PART - II

SECTION - I

GENERAL AND THEORETICAL
PART - II

POSSIBLE ANTITUBERCULAR COMPOUNDS

SECTION : I (Possible Antitubercular compounds)
General and Theoretical

1. Antitubercular agents:

Tuberculosis is caused by an acid fast organism or mycobacterium, so called because, after being stained with a specific dye, it is not easily decolorized by acids and because some of its metabolic products, the high molecular weight mycolic acids, are not attacked by hot dilute sulphuric acid. The bacillus is rich in lipids, and a lipid layer or capsule is said to have been discerned under the electron microscope. This organism was first isolated by KOCH in 1882.

In contrast to other infections of more acute nature, tuberculosis usually is a chronic progressive disease which propagates in a complex manner. The slow life cycle of the tubercle bacillus may cause, in part, the irregular growth of the lesions which are produced by some of the excretion products of the bacillus. In internal organs these lesions may lead to cavities which are not properly perfused by the circulation. The bacillary foci within them are so hard to reach with drugs that many clinicians doubt the value of chemotherapy in the treatment of old established lesions. In pulmonary tuberculosis in rabbits inhalation of active
drugs in the form of a fog or aerosole has produced acceptable results.

In miliary tuberculosis the infection is spread by the circulation, and the bacilli should be attacked by drugs readily. Yet, only few cases of recovery are on record. In older lesions the bacilli often encapsule themselves in calcified envelopes consisting largely of calcium salts of fatty acids excreted by the organisms. They may remain dormant in these calcifications for decades, and this condition can bring about new outbreaks of the disease if the calcified layers are upset. Certain chemicals such as inorganic iodides are contraindicated in tuberculosis because they tend to destroy the calcified capsules, perhaps by formation of soluble calcium iodide. These facts contribute to the difficulties of antitubercular chemotherapy.

2. Serology:

While the organism of the host can build up some resistance to the antigenic tubercular protein, certain individuals become hypersensitized. Nevertheless, at least two tubercular sera have been produced and widely used. One is tuberculin which is used as a diagnostic tool in recognizing a previous infection.
The other one, the Bacillus Calmette-Guerin (BCG) serum, is now being tested for its possible immunizing action. In laboratory animals, especially guinea pigs, defense mechanism rarely exist, and with every experimental infection the animals are exposed not only to the destructive action of the bacilli but also to the antigenic properties of their protein. Cortisone has been found to increase the resistance of susceptible rabbits to tuberculosis.

3. Testing methods:

The greatest drawback to a thorough examination of all aspects of the chemotherapy of tuberculosis has been the lack of an adequate and reliable pharmacological test. A number of synthetic solid or emulsion media are known for tubercle bacilli and may be used for in vitro testing, for instance the modified Proskauer and Beck medium which consists of 0.5% K₂SO₄, 0.15% Mg-citrate, and 2% glycerol at pH 7.0. Another synthetic medium containing a detergent spreading agent has been described by Dubos(26).

Of the in vivo tests now being used, the most critical and reliable ones are probably those of Feldman and Hinshaw(34).

Theoretical classification of Drugs in Use:

The early search for effective antitubercular drugs was based on trial and error. Dozens of different classes
of compounds have been investigated. Among some typical are vitamins and Hormones, Alkaloids, Inorganic and metalorganic drugs are listed below:

(A) **Vitamin and Hormones**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>(21,38)</td>
</tr>
<tr>
<td>±</td>
<td>(71)</td>
</tr>
<tr>
<td>+</td>
<td>(9)</td>
</tr>
<tr>
<td>±</td>
<td>(8,31,33)</td>
</tr>
</tbody>
</table>

(B) **Alkaloids**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>±</td>
<td>(12)</td>
</tr>
<tr>
<td>+</td>
<td>(80)</td>
</tr>
<tr>
<td>±</td>
<td>(51)</td>
</tr>
<tr>
<td>+++</td>
<td>(45,42)</td>
</tr>
</tbody>
</table>

(C) **Inorganic and Metal organic drugs**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na₃AuS₂P₃ (Sanocrysin)</td>
<td>++</td>
<td>(67)</td>
</tr>
<tr>
<td>Ag-Aeriflavin, Ag-proflavine</td>
<td>±</td>
<td>(70)</td>
</tr>
<tr>
<td>FeCl₃</td>
<td>±</td>
<td>(50)</td>
</tr>
<tr>
<td>Silica</td>
<td>±</td>
<td>(14)</td>
</tr>
<tr>
<td>Cu-thiouremith-Na-benzoate</td>
<td>+</td>
<td>(66,50)</td>
</tr>
<tr>
<td>Germanium Dioxide</td>
<td>±</td>
<td>(65)</td>
</tr>
</tbody>
</table>

(D) **Phenols and Aromatic ethers**

Many phenolic compounds, their esters and ethers possess bactericidal properties in experimental tuberculosis.
infections(15). Burger and Bernheim studied significant
tuberculostatic specificity exhibited by series of halogenated
dialkylaminoalkyl phenyl ethers of the type -

![Chemical Structure](image)

(35) Friedman, Braitberg and others studied
tuberculostatic activities of substituted 2-Alkoxy pyridines.

(E) Benzothiazole derivatives:
Several simple amino derivative of benzothiazole
have been found to have considerable in vitro activity(39).

(F) Diarylamines:
Diphenylamine inhibits the vital oxidative functions
of tubercle bacilli. Basic dyes, especially Indamane-Blue
(extra) and deeply colored 2-Anilino-3-imino-5-phenylphenazines(6) inhibits the growth of tubercle bacilli at a
concentration of 1x10^{-6}.

(G) Aliphatic acids:
Stanley, Adams, and their co-workers(1,73) observed
that various fatty acids, which may or may not contain ring
structure are tuberculostatic in vitro provided that a
relatively narrow range of the molecular weight be retained.
(H) Aromatic sulfones:

The introduction of the highly bacteriostatic bis-(4-aminophenyl)-sulfone(16) was significant in antitubercular chemotherapy. Promin and Diasone have relatively favorable therapeutical indices and clinical trials of these drugs have become feasible.

A series of heterocyclic sulfones, synthesised by Bambas(7) of which promizole is found least toxic and most effective drugs(37).

(I) Thiosemicarbazones:

Sulphathiazole is only useful drug which exhibit some antitubercular activity in vitro, and hence thiazole moiety is important part for this activity.

Benzal thiosemicarbazone, showed good tuberculostatic activity. It was Domagk(24) who singled out the thiosemicarbazone of p-acetamidobenzaldehyde as a most promising drug. The thiosemicarbazone of 4-aminosalicylaldehyde inhibits the in vitro growth of tubercle bacilli as effectively as streptomycin(25).

(J) Tuberculostatic Antibiotics:

The toxicity of most of these antibiotics prohibits clinical studies with the notable exception of Streptomycin.
Its bactericidal(64) action and low toxicity has led to its manufacture. The significance of Neomycin and other tuberculostatic Antibiotics possess high antitubercular activity even against streptomycin-resistant stains of bacteria, but it is quite toxic(28,43). The antibiotic viomycin from streptomyces flordiae shows similar properties(3).

(K) Thioureas and their derivatives:

Thiourea and its derivatives are tuberculostic. Thiourea itself possesses a slight but definite activity in vitro, which is enhanced by appropriate substitution as in allyl thiourea(41) and especially in p-aminobenzene sulphonyl thiourea(49). Discovery of N-N'-di-(p-n-butoxy phenyl) thiourea and related compounds are found to be having outstanding tuberculous activity and has been confirmed by a series of N-N'-diaryl thiourea(17).

In 1944 a patent(13) was issued for copper compounds made from thiourea benzoic acids which were said to be active in treating tuberculosis.

In 1952 a number of thiourea derivatives of p-amino salicylic acid in in vitro studies were found to be equally active or more active than the acid itself(63). Further 4-4' diethoxy thiocarbanilide was found to possess high antitubercular activity in mice infected with bacillus H37RV (47,48).
Mechanism of Antituberculous Action:

There is at present no established mechanism for the activity of any of the antituberculous agents despite considerable speculation and the elaboration of a number of theories. The thiosemicarbazones, the thioureas, the thio oxamic acids, p-aminosalicylic acid and Isoniazid are thought to own their antitubercular activity, owing to their ability to form stable complexes with certain heavy metals such as copper and iron, which are essential to the metabolic processes of tubercle bacillus (13, 20, 22, 36, 28, 71).

Bergel considers the antituberculous activity of a compound as a function of its antioxidant activity(5). Streptomycin is believed to inhibit tubercle bacillus by a mechanism which involves the oxidation of fatty acid(79). Isoniazid is considered to be an antimetabolite(5). Another view suggests that the antitubercular activity of isoniazid may be related to its activity to displace Niacinamide from diphosphopyridine nucleotide (DPN) to form an Isoniazid analog of DPN.

Antitubercular compounds: (Previous work):

Acylthiocarbamides gave an expressed antitubercularostatic effect in mice and guinea-pigs with no toxic effect.

\[ \text{iso-Pr-CH}_2\text{-CH}_2\text{-O-} \begin{array}{c} \text{NHCS.NH.CO}_2\text{C}_2\text{H}_5 \end{array} \]
Above title compound was synthesized by Toldy, L; and others(76).

Chemotherapeutic effect of antitubercular agents such as Kanamycin and ethambutol was studied by Ohta; and Yoshiko(54) against tubercle bacilli in the resting state on animals.

Toxicity of Tuberactionomycin was studied by Akiyoshi, Masatoyo Sato, Kiichi(2), who isolated it from streptomyces griseoverticillatus tuberacticus, it exhibited mild toxicity in guinea-pigs less than that of Viomycin, Kanamycin and Capreomycin.

It was Kharizanova T; and others(44) who studied activity and Virulence of Mycobacterium tuberculosis treated in vitro.

Ultra structure of some strains of Mycobacterium tuberculosis (isolated from patients) with different sensitivity to Isoniazid and streptomycin was studied by Radanov, R; and others(59).

Deshpande S.M; Singh A.K.(23), who synthesized N-N'-di-9-acridino-6-diamino alkane dihydrochloride as potential antibacterial, antitubercular and antileprotic agents.

Antibacterial activity of dihydro-1,3-oxazine derivatives condensed with aromatic rings in position 5;6 by Chylinska J.B. and others(17) and have marked
Antituberculosis activity in mice and guinea pigs, infected with various strains of Mycobacterium tuberculosis below 2 mcg/ml. in vitro.

Effect of dimethyl sulfoxide on tubercle bacilli resistant to isonicotinic acid hydrazide studied by Ropek and Cowon (61) shows tuberculostatic activity in vitro with low toxicity to the host cells.

Voinescu R, and others studied (81) Rifampicin activity on tubercle bacilli in vitro.

Wei Peter H.L. and Bell Stanley C; have patented thiazolo(3,2-a) benzimidazole compounds of the type I & II.

\[
\text{(I)}
\]

\[
\text{(II)}
\]

where I and II have antitubercular and central nervous depressant activity. (77)
Berdinskii I.S. (10) and others have synthesized substituted hydrazides of hydroxy carboxylic acids. Chlorophenyl hydrazides of diaryl and dialkyl glycolic acids such as Cl.C₆H₄NH.NH.CO.C.R₂.OH (I) and Cl.C₆H₄N.X.NH.CO.CR₂OH (II). These compounds show antitubercular activity higher for para than meta isomers, they also possess 80% antispasmodic activity.

Experimental study of the antitubercular activity of Butomelide of following type was studied by Pershin G.N. (56) and Zykova, T.N. It is much more active than ethoxide in mice tuberculosis.

\[
\text{Structure anti-bacterial activity relations of aryl thioxamides and Tuberculosis activity in vitro of some arylvinylene thioamides was studied by Tornetta B; and others(75).}
\]

Wang Lynn and Takayamakuni studied relation between the uptake of Isoniazid and its action on in vivo, mycolic acid synthesis in Mycobacterium tuberculosis.

Utilization of MH (Maleic hydrazide) as antituber in growing Chines Yams, was studied by Satoh I. Chiro, Tanabe, Kenji (62).
2-thiazolecarboxyhydrazide has shown tuberculostatic activity(12).

Bavin and his coworkers(89) claim that 1-Dinito-
nyl-2-(o-hydroxy) benzylidine hydrazine is better than
isoniazid, because it is almost as active as the latter and
much less toxic.

p-(Benzene sulphonamide)benzoic hydrazides(29),
iso-nicotinoyl hydrazones and N'-isonicotinoyl-N"-
cycloalkylylhydrazines(61); Dibutylglycolic acid hydrazides
(42); (Pyrid-2-yl)aliphatic acid hydrazides(58); R2N(CH2)n
COMNH2(27), N2-substituted isonicotinic acid hydrazide(52),
2-hydroxy-4- and 2-hydroxy-5-alkoxy-benzhydrazides; 1-(3,4-
methylenedioxyphene-ethyl)-4-ethoxycarbonylmethyl-5-
pyrazolone hydrazide (46); 2-(2,5-dimethyl-1-pyroyl)
benzhydrazides (84) and 2-Amilino 1,3,4 thiadiazoly-5-
acetyl hydrazide (68) have been prepared and tested for their
tuberculostatic activity.

Mizzoni(53) prepared 2-phenylimino-3-phenyl-
4-thiazolidinone and its derivatives and reported them as
antitubercular or antileprotic agents.

Several 4-thiazolidinone derivatives have been
found by Mizzoni and Eismann(28, 34) to be antitubercular
agents.

Brown et al.(14) prepared 3-aryl and -3-benzyl
Rhodanines and -3-benzyl, 2,4, thiazolidinediones. They found
that 3-aryl substituted compounds exhibited bacteriostatic activity.

N-N'-bis-(2-hydroxy ethyl) derivatives of ethylenediamine containing thiamide groups are reported as potential antitubercular(57).

Hydrazone derivatives of 2,4, thiazolidine diones obtained from thiosemicarbazones by reaction with chloroacetic acid show tuberculostatic activity, though lower than original thiosemicarbazone. Maximum activity was observed where \( R' = H, R = O\)-hydroxyphenyl(60).

\[
\begin{align*}
R' & \quad \text{NH} \\
R - C = N - N - & \quad \text{CO} \\
& \quad \text{CH}_2 \\
& \quad \text{S}
\end{align*}
\]

3-amino-Rhodamine and its derivative are useful as effective tuberculostatic and fungistatic agents(78).

2-hydroxyimino-3-phenyl-4-thiazolidinones has been found to be active against Mycobacterium tuberculosis(74).

2-anilino-1,3,4 thiadiazoyl-5-acetyl-hydroxy(62) have been prepared and tested for the tuberculostatic activity.

4-4'-bis(hydrazine)diphenyl methane(77) have been synthesised and possess antituber activity.

Antitubercular activity of sulfoniy benzothiazole
was considerably active at 1 µg/ml against Mycobacterium tuberculosis H$_{37}$Rv (18).

Pyridine-4-thiocarboxamide shows antituberculous activity in vitro (72).

HCl-salts of N-N'-bis(β-hydroxy alkyl) diamine studied by Butula et al. (11) as useful a tuberculostatic.

El-sebai et al. (32) synthesized some new acid hydrazides structurally related to certain tuberculostatic agents such as isonicotinic hydrazide.

El-sebai et al. (30) synthesized some isoniazid derivative as potential tuberculostatic agents. Such as Isonicotinyl hydrazono acetyl arylamines.

From these observations we were led to synthesize series of compounds having benzyloxy oxamide moiety; in order to investigate the tuberculostatic activity of above products with a hope to evaluate some structural relationship with the activity.

Section - I
(Possible antituber compounds)

\[
\text{EtOH} \xrightarrow{H_2N(CH_2)_3NMMe_2} \text{EtCOOCOC}_2H^+ \xrightarrow{H_2O} \text{Y-CH}_2O-\text{NHCOCOOCH}_2H^+ \xrightarrow{\text{EtOH}} \text{Y-CH}_2O-\text{NHCOCO}N(CH_2)_3NMMe_2.HCl}
\]

Ethyl-N(4-Sub.-benzyloxy)-Phenyloxamide
(From Part - I)

\[
\text{Y-CH}_2O-\text{NHCOCO}N(CH_2)_3NMMe_2.HCl}
\]

[NN'-Di-Me-amino-propyl-(4-sub-benzyloxy)-phenyl-oxamide.
-HCl] Where Y = H, 4-CH$_3$, 4-OCH$_3$, 4-Cl, 4-Br.
EXPERIMENTAL

1. Preparation of sub-Benzylloxyanilines:
   (See Part I - experimental)

2. Preparation of subst-Ethyl-N^-sub-benzylox^oxaml^'te:
   (See Part I - experimental)

3. Preparation of possible antitubercular compounds:

   General Procedure:
   
   0.01 M of 5-Ethyl-N-benzyloxy oxamide was taken in a 250 ml R.B.Flask, fitted with a reflux condenser and 0.01 M dimethyl propylamine in absolute alcohol 10 ml, was slowly added, the mixture was refluxed on a waterbath for 1 hr. After cooling the reaction mixture the product obtained was filtered through water suction pump, dried and recrystallised from Absolute Alcohol yield (80%). The mother liquor partly evaporated under reduced pressure, gave a second crop with little impurities (10%) which on successive recrystallization from absolute ethanol approved more of the same product. Total yield is (90%). Reactions are as follows:

\[
\begin{array}{c}
\text{Y} \quad \text{CH}_2\text{O} \quad \text{NH-CO-CO-OC}_2\text{H}_5 \\
\xrightarrow{\text{EtOH}} \quad \text{H}_2\text{N(CH}_2\text{)}_3\text{NMe}_2 \\
\text{Ethyl-N-(4-Sub-benzyloxy)-Phenyl-oxamide}
\end{array}
\]

(From - Part - I)
PART - II

SECTION - I

EXPERIMENTAL
REFERENCES

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PART - II

SECTION - II

GENERAL
Where, \( Y = H; 4\text{-Cl}; 4\text{-Br}; 4\text{-Me}; 4\text{-OCH}_3 \)

By this general method the compounds prepared are described in table given below No. 1. Some compounds are for testing purpose converted into their Hydrochloride salts.
TABLE 1

\[
\begin{align*}
\text{R} & \quad \text{M.P.} \quad \text{Molecular} \quad \text{Mol. Wts.} \quad \% \text{ of} \quad \text{Nitrogen} \\
 & \quad ^\circ \text{C} \quad \text{formula} \quad \text{in} \quad \text{Calc.} \quad \text{Found} \\
\text{p-H} & \quad \text{98} \quad \text{355} \quad 11.83 \quad 11.84 \\
(\text{HCl salt}) & \quad \text{208} \quad \text{C}_{20}\text{H}_{25}\text{N}_{3}\text{O}_{3} \\
\text{p-CH}_{3} & \quad \text{140} \quad \text{369} \quad 11.39 \quad 11.40 \\
(\text{HCl salt}) & \quad \text{189} \quad \text{C}_{21}\text{H}_{27}\text{N}_{3}\text{O}_{3} \\
\text{p-Cl} & \quad \text{185} \quad \text{389.5} \quad 10.78 \quad 10.77 \\
(\text{HCl salt}) & \quad \text{211} \quad \text{C}_{20}\text{H}_{24}\text{N}_{3}\text{O}_{3}\text{Cl} \\
\text{p-Br} & \quad \text{150} \quad \text{434} \quad 9.69 \quad 9.70 \\
\text{p-OCH}_{3} & \quad \text{144} \quad \text{385} \quad 10.96 \quad 10.94 \\
\end{align*}
\]

All these compounds were crystallized from benzene.
Part - II

(Section - II)

Oxamides, Semioxamides, Oxamazones and Bis-Hydrazides

General:

It is known that some esters, such as the Alkyl oxalates, give an immediate precipitate of the amide when treated with 30% solution of ammonia. Although this reaction does not generally proceed so easily with the majority of esters, it can nevertheless be employed as a fairly general method of preparation if the experimental conditions are modified. Thus the methyl esters of n-butyric acid and its immediate homologues give the corresponding amides in fairly good yield by agitation with 30% solution of ammonia at room temperature for 12-30 hrs. If the amides are soluble in water, they can be isolated from the product by extraction with chloroform. The reaction of the higher homologues with aq. NH$_3$ is much slower and not very satisfactory. The amides of some aromatic acids may be obtained by similar process (H. Meyer, Monatsh., 1906, 27, 31). This type of preparation has been used successfully for the preparation of a number of hydrazides, by using hydrazine hydrate in place of ammonia.

Hydrazine derivatives other than the aryl and arylalkyl hydrazines are frequently employed for the characterisation and recognition of carbonyl compounds of
these, semicarbazide, $\text{NH}_2\text{CO.NH.NH}_2$ gives crystalline condensation products with most aldehydes and ketones and is extensively used; other reagents less commonly employed are thiosemicarbazide $\text{NH}_2\text{CS.NH.NH}_2$, benzoylhydrazine, Ph.CO.NH.NH$_2$ and its nitrosubstituted derivatives, semioxamazide $\text{NH}_2\text{CO.CO.NH.NH}_2$ and aminoguanidine $\text{NH}_2\text{N.C.NH.NH}_2$. Semi oxamazide has been used for the characterisation of aldehydes when the semicarbazones are not satisfactory (Kerp and Unger, Ber, 1897, 30, 585; Perf. and Essential Oil Record, 1919, 10, 39).

The reaction appears to be a general one for aldehydes, for ketone special precautions are necessary, suitable experimental conditions with this object are described by Wilson and Pickering (J. 1923, 123, 391; 1924, 125, 1152).

Theoretical:

The preparation of hydrazides by interaction of esters and hydrazine hydrate is quite straightforward and proceeds in good yields. In many cases, simple addition of hydrazine-hydrate to the liquid esters suffices to cause the precipitation of hydrazide. P.A.S. Smith, Org. Reactions, 3, 337 (1946)

If the esters are insoluble for solids, or more prolonged treatment is required usually in the presence of an
alcohol, as the preparation of terephthalic hydrazide.
(Preparative Methods of polymer chemistry, p. 103 New York, 1961).

General methods for preparation of hydrazides:

1. Preparation of 1-substituted hydrazides by addition of sodamide to N-chloroacetanilides:

$$\text{W.F. Short, J. Chem. Soc. 119, 1446 (1921)}$$

$$\begin{align*}
\text{N} & - \text{C} - \text{CH}_3 + \text{NaNH}_2 \rightarrow \\
\text{Cl} & = \text{O} \\
\end{align*}$$

2. Preparation of azines and Dihydrazide from malonic ester derivatives:

$$\text{C.N. O' Callaghan and D. Twomey, Proc. Roy. Irish, Acad, 63, No. 12, 217 (1964)}$$

$$\text{R. West, M. Ishikawa and R.E. Bailey, J. Am. Chem. Soc. 88, 4648 (1966)}$$

$$\begin{align*}
\text{Me}_2\text{N} - \text{C} - \text{H} = \text{C} & \text{CO}_2\text{C}_2\text{H}_5 + \text{NH}_2\cdot\text{NH}_2(\text{H}_2\text{O}) \rightarrow \\
\text{Me}_2\text{N} & \text{N} - \text{N} = \text{C} - \text{H} \\
\end{align*}$$
Hydrazones:


The preparation of acyl hydrazone from hydrazides has been described by L. Spialter, D.H; O'Brien, G.L. Untereiner, and W.A. Rush [J.Org.Chem. 30, 3278 (1965)].

The reaction of hydrazine with carbonyl compounds frequently leads to the formation of azines, if an excess of carbonyl starting material is present. However, with an excess of hydrazine the simple hydrazone can be prepared (H.L. Lochte, W.A. Noyes, and J.R.Bailey; J.Am.Chem.Soc. 44, 2526 (1922).

General Methods for preparations of Hydrazones:
Vvedenskii V.M. (65) and others synthesized various hydrazides from parahnic acid by hydrazinolysis, i.e.
Parahnic acid (I) reacted with BZNH.NH2 and Ph2N.NH2 to give H2N.CO.NHCO.CO.NH-NR1R2 where (R = H, R' = Bz, R = R' = Ph) dihydrazide were obtained from (I) and Bz-NHNH2 and Isoniazid. (I) with oxalic acid and adipic acid dihydrazide gave (H2N.CO.NH.CO.CO.NH.NH.CO2)(CH2)n, n = 0, 4. The hydrooxamic acid H2N.CO.NH.CO.CO.NH.OH was prepared from I and OH.NH2.HCl.
A.S. Shawali (42) and others synthesised oxamic arylhydrazides by the acidic hydrolysis of $N^3-N^3$-Disubstituted Aminohydrazones. Shindo (44) and coworkers synthesized 5-substituted 2-aminobenzophenone hydrazones which inhibit the central nervous system, the title compounds are of the type given as below.

\[
\begin{array}{c}
\text{Perronnet (31) and others synthesized 2- \text{(phosphorylthio)acetohydrazides which are useful as acaricides.}}
\end{array}
\]

It was Zakalynzhnyi M.V. (69) who synthesized bis-(Arylmethylene)deri. of ethylene 1-2-dioxamic acid dihydrazide for their biological activity and were found inactive in vitro against acid resistant saprophyte $B_5$ and human and bird tuberculosis bacillic at 1:1000 dilution; the title compounds are of the following type,

\[
\begin{array}{c}
H_2N\text{.NH.CO.CO.NH.CH}_2\text{.CH}_2\text{.NH.CO.CO.NH.NH}_2(I) \text{ condensed with R-CHO to give the corresponding (R-CH = N.NH.CO.CO. NH.CH}_2\text{)}_2 (II). \text{ Some biological active compounds synthesized by Berdinskii I.S. (11) and others of the type substituted hydrazides of hydroxy carboxylic acids, chlorophenylhydra-}
\end{array}
\]
zides of diaryl- and dialkyl glycolic acids, 
\(\text{Cl.C}_6\text{H}_4-\text{NH.NH.CO.CR}_2\text{-OH(I)}\) and \(\text{Cl.C}_6\text{H}_4-\text{NX.NH.CO.CR}_2\text{OH(II)}\) shows antitubercular activity higher for para than meta isomers; they also possess 80% antispasmodic activity.

P.A. Petyumin (35) (USSR) synthesised acyl derivative of the N-butyloxamic acid phenyl hydrazide for analgesic activity (Ph.NH.NH.CO.CO.NH.Bu); their Morphilino HCl salt was having greater analgesic activity than that of amidopyrine.

Storozheva A.V.(51) and others synthesized some analgesic and antitubercular active compounds of acyl derivative of arylhydrazides of N-substituted oxamic acid. The reaction of \(\text{R-C}_6\text{H}_4\text{-CO.N.Ph.CO.N.Ph.NH.CO.CO}_2\text{Et(I)}\) with \(\text{R'}-\text{NH}_2 (\text{R'} = \text{Alkyl, Aralkyl})\) gave \(\text{R-C}_6\text{H}_4\text{-CO.N.Ph.NH.CO.CO.NH.R'} (\text{II})\). Thus II exhibited analgesic and antitubercular activity. It was Westermann and other(67) who studied \(N^{15}\)-labelled Urea and oxamide as fertilizers. P.A. Petyumin has synthesized Arylsulphonyl oxamides(34).

Structural antibacterial activity relations of aryl thiooxamides shows tuberculostatic activity in vitro(58).

Utilization of M3 (Maleic hydrazide) as antituber-in growing Chines Yam) was studied by Satosh, I. Chiro, Tunabe, Kenji(45).
2-thiazolecarboxyhydrazide has shown tuberculostatic activity (9).

Bavin and his coworkers (7,8) claim that 1-Isonicotinyl-2-(o-hydroxy) benzylidine hydrazine is better than Isoniazid, because it is almost as active as the latter and much less toxic.

p-(Benzene sulphonamido-) benzoic Hydrazides (16); Isonicotinoyl hydrazones and N'-isonicotinoyl-N''-cycloalkylhydrazines, dibutylglycolic acid hydrazide (22), (Pyrid-2-yl)aliphatic acid hydrazides, R₂N(CH₂)₅CO.NH.NH₂ (15), N²-substituted isonicotinic acid hydrazide (27), 2-hydroxy-4-and-2-hydroxy-5-alkoxybenzhydrazide (55), 1-(3-4-methylene-dioxyphene-ethyl)-4-ethoxy carbonyl methyl-5-pyrazolone hydrazide (24), 2-(2-5-dimethyl-1-pyroyl)benz hydrazides (68), and 2-amilino-1,3,4-thiadiazolyl-5-acetyl hydrazide (45) have been prepared and tested for their tuberculostatic activity.

Petyumin has also synthesized Basic amides of alkoxy-oxamitic acid (34).

David Libermann and others studied chemotherapy of tuberculosis of acid hydrazides and hydrazones (13).

Derivatives of semioxamazide (I) (66) with carbonyl compounds, possess the advantage of facile hydrolysis, thus permitting easy regeneration of the aldehyde or ketone 5-substituted semioxamazides have been suggested as reagent.
for the identification of carbonyl compounds, but 5-phenyl semioxamazide\(^{(56,39)}\) and 5-methylsemioxamazide formed derivatives which have uniformly high M.P. 5-(\(\alpha\)-phenylethyl) semioxamazide\(^{(30)}\) possesses more satisfactory M.P.

Mizzoni\(^{(28)}\) prepared 2-phenylimino-3-phenyl-4-thiazolidinone and its derivatives and reported them as antitubercular or antileprotic agents.

Several 4-thiazolidinone derivatives have been found by Mizzoni and Eisman \(^{(14,29)}\) to be antitubercular agents.

Brown et al\(^{(6)}\) prepared 3-aryl and 3-benzyl Rhodanines and 3-benzyl 2,4, thiazolidinediones. They found that 3-aryl-substituted compounds exhibited bacteriostatic activity.

N-N-bis-(2-hydroxyethyl) derivatives of ethylene-diamine containing thioamide group are reported as potential antitubercular\(^{(33)}\).

Hydrazone derivatives of 2,4,thiazolidinediones obtained from thiosemicarbazones by reaction with chloroacetic acid show tuberculostatic activity, though lower than original thiosemicarbazone. Maximum activity was observed
where \( R' = H, R = \text{0-hydroxyphenyl} \). 

\[
\begin{align*}
\text{R' & } \text{H} \\
\text{R - C = N - N & } \text{C S} \\
\text{NH & CO} \\
\text{CH}_2
\end{align*}
\]

3-amino Rhodanine and its derivatives are useful as effective tuberculostatic and fungistatic agents (59).

2-hydroxyimino-3-phenyl4-thiazolidinone has been found to be active against mycobacterium tuberculosis (57). Following compounds are also exhibiting tuberculostatic property then are 1-2 Bis (R-substituted)perhydro-pyridazine-3,6-diones (18), 4-methythiazolyl-2-hydrazides and 4-alkoxybenzal-hydrazides of 2-alkoxy-5-bromo-benzoic acid (4); N'- (Methoxy thiocarbonyl) hydrazide and N'- (Methoxy thiocarbonyl)-N^2-4'-chlorobenzaldehyde hydrazone (1). Oxanilic hydrazone rearrangement was observed by shawali, A et al. (43).

Hydrazone derivative acts as useful fungicide as observed by Butta et al. (10).

4-4'-bis(Hydrazine)diphenyl methane (53), 4-alkoxyphenyl alkane carboxylic acid-hydrazides (5), Indol-2-(or 3)-ylkyl hydrazides (32) L-N-carbobenzyloxy glutamic acid-5-hydrazide (60), cyanoacetic acid hydrazide and cyanoacetic acid hydrazones of the lower carbonyl groups (41); N-(4-methyl
piperazine)-9-Xanthene carboxamide (19); 3-4-dimethoxy-6-chlorobenzoic hydrazide (58), Hydrazide of Et-\(\text{O} \)-\((N\text{-azacylalkyl})\)-propionates (12), Me\(\text{CO}_2\)-Ph-Ph-NH-NH\(_2\) (52) (2-oxo-3-indolinyldene) hydrazides of alkenoic acids (61), p-(bis-chloroethyl) amino benzylidene hydrazide of N-acetyl-tryptophan (23); \(\text{O}\)-alkyl-\(\text{O}\)-(p-Bromo benzy1 acetohydrazide) (38), 1-(\(\text{O}\)-hydroxy propionyl)-2-phenyl-ethyl hydrazides stearoyl hydrazide (62), N-benziloyl-N\(^1\)-(2-piperidinoethyl) hydrazine (64), Hydrazides of 3-pyridazine carboxylic acid (46), 6-hydroxy-4-quinoliniline hydrazide (3), 2-(3-4-dihydroxy benzyl)-hydrazide (20), 2,6-dihydroxy isonicotinic acid hydrazide (47), Fluurene-9-carboxylic acid hydrazide (48), -Ureidobutyric acid hydrazide (25), 5-Methyl-2-flurohydrazide (26) and 2-benzo-thiazolyl carboxylic acid hydrazides (37) have been synthesized; some of them possess physiological activity.

From these observations we were led to synthesize series of compounds having semi-oxamizide structure containing benzyloxy moity along with structurally related Bis-hydrazides, and semioxamazones of carbonyl compounds in order to investigate the tuberculostatic activity of the above products with a hope to evaluate some structure relationship with the activity.
PART - II

SECTION - II

EXPERIMENTAL
Section II

(Semi-oxamazides and semi-oxamazones)

(a) Y—\( \text{CH}_2\text{O} \)-\( \text{NHCOCONHN} \)

[\text{Ethyl-N}(4\text{-Sub.-benzyloxy})\text{Phenyl-oxamide}]

(From Part - I)  (I)

(b) (I) + (II) Ethylene glycol

in ethylalcohol

\[ \xrightarrow{\text{Reflex}} \]

[\( \text{NH}_{\text{NH}} \)]

[\text{N-(4-Sub.-benzyloxy)-phenyl-Bis-Hydrazide}]

(III)

(c) (II) + R-CHO I\(_2\) in C\(_6\)H\(_6\)

(Aldehyde)

\[ \xrightarrow{\text{Reflex}} \]

\( \text{Y} \)

\( \text{CH}_2\text{O} \)-\( \text{NHCOCONHN} \)

(IV)
Benzylidine derivative of-
-N-(4-sub.benzylxy)phenyl-oxamic acid-
carbonyl Hydrazones

(II) + R-CO-R' \xrightarrow{I_2 \text{ in } C_6H_6} \text{(Ketone)}

![Chemical Structure]

(V)

IV & V are semioxamazones of aldehydes and Ketones

Where Y = same as in Section - I.

Aldehydes taken: Benzaldehyde, Salicyaldehyde,
Cinnamaldehyde, vanillin, Furfural,
Anisaldehyde, n-butyraldehyde.

Ketones taken: Acetone, Me-ethyl ketone,
Cyclohexanone, Benzophenone,
Acetophenone
Experimental

Oxamides; semi-oxamazides; and semi oxamazones

1. Preparation of Benzyloxy anilines
   Refer Part - I (experimental)

2. Preparation of Benzyloxyaniline ester
   Refer Part - I (experimental)

3. Preparation of semi-oxamazides

3. Preparation of substituted benzyloxy-semi oxamazides:
   Procedure: To a solution of 20 gms (0.1 M) of the benzyloxy oxamate in 200 ml absolute EtOH, was added with stirring 6.0 gm. (0.1 M) of 85% Hydrazine Hydrate. A gelatinous precipitates formed immediately and entire content of the reaction flask becomes semi-solid. The crude product was dissolved in minimum quantity of absolute alcohol. The solution was filtered to remove traces of dihydrazides of oxalic acid. The very fine needles which separated from the filtrate were recrystallized from the ethanol, to give 20.5 gm. 93% of benzyloxy semi-oxamazide, compounds are described in table No. 1.

\[
\text{Et-(4-sub.-benzyloxy)-phenyl oxamate} + \text{Hydrazine Hydrate} \rightarrow \text{5-(4-sub.-benzyloxy)-phenyl-semi-oxamazide}
\]

Where, \( Y = \text{H, 4-Cl; 4-Br; 4-Me; 4-OCH}_3 \)
**TABLE 1**

\[
R- \begin{array}{c}
\text{C}_6\text{H}_4
\end{array}
\text{--CH}_2\text{--O--} \begin{array}{c}
\text{C}_6\text{H}_4
\end{array}
\text{--NH\cdot CO\cdot CO\cdot NH\cdot NH}_2
\]

\[\text{L-5-(4-Sub-benzyloxy)phenyl-Semioxamazides}\]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Nitrogen Cal. Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. p-H</td>
<td>212</td>
<td>C_{15}H_{15}N_{3}O_{3}</td>
<td>285</td>
<td>14.73</td>
<td>14.74</td>
</tr>
<tr>
<td>2. p-CH_{3}</td>
<td>204</td>
<td>C_{16}H_{16}N_{3}O_{3}</td>
<td>308</td>
<td>13.63</td>
<td>13.64</td>
</tr>
<tr>
<td>3. p-Cl</td>
<td>222</td>
<td>C_{15}H_{14}N_{3}O_{3}Cl</td>
<td>319.5</td>
<td>13.16</td>
<td>13.18</td>
</tr>
<tr>
<td>4. p-Br</td>
<td>200</td>
<td>C_{15}H_{14}N_{3}O_{3}Br</td>
<td>364</td>
<td>11.53</td>
<td>11.54</td>
</tr>
<tr>
<td>5. p-OCH_{3}</td>
<td>164</td>
<td>C_{16}H_{16}N_{3}O_{4}</td>
<td>324</td>
<td>12.90</td>
<td>12.97</td>
</tr>
</tbody>
</table>

All compounds were crystallized from Absolute EtOH.
Preparation of substituted benzyloxy-Bis-Hydrazides:

0.01 M substituted semi oxamazide (II) was condensed with 0.01 M symmetrically substituted benzyloxy phenyl oxamide (I) in 15 ml absolute EtOH, in presence of ethylene glycol (CH₂OH)₂ (1 ml.). Refluxed for 1 hr. The mixture was filtered, cooled to get needle shape crystals, compounds were purified in absolute alcohol. Reactions were stated as below. Compounds are described in table No. 2.

\[
\begin{align*}
Y \quad & \quad \text{CH}_2\text{-O-} \quad \text{NH} \cdot \text{CO} \cdot \text{CO.} \text{OC}_2\text{H}_5 \\
\text{(I)}
\end{align*}
\]

EtOH Ethylene glycol

\[
\begin{align*}
\text{H}_2\text{N} \cdot \text{NH} \cdot \text{CO} \cdot \text{CO} \cdot \text{NH} \cdot \text{O-CH}_2\text{-} \quad \text{Y} \\
\text{(II)}
\end{align*}
\]

\[
\begin{align*}
\text{Y} \quad & \quad \text{CH}_2\text{-O-} \quad \text{NH} \cdot \text{CO} \cdot \text{CO} \cdot \text{NH}_2 \\
\text{(III)}
\end{align*}
\]

Where, \( Y = \text{H}; 4-\text{CH}_3; 4-\text{Cl}; 4-\text{Br}; 4-\text{Me}; 4-\text{OCH}_3 \)
TABLE 2

\[
\begin{array}{c}
\begin{array}{c}
\text{R} \\
\text{CH}_2\text{O} \\
\text{NH-CO.CO.NH}_2
\end{array}
\end{array}
\]  
\[
\text{N}(4\text{-substituted-benzylxy})\text{phenyl-Bis-Hydrazides}
\]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>M. P. °C</th>
<th>Molecular formula</th>
<th>Molecular wts. gms.</th>
<th>% of Cal. N</th>
<th>Found N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>185\text{a}</td>
<td>C\text{\textsubscript{30}}\text{H}\text{\textsubscript{26}}N\text{\textsubscript{4}}O\textsubscript{6}</td>
<td>538</td>
<td>10.41</td>
<td>10.41</td>
</tr>
<tr>
<td>2</td>
<td>p-CH\textsubscript{3}</td>
<td>145\text{b}</td>
<td>C\text{\textsubscript{31}}H\text{\textsubscript{27}}N\text{\textsubscript{4}}O\textsubscript{6}</td>
<td>551</td>
<td>10.16</td>
<td>10.15</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>173\text{a}</td>
<td>C\text{\textsubscript{30}}H\text{\textsubscript{24}}N\text{\textsubscript{4}}O\textsubscript{6}Cl\textsubscript{2}</td>
<td>607</td>
<td>9.22</td>
<td>9.22</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>165\text{a}</td>
<td>C\text{\textsubscript{30}}H\text{\textsubscript{24}}N\text{\textsubscript{4}}O\textsubscript{6}Br\textsubscript{2}</td>
<td>696</td>
<td>7.86</td>
<td>7.86</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH\textsubscript{3}</td>
<td>181\text{b}</td>
<td>C\text{\textsubscript{31}}H\text{\textsubscript{27}}N\text{\textsubscript{4}}O\textsubscript{7}</td>
<td>567</td>
<td>9.87</td>
<td>9.87</td>
</tr>
</tbody>
</table>

\text{a. crystallized from EtOH} \quad \text{b. crystallized from C\textsubscript{6}H\textsubscript{6}}
(5) **Preparation of semi-oxamazones:** Condensation of semi-
oxamazide with Aldehydes and Ketones

**Procedure:** To 0.1 gm. of aldehyde or ketone in 20 ml anhydrous benzene was added 0.2 to 0.5 gm. of the reagent. A crystal of I₂ was added and the reaction mixture was refluxed for 5 to 10 minutes (till substance dissolved), vigorous anhydrous conditions were maintained for the success of the reaction, to get semi-oxamazones. The derivative obtained, crystalized out when C₆H₆ solution was cooled. If the derivative was too soluble in C₆H₆, the addition of low B.P. petroleum ether was added to cause precipitation. Absolute alcohol is successful solvent for aldehyde derivatives but benzene or petroleum ether are necessary for ketone derivatives; all of which were readily hydrolysed. All these are slightly coloured substances compounds are described in tables No. 3 to 14.

\[
\begin{align*}
Y - &\begin{array}{c}
\text{Phenyl} \\
\text{OR} \\
\text{Alkyl}
\end{array} - \text{CH₂-O} - &\begin{array}{c}
\text{Phenyl}
\end{array} - \text{NH-CO-CO.NH-N} = C
\end{align*}
\]

Benzylidine derivatives of carbonyl hydrazones of N-(4-substituted benzyloxy)-phenyl-oxamic acid

Where, \( Y = H; 4-\text{CH₃}; 4-\text{Cl}; 4-\text{Br}; 4-\text{OCH₃} \)
TABLE 3

Name of carbonyl compound: Benzaldehyde (A.R.)

\[
\begin{align*}
\text{Benzylidine deri. of: } & \text{N}^4(4\text{-sub.benzyloxy})\text{-phenyl-} \\
& \text{oxamic acid-phenyl-Hydrazone}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Cal.</th>
<th>Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>250</td>
<td>C_{22}H_{19}N_{3}O_{3}</td>
<td>373</td>
<td>11.27</td>
<td>11.28</td>
</tr>
<tr>
<td>2</td>
<td>p-Me</td>
<td>221</td>
<td>C_{23}H_{21}N_{3}O_{3}</td>
<td>387</td>
<td>10.82</td>
<td>10.81</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>275</td>
<td>C_{22}H_{18}N_{3}O_{3}Cl</td>
<td>406.5</td>
<td>10.31</td>
<td>10.30</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>233</td>
<td>C_{22}H_{18}N_{3}O_{3}Br</td>
<td>451</td>
<td>9.31</td>
<td>9.32</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH_3</td>
<td>252</td>
<td>C_{23}H_{21}N_{3}O_{3}</td>
<td>403</td>
<td>10.42</td>
<td>10.43</td>
</tr>
</tbody>
</table>

All these were crystallized from C_{6}H_{6}. 
Name of carbonyl compound: Salicylaldehyde

Benzylidine deri. of: \( N-\left[4-(4'-\text{sub.-benzyloxy})\right]-\text{phenyl-oxam}
\)

acid-salicyl-Hydrazone

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R [\text{(Para)}]</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Cal. N</th>
<th>Found N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>283</td>
<td>( C_{22}H_{19}N_{3}O_4 )</td>
<td>389</td>
<td>10.80</td>
<td>10.81</td>
</tr>
<tr>
<td>2</td>
<td>p-CH(_3)</td>
<td>222</td>
<td>( C_{23}H_{21}N_{3}O_4 )</td>
<td>403</td>
<td>10.42</td>
<td>10.42</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>211</td>
<td>( C_{22}H_{18}N_{3}O_4)Cl</td>
<td>422.5</td>
<td>9.93</td>
<td>9.95</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>185</td>
<td>( C_{22}H_{18}N_{3}O_4)Br</td>
<td>467(^\circ)</td>
<td>8.98</td>
<td>9.98</td>
</tr>
<tr>
<td>5</td>
<td>p-0CH(_3)</td>
<td>265</td>
<td>( C_{23}H_{21}N_{3}O_5 )</td>
<td>419</td>
<td>10.02</td>
<td>10.08</td>
</tr>
</tbody>
</table>

All these were crystallized from Absolute EtOH
TABLE : 5

Name of carbonyl compound : Cinnamaldehyde

\[
R - \begin{array}{c}
\text{\textacyclic} \\
\text{\textacyclic}
\end{array}
- \begin{array}{c}
\text{\textacyclic} \\
\text{\textacyclic}
\end{array}
- \begin{array}{c}
\text{\textacyclic} \\
\text{\textacyclic}
\end{array}
\]

Benzylidine deri. of : \(\text{N}^4\text{-(4'-sub.benzyloxy)-7-phenyl-oxamic acid-cinnamyl Hydrazine}\)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts.</th>
<th>% of Cal.</th>
<th>Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>273</td>
<td>(\text{C}<em>{25}\text{H}</em>{21}\text{N}<em>{3}\text{O}</em>{3})</td>
<td>399.5</td>
<td>10.52</td>
<td>10.53</td>
</tr>
<tr>
<td>2</td>
<td>p-CH(_3)</td>
<td>258</td>
<td>(\text{C}<em>{25}\text{H}</em>{23}\text{N}<em>{3}\text{O}</em>{3})</td>
<td>413.5</td>
<td>10.16</td>
<td>10.17</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>275</td>
<td>(\text{C}<em>{24}\text{H}</em>{20}\text{N}<em>{3}\text{O}</em>{3}\text{Cl})</td>
<td>432.5</td>
<td>9.70</td>
<td>9.70</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>225</td>
<td>(\text{C}<em>{24}\text{H}</em>{20}\text{N}<em>{3}\text{O}</em>{3}\text{Br})</td>
<td>447.5</td>
<td>9.39</td>
<td>9.40</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH(_3)</td>
<td>273</td>
<td>(\text{C}<em>{25}\text{H}</em>{23}\text{N}<em>{3}\text{O}</em>{4})</td>
<td>429.5</td>
<td>9.79</td>
<td>9.79</td>
</tr>
</tbody>
</table>

All these were crystallized from Dry \(\text{C}_6\text{H}_6\)
TABLE: 6

Name of carbonyl compound: Vanillin (m-methoxy-p-OH-benzaldehyde)

![Chemical structure of Vanillin](attachment:image.png)

Benzylidene deri. of: N-[4(4'-sub.benzylxy)-phenyl-oxamic acid-Vanilin Hydrazone

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Cal. Nitrogen</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>280</td>
<td>C_{23}H_{21}N_{3}O_{5}</td>
<td>419</td>
<td>10.02</td>
<td>10.08</td>
</tr>
<tr>
<td>2</td>
<td>p-CH₃</td>
<td>210</td>
<td>C_{24}H_{23}N_{3}O_{5}</td>
<td>433</td>
<td>9.70</td>
<td>9.70</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>218</td>
<td>C_{23}H_{20}N_{3}O_{5}Cl</td>
<td>425.5</td>
<td>9.27</td>
<td>9.28</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>175</td>
<td>C_{23}H_{20}N_{3}O_{5}Br</td>
<td>497</td>
<td>9.45</td>
<td>9.45</td>
</tr>
<tr>
<td>5</td>
<td>p-CH₃</td>
<td>200</td>
<td>C_{24}H_{23}N_{3}O_{6}</td>
<td>449</td>
<td>9.35</td>
<td>9.36</td>
</tr>
</tbody>
</table>

All these were crystallized from Absolute EtOH.
TABLE : 7

Name of carbonyl compound : Furfural

\[ \begin{array}{cccccc}
\text{Sr. No.} & \text{R (Para)} & \text{M.P.} & \text{Molecular formula} & \text{Mol. wts. gms.} & \text{Cal.} & \text{Found} \\
\hline
1 & p-H & 189 & C_{20}H_{17}N_{3}O_{4} & 363 & 11.57 & 11.58 \\
2 & p-CH_3 & 240 & C_{21}H_{19}N_{3}O_{4} & 377 & 11.14 & 11.14 \\
3 & p-Cl & 246 & C_{20}H_{16}N_{3}O_{4}Cl & 396.5 & 10.58 & 10.60 \\
4 & p-Br & 265 & C_{20}H_{16}N_{3}O_{4}Br & 441 & 9.53 & 9.63 \\
5 & p-CH_3 & 220 & C_{21}H_{19}N_{3}O_5 & 393 & 10.69 & 10.72 \\
\end{array} \]

All these were crystallized from Absolute EtOH
Name of carbonyl compound: Anisaldehyde

![Diagram of chemical structure](image)

Benzylidene deri. of: \(\text{N-}4-(4'-\text{sub. benzyl oxy})\text{-phenyl-oxamic acid-Anisyl-Hydrazone}\)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R \text{(Para)}</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Cal.</th>
<th>Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>265</td>
<td>(\text{C}<em>{23}\text{H}</em>{21}\text{O}_4\text{N}_3)</td>
<td>403</td>
<td>10.42</td>
<td>10.43</td>
</tr>
<tr>
<td>2</td>
<td>p-CH(_3)</td>
<td>207</td>
<td>(\text{C}<em>{24}\text{H}</em>{23}\text{O}_4\text{N}_3)</td>
<td>417</td>
<td>10.07</td>
<td>10.08</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>155</td>
<td>(\text{C}<em>{23}\text{H}</em>{20}\text{O}_4\text{N}_3\text{Cl})</td>
<td>436.5</td>
<td>9.61</td>
<td>9.62</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>220</td>
<td>(\text{C}<em>{23}\text{H}</em>{20}\text{O}_4\text{N}_3\text{Br})</td>
<td>481</td>
<td>8.73</td>
<td>8.74</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH(_3)</td>
<td>275</td>
<td>(\text{C}<em>{24}\text{H}</em>{23}\text{O}_5\text{N}_3)</td>
<td>433</td>
<td>9.69</td>
<td>9.69</td>
</tr>
</tbody>
</table>

All these were crystallized from Absolute EtOH
### Table 9

Name of carbonyl compound: m-butyraldehyde

![Chemical Structure](attachment://structure.png)

Benzylidene deri. of: \(N-2-4-(4'-sub. benzoyloxy)phenyl- oxamic acid-n-butyryl-Hydrazone\)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wt. gms.</th>
<th>% of Cal.</th>
<th>Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>228</td>
<td>(C_{19}H_{21}O_{3}N_3)</td>
<td>339</td>
<td>12.39</td>
<td>12.40</td>
</tr>
<tr>
<td>2</td>
<td>p-CH₃</td>
<td>198</td>
<td>(C_{20}H_{23}O_{3}N_3)</td>
<td>353</td>
<td>11.90</td>
<td>12.00</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>235</td>
<td>(C_{19}H_{20}O_{3}N_3Cl)</td>
<td>372.5</td>
<td>11.26</td>
<td>11.30</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>212</td>
<td>(C_{19}H_{20}O_{3}N_3Br)</td>
<td>417</td>
<td>10.07</td>
<td>10.10</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH₃</td>
<td>210</td>
<td>(C_{20}H_{23}O_{4}N_3)</td>
<td>369</td>
<td>11.39</td>
<td>11.40</td>
</tr>
</tbody>
</table>

All these were crystallized from Dry \(C_6H_6\).
TABLE : 10

Name of carbonyl compound : Acetone

\[
\begin{array}{c}
R - H - CH_2 - 0 - \text{Benzylidene deri. of : N} \quad - \text{sub.benzyloxy} \quad - \text{phenyl-oxamic acid} - \text{Acetone-Hydrazone}
\end{array}
\]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Cal. Nitrogen</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>170</td>
<td>C_{18}H_{19}N_{3}O_{3}</td>
<td>325</td>
<td>12.93</td>
<td>12.96</td>
</tr>
<tr>
<td>2</td>
<td>p-CH₃</td>
<td>183</td>
<td>C_{19}H_{21}N_{3}O_{3}</td>
<td>339</td>
<td>12.39</td>
<td>12.36</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>212</td>
<td>C_{18}H_{16}N_{3}O_{3}Cl</td>
<td>358.5</td>
<td>11.69</td>
<td>11.70</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>195</td>
<td>C_{18}H_{19}N_{3}O_{3}Br</td>
<td>403</td>
<td>10.42</td>
<td>10.40</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH₃</td>
<td>252</td>
<td>C_{19}H_{21}N_{3}O_{4}</td>
<td>355</td>
<td>11.83</td>
<td>11.80</td>
</tr>
</tbody>
</table>

All these were crystallized from Dry C₆H₆.
### Table 11

**Name of carbonyl compound**: Me-Et-Ketone

![Chemical Structure](image)

**Benzylidine deri. of**: \(N-\bigcirc-(4'-\text{sub. benzyloxy})/-\text{phenyl-oxamic acid} - \text{Me-Et-ketone-Hydrazone}

<table>
<thead>
<tr>
<th>Sr. R No. (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Cal. N</th>
<th>Found N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 p-H</td>
<td>176</td>
<td>(C_{19}H_{21}N_3O_3)</td>
<td>339</td>
<td>12.37</td>
<td>12.40</td>
</tr>
<tr>
<td>2 p-CH(_3)</td>
<td>259</td>
<td>(C_{20}H_{23}N_3O_3)</td>
<td>353</td>
<td>11.90</td>
<td>11.92</td>
</tr>
<tr>
<td>3 p-Cl</td>
<td>200</td>
<td>(C_{19}H_{20}N_3O_3)</td>
<td>372.5</td>
<td>11.26</td>
<td>11.30</td>
</tr>
<tr>
<td>4 p-Br</td>
<td>170</td>
<td>(C_{19}H_{20}N_3O_3)</td>
<td>417</td>
<td>10.07</td>
<td>10.10</td>
</tr>
<tr>
<td>5 p-OC(_3)</td>
<td>256</td>
<td>(C_{20}H_{23}N_3O_4)</td>
<td>369</td>
<td>11.39</td>
<td>11.42</td>
</tr>
</tbody>
</table>

All these were crystallized from Absolute EtOH.
TABLE : 12

Name of carbonyl compound: Cyclohexanone

Benzylidine deri. of: $N-(4\text{'-sub.benzyloxy})$-$\text{phenyl}$-oxamic acid-cyclohexanone-Hydrazone

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>$R$</th>
<th>M.P. $^\circ C$</th>
<th>Molecular formula</th>
<th>Mol. wt. gms.</th>
<th>% of Cal. N</th>
<th>Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>205</td>
<td>$C_{21}H_{23}O_3N_3$</td>
<td>365</td>
<td>11.50</td>
<td>11.56</td>
</tr>
<tr>
<td>2</td>
<td>p-CH$_3$</td>
<td>212</td>
<td>$C_{22}H_{25}O_3N_3$</td>
<td>380</td>
<td>11.65</td>
<td>11.68</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>210</td>
<td>$C_{21}H_{22}O_3N_3Cl$</td>
<td>399.5</td>
<td>10.51</td>
<td>10.55</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>196</td>
<td>$C_{21}H_{22}O_3N_3Br$</td>
<td>444</td>
<td>9.46</td>
<td>9.46</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH$_3$</td>
<td>229</td>
<td>$C_{22}H_{25}O_4N_3$</td>
<td>396</td>
<td>10.57</td>
<td>10.60</td>
</tr>
</tbody>
</table>

All these were crystallized from Absolute EtOH.
Table: 13

Name of carbonyl compound: Benzophenone

Benzylidene deri. of: N-[^4-(4'-sub.benzylxy)]^-phenyl-oxamic acid-Benzophenone-Hydrazone

![Chemical structure](attachment:image.png)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Molecular wts. gms.</th>
<th>% of Cal.</th>
<th>Nitrogen Pound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>248</td>
<td>C₂₈H₂₃N₃O₃</td>
<td>449</td>
<td>9.35</td>
<td>9.36</td>
</tr>
<tr>
<td>2</td>
<td>p-CH₂</td>
<td>222</td>
<td>C₂₉H₂₅N₃O₃</td>
<td>463</td>
<td>9.07</td>
<td>9.07</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>258</td>
<td>C₂₈H₂₂N₃ClO₃</td>
<td>482.5</td>
<td>8.69</td>
<td>8.69</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>220</td>
<td>C₂₈H₂₂N₃O₃Br</td>
<td>529.5</td>
<td>7.97</td>
<td>7.97</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH₃</td>
<td>215</td>
<td>C₂₉H₂₅N₃O₄</td>
<td>479</td>
<td>8.76</td>
<td>8.76</td>
</tr>
</tbody>
</table>

All these were crystallized from Absolute EtOH.
Table 14

Name of carbonyl compound: Acetophenone

![Chemical structure of benzylidine deri. of N-\(4\)-(4'-sub.benzyloxy)\-phenyl oxamic acid-Acetophenone-Hydrazone]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R (Para)</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Mol. wts. gms.</th>
<th>% of Cal. Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-H</td>
<td>250</td>
<td>(C_{23}H_{21}O_3N_3)</td>
<td>387</td>
<td>10.82</td>
</tr>
<tr>
<td>2</td>
<td>p-CH₃</td>
<td>217</td>
<td>(C_{24}H_{23}O_3N_3)</td>
<td>401</td>
<td>10.47</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>215</td>
<td>(C_{23}H_{20}O_3N_3Cl)</td>
<td>420.5</td>
<td>10.01</td>
</tr>
<tr>
<td>4</td>
<td>p-Br</td>
<td>234</td>
<td>(C_{23}H_{20}O_3N_3Br)</td>
<td>465</td>
<td>9.13</td>
</tr>
<tr>
<td>5</td>
<td>p-OCH₃</td>
<td>225</td>
<td>(C_{24}H_{23}N_3O_4)</td>
<td>417</td>
<td>10.07</td>
</tr>
</tbody>
</table>

All these were crystallized from Absolute EtOH
PART - II

SECTION - II

REFERENCES
REFERENCES

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    Cercetari, Stimnt, Ser, Stinle, Chim, 2, 157-68.
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    (Russ). Chem. Abstr. 28, April, No. 9, pp.110801(e) 
    (1973).
PART - II

SECTION - III

INTRODUCTION
INTRODUCTION

Organic compounds containing sulphur and hydrogen in their molecules are generally indicated as 'thio' compounds. Since according to I.U.P.A.C. system of Nomenclature, the -SH group is known as 'thio' group and the suffix of these series are 'thiols', i.e. sulphur analogous of the alcohols, are usually indicated as thio compounds. Various types of organic compounds of this class are known today having the wider range of applications in various fields of industries and pharmaceuticals.

Thioureas, substituted thioureas, and their derivatives have played an important role in the development of almost every branch of chemistry. Their applications on commercial base have been found to be fruitful in dyestuffs, plastics, photography, preservatives, elastomers, and in textile industries. Their applications also have been observed with successful results in medicine and pharmaceuticals, especially from the biological point of view, it has been observed that these compounds possesses biological properties such as Bacteriostatic(121), Tuberculostatics(24), Insecticidal(39), Antithyroid(4), Anthelminitics(134), Rodenticidal and Fungitoxic(144).
In the analytical field, thioureas are of great value in the characterisation of organic amines. These thioureas, which show sharp M.P., have the ability to form crystalline complexes with the branched hydrocarbons and acyclic structures have led to their use in the separation of mixtures of organic compounds (2, 63, 64, 65, 92, 107).

Certain (57) thioureas give brilliant colored microcrystalline compounds with Fehling solutions that can be isolated before the copper sulphide is formed.

The thiourea system is numbered as shown below:

\[ \begin{array}{c}
N \quad S \quad N \\
R' \quad C \quad R'' \\
R'''
\end{array} \]

Sulphur substituted thioureas are referred to as Pseudo-thioureas rather than iso-thioureas.

**Physiological Activity:**

(1) **Antitubercular Activity:**

Thiourea and its derivatives are tuberculostatic (24). Thiourea itself possesses a slight but definite activity in vitro, which is enhanced by appropriate substitution as in allyl thiourea (83) and especially in p-aminobenzene sulphonyl thiourea (99).

Discovery of N-N''-di-(p-n-butoxy phenyl) thiourea
and related compound are found to be having outstanding tuberculostatic activity (100). N-N''-diaryl thiourea (28), 4'-4' dialkoxy thio-carbanilides have been found to be active against human Leprosy (29). Certain diaryl thioureas and related sulfur compound were found to be active against Influenza virus infection in mice (30). On account of these various biological properties, the preparation of new thioureas derivatives was developed.

A favorable result was observed by Chillean workers (24, 158), who reported that thiourea itself possesses significant tuberculostic activity. Many thiourea derivatives have been tested for antitubercular activity. Some showed no activity at all (71, 80, 149), while others were found promising in vitro studies (16, 26, 77, 137, 150).

In 1944 a patent (13) was issued for copper compound made from thioureido benzoic acids which were said to be active in treating tuberculosis, since bacteria such as tubercle bacilli contain a large amounts of lipoidal tissues, long chain alkyl thioureas which are lipid soluble were suggested by Massie (98) as therapeutic agents. However, excluding the sulphonyl thioureas, very little success was found in the treatment of tuberculosis, with this class of compound until very recently.

In 1952, number of thiourea deriv of p-amino salicylic
acid in *in vitro* studies were found to be equally active or more active than the acid itself (3, 85, 127).

Maximum activity was observed in the compounds of the type

\[
\text{HOOC} \bigg\longrightarrow \text{NHCSNHR} \quad \text{where } R = \text{Aryl}
\]

From the comparative view it was observed that ortho and m-amino salicylic acids were found to be less active or not active at all than that of p-aminosalicylic acid. If \( R = \) aliphatic, activity completely dropped. The above \( R = \text{Aryl} \), was found to prolong life in animal studies but although the disease was arrested, it did not produce a complete cure. Further 4-4'-diethoxy thiocarbanilide was found to possess high antitubercular activity in mice infected with *bacillus H_{37}RV* (99, 100).

2. **Antibacterial activity:**

In 1906 the parent compound urea (113) was first mentioned as a bacteriostat and was reviewed in 1944. It possesses bacteriostatic (135, 154) properties. This property was also observed in isothiocyanates, namely Allyl isothiocyanates and benzyl isothiocyanate (40). It seems that benzyl isothiocyanates are much more active than the phenyl derivatives (40).
3. **Antithyroid activity:** One of the most widely studied aspects of thioureas and its derivatives has been their antithyroid activity (122). Certain generalities reported in several of the publications (80, 100, 103) are in agreement. Thiourea has approximately 1/10th activity of thiouracil. Pseudothioureae are inactive but incorporation of the thioureas moiety into ring not involving the sulphur seems to increase the potency (155).

4. **Hypnotic and Anesthetic properties:**

Thioureas of the general formula $R''\cdot C_6H_4-N(R)-C-N-R'R''$ have been patented (25) as hypnotics, and suitable for use as general or local anesthetics.

This patent specifies those compound in which $R = \text{Alkyl or Alkenyl (less than 8\text{-atoms})}$

$R'$ and $R'' = \text{H, Alkyl or Alkenyl (more than 8\text{-atoms})}$ and $R'''' = \text{Alkyl radical of 1 to 8 carbon atoms}$.

5. **Anthelminitic activity:**

The anthelminitic activity of thioureas have been reviewed recently, aromatic heterocyclic compound with quaternary nitrogen in the nucleus are said to have similar activity (128).

2-Carbethoxy phenyl thioureas showed remarkable Vermicidal activity.
1-Napthyl thioureas has been found to be effective against intestinal parasites in man and dog(70).

6. **Insecticidal properties:**

Thiocarbamido D.D.T. is more effective than D.D.T. against bed bugs, although its action is of shorter duration(156).

1-Allyl-3-(4-Cl-2-methyl-phenyl)-thioureas has been claimed to be effective in controlling the Japanese beetle or the Mexican jumping bean beetle(14).

2-Benzyl-1-(1-Napthyl)-thioureas and its chloro deriv. were found to be effective against Altogemus piccus and Tinia pellonella(101).

(7) **Rodenticidal activity:**

α-Napthyl thiourea (ANTU) is well known as rat poison, its success is based on the fact that it is much more toxic to rats that it is to cats, fowls etc.(17). It also produces hyperglycemia in rats and Guinea pigs(53,54).

8. **Miscellaneous Activities:**

A number of other biological properties have been observed.

4',4'-diaminophenyl thioureas have been found to have inhibitory effect on experimental cancer in mice(157).

1-Alkyl-3-guanyl-thioureas shows antipyretic properties
but having greater toxicity (136).

1-Methyl-pseudo-thiourea displays appreciable anticuscare activity (61, 120). It does not affect on blood pressure (16, 22) since this varies with the compound and animal.

Recently, compounds of the type \( R-NHCONH-COCH_2-CN \), where \( R \) and \( R'' \) are Alkyl and Aryl group have been claimed to be useful as cardiovascular diuretic and chemotherapeutic agents (114).

**Importance of Benzyl and Benzyloxy groups**

Several well known drugs like penicillin, marfanil, Hibicon, and Hibital contain a benzyl group (-CH \(_2\)Ph) as a part of their molecules.

In previous Biological activity part we have observed that benzyl thiourea shows a remarkable properties such as antithyroids, antituber and antibacterial.

1:3:4 thiazolidones containing benzyl group shows aericidal activity (142).

N-Benzyl Nicotinamide and Hypamin shows powerful antispasmodic activity. Above observations indicate the importance of Benzyl group as contributing to medicinal properties of the compounds.

Alkoxy substituted benzoic acid esters of the type
R-CO-O-C₆H₄-CH₂-CH(OH)-CH₂-N-R'-R have been found to possess local anesthetic properties(18).

Basic ester of the type p-R-O-C₆H₄-CO0(CH₂)₄-R-HCl have been found to have anesthetic properties(72).

Importance of benzyloxy group is evidenced from the work of Borovansky, Sekera et al. as well as from the work of Shigematsu(131, 15).

Importance of benzyloxy group is further supported from the work of Ellenbogen, Leonmarkly, Elizabeth (58) et al., they have reported inhibition of enzyme activity of the in vitro NSD-loss.

Trivedi and Shah (145) synthesized various basic amides containing benzyloxy group and observed that some of them were tested and found to possessed great irritancy and toxicity, on the smooth muscles. The results found more potent than cocaine or procaine and Lidocaine. All produced aspasm on the smooth muscles.

Toldy L; Solyom S; and others (147) synthesized thiourea derivative of the type iso-Pr-CH₂-CH₂-O- -CS.NH.CO.C₂H₅ with the tuberalostatic action.

Acylthiocarbamides gave an expressed antituberculostatic effect in mice and guinepigs with no toxic effect.
Burkard, Willy and others (27) studied Antimalerial and enzyme inhibiting 1-(2-thiazoyl)-thiourea derivative of the type

\[
\begin{align*}
R' &= \text{Me or Pr} \\
R &= \text{H or Me} \\
NRR' &= \text{Morpholino/Piperidino}
\end{align*}
\]

on mice on oral administration.

Anticonvulsant activity was observed by Ram Vishnuji and others (119) by synthesizing some new thioureas and guanidines derived from butyl and iso-butyl-p-aminobenzoates.
PART - II

SECTION - III

THEORETICAL
Theoretical:

(A) Preparation of Thiourea derivatives:

There are several common syntheses for derivative of thiourea. Many variations have been applied to each of these when needed. As might be expected, certain advantages and disadvantages arise from the use of any one of these methods of preparation described below:

(A) \( \text{CS}_2 \) and an amine:

\[
\text{CS}_2 + 2\text{R-NH}_2 \rightarrow \text{R-HNCSNH}_2 + \text{H}_2\text{S}
\]

The most reasonable course for the reaction seems to be:

(i) \( \text{R-NH}_2 + \text{CS}_2 \rightarrow \text{R-NH-CS-SH} \)

(ii) \( \text{R-NH-SH} + \text{R-NH}_2 \rightarrow (\text{R-NH-C-S})^- (\text{NH}_3)^+ \)

(iii) \( (\text{R-NH-C-S})^- (\text{NH}_3)^+ \xrightarrow{\text{heat}} \text{RNC} + \text{R-NH}_2 + \text{H}_2\text{S} \)

The above mechanism is supported by the fact that dithiocarbamic acids are formed when \( \text{CS}_2 \) reacts with amines and their salts are isolated (19, 36, 67, 86, 96).

The most common application of this method is to
synthesize substituted benzyloxy-semi-oxamazides thioureas.

(B) Thiophosgene and an Amine:

Primary amines with thiophosgene to give either an isothiocyanate or a 1:3 disubstituted thiourea; depending upon the ratio of the reactions.

\[
\text{CSCl}_2 + R\text{-NH}_2 \rightarrow R\text{-NCS} + 2\text{HCl} \\
\text{CSCl}_2 + 2R\text{-NH}_2 \rightarrow R\text{HNCSNHR} + 2\text{HCl}
\]

Secondary amines give only symmetrical thioureas.

The mechanism of these reaction has been explained in the following manner(55).

\[
R\text{-R'-NH} + \text{CSCl}_2 \rightarrow (\text{RR'NHClCSCl}) \\
\text{RR'NCSCl} + \text{HCl}
\]

(I)

a) When R' is not H, or if R' is H and I is stable

\[
I + \text{RR'NH} \rightarrow \text{RR'NCSRR'} + \text{HCl}
\]

b) When R' = H and I is unstable

\[
\text{RHNCSCl} \rightarrow \text{RNCS} + \text{HCl} \\
\text{RNCS} + H_2\text{NR} \rightarrow \text{R-NHCSNHR}
\]

Thus, 1° amines may go either route(a) or route(b), whereas 2° amines can proceed only by way of route(a).

Proof of this mechanism lies in the fact that I has been isolated and identified in certain instances even when R' is H, when a 2° amine is used in a 1:1 ratio with thiophosgene.
The reaction stops short at the thiocarbonyl chloride stage and I is often quite stable.

Because of the objectional nature of thiophosgene this method is usually reserved for those instances other methods do not work, for example the conversion of aromatic amines with strong negative substitution (76) and of 2° amines to the corresponding symmetrical thioureas where other methods do not work.

c) Organic Isothiocyanates and an amine:

\[ R-\text{NCS} + R' R'' \text{NH} \rightarrow R-\text{NH-CS-NR'} R'' \]

This is the most common method of preparing unsymmetrical thiourea. Ammonia, 1° amine, or 2° amine may be used and R-R' or R'' may be aromatic, Aliphatic, Alicyclic or heterocyclic.

R may also be acyl, in this way 1-mono, 1:1 or 1:3 disubstituted thioureas and 1:1:3 trisubstituted thioureas have been synthesized. Because of the simplicity of the reaction and since most thioureas are solids, it is also a widely used methods for characterizing amines (20, 21, 31, 64, 74, 78, 79, 111). Conversely, isothiocyanates may be characterized by conversion to a thiourea with ammonia or an amine (91).

Studies have been made to determine the effect of nuclear substitution on the reactivity of aryl isothiocyanates (26).
Conclusions were based upon the ease of urethane formation, when the isothiocynates and alcohol were refluxed. It was found that halogen, nitro, m-methoxy and m-ethoxy groups accelerated the rate of the reaction, whereas alkyl and p-methoxy groups retarded it.

The effect of more than one substituent is additive.

m-Substituted compounds are always more reactive than their o- and p-isomers. Acyl isothiocynates are more reactive than alkyl or Aryl, for example, diphenylamine adds only to acyl isothiocynates. Addition is usually carried out in the presence of a solvent such as alcohol. Frequently the reaction is exothermic and cooling may be necessary to keep it from getting out of hand. In some cases it is necessary to heat the mixture and then a higher alcohol or preferably on inert solvent such as benzene or toluene may be used.

Use of alcohol as solvent, when a long reflux period is required may cause urethane formation between the alcohol and isothiocynates, to predominate over the desired thioureas synthesis. Pyridine has also used successfully as a solvent (3, 37). The thioureas often precipitate from the cooled reaction mixture, since in most cases it is less soluble than the starting material.
In addition to urethane formation, another complication may arise. The following exchange has been observed in a number of instances (160).

\[ 2RNCs + R'-NH_2 \rightarrow R'NCS + (RHN)_2CS \]
\[ 2RNCs + (R'-NH)_2CS \rightarrow 2R'NCS + (RHN)_2CS \]

Since, similarly substituted thioureas melt at nearly the same temperature and isomorphism may make mixed m.p. unreliable, elemental analysis or an infra red spectrum is often essential in the identification of the reaction product.

d) Alkali thiocyanate and Amine Hydrochloride:

It has long been known that heating ammonium thiocyanate at 160°C for several hours causes it to rearrange to thiourea (82). The same rearrangement occurs when the ammonium ion is mono or disubstituted (47) but not when it is tri or tetra substituted. Use is made of this rearrangement in preparing 1-mono, substituted and 1:1-disubstituted thioureas (129, 134, 93, 112, 123, 115, 44, 46, 51, 73, 95, 105).

\[ R'-R-NH + HCl + NH_4SCN \rightarrow NH_4Cl + R'NH_2SCN \]
\[ R'\text{NH}_2SCN \rightarrow R'NCS NH_2 \]

The reaction can be carried out in either,
(a) an inert organic solvent (51, 129) or
(b) aqueous medium (44, 51, 94).
(i) Chlorobenzene is commonly used as solvent. It is saturated with HCl, and the amine and thiocynate are added. The mixture is then heated at 110°-120°C. The length of time depending on the components organic salts are removed by filtration and the product is isolated from the filtrate.

(ii) One mole of amine is dissolved in water containing 1.3 mole of HCl. Ammonium thiocynate is added and after a reflux period the solution is evaporated to dryness on a steam bath. The residue is heated for several additional hours, taken up in benzene and washed with dil. HCl. Evaporation of dried benzene layer yields the product.

Both methods are simple to use and suitable for aromatic and aliphatic amines.

e) Thioureas and Organic halides:

Thioureas react with acyl, alkyl, aralkyl and heterocyclic halides to give thiourea derivatives. It has been observed on many occasions that when thiourea is treated with acylhalides 5-acylation occurs first. Then upon being heated or sometimes merely upon standing at room temperature, the acyl group transfers to an N-position. In other case, the transformation is so rapid that the S-substituted compound is never discernible. However, when an S-Alkyl pseudo-thiourea is heated with an acyl halide in presence of a weak base when N-acyl S-Alkyl
pseudo thiourea results, indicating direct N-acylation (34, 130).

When diacylation occurs by this method it gives a 1-1-diacyl thiourea in preference to a 1:3 diacyl thiourea. Monoaryl thioureas upon treatment with an acyl halide give first the S-acyl-N-aryl compound. Heating converts this first to the 1-aryl-1-acyl and finally to the 1-aryl-3-acyl thiourea.

Alkyl, arylkyl and heterocyclic halides give stable S-substituted products with thioureas and this is the most common method of preparing pseudothioureas. The reaction may be carried out by mixing a 1:1 molar ratio of the reactants directly in an inert solvent (6, 10, 41) or in anhydrous ethanol (23, 16, 66). Almost quantitative yield of hydrobromide or hydrochloride salts are obtained when the halide used in the bromide or iodide.

Alkyl chlorides are less reactive and certain adjustment must be made at times in the procedure to give optimum yields of the corresponding hydrochloride. To obtain the free base of the pseudo-thiourea the salt is washed with dil. alkali. Other common alkylating reagents such as dimethyl sulphate (13, 139) or esters of p-toluene sulphonie acid (89) can be used to prepared S-alkyl pseudo thioureas as the corresponding salts. Pseudo-thioureas can be prepared from mono, di, and -tri; but not from tetrasubstituted
thioureas. This is true because at least one ureido nitrogen is essential for the tautomerism which must occur with S-substitution.

\[
R-NH-C-N-R'\,R'' \quad \text{RN} = \text{C} - \text{NR'}\,R''
\]

The salts of pseudo thioureas are referred to as pseudo thiourenium salts. Thus, the hydrochloride of 2-methyl pseudo thiourea is methyl pseudo thiouronium chloride etc.

The 2-benzyl homolog is benzyl pseudo thiouronium chloride etc. In the literature several structural formulas are used for these compounds.

\[
(R-SC(=NH)-NH_2\,HCl) \\
\quad \quad \quad \quad \quad \quad \quad \downarrow \\
(RSC(=NH)NH_3)^+ \text{ Cl}^- \\
\quad \quad \quad \quad \quad \quad \quad \downarrow \\
(RSC(=NH_2)NH_2)^+ \text{ Cl}^-
\]

Because of the simplicity of their preparation pseudo thiouronium salts of alkyl or arylkyl (110, 7, 12, 75, 84) or heterocyclic (11, 102, 116, 127, 140) halides are often used in characterizing these compounds. Some of the more common pseudo thiouronium compounds, e.g. benzyl and 4-chlorobenzyl pseudo thiouronium halides are often used in identifying carboxylic acids by conversion to the salts of the latters (38, 87, 71, 146, 159, 151).
Sulphonic acids can be characterized in the same way (141).

(F) Some special synthesis of substituted thioureas:

A great number of special synthesis for thiourea derivatives have been reported. Many of these are specific for a single compound while others are of general nature.

1:3 Diaryl thioureas can be prepared by heating primary Amine with salts of tri-thio-carbonic acid. Heavy metal salts have been especially recommended (52). This method appears to have little advantage and requires more steps. 

\[
2CS_2 + 2C_6H_5NH_2 + 2NaOH \rightarrow SC(NHC_6H_5)_2 + Na_2CS_3 + H_2O
\]

\[
Na_2CS_3 + MCl_2 \xrightarrow{aq. medium} MCS_3 + 2NaCl (M = Heavy metal)
\]

\[
MCS_3 + 2RNH_2 \rightarrow CS(NHR)_2 + MS + H_2S
\]

However, an interesting variation is,

\[
Na_2CS_3 + 2ArNO + H_2O \rightarrow SC(NHAr)_2 + Na_2S_3O_3
\]

This has been successfully used in preparing 1-3 bis-(4-hydroxyphenyl) and 1-3 bis-(4-methyl amino phenyl) thiourea from 4-nitrosophenyl and 4-nitrosodimethylamiline respectively (90).

The addition of a sulphide to an unsaturated bond has also been used in preparing thioureas. Cynothiourea can
be prepared by heating a metal dicyanamide with $\text{H}_2\text{S}$ (98).

Pseudo thioureas are formed by heating a mercaptan and cyanamide (125, 126) in aqueous or alcoholic medium.

\[
\text{CH}_3\text{SH} + (\text{C}_2\text{H}_5)_2\text{NCN} \xrightarrow{\text{water}} (\text{C}_2\text{H}_5)_2\text{NC(SCH}_3) = \text{NH}
\]

It has also been observed that the sulphur of a 1:3 disubstituted thiourea will add to an acetylene bond to give a pseudo thiourea salt in acid medium (33).

\[
\text{R-NH-CS-NH-R'} + \text{B-C=CH} \xrightarrow{\text{acid medium}} \text{R-NH(R'N=)CSCH=CH.B + HA}
\]

In some cases it has been found possible to heat thiourea and a (1°) amine and obtain 1-mono-substituted thiourea (109, 118).

Small yields of symmetrical disubstituted thioureas have also been observed in this reaction. From these observations, we were led to synthesize series of compounds having a thioureido moiety, containing benzyloxy group, along with semi-oxamazide moiety, in order to investigate the tuberculostatic activity of above products with a hope to evaluate some structural relationship with the activity.
Section - III
(Substituted thioureas)

Compound (II), from the section - III + substituted phenyl isothiocynates

\[ \text{Y} \text{CH}_2\text{O} \text{NCS} \xrightarrow{\text{heat}} \text{C}_2\text{H}_2\text{OH} \]

substituted phenyl isothiocynates

\[ Y\text{-}N\text{HCO}.\text{CO.NH.NH.CS.NH} \text{CH}_2\text{O} \text{NCS} \]

N-(4-phenyl)thioureido-N-(4'-sub. benzyl oxy)phenyl-oxamide

Where \( Y \) = same as above in Section I
and \( X \) = H; 4-Cl; 3-Cl; 4-Br; 4-I; 4-Me; 3-Me; 4-OC\(_3\)H\(_2\)

Isothiocyanates: Theoretical

There are various methods available in literature for the preparation of isothiocyanates, also called "mustard oils". These are:

(A) By the interaction of Alkyl halides and metallic thiocyanates, Alkyl thiocyanates will be formed which on rearrangement will give isothiocyanates(124).
(B) By the decomposition of substituted thioureas by hot mineral acids\(^{(104)}\), acetic anhydride\(^{(153)}\) or by heating in a suitable inert solvent\(^{(8)}\).

(C) By the action of thiophosgene on a primary amine. This reaction proceeds via the formation of thiocarbamyl chloride which eliminates hydrogen chloride to form the isothiocyanate\(^{(56)}\).

\[
\begin{align*}
R - NH_2 + CS\text{Cl}_2 &\rightarrow (R - NH - \overset{\text{C}}{\text{C}} - \overset{\text{O}}{\text{Cl}}) + H\text{Cl} \\
R - N &\rightarrow C = S + H\text{Cl}
\end{align*}
\]

(D) From salts of dithiocarbamic acid:

Salts of dithiocarbamic acid obtained by the reactions of carbon disulphide and alkali hydroxides or ammonia with primary amines are smoothly cleaved to isothiocyanates by heavy metals salts\(^{(42)}\) chloroformate esters\(^{(106)}\), phosgene \(^{(138)}\), or iodine\(^{(81)}\).

\[
R - NH - \overset{\text{C}}{\text{S}}\text{NH}_4 + \text{Pb(NO}_3\text{)}_2 \rightarrow R - N = C = S + \text{NH}_4\text{NO}_3 + \text{HNO}_3 + \text{PbS}
\]

The decomposition of Ammonium or sodium dithiocarbamate by ethylchloroformate (ethyl chlorocarbonate) is often called Andreasch Kaluza synthesis for isothiocyanates\(^{(1)}\). The reaction has been represented as follows:
For the purpose of the present work the procedure of Dains, Brewster and Olandy (42) was adopted and the product was isolated by steam distillation after addition of lead nitrate.

The isothiocyanates thus prepared are shown below:

\[ R \cdot N = C = S \]

where \( R = C_6H_5 \); and \( m - p - \text{CH}_3C_6H_4 \); 
\( m - p - \text{OCH}_3C_6H_4 \); 
\( -p - \text{OC}_2H_5C_6H_4 \); 
\( m - p - \text{Cl} - C_6H_4 \); 
\( p - \text{Br} - C_6H_4 \); 
\( p - \text{I} - C_6H_4 \);

(vide experimental)

**Synthesis of Isothiocyanates:**

Various isothiocyanates required for the work described in this part of the thesis were prepared according to Dains, Brewster, and Olandy as described in Org. Syn. coll. vol. I, 447, 1948.

The reactions are as under:
\[
R - NH_2 + CS_2 + NaOH \rightarrow R - NH^- - C - S - Na + H_2O \\
R - NH - C - S - Na + Pb(\text{NO}_3)_2 \rightarrow R - N = C = S + Na\text{NO}_3 \\
\]

Isothiocyanates thus prepared are tabulated below:

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>B.P. °C</th>
<th>M.P. °C</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>C_6H_5^-</td>
<td>121/35 mm</td>
<td>-</td>
<td>(9) Bigelow</td>
</tr>
<tr>
<td>2.</td>
<td>m-CH_3-C_6H_4^-</td>
<td>244/733 mm</td>
<td>-</td>
<td>(55) Dyson and George</td>
</tr>
<tr>
<td>3.</td>
<td>p-CH_3-C_6H_4^-</td>
<td>-</td>
<td>26-27 °C</td>
<td>(55) Dyson and George</td>
</tr>
<tr>
<td>4.</td>
<td>p-Br-C_6H_4^-</td>
<td>-</td>
<td>(60°C-61°C) (42) Dains, Brewster and Olander</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>4-Cl-C_6H_4^-</td>
<td>-</td>
<td>43°C</td>
<td>Dains-Hofmann A.W., Ber, 13, 14, (1880)</td>
</tr>
<tr>
<td>6.</td>
<td>3-Cl-C_6H_4^-</td>
<td>120/10 mm</td>
<td>-</td>
<td>(35) Cogil &amp; Johnson</td>
</tr>
<tr>
<td>7.</td>
<td>4-MeO-C_6H_4^-</td>
<td>111/5 mm</td>
<td>-</td>
<td>(55) Dains Brewster and Olander ibid, 448 (1963)</td>
</tr>
<tr>
<td>8.</td>
<td>4-I-C_6H_4^-</td>
<td>-</td>
<td>63°C</td>
<td>(43) Dains Brewster and Olander ibid, 448 (1963)</td>
</tr>
<tr>
<td>9.</td>
<td>4-OEt-C_6H_4^-</td>
<td>-</td>
<td>75-76 °C</td>
<td>(55) Dyson &amp; G. M. and George H.J. J.Org. Chem. 1702 (1924)</td>
</tr>
</tbody>
</table>
PART - II

SECTION - III

EXPERIMENTAL
PART - II
(Section - III)
Thioureas
Experimental
1. Preparation of Benzyloxy anilines.
   (See part - I, experimental)
2. Preparation of sub-benzyloxy oxamides.
   (See part - I, experimental)
3. Preparation of semi-oxamazide.
   (See part - II; Section II)
4. Preparation of substituted thioureas:
   (Condensation of isothiocyanates (Aryl) with semi-oxamazides)

Procedure: 0.01M of semioxamazide in 10 ml EtOH was taken in a 250 ml R.B. flask, fitted with a reflux condenser and 0.01 M substituted phenyl isothiocyanates in absolute EtOH 10 ml, was slowly added; the mixture was refluxed on a water bath for 1 hr. After cooling the reaction mixture the product obtained was filtered at pump, dried and recrystallized from absolute EtOH; yield is (78% to 84%); the mother liquor on evaporation under vaccum yielded second crop 8% to 9%. Total yield about 92%.

By this general method thioureas prepared are as described in table Nos.1 to 5.
5-(4-sub.benzyloxy)phenyl-semi-oxamazide

\[
\text{Ethanol} \xrightarrow{\text{reflux}} \text{sub-phenyl isothiocyanates}
\]

\[
\begin{array}{c}
\text{N-(4-phenyl)thioureido-N'(4-sub.benzyloxy)-phenyl oxamide} \\
\text{where, } Y = H; 4-Cl; 4-Br; 4-CH_3; 4-OCH_3 \\
R = H; 4-Cl; 3-Cl; 4-CH_3; 3-CH_3; 4-Br; 4-I; 4-OCH_3, 4-O\text{C}_2\text{H}_5.
\end{array}
\]
TABLE 1

\[
\begin{aligned}
R &- CH_2-O - R' \\
\hline
% & \text{Molar formula} & \text{Mol. wts.} & \% \text{of Nitrogen} & \% \text{of Sulphur} \\
\hline
H & Aniline & 150 & C_{22}H_{19}O_3N_3S & 405 & 10.37 & 10.28 & 7.90 & 7.90 \\
H & p-toluidine & 168 & C_{23}H_{21}O_3N_3S & 418 & 10.05 & 10.10 & 7.48 & 7.48 \\
H & m-toluidine & 177 & C_{23}H_{21}O_3N_3S & 418 & 10.05 & 10.08 & 7.48 & 7.48 \\
H & p-Phenatidine & 182 & C_{24}H_{23}O_4N_3S & 449 & 9.35 & 9.36 & 7.12 & 7.13 \\
H & p-Chloroaniline & 176 & C_{22}H_{18}O_3N_3S\cdot Cl & 439.5 & 9.56 & 9.57 & 7.28 & 7.28 \\
H & m-Chloroaniline & 211 & C_{22}H_{18}O_3N_3S\cdot Cl & 439.5 & 9.56 & 9.56 & 7.28 & 7.29 \\
H & p-Bromoaniline & 178 & C_{22}H_{18}O_3N_3S\cdot Br & 484 & 8.68 & 8.68 & 6.62 & 6.22 \\
H & p-Iodoaniline & 205 & C_{22}H_{18}O_3N_3S\cdot I & 531 & 7.90 & 7.91 & 6.91 & 6.92 \\
\end{aligned}
\]

\[N-(4-phenyl)-Thioureido-N'(4-benzylxoy)phenyloxamide\]
TABLE : 2

\[
\begin{align*}
\text{N-}\{4-\text{phenyl}\}-\text{Thioureido-N'\{4-Methylbenzoyloxy\}phenyloxamide}\end{align*}
\]

<table>
<thead>
<tr>
<th>R of Thiourea</th>
<th>Molecular formula</th>
<th>Mol. % of wts. Nitrogen</th>
<th>Cal. Found %</th>
<th>Mol. % of Sulphur</th>
<th>Cal. Found %</th>
<th>gms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃ Aniline</td>
<td>C₂₃H₂₁O₃N₃S</td>
<td>419</td>
<td>10.02</td>
<td>10.00</td>
<td>7.63</td>
<td>7.63</td>
</tr>
<tr>
<td>CH₃ p-toluidine</td>
<td>C₂₄H₂₁O₃N₃S</td>
<td>432</td>
<td>9.69</td>
<td>9.70</td>
<td>7.38</td>
<td>7.39</td>
</tr>
<tr>
<td>CH₃ m-toluidine</td>
<td>C₂₄H₂₂O₃N₃S</td>
<td>432</td>
<td>9.69</td>
<td>9.70</td>
<td>7.38</td>
<td>7.38</td>
</tr>
<tr>
<td>CH₃ p-Anisidine</td>
<td>C₂₄H₂₂O₄N₃S</td>
<td>448</td>
<td>9.37</td>
<td>9.40</td>
<td>6.94</td>
<td>6.95</td>
</tr>
<tr>
<td>CH₃ p-Phenalidine</td>
<td>C₂₅H₂₅O₄N₃S</td>
<td>463</td>
<td>9.06</td>
<td>9.07</td>
<td>6.91</td>
<td>6.91</td>
</tr>
<tr>
<td>CH₃ p-Chloroaniline</td>
<td>C₂₃H₁₉O₃N₃SCL</td>
<td>453</td>
<td>9.27</td>
<td>9.28</td>
<td>7.06</td>
<td>7.06</td>
</tr>
<tr>
<td>CH₃ m-Chloroaniline</td>
<td>C₂₃H₁₉O₃N₃SCL</td>
<td>453</td>
<td>9.27</td>
<td>9.27</td>
<td>7.06</td>
<td>7.06</td>
</tr>
<tr>
<td>CH₃ p-Bromoaniline</td>
<td>C₂₃H₁₉O₃N₃SBr</td>
<td>498</td>
<td>8.43</td>
<td>8.43</td>
<td>6.42</td>
<td>6.42</td>
</tr>
<tr>
<td>CH₃ p-Iodoaniline</td>
<td>C₂₃H₁₉O₃N₃SI</td>
<td>545</td>
<td>7.70</td>
<td>7.71</td>
<td>5.87</td>
<td>5.67</td>
</tr>
</tbody>
</table>
\[ N-(4\text{-phenyl})\text{Thioureido-}N'-(4\text{-chloro-benzylxy})\text{phenyl-oxamide} \]

<table>
<thead>
<tr>
<th>Para R'</th>
<th>M.P.</th>
<th>Molecular formula</th>
<th>Mol. % of wts.</th>
<th>% of Nitrogen</th>
<th>Sulphur</th>
</tr>
</thead>
<tbody>
<tr>
<td>R of phenyl of Thiourea</td>
<td>0°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl Aniline</td>
<td>180</td>
<td>( C_{22}H_{18}O_3N_3SCl )</td>
<td>439.5</td>
<td>9.55</td>
<td>0.56</td>
</tr>
<tr>
<td>Cl p-toluidine</td>
<td>240</td>
<td>( C_{23}H_{20}O_3N_3SCl )</td>
<td>452.5</td>
<td>9.28</td>
<td>6.91</td>
</tr>
<tr>
<td>Cl m-toluidine</td>
<td>230</td>
<td>( C_{23}H_{20}O_3N_3SCl )</td>
<td>452.5</td>
<td>9.28</td>
<td>6.91</td>
</tr>
<tr>
<td>Cl p-anisidine</td>
<td>182</td>
<td>( C_{23}H_{20}O_4N_3SCl )</td>
<td>468.5</td>
<td>8.96</td>
<td>6.82</td>
</tr>
<tr>
<td>Cl p-Phenatidene</td>
<td>222</td>
<td>( C_{24}H_{22}O_4N_3SCl )</td>
<td>483.5</td>
<td>8.68</td>
<td>6.62</td>
</tr>
<tr>
<td>Cl p-Chloroaniline</td>
<td>224</td>
<td>( C_{22}H_{17}O_3N_3SCl )</td>
<td>474</td>
<td>8.85</td>
<td>6.74</td>
</tr>
<tr>
<td>Cl m-Chloroaniline</td>
<td>229</td>
<td>( C_{22}H_{17}O_3N_3SCl )</td>
<td>474</td>
<td>8.85</td>
<td>6.74</td>
</tr>
<tr>
<td>Cl p-bromoaniline</td>
<td>196</td>
<td>( C_{22}H_{17}O_3N_3SClBr )</td>
<td>528.5</td>
<td>7.94</td>
<td>6.05</td>
</tr>
<tr>
<td>Cl p-iodoaniline</td>
<td>234</td>
<td>( C_{22}H_{17}O_3N_3SLCL )</td>
<td>565.5</td>
<td>7.42</td>
<td>5.65</td>
</tr>
</tbody>
</table>
TABLE 4

\[
\text{R} - \begin{array}{c}
\text{CH}_2\text{O} \\
\end{array} \rightarrow \begin{array}{c}
\text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{NH} \cdot \text{CS} \cdot \text{NH} \cdot \text{R}'
\end{array}
\]

\[\text{N-}(\text{4-phenyl)Thioureido-} (\text{4-Bromo-benzylxy}) \cdot \text{phenyl-oxamide}\]

<table>
<thead>
<tr>
<th>Para R' Substituting R of Phenyl Ring</th>
<th>M.P. of Thiourea C</th>
<th>Molecular formula</th>
<th>Mol. % of wts. Nitrogen</th>
<th>Cal. % of Sulphur gms.</th>
<th>Found % of Nitrogen Cal.</th>
<th>Found % of Sulphur Cal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br Aniline</td>
<td>170</td>
<td>(\text{C}<em>{22}\text{H}</em>{18}\text{O}_3\text{N}_3\text{SBr})</td>
<td>484</td>
<td>8.48</td>
<td>6.61</td>
<td>6.61</td>
</tr>
<tr>
<td>Br p-toluidine</td>
<td>165</td>
<td>(\text{C}<em>{23}\text{H}</em>{20}\text{O}_3\text{N}_3\text{SBr})</td>
<td>497</td>
<td>8.44</td>
<td>6.43</td>
<td>6.44</td>
</tr>
<tr>
<td>Br m-toluidine</td>
<td>160</td>
<td>(\text{C}<em>{23}\text{H}</em>{20}\text{O}_3\text{N}_3\text{SBr})</td>
<td>497</td>
<td>8.44</td>
<td>6.43</td>
<td>6.43</td>
</tr>
<tr>
<td>Br p-anisidine</td>
<td>155</td>
<td>(\text{C}<em>{23}\text{H}</em>{20}\text{O}_4\text{N}_3\text{SBr})</td>
<td>513</td>
<td>7.81</td>
<td>6.23</td>
<td>6.24</td>
</tr>
<tr>
<td>Br p-phenatidine</td>
<td>162</td>
<td>(\text{C}<em>{24}\text{H}</em>{22}\text{O}_4\text{N}_3\text{SBr})</td>
<td>528</td>
<td>7.95</td>
<td>6.06</td>
<td>6.06</td>
</tr>
<tr>
<td>Br p-Chloro-aniline</td>
<td>168</td>
<td>(\text{C}<em>{22}\text{H}</em>{17}\text{O}_3\text{N}_3\text{SBr})</td>
<td>513</td>
<td>8.28</td>
<td>6.17</td>
<td>6.17</td>
</tr>
<tr>
<td>Br m-Chloro-aniline</td>
<td>172</td>
<td>(\text{C}<em>{22}\text{H}</em>{17}\text{O}_3\text{N}_3\text{SBr})</td>
<td>518</td>
<td>8.28</td>
<td>6.17</td>
<td>6.17</td>
</tr>
<tr>
<td>Br p-bromo-aniline</td>
<td>160</td>
<td>(\text{C}<em>{22}\text{H}</em>{17}\text{O}_3\text{N}_3\text{SBr}_2)</td>
<td>563</td>
<td>9.39</td>
<td>5.68</td>
<td>6.68</td>
</tr>
<tr>
<td>Br p-iodo aniline</td>
<td>150</td>
<td>(\text{C}<em>{22}\text{H}</em>{17}\text{O}_3\text{N}_3\text{SBr}_2)</td>
<td>610</td>
<td>6.87</td>
<td>5.23</td>
<td>6.23</td>
</tr>
</tbody>
</table>
TABLE 5

\[
\text{R} - \text{CH}_2\text{-O} - \text{NHCO.CO.NH-CS.NH-R'}
\]

\[
\text{N-(4-phenyl)Thioureido-N'- (4-Methoxy-benzylol)-phenyl-oxamide}
\]

<table>
<thead>
<tr>
<th>Para R'</th>
<th>R' of Phenyl Thiourea</th>
<th>Mol. % of</th>
<th>% of</th>
<th>Mol. % of</th>
<th>% of</th>
<th>Molecular formular</th>
<th>% of</th>
<th>% of</th>
<th>% of</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>Aniline</td>
<td>166</td>
<td>C_{23}H_{21}O_N_3S</td>
<td>435</td>
<td>9.65</td>
<td>9.65</td>
<td>7.35</td>
<td>7.35</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>p-toluidine</td>
<td>195</td>
<td>C_{24}H_{23}O_N_3S</td>
<td>448</td>
<td>9.37</td>
<td>9.38</td>
<td>7.14</td>
<td>7.14</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>m-toluidine</td>
<td>181</td>
<td>C_{24}H_{23}O_N_3S</td>
<td>448</td>
<td>9.37</td>
<td>9.37</td>
<td>7.14</td>
<td>7.14</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>p-anisidine</td>
<td>175</td>
<td>C_{24}H_{23}O_N_3S</td>
<td>464</td>
<td>9.05</td>
<td>90.5</td>
<td>6.89</td>
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<tr>
<td>OMe</td>
<td>p-phenatidine</td>
<td>170</td>
<td>C_{25}H_{25}O_N_3S</td>
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<td>8.76</td>
<td>8.77</td>
<td>6.99</td>
<td>6.99</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>p-Chloro-aniline</td>
<td>165</td>
<td>C_{23}H_{20}O_N_3Cl</td>
<td>469</td>
<td>10.05</td>
<td>10.10</td>
<td>6.82</td>
<td>6.82</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>m-Chloro-aniline</td>
<td>158</td>
<td>C_{23}H_{20}O_N_3Cl</td>
<td>469</td>
<td>10.05</td>
<td>10.10</td>
<td>6.82</td>
<td>6.82</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>p-bromo-aniline</td>
<td>155</td>
<td>C_{23}H_{20}O_N_3Br</td>
<td>514</td>
<td>8.16</td>
<td>8.17</td>
<td>6.22</td>
<td>6.22</td>
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</tr>
<tr>
<td>OMe</td>
<td>p-iodo-aniline</td>
<td>220</td>
<td>C_{23}H_{20}O_N_3I</td>
<td>561</td>
<td>7.48</td>
<td>7.49</td>
<td>5.70</td>
<td>5.71</td>
<td></td>
</tr>
</tbody>
</table>
PART - II

SECTION - III

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REFERENCES

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