PART - III - A

GENERAL INTRODUCTION
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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 disease 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 (68, 96). 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 (53). 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 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 (20) 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 (102, 103).
SYNTHETIC TUBERCULOSTATICS:

(A) Sulphur containing Organic Compounds:

(i) Sulphones:

The pioneering work of Rist (97), and Feldmann (39) 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 (91, 119).

(ii) Thiosemicarbazones:

The best known tuberculostat of thiosemicarbazone series is p-acetamidobenzaldehyde thiosemicarbazone, also known as Tb I (Tibione), (32). 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 (22).

\[ \text{CH}_3\text{CONH-} \quad \text{CH-NNHCSNH}_2 \]

p-acetamidobenzaldehyde thiosemicarbazone
(Tibione)

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 (41, 50).
(iii) Thioureas:

In 1941, Mayer (78) 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 (34, 61, 69, 132).

4-Ethoxy-4'-isobutoxy and 4-n-butoxy-4'-dimethylamino thiocarbanilides were found to exceed PAS or Streptomycin and approach isoniazid in activity (34).

Buu-Hoi et al. (15) confirmed the in vitro activity of diarylthioureas and also reported that 4,4'-dialkoxythioureas possess antileprotic activity (13, 29). N-Aryl-N'-(2-(4-arylthiazolyl)) thioureas (10), N-aryl-N'-2-pyrimidyl-thioureas (92), $R^1-C_6H_4NHCSNHC_6H_4-CH_2CH_2R^2$ ( $R^1$ is normal or branched C$_4$-alkyl or alkoxy group and $R^2$ is piperidino or
morpholino group (37), N-alkylthioethyl-N'-aryl-thioureas (95), N- [β-(5-methoxyindol-3-yl)ethyl] thiourea, N,N'-bis[β-(5-methoxyindol-3-yl)ethyl] thiourea (89), p-alkoxy-1-benzyl-3-(p-alkoxyphenyl) thioureas (94), N-phenyl-N'-pyridylalkenylphenyl or N-phenyl-N'-pyridyl-alkenylphenyl thioureas (38) exhibit antitubercular activity.

(iv) Thiazolines and Thiazolidinones:

Eisman et al., (34, 35) found that thiazolines II and thiazolidinones 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 in vivo activity against tuberculous infection in experimental animals. The activity seems to reach a peak where the ether group is isopentyl oxy (i.e. R = isoo-C_5H_{11}). The ether group can be replaced by an alkyl group as well as by dialkylamino group with retention of activity.

\[
\begin{align*}
\text{I} & \quad \text{p-RO-C}_6\text{H}_4\text{NHGSNHC}_6\text{H}_4\text{-OR-p} \\
\text{II} & \quad \text{p-RO-C}_6\text{H}_4\text{-N=CH-C}_6\text{H}_4\text{-OR-p} \\
\text{III} & \quad \text{p-RO-C}_6\text{H}_4\text{-N=CH-C}(\text{CO})\text{C}_6\text{H}_4\text{-OR-p}
\end{align*}
\]
Sulphanilyl derivatives of thiazoline derivatives exhibit vigorous bactericidal action against pneumococci and gonococci (49, 65, 111).

Buu-Hoi et al., (16) have synthesized antiviral thiazoline derivatives by condensing 3-halo ketones with N,N'-diaryl thioureas. 2-(2-Propynylthio)-2-oxazolines and thiazolines can be used as nematocides (51). Miyama (80) found heavy metal derivatives of thiazolines to exhibit ascaricidal activity. Mizzoni (81) suggested the use of diquaternary thiazoline ammonium compounds as ganglionic-blocking agents. 2-Anilino-2-thiazolines are useful as anesthetics (122).

2-Imino-4-thiazoline derivatives show spasmolytic, antidiuretic and bacteriostatic activity (5). 2-Imino-4-thiazoline derivatives are useful as fungicides, bactericides and insecticides (23).

Buu-Hoi et al., (17) prepared several 4-oxo-$\triangle^2$-thiazoline-2-ylhydrazones possessing tuberculostatic activity.

2-Alkylidene or arylidene-hydrazono-4-thiazolidinones (113), 2-(o-hydroxybenzylidene)-hydrazono-4-thiazolidinones (112), 5-arylidene-2,4-thiazolidinedione-2-benzylidene hydrazono (123) have been prepared and tested for their tuberculostatic activity.

Trivedi et al., (116) have synthesized several 4-oxo-3-aryl-5-substituted thiazoline-2-ylhydrazones from the 4-aryl-thiosemicarbazones and $\alpha$-halo acids with a view to study their physiological activity.
Modi and Trivedi (83) prepared 2-aryloxyethylimino-3-aryloxyethyl-4-aryl-4-thiazolines to study their physiological activity.

3-Aryl-2-arylimino-4-(p-bromophenyl)-4-thiazolines have been prepared which possess fungicidal activity (27).

2-Imino-3-(p-ethoxyphenyl)-4-methyl-4-thiazoline, 2-benzylimino-3-(p-ethoxyphenyl)-4-methyl-4-hydroxythiazolidine and 2-γ-pyridylimino-3-(p-ethoxyphenyl)-4-methyl-4-hydroxythiazolidine have been synthesized with a view to study their physiological activity (84).

Dash and Mahapatra (28) prepared 2-arylimino-3-aryl-4-methyl-5-carbethoxy-4-thiazolines and their mercurated derivatives as possible fungicides.

3-Amino-2-imino-4-(5-nitro-2-furyl)-4-thiazoline hydrochloride is useful in veterinary medicine (86).

2-Arylimino-3-aryl-4-alkyl-4-thiazolines (70), 2-phenylimino-3-isonicotinoylamino-4-phenyl-4-thiazoline (11), 2-(R'N-substituted)-3-(R'-substituted)-4-(R-substituted)-thiazole-4-ines (54), 4-arylamino-4-thiazolines (74),
2-(p-carboxy)phenylimino-3-phenyl-4-methyl-4-thiazoline (6), 2-imino-3-aryl-4-amino-5-carbethoxy-4-thiazolines (105), and Et-4-allylthiourea-3-aryl-2-imino-4-thiazoline-5-carboxylates have been synthesized to study their physiological properties.

Werbel (130) prepared 5-nitro-4-thiazolin-2-ylidene-ureas which are active against schistosomes and trichomonides.

5-Phenyl-3-methyl-2-(methylimino)-thiazolines possess hypotensive activity (75).

4-(p-Chlorophenyl)-4-hydroxy-5-thiazolidine acetic acids and their esters have been synthesized as possible antitubercular and central nervous depressant (128).

2-(o,o-diethylthiophosphonolimino)-3-methyl-4-thiazoline possess insecticidal and acaricidal properties (79).
Soggero and Metzger (99) 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 anti-radiation drugs (55). 2-Benzylimino-3-benzyl-4-aryl-Δ4-thiazoline hydrobromides are synthesized as possible anti-tuberculars (67).

(B) Hydroxybenzoic acids:

(i) PAS Derivatives:

Guided by Bernheim's observation (9) that the oxygen uptake of tubercle bacillus is increased under the influence of benzoates and salicylates, Lehmann (73) discovered that p-aminosalicylic acid (PAS) was markedly tuberculostatic. It is extensively used in clinical tuberculosis, because of its low toxicity. 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 (118) to the study of closely
related salicylhydroxamic acid. He announced the discovery of the tuberculostatic 3-bromosalicylhydroxamic acid and 3-hydroxy-2-naphthylhydroxamic acid, the first being as active as streptomycin.

3-Bromosalicylhydroxamic acid

3-Hydroxy-2-naphthylhydroxamic acid

(C) Pyridine Carboxylic Acid Derivatives:

Among the pyridine derivatives, isonicotinic acid hydrazide (42) 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.
Pyrazinecarboxamide (71, 98), pyridazine-3-carboxamide (98) and phthalylhydrazide (66) have shown tuberculostatic activity. Surface active agents of the type of Triton have been reported to exhibit tuberculostatic activity (25, 108).

Panisset and coworkers (87) 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.

Menadione
or
2-Methyl-1,4-naphthoquinone
Antibiotics also show tuberculostatic activity. Amongst these streptomycin and dihydrostreptomycin are the most important. Neomycin, though active is accompanied by great toxicity. Oxytetracycline, Viomycin and Cycloserine which elicit antituberculous activity.

**MECHANISM OF ANTITUBERCULOUS ACTION**

There is at present no established mechanism for the activity of any of the antituberculour 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 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 bacilli (14, 21, 26, 43, 77, 109). Bergel considers the antituberculous activity of a compound as a function of its antioxident
activity (8). Streptomycin is believed to inhibit tubercle bacillus by a mechanism which involves the oxidation of fatty acids (117). Isoniazid is considered to be an antimetabolite (4, 131). Another view suggests that the antituberculair activity of isoniazid may be related to its activity to displace niacinamide from diphosphopyridine nucleotide (DPN) to form an isoniazid analog of DPN.
Thiazolines, especially aryl substituted thiazolines are active against tubercular bacilli. A carboxyl group in a thiazoline ring would increase its solubility. With this in view 3-aryl-2-arylimino-4-aryl-\(\Delta^4\)-thiazoline-5-acetic acids (as hydrobromides) have been prepared by condensation of diarylthioureas with \(\beta\)-bromo-\(\beta\)-arylpionic acids in absolute alcohol.

Where: 
- \(X=H; o-m-p-CH_3; o-m-p-Cl; p-Br; o-p-OCH_3\)
- \(Y=H; p-CH_3; p-C_3H_5; p-OCH_3; p-OCH_3; p-OCH_3; p-n-OCH_3; p-n-OCH_3; 2,6-(CH_3)_2\)
**THEORETICAL**

Thiazolines are related to thiazoles as shown below:

- 2-Thiazoline
- or
- 4,5-dihydro-thiazole

- 3-Thiazoline
- or
- 2,5-dihydro-thiazole

- 4-Thiazoline
- or
- 2,3-dihydro-thiazole

**2-Thiazolines:**

Relatively few 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 tautomerism and, therefore, can be considered as derivatives of thiazolidines.
Where X = S, O or RN.

Some of the important methods for the preparation of 2-thiazolines are as follows:

(i) By heating a thioamides with alkylene dibromide, 2-thiazolines are obtained (47, 90, 93, 101).

\[ \text{R-C-SH} + \text{Br-CH}_2 \xrightarrow{\text{Reaction}} \text{R-C-S-CH}_2 \]

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-haloalkylamine salt (12, 31, 48, 52, 101, 110, 120).

\[ \text{R-C-SH} + \text{Br-CH-R'} \xrightarrow{\text{Reaction}} \text{R-C-S-CH-R'} \]

(ii) 2-Mercaptoethylamines also react with thioamides, esters or iminoesters to yield 2-thiazoline derivatives. This method is particularly successful with cysteine and its derivatives (24, 59, 64, 104).
(iii) 2-Mercaptoalkylamides when cyclised with phosphorus pentoxide, phosphorus pentachloride or phosphorus pentasulphide give 2-thiazolines (44).

\[
\begin{align*}
\text{CH}_2\text{NH-CO-R} & \xrightarrow{\text{P}_2\text{O}_5} \text{R-C} \\
\text{CH}_2-3\text{H} & \\
\end{align*}
\]

Certain acylated di-β-aminoethyl sulphide and disulphide also are cyclised in a similar way.

\[
\begin{align*}
\left[ \begin{array}{c}
\text{CH}_2\text{NH-CO-R} \\
\text{CH}_2-3\text{H}
\end{array} \right] & \xrightarrow{\text{PCl}_5} \text{R-C} \\
& \end{align*}
\]

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

(vi) N-(2-substituted alkyl)amides when treated with phosphorus pentasulphide give 2-thiazoline derivatives (1, 30, 31, 104, 107, 129).

\[
\begin{align*}
\text{R-CNHCH}_2\text{X} & \xrightarrow{\text{P}_2\text{S}_5} \text{R-C} \\
& \end{align*}
\]

Where \(X=\text{Halogen, hydroxyl or acetoxy groups.}\)
(v) Phenols and allyl isothiocyanates react in the presence of mineral acids or aluminium chloride at low temperature to yield p-2-thiazolinine phenols (58).

\[
\text{C}_6\text{H}_5\text{OH} + \text{CH}_2=\text{CHCH}_2\text{NGS} \xrightarrow{\text{H}_2\text{SO}_4, 0-5^\circ\text{C}} \text{C}_6\text{H}_5\text{O}-\text{S} \quad \text{CH}=\text{CH}_2
\]

\[
\text{p-HO-C}_6\text{H}_4-\text{S} \quad \text{CH} \quad \text{CH}_3 \leftarrow \quad \text{C}_6\text{H}_5\text{O}-\text{N} \quad \text{CH}_2 \quad \text{CH}_2
\]

(vi) 2-Amino-2-thiazolines are prepared readily by heating 2-haloalkylamine with thiocyanate or by the cyclisation of allyl thioureas (45).

\[
\text{CH}_2\text{NH}_2\cdot\text{HCl} \quad + \quad \text{KCN} \quad \xrightarrow{\text{CH}_2\text{Br}} \quad \text{H}_2\text{N} \quad \text{CH}_2
\]

\[
\text{CH}_2=\text{CH} \quad \text{NH}_2 \quad \xrightarrow{\text{HBr}} \quad \text{H}_2\text{N} \quad \text{CH}_3 \quad \text{CH}_2
\]

(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 (40, 45).
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-dihydrobenzothiazole in which 4,5-double bond is a part of benzene ring.

2,3-dihydrobenzothiazole

(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 (2,36, 72, 100).
(ii) Benzothiazoles react with two molecules of dimethyl or diphenyl ketene to give 4-thiazoline derivatives (3).

\[
\text{S}\begin{array}{c}
\text{N} \\
\text{S}
\end{array} + (R)_2C=O \rightarrow \text{S}\begin{array}{c}
\text{N} \\
\text{R}
\end{array}
\]

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-mercaptothiazoles can exist in tautomeric forms, one form being the 4-thiazolines (II, R=H, X=O, S or NH). When the ring nitrogen is substituted by alkyl or aryl group (II, R=alkyl or aryl group), the compounds become true thiazoline.

\[
\begin{array}{c}
\text{X} \\
\text{C}
\end{array} \begin{array}{c}
\text{S} \\
\text{N} \\
\text{CH}
\end{array} \quad \leftrightarrow \quad \begin{array}{c}
\text{X} \\
\text{C}
\end{array} \begin{array}{c}
\text{S} \\
\text{N} \\
\text{CH}
\end{array} \quad \begin{array}{c}
\text{R}
\end{array}
\]

(1) Thiazole \hspace{1cm} (II) Thiazoline (Tautomeric form)

\(X=\text{OH}, \text{SH or NH}_2\) \hspace{1cm} (R=H, X=O, S or NH)

True Thiazoline \hspace{1cm} (R=alkyl or aryl)

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-Aminothiazole:

Alkylation of 2-aminothiazole 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 iminothiazolines (33, 57, 62, 85, 115, 124, 133).

Irving and Kaye (63) prepared N,N-disubstituted-2-aminothiazoles by alkylation of N-substituted-2-aminothiazoles in presence of lithium amide. This method was found to be satisfactory for the preparation of secondary amines from 2-aminothiazole. 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 the appropriately substituted thiourea and \( \gamma \)-halo carbonyl compound (33, 62).

(ii) By hydrolysis with hydrochloric acid at 200°C, followed by identification of the amines that are produced by the rupture of the thiazole ring (57, 115, 121, 133).

(iii) By treatment with carbon disulphide at 200°C towards which the 2-amino isomers are relatively resistant whereas the 2-imino yields a 2-thioxo-4-thiazoline (2-thiothiazolone) and an aryl isothiocyanate (124, 126).
(iv) By coupling with diazonium salts, which occurs readily with 2-aminothiazoles when the 5-position is unsubstituted whereas 2-iminothiazolines are inert (124, 126).

2-imino-4-thiazolines have been prepared by Gregory (121) 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., (114) prepared 2-imino-3,5-diphenyl-4-aminothiazoline by the condensation of α-cyanobenzyl benzene-sulphonate with thiourea.

Bayer and Ruhlig (7) synthesized 3-substituted-2-imino-4-thiazolines from α-thiocyanato ketones.

Buu-Hoi, (18) prepared 3-aryl-2-arylimino-4-(2'-phenothiazinyl) -4'-thiazolines from α-thiocyanato ketones.

Bayer and Ruhlig (7) synthesized 3-substituted-2-imino-4-thiazolines from α-thiocyanato ketones.
1,3-Disubstituted thioureas react with α-halocarbonyl compounds to form 2-iminothiazolines (60, 62, 76, 85, 115, 124, 125).

When the two nitrogen substituents are dissimilar, two isomeric thiazolines are possible, depending upon the direction of ring closure, only one form is obtained (62).
Buu-Hoi (19) has condensed unsymmetrical \(NN'\)-diaryl-thioureas with \(\omega\)-halo ketones. In every instance, only one of the two possible 3,4-diaryl-2-arylimino-\(\triangle\)-thiazolines was obtained; from the results of Von Walther's degradation (127) of similar unsymmetrical compounds, it can be assumed that the arylimino-radical in the thiol form of unsymmetrical thioureas involves the more bulky aryl group.

\[
\begin{align*}
\text{Ar}^I \cdot &-N=\text{C} \\
\text{NH} & \\
\text{Ar} &
\end{align*}
\quad + \quad
\begin{align*}
\text{Br}-\text{CH} & \\
\text{HO}-\text{C}-\text{Ar}'' & \\
\text{Ar} &
\end{align*}
\rightarrow
\begin{align*}
\text{Ar}^I \cdot &-N=\text{C} \\
\text{NH} & \\
\text{Ar} &
\end{align*}
\]

Mizzi and Eisman (82) have prepared 3-(p-isopentyloxyphenyl)-2-(p-isopentyloxyphenyl)imino-4-methyl-4-thiazoline hydrochloride by the condensation of 1,3-bis(isopentyloxyphenyl)-2-thiourea with chloroacetone in absolute alcohol.

\[
\begin{align*}
\text{SH} & \\
\text{NH} & \\
\text{C}_6\text{H}_4\text{O}\text{C}_5\text{H}_{11} \cdot \text{iso}-p
\end{align*}
\quad + \quad
\begin{align*}
\text{Cl}-\text{CH} & \\
\text{HO}-\text{C}-\text{CH}_3 & \\
\text{C}_6\text{H}_4\text{O}\text{C}_5\text{H}_{11} \cdot \text{iso}-p
\end{align*}
\rightarrow
\]

\[
\begin{align*}
\text{SH} & \\
\text{NH} & \\
\text{C}_6\text{H}_4\text{O}\text{C}_5\text{H}_{11} \cdot \text{iso}-p
\end{align*}
\]

Bartoszewski and Jerzmanowska (5) have condensed differently substituted sym. diarylthioureas 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-aryl-2-arylimino-4-aryl \( \Delta^4 \)-thiazoline-5-acetic acid hydrobromides have been prepared by the condensation of sym. diarylthioureas with \( \beta \)-bromo-\( \beta \)-arylpropionic acids in absolute alcohol.

Where: \( X=H; \) o-m-p-CH\(_3\); o-m-p-Cl; p-Br; o-p-OC\(_2\)H\(_5\);

\( p-OC_2H_5; p-n-OC_3H_7; p-n-OC_4H_9; 2,6-(CH_3)_2 \).

\( Y=H; p-CH_3; p-Cl; p-OCH_3; p-OC_2H_5; p-n-OC_3H_7; p-n-OC_4H_9 \).

Compounds prepared are shown in the table.
### Table 3.1

3-Aryl-2-arylimino-4-aryl-$\Delta^4$-thiazoline-5-acetic acid hydrobromides:

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

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>Y</th>
<th>M.P. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>H</td>
<td>H</td>
<td>210</td>
</tr>
<tr>
<td>2.</td>
<td>o-CH$_3$</td>
<td>H</td>
<td>175</td>
</tr>
<tr>
<td>3.</td>
<td>m-CH$_3$</td>
<td>H</td>
<td>222</td>
</tr>
<tr>
<td>4.</td>
<td>p-CH$_3$</td>
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<td>228</td>
</tr>
<tr>
<td>5.</td>
<td>o-Cl</td>
<td>H</td>
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<tr>
<td>6.</td>
<td>m-Cl</td>
<td>H</td>
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<tr>
<td>7.</td>
<td>p-Cl</td>
<td>H</td>
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</tr>
<tr>
<td>8.</td>
<td>p-Br</td>
<td>H</td>
<td>85</td>
</tr>
<tr>
<td>9.</td>
<td>o-OCH$_3$</td>
<td>H</td>
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</tr>
<tr>
<td>10.</td>
<td>p-OCH$_3$</td>
<td>H</td>
<td>155</td>
</tr>
<tr>
<td>11.</td>
<td>p-OC$_2$H$_5$</td>
<td>H</td>
<td>138</td>
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<td>12.</td>
<td>p-n-OC$_3$H$_7$</td>
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<td>205</td>
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<tr>
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<td>------------------</td>
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<td>----------------------</td>
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<tr>
<td>13.</td>
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<tr>
<td>14.</td>
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</tr>
<tr>
<td>15.</td>
<td>H</td>
<td>p-CH_3</td>
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<td>p-Cl</td>
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</tr>
<tr>
<td>17.</td>
<td>H</td>
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<td>18.</td>
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<td>21.</td>
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<td>22.</td>
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<td>25.</td>
<td>p-n-OC_4H_9</td>
<td>p-n-OC_4H_9</td>
<td>181</td>
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</table>
EXPERIMENTAL

p-n-Alkoxyanilines and isothiocyanates required for the preparation of symmetrical 1,3-diaryl-2-thioureas were prepared as described in experimental Part I.

GENERAL METHOD FOR THE PREPARATION OF SYMMETRICAL 1,3-DIARYL-2-TIIOUREAS:

A mixture of substituted aryl isothiocyanate (0.01 mole) and appropriate substituted arylamine (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 recrystallized from ethyl alcohol (Buu-Hoi, NG. PH., Xuong, NG. D., and Nam, NG.H., J. Chem. Soc., 1573, 1955).

Following symmetrical thioureas were prepared by the above method.
### SYMMETRICAL 1,3-DIARYL-2-ThIOUREAS

\[ x-C_6H_4NH_2NH_2C_6H_4-x \]

<table>
<thead>
<tr>
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<th>Reference</th>
</tr>
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<td>m-CH₃</td>
<td>112</td>
<td>-do-</td>
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<td>4.</td>
<td>p-CH₃</td>
<td>176</td>
<td>-do-</td>
</tr>
<tr>
<td>6.</td>
<td>m-Cl</td>
<td>131</td>
<td>-do-</td>
</tr>
<tr>
<td>7.</td>
<td>p-Cl</td>
<td>176</td>
<td>-do-</td>
</tr>
<tr>
<td>8.</td>
<td>p-Br</td>
<td>188</td>
<td>-do-</td>
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<tr>
<td>No.:</td>
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<td>M.P.: o°C</td>
<td>Reference</td>
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<td>------</td>
<td>------------</td>
<td>-----------</td>
<td>-----------------------------------------------</td>
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<tr>
<td>11.</td>
<td>p-OCH₂H₅</td>
<td>170</td>
<td>—do—</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF β-ARYLOXYPROPIONIC ACIDS

In a dry 1 litre three-necked flask, fitted with a mechanical stirrer and two efficient reflux condensers, were placed substituted benzene (2.24 moles) and succinic anhydride (34 g., 0.34 mole). The mixture was stirred and finely powdered anhydrous aluminium chloride (100 g.) was added all at once. After addition of aluminium chloride, the mixture was stirred and heated for half an hour in an oil bath to gentle refluxing. After cooling the flask, in a bath of cold water, water (150 ml.) and concentrated hydrochloric acid (50 ml.) were slowly added by separatory funnel which was inserted into the top of one of the condensers. Substituted benzene was separated by steam distillation. The hot mixture was transferred to a 600 ml. beaker; the acid was separated as a colourless oil, which soon solidified. The acid was filtered at the pump, and washed with cold dilute hydrochloric acid (100 ml.) and then with cold water (100 ml.). The crude acid was dissolved in a solution of 40 g. of anhydrous sodium carbonate in 250 ml. of water by boiling for ten minutes; the solution was filtered and treated with 2 g. of decolourising carbon and filtered at the pump. The hot filtrate was transferred to a 1 litre beaker, cooled to about 50°C, and cautiously acidified with 65-70 ml. of concentrated

Following β-arylpropionic acids have been synthesised by the above method.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>M.P.</th>
<th>Reference</th>
</tr>
</thead>
</table>
Alkyl bromides required for the preparation of n-alkyl phenyl ethers were prepared as described in Experimental Part 1.

**GENERAL METHOD FOR THE PREPARATION OF n-ALKYL PHENYL ETHERS:**

Into a dry one litre round bottomed flask provided with water condenser in which ethyl alcohol (250 ml, 3.7 mole) was taken and sodium pieces (11.5 g., 0.5 mole) were added from the top of the condenser. To control the vigorous reaction, the round bottomed flask was kept in a water bath. Phenol (47 g., 0.5 mole) in 50 ml. of absolute alcohol was added to the reaction mixture. Into a small separatory funnel supported by grooved cork on the top of the condenser, in which alkyl bromide (0.73 mole) was placed and this was added with shaking to the reaction mixture. The reaction mixture was heated for about three hours. The reaction mixture then was poured into water. The organic layer was separated. It was washed with 10% sodium hydroxide solution, then successively with water, dilute sulphuric acid and water. It was dried over anhydrous magnesium sulphate and distilled under reduced pressure.

Following n-alkyl phenyl ethers were prepared by this method.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>B.P. °C</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td>2.</td>
<td>n-Propyl phenyl ether</td>
<td>188</td>
<td><em>do</em></td>
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<tr>
<td>3.</td>
<td>n-Butyl phenyl ether</td>
<td>207-208</td>
<td><em>do</em></td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF β-ALKOXYAROYLPROPIONIC ACIDS:

Into a dry 1 litre three-necked flask, fitted with an efficient mercury sealed stirrer, a reflux condenser attached to a gas absorption device, were placed n-alkyl phenyl ether (2.24 moles) in carbon disulphide and succinic anhydride (34 g., 0.34 mole). The mixture was stirred and finely powdered anhydrous aluminium chloride (100 g.) was added all at once. After addition of aluminium chloride, the 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. The excess of n-alkyl phenyl ether and carbon disulphide were removed by steam distillation. The hot mixture was transferred to a 600 ml. beaker; the acid separated as a colourless oil, which soon solidified. The acid was filtered, washed with cold dilute hydrochloric acid (100 ml.), and then with cold water (100 ml.). The crude acid was dissolved in a solution of 40 g. of anhydrous sodium carbonate in 250 ml. of water by boiling for ten minutes; the solution was filtered and treated with 2 g. of decolourising carbon and was filtered at the pump. The hot filtrate was transferred to a 1 litre beaker, cooled to about 50°C, and acidified with 65-70 ml. of concentrated hydrochloric acid. The acid was filtered, washed with cold water and dried (Vogel, I., Practical Organic Chemistry, 3rd Edition, Longmans, Green & Co. Ltd., P. 737, 1968).
Following β-alkoxyacylpropionic acids were prepared by this method.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>B.P.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td>β-(p-n-Propoxybenzoyl)propionic acid.</td>
<td>118</td>
<td>-do-</td>
</tr>
<tr>
<td>4.</td>
<td>β-(p-n-Butoxybenzoyl) propionic acid.</td>
<td>112</td>
<td>-do-</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF

$\beta$-BROMO-$\beta$-AROYLPROPIONIC ACIDS:

$\beta$-Aroylpropionic acid (0.1 mole) was dissolved in hot chloroform (80 ml.), and bromine (4 ml.) in 30 ml. chloroform was added slowly with constant shaking. Heating was continued until the bromine was absorbed. The chloroform solution was washed four times with water, dried and the solvent removed. The acid was usually left as an oil which crystallized on addition of carbon disulphide or petroleum ether (Knott, E. B., J. Chem. Soc., 455-60, 1945).
Following \( \beta \)-bromo-\( \phi \)-aroylpropionic acids were prepared by this method.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>( M \cdot P \cdot )</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>( \beta )-Bromo-( \phi )-benzoyl-( \phi )-propionic acid.</td>
<td>126</td>
<td>Rice, G. P., J. Am. Chem. Soc., 45, 222 (1923).</td>
</tr>
<tr>
<td>3.</td>
<td>( \beta )-Bromo-( \phi )-(p-chlorobenzoyl)-( \phi )-propionic acid.</td>
<td>115</td>
<td>—do—</td>
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<tr>
<td>4.</td>
<td>( \beta )-Bromo-( \phi )-(p-methoxybenzoyl)-( \phi )-propionic acid.</td>
<td>114</td>
<td>Bougault, A. Ch., 15(8), 514 (1908).</td>
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<tr>
<td>6.</td>
<td>( \beta )-Bromo-( \phi )-(p-n-propoxy-benzoyl)propionic acid.</td>
<td>141</td>
<td>Not reported.</td>
</tr>
<tr>
<td>7.</td>
<td>( \beta )-Bromo-( \phi )-(p-n-butoxy-benzoyl)propionic acid.</td>
<td>146</td>
<td>Not reported.</td>
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</table>

Percent bromine

<table>
<thead>
<tr>
<th>Found</th>
<th>Required</th>
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<tbody>
<tr>
<td>* 25.1</td>
<td>25.3</td>
</tr>
<tr>
<td>** 24.2</td>
<td>24.3</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF 3-ARYL-2-ARYLIMINO-4-
-ARYL-Δ4-THIAZOLINE ACETIC ACID HYDROBROMIDES:

A mixture of sym, 1,3-diaryl thiourea (0.034 mole) and
β-bromo-β-arylpipionic acid (0.036 mole) in 150-200 ml. of
anhydrous alcohol was refluxed for five 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 recrystallized from absolute alcohol-ether. The
yield was 60 to 70 per cent (Mizzoni, R.H., Eisman, P.C.,

Compounds prepared are shown in the table.
## TABLE - 3.2

### 3-ARYL-2-ARYLIMINO-4-ARYL- 4-THIAZOLINE ACETIC ACID HYDROBROMIDES:

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>Y</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Per cent Sulphur</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>Found</td>
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<td>H</td>
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<td>C\textsubscript{23}H\textsubscript{19}N\textsubscript{2}O\textsubscript{2}SBr</td>
<td>6.8</td>
</tr>
<tr>
<td>2.</td>
<td>o-CH\textsubscript{3}</td>
<td>H</td>
<td>175</td>
<td>C\textsubscript{25}H\textsubscript{23}N\textsubscript{2}O\textsubscript{2}SBr</td>
<td>6.4</td>
</tr>
<tr>
<td>3.</td>
<td>m-CH\textsubscript{3}</td>
<td>H</td>
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<td>C\textsubscript{25}H\textsubscript{23}N\textsubscript{2}O\textsubscript{2}SBr</td>
<td>6.5</td>
</tr>
<tr>
<td>4.</td>
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<td>H</td>
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<td>6.3</td>
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<tr>
<td>5.</td>
<td>o-Cl</td>
<td>H</td>
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<td>C\textsubscript{23}H\textsubscript{17}N\textsubscript{2}O\textsubscript{2}SBr</td>
<td>5.9</td>
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<tr>
<td>6.</td>
<td>m-Cl</td>
<td>H</td>
<td>240</td>
<td>C\textsubscript{23}H\textsubscript{17}N\textsubscript{2}O\textsubscript{2}SBr</td>
<td>5.9</td>
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</table>

**Required Found**
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<tbody>
<tr>
<td>7.</td>
<td>p-Cl</td>
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<td>p-Br</td>
<td>H</td>
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<td>C_{23}H_{17}N_{2}O_{2}SBr_{2}</td>
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<tr>
<td>9.</td>
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<td>138</td>
<td>C_{25}H_{23}N_{2}O_{4}SBr</td>
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<tr>
<td>10.</td>
<td>p-OCH_{3}</td>
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<td>155</td>
<td>C_{25}H_{23}N_{2}O_{4}SBr</td>
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<tr>
<td>11.</td>
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<tr>
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<td>C_{29}H_{31}N_{2}O_{4}SBr</td>
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<tr>
<td>13.</td>
<td>p-n-OCH_{4}H_{9}</td>
<td>H</td>
<td>140</td>
<td>C_{31}H_{35}N_{2}O_{4}SBr</td>
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</tr>
<tr>
<td>14.</td>
<td>2,6-(CH_{3})_{2}</td>
<td>H</td>
<td>252</td>
<td>C_{27}H_{27}N_{2}O_{4}SBr</td>
<td>6.0</td>
</tr>
<tr>
<td>15.</td>
<td>H</td>
<td>p-CH_{3}</td>
<td>156</td>
<td>C_{24}H_{21}N_{2}O_{2}SBr</td>
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<tr>
<td>16.</td>
<td>H</td>
<td>p-Cl</td>
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</tr>
<tr>
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<td>-------</td>
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<td>------------------</td>
</tr>
<tr>
<td>17</td>
<td>H</td>
<td>p-OC₃H₅</td>
<td>150</td>
<td>C₄H₈N₂O₂SBr</td>
<td>6.3</td>
</tr>
<tr>
<td>18</td>
<td>H</td>
<td>p-OC₂H₅</td>
<td>95</td>
<td>C₅H₁₀N₂O₂SBr</td>
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<td>C₆H₁₂N₂O₂SBr</td>
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</tr>
<tr>
<td>20</td>
<td>H</td>
<td>p-OC₂H₅</td>
<td>105</td>
<td>C₇H₁₄N₂O₂SBr</td>
<td>5.8</td>
</tr>
<tr>
<td>21</td>
<td>O-OC₃H₅</td>
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<td>173d</td>
<td>C₆H₁₄N₂O₂SBr</td>
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</tr>
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<td>O-OC₃H₅</td>
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<td>26</td>
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<td>27</td>
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<td>C₁₁H₂₂N₂O₂SBr</td>
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<tr>
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<td>31</td>
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<td>181</td>
<td>C₁₁H₂₂N₂O₂SBr</td>
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</table>
***************
* PART-III-A *
* REFERENCES *
***************


: REFERENCES : 

44. Gabriel, S., Ber., 49, 1110 (1916).
45. Gabriel, S., Ber., 22, 1139, 2984 (1889).
46. Gabriel, S., Ber., 50, 804 (1917); ibid., 47, 1866 (1914).
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PART III-B
GENERAL INTRODUCTION AND THEORETICAL
The discovery of the tuberculostatic activity of isoniazid (INH) and its derivatives marks a major advance in the chemotherapy of tuberculosis. In connection with a study of pyridine-carboxylic acid derivatives as potential tuberculostats, Fox (25, 26) attempted to prepare isonicotinaldehyde thiosemicarbazone by a modification of the McFadyen-Stevens reaction (41).

In this reaction, methylisonicotinate is converted to isonicotinylhydrazine which, in turn, is treated with benzene-sulfonyl chloride to give l-isonicotinyl-2-benzenesulfonylhydrazine. Alkaline decomposition of the latter in the presence of thiosemicarbazide gives the desired thiosemicarbazone and its benzenesulfonyl derivative are pyridinecarboxylic acid derivatives, Fox investigated their tuberculostatic potential. The benzenesulfonyl derivative was inactive, but isonicotinylhydrazine (isoniazid) proved to be far more active than any other known substance, whether synthetic or antibiotic (24).
A large number of reports on the activity of isoniazid in both experimental and clinical tuberculosis have appeared in the literature. It is highly active in very small doses (31). Widespread clinical application has shown it to be relatively nontoxic and well tolerated (17, 49, 50) although side-reactions including central nervous stimulation (44, 49, 50), peripheral neuritis (8, 9, 40) and gastric intolerance (8) have been reported.

2-Thiazolecarboxhydrazide has shown tuberculostatic activity (7).

The isopropyl derivative, iproniazid (23), which has a tuberculostatic activity of the same order as isoniazid in animals (31) but is reported to be more active in humans (10, 13). Unfortunately, its use is accompanied by a higher incidence of toxic side-reactions.

\[
\text{CONHNHCH(CH}_3\text{)}_2
\]

In an attempt to prepare a methylene derivative by interacting isoniazid with formaldehyde, Fox (27) obtained an insoluble product which proved to be hexahydro-1,3,5-triisonicotinamido-s-triazine.
This compound has approximately one-third the activity and one-twentieth the toxicity of isoniazid (30) but its chief clinical advantage seems to lie in the fact that its action is prolonged and that one dose per day produces the desired effect (38).

Bavin and his coworkers (5,6) claim that 1-isonicotinyl-2-(o-hydroxy)benzylidenehydrazine is better than isoniazid because it is almost as active as the latter and much less toxic.

Similar claims of superiority have been made for D-glucuronolactone isonicotinylhydrazine (12,29) and for 1-isonicotinyl-2-(3,4-dimethoxybenzal)hydrazine (46,47).
Isoniazid treated with phosgene gives 5-(4-pyridyl)-1,3,4-oxidazolone (66), which is claimed to be less toxic and somewhat more active than isoniazid in guinea pigs infected with strain H37 Rv (68).

2-Methyl-2-(p-chloroethyl) acid hydrazide (61), RR'RCONHNHR' (19), 1-trimethylacetyl-2-benzylhydrazine (22) and Nβ-alkylhydrazides of amino acids (32) are useful as antidepressants.
1,2-Bis(R-substituted)-perhydropyridazine-3,6-diones (18), 4-methylthiazolyl-2-hydrazides and 4-alkoxybenzalhydrazides of 2-alkoxy-5-bromobenzoic acids (3), \(N^1\)-methoxythiocarboxylhydrazide and \(N\)-methoxythiocarboxyl-\(N^2\)-4'-chlorobenzaldehyde hydrazone (1), 4,4'-bis(hydrazine) diphenylmethane (58), 4-alkoxyphenylalkane carboxylic acid hydrazides (4), Indol-2(or 3)-ylalkyl hydrazides (43), L-N-carbobenzyloxyglutamic acid 5-hydrazide (62), cyanoacetic acid hydrazide and cyanoacetic acid hydrazones of the lower carboxyl groups (51), N-(4-methylpiperazino)-9-xanthene carboxamide (28), 3,4-dimethoxy-6-chlorobenzoic hydrazide (59), hydrazide of Et \(\alpha\)-(N-azacycloalkyl)propanoates (14), \(\text{Me}_3\text{CO}_2\text{G-Phe-Phe-NHNNH}_2\) (57), 2-oxo-3-indolylmethylene hydrazides of alkanoic acids (63), p-(bis-p-chloroethyl)amino benzylidene hydrazide of N-acetyltryptophan (35), \(\alpha\)-allyl-\(\alpha\)-(p-bromobenzyl)acetoxyhydrazide (45), 1-(\(\alpha\)-hydroxypropionyl)-2-phenylethyl hydrazine (20), 1-methyl-2-(3-chlorobutten-2-yl)hydrazine (21), acylhydrazides, stearoyl hydrazide (64), N-benziloyl-N'-(2-piperidinoethyl) hydrazine (67), hydrazides of 3-pyridazinecarboxylic acid (55), 6-hydroxy-4-quinolinic hydrazide (2), 2-(3,4-dihydroxybenzyl) hydrazide (33), 2,6-dihydroxyisonicotinic acid hydrazide (53), fluorene-9-carboxylic acid hydrazides (65), 2,6-dihydroxyisonicotinic acid hydrazides (54), \(\gamma\)-ureidobutyric acid hydrazides (37), 5-methyl-2-furohydrazide (39) and 2-benzothiazolyl carboxylic acid hydrazides (48) have been synthesized. Some of them possess physiological activity.
Some important methods for the preparation of acid hydrazides are discussed below:

1. **Condensation of Acid and Hydrazine** :

   \[
   R\text{-COOH} + H_2N\text{NH}_2 \rightarrow R\text{-CONHNH}_2 - \text{H}_2\text{O} \quad \text{[Reaction]} \]

   This is obviously the simplest method (Dan. Pat. 87,228, 1959, Holger B. Thomassen; C.A., 54, 7742, 1960).

2. **Condensation of Ester and Hydrazine** :

   \[
   R\text{-COOC}_2\text{H}_5 + \text{NH}_2\text{NH}_2 \rightarrow R\text{-CONHNH}_2 \quad \text{[Reaction]} \]

   The reaction is carried out by heating the ester with hydrazine hydrate solution. The yields of hydrazides are usually excellent (Sah and Chang Ber., 69, 2763, 1936).

3. **Condensation of Acyl chloride and Hydrazine** :

   In this process acid hydrazides may be prepared by the action of hydrazine hydrate on acyl chlorides. (Span. Pat. 202,450, 1952, D.Magrane, S.A.; C.A., 50, 17323, 1956).
**PRESENT WORK**

Isoniazid is active against tubercular bacilli. With this in view 3-aryl-2-arylimino-4-aryl-Δ⁴-thiazoline-5-acetic acid hydrazides have been prepared from 3-aryl-2-arylimino-4-aryl-Δ⁴-thiazoline-5-ethyl acetates. These esters have been prepared by condensation of diarylthioureas with ethyl-φ-bromo-φ-arylpropionates in absolute alcohol. The ethyl esters of thiazoline acetic acids obtained, on treatment with hydrazine hydrate gave hydrazides.

Where: $X = H; \text{o-m-p-CH}_3; \text{o-m-p-Cl} ; \text{p-Br} ; \text{o-p-OCH}_3 ; \text{p-OC}_2H_5 ; \text{p-n-OCH}_3; \text{p-n-OC}_3H_7; \text{p-n-OC}_4H_9; \text{2,6-(CH}_3)_2$.

$Y = H; \text{p-CH}_3 ; \text{p-Cl} ; \text{p-OCH}_3 ; \text{p-OC}_2H_5; \text{p-n-OC}_3H_7; \text{p-n-OC}_4H_9.$
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<tr>
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* PART - III-B *
* EXPERIMENTAL *
* * * * * * * * * * * * * * * * * * *
EXPERIMENTAL

β-Bromo-β-aroylpropionic acids required for the preparation of ethyl-β-bromo-β-aroylpropionates were prepared as described in Experimental Part-III-A.

GENERAL METHOD FOR THE PREPARATION OF ETHYL-β-BROMO-β-AROYLPROPIONATES:

Into a dry 500 ml. flask, fitted with a reflux condenser, were placed β-bromo-β-aroyl propionic acid (30 g.), absolute alcohol (80 g., 101 ml.) and concentrated sulphuric acid (5 g., 2.7 ml.). The mixture was heated to boiling for four hours. The excess alcohol was distilled off and the residue was poured into about 250 ml. of water contained in a separatory funnel. The organic layer was separated, washed with a strong solution of sodium bicarbonate, and water, and the ester was dried over anhydrous magnesium sulphate (Vogel, I., Practical Organic Chemistry, 3rd Edition, Longmans, Green & Co. Ltd., p. 781, 1968).
Symmetrical 1,3-diaryl-2-thioureas required for the preparation of 3-aryl-2-arylimino-4-aryl-$\Delta^4$-thiazoline ethyl acetate were prepared as described in Experimental Part III-A.

3-Aryl-2-arylimino-4-aryl-$\Delta^4$-thiazoline ethyl acetates required for the preparation of 3-aryl-2-arylimino-4-aryl-$\Delta^4$-thiazoline acetic acid hydrazides were prepared as described in Experimental Part III-A.

**GENERAL METHOD FOR THE PREPARATION OF 3-ARYL-2-ARYLIMINO-4-ARYL-$\Delta^4$-THIAZOLINE ACETIC ACID HYDRAZIDES:**

A mixture of the crude ethyl ester of 3-aryl-2-arylimino-4-aryl-$\Delta^4$-thiazoline acetic acid hydrobromide (0.034 mole) in 20 ml. of ethyl alcohol and hydrazine hydrate (0.08 mole, 85 per cent) was refluxed for six hours. The reaction mixture was then poured into about 250 ml. of cold water. The product was filtered, washed with cold water and dried. The yield was 80 per cent. Acid hydrazides were recrystallized from absolute alcohol (Pearl, I.A., and Beyer, D.L., J. Am. Chem. Soc., 77, 3661, 1955).

Compounds prepared are shown in the table.
### TABLE 3.4

**3-ARYL-2-ARYLIMINO-4-ARYL-4'-THIAZOLINE ACETIC ACID HYDRAZIDES:**

![Chemical Structure](image)

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