PART II

GENERAL INTRODUCTION
Historically, as is evidenced by archaeological discoveries of skeletons with tuberculous lesions, tuberculosis has plagued mankind since remote antiquity and all through the subsequent ages has stood high on the list of man-killing diseases. Even to-day, it kills several million people early throughout the world, and causes more death than any other infectious diseases without intermediate vectors. Tuberculosis ranks seventh among the causes of death and is number one killer of persons between fifteen and forty-five years of age.

The causative organism, first isolated by Koch in 1882, is a fungus like bacterium, known as Mycobacterium tuberculosis or tubercle bacillus. The organisms causing tuberculosis in men, cattles and birds are sufficiently different to be recognisable as human, bovine and avian types. Though selective, these types are not rigidly exclusive in their choice of host. Bacillus of human leprosy (Mycobacterium leprae) is related to Mycobacterium tuberculosis, both belonging to the group known as "ACID-FAST-BACILLI".

The tubercle bacilli infect any tissue or organ, in addition to the pulmonary form which accounts for about 90 per cent of tuberculosis.

Tuberculosis is a chronic disease. The tubercle bacillus is a slow-growing organism which does not elicit a
sharp and massive reaction from the host and in this way tuberculosis differs from common bacterial infections. It is known that the tubercle bacillus can live for years in the host without provoking an all-or-none struggle. Tuberculosis is a communicable disease which has existed as a more or less constant stress on the human organism for hundreds of years and has left us a legacy of high resistance. The effect of such high resistance on an invasion by a slow-growing but persistent organism is to prolong the struggle, i.e. to make the disease chronic. Communities which are exposed to tuberculosis for the first time die at a fantastic rate.

In tuberculosis there is extensive tissue destruction and live, virulent bacilli become isolated in the cavities and debris of necrotic tissue where they are relatively immune to chemotherapeutic attack. The capsule theory, which assumes that the bacilli get protected, because of the fat-capsule has been proved to be wrong as modern work disproves the presence of waxy capsule surrounding the tubercle bacillus (63, 84.). The problem of getting the drug to the organism is still important because of the mechanical barriers imposed by cavities, avascular areas, necrotic and fibrotic tissue, caseation and intracellular character of the infection. These barriers may also be responsible for the emergence of resistant strains, a phenomenon which has been a major stumbling block in the chemotherapy of tuberculosis.
MODERN TESTING OF TUBERCULOSTATIC DRUGS:

(A) The *in vitro* test consists, in the main, of seeding tubercle bacilli into a synthetic culture medium which contains graded concentration of the substance to be tested, ranging from zero concentration for control purposes to concentrations approaching the toxic dose. The retardation of the rate of growth at the various concentrations is an index of the tuberculostatic efficacy of the substance.

(B) The *in vivo* test consists of inoculating mice, guinea pigs or rabbits with bovine or human types of virulent tubercle bacilli. Some of the infected animals are then treated orally or parenterally at various dose levels with the substance to be tested while others, untreated, are maintained as controls. A widely used technique involves following the pathology of the disease process by sacrificing treated and untreated infected animals at regular intervals and determining the extent to which the infection has spread to various organs. The ability of a substance to contain the original infection or minimize organ involvement is taken as an index of its tuberculostatic activity. The method of introducing a tuberculous infection in animals is an important determinant in the character of the disease process. An intranasal inoculation in mice produces a disease which is much more resistant to streptomycin than that produced by the intravenous route (49). Thus, each route requires the establishment of different criteria for the disease process. Usually H37 Rv strain is
used for experimental tuberculosis. *In vitro* test, though providing a quick inexpensive screening method, must always be followed by *in vivo* tests, as many times, compounds active *in vitro* are inactive in the animals and what is much worse, some compounds active *in vivo* are inactive in some *in vitro* tests.

**TREATMENT WITH VACCINES:**

It is known that the acquired resistance to highly virulent organisms can be induced through the medium of avirulent strains. With these ideas in mind, Calmette (18) developed, from a virulent strain of bovine tubercle bacilli by means of prolonged culture outside the body, an attenuated strain which lost its power to produce progressive tuberculosis in animals. This attenuated strain known as bacillus Calmette-Guerin, or BCG, has been administered to millions of humans in the hope of producing prophylaxis. To-date there is no conclusive evidence that vaccination with BCG confers acquired resistance on human beings, but it is considered probable that it is of some benefit (90, 91).

**SYNTHETIC TUBERCULOSTATS:**

(A) **Sulphur containing Organic Compounds:**

(1) **Sulphones:**

The pioneering work of Rist (85) and Feldmann (35) on sulphone derivatives opened the modern era in the chemotherapy of tuberculosis. In general, the sulphones are not active
enough to serve as the sole chemotherapeutic agents in clinical tuberculosis. It is interesting to note however that they have found useful application in leprosy (79, 105).

(ii) **Thiosemicarbazones** :

The best known tuberculostat of thiosemicarbazone series is p-acetamidobenzaldehyde thiosemicarbazone, also known as Tb I (Tibione), (28). Until the advent of hydrazides, Tibione was the most active of the synthetic tuberculostats in clinical use, mainly in pulmonary and mucus membrane tuberculosis. Its clinical use, however is hampered by a considerable number of very severe side reactions (20).

![p-acetamidobenzaldehyde thiosemicarbazone (Tibione)](image)

(iii) **Thioureas** :

In 1941, Mayer (70) investigated the hypothesis that the close morphological relationship between Mycobacteria and fungi might extend to their biochemistry, so that compounds with antifungal activity might also be tuberculostatic. Study of thiourea derivatives confirmed this hypothesis (30, 56, 64, 116.).

4-Ethoxy-4'-isobutoxy and 4-n-butoxy-4'-dimethylamino thiocarbanilides were found to exceed PAS or Streptomycin and approach isoniazid in activity (30).
Buu-Hoi et al., (13) confirmed the in vitro activity of diaryl thioureas and also reported that 4-4'-dialkoxy thioureas possess antileprotic activity (25, 11.). N-Aryl-N′-[2-(4-aryltiazolyl)] thioureas (9), N-aryl-N′-2-pyrimidylthioureas (80), R′-C₆H₄NHCSNH-C₆H₄-CH₂CH₂R² (R¹ is normal or branched C₄-alkyl or alkoxy group and R² is piperidino or morpholino group) (33), N-alkylthioethyl-N′-aryltioureas (83), N-β-(5-methoxyindol-3-yl)ethyl] thiourea, N-N′-bis[β-(5-methoxyindol-3-yl)ethyl] thiourea (77), p-alkoxy-1-benzyl-3-(p-alkoxyphenyl)-thioureas (82), N-phenyl-N¹-pyridylalkenylphenyl- or N-phenyl-N¹-pyridylalkynylphenyl thioureas (34), exhibit antitubercular activity.

(iv) Thiazolines and Thiazolidones:

Eisman et al., (31, 30.) found that thiazolines II and thiazolidones III were more active than the corresponding Sym. thioureas I from which these were prepared. It was observed that substances containing ether function on the aromatic ring
within the range of C$_3$ to C$_6$ possessed good \textit{in vivo} activity against tuberculous infection in experimental animals. The activity seems to reach a peak where the ether group is isopentyloxy (i.e. R = iso-C$_5$H$_{11}$). The ether group can be replaced by an alkyl group as well as by dialkyl amino group with retention of activity.

\begin{equation}
p-\text{RO-C}_6\text{H}_4\text{NHCSNH-C}_6\text{H}_4\text{-OR-p}
\end{equation}

\begin{center}
\text{I}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (s) at (0,0) {S};
\node (ch) at (0.5,0) {CH};
\node (n) at (1.5,0) {N};
\node (c) at (2,0) {C$_6$H$_4$-OR-p};
\node (c1) at (1.5,1) {C$_4$H$_3$};
\node (c2) at (2,1) {C$_6$H$_4$-OR-p};
\node (c3) at (0.5,1) {N};
\node (c4) at (0,1) {N};
\draw (s) -- (c);
\draw (c) -- (c1);
\draw (c1) -- (n);
\draw (n) -- (c2);
\draw (c2) -- (c3);
\draw (c3) -- (c4);
\draw (c4) -- (s);
\end{tikzpicture}
\end{center}

\begin{center}
\text{II}
\end{center}

\begin{equation}
p-\text{RO-C}_6\text{H}_4\text{-N=C}
\end{equation}

\begin{center}
\begin{tikzpicture}
\node (s) at (0,0) {S};
\node (ch2) at (0.5,0) {CH$_2$};
\node (n) at (1.5,0) {N};
\node (c) at (2,0) {C$_6$H$_4$-OR-p};
\node (c1) at (1.5,1) {N};
\node (c2) at (2,1) {CO};
\node (c3) at (0.5,1) {N};
\node (c4) at (0,1) {C$_6$H$_4$-OR-p};
\draw (s) -- (c);
\draw (c) -- (c1);
\draw (c1) -- (c2);
\draw (c2) -- (n);
\draw (n) -- (c3);
\draw (c3) -- (c4);
\draw (c4) -- (s);
\end{tikzpicture}
\end{center}

\begin{center}
\text{III}
\end{center}

\textbf{Sulphanilyl derivatives of thiazoline derivatives exhibit vigorous bactericidal action against pneumococci and gonococci (45, 60, 97.).}

\textbf{Buu-Hoi et al., (14) have synthesized antiviral thiazoline derivatives by condensing }\omega\text{-halo ketones with }\text{N,}\text{N'}\text{-diaryl thioureas. 2-(2-Propynylthio)-2'-oxazolines and -thiazolines can be used as nematocides (47). Miyama (71) found heavy metal}
derivatives of thiazolines to exhibit ascaricidal activity. Mizzoni (72) suggested the use of diquaternary thiazoline ammonium compounds as ganglionic-blocking agents. 2-Anilino-2-thiazolines are useful as anaesthetics (108).

2-Imino-4-thiazoline derivatives show spasmolytic, antidiuretic and bacteriostatic activity (5). 2-Imino-4-thiazolone derivatives are useful as fungicides, bactericides and insecticides (21).

Buu-Hoi et al., (15) prepared several 4-oxo-Δ²-thiazoline-2-ylhydrazones possessing tuberculostatic activity.

2-alkylidene or arylidene-hydrazono-4-thiazolidones (99), 2-(o-hydroxybenzylidene)-hydrazono-4-thiazolidones (98), 5-arylidene-2',4-thiazolidione-2-benzylidene hydrazono (109) have been prepared and tested for their tuberculostatic activity.

Trivedi et al., (102) have synthesized several 4-oxo-3-aryl-5-substituted thiazoline-2-ylhydrazones from the 4-aryl-thiosemicarbazones and α-halo acids with a view to study their physiological activity.

Roggero and Metzger (87) cyclised N-(α-hydroxyalkyl) thiobenzamides to 2-thiazoline derivatives.

2-Amino-1-alkanethiols, 1-amino-2-alkanethiols, 2-thiazolines and 2-thiazoline-2-thiols are useful as antiradiation drugs (50). 2-Benzylimino-3-benzyl-4-aryl-Δ¹-thiazoline hydrobromides are synthesised as possible antituberculars (62).
(B) Hydroxy-benzoic Acids:

(i) PAS Derivatives:

Guided by Bernheim's observation (8) that the oxygen uptake of tubercle bacillus is increased under the influence of benzoates and salicylates, Lehmann (67) discovered that p-aminosalicylic acid (PAS) was markedly tuberculostatic. It is extensively used in clinical tuberculosis,

\[
\begin{align*}
\text{H}_2\text{N}\text{-} & \\
\text{-} & \\
\text{O} & \\
\text{H} & \\
\text{COOH}
\end{align*}
\]

because of its low toxicity and when combined with streptomycin it reduces the development of resistant strains. Many variations in the structure of PAS have been investigated but so far none seems to be notably superior to the parent compound.

(ii) Hydroxamic Acids:

The investigation in the field of p-aminosalicylic acid derivatives led Urbanski (104) to the study of closely related salicyl-hydroxamic acid. He announced the discovery of the tuberculostatic 3-bromosalicylhydroxamic acid and 3-hydroxy-2-naphthylhydroxamic acid, the first being as active as streptomycin.
Among the pyridine derivatives, isonicotinic acid hydrazide (38) has been found to be the most powerful synthetic tuberculostat. It is the most extensively used synthetic tuberculostat and is relatively non-toxic and is well tolerated.

Isonicotinic acid hydrazide

Isoniazid confirms remarkably to the criteria for an effective tuberculostat. It does penetrate barrier interposed between the tubercle bacilli and the vital tissues of the host. The discovery of the tuberculostatic activity of isoniazid is a major advance in the chemotherapy of tuberculosis.

Following the discovery of the tuberculostatic activity of p-acetamidobenzaldehyde thiosemicarbazone, a large
number of thiosemicarbazones containing pyridine ring have also been investigated for the tuberculostatic activity (37, 46.).

(D) Miscellaneous Compounds:

Pyrazine carboxamide (65, 86.), Pyridazine-3-carboxamide (86), and phthalyl hydrazide (61) have shown tuberculostatic activity. Surface active agents of the type of Triton have been reported to exhibit tuberculostatic activity (23, 94.).

Panisset and co-workers (75) investigated the tuberculostatic activity of synthetic K-vitamins, menadione and Synkayvite (tetrasodium 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester) in mice infected with human H37 Rv strain and with bovine Ravenel strain and found menadione to be active against human type of organism and Synkayvite to be active against the bovine type, but the activity is of very low order.
Antibiotics also show tuberculostatic activity.
Amongst these streptomycin and dihydrostreptomycin are the most important. Neomycin, though active, is accompanied by great toxicity.

**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 hydroxamic acids, p-aminosalicylic acid and isoniazid are thought to owe 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 (12, 19, 24, 39, 69, 95.). Bergel considers the antituberculous activity of a compound as a function of its antioxidant activity (7). Streptomycin is believed to inhibit tubercle bacillus by a mechanism which involves the oxidation of fatty acids (103). Isoniazid is considered to be an antimetabolite (4, 115.). 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 isoniazide analog of DPN.
PRESENT WORK

As thiazolines containing alkoxyphenyl group have shown strong antitubercular activity (73), and as aryloxyalkyl group has been found to impart a wide variety of physiological activities (4, 11, 13, 15, 29, 31, 40, 78, 81, 86, 96, 105, 108.: Part III A) and as 2-aryl-3-aryloxyalkyl-4-thiazolidones have shown very strong antiflammatory activity (P.B. Patel, Ph.D. Thesis, Guj. Uni. 1968) it was of considerable interest to prepare thiazolines containing aryloxyalkyl group. With this in view 2-aryloxyethylimino-3-aryloxyethyl-4aryl-Δ₄-thiazolines (as hydrohalides) have been prepared by condensation of 1-aryloxyethyl-3-aryloxyethyl-2-thioureas with phenacyl halides.

\[
\begin{align*}
R-C_6H_4O(CH_2)_2N=C\overset{\text{SH}}{\text{NH(CH_2)_2OC_6H_4R}} + & \quad \text{Br-CH} \\
& \quad \text{HO-C-C_6H_4-R'} \\
\rightarrow & \quad \text{R-C_6H_4O(CH_2)_2N=C-C_6H_4-R'} \\
& \quad (\text{CH}_2)_2OC_6H_4R
\end{align*}
\]

R = H; 2-4-Cl; 2-4-CH₃; 2,4-3,4-(CH₃)₂; 2,4-(Cl)₂; 2-CH₃-4-Cl
R' = H; 4-Cl; 4-OCH₃
PART II

THEORETICAL
THEORETICAL PART II

Thiazolines are related to thiazoles as shown below:

Thiazole

\[
\begin{align*}
\text{H}^2
\end{align*}
\]

2-Thiazoline

\[
\begin{align*}
\text{H}^2
\end{align*}
\]

4,5-dihydro-thiazole

3-Thiazoline

\[
\begin{align*}
\text{H}_2\text{C}^2
\end{align*}
\]

or

2,5-dihydro-thiazole

4-Thiazoline

\[
\begin{align*}
\text{H}_2\text{C}^2
\end{align*}
\]

or

2,3-dihydro-thiazole

2-Thiazolines:

Relatively few types of 2-thiazolines are known. Substituents in the 4 and 5 positions are limited chiefly to alkyl and phenyl groups. A number of 2-alkyl and 2-aryl derivatives are also known. The 2-thiazolines that carry a functional group such as mercapto, hydroxy or amino in the 2 position can undergo tautomeration and, therefore, can be considered as derivatives of thiazolidines.

\[
\begin{align*}
\text{HX-CH,} & \quad \text{N---CH,} & \quad \% \quad \text{-CH,} & \quad \text{"NH---CH,}
\end{align*}
\]

Where \( X = S, O, \) or \( RN \)
Some of the important methods for the preparation of 2-thiazolines are as follows:

(i) By heating a thioamide with alkylene dibromide, 2-thiazolines are obtained (43, 78, 81, 89).

\[
\begin{align*}
R-C\overset{SH}{\longrightarrow}N\overset{NH}{\longrightarrow}B_r-CH_2 & \rightarrow R-C\overset{S}{\longrightarrow}N\overset{CH_2}{\longrightarrow} \\
R-C & \overset{SH}{\longrightarrow}N\overset{NH}{\longrightarrow}B_r-CH_2
\end{align*}
\]

This method is useful for the preparation of 2-alkyl/aryl-2-thiazolines. Thiazoline formation occurs more smoothly and in better yield by the reaction of a thioamide with a 2-haloalkylamino salt (10, 27, 44, 48, 89, 96, 106).

(ii) 2-Mercaptoethyl amines also react with thioamides, esters, or imino-esters to yield 2-thiazoline derivatives. This method is particularly successful with cysteine and its derivatives (22, 54, 59, 92).

\[
\begin{align*}
R-C\overset{SH}{\longrightarrow}N\overset{NH}{\longrightarrow}B_r-CH-R' & \rightarrow R-C\overset{S}{\longrightarrow}N\overset{CH-R'}{\longrightarrow} \\
R-C & \overset{SH}{\longrightarrow}N\overset{NH}{\longrightarrow}B_r-CH-R'
\end{align*}
\]

(iii) 2-Mercaptoalkylamides when cyclised with phosphorus pentoxide, phosphorus pentachloride or phosphorus pentasulphide give 2-thiazolines (40).
Certain acylated di-β-aminoethyl sulphide and disulphide also are cyclised in a similar way.

Method (ii) can be considered as a variant of this method.

(iv) N-(2-substituted alkyl) amides when treated with phosphorous pentasulphide give 2-thiazoline derivatives (1, 26, 27, 92, 93, 114).

(v) Phenols and allyl isothiocyanates react in the presence of mineral acids or aluminium chloride at low temperature to yield p-2-thiazolinine phenols (53).
(vi) 2-Amino-2-thiazolines are prepared readily by heating 2-haloalkyl amine with thiocyanate or by the cyclisation of allyl thioureas (41).

(vii) 2-Mercapto-2-thiazolines are readily prepared by methods similar to those employed for 2-amino derivatives. 2-Haloalkylamines react with carbon disulphide to yield 2-mercapto-2-thiazolines (36, 41, 42.).
4-Thiazolines:

Simple 4-thiazoline or its homologues with only alkyl substituent in 2, 4 or 5 positions are unknown. The simplest known 4-thiazolines are the 2,3-dihydrobenzo-thiazole in which 4,5 double bond is a part of benzene ring.

![2,3-dihydrobenzo-thiazole](image)

(i) Benzothiazoline can be obtained on reacting the aldehydes with o-aminothiophenol in the presence of pyridine. The thiazoline obtained is extremely labile towards oxidation, and gets converted into benzothiazole (2, 32, 66, 88).

(ii) Benzothiazoles react with two molecules of dimethyl or diphenyl ketene to give 4-thiazoline derivatives (3).
There are many compounds which can be represented as derivatives of 4-thiazolines but which are commonly classified as true thiazoles or as thiazolidines. 2-Amino, 2-hydroxy and 2-thiomethyl thiazoles can exist in tautomeric forms, one form being the 4-thiazolines (II, $R = \text{H}$, $X = 0$, $S$, or $\text{NH}$). When the ring nitrogen is substituted by alkyl or aryl group (II, $R = \text{Alkyl or aryl group}$), the compounds become true thiazoline.

![Diagram of thiazole and thiazoline structures](image)

In a similar way 4-oxo-thiazolidine with at least one hydrogen at 5 position can be considered to be 4-hydroxy-4-thiazoline.
Alkylation of 2-Amino-Thiazole:

Alkylation of 2-amino-thiazole can occur either at the amino group or at the cyclic nitrogen depending upon the conditions. In the absence of any condensing agents or in the presence of such agents as aqueous alkali and potassium carbonate, alkylation gives an unstable salt, which on treatment with bases yield imino-thiazolines (29, 52, 57, 74, 101, 110, 117.).

Irving and Kaye (58) prepared N,N-disubstituted-2-amino thiazoles by alkylation of N-substituted-2-amino-thiazoles in presence of lithium amide. This method was found to be satisfactory for the preparation of secondary amines from 2-amino thiazole. In absence of condensing agent N-alkylated products were isolated.
This product is different from the one having the alkyl group on the exocyclic nitrogen. This is proved as follows:

(i) By synthesising the compounds from appropriately substituted thiourea and \(\alpha\)-halo carbonyl compound \((29, 57.)\)

(ii) By hydrolysis with hydrochloric acid at 200\(^{\circ}\), followed by identification of the amines that are produced by the rupture of the thiazole ring \((52, 101, 107, 117.)\)

(iii) By treatment with carbon disulphide at 200\(^{\circ}\) towards which the 2-amino isomers are relatively resistant
whereas the 2-imino yields a 2-thioxo-4-thiazoline (2-thiathiazolone) and an aryl isothiocyanate (110, 112).

(iv) By coupling with diazonium salts, which occurs readily with 2-amino thiazoles when the 5 position is unsubstituted whereas 2-imino thiazolines are inert (110, 112).

2-Imino-4-thiazolines have been prepared by Gregory (107) by condensing an α-thiocyanate carbonyl compound with a primary amine or its salts and azeotropically removing the water formed during the course of reaction.

Taylor et al., (100) prepared 2-imino-3,5-diphenyl-4-amino thiazoline by the condensation of α-cyanobenzyl benzene sulphonate with thiourea.
Bayer and Ruhlig (6) synthesised 3-substituted 2-imino-4-thiazolines from \( \alpha \)-thiocyanato ketones.

Buu-Hoi (16) prepared 3-aryl-2-aryl-imino-4-(2'-phenoxathiinyl)-4-thiazoline by refluxing for one hour equimolar amounts of 2-\( \omega \)-bromoacetylphenoxathiin and the appropriate \( N,N' \)-diaryl thioureas in ethyl alcohol.

Where \( Ar = \text{phenyl} \)
1,3-Disubstituted thioureas react with α-halocarbonyl compounds to form 2-imino-thiazolines (55, 57, 68, 74, 101, 110, 111).

\[
\begin{align*}
S & \quad R-N=C \quad \text{SH} \\
& \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 

Buu-Hoi (17) has condensed unsymmetrical NN'-diaryl thioureas with α-halo ketones. In every instance, only one of the two possible 3,4-diaryl-2-arylimino-△-thiazolines was obtained; from the results of Von Walther's degradation (113) of similar unsymmetrical compounds, it can be assumed that the aryl-imino-radical in the thiol form of unsymmetrical thioureas involves the more bulky aryl group.
Mizzoni and Eisman (73) have prepared 3-\((p\text{-isopentyloxyphenyl})\)-2-\((p\text{-isopentyloxyphenyl})\)-imino-4-methyl-4-thiazoline hydrochloride by the condensation of 1,3-bis-(isopentyloxyphenyl)-2-thiourea with chloroacetone in absolute alcohol.

Bartoszewski and Jerzmanowska (5) have condensed differently substituted sym. diaryl thioureas with chloroacetone and obtained in some cases two isomeric 2-arylimino-3-aryl-4-methyl-4-thiazoline derivatives. They arrived at the structure on the basis of its reaction with carbon disulphide.
The degradation products and the corresponding aryl isothiocyanates were isolated and identified.

Several 3-aryloxyethyl-2-aryloxyethyl-imino-4-aryl-thiazoline hydrobromides/hydrochlorides have been prepared by the condensation of symmetrical 1,3-diaryloxyethyl-2-thioureas with substituted phenacyl bromides/chlorides in absolute alcohol.

\[ \text{R} \cdot \text{C}_6\text{H}_4(\text{CH}_2)_2 \text{N}=\text{C}(\text{CH}_2)_2\text{OC}_6\text{H}_4 \cdot \text{R}^* \]

\[ \text{R} \cdot \text{C}_6\text{H}_4(\text{CH}_2)_2 \text{N}=\text{C}(\text{CH}_2)_2\text{OC}_6\text{H}_4 \cdot \text{R}^* \]

\[ \text{R} = \text{H} ; 2-/4-\text{Cl} ; 2-/4-\text{CH}_3 ; 2,4-/3,4-(\text{CH}_3)_2 ; 2,4-(\text{Cl})_2 ; 2-\text{CH}_3-4-\text{Cl} \]

\[ \text{R}^* = \text{H} ; 4-\text{Cl} ; 4-\text{OCH}_3 \]

Compounds prepared are shown in the table.
TABLE B-I

3-β-ARYLOXYETHYL-2-β-ARYLOXYETHYL-IMINO-4-ARYL- Δ -THIAZOLINE HYDROBROMIDES/HYDROCHLORIDES

\[
\text{R-}C_6H_4O(CH_2)_2\text{N=CH-N}C_6H_4\text{R'}
\]

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>R'</th>
<th>A</th>
<th>M.P. degree C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>H</td>
<td>H</td>
<td>HBr</td>
<td>138-39</td>
</tr>
<tr>
<td>2.</td>
<td>2-C1</td>
<td>H</td>
<td>HCl</td>
<td>140</td>
</tr>
<tr>
<td>3.</td>
<td>4-C1</td>
<td>H</td>
<td>HBr</td>
<td>161</td>
</tr>
<tr>
<td>4.</td>
<td>2-CH₃</td>
<td>H</td>
<td>HBr</td>
<td>142</td>
</tr>
<tr>
<td>5.</td>
<td>4-CH₃</td>
<td>H</td>
<td>HBr</td>
<td>154</td>
</tr>
<tr>
<td>6.</td>
<td>2-CH₃-4-C1</td>
<td>H</td>
<td>HBr</td>
<td>107</td>
</tr>
<tr>
<td>7.</td>
<td>2,4-(Cl)₂</td>
<td>H</td>
<td>HBr</td>
<td>155</td>
</tr>
<tr>
<td>8.</td>
<td>2,4-(CH₃)₂</td>
<td>H</td>
<td>HBr</td>
<td>157</td>
</tr>
<tr>
<td>9.</td>
<td>3,4-(CH₃)₂</td>
<td>H</td>
<td>HBr</td>
<td>160-61</td>
</tr>
<tr>
<td>10.</td>
<td>H</td>
<td>4-C1</td>
<td>HBr</td>
<td>173</td>
</tr>
<tr>
<td>11.</td>
<td>2-C1</td>
<td>4-C1</td>
<td>HBr</td>
<td>148</td>
</tr>
<tr>
<td>12.</td>
<td>4-C1</td>
<td>4-C1</td>
<td>HBr</td>
<td>194-95</td>
</tr>
<tr>
<td>13.</td>
<td>2-CH₃</td>
<td>4-C1</td>
<td>HBr</td>
<td>107</td>
</tr>
<tr>
<td>14.</td>
<td>4-CH₃</td>
<td>4-C1</td>
<td>HBr</td>
<td>170</td>
</tr>
<tr>
<td>No.</td>
<td>R</td>
<td>R'</td>
<td>A</td>
<td>M.P. degree C</td>
</tr>
<tr>
<td>-----</td>
<td>------------</td>
<td>-----------</td>
<td>----</td>
<td>---------------</td>
</tr>
<tr>
<td>15.</td>
<td>2-CH₃-4-Cl</td>
<td>4-Cl</td>
<td>HBr</td>
<td>115</td>
</tr>
<tr>
<td>16.</td>
<td>2,4-(CH₃)₂</td>
<td>4-Cl</td>
<td>HBr</td>
<td>174</td>
</tr>
<tr>
<td>17.</td>
<td>3,4-(CH₃)₂</td>
<td>4-Cl</td>
<td>HBr</td>
<td>165</td>
</tr>
<tr>
<td>18.</td>
<td>H</td>
<td>4-OCH₃</td>
<td>HCl</td>
<td>154</td>
</tr>
<tr>
<td>19.</td>
<td>2-C₁</td>
<td>4-OCH₃</td>
<td>HCl</td>
<td>138-39</td>
</tr>
<tr>
<td>20.</td>
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<td>4-OCH₃</td>
<td>HCl</td>
<td>213</td>
</tr>
<tr>
<td>21.</td>
<td>2-CH₃</td>
<td>4-OCH₃</td>
<td>HCl</td>
<td>124</td>
</tr>
<tr>
<td>22.</td>
<td>4-CH₃</td>
<td>4-OCH₃</td>
<td>HCl</td>
<td>153-54</td>
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<tr>
<td>23.</td>
<td>2-CH₃-4-Cl</td>
<td>4-OCH₃</td>
<td>HCl</td>
<td>85</td>
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<td>24.</td>
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<td>4-OCH₃</td>
<td>HCl</td>
<td>111</td>
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<tr>
<td>25.</td>
<td>3,4-(CH₃)₂</td>
<td>4-OCH₃</td>
<td>HCl</td>
<td>223</td>
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</tbody>
</table>
PART II

EXPERIMENTAL
EXPERIMENTAL PART II

Aryloxyethyl amines and isothiocyanates required for the preparation of symmetrical 1,3-diaryloxyethyl-2-thioureas were prepared as described in Experimental Part I.

GENERAL METHOD FOR THE PREPARATION OF SYMMETRICAL 1,3-DIARYLOXYETHYL-2-THIOUREAS:

A mixture of aryloxyethyl isothiocyanate (0.01 mole) and appropriate aryloxyethyl amine (0.01 mole) in absolute alcohol (25-40 ml.) was heated to boiling for a few minutes and kept overnight. In most cases thiourea was obtained as a crystalline solid. It was recrystallised from ethyl alcohol (Buu-Hoi et al., J. Chem. Soc., 1955, 1573).

Following symmetrical thioureas were prepared by the above method:

SYMMETRICAL 1,3-DIARYLOXYETHYL-2-THIOUREAS

R-C$_6$H$_4$OCH$_2$NHCNSNHCH$_2$OC$_6$H$_4$-R

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>M.P. degree $^\circ$ C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>2-Cl</td>
<td>93</td>
<td>-do-</td>
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<td>Sr. No.</td>
<td>R</td>
<td>M.P. degree °C</td>
<td>Reference</td>
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<td>--------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>4.</td>
<td>2-CH₃</td>
<td>117-18</td>
<td>-do-</td>
</tr>
<tr>
<td>5.</td>
<td>4-CH₃</td>
<td>131</td>
<td>-do-</td>
</tr>
<tr>
<td>6.</td>
<td>2-CH₃-4-Cl</td>
<td>152</td>
<td>-do-</td>
</tr>
<tr>
<td>7.</td>
<td>2,4-(Cl)₂</td>
<td>105</td>
<td>-do-</td>
</tr>
<tr>
<td>8.</td>
<td>2,4-(CH₃)₂</td>
<td>134</td>
<td>-do-</td>
</tr>
<tr>
<td>9.</td>
<td>3,4-(CH₃)₂</td>
<td>118</td>
<td>Not reported so far.</td>
</tr>
</tbody>
</table>

**GENERAL METHOD FOR THE PREPARATION OF SUBSTITUTED PHENACYL BROMIDES:**

To 20 g. of substituted acetophenone, dissolved in 30 g. glacial acetic acid, 28 g. bromine was added slowly with constant shaking. If, towards the end of the reaction, the hydrobromic acid was not given off readily, the reaction flask was put in hot water for a few minutes. At the end of the reaction, the reaction mixture was poured into ice water, allowed to stand for an hour and filtered. The yield of substituted phenacyl bromide was about 75 per cent. For further purification the phenacyl bromides were crystallised from hot alcohol (Reid, J. Am. Chem. Soc., 1919, 40, 75).
Following substituted phenacyl bromides have been synthesised by the above method:

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>M.P. degree C</th>
<th>Reference</th>
</tr>
</thead>
</table>

PREPARATION OF CHLOROACETYLCHLORIDE:

In a round bottomed flask fitted with the fractionating column was placed monochloro acetic acid (0.25 mole) and benzoyl chloride (0.325 mole). The mixture was heated to boiling. The acid chloride was slowly distilled off at 105-7°C. The yield was about 70 per cent (Brown, J. Am. Chem. Soc., 1938, 60, 1325 quoted from Experimental Chemistry by Fieser).

PREPARATION OF p-METHOXY PHENACYL CHLORIDE:

In a dry 500 ml. three-necked flask, fitted with an efficient mercury sealed stirrer, a separatory funnel and a reflux condenser attached to a gas absorption device, were placed finely powdered anhydrous aluminium chloride (40 g.) and freshly distilled anisole (1.13 mole) in carbon disulphide.
To this, freshly distilled acid chloride (0.36 mole) was added dropwise through the separatory funnel within half an hour. During the addition of acid chloride, the reaction mixture was stirred vigorously. After completing the addition of acid chloride, the reaction mixture was stirred and heated for one hour on a water bath at 50°C. The reaction mixture was decomposed with a mixture of 500 g. of crushed ice and 300 ml. of concentrated hydrochloric acid and the phenacyl chloride was extracted with ether. The ether extract was washed with 50 ml. of 10 per cent sodium hydroxide solution and then with water. The organic layer was separated and dried with anhydrous magnesium sulphate or calcium chloride. The crude phenacyl chloride, obtained after the removal of ether, was purified by recrystallisation from alcohol, M.P. 102°C. (Vogel, Practical Organic Chemistry, 1959, page 729; Kunckell and Johannsen, Ber., 30, 1715 (1897)).
GENERAL METHOD FOR THE PREPARATION OF:

\[ \text{3-\(\beta\)-ARYLOXYETHYL-2-\(\beta\)-ARYLOXYETHYL-IMINO-4-ARYL-\(\Delta^1\)-THIAZOLINE HYDROBROMIDES/HYDROCHLORIDES} \]

A mixture of sym. \(\beta\)-phenoxyethyl thiourea (0.034 mole) and substituted phenacyl bromide/chloride (0.036 mole) in 150-200 ml. of anhydrous alcohol was refluxed for 4-5 hours on a water bath. The solution was concentrated to about 50 ml. and diluted with sodium dried ether. The substance obtained on chilling was filtered and recrystallised from absolute alcohol-ether. The yield was 60 to 70 per cent (Mizzoni et al., J. Am. Chem. Soc., 1958, 80, 3473).

Compounds prepared are shown in the tables.
TABLE B-II

3-β-ARYLOXYETHYL-2-β-ARYLOXYETHYLMINO-4-PHENYL-Δ-

THIAZOLINE HYDROBROMIDES

<table>
<thead>
<tr>
<th>No.</th>
<th>Compds. (R =)</th>
<th>M.P. degree C</th>
<th>Molecular Formula</th>
<th>Per cent Sulphur</th>
<th>Found</th>
<th>Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>H</td>
<td>138-39</td>
<td>C_{25}H_{25}O_{2}N_{2}BrS</td>
<td>6.5</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>2-Cl</td>
<td>140</td>
<td>C_{25}H_{23}O_{2}N_{2}Cl_{3}S</td>
<td>6.5</td>
<td>6.1</td>
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</tr>
<tr>
<td>3.</td>
<td>4-Cl</td>
<td>161</td>
<td>C_{25}H_{23}O_{2}N_{2}Cl_{2}BrS</td>
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<td>5.7</td>
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<tr>
<td>4.</td>
<td>2-CH₃</td>
<td>142</td>
<td>C_{27}H_{29}O_{2}N_{2}BrS</td>
<td>6.1</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>4-CH₃</td>
<td>154</td>
<td>C_{27}H_{29}O_{2}N_{2}BrS</td>
<td>6.2</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>2,4-(CH₃)₂</td>
<td>157</td>
<td>C_{29}H_{33}O_{2}N_{2}BrS</td>
<td>5.6</td>
<td>5.8</td>
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<tr>
<td>7.</td>
<td>3,4-(CH₃)₂</td>
<td>160-61</td>
<td>C_{29}H_{33}O_{2}N_{2}BrS</td>
<td>5.9</td>
<td>5.8</td>
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<tr>
<td>8.</td>
<td>2,4-(Cl)₂</td>
<td>155</td>
<td>C_{25}H_{21}O_{2}N_{2}Cl_{4}BrS</td>
<td>5.0</td>
<td>5.1</td>
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<tr>
<td>9.</td>
<td>2-CH₃-4-Cl</td>
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<td>5.3</td>
<td>5.4</td>
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</tr>
</tbody>
</table>
### TABLE B-III

3-β-ARYLOXYETHYL-2-β-ARYLOXYETHYLIMINO-4-p-CHLOROPHENYL-Δ^4-

**THIAZOLINE HYDROBROMIDES**

![Chemical Structure]

<table>
<thead>
<tr>
<th>No.</th>
<th>Compds. (R= )</th>
<th>M.P. degree C</th>
<th>Molecular Formula</th>
<th>Per cent Sulphur Found</th>
<th>Per cent Sulphur Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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<td>C_{25}H_{24}O_{2}N_{2}ClBrS</td>
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<td>6.0</td>
</tr>
<tr>
<td>2.</td>
<td>2-Cl</td>
<td>148</td>
<td>C_{25}H_{22}O_{2}N_{2}Cl_{3}BrS</td>
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<td>5.3</td>
</tr>
<tr>
<td>3.</td>
<td>4-Cl</td>
<td>194-95</td>
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<td>5.2</td>
<td>5.3</td>
</tr>
<tr>
<td>4.</td>
<td>2-CH₃</td>
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<td>C_{27}H_{28}O_{2}N_{2}ClBrS</td>
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<td>5.7</td>
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<tr>
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<td>4-CH₃</td>
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<td>5.7</td>
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<tr>
<td>6.</td>
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<td>5.3</td>
<td>5.5</td>
</tr>
<tr>
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<td>C_{29}H_{32}O_{2}N_{2}ClBrS</td>
<td>5.4</td>
<td>5.5</td>
</tr>
<tr>
<td>8.</td>
<td>2-CH₃-4-Cl</td>
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<td>C_{27}H_{26}O_{2}N_{2}Cl_{3}BrS</td>
<td>5.0</td>
<td>5.1</td>
</tr>
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</table>
TABLE B-IV

3-β-ARYLOXYETHYL-2-β-ARYLOXYETHYLIMINO-4-p-METHOXYPHENYL-Δ4-
THIAZOLINE HYDROCHLORIDES

<table>
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<th>No.</th>
<th>Compds. (R =)</th>
<th>M.P. degree C</th>
<th>Molecular Formula</th>
<th>Per cent Sulphur Found</th>
<th>Required</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>H</td>
<td>154</td>
<td>C_{26}H_{27}O_{3}N_{2}ClS</td>
<td>6.2</td>
<td>6.1</td>
</tr>
<tr>
<td>2.</td>
<td>2-Cl</td>
<td>138-39</td>
<td>C_{26}H_{25}O_{3}N_{2}Cl_{3}S</td>
<td>5.2</td>
<td>5.4</td>
</tr>
<tr>
<td>3.</td>
<td>4-Cl</td>
<td>213</td>
<td>C_{26}H_{25}O_{3}N_{2}Cl_{3}S</td>
<td>5.1</td>
<td>5.4</td>
</tr>
<tr>
<td>4.</td>
<td>2-CH₃</td>
<td>124</td>
<td>C_{28}H_{31}O_{3}N_{2}ClS</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>5.</td>
<td>4-CH₃</td>
<td>153-54</td>
<td>C_{28}H_{31}O_{3}N_{2}ClS</td>
<td>5.7</td>
<td>5.8</td>
</tr>
<tr>
<td>6.</td>
<td>2,4-(CH₃)₂</td>
<td>111</td>
<td>C_{30}H_{35}O_{3}N_{2}ClS</td>
<td>5.6</td>
<td>5.5</td>
</tr>
<tr>
<td>7.</td>
<td>3,4-(CH₃)₂</td>
<td>223</td>
<td>C_{30}H_{35}O_{3}N_{2}ClS</td>
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<td>5.5</td>
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<tr>
<td>8.</td>
<td>2-CH₃-4-Cl</td>
<td>85</td>
<td>C_{28}H_{29}O_{3}N_{2}Cl_{3}S</td>
<td>5.2</td>
<td>5.1</td>
</tr>
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