time. By this method, 2-mercapto benzimidazole¹⁰⁴ and 5-chloro¹¹¹, 4-methyl¹¹² and 5-methyl derivatives of 2-mercapto benzimidazole have been prepared.

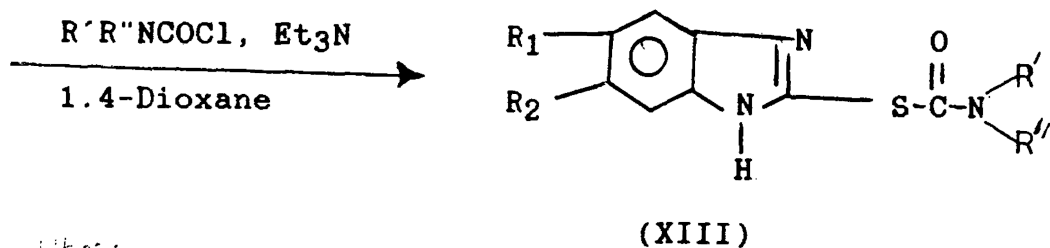
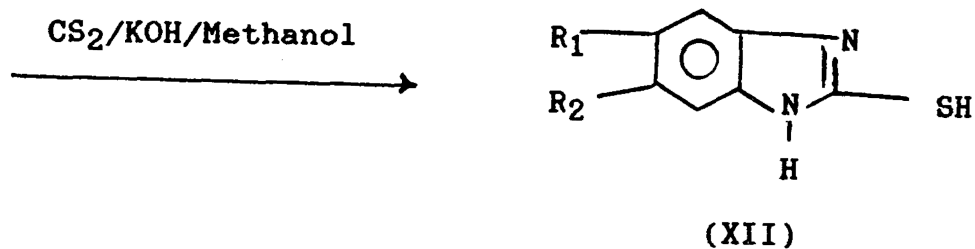
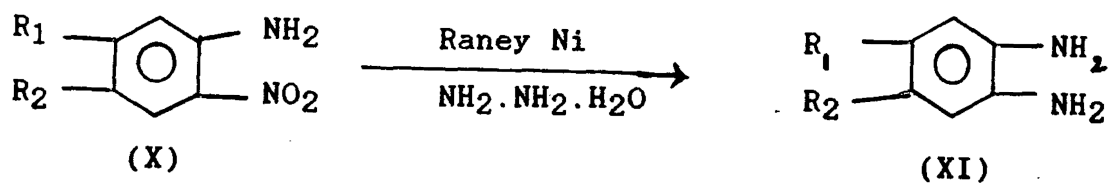
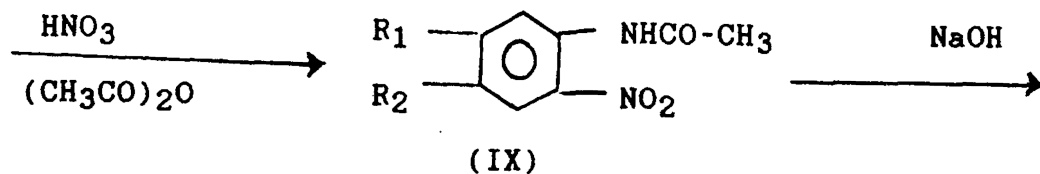
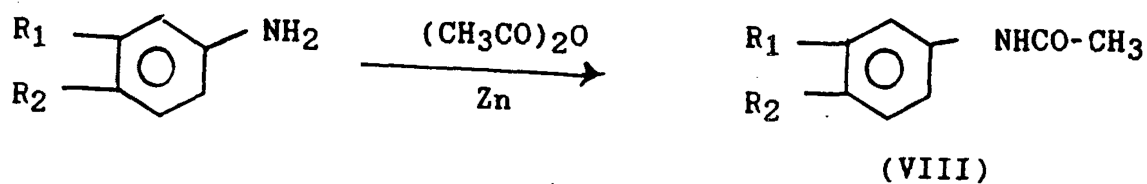
In the present investigation, 5,6-disubstituted 2-mercapto benzimidazoles were prepared by the following manner:-

3,4 Disubstituted acetanilides (VIII) were nitrated at 0-5 °C to give 2-nitro-4,5-disubstituted acetanilides (IX), which on further hydrolysis gives 2-nitro-4,5-disubstituted amines (X). The nitro derivative on reduction with hydrazine hydrate in presence of Raney nickel gives 4,5-disubstituted o-phenylene diamine (XI). These o-phenylene diamines on condensation with K-methyl xanthate under reflux conditions gives 2-mercapto benzimidazoles (XII).

The 5,6-disubstituted-2-mercapto benzimidazoles obtained as above were condensed with N,N-dialkyl carbamoyl chlorides in presence of triethylamine and using 1,4 dioxane as a solvent to give the desired compounds (XIII).

The schematic diagram leading to the formation of the title compounds summarising the various reactions discussed so far is given in the scheme II.

Scheme II



Where

$R_1 = \text{H, Cl, NO}_2$

$R_2 = \text{H, Cl, OCH}_3$

$R' = R'' = \text{CH}_3, \text{C}_2\text{H}_5$

PART - III

SECTION - B

EXPERIMENTAL

This section deals with the synthesis of 5,6 disubstituted 2-(N,N - dialkyl thiocarbamido) benzimidazoles which involves the following steps:

- (1) Preparation of substituted acetanilides
- (2) Preparation of nitro derivatives of substituted acetanilides
- (3) Hydrolysis of substituted nitro acetanilides
- (4) Preparation of substituted o-phenylene diamines
- (5) Preparation of 2-mercapto-5,6-disubstituted benzimidazoles
- (6) Preparation of 5,6-disubstituted 2-(N,N - dialkyl thiocarbamido) benzimidazoles.

(1) Preparation of 3,4 dichloro acetanilide :-

In a 500 ml round bottomed flask equipped with a reflux condenser was placed 3,4 dichloro aniline (33 gms, 0.2 moles), acetic anhydride (23 gms, 21 ml, 0.2 moles), acetic acid 14 gms (14 ml, 0.2 moles) and 0.1 gm of zinc dust. The reaction mixture was refluxed for 30 minutes and then was allowed to cool down at room temperature. It was then poured onto 500 ml of ice-water mixture. The solid separated was filtered, washed with cold water and dried. It was then recrystallised from 40 % aqueous ethanol.

Yield : 36 gms (88 %)

m.p. : 119-120 °C.

(Lit. m.p.¹¹³ : 121 °C.)

Preparation of 4,5 dichloro 2-nitro acetanilide:-

In a 1 l three necked round bottomed flask equipped with a mechanical stirrer, dropping funnel and a thermometer was placed of 3,4 dichloro acetanilide (48 gms, 0.235 moles) in 468 ml conc. H_2SO_4 . It was cooled to 0 °C. To this 21.4 ml of ethyl nitrate was added dropwise maintaining the temperature between 0-2 °C. The reaction mixture was stirred for two hours at the same temperature. It was then poured onto 1 kg of crushed ice with stirring. The solid separated was filtered, washed with cold water and dried. It was recrystallised from ethanol.

Yield : 36 gms (61.3 %)

m.p. : 123-5 °C.

Lit. m.p.^{113a,b,c} : 122-4 °C).

Preparation of 4,5 dichloro 2-nitro aniline:-

To a solution of 4,5 dichloro 2-nitro acetanilide (24.9 gms, 0.1 mole) in 30 ml boiling ethanol was added a solution of potassium hydroxide (5.6 gms, 0.1 mole) in 10 ml water. The reaction mixture was refluxed for 40 minutes and cooled. The alcohol was distilled out under vacuum. The residue was poured onto 200 gms of crushed ice and made slightly acidic with dilute hydrochloric acid. The solid separated out was filtered washed with cold water and dried. It was further recrystallised from ethanol.

Yield : 12 gms (58 %)

m.p. : 176-8 °C.

Lit. m.p.¹¹³ : 178-9 °C.

Preparation of 4,5 dichloro o-phenylene diamine :-

In a 100 ml three necked round bottomed flask equipped with a mechanical stirrer, dropping funnel and a reflux condenser was placed 1 gm of Raney Nickel and 80 % hydrazine hydrate (10 ml, 0.16 mole) in 30 ml ethanol. The mixture was heated at 40-50 °C. To this 4,5 dichloro 2- nitro aniline (10 gms, 0.05 mole) in 25 ml alcohol was added dropwise. The reaction mixture was refluxed for 4 hours till the reduction was complete. The solution was filtered and the ethanol was distilled out under vacuum. The oil obtained was recrystallised from benzene-pet. ether (60-80) mixture.

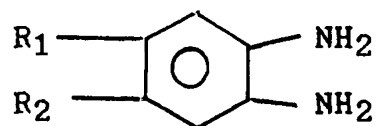
Yield : 4.9 gms (55 %)

m.p. : 60-2 °C.

Lit. m.p.¹¹⁵ : 58-60 °C).

TABLE 5

SUBSTITUTED o-PHENYLENE DIAMINES



SR.NO.	R_1	R_2	m.p. °C		YIELD %	REF
			OBSERVED	REPORTED		
1.	H	H	-	-	58	113
2.	H	Cl	75-76	73-74	68	113
3.	Cl	Cl	60-62	58-60	55	115
4.	H	NO_2	197-198	196-198	58	116
5.	H	OCH_3	248-249	246-248	56	114

Preparation of 2-mercapto-5,6-dichloro benzimidazole :-

To potassium hydroxide (5.6 gms, 0.1 mole) was added 150 ml ethanol and 30 ml water. The mixture was warmed on waterbath till all the solid goes into the solution. To this cold solution was added carbon disulfide (13.5 gms, 11 ml, 0.17 mole) with stirring.

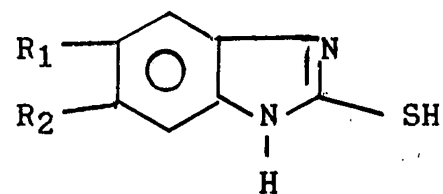
In a 250 ml three necked round bottomed flask equipped with a dropping funnel and a reflux condenser was placed 4,5-dichloro o- phenylene diamine (18 gm, 0.1 mole) in 200 ml ethanol. To this above potassium ethyl xanthate solution was added dropwise. The mixture was further refluxed for 6 hours until fumes of hydrogen sulfide gas ceases. The reaction mixture was cooled and then concentrated under vacuum to remove most of the ethanol. The oil obtained was diluted with water and then neutralised with dilute hydrochloric acid. The solid separated was filtered, washed with water and dried. It was then recrystallised from ethanol.

Yield : 16.5 gms (75 %)

m.p. : 332-4 °C.

(Lit. m.p.¹²² : 335 °C.)

TABLE 6

5.6 DISUBSTITUTED 2-MERCAPTBPENZIMIDAZOLES

SR.NO.	R ₁	R ₂	m.p. °C		YIELD %		REF
			OBSERVED	REPORTED	OBSERVED	REPORTED	
1	H	H	302-303	303-304	84-86	87	120
2	H	Cl	304-306	305(d)	85	88	117
3	Cl	Cl	332-334	335	75	89	122
4	H	NO ₂	281-282	282	84	90	119
5	Cl	SC ₃ H ₇	179-80	179	80	91	123
6	H	C ₆ H ₅ CO	172	-	80	-	-
7	H	OCH ₃	300-302	302-305	58	-	120, 121

Preparation of 5,6 dichloro -2-N,N-(diethylthiocarbamido) benzimidazole

In a 100 ml three necked flask equipped with a dropping funnel, mechanical stirrer and a reflux condenser was placed a solution of 5,6 dichloro 2-mercapto benzimidazole (0.438 gm, 0.002 mole) in 10 ml dry 1,4 dioxane and triethylamine (0.003 mole, 0.10 gm). It was stirred at 40-50 °C for about 15 minutes. To this N, N-diethylcarbamoyl chloride (0.135 gms 0.20 ml, 0.003 mole) in 10 ml dry 1,4 dioxane was added dropwise with stirring. The reaction mixture was stirred at 50-60 °C for about two hours. It was kept overnight at room temperature. The solution was poured onto 100 gms of crushed ice. The solid separated was filtered, washed with water and dried. It was then purified by column chromatography using 60-120 mesh silica gel and chloroform as an eluant.

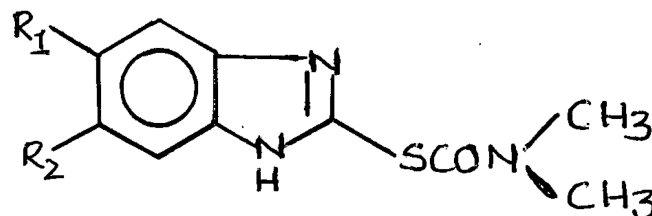
Yield : 0.4 gms (63 %)

m.p. : 145-7 °C

Elemental Analysis :	Required	Found
C %	45.28	45.23
H %	4.08	3.73
N %	13.20	12.86

In a similar manner different 5,6 disubstituted 2-mercapto benzimidazoles were condensed with N,N- dialkyl carbamoyl chloride to obtain the respective final benzimidazole compounds whose physical data are represented in Table 7 and 8.

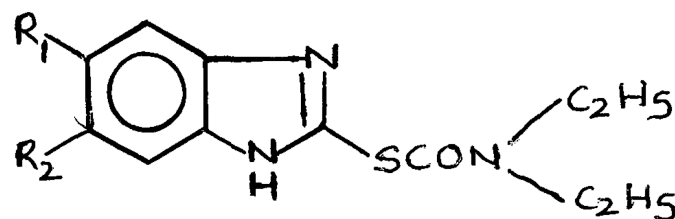
TABLE 7

5,6-DISUBSTITUTED -2-(N,N-DIMETHYL THIOCARBAMIDO) BENZIMIDAZOLES

SR. NO.	R ₁	R ₂	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
							REQUIRED			-	FOUND	
							C	H	N	C	H	N
1	H	H	C ₁₀ H ₁₁ N ₃ OS	221	112-3	65	54.29	4.97	19.00	54.85	4.35	19.53
2	Cl	H	C ₁₀ H ₁₀ ClN ₃ OS	255.5	138-9	57	46.96	3.91	16.43	47.14	4.05	16.57
3	Cl	Cl	C ₁₀ H ₉ Cl ₂ N ₃ OS	290	165-7	53	41.37	3.10	14.48	41.23	3.33	14.76
4	CH ₃	H	C ₁₁ H ₁₃ N ₃ OS	235	108	48	56.17	5.53	17.87	55.85	5.75	18.04
5	OCH ₃	H	C ₁₁ H ₁₃ N ₃ O ₂ S	251	126-7	42	52.58	5.17	16.73	52.37	4.88	16.53
6	OC ₂ H ₅	H	C ₁₂ H ₁₅ N ₃ O ₂ S	265	128	49	54.33	5.66	15.84	54.32	5.23	16.12
7	NO ₂	H	C ₁₀ H ₁₀ N ₄ O ₃ S	266	113-5	58	45.11	3.75	21.05	44.53	3.17	20.68
8	C ₆ H ₅ CO	H	C ₁₇ H ₁₅ N ₃ O ₂ S	325	133-5	65	62.76	4.61	12.92	62.89	4.22	13.04
9	SC ₃ H ₇	Cl	C ₁₃ H ₁₆ ClN ₃ OS ₂	329.5	157-8	61	47.34	4.85	12.74	47.56	5.11	12.88
10	C ₆ H ₅ CH ₂ SCl		C ₁₇ H ₁₆ ClN ₃ OS ₂	377.5	148-9	54	54.03	4.23	11.12	53.86	3.96	10.85

TABLE 8

5,6-DISUBSTITUTED -2-(N,N-DIETHYL THIOCARBAMIDO) BENZIMIDAZOLES



SR. NO.	R ₁	R ₂	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
							REQUIRED			FOUND		
							C	H	N	C	H	N
1	H	H	C ₁₂ H ₁₅ N ₃ OS	249	152-3	45	57.83	6.02	16.86	57.25	5.45	17.43
2	Cl	H	C ₁₂ H ₁₄ ClN ₃ OS	283.5	118-9	67	50.79	4.93	14.81	50.54	5.05	14.57
3	Cl	Cl	C ₁₂ H ₁₃ Cl ₂ N ₃ OS	318	145-7	63	45.28	4.08	13.20	45.23	3.73	12.86
4	CH ₃	H	C ₁₃ H ₁₇ N ₃ OS	263	128	58	59.31	6.46	15.96	59.65	6.75	16.04
5	OCH ₃	H	C ₁₃ H ₁₇ N ₃ O ₂ S	279	136-7	52	55.91	6.09	15.05	55.77	5.88	14.83
6	OC ₂ H ₅	H	C ₁₄ H ₁₉ N ₃ O ₂ S	293	112	39	57.33	6.48	14.33	57.52	6.23	14.12
7	NO ₂	H	C ₁₂ H ₁₄ N ₄ O ₃ S	294	133-5	68	48.97	4.76	19.04	48.33	4.17	18.48
8	C ₆ H ₅ CO	H	C ₁₉ H ₁₉ N ₃ O ₂ S	353	138-9	55	64.58	5.38	11.89	64.79	5.22	12.04
9	SC ₃ H ₇	Cl	C ₁₅ H ₂₀ ClN ₃ OS ₂	357.5	147-8	60	50.34	5.59	11.74	50.56	5.3	11.88
10	C ₆ H ₅ CH ₂ SCl		C ₁₉ H ₂₀ ClN ₃ OS ₂	405.5	123-4	56	56.22	4.93	10.35	55.86	4.96	10.58

SPECTRAL ANALYSIS OF 5,6 disubstituted -2-N,N-(dialkyl
thiocarbamido) benzimidazole

5-BENZOYL-2-N,N -(DIMETHYLTHIOCARBAMIDO) BENZIMIDAZOLE

(COMPOUND NO. 8 , TABLE NO. 7)

IR (KBr cm^{-1})

3040 (-NH), 2980 (-CH₃), 1640 (C=O), 1580 (ARM),
1240 (-N-C=O), 1100 (N-C-S),

5-NITRO-2-N,N -(DIMETHYLTHIOCARBAMIDO) BENZIMIDAZOLE

(COMPOUND NO. 7 , TABLE NO. 7)

IR (KBr cm^{-1})

3120 (-NH), 2940 (-CH₃), 1630 (C=O), 1620 (ARM),
1530 and 1330 (NO₂), 1260 (-N-C=O), 1100 (N-C-S),

PMR (CdCl₃) δ :

3.142 - 3.238 (s, 6H, -CH₃) 7.571 - 8.60 [m, 3H, Ar-H]
12.076-12.192 (d, 1H, -NH).

MS

m/z : 266 (m⁺)

2-N,N -(DIETHYLTHIOCARBAMIDO) BENZIMIDAZOLE

(COMPOUND NO. 1 , TABLE NO. 8)

IR (KBr cm^{-1})

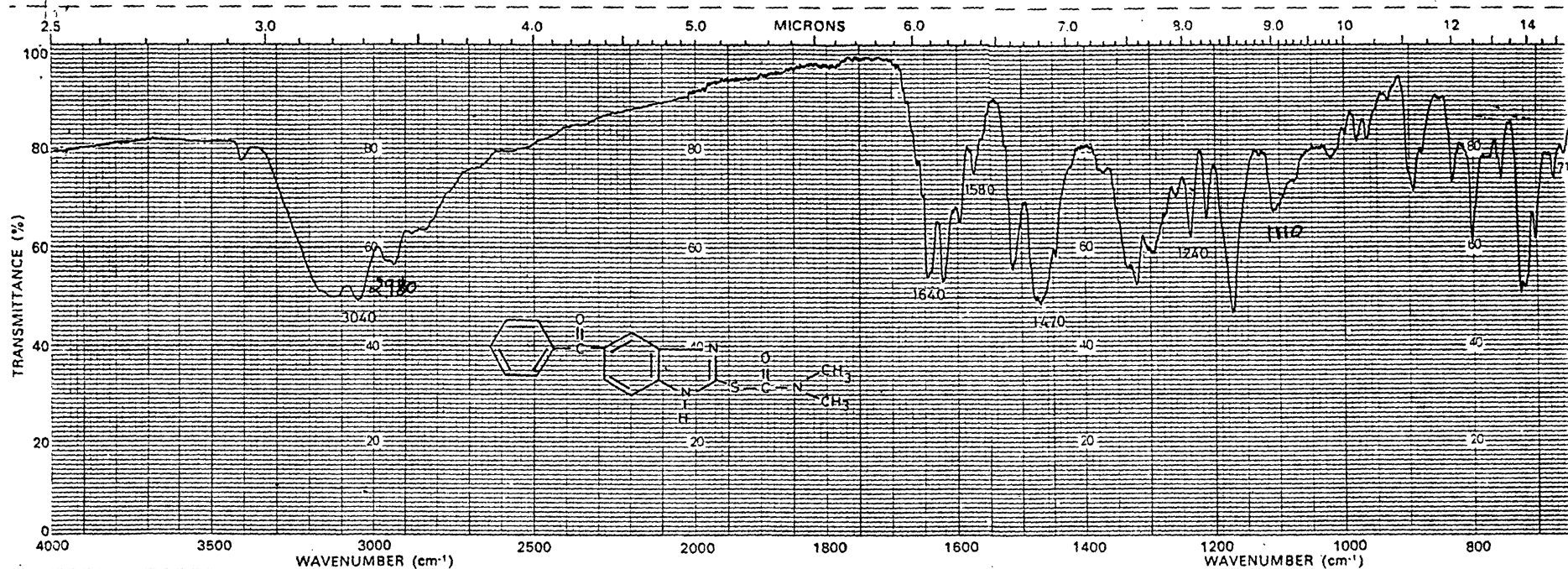
3000 (-NH), 2980 (-C₂H₅), 1670 (C=O), 1590 (ARM),
1240 (-N-C=O), 1120 (N-C-S),

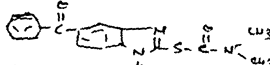
PMR (CdCl_2) δ :

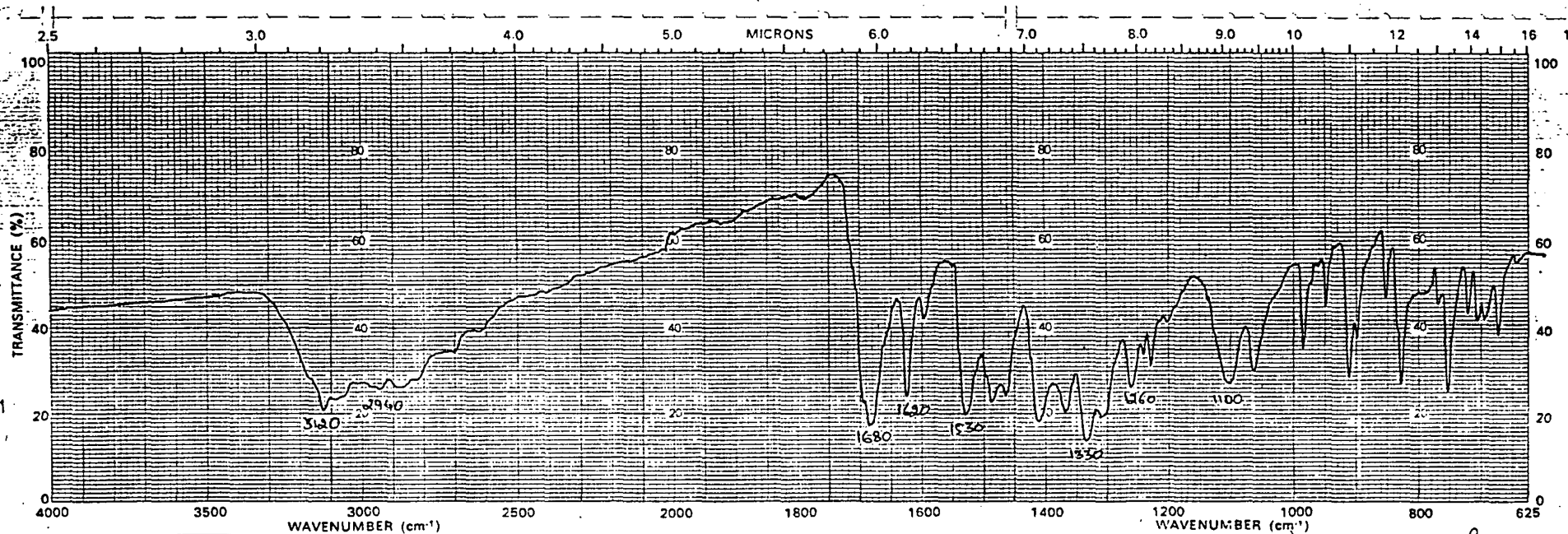
1.12-1.28 (t, 6H, -CH₂CH₃), 3.28-3.52 (q, 4H, -CH₂CH₃),
7.12-7.56 [m, 4H, 4H, AR-H)]

MS

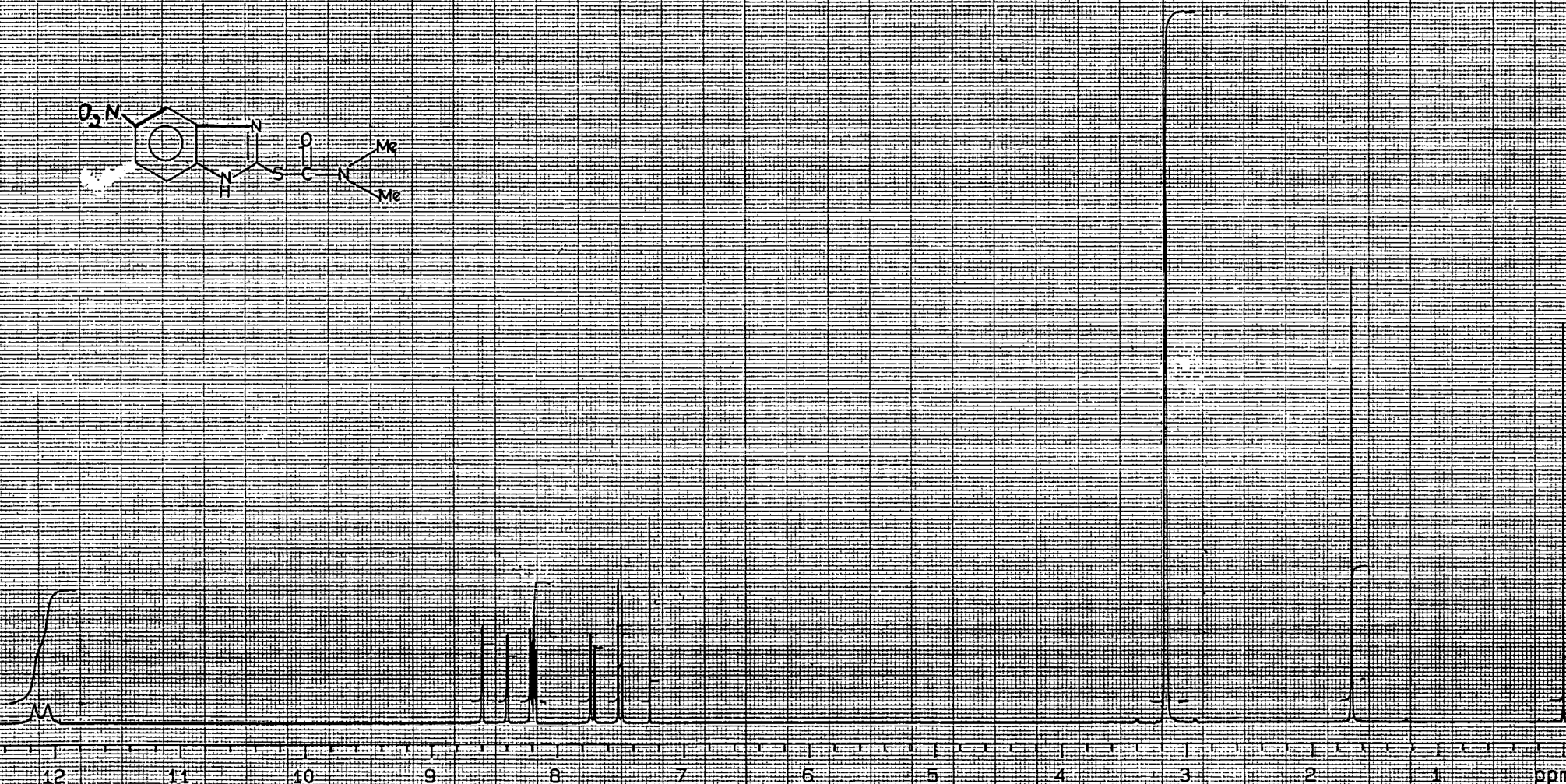
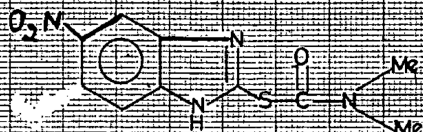
m/z : 249 (m⁺)



SAMPLE 	SOLVENT <u>KBr</u>	REMARKS	SCAN SPEED <u>Medium</u>	OPERATOR <u>W. J. G.</u>
	CONCENTRATION <u>1%</u>		SLIT <u>Normal</u>	DATE <u>2/10/67</u>
ORIGIN	CELL PATH	CHART NO. 472-5089	TRUEGRAPH CHARTS BY LTD.	
	REFERENCE			



SAMPLE <chem>CC(=O)N1C=CC(=O)N1</chem>	SOLVENT	RD	REMARKS	SCAN SPEED	Medium	OPERATOR	SDP
	CONCENTRATION	1%		SLIT	Normal	DATE	25.1.1982
	CELL PATH						
	REFERENCE						
ORIGIN	CHART NO. 472-5089			TELEGRAPH (EXPORT) LTD.		REF. NO.	



Nucleus H1 Freq. 299.9486 MHz
 Spec. Width 6997.9 Hz Offset 1600.0 Hz
 Acq. Time 4.001 sec Delay 0 sec
 Pulse Width 8.0 sec Transients 32

Nucleus H1 Offset 315.9 Hz
 Mode n Power 20 dB
 Modulation: Mode c Freq. 200 Hz
 Pulse Width μsec Power Mode not used

PLOT/PROCESSING
 FN not used RE sec CD sec
 LB 0.100 Hz / not used sec CCD sec
 Width 3952.7 Hz/ppm Start 38.4 Hz/ppm
 Reference sec

EXPERIMENT
 Pulse Sequence g2pul
 Tube O.D. mm
 Temp. not used °C
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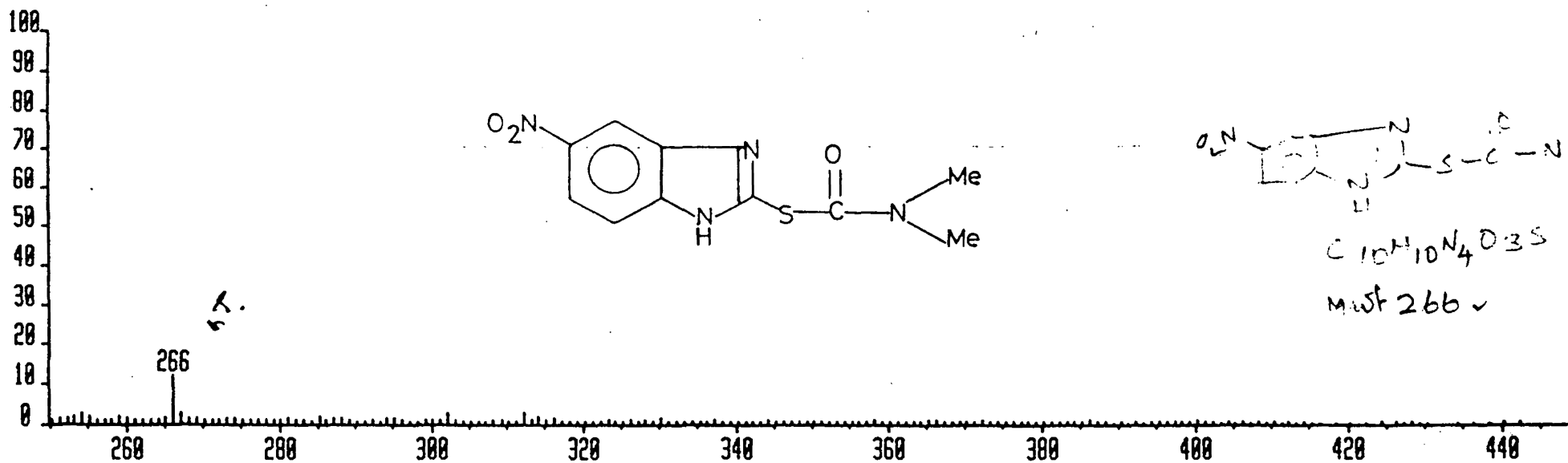
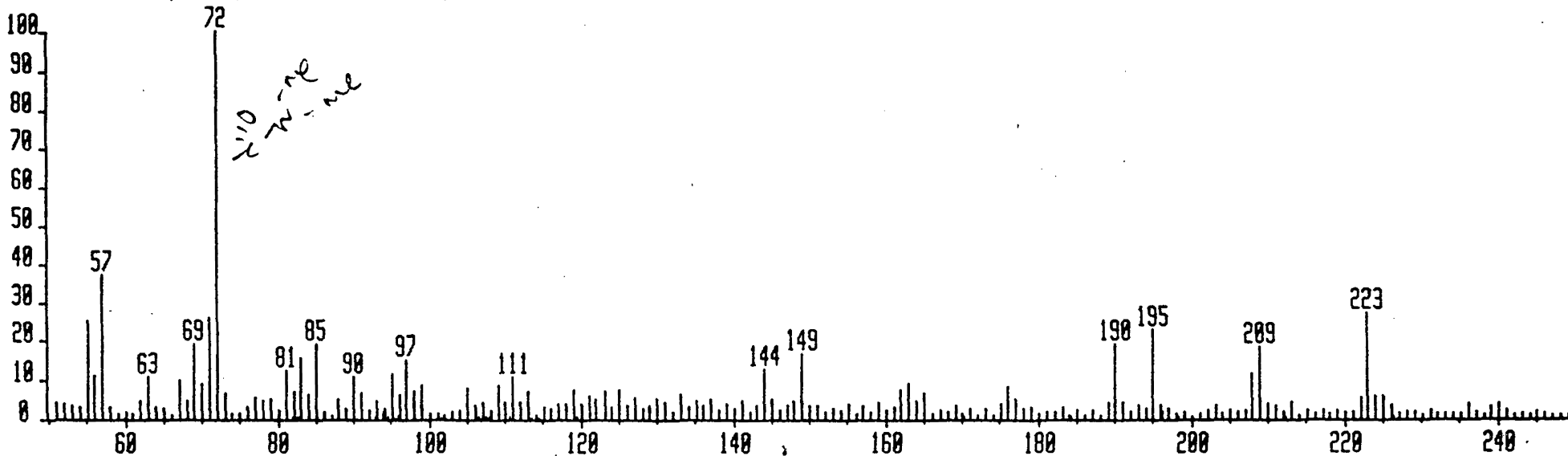
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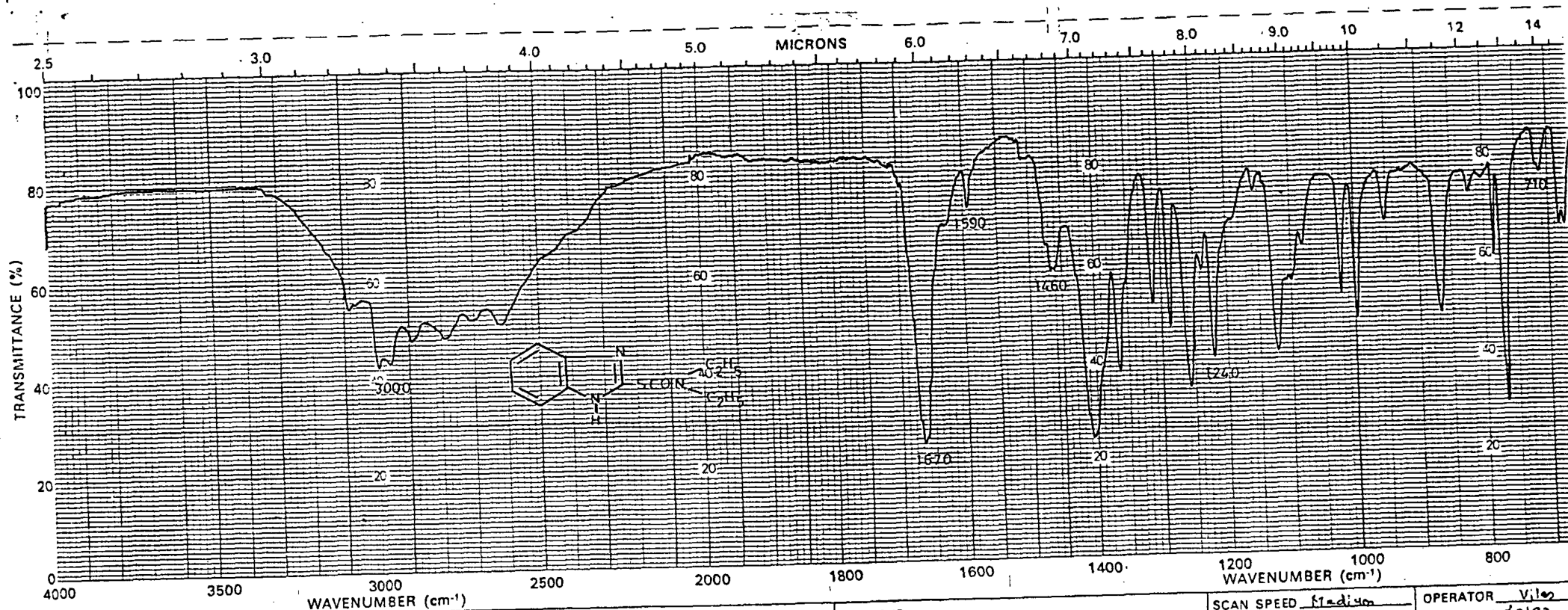
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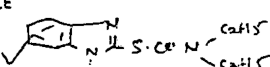
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CHART NO. 323
SAMPLE

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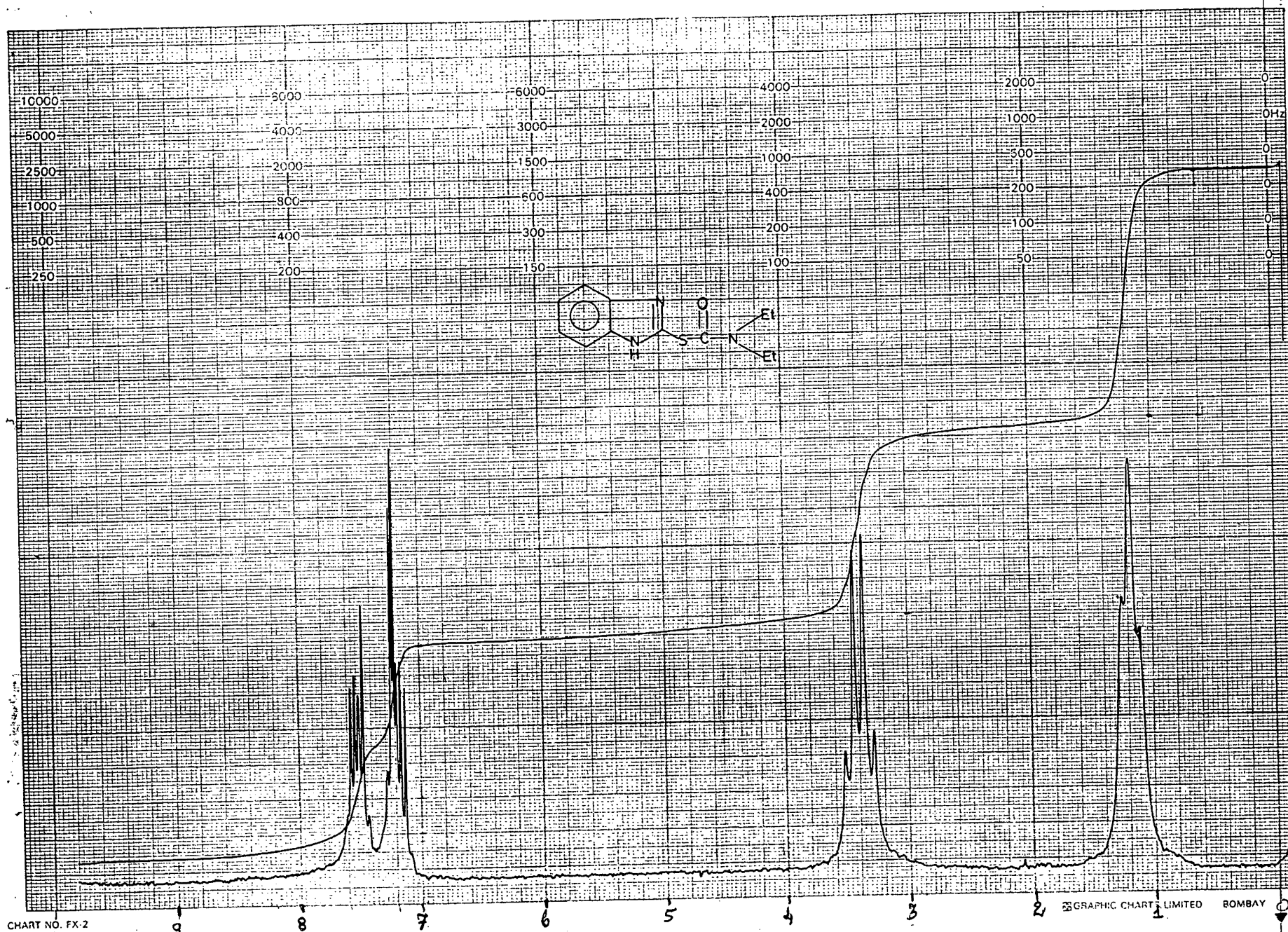
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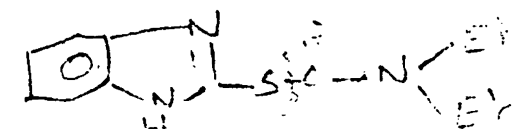
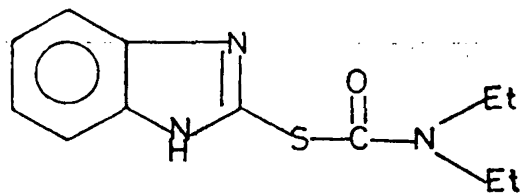
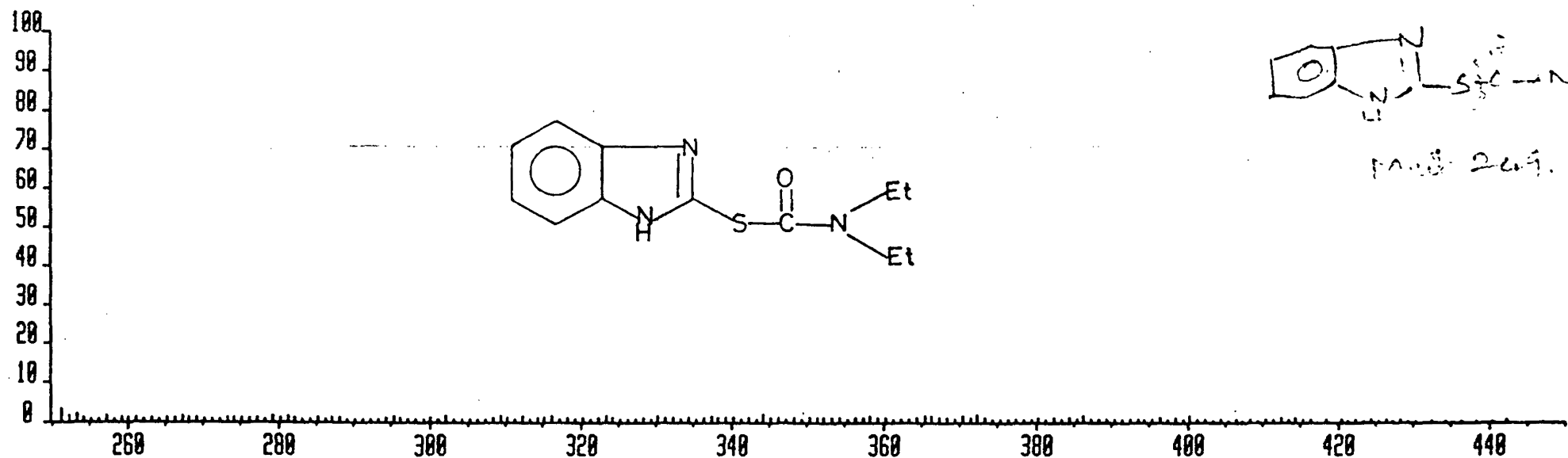
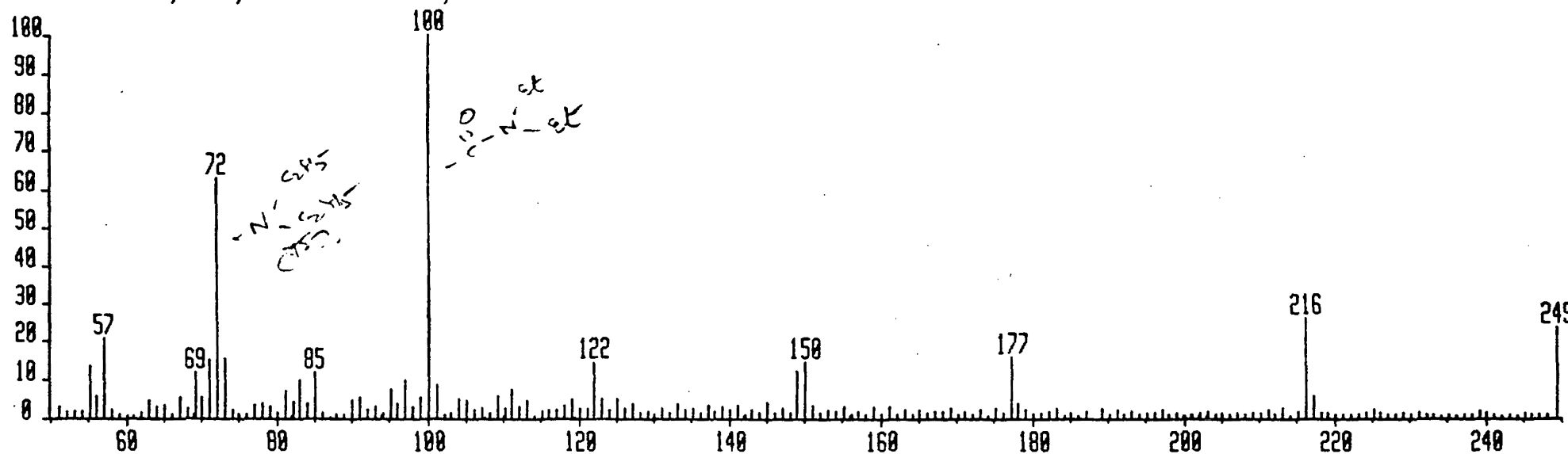
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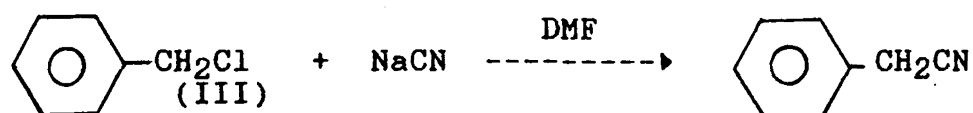
PART - IV

SECTION - A

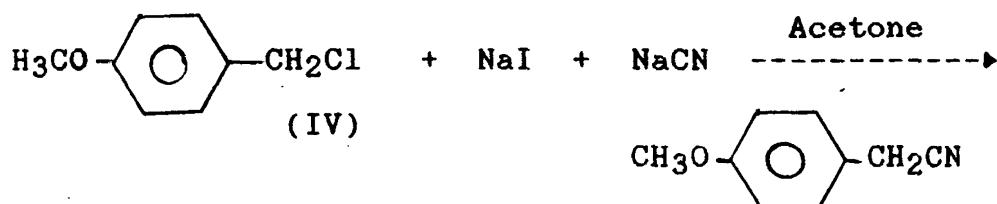
(a) CHEMISTRY OF NITRILES

The yields in such cases vary from 75-90 %. The solvent - alcohol, accelerates the reaction very slowly and higher boiling solvents like ethylene glycol¹²⁶, methyl cellosolve¹²⁷, tetrahydrofurfuryl alcohol¹²⁸ and DMF improves the yields; but with secondary halides, their yields are low and tertiary halides give little or

no nitriles. The conversion of aralkyl halides (III) into nitriles is accomplished best with sodium or cuprous cyanide with pyridine, quinoline, dimethyl formamide¹²⁹ and N-methyl pyrrolidine¹³⁰ as solvents. The reaction time can be shortened by the addition of small amount of a nitrile and traces of copper sulphate as a catalyst.



While, halide like anisyl chloride (IV) gives its nitrile in 75 % yield when it is treated with sodium iodide and sodium cyanide in dry acetone¹³¹.

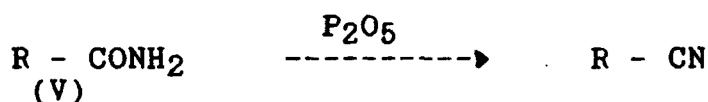


b) From heterocyclic halides :

The halides of pyridine¹³², quinoline¹³³ yield nitrile satisfactorily with cuprous cyanide alone¹³⁰.

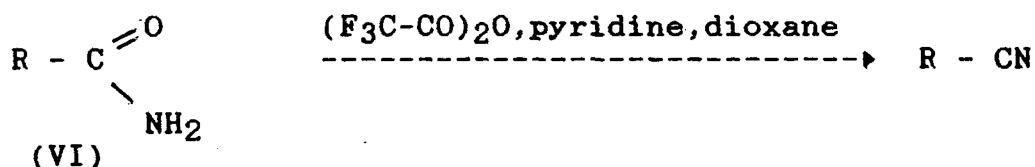
2) From amides :

The preparation of nitriles by the removal of water from amides (V), can be performed in 60-70 % yields by using usual dehydrating agents like phosphorous pentoxide¹³⁴ or phosphorous pentachloride¹³⁵.



Sometimes, dehydrating agents like carbonyl chloride¹³⁶, benzene and p-toluene sulphonyl chloride¹³⁴⁻⁷, phosphorous oxychloride are used in the nucleophilic solvents such as pyridine or tertiary amines. Even addition of salts like sodium chloride¹³⁸ or sodium metabisulphite¹³⁹ to phosphorous oxychloride, enhance the effectiveness of the reagents.

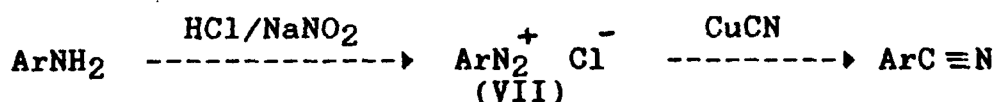
The recent convenient synthesis of nitriles¹⁴⁰ under mild conditions, makes use of the trifluoroacetic anhydride/ pyridine system, which leads to a rapid amide (VI) to nitrile transformation with 85-95 % yields.



Where R = CH₃, p-OMe-C₆H₄, p-NO₂-C₆H₄, pyridyl, etc.

3) From diazonium salts (Sandmeyer's reaction) :

The replacement of aromatic amino groups by cyanide, is obtained in 65-85% yields by the action of cuprous cyanide with diazonium salts (VII).



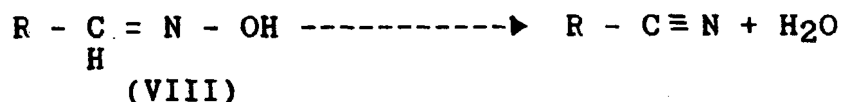
Double or complex salts of cuprous cyanide such as $\text{Na}_3\text{Cu}(\text{CN})_5\text{NH}_3$ ¹⁴¹ have also been employed to a great extent. While, carrying out the reaction, it is important to neutralize the diazonium salt before addition to the cyanide solution, in order to avoid the escape of hydrogen cyanide. o-Tolunitrile¹⁴² can be obtained by this procedure in 64-70 % yield.

4) From aldehydes :

Many methods have been reported for the conversion of aldehydes to nitriles e.g. (a) dehydration of aldoximes using dicyclohexyl carbodiimides¹⁴³, carbonyl biimidazole¹⁴⁴, or phosgene immonium chloride¹⁴⁵, (b) 1,2 elimination of o-substituted aldoxime^{146,147} and (c) 1,2 elimination of $\text{R}-\text{CH}=\text{N}-\text{N}^+ \begin{array}{c} | \\ (\text{CH}_3)_3\text{I}^- \end{array}$ ¹⁴⁸ and $\text{R}-\text{CH}=\text{N}-\text{tosyl}$ by base¹⁴⁹.

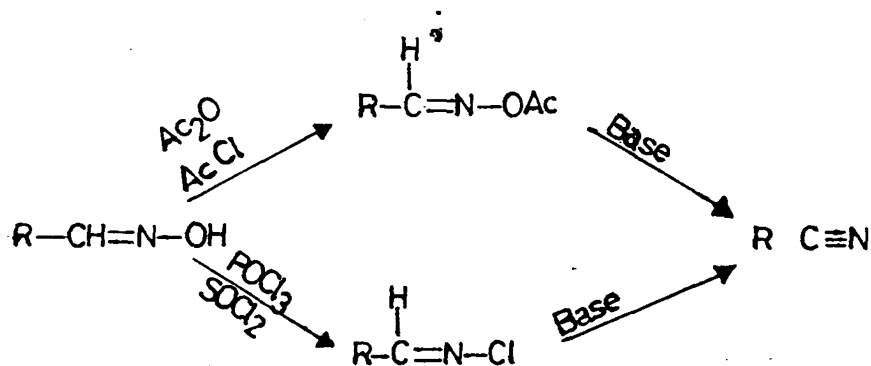
Method A is discussed under the title 'dehydration of aldoximes' and method B and C are discussed under the headings "1,2 -elimination of o-substituted aldoximes; while other methods D and E are described under "1,2- elimination of $\text{R}-\text{CH}=\text{N}-\text{N}^+(\text{CH}_3)_3$ and $\text{R}-\text{CH}=\text{N}-\text{Cl}$ ".

Method - A (Dehydration of aldoximes):



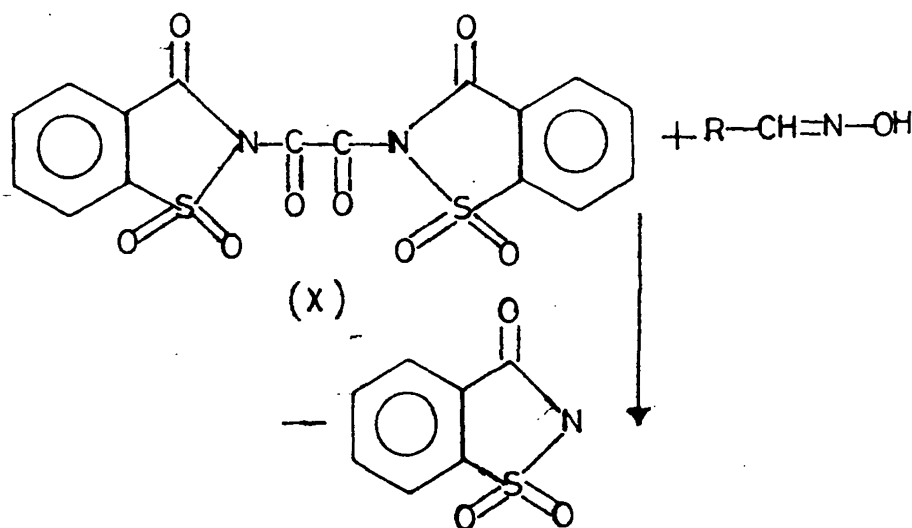
The dehydration of aldoximes (VIII) represents one of the preparative method for nitriles from corresponding aldehydes. Large number of dehydrating agents are employed to accomplish the dehydration of aldoximes¹⁵⁰ e.g, acetic anhydride, phosphorous

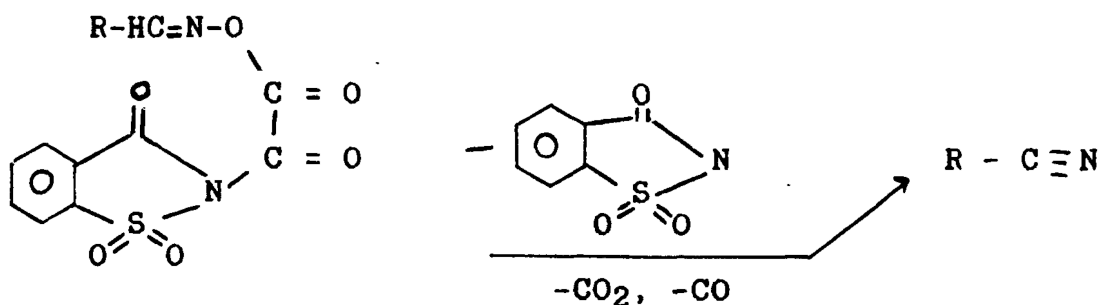
halides, phosphoric oxides, thionyl chloride, acetyl chloride, etc. In all these cases, the dehydrating agents forms a reactive complex (IX) which renders the aldoximes to lose a water molecule easily.



Recently, new dehydrating agents have been introduced e.g., dicyclohexyl carbodiimides¹⁴³, carbonyl biimidazole¹⁴⁴, and phosgene immonium chlorides¹⁴⁵.

Very recently, Kitagawa T. *et. al*¹⁵¹ described new dehydrating agent, 2,2' - oxalyldi (o-sulfobenzimide) (ODS) (X) for convenient one-pot synthesis of nitriles from aldoximes. The possible proposed mechanism was as follows:



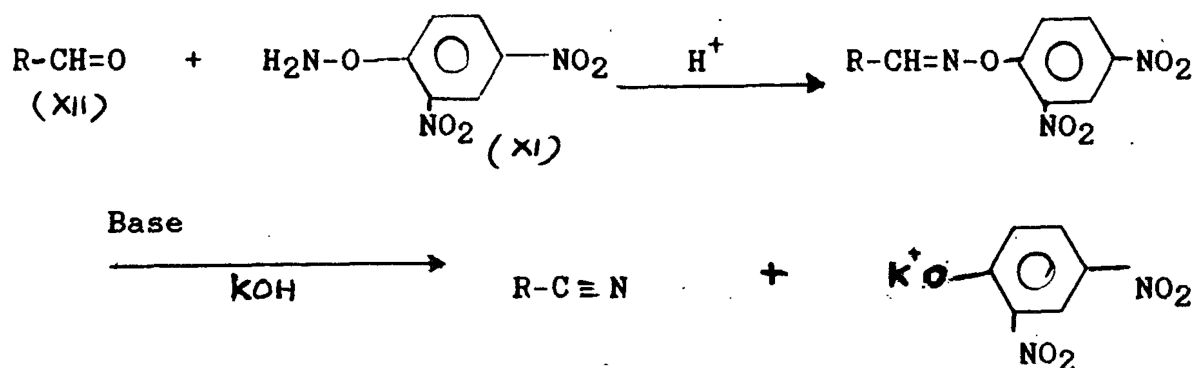


These reagents are highly reactive and involves very clean reaction at room temperature or cold temperature.

Methods B and C : (1.2 = Elimination of o - substituted aldoximes) :

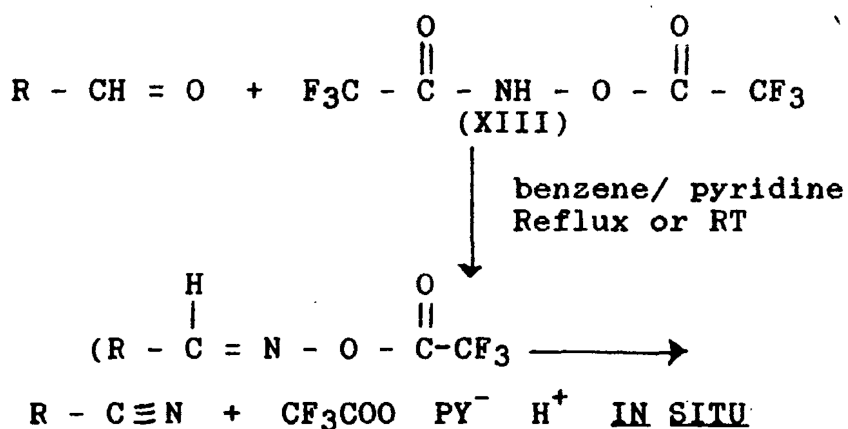
(B) This is the method recently developed by Miller *et. al*¹⁴⁷ for accomplishing the conversion of aldehydes to nitriles. This method differs from other routine methods in the fact that the experimentalist need not isolate and purify the intermediate oximes or related aldehyde derivatives, although he may do so, if he wishes. This method, therefore, saves one step in the aldehyde to nitrile conversion.

The development of efficient amino protecting groups facilitated the synthesis of a variety of sensitive compounds, including o-substituted hydroxyl amines¹⁵². Although a number of these are highly unstable¹⁵³, others have significant synthetic utility. Their electrophilic character has been exploited in their increasing use as aminating agents^{154,156}. Their nucleophilicity has been demonstrated by their reaction with ketones to form substituted oximes. Thus, 2,4 - dinitrophenyl hydroxyl amine (XI) can be reacted with aromatic or alkyl aldehydes (XII) to form corresponding o-substituted aldoximes.



Nitriles can be prepared from these o-substituted aldoximes by 1,2 - elimination reaction using excess base [KOH or $\text{N}(\text{C}_2\text{H}_5)_3$] as shown above. The development of a deep yellow to red colour of the 2,4 - dinitrophenolate ion indicates the extent of completion of the reaction.

(C) This method is a one-step synthesis involving the use of O-N-bis (trifluoroacetyl)hydroxyl amine (XIII) as one of the reagent as follows :



The reaction conditions are very mild and directly affords nitrile, eliminating the intermediate step¹⁵⁷. The yields are in the range of 70-90 %.

The reagent could be obtained by reacting trifluoroacetic anhydride with hydroxylamine hydrochloride in suitable solvents. The intermediate aldoxime is so unstable that it could not be isolated and instantly decomposed to furnish nitrile; thus, eliminating the intermediate step.

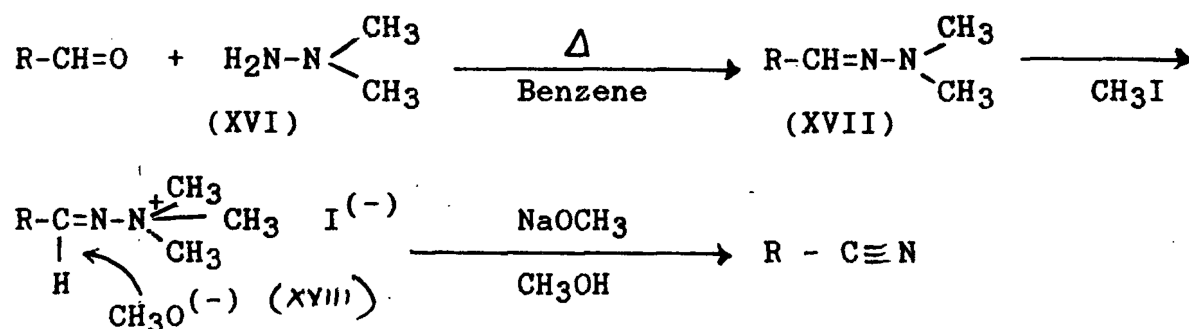
Methods D and E : 1.2 - Elimination of $R-CH=N-N^+(CH_3)_3^-$ and $R-CH=N-Tosyl$ by base :

While working with reactions of 2,2-dimethyl-1,2 dihydrophthalazinium iodide (XIV), Smith *et. al*¹⁴⁸ observed that the quaternary salts were decomposed with aqueous sodium hydroxide and isolated N,N-dimethylamino o-toluenitrile (XV). This interesting transformation could be explained as follows:



It seems that the quaternary salts (XIV) must be undergoing β -elimination reaction due to the abstraction of β -hydrogen atom which is highly acidic because of the cyclic hydrazimine character by the base. Therefore, this observation was further exploited to synthesize number of nitriles using β -eliminating reaction of N,N-dimethyl hydrazonium salts of substituted aryl aldehydes. Thus, it was not established that aryl aldehydes could be reacted with N,N-dimethyl hydrazine (XVI)

to obtain corresponding hydrazones (XVII) which instantly undergo quaternization with methyl iodide to give required hydrazonium quaternary salts (XVIII). These, on treatment with methanolic sodium methoxide, give nitriles as shown below in the range of 70-90 % yields.



The rate of reaction of base hydrolysis depends upon the extent of acidic character of α -hydrogen atom. The versatility coupled with the simplicity of the experimental procedure, should establish this method as one, having considerable utility.

Among the nitrogen containing derivatives of aldehydes which have been utilised in preparing nitriles, the oxime derivatives were the most successfully used in our present work to prepare substituted phenyl nitriles.

All the substituted phenyl nitriles were obtained from their corresponding substituted aldehydes by first converting them to aldoximes, followed by dehydration to get nitriles.

The oximes were synthesized by condensing corresponding aldehydes at reflux temperature with a solution of hydroxylamine hydrochloride in ethanol, in presence of aqueous solution of sodium carbonate. In some cases, where oximes do not precipitate out, the reaction mixture has to be saturated with gaseous carbon dioxide and cooled to get the oximes in very good yields. These

oximes give respective nitriles in the range of 55-90 % yields after dehydration with 94-96 % acetic anhydride. 158-161

The simple benzonitrile¹⁶² was prepared in 61 % yield by converting aniline (0.32 moles) to its diazonium salt, followed by reaction with potassium cuprous cyanide solution as per Sandmayer's reaction conditions.



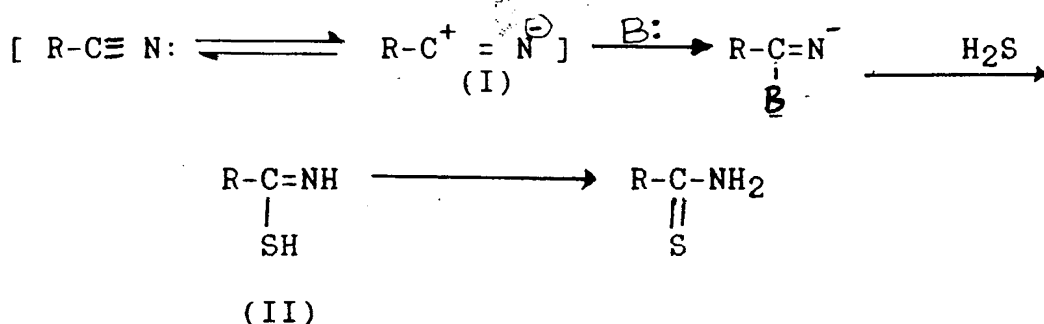
PART - IV

SECTION - A

**(b) CHEMISTRY
OF
THIOAMIDES**

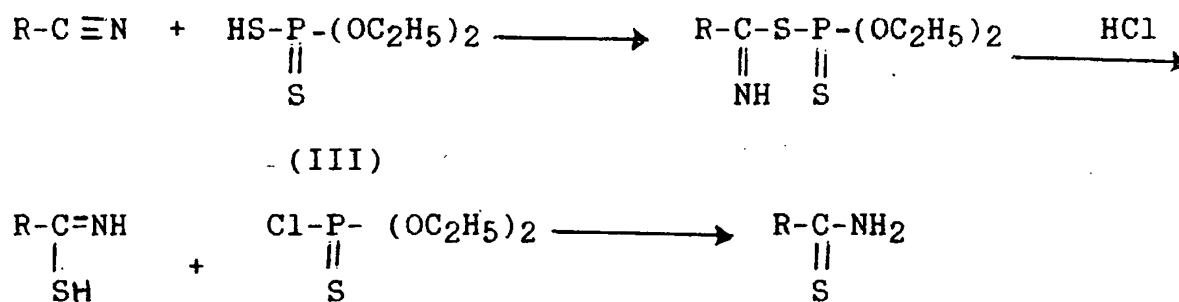
REACTION OF NITRILES WITH H₂S GAS AND THIOLS :

The syntheses of thiocarboxamides (II) of nitriles is known. The reaction requires high hydrogen sulphide concentration. It is catalysed by bases and generally favoured by water elimination. Water soluble sulphides or polysulphides can be used instead of hydrogen sulphide. The base catalysed addition of hydrogen sulphide to nitrile (I) could be as :



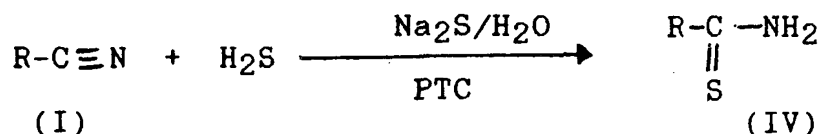
Suitable catalysts includes aliphatic amines, pyridine, alkoxides and KSH.¹⁶³ Fairfull *et al* ¹⁶⁴ got very good yields by addition of hydrogen sulphide to aromatic nitriles in presence of pyridine and triethylamine.

Good yields are obtained by addition of O,O-diethyl phosphoro dithioic acid (III) (ethanol + P₂S₅) to nitriles.¹⁶⁵ The SP bond is cleaved by HCl.



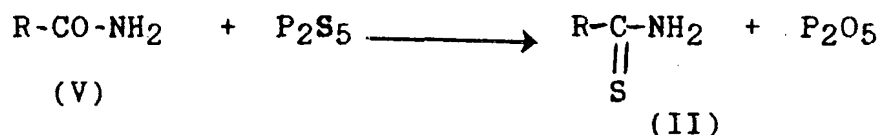
The general procedure of thioamides (IV) synthesis consisting of the base catalysed ion of nitriles (I) with hydrogen sulphide in polar organic solvents has been modified by Cassar *et al*.¹⁶⁶

An organic solution of Na_2S is employed as a phase transfer catalyst for the addition of H_2S into the nitrile function. Thus the system which consists of three phases viz aqueous, organic and H_2S gas provides aromatic thioamides in high yields.



SULPHURISATION OF AMIDES :

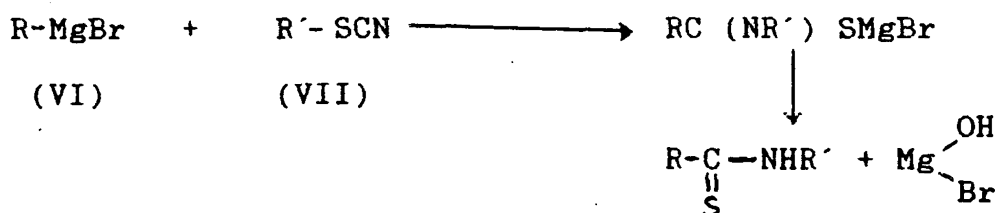
The general method employed for the preparation of thio-carboxamides (II) involves the replacement of O in carboxamide (V).



The most useful reagent for this replacement is P_2S_5 . It was also found that presence of K-thiophosphate along with P_2S_5 enhances the yield.

ADDITION OF NUCLEOPHILE TO ISOTHIOCYANATE :-

Isothiocyanate (VII) react with Grignard reagent (VI) and substituted hydrocarbons under mild conditions leads to thiocarboxamide.¹⁶⁷



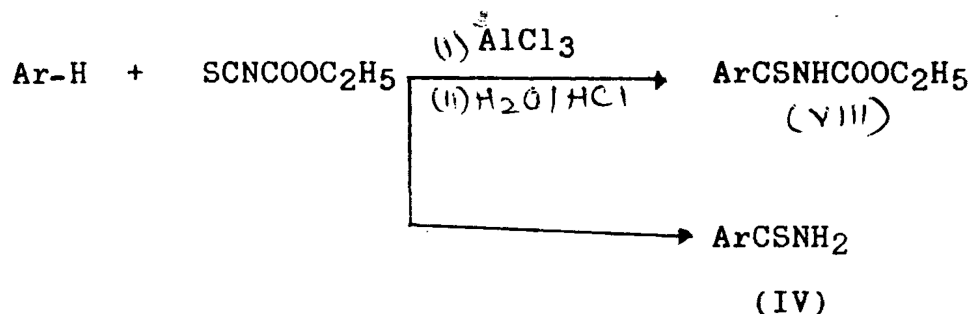
Sachs and Loevy used this method first and then Warall used this to prepare a large number of N-substituted thiovaleramides.

ONE STEP SYNTHESIS :

Friedal Craft's thioacylation with ethoxy carbonyl isothiocyanate :

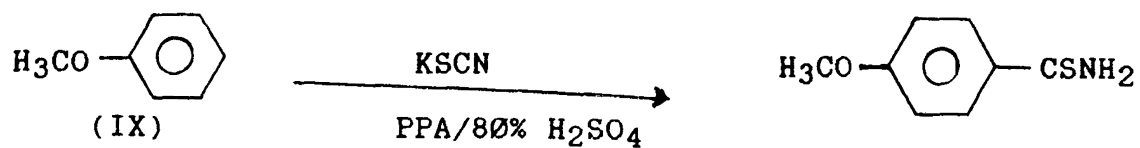
It was found that ethoxy carbonyl isothiocyanate reacts with various aromatic compounds in presence AlCl_3 .¹⁶⁸ The yields of N-ethoxy carbonyl thioamides or thioamides depend on the following conditions :

- (i) For thioamides to be the major product molar ratio of AlCl_3 to isothiocyanate should be 2:1.
- (ii) While low reaction temperature favours formation of N-ethoxy carbonyl thioamide (VIII), larger the period of time favours the synthesis of thioamide (IV).



Thus the above methods allow preparation of certain thioamide in one step from aromatic compounds. This therefore subjects it to the usual limitations of the Friedal Craft's reaction. But due to its simplicity and satisfactory yields it compares favourably with other methods of preparation¹⁶⁹.

Thioamides can also be prepared by heating anisole or veratrole (IX) at 60° in presence of polyphosphoric acid (PPA) or 80 % sulphuric acid with KSCN.¹⁷⁰



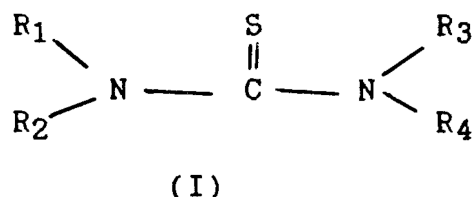
In case of PPA, thioamides were obtained in 50 % yield while it increases by 5 % if 80 % sulphuric acid is used.

PART - IV

SECTION - A

**(c) CHEMISTRY
OF
THIOUREAS**

Thioureas are generally represented by the structure (I)

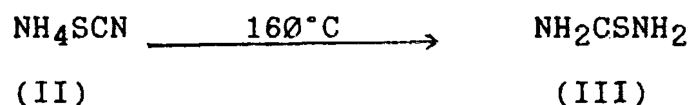


The chemistry essentially deals with the reaction promoted by the nucleophile reactivity of these compounds, the centre of the reaction being located either at S-atom or N-atom. Formation of the thiazole ring with a haloacetyl group is of pharmaceutical importance.

GENERAL METHODS OF SYNTHESIS :-

(a) Action of alkali thiocyanate on amine hydrochlorides :

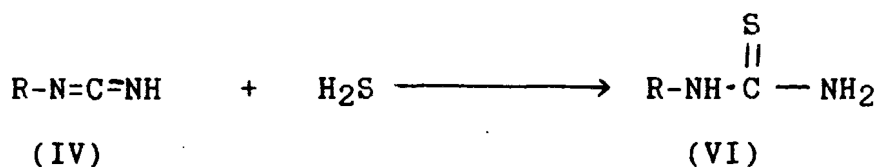
When ammonium thiocyanate (II) is heated at 160°C for several hours it rearranges to give thioureas (III).

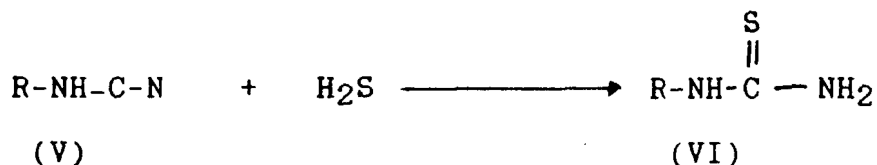


A mixture of primary amine and ammonium thiocyanate is heated in presence of hydrochloric acid in an inert solvent or in an aqueous medium to give substituted thioureas.

(b) Thiohydrolysis of carbodi-imides and cyanamides :

On passing hydrogen sulphide gas to substituted carbodi-imides (IV), ^{and} cyanamides (V), corresponding thioureas (VI) are formed.

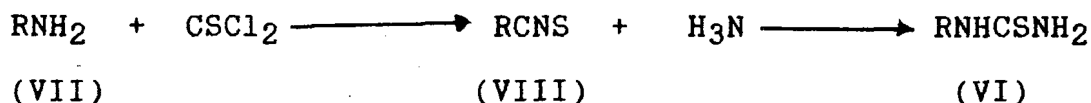




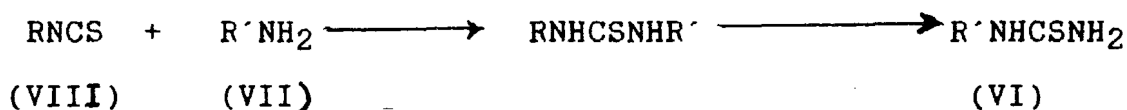
The reaction is mostly dependent on the ability of carbodiimides and cyanamides to add to H_2S .

(c) Action of isothiocyanate on ammonia or primary amine :

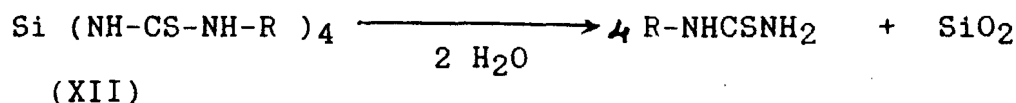
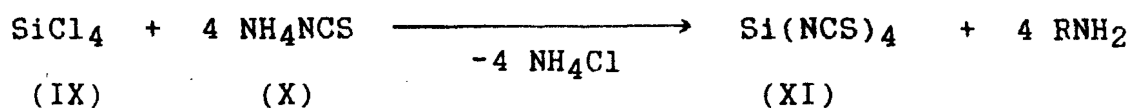
(i) Primary amines (VII) react with thiophosgene to give isothiocyanates (VIII) which further reacts with ammonia to give corresponding thioureas.



(ii) Isothiocyanates (VIII) reacts with primary amines (VII) to give unsymmetric 1,3 disubstituted thioureas. Substituted isothiocyanates are chosen such that after disubstituted product is formed the substituted group can be easily removed by hydrolysis or heterolysis to obtain monosubstituted thioureas of corresponding primary amine.

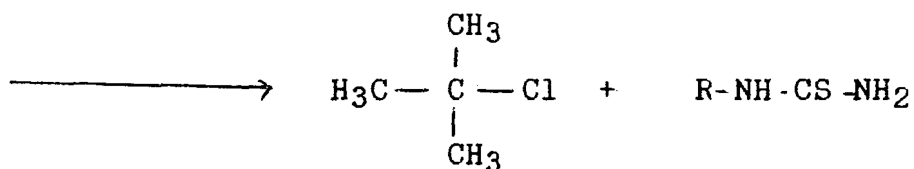
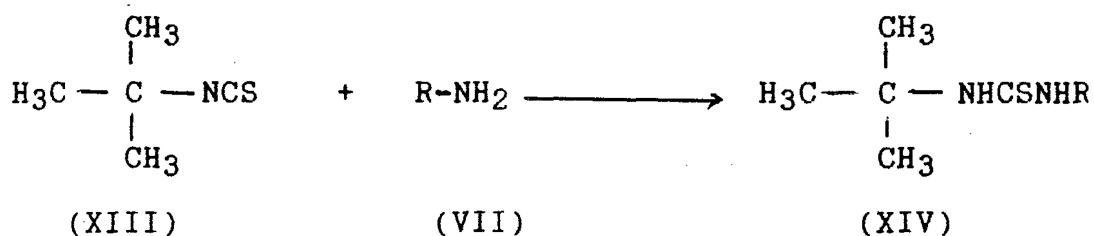


Neville et al ¹⁷¹ have reported a method using silicon tetrathiocyanate (XI) as a thiocarbonylating agent. It is prepared by

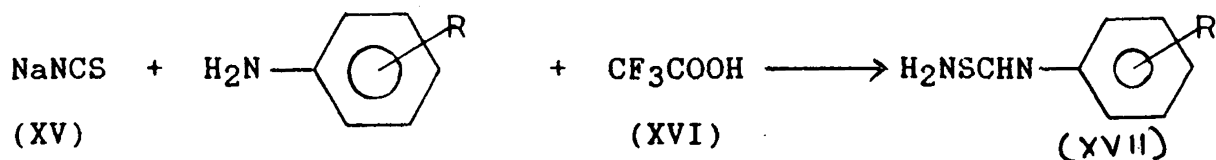


the action of ammonium thiocyanate (X) on silicon tetrachloride (XI) in benzene which on treatment with primary amine yields a silicon complex (XII) which on further hydrolysis give monosubstituted thioureas.

Vijaykumaran Nair ¹⁷² has reacted tertbutylisothiocyanate (XIII) with substituted aromatic, aliphatic and heterocyclic primary amines (VII) to give disubstituted unsymmetric thioureas (XIV) which on acid hydrolysis gives respective monosubstituted thioureas.



Loev *et al* ¹⁷³ have synthesized monosubstituted thioureas (XVII) by the the action of isothiocyante (XV) on appropriate aromatic amines in presence of trifluoroacetic acid (XVI) using benzene or toluene as a solvent.



Rasmussen *et al* have recently reported improved procedures for the preparation of cycloalkyl, arylalkyl and arylthioureas by the action of benzoyl isothiocyanate on anilines in acetone and debenzoylation of the resultant N-aryl, N-benzoyl thioureas with 5% aqueous NaOH.¹⁷⁴

PART - IV

SECTION - A

**(d) CHEMISTRY
OF
THIAZOLES**

The thiazole ring (I) was first described by Hantzsch and Weber in 1887, as "the pyridine of the thiophene series".



(I)

The high reactivity of the thiazole molecule is due to the groups attached to the carbon atom placed between sulphur and nitrogen. They proposed the prefix *meso* for this position in the normal azole series.

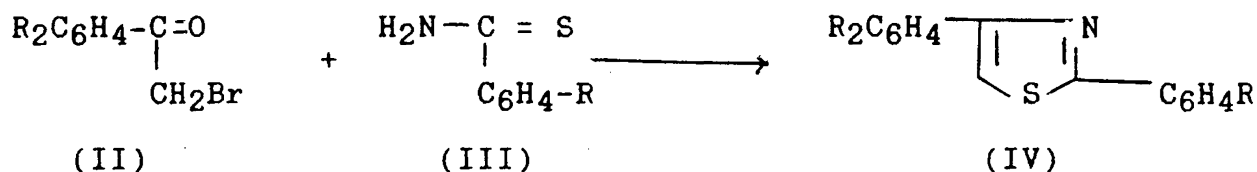
Although unsubstituted thiazole is not found in nature, naturally occurring thiazoles are numerous. Their origin has often been related to the cyclisation of a peptide chain at cysteine residue with formation of a thiazoline ring.¹⁷⁵

Several antibiotics such as Althomycin¹⁷⁶ and Micrococcin¹⁷⁷ contains thiazole rings as do many metabolites of living organisms. Numerous natural aromas such as tomato¹⁷⁸ contains thiazole derivatives. Thiazoles have been separated from bases of some petroleums. Many thiazole derivatives possess biological activity and numerous medicaments contain a thiazole ring in their structure.

GENERAL METHODS OF SYNTHESSES :

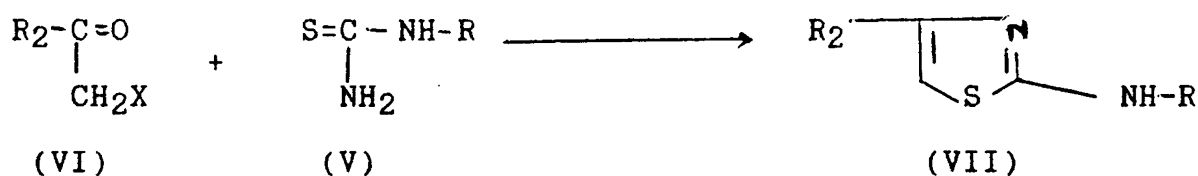
(1) 2,4 DIARYL THIAZOLES (IV) :

These were prepared in 1950 by Erylenmeyer *et al*¹⁷⁹ from thiobenzamide (III) and -w bromo acetophenones (II) in alcoholic solutions with yields of the order of 50-80%.



(2) 2-MONOSUBSTITUTED AMINO THIAZOLES (VII):

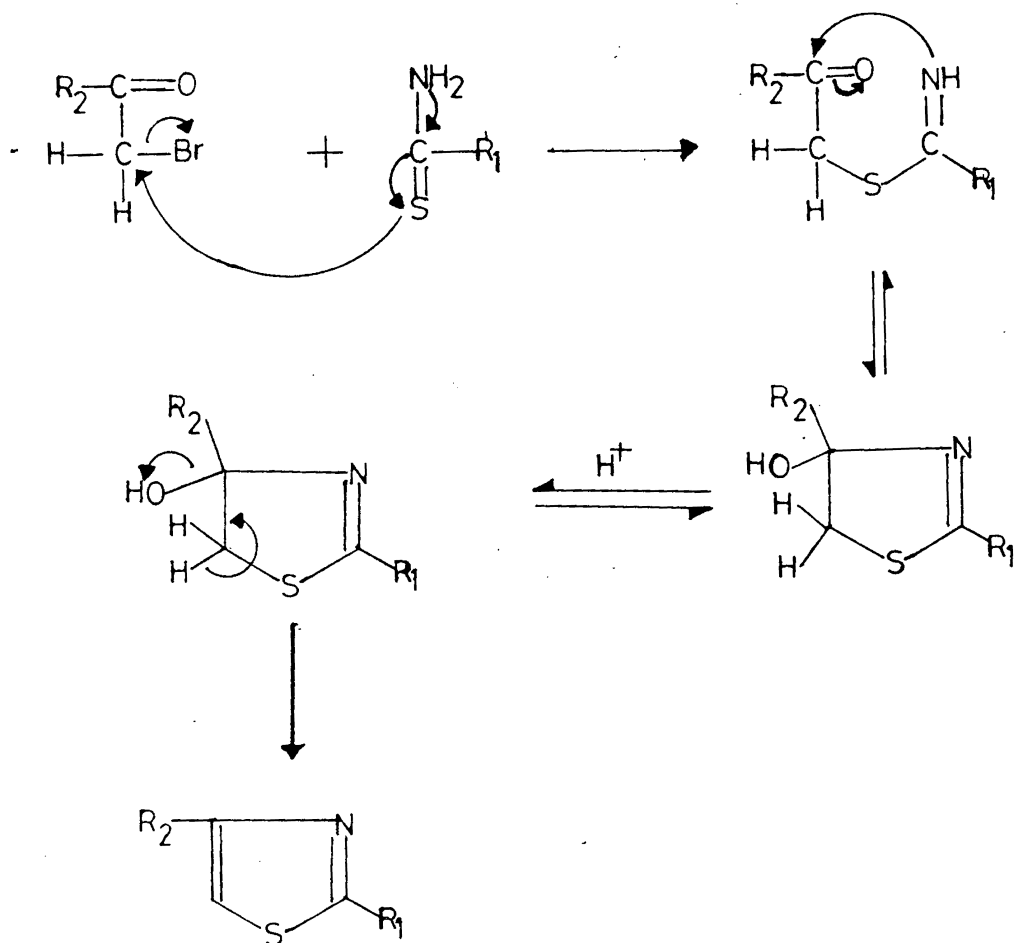
The cyclisation of N-monosubstituted thioureas (V) with halocarbonyl compounds give (VI) 2-monosubstituted amino thiazoles.^{180,181}



Mechanism of syntheses (Hantzsch's synthesis) :

The first step in the reaction is the formation of an acyclic intermediate by nucleophilic attack of the S-atom by one of its lone pair of electrons on the halogen carrying C-atom to form a C-S-C bond.

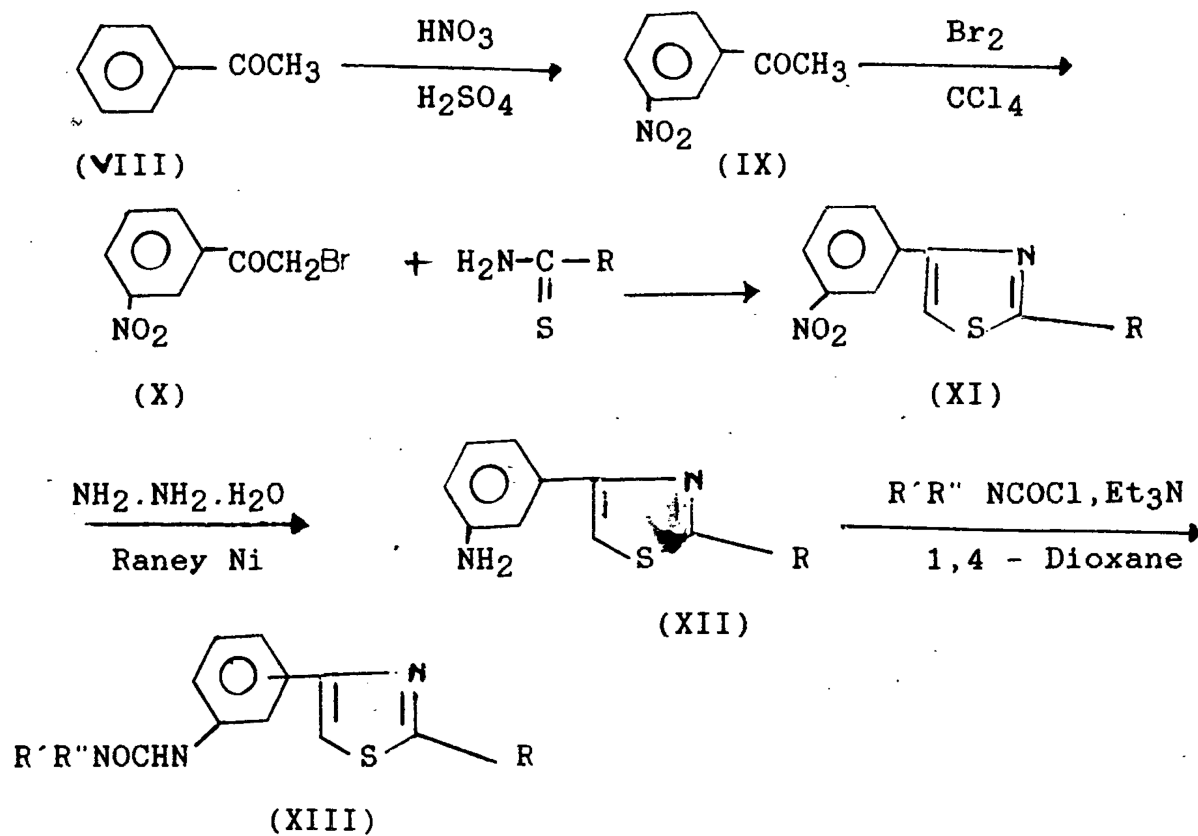
In the second step, the lone pair of electrons of N- atoms attacks the carbon carrying the carbonyl function, giving rise to a new cyclic intermediate. This intermediate upon treatment by acid lead to the thiazole molecule^{182,183}.

PROBABLE MECHANISM

In the present investigation various thiazoles have been prepared by employing the Hantzsch synthesis. Acetophenone (VIII) was treated with nitrating mixture at 0-5°C to give the *m*-nitroacetophenone (IX) which was then brominated in presence of AIBN as a catalyst using CCl₄ as a solvent at 50-55°C. The haloketone (X) thus obtained was treated with substituted thioureas/thioamides to give the 2-substituted anilino/phenyl thiazoles (XI). The nitro group of the thiazole moiety was reduced in presence of Raney Nickel and hydrazine hydrate. The amino derivatives (XII) thus obtained was condensed with N,N-dialkyl carbomoyl chlorides in presence of triethylamine using 1,4 dioxane as a solvent to get the desired compounds (XIII).

The schematic diagram leading to the formation of the title compounds summarising the various reactions discussed so far is given in the scheme III.

Scheme III



$\text{R}' = \text{R}'' = \text{CH}_3, \text{C}_2\text{H}_5$

$\text{R} =$ Substituted phenyl, substituted anilino etc.

PART - IV

SECTION - B

EXPERIMENTAL

This section deals with the synthesis of desired derivatives of 2-substituted phenyl/anilino-4[m-(N,N-dialkyl-urido)-phenyl] thiazoles which involves following steps:

- (1) Preparation of substituted nitriles
- (2) Preparation of substituted thioamides
- (3) Preparation of substituted thioureas
- (4) Preparation of m-nitro acetophenone
- (5) Preparation of w-bromo m-nitro acetophenone
- (6) Preparation 2-substituted phenyl/anilino 4-m-nitro phenyl thiazoles
- (7) Preparation of 2-sustituted phenyl/anilino 4-m-amino phenyl thiazoles
- (8) Preparation of 2-(substituted aryl/anilino)-4[m-(N,N-dialkyl-urido)-phenyl] thiazoles

3.4 Dimethoxybenzaldehyde (Veratraldehyde)

A one litre three necked round bottomed flask equipped with two dropping funnels, and condenser and mercury sealed mechanical stirrer, was mounted on a steam bath. In this, was placed boiling water (45 ml) and 3-methoxy-4-hydroxy benzaldehyde (Vanillin) (18.2 g; 0.12 mole). To a well stirred previously heated turbid mixture of this vanillin, was added a boiling solution (30 ml) of sodium hydroxide (15 g in 75 ml water; 0.375 mole) and dimethyl sulphate (18.9 g; 0.15 mole) just rapidly enough to maintain the gentle ebullition which started after adding 2-3 ml of dimethyl sulphate. After complete addition, the mixture was heated for 45 minutes. At this stage, the reaction mixture was acidic. Then sodium hydroxide (6 ml) was added to make it alkaline (turbid solution when acidic and clear when alkaline). Alternate additions of dimethyl sulphate and alkali were repeated with same quantities of each as earlier two times until the addition of dimethyl sulphate (34.5 g; 26.6 ml; 0.27 mole) was completed. After the last addition, the reaction mixture was made alkaline by adding sodium hydroxide solution (15 ml) and stirred for one hour. The reaction mixture was extracted with ether, the ether layer was washed with water, dried and evaporated. The veratraldehyde was collected as pure oily product after subjecting it to fractional distillation under reduced pressure.

Yield : 16.9 g (84.5 %); m.p. 43°C; b.p. 153-54 °C/8 mm. (Lit. m.p. 43-44°C.¹⁸⁴

Veratronitrile (3,4- Dimethoxy benzonitrile) :

A 500 ml three necked round bottomed flask, provided with a mercury sealed stirrer, a dropping funnel and a condenser, was mounted on a steam bath. In this was placed veratraldehyde (8.3 g; 0.05 mole) dissolved in 95 % warm ethanol (30 ml) and was added a warm solution of hydroxylamine hydrochloride (4.2 g; 0.06 mole) in water (5 ml). After stirring for five minutes, a solution of sodium hydroxide (3 g; 0.075 mole) in water (40 ml) was added. The mixture was stirred for additional ten minutes and kept at room temperature for three hours. Then crushed ice (25 g) was added in it. The separated aldoxime was filtered, washed with cold water and dried.

Yield : 8 g (88 %)

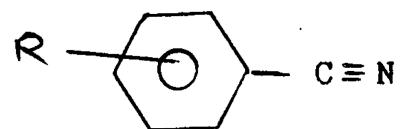
The Veratraldoxime (8 g; 0.04 mole) was heated on a burner with acetic anhydride (100 g; 94 %) in 250 ml round bottomed flask equipped with a condenser. The mixture was refluxed for 1 hr, cooled to room temperature, it was poured on crushed ice with stirring. The separated compound was filtered, washed with cold water and crystallised from ethanol.

Yield : 6 g (78.5 %); m.p. 65 °C.

(Lit. m.p. 66-67°C)¹⁸⁴

TABLE 9

SUBSTITUTED NITRILES



SR.NO.	R	m.p. °C		YIELD %	REF
		OBSERVED	REPORTED		
1.	4 - Cl	91	93	88	185
2.	4 - OCH ₃	55-57	57	70	184
3.	4 - CH ₃	38	42	71	186
4.	3,4 - OCH ₃	65	66-67	78	184

PREPARATION OF THIOBENZAMIDE

In a 100 ml conical flask was placed benzonitrile (10.3 gm, 0.1 mole), pyridine (20 ml) and triethylamine (10.1gm, 0.1 mole). Dry hydrogen sulphide gas was passed to it for six hours at room temperature in a steady flow. It was then poured onto water with stirring. The solid separated was filtered, washed with water and dried. It was recrystallised from benzene.

Yield :- 8.0 gms (58 %)

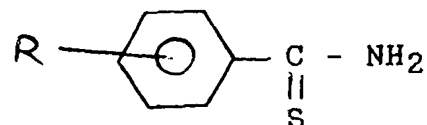
m.p. :- 115-6 °C

Lit. m.p.¹⁶⁴ :- 116 °C

Other thioamides were prepared from the corresponding substituted nitriles by using the same method.

TABLE 10

THIOAMIDES



SR.NO.	R	m.p. °C		YIELD %		REF
		OBSERVED	REPORTED	OBSERVED	REPORTED	
1.	Phenyl	115-116	116	58	58.4	164
2.	4-Chlorophenyl	129-131	129-130	50	-	164
3.	4-Methoxyphenyl	148	149	70	-	164
4.	4-Methylphenyl	166	167	78	-	164
5.	3,4- Dimethoxyphenyl	183	185	68		164

PREPARATION OF (p-CHLOROPHENYL) THIOUREA :-

A mixture of ammonium thiocyanate (16.72 gm, 0.22 mole) and freshly distilled acetone (200 ml) was placed in 500 ml three necked round bottomed flask, equipped with a condenser, mechanical stirrer and a dropping funnel. To this freshly distilled benzoyl chloride (28 gms, 0.1 mole) was added dropwise with stirring. After the addition is over the mixture was refluxed for 5 minutes. A solution of p-chloroaniline (21 gms, 0.2 mole) in dry acetone (50 ml) was added such that the solution refluxed gently. The refluxing was continued further for one hour. It was cooled and poured into 1 liter of water. The resulting precipitate was filtered and dried.

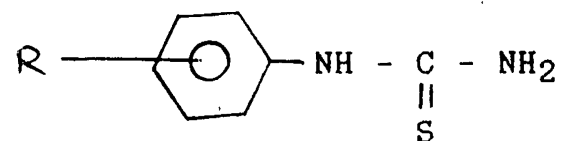
Yield : 21 gms (56 %)

m.p. : 176-8 °C

Lit. m.p.¹⁷⁴ : 176-8°C)

Other thioureas were prepared from the corresponding substituted benzoyl chlorides by the same method.

TABLE 11

THIOUREAS

SR.NO.	R	m.p. °C		YIELD %		REF
		OBSERVED	REPORTED	OBSERVED	REPORTED	
1.	H	154-156	154-155	48	52	174
2.	4-Cl	176-178	176-178	56	-	174
3.	4-CH ₃	186	182	54	-	173
4.	3,4-DiCl ₂	206-207	199-203	42	-	174
5.	4-OCH ₃	213-214	212-214	45	-	173

PREPARATION OF *m*-NITRO ACETOPHENONE :

In a one litre three necked round bottomed flask equipped with a mechanical stirrer, thermometer and a dropping funnel was added freshly distilled acetophenone 60 gms (58 ml, 0.5 mole) at 10-15°C. The mixture was allowed to cool to -10 °C. Nitrating mixture containing 60 ml fuming nitric acid (d:1.52) and 135 ml concentrated sulphuric acid was added dropwise with stirring to this at the same temperature within 2 hours. After the addition is over the mixture was stirred at -5°C for about one hour. The reaction mixture was poured onto crushed ice whereby crude *m*-nitroacetophenone at once precipitated. It was allowed to stand for one hour and then filtered, washed with water until free from acids, dried. It was then recrystallised from aqueous acetic acid.

Yield : 49 gms (60 %)

m.p. : 75-77°C

(Lit. m.p.¹⁸⁷ : 76-78°C)

Preparation of *p*-bromo *m*-nitroacetophenone :

In a 250 ml three necked round bottomed flask equipped with a mechanical stirrer, dropping funnel and a reflux condenser was dissolved *m*-nitroacetophenone (40 gms, 0.24mole) in 200 ml of carbon tetrachloride by warming it to 50-60 °C. To this bromine (48 gms, 16ml, 0.3 mole) was added dropwise at the same temperature within one hour. It was then cooled to room temperature. The solid separated was stirred with a solution of sodium bicarbonate (1 gm) and sodium sulphate (1 gm) for half an hour. The solid was filtered, washed with water and dried. It was recrystallised from carbontetrachloride.

Yield : 48 gms (81 %)

m.p. : 95-6 °C

(Lit. m.p.¹⁸⁸ : 94-96 °C)

PREPARATION OF 2-PHENYL-4-(*m*-NITROPHENYL) THIAZOLE :

A mixture of *w*-bromo, *m*-nitroacetophenone (0.732 gms, 0.003 mole) and thiobenzamide (0.411 gms, 0.003 mole) in dry ethanol was reflux in a 100 ml round bottomed flask equipped with a refluxed condenser for six hours. The excess of solvent was removed. The solid separated was neutralised by aqueous ammonia in cold condition. The solid separated was filtered, washed with cold water until free from ammonia and dried. It was recrystallised from ethanol.

Yield : 0.465 gms (55 %)

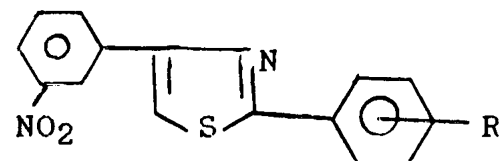
m.p. : 122-3 °C

ELEMENTAL ANALYSIS

	Required	Found
% C	63.82	63.45
% H	3.55	3.15
% N	9.93	9.63

TABLE 12

2-SUBSTITUTED ARYL -4-[m-(NITROPHENYL)] THIAZOLES



SR. NO.	R	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
						C	H	N	C	H	N
1	H	C ₁₅ H ₁₀ N ₂ O ₂ S	282	122-3	55	63.82	3.55	9.93	63.45	3.15	9.63
2	4-Cl	C ₁₅ H ₉ ClN ₂ O ₂ S	316.5	188-9	47	56.87	2.84	8.85	56.24	3.35	8.37
3	4-OCH ₃	C ₁₆ H ₁₂ N ₂ O ₃ S	312	168-9	58	61.54	3.85	8.78	61.65	3.75	9.04
4	4-CH ₃	C ₁₆ H ₁₂ N ₂ O ₂ S	296	146-7	52	64.86	3.17	9.45	64.77	3.88	9.53
5	4-N(CH ₃) ₂	C ₁₇ H ₁₅ N ₃ O ₂ S	325	102-3	49	62.77	4.62	12.92	62.22	4.13	12.42
6	3,4-OCH ₃	C ₁₇ H ₁₄ N ₂ O ₄ S	342	152-3	48	59.65	4.09	8.19	59.83	4.37	7.98
7	2,4-OCH ₃	C ₁₇ H ₁₄ N ₂ O ₄ S	342	146-8	45	59.65	4.09	8.19	60.19	4.22	8.24

PREPARATION OF 2-PHENYL -4-(*m*-AMINOPHENYL) THIAZOLE :

To a solution of 2-phenyl-4-(*m*-nitrophenyl) thiazole (0.451 gms, 0.0016 mole) in 25 ml dry ethanol in 100 ml round bottomed flask equipped with a reflux condenser was added about 0.4 gms of Raney Nickel and 10 ml of hydrazine hydrate slowly. The reaction mixture was refluxed gently for six hours. It was filtered hot. The excess of solvent was removed. The residue obtained was dissolved in chloroform and washed with water to remove excess of hydrazine hydrate. The chloroform extract was dried over sodium sulphate. The chloroform was removed under vacuum to get the desired compound.

Yield : 0.365 gms (91 %)

oil obtained
TLC : Single spot
(Chloroform) /

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PREPARATION OF 2-(PHENYL)-4-[*m*-(N,N-DIETHYL-CARBOXYMETHYL)AMINO]PHENYL] THIAZOLE :**PHENYL] THIAZOLE :**

In a 100 ml three necked round bottomed flask equipped with a reflux condenser, mechanical stirrer and a dropping funnel was placed a solution of 2-phenyl-4-(*m*-aminophenyl) thiazole (0.151 gms, 0.0006 mole) in 10 ml of dry 1,4 dioxane. To this triethylamine (0.06 gm, 0.0006 mole) was added. The mixture was stirred at 50-60 °C for about half an hour. N,N-diethyl carbamoyl chloride (0.088 gm, 0.00065 mole) in 10 ml of 1,4 dioxane was added dropwise to the above mixture at the same temperature. The reaction mixture was stirred for further two hours at the same temperature. It was then kept overnight at room temperature. It was poured on to crushed ice. The solid separated was filtered, washed with water and dried. It was purified by column chromatography using 60-120 mesh silica gel and chloroform as an eluant.

Yield : 0.113 gms (54 %)

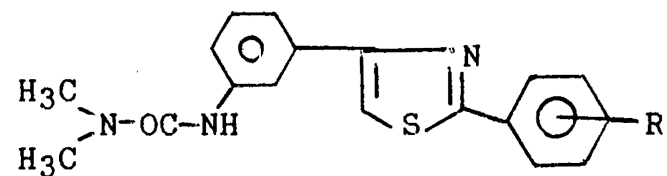
m.p.: 117-8°C

ELEMENTAL ANALYSIS

	Required	Found
% C	68.37	68.45
% H	5.98	5.55
% N	11.96	11.63

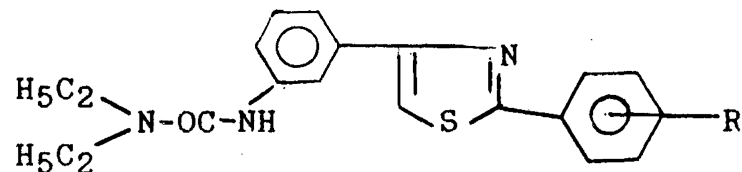
All the compounds listed in the table no. 13 were prepared by the same method and their physical data characterised.

TABLE 13

2-SUBSTITUTED ARYL -4-[m-(N,N-DIMETHYLUREIDO PHENYL)] THIAZOLES

SR. NO.	R	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
						C	H	N	C	H	N
1	H	C ₁₈ H ₁₇ N ₃ OS	323	122-3	55	66.87	5.26	13.00	66.45	5.55	13.23
2	4-Cl	C ₁₈ H ₁₆ ClN ₃ OS	357.5	188-9	47	60.41	4.47	11.74	60.94	3.05	11.27
3	4-OCH ₃	C ₁₉ H ₁₉ N ₃ O ₂ S	353	138	58	64.58	5.38	11.8	64.65	5.75	12.04
4	4-CH ₃	C ₁₉ H ₁₉ N ₃ OS	337	146-7	52	67.65	5.63	12.46	67.77	5.88	12.83
5	4-N(CH ₃) ₂	C ₂₀ H ₂₂ N ₄ OS	366	102-3	49	65.57	6.01	15.30	66.12	6.53	14.82
6	3,4-OCH ₃	C ₂₀ H ₂₁ N ₃ O ₃ S	383	123-5	48	62.66	5.48	10.97	62.83	5.57	10.78
7	2,4-OCH ₃	C ₂₀ H ₂₁ N ₃ O ₃ S	383	128-9	45	62.66	5.48	10.97	62.79	5.22	11.04

TABLE 14

2-SUBSTITUTED ARYL -4-[m-(N,N DIETHYLUREIDO)-PHENYL] THIAZOLES

SR. NO.	R	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
						REQUIRED			FOUND		
						C	H	N	C	H	N
1	H	C ₂₀ H ₂₁ N ₃ OS	351	117-8	54	68.37	5.98	11.96	68.45	5.55	11.63
2	4-Cl	C ₂₀ H ₂₀ ClN ₃ OS	385.5	178-9	57	62.25	5.18	10.89	62.84	5.65	10.37
3	4-OCH ₃	C ₂₁ H ₂₃ N ₃ O ₂ S	381	158	48	66.14	6.03	11.02	66.35	5.75	11.04
4	4-CH ₃	C ₂₁ H ₂₃ N ₃ OS	365	126-7	52	69.04	6.30	11.50	69.47	6.18	11.83
5	4-N(CH ₃) ₂	C ₂₂ H ₂₆ N ₄ OS	394	112-3	59	67.00	6.59	14.21	66.42	6.13	14.62
6	3,4-OCH ₃	C ₂₂ H ₂₅ N ₃ O ₃ S	411	143-5	46	64.23	6.08	10.22	63.83	6.37	9.98
7	2,4-OCH ₃	C ₂₂ H ₂₅ N ₃ O ₃ S	411	138-9	45	64.23	6.08	10.22	64.69	6.22	10.04

PREPARATION OF (*p*-CHLOROANILINO)-4-(*m*-NITROPHENYL) THIAZOLE :

A mixture of *w*-bromo,*m*-nitroacetophenone (0.732 gm, 0.003 mole) and *p*-chlorophenyl thiourea (0.559 gm, 0.003 mole) was dissolved in dry ethanol (25 ml) and was refluxed for six hours. The solid separated on evaporation of excess of solvent was neutralised by using aqueous ammonia in cold condition. The free thiazole thus obtained was filtered, washed with water till free from ammonia and dried. It was then purified from ethanol.

Yield : 0.537 gm, (54 %)

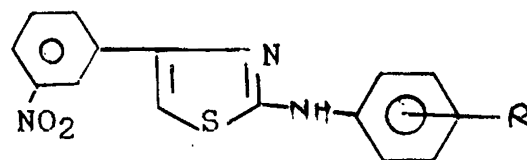
m.p. : 175-6°C

ELEMENTAL ANALYSIS

	Required	Found
% C	54.30	54.54
% H	3.02	3.19
% N	12.67	12.37

All the compounds listed in the table no. 15 were prepared by the same method and their physical data characterised.

TABLE 15

2-SUBSTITUTED ANILINO -4-[m-(NITROPHENYL)] THIAZOLES

SR. NO.	R	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
						REQUIRED			FOUND		
						C	H	N	C	H	N
1	H	C ₁₅ H ₁₁ N ₃ O ₂ S	297	122-3	48	60.61	3.70	14.14	60.15	3.26	13.63
2	4-Cl	C ₁₅ H ₁₀ ClN ₃ O ₂ S	331.5	175-6	54	54.30	3.02	12.67	54.54	3.19	12.37
3	4-CH ₃	C ₁₆ H ₁₃ N ₃ O ₂ S	311	120-2	43	61.74	4.18	13.50	61.43	4.33	13.86
4	3,4-Cl ₂	C ₁₅ H ₉ Cl ₂ N ₃ O ₂ S	366	128	58	49.18	2.46	11.48	49.35	2.75	11.64
5	4-OCH ₃	C ₁₆ H ₁₃ N ₃ O ₃ S	327	99-102	42	58.72	3.98	12.84	58.57	4.18	12.63
6	4-OC ₂ H ₅	C ₁₇ H ₁₅ N ₃ O ₃ S	341	115-6	49	59.82	4.40	12.32	59.32	3.83	12.81
7	3-OC ₂ H ₅	C ₁₇ H ₁₅ N ₃ O ₃ S	341	143-5	46	59.82	4.40	12.32	60.13	4.57	12.58
8	3-OCH ₃	C ₁₆ H ₁₃ N ₃ O ₃ S	327	128-9	45	58.72	3.98	12.84	58.69	4.22	13.04
9	2-OCH ₃	C ₁₆ H ₁₃ N ₃ O ₃ S	327	122-3	43	58.72	3.98	12.84	58.89	3.62	12.94

PREPARATION OF 2-(p-CHLOROANILINO)-4-(m-AMINOPHENYL) THIAZOLE :

The solution of 2-chloranilino -4-(m-nitrophenyl)thiazole (0.596gm, 0.0018 mole) in 25 ml of dry alcohol was placed in 100 ml round bottomed flask equipped with a reflux condenser. To this about 0.4 gm of Raney Nickel and 10 ml of hydrazine hydrate was added slowly. The reaction mixture was refluxed gently for six hours. It was filtered hot and the excess of solvent was removed under vacuum. The residue obtained was dissolved in chloroform and washed with water to remove excess of hydrazine hydrate. The chloroform extract was dried over sodium sulphate and was then concentrated under vacuum to get the desired compound.

Yield : 0.532 gm (98 %)

m.p. : Oil obtained
TLC : Single spot
(Chloroform)

PREPARATION OF 2-(p-CHLOROANILINO)-4-(N,N-DIMETHYL-UREIDO)PHENYL] THIAZOLE :

In a 100 ml round bottomed flask equipped with a reflux condenser, mechanical stirrer and dropping funnel was placed a solution of 2-(p-chloroanilino)-4-(*m*-aminophenyl) thioazole (0.241 gm, 0.0008 mole) in 10 ml of dry 1,4 dioxane and triethylamine (0.08 gm, 0.0008 mole). The mixture was warmed at 50-60 °C for half an hour. To this N,N-dimethyl carbamoyl chloride (0.092 gm, 0.00085 mole) in 10 ml dry 1,4 dioxane was added dropwise at the same temperature in 15 minutes. The mixture was stirred at 50-60 °C for two hours and was kept overnight at room temperature. It was poured onto crushed ice. The solid separated was filtered, washed with water and dried. It was purified by column chromatography using 60-120 mesh silica gel and chloroform as an eluant.

Yield : 0.160 gm (54 %)

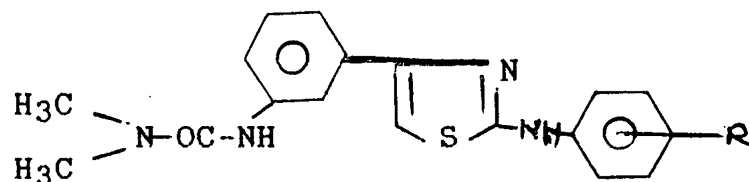
m.p.: 158-9°C

ELEMENTAL ANALYSIS

	Required	found
% C	57.98	57.54
% H	4.56	4.19
% N	15.03	15.37

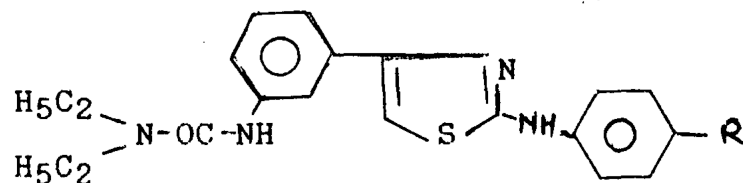
TABLE 16

2-SUBSTITUTED ANILINO -4-[m-(N,N-DIMETHYLREIDO)PHENYL] THIAZOLES



SR. NO.	R	MOLECULAR FORMULA	M. W.	m.p. °C	YIELD %	ELEMENTAL ANALYSIS					
						REQUIRED		N	FOUND		
						C	H		C	H	N
1	H	C ₁₈ H ₁₈ N ₄ OS	338	122-3	48	63.90	5.32	16.56	64.45	5.85	17.03
2	4-Cl	C ₁₈ H ₁₇ ClN ₄ OS	372.5	158-9	54	57.98	4.56	15.03	57.54	4.19	15.37
3	4-CH ₃	C ₁₉ H ₂₀ N ₄ OS	352	145-7	43	64.77	5.68	15.90	64.43	5.73	15.86
4	3,4-Cl ₂	C ₁₈ H ₁₆ Cl ₂ N ₄ OS	407	128	58	53.07	3.93	13.76	53.35	3.75	13.64
5	4-OCH ₃	C ₁₉ H ₂₀ N ₄ O ₂ S	368	136-7	42	61.95	5.43	15.21	61.57	5.18	14.83
6	4-OC ₂ H ₅	C ₂₀ H ₂₂ N ₄ O ₂ S	382	115-6	49	62.82	5.75	14.65	62.53	5.23	14.12
7	3-OC ₂ H ₅	C ₂₀ H ₂₂ N ₄ O ₂ S	382	143-5	46	62.82	5.75	14.65	63.13	5.57	14.88
8	3-OCH ₃	C ₁₉ H ₂₀ N ₄ O ₂ S	368	128-9	45	61.95	5.43	15.21	61.69	5.22	15.04
9	2-OCH ₃	C ₁₉ H ₂₀ N ₄ O ₂ S	368	122-3	43	61.95	5.43	15.21	62.09	5.62	14.94

TABLE 17

2-SUBSTITUTED ANILINO-4-[m-(N,N-DIETHYLUREIDO)PHENYL] THIAZOLES

SR. NO.	R	MOLECULAR FORMULA	M. W.	m. p. °C	YIELD %	ELEMENTAL ANALYSIS					
						REQUIRED			FOUND		
						C	H	N	C	H	N
1	H	C ₂₀ H ₂₂ N ₄ OS	366	148-9	48	65.57	6.01	15.30	65.25	5.85	15.63
2	4-Cl	C ₂₀ H ₂₁ ClN ₄ OS	400.5	178-9	45	59.92	5.24	13.98	59.54	5.19	14.07
3	4-CH ₃	C ₂₁ H ₂₄ N ₄ OS	380	138-40	53	66.31	6.31	14.73	66.83	5.73	15.26
4	3,4-Cl ₂	C ₂₀ H ₂₀ Cl ₂ N ₄ OS	435	124	37	55.17	4.59	12.87	55.35	4.75	13.04
5	4-OCH ₃	C ₂₁ H ₂₄ N ₄ O ₂ S	396	138	52	63.63	6.06	14.14	63.57	5.88	13.83
6	4-OC ₂ H ₅	C ₂₂ H ₂₆ N ₄ O ₂ S	410	112-3	40	64.39	6.34	13.65	64.72	6.23	13.32
7	3-OC ₂ H ₅	C ₂₂ H ₂₆ N ₄ O ₂ S	410	146-8	36	64.39	6.34	13.65	64.83	6.87	13.18
8	3-OCH ₃	C ₂₁ H ₂₄ N ₄ O ₂ S	396	126-8	55	63.63	6.06	14.14	63.69	6.22	14.04
9	2-OCH ₃	C ₂₁ H ₂₄ N ₄ O ₂ S	396	132-3	46	63.63	6.06	14.14	63.88	6.36	14.28

SPECTRAL ANALYSIS OF 2-(SUBSTITUTED ARYL/ANILINO)-4-[m-(N,N-DIALKYL URIEDO)-PHENYL] THIAZOLE

2-PHENYL-4-[m-(N,N-DIETHYLURIEDO)-PHENYL] THIAZOLE
(COMPOUND NO. 1 , TABLE NO. 14)

IR (KBr cm^{-1})

3300 (-NH), 2980 (-CH₂CH₃), 1630 (C-O-N<), 1610 1460 1050
(THIAZOLE), 1500 (-NHCO).

2-(4'-~~Methoxy~~)phenyl-4-[m-(N,N-DIMETHYLURIEDO)-PHENYL] THIAZOLE
(COMPOUND NO. 3 , TABLE NO. 13)

IR (KBr cm^{-1})

3320 (-NH), 2940 (-CH₃), 1650 (C-O-N<), 1600 1470 1030
(THIAZOLE), 1550 (-NHCO).

2-(4-CHLOROANILINO)-4-[m-(N,N-DIETHYLURIEDO)-PHENYL] THIAZOLE
(COMPOUND NO. 2 , TABLE NO. 17)

IR (KBr cm^{-1})

3240 (-NH), 3000 (-C₂H₅), 1630 (C-O-N<), 1600 1480 1040
(THIAZOLE), 1530 (-NHCO).

PMR (CdCl₃) δ :

1.20 - 2.46 (t, 6H, -CH₂CH₃), 3.33 - 3.46 (q, 4H, -CH₂CH₃)

6.35 - 7.84 [m, 11H (2H, -NH-) (8H, Ar-H) (1 H, thiazole, C₅H)]

2-(4-Methoxyphenyl)-4-[m-(N,N-DIMETHYLURIEDO)-PHENYL] THIAZOLE
(COMPOUND NO. 3, TABLE NO. 14)

IR (KBr cm^{-1})

3360 (-NH), 2980 ($-\text{C}_2\text{H}_5$), 1650 ($\text{C}-\text{O}-\text{N}<$), 1590 1480 1050
(THIAZOLE), 1550 (-NHCO).

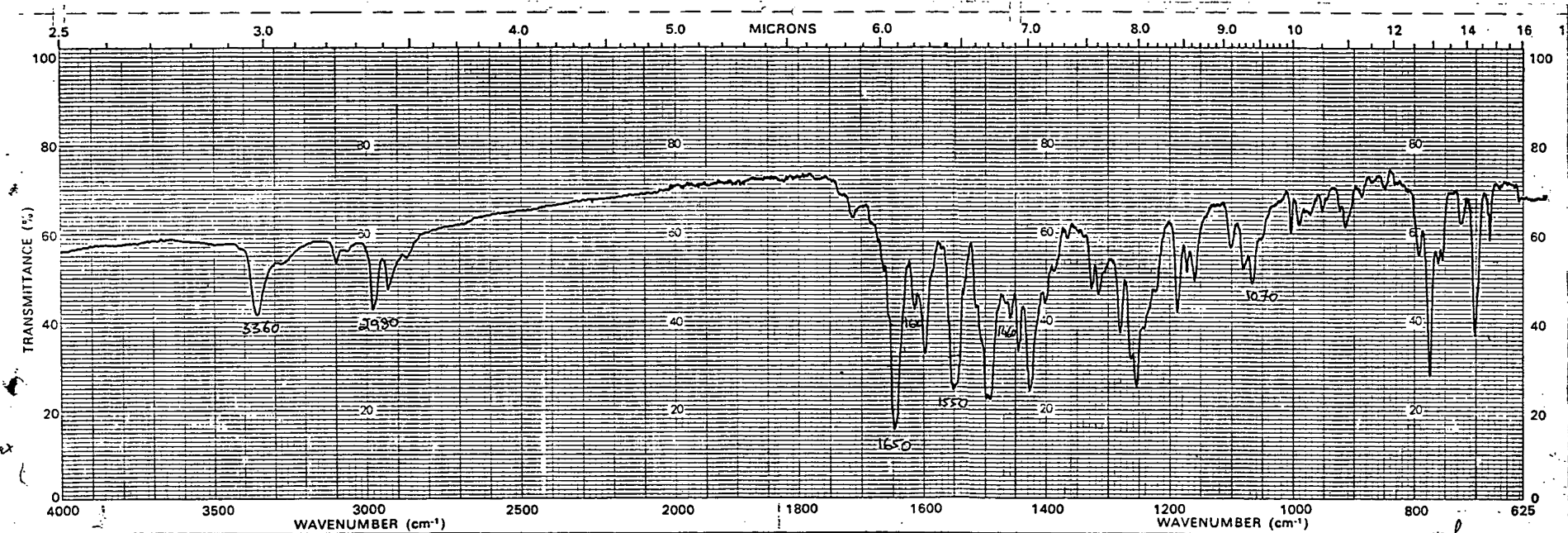
2-(4-METHOXYANILINO)-4-[m-(N,N-DIETHYLURIEDO)-PHENYL] THIAZOLE
(COMPOUND NO. 5, TABLE NO. 17)

IR (KBr cm^{-1})

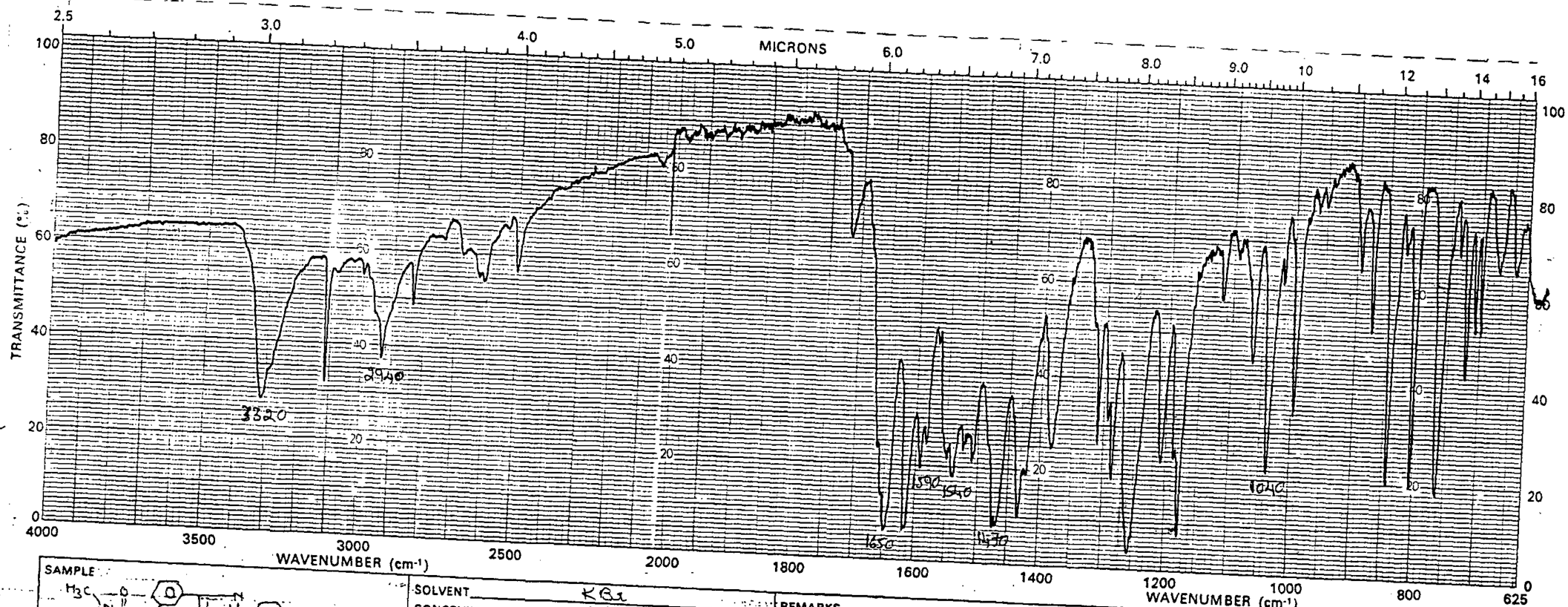
3340 (-NH), 3020 ($-\text{C}_2\text{H}_5$), 1650 ($\text{C}-\text{O}-\text{N}<$), 1600 1480 1065
(THIAZOLE), 1530 (-NHCO).

PMR (CdCl_3) δ :

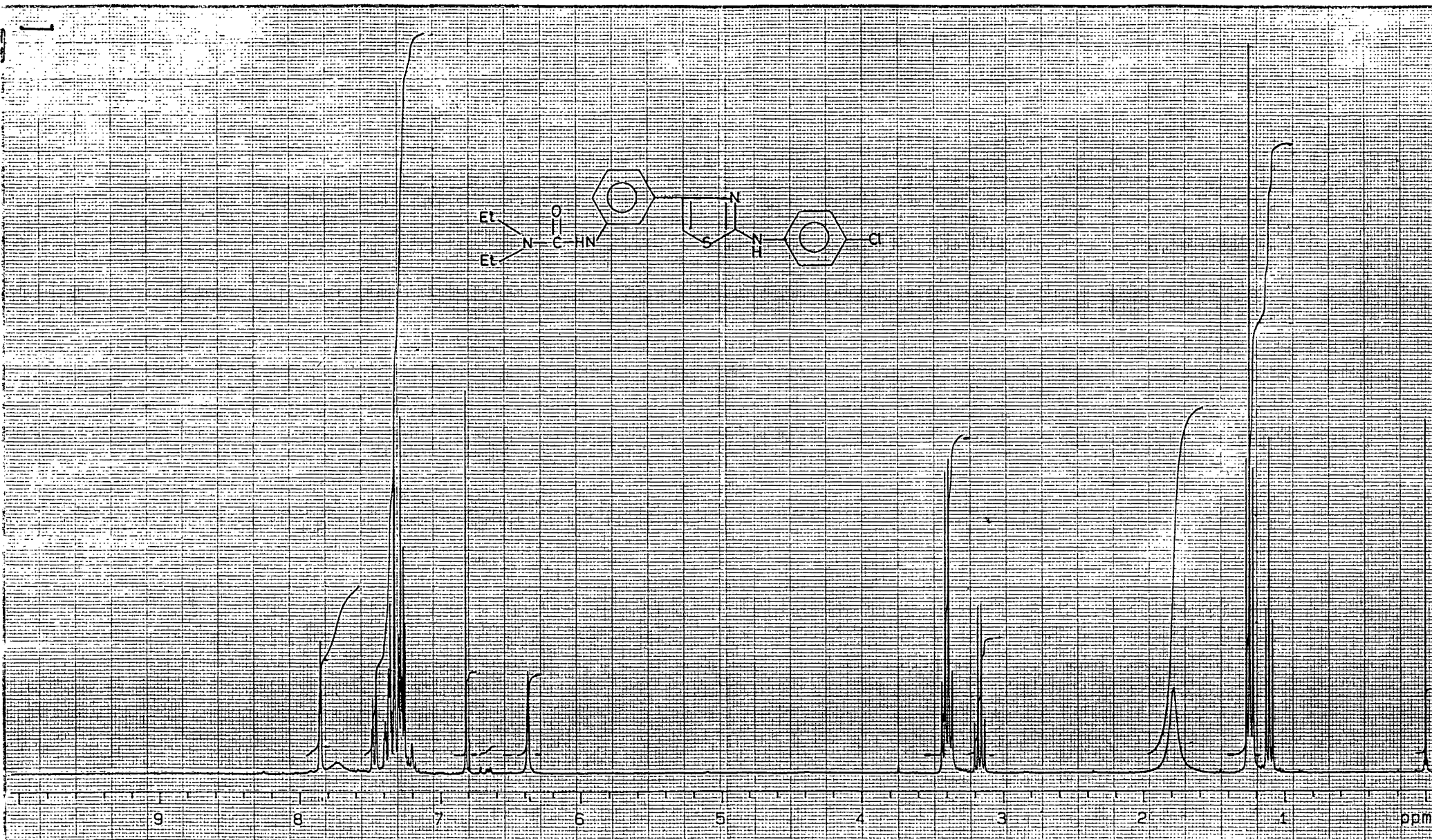
1.225 - 1.275 (t, 6H, $-\text{CH}_2\text{CH}_3$), 3.35 - 3.425 (q, 4H, $-\text{CH}_2\text{CH}_3$)
3.825 (s, 3H, $-\text{OCH}_3$), 6.425 - 7.975 [m, 11H, (2H, -NH-)
(8H, Ar-H), (1H, thiazole, C_5H)



SAMPLE <chem>C1=CC=C2C(=C1)N(C=NC2=O)C3=CC=CC=C3</chem> ORIGIN	SOLVENT	REMARKS CHART NO. 472 5089 TRUEGRAPH CHARTS PVT. LTD.	SCAN SPEED	OPERATOR
	CONCENTRATION		SLIT	DATE
	CELL PATH			
	REFERENCE			REF. NO.



SAMPLE <chem>CC(=O)Nc1ccc2c(c1)sc(c2)COC</chem> ORIGIN	SOLVENT	KBr	REMARKS	SCAN SPEED	Medium	OPERATOR W. B. B.
	CONCENTRATION	1%		SLIT	Normal	
	CELL PATH					
	REFERENCE					
CHART NO. 472-5089			TRUEGRAPH CHARTS PVT. LTD.	DATE		25/10/94
REF. NO.						



OBSERVE
Nucleus H1 Freq 299.9486 MHz
Spc. Width 6997.9 Hz Offset 1600.0 Hz
Acq. Time 4.00 sec Delay 0 sec
Pulse Width 8.0 ° Transients 120

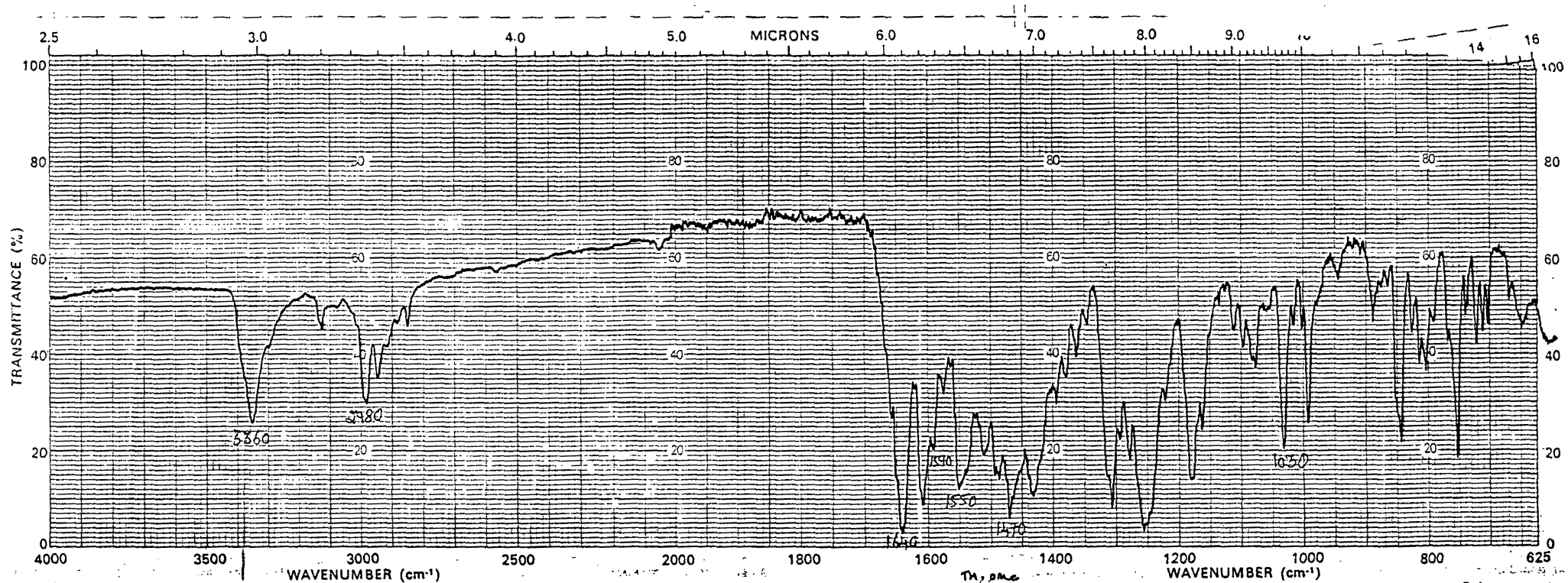
DECOUPLE
Nucleus H1 Offset 315.9 Hz
Mode n Power 20 dB
Modulation Mode c Freq. 200 Hz
Pulse Width μsec Power Mode not used

PLOT/PROCESSING
FN not used RE sec CD sec
LB 0-100 Not used sec CD sec
Width 3045.0 Hz ppm Corr 28.4 Hz/ppm
Reference _____

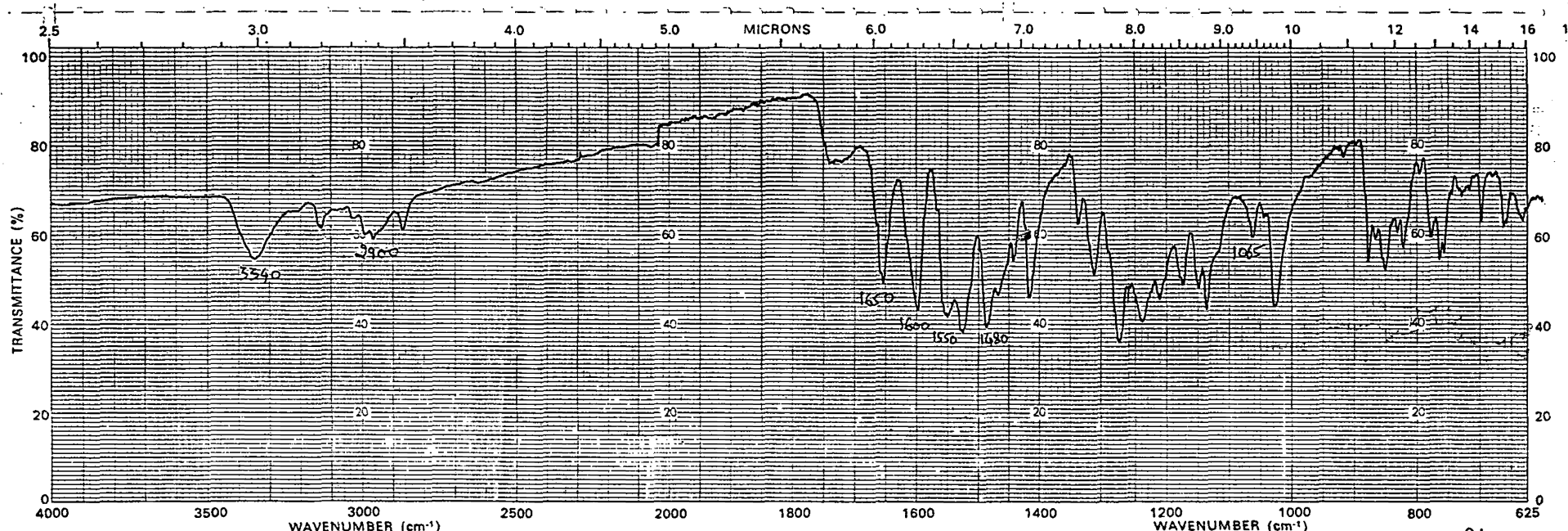
EXPERIMENT
Pulse Sequence s2pu1
Tube O.D. _____ mm
Temp. not used °C
Solvent CDCl3

SAMPLE
SDP5
Haffkine Inst.

Number _____
File sdp5.fid
Date Jul-6 94
VXRO 300



SAMPLE <chem>CC(=O)Nc1ccc(OC)cc1</chem> ORIGIN	SOLVENT	KB	REMARKS	SCAN SPEED	Medium	OPERATOR	SPJAV
	CONCENTRATION	1%		SLIT	Normal	DATE	12/6/24
	CELL PATH		CHART NO. 472 5089			REF. NO.	
	REFERENCE		TRUEGRAPH CHARTS PVT. LTD.				



SAMPLE <chem>NC(=O)Nc1ccc(NC(=O)Nc2ccc(N)cc2)cc1</chem> ORIGIN	SOLVENT	KBr	REMARKS CHART NO. 472 5089	SCAN SPEED	Medium	OPERATOR	Sofala
	CONCENTRATION	1%		SLIT	Normal	DATE	12/6/94
	CELL PATH						
	REFERENCE						

TRUEGRAPH CHARTS PVT. LTD.



10 9 8 7 6 5 4 3 2 1 ppm

OBSERVE
Nucleus H1 Freq. 299.9486 MHz
Spoc. Width 8997.9 Hz Offset 1600.0 Hz
Acq. Time 4.00 sec Delay 0 sec
Pulse Width 8.0 sec Transients 48

DECOUPLE
Nucleus H1 Offset 315.9 Hz
Mode n Power 20 dB
Modulation Mode c Freq. 200 Hz
Pulse Width μsec Power Mode not-used

PLOT/PROCESSING
PN not-used RE sec CD sec
LB 0.100 Hz Not-used^{sec} CCD
Width 3056.6 Hz/ppm Start 29.0 Hz/ppm
Reference

EXPERIMENT
Pulse Sequence e2pu1
Tube O.D. mm
Temp. not-used °C
Solvent CDCl3

SAMPLE
SDP6
Haffkine Inst.

Number
File edp6-f1d
Date Jul 6 94
VXRO 300

PART - V

**BIOLOGICAL RESULTS
AND
DISCUSSION**

The compounds synthesized in the present study have been subjected to antibacterial and antifungal screening based on their structural features.

The *in vitro* testing of these compounds was carried out against various species of Gram positive and Gram negative bacteria viz. *Staphylococcus aureus* (ATCC 10148), *Salmonella typhi* (NCTC 786) and against fungal cultures of *Candida albicans*, *T. rubrum* and *T. mentagrophytes*.

In part II, the syntheses of 5,6 disubstituted 2-(N,N-dialkyl thiocarbamido) benzothiazoles have been described. These compounds were subjected to antibacterial and antifungal screening against *S. aureus*, *S. typhi* and *C. albicans*, *T. mentagrophytes*, *T. rubrum* respectively.

In part III, the syntheses of 5,6 disubstituted 2-(N,N-dialkyl thiocarbamido) benzimidazoles have been reported. These compounds were screened for their antibacterial and antifungal activity against the above mentioned cultures.

In part IV, the syntheses of 2-(substituted phenyl/anilino) 4-[m-N,N dialkyl ureido) phenyl]-thiazoles have been described. These compounds were tested for their antibacterial and antifungal activity against the above mentioned cultures.

SCREENING AGAINST BACTERIAL INFECTIONS :

The test compounds have been subjected to *in vitro* screening by the tube dilution technique against various species

of Gram positive and Gram negative bacteria viz. *S. aureus*, *E.coli*, and *S. typhi*. Using Mueller-Hinton broth as the culture medium.

Screening procedure :

Sterile Mueller-Hinton broth (4.35 ml) was dispersed in each borosilicate test tube (150 X 20 mm). The test compounds (20 mg) were dissolved in a suitable solvent (10 ml) such as DMF, dilute HCl, ethanol etc. as the case may be.

The serial dilution were made in such a way as to give various final drug concentrations of 200, 100, 50 ug/ml etc. The inoculum of standard suspension (0.1 ml) of the desired bacterial strain (*S. aureus*, *E. coli*, *S. typhi*) containing 10^6 bacilli/ml was added at the end. The tubes were incubated at 37°C for 24 hours and then examined for the presence or absence of the growth of the test organisms. The lowest concentration which showed no visible growth was taken as end point.

Control tubes with ampicillin as standard drug and tubes with out any drug were kept for comparision. Also the solvent used for dissolving the subjected under study were simillarly tested to see that they did not affect the growth of the culture at the concentration wsed under these experimental conditions. Ampicillin inhibited the growth of the *S. aureus*, *E.coli*, *S.typhi* at the concentration of 0.5, 2 and 4 ug/ml respectively.

SCREENING AGAINST FUNGAL INFECTIONS

The organisms employed in the test were *Candida albicans*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*. These organisms were maintained on Sabouraud's agar slants by regular subculturing. *C. albicans* was subcultured every week and the rest of the organisms at the interval of 12 days.

Test medium

The liquid medium described by Schraufstatter et. al was used for screening the compounds for their antifungal activity. The final pH of the medium was adjusted to 5.2. This test medium was dispensed in requisite amounts varying from 4.4 to 4.85 ml in sterile tubes. To these tubes were added the requisite test solutions in graded concentrations varying from 200 ug/ml to 20 ug/ml.

Preparation of inoculum

Candida albicans

A 48 hours old growth on Sabouraud's agar slant was suspended in 4-5 ml of the test medium with the help of platinum loop. The cell count of suspension (yeast phase) was carried out using Naubaur chamber and then diluted with requisite volume of the medium to give a final concentration of 5×10^6 cells per ml.

T. rubrum and *T. mentagrophytes*

To a 12 to 14 days old growth on Sabouraud's agar slant, 5 ml of sterile test medium and 3-4 sterile glass beads (3 mm diameter) were added and gently shaken for about 10 minutes. The supernatant was decanted into another sterile tube and the count of spores in the suspension was carried out using Neubauer chamber. Final strength of the inoculum was adjusted to 5×10^6 spores per ml, using test medium.

Method

To each test tube was added 0.1 ml of standardised inoculum of the test organisms. The tubes were then incubated at room temperature (28-30°) in a dark place. The presence or absence of the growth was noted visually after 7 days in case of *C. albicans* and after 14 days in case of *T. rubrum* and *T. mentagrophytes*.

Miconazole Nitrate was used as a standard compound for the antifungal screening programme. It is active against *Candida albicans*, *T. mentagrophytes* and *T. rubrum* at a concentration of 0.625 ug/ml.

RESULT AND DISCUSSION

PART II : 5.6 DISUBSTITUTED 2-(N,N DIALKYL THIOCARBAMIDO) BENZOTHAZOLES

ANTIBACTERIAL AND ANTIFUNGAL SCREENING

Most of the compounds in these type of compounds were found to be inactive against Gram positive and Gram negative bacteria except one. In table no. (18) Compound 5, was found to be moderately active at the concentration of 100 ug/ml against *S. aureus*.

The antifungal testing results shows good pattern as compared to the antibacterial screening. Compound no. 3 Table no. 18 shows activity at the concentration 50 ug/ml against *C.albicans*, and *T. rubrum* whereas compounds 4 and 5 shows activity at the concentration of 100 and 50 ug/ml against *T.rubrum* respectively.

In Table no. (19), compound no 3, 5 was found to be active at the concentration of 50 ug/ml against *T. rubrum* and *C.albicans* respectively. Compound no. 4 has shown activity at 100 ug/ml concentration against *T. rubrum* while compound 8 is active against *C. albicans* at a concentration of 200 ug/ml.

The testing results as given in the tables 18 and 19, show that antifungal activity is enhanced by the substitution of electronegative atom in the aromatic ring system. In table 18, the dichloro and fluoro substituted compounds (no. 3 and 5 respectively) have shown the highest activity while the electron

donating methoxy substituted compound (no.4) has registered a lower activity.

Similarly, from table 19, it is observed that the dichloro and fluoro substituted compounds (no. 3 and 5 respectively) have shown the highest activity. viz., active at 50 ug/ml against *C. albicans* and *T. rubrum*. The activity exhibited by the mono chloro substituted compound (no.2) is the same as that exhibited by the methoxy substituted compound (no.4) albeit against different species of fungi. This probably indicates the need for stronger electronegative substitutions for imparting activity in this series.

PART III: 5.6 DISUBSTITUTED 2-(N,N-DIALKYL THIOCARBAMIDO)
BENZIMIDAZOLES

ANTIBACTERIAL AND ANTIFUNGAL SCREENING:

Only one compound (compound no. 8 of Table no. 21) has shown activity against *S.aureus* at the concentration of 100 ug/ml.

Compound no. 8 of Table no. (20) and (21), has shown activity against *C. albicans* and *T. mentagrophytes* at the concentration of 50 ug/ml. This compound exhibits a similar structure as that of mebendazole in which a benzoyl group is directly attached to the benzimidazole moiety.

Compound no. 7 (Table no. 20) shows moderate activity against *T. rubrum* at a concentration of 100 ug/ml. whereas compound no. 10 (Table no. 21) is active at the

concentration of 50 ug/ml. In both these compounds, electronegative groups such as NO₂ and Cl are attached to benzimidazole moiety.

The testing results as given in the tables 20 and 21, reveal that most compounds of these series are inactive against the bacterial and fungal strains. But once again the activity appears to depend on the electronegativity of the substitution in the aromatic ring system.

In table 20, only two compounds have been found active (nos. 7 and 8) both viz., NO₂ and C₆H₅CO respectively. Following the same reasoning it is seen that in table 21, the active compounds (nos. 7, 8 and 10) have electronegative substitutions such as NO₂, C₆H₅CO and C₆H₅CH₂S respectively.

PART IV : 2-(SUBSTITUTED PHENYL/ANILINO)-4-[m-N,N-DIALKYL UREIDO] PHENYL] THIAZOLES.

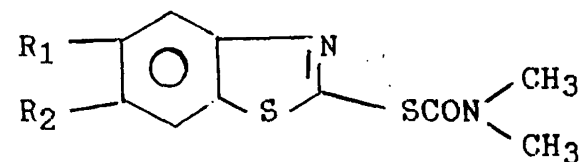
A study of the testing results in tables 22 to 25 show that these series of compounds are by and large completely inactive against fungal strains.

The antibacterial testing results of the compounds in tables 22 and 23, with the aryl substitution in the 2-position of the thiazole ring exhibit interesting results, with activity being favoured by electron donating substitution in the phenyl ring. In table 22, the highest activity of 50 ug/ml is recorded by the 4-OCH₃ substitution (no.3) while the unsubstituted and 3-OCH₃ substitutions (no. 1 and 6) are active at 100 ug/ml.

Quite similar trends are exhibited by the compounds shown in table 23. The highest activities are recorded by the unsubstituted and the 3-OCH₃ (no. 1 and 6) while the 4-OCH₃ (no.3) substituted compound is active at 100 ug/ml.

In the series of compounds represented in tables 24 and 25, the thiazole heterocycle exhibits various anilino substitutions in the 2-position. The results appear mixed with the N,N-diethyl substituted compounds being more active than the N,N-dimethyl substituted ones. The activity results do not indicate a preference for either the electron donating or withdrawing groups. Interestingly the highest activity of 50 ug/ml has been shown by compound no. 7 in both tables 24 and 25 with the 3-OC₂H₅ substitution. The 4-Cl substituted product in table 24 (no. 2) is also active at 50 ug/ml. The other active compounds in table 25 all exhibit antibacterial activity at 100 ug/ml.

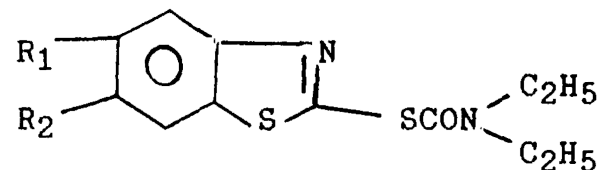
TABLE 18

5,6-DISUBSTITUTED-2-(N,N-DIMETHYL THIOCARBAMIDO)BENZOTHAZOLES

SR. NO.	R ₁	R ₂	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	-
2.	H	Cl	-	-	-	-	-
3.	Cl	Cl	-	-	50	-	50
4.	H	OCH ₃	-	-	-	-	100
5.	H	F	100	-	-	-	50
6.	NO ₂	F	-	-	-	-	-
7.	H	OC ₄ H ₉	-	-	-	-	-
8.	H	OC ₂ H ₅	-	-	-	-	-

- = INACTIVE AT > 200

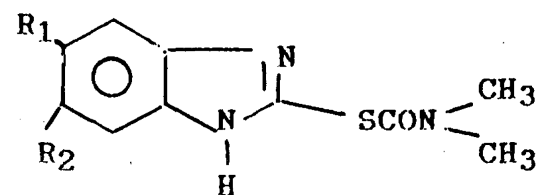
TABLE 19

5,6-DISUBSTITUTED-2-(N,N-DIETHYL THIOCARBAMIDO) BENZOTHAZOLES

SR. NO.	R ₁	R ₂	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	-
2.	H	Cl	-	-	100	-	-
3.	Cl	Cl	-	-	50	-	50
4.	H	OCH ₃	-	-	-	-	100
5.	H	F	-	-	50	-	50
6.	NO ₂	F	-	-	-	-	-
7.	H	OC ₄ H ₉	-	-	-	-	-
8.	H	OC ₂ H ₅	-	-	200	-	-

- = INACTIVE AT > 200

TABLE 2c

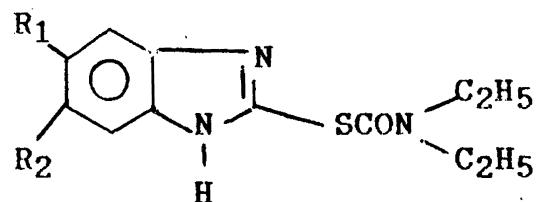
5.6-DISUBSTITUTED-2-(N,N-DIMETHYL THIOCARBAMIDO) BENZIMIDAZOLES

SR. NO.	R	R'	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	-
2.	Cl	H	-	-	-	-	-
3.	Cl	Cl	-	-	-	-	-
4.	CH ₃	H	-	-	-	-	-
5.	OCH ₃	H	-	-	-	-	-
6.	OC ₂ H ₅	H	-	-	-	-	-
7.	NO ₂	H	-	-	-	-	100
8.	C ₆ H ₅ CO	H	-	-	50	50	-
9.	SC ₃ H ₇	Cl	-	-	-	-	-
10.	C ₆ H ₅ CH ₂ S	Cl	-	-	-	-	-

- = INACTIVE AT > 200

TABLE 21

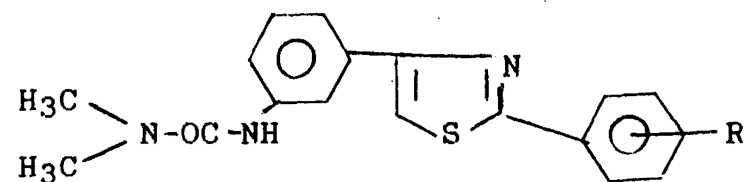
5,6-DISUBSTITUTED-2-(N,N-DIETHYL THIOCARBAMIDO) BENZIMIDAZOLES



SR. NO.	R	R'	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	100
2.	Cl	H	-	-	-	-	-
3.	Cl	Cl	-	-	-	-	-
4.	CH ₃	H	-	-	-	-	-
5.	OCH ₃	H	-	-	-	-	-
6.	OC ₂ H ₅	H	-	-	-	-	-
7.	NO ₂	H	-	-	50	-	-
8.	C ₆ H ₅ CO	H	100	-	50	50	-
9.	SC ₃ H ₇	Cl	-	-	-	-	-
10.	C ₆ H ₅ CH ₂ S	Cl	-	-	-	50	-

TABLE 22

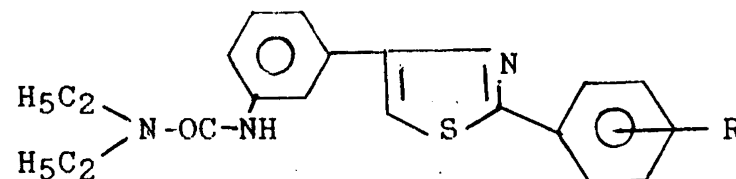
2-(SUBSTITUTED ARYL)-4-[m-(N,N-DIMETHYLUREIDO) PHENYL]-THIAZOLES



SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	100	-	-	-	-
2.	4-Cl	-	-	-	-	-
3.	4-OCH ₃	50	-	-	-	-
4.	4-CH ₃	-	-	-	-	-
5.	4-N(CH ₃) ₂	-	-	-	-	-
6.	3,4-OCH ₃	100	100	-	-	-
7.	2,4-OCH ₃	-	-	-	-	-

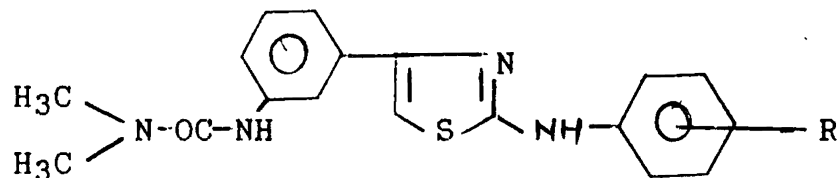
- = INACTIVE AT > 200

TABLE 23

2-(SUBSTITUTED ARYL)-4-[m-(N,N-DIETHYLUREIDO) PHENYL]-THIAZOLES

SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	50	-	-	-	-
2.	4-Cl	-	-	-	-	-
3.	4-OCH ₃	-	100	-	-	-
4.	4-CH ₃	-	-	-	-	-
5.	4-N(CH ₃) ₂	-	-	-	-	-
6.	3,4-OCH ₃	50	50	-	-	-
7.	2,4-OCH ₃	-	-	-	-	-
- = INACTIVE AT > 200						

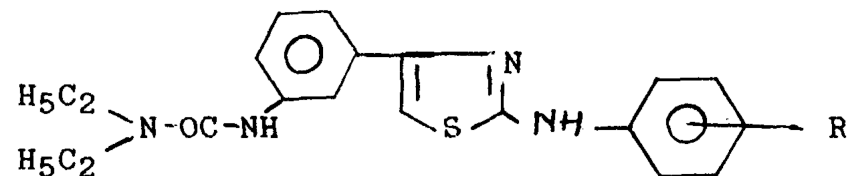
TABLE 24

2-(SUBSTITUTED ANILINO)-4-[m-(N,N-DIMETHYLUREIDO) PHENYL]-THIAZOLES

SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	-	100	-	-	-
2.	4-Cl	50	-	-	-	-
3.	4-CH ₃	-	-	-	-	-
4.	3,4-Cl ₂	-	-	-	-	-
5.	4-OCH ₃	-	-	-	-	-
6.	4-OC ₂ H ₅	-	-	-	-	-
7.	3-OC ₂ H ₅	-	50	-	-	50
8.	3-OCH ₃	-	-	-	-	-
9.	2-OCH ₃	-	-	-	-	-

- = INACTIVE AT > 200

TABLE 25

2-(SUBSTITUTED ANILINO)-4-[m-(N,N-DIETHYLUREIDO) PHENYL]-THIAZOLES

SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	100	-	-	-	-
2.	4-Cl	-	100	-	-	-
3.	4-CH ₃	-	-	-	-	-
4.	3,4-Cl ₂	100	100	-	-	-
5.	4-OCH ₃	-	100	-	-	-
6.	4-OC ₂ H ₅	-	-	-	-	-
7.	3-OC ₂ H ₅	-	50	-	-	-
8.	3-OCH ₃	-	-	-	-	-
9.	2-OCH ₃	-	-	-	-	-

- = INACTIVE AT > 200

PART - V.

CONCLUSION

In the present investigation, novel heterocyclic molecules have been synthesized which have been screened for their possible therapeutic value against fungal and bacterial infections.

The synthesized compounds have been described in three parts and all of them have been tested against various fungal and bacterial strains. In Part II various 5,6 disubstituted 2-N,N-dialkylthiocarbamido benzothiazoles have been synthesized and tested for their biological activity, the results of which are given in table 18 and 19. These series of compounds are practically inactive against the bacterial strains.

The antifungal results show that in both the series viz., N,N-dimethyl and diethyl, the activity is influenced by the electronegativity of the substituents in the aromatic ring. Greater the electronegativity, better is the activity, with N,N-diethyl series generally being more active than the N,N-dimethyl ones.

In part III, the syntheses of 5,6-disubstituted-2-N,N-dialkyl thiocarbamido benzimidazoles have been described. The testing results (table 20 and 21) once again reveal that the compounds are inactive against the bacterial strains. The antifungal activity is favoured by the presence of an electron withdrawing group in the phenyl ring and yet again the N,N-diethyl series have shown better activity than the N,N-dimethyl series. The benzoyl substituted compound in both series have shown the highest and identical activity against the different fungal strains.

Part IV describes the syntheses of 2-substituted aryl/anilino -4-[m-(N,N-dialkylureido) phenyl] thiazoles. The biological activity against fungal and bacterial reveal the following trends.

(i) This series is inactive against the various fungal strains viz. *C.albicans*, *T. mentagrophytes*, *T. rubrum*.

(ii) The antibacterial activity of compounds which exhibit the substituted phenyl moiety in the 2-position of the thiazole ring (table 22 and 23) is favoured by the presence of electron donating substituent.

(iii) The antibacterial activity results of compounds which exhibit the substituted anilino moiety in the 2-position of the thiazole ring (table 24 and 25) do not show a definite trend towards ascertaining the nature of substituents which could enhance activity.

In conclusion it may be stated that the present study has not resulted in the discovery of new molecules which could be used against fungal and bacterial infections. Some compounds have indeed exhibited biological activity but they are quite low as compared to the activity of the standard compounds. Quite possibly further structural modifications are necessary to enhance the activities of the compounds synthesized herein.

PART - V

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SYNOPSIS



SYNOPSIS

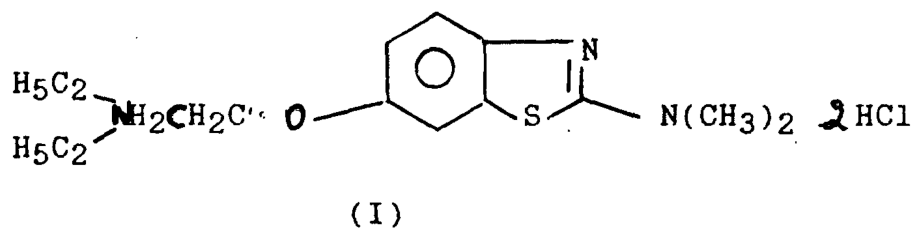
Heterocyclic compounds have time and again proved themselves to be invaluable in the field of medicinal chemistry. Several heterocyclic derivatives find important applications in the compounds of therapeutic value. The benzimidazoles are synonymous with anthelmintic agents, thiazoles are useful for several purposes ranging from antibacterial to immuno-suppressive agents. pyridines are found in antiulcer and antitubercular compounds; while, isoxazoles find applications in penicillins and semisynthetic antibiotics. The list could be endless.

Microbial infections have tormented mankind in various forms since ancient times. Tuberculosis and leprosy are well documented since the biblical era. While other manifestations of such infections are caused by bacterial, viral and fungal diseases. Heterocyclic derivatives play an important role in the control of various microbial diseases and hence, in this present study a new series of heterocyclic agents have been synthesized and studied for their properties as antibacterial and antifungal agents.

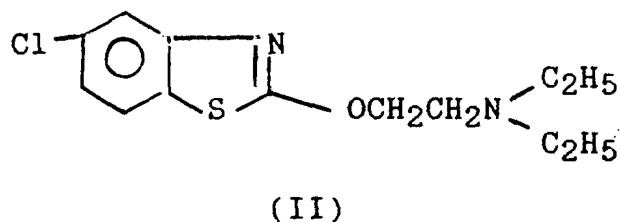
The thesis would consists of 'Introduction', 'Review of literature' and 'Plan of work' in Part I. Further, it would be subdivided into different parts as summerized here.

Part-II: SYNTHESSES OF 5,6-DISUBSTITUTED-2-(N,N-DIALKYLTHIOCARBAMIDO) BENZOTHIAZOLES

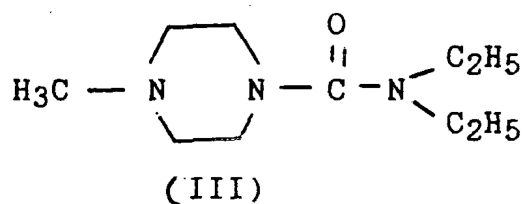
The literature survey reveals that Diamthazole dihydrochloride (I) containing benzothiazole derivatives moiety shows antifungal activity¹.



Halethazole (II) is another benzothiazole derivative having chloro substitution at 5-position which shows antifungal activity².

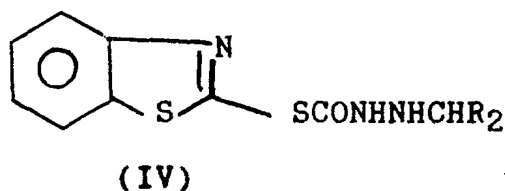


N,N-Diethyl carbamazine (Hetrazan) (III) having N,N-diethyl carbamoyl linkage is a well marked antifilarial agent³.

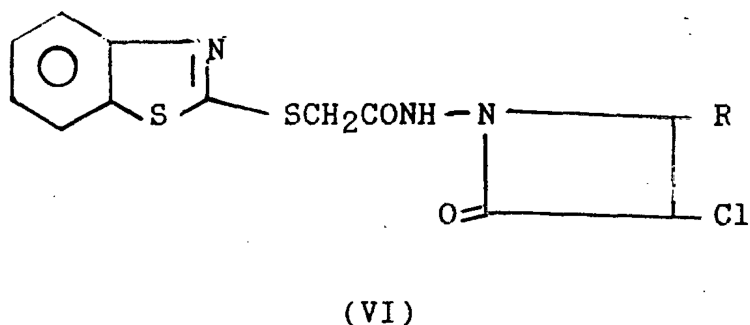
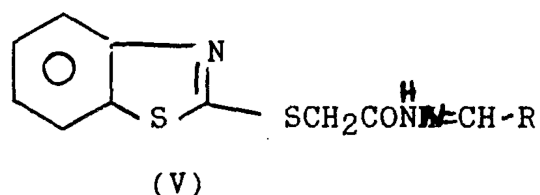


Besides Hetrazan (III), Diamthazole dihydrochloride (I) and Halethazole (II) also have N,N-dialkyl linkage as the side chain.

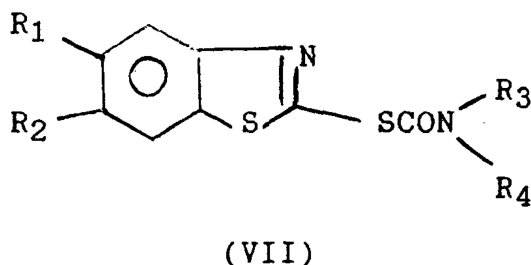
Very recently, Asaad and Falmy⁴, synthesized benzothiazoles of type (IV) having thiocarbamoyl linkage at 2-position and were found to show inhibition zone of 9-18 mm on various bacteria at a concentration of 0.01 g/100 ml.



Further, benzothiazoles of type (V) and (VI) having acetamidothio (S-CH₂CONH-) linkage at the 2-position were found to exhibit moderate to good antibacterial and antifungal activity⁵.



Thus, a combination of various substituted benzothiazoles with N,N-dialkyl carbamoyl linkage (VII) have been effected so as to study their antibacterial and antifungal properties.



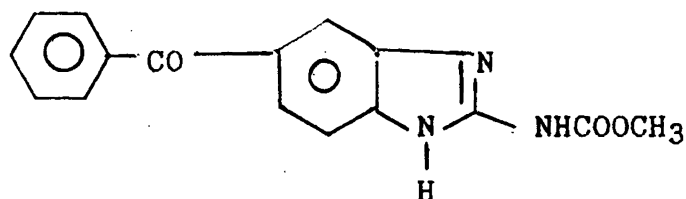
Where R₁ = H, Cl, NO₂

R₂ = H, Cl, F, OCH₃

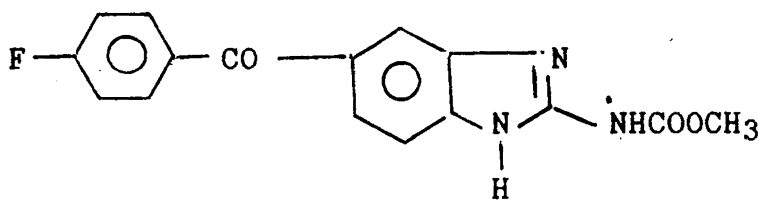
R₃ = R₄ = CH₃, C₂H₅

Part-III: SYNTHESIS OF 5,6-DISUBSTITUTED-2-(N,N-DIALKYL
THIOCARBAMIDO) BENZIMIDAZOLES

A number of benzimidazole derivatives have demonstrated a broad spectrum of significant biological activity such as mebendazole⁶ (VIII) and flubendazole (IX)⁷.

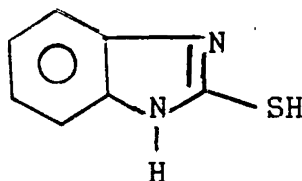


(VIII)



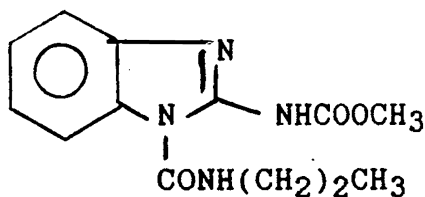
(IX)

2-Mercapto benzimidazole (X) itself is a bacteriostatic and antifungal agent⁸.



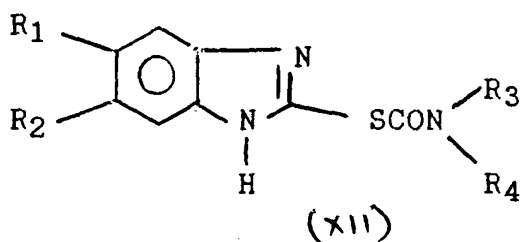
(X)

Benomyl (XI) is another antifungal compound having benzimidazole moiety with a carbamido linkage⁹.



(XI)

Thus, considering the importance of dialkyl carbamoyl linkage as effective synthons in preparing compounds of medicinal value, several substituted benzimidazoles have been condensed with N,N-dialkyl carbamoyl chloride. The resultant compounds depicted as (XII) have been then screened for their antibacterial and antifungal properties.

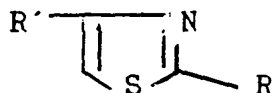


Where $R_1 = H, Cl$ $R_2 = H, Cl, F, OCH_3$
 $R_3 = R_4 = CH_3, C_2H_5$

Part-IV: SYNTHESIS OF 2-SUBSTITUTED ARYL/ANILINO-4-[m-(N,N-DIALKYLUREIDO)PHENYL] THIAZOLES

Thiazole derivatives have significant chemotherapeutic activities. Compounds such as vitamin B₁, sulphathiazole, promizole, thiabendazole, tramisole, contains thiazole ring having outstanding value for the treatment of a variety of bacterial protozoal and anthelmintic infections.

Prabhu et al.¹⁰ have reported that 2,4-disubstituted thiazoles (XIII) have shown good response against tubercule bacilli.



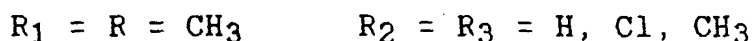
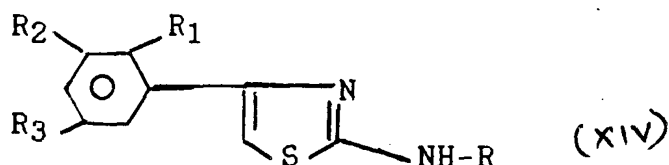
$R = \text{Alkyl, Aryl}$

$R' = 2\text{-Piperazinyl,}$

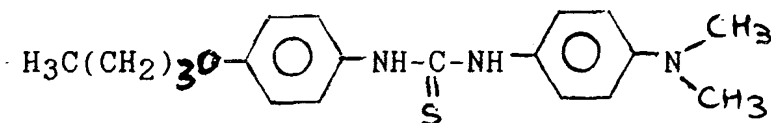
$5\text{-Nitro-2-furfuryl-ladamentyl}$

(XIII)

Recently, Grafe *et al.* reported 4-substituted phenyl 2-substituted aminothiazoles as antiviral agents¹¹ (XIV).

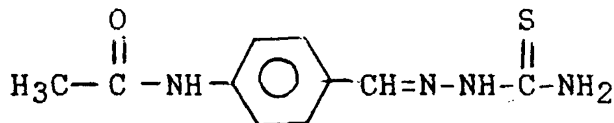


As explained in the earlier part, N,N-dialkyl carbamoyl linkage enhances biological activity of the compounds, also among thioureas, the thiocarbanilides are more potent antibacterial agents. Phenyl thioureas, with substitution at *p*-position of the phenyl ring increases the activity for e.g., *p*-butoxy *p*'-dimethylamino thiocarbanilide (XV) has the highest antitubercular activity in mice¹².



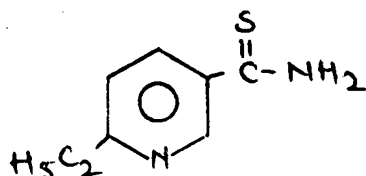
(XV)

The most active compound among thioureas is thiacetazone (XVI), which was as active as streptomycin and one-tenth as active as INH¹³.



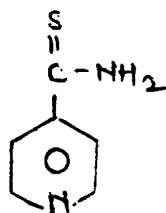
(XVI)

In the thioamide derivatives ethionamide (XVII) is a good antitubercular agent. Its activity is about twice as streptomycin¹⁴.



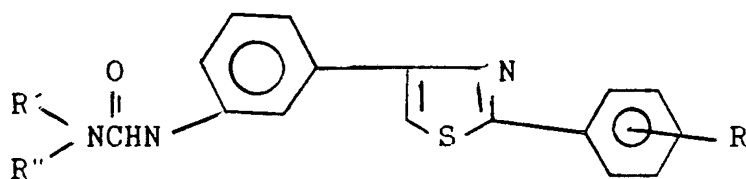
(XVII)

Thioisonicotinamide (XVIII) is another example in the class of thioamides found to be active against INH-resistant as well as INH-susceptive tubercle bacilli¹⁵.



(XVIII)

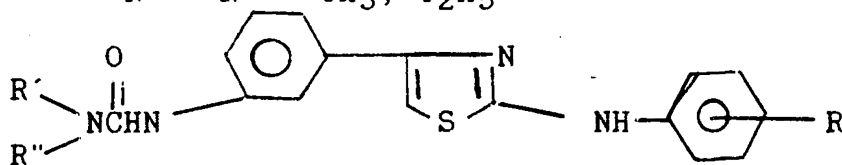
Thus, merging all the above facts into one moiety a series of following types of compounds (XIX) and (XX) were synthesized and their bactericidal and antifungal properties were studied.



(XIX)

R = H, Cl, CH₃, OCH₃, CH₃ etc

R' = R'' = CH₃, C₂H₅



(XX)

R = H, Cl, CH₃, OCH₃, CH₃ etc

R' = R'' = CH₃, C₂H₅

Part-V

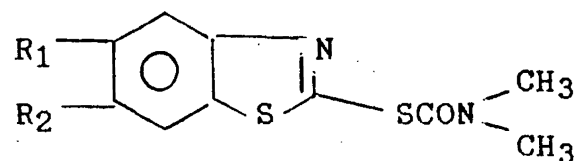
The structures of all the above-mentioned compounds have been confirmed by elemental and spectral studies and results obtained are found satisfactory. Overall seventy compounds are prepared.

These compounds have been screened for *in vitro* antimicrobial activities by the tube dilution method against various species of Gram-positive and Gram-negative bacteria *viz.*, *Staph. aureus*, *S. typhi* and *E. coli*. The culture medium used in the screening was Mueller-Hinton broth. MIC was found in the range of 50-200 ug/ml. Ampicillin was used as standard drug.

In vitro antifungal activity for the above compounds have been carried out by the tube dilution method against *C. albicans*, *T. rubrum* and *T. mentagrophytes*. The standard drug used was Miconazole. MIC was found in the range of 50-200 ug/ml.

The biological results are discussed as follows :-

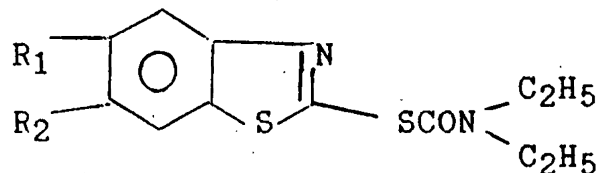
TABLE 1

5,6-DISUBSTITUTED-2-(N,N-DIMETHYL THIOCARBAMIDO)BENZOTHAZOLES

SR. NO.	R ₁	R ₂	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	-
2.	H	Cl	-	-	-	-	-
3.	Cl	Cl	-	-	50	-	50
4.	H	OCH ₃	-	-	-	-	100
5.	H	F	100	-	-	-	50
6.	NO ₂	F	-	-	-	-	-
7.	H	OC ₄ H ₉	-	-	-	-	-
8.	H	OC ₂ H ₅	-	-	-	-	-

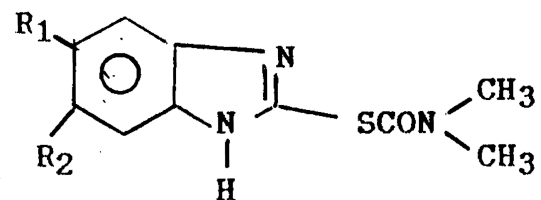
- = INACTIVE AT > 200

TABLE 2

5,6-DISUBSTITUTED-2-(N,N-DIETHYL THIOCARBAMIDO) BENZOTHAZOLES

SR. NO.	R ₁	R ₂	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	-
2.	H	Cl	-	-	100	-	-
3.	Cl	Cl	-	-	50	-	50
4.	H	OCH ₃	-	-	-	-	100
5.	H	F	-	-	50	-	50
6.	NO ₂	F	-	-	-	-	-
7.	H	OC ₄ H ₉	-	-	-	-	-
8.	H	OC ₂ H ₅	-	-	200	-	-

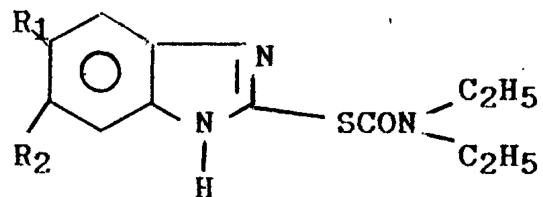
TABLE 3

5,6-DISUBSTITUTED-2-(N,N-DIMETHYL THIOCARBAMIDO) BENZIMIDAZOLES

SR. NO.	R ₁	R ₂	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	-
2.	Cl	H	-	-	-	-	-
3.	Cl	Cl	-	-	-	-	-
4.	CH ₃	H	-	-	-	-	-
5.	OCH ₃	H	-	-	-	-	-
6.	OC ₂ H ₅	H	-	-	-	-	-
7.	NO ₂	H	-	-	-	-	100
8.	C ₆ H ₅ CO	H	-	-	50	50	-
9.	SC ₃ H ₇	Cl	-	-	-	-	-
10.	C ₆ H ₅ CH ₂ S	Cl	-	-	-	-	-

- = INACTIVE AT > 200

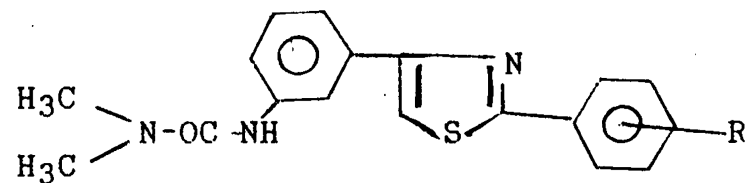
TABLE 4

5,6-DISUBSTITUTED-2-(N,N-DIETHYL THIOCARBAMIDO) BENZIMIDAZOLES

SR. NO.	R ₁	R ₂	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	H	-	-	-	-	100
2.	Cl	H	-	-	-	-	-
3.	Cl	Cl	-	-	-	-	-
4.	CH ₃	H	-	-	-	-	-
5.	OCH ₃	H	-	-	-	-	-
6.	OC ₂ H ₅	H	-	-	-	-	-
7.	NO ₂	H	-	-	50	-	-
8.	C ₆ H ₅ CO	H	100	-	50	50	-
9.	SC ₃ H ₇	Cl	-	-	-	-	-
10.	C ₆ H ₅ CH ₂ S	Cl	-	-	-	50	-

- = INACTIVE AT > 200

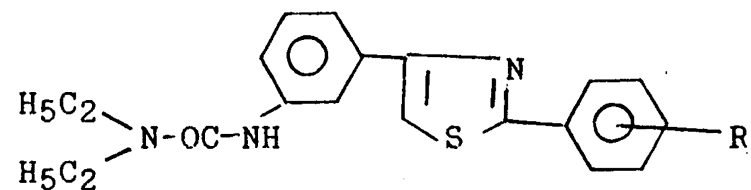
TABLE 5

2-(SUBSTITUTED ARYL)-4-[m-(N,N-DIMETHYLUREIDO) PHENYL]-THIAZOLES

SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	100	-	-	-	-
2.	4-Cl	-	-	-	-	-
3.	4-OCH ₃	50	-	-	-	-
4.	4-CH ₃	-	-	-	-	-
5.	4-N(CH ₃) ₂	-	-	-	-	-
6.	3,4-OCH ₃	100	100	-	-	-
7.	2,4-OCH ₃	-	-	-	-	-

- = INACTIVE AT > 200

TABLE 6

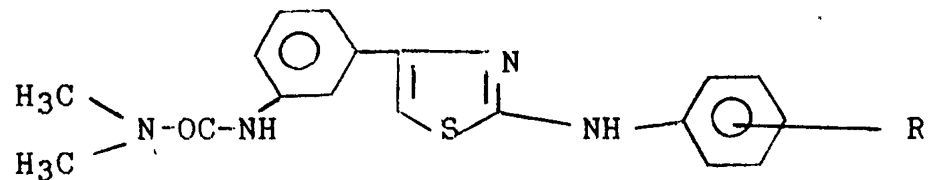
2-(SUBSTITUTED ARYL)-4-[m-(N,N-DIETHYLUREIDO) PHENYL]-THIAZOLES

SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	50	-	-	-	-
2.	4-Cl	-	-	-	-	-
3.	4-OCH ₃	-	100	-	-	-
4.	4-CH ₃	-	-	-	-	-
5.	4-N(CH ₃) ₂	-	-	-	-	-
6.	3,4-OCH ₃	50	50	-	-	-
7.	2,4-OCH ₃	-	-	-	-	-

- = INACTIVE AT > 200

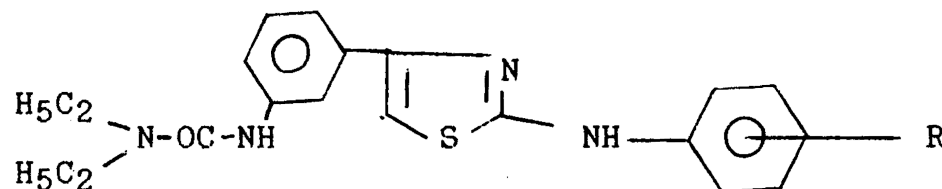
TABLE 7

2-(SUBSTITUTED ANILINO)-4-[m-(N,N-DIMETHYLUREIDO) PHENYL]-THIAZOLES



SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	-	100	-	-	-
2.	4-Cl	50	-	-	-	-
3.	4-CH ₃	-	-	-	-	-
4.	3,4-Cl ₂	-	-	-	-	-
5.	4-OCH ₃	-	-	-	-	-
6.	4-OC ₂ H ₅	-	-	-	-	-
7.	3-OC ₂ H ₅	-	50	-	-	50
8.	3-OCH ₃	-	-	-	-	-
9.	2-OCH ₃	-	-	-	-	-
- = INACTIVE AT > 200						

TABLE 8

2-(SUBSTITUTED ANILINO)-4-[m-(N,N-DIETHYLUREIDO) PHENYL]-THIAZOLES

SR. NO.	R	S.aureus	S.typhi	C.albicans	T.mentagrophytes	T.rubrum
1.	H	100	-	-	-	-
2.	4-Cl	-	100	-	-	-
3.	4-CH ₃	-	-	-	-	-
4.	3,4-Cl ₂	100	100	-	-	-
5.	4-OCH ₃	-	100	-	-	-
6.	4-OC ₂ H ₅	-	-	-	-	-
7.	3-OC ₂ H ₅	-	50	-	-	-
8.	3-OCH ₃	-	-	-	-	-
9.	2-OCH ₃	-	-	-	-	-

- = INACTIVE AT > 200

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