SYNTHESIS
OF
ORAL HYPOGLYCEMIC AGENTS

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To

SHAGUFTA
Preface

The pioneering work of Loubatierers on 1,3,5-thiadiazoles and the subsequent discovery of the sulphonylureas gave a great Phillip to the search for oral hypoglycemic compounds. Although the intensification of work in this field has yielded rich dividends there are still several lacunae in our understanding of the problem and the best compounds available, so far, are from being the ideal ones. The search for more potent and less toxic oral hypoglycemic agents, therefore, continues.

The work now presented describes the synthesis of further series of possible oral hypoglycemic agents with a view to elucidate the structure activity relationships among the various types of compounds prepared. Ultra-violet, infrared and nuclear magnetic resonance spectroscopic evidences were obtained in support of the postulated structures and reaction mechanisms wherever ambiguities were met with.

Following the introduction, the thesis has been divided broadly into five chapters; the first four chapters deal independently with the theoretical aspects and experimental procedures for the preparation of the respective
groups of compounds. The last chapter details the biological findings and is followed by the conclusions drawn from these results.

I wish to take this opportunity of thanking Dr. A.R. Kidwai, Professor and Head of the Department of Chemistry, Aligarh Muslim University, Aligarh, for guidance and valuable suggestions and Dr. M.L. Dhar, Director, Central Drug Research Institute, Lucknow, for permission and constant encouragement to carry out the work embodied in this thesis and for laboratory facilities.

I am grateful to Dr. Nitiya Nand and Dr. S.P. Popli of Central Drug Research Institute, Lucknow for their keen interest throughout the course of this work.

My thanks are due to Dr. S.K. Mukherjee of this Institute for evaluating the compounds presented in this thesis for hypoglycemic effects.

I have also to thank Mr. J. Saran, Mr. P.N. Khanna, Mr. B.N. Zaidi and Mrs. S. Banerji for microanalyses.

(A. SHOEB)
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General Introduction
Diabetes as a distinct disease was recognized in India at least two thousand years ago. An interesting review of the early history of diabetes including the early writings of ancient Hindus, Arabs, Chinese and the Japanese is given by Barach. Despite its recognition for so many centuries, little was accomplished in the way of understanding the pathology of this disease. Upto the 18th century, the only test for glycosuria was by tasting the urine! It took over two hundred years to go from this crude method of detection of sugar to the modern rapid and accurate method of Nelson-Somogyi for the technique of the blood sugar determination. The understanding of the disease was put on a scientific footing by Dobson who in 1776 demonstrated that diabetic blood is sweet and that diabetic urine contains sugar that ferments.

A further milestone in this direction was the demonstration in 1889 by Von Mering and Minkowski that the removal of pancreas causes a disease similar to that characterised by ancient Assyrians and Babylonians by thirst, a large output of sweet urine and gradual wasting
inspite of voracious appetite.

The progress during the last fifty years has been phenomenal. The discovery of new techniques has opened up fields which hitherto could not be attempted. It is now known that islets of Langerhans, in the pancreas, secrete a hormone, insulin, which is responsible for the regulation of glucose concentration in the blood and that any imbalance in the availability of insulin causes a disturbance in glucose metabolism leading to hyper- or hypoglycemia.

Banting and Best\(^{2-4}\) of Toronto were the first to isolate this active principle from acid-alcohol extracts of frozen pancreas and they demonstrated that its injection alleviated the symptoms of acute diabetes by restoring the blood-sugar level to normal. The problem of the painful and frequent administration of insulin was partly overcome in later years by suitable preparations of long-acting insulins; protamine-zinc-insulin can, by suitable adjustment of pH, control blood sugar level over twenty-four hours. Insulin proved to be the saving of many a diabetic and allowed him or her to lead a normal life. However, its use over prolonged periods showed that quite often, this control of diabetic state did not extend to certain pathogenic complications of blood vessels, kidneys and eyes. Whether these complications were dependent on the degree of control of the blood sugar levels or were only partly related to
the diabetic control is still a matter of controversy. These observations led, however, to intensive work on the etiology of diabetes and it is now accepted that it is a functional and multiple etiological defect rather than just organic islet cell deficiency.\textsuperscript{5-14}

The above mentioned complications due to prolonged insulin therapy which began to mar the success story of Banting's great discovery coupled with the (i) difficulty of insulin administration, (ii) the new concept about the nature of diabetes itself, and (iii) the startling though accidental discovery of the hypoglycemic properties of some of the sulfonamide derivatives, which were found orally active, led a renewed and concerted effort by chemists and biologists as has few parallels in the field of modern therapeutics.

Although superior in its method of administration, any oral substitute would still have to be at least equal to insulin both in its hypoglycemic action and lack of serious side effects. The search for these compounds has been made in the following two directions.

I. Herbal drugs, and

II. Synthetic drugs

I. \textbf{Herbal drugs}

Extracts and decoctions of different parts of
plants, such as juice extracts of onion and garlic, root extract of Coccinia indica, the decoction of the leaves of Eucalyptus, Gymnema sylvestre R.Br. and Rivea cuneata Wight, the leaf extract of Pterocarpus marsupium Roxb., the seed extract of Securigera securideca and the whole plant extract of Scoparia dulica have been studied. None of these extracts have, however, been found to possess activity as would warrant their clinical application.

One of the most thoroughly examined plants in this connection is Vinca rosea (Catharanthus roseus). Its considerable reputation in folk-lore medicine stems from its reported use as an oral hypoglycemic agent. However, both experimental and limited clinical investigations had been disappointingly negative. During the course of investigations of this plant in several laboratories, various alkaloid and non-alkaloid fractions were tested for their ability to lower blood sugar. Evidently, because of their inherent toxicities as well as the masking of the properties because of accompanying compounds, it was not possible to obtain experimental verification with the crude extracts or the fractions used.

As a result of the classic work done by Svoboda and his group in the Eli Lilly Laboratories and Noble, Beer and Cutts in Canada it has now been possible to obtain fifty-five alkaloids in the pure form. The assay
of the pure compounds has shown interesting results. These indicate that catharanthine (HCl) (I), leurosine (H₂SO₄), lochnerine (II), tetrahydroalstonine (III), vindoline and vindolinine (·2HCl) (IV, V) produce varying degrees of blood-sugar lowering effect."³⁵ It seems highly probable, therefore, that the continued use of various galenical preparations of Vinca rosea in indigenous medicine as an oral hypoglycemic agent is not completely without merit.
In addition, Collip's glucokinin; phaseolin out of beans and bean pod; aspergillin from *Aspergillus niger*; aqueous extract of *Carchorus olitorius* containing traces of sulfur and zinc but no nitrogen; mystilllin out of blue-berries; antimellin which is a glycoside out of jambul fruits; lupanine from *Lupinus albus* and galegine which is isoamylene guanidine from *Galega officinalis*, are worth mentioning. Most of these have proved ineffective in human diabetes.

A new impetus to re-examine drugs from plant sources was evoked following the interesting findings that a drug may be ineffective in experimental animals (depancreatized or alloxan poisoned) but it may show promise where pancreas and its harmones are intact, though impaired, by enhancing the insulin activity as well as by inhibiting its peripheral degradation.

Revival of interest resulted in the systematic investigation of more plants, and from the fruits of *Blighia sapida*, two active principles, Hypoglycing A and B were isolated and these were found to possess marked hypoglycemic activity. Hypoglycin A has been characterised as \( \alpha\)-amino-\( \beta\)-(2-methylene cyclopropyl) propionic acid (VI, \( R=\text{OH} \)), while hypoglycin B is L-glutamylhypoglycin A (VI, \( R=\text{glutamic acid residue} \)). Both have been synthesised. Their hypoglycemic action does not seem to depend on the
presence of insulin because alloxan-diabetic and
depancreatized animals respond to these equally well.

None of these herbs has, however, shown activity
high enough to merit clinical use. The hypoglycemic action
in most cases, when it could be confirmed at all, was nor-
mally not greater than what could be achieved by dietary
regimens; none was as effective as insulin and most had
severe toxic side effects.

II. Synthetic drugs

Search for hypoglycemic compounds in the
synthetic field has been carried out mostly on empirical
lines. In the description that follows it is not claimed
that the various types of compounds that have shown hypo-
glycemic property are all included but the wide variety of
chemical structures that have shown such activity bear
testimony to the difficulties inherent in drug research
and to the role of chance observation in this field.

(a) Salicylic acid and its derivatives: Hypo-
glycemic effect produced by salicylic acid has been known
for a considerable time and acetyl-salicylic acid was widely
used in diabetes in pre-insulin era. Its use, however, was discontinued long before the introduction of insulin because the doses required produced one or another effect of salicylism.

Recently, interest in this subject has been revived in U.K. by Reid and co-workers. They observed that acetyl salicylic acid potentiates the action of insulin. Stowers et al. have observed a similar potentiating effect of calcium acetylsalicylate when used together with a sulfonyl urea.

Salicylates are considered to exhibit their effect because of their action on the adrenal secretions and on a variety of tissue enzymes. The exact mechanism by which the hypoglycemic effect is obtained is still not clear. The best explanation appears to be that salicylates interfere with some step at the terminal portion of the respiratory chain. This type of action at the cell level seems to break down the barrier to ready glucose entry into certain tissues.

(b) Antihistaminics and sympatheticolytics having hypoglycemic activity: It is known that histamine - or guanidine - induced hyperglycemia can be countered by the use of ergotamine. Further, this drug gives rise side effects like tremor, headache, perspiration and dizziness which are also the symptoms of hypoglycemia. These
observations have led to the search for hypoglycemic activity amongst the known antihistaminics and sympathetico lytics. Ergotamine (VII), Antistin (VIII), Regitin (IX) and Priscol (X) were accordingly tested.

Although all these compounds showed some hypoglycemic activity, none of these is of any practical value in diabetes therapy. Some of these have, however, been used for the treatment of allergy in diabetic patients.

(c) Guanidine and its derivatives: The blood-sugar lowering ability of guanidines was one of the fruitful scientific chance observations and owes its discovery to Watanabe in 1918. Subsequently, Frank et al. were the first to attempt a systematic study of the structure-activity relationships in the guanidine series of compounds. Later Bischoff et al., Slotta and Hesse
and quite recently Shapiro have joined the search. Their researches revealed that all effective guanidines have the following general formula (XI):

\[
\text{NH} \\
\text{R-NH-C-NH}_2 \\
\text{XI}
\]

Chemically guanidine derivatives can be classified into three sub-groups:

(1) **Monoguanides**: Guanidine (XI; \( R = H \)) administered in the form of its hydrochloride was used as an effective hypoglycemic agent in the pre-insulin era. Its action on the blood-sugar of rats was first described by Watanabe and subsequently a series of natural and synthetic guanidine derivatives were given clinical trials against diabetes.

Galegine (XII), the guanide isolated from the seeds of *Galaga officinalis* was found to have a significant blood-sugar lowering effect when administered by mouth and agmatine (XIII), present in herring sperm, was found to be hypoglycemic. These two compounds were more effective and less toxic than guanidine itself and this observation led to the synthesis of a series of substituted guanidines, particularly the diguanides and biguanides.
Bischoff, Sahyun and Long$^{71}$ prepared a number of fatty acid derivatives of guanidines, but these, though non-toxic, were found to be completely ineffective. The inactivity of these compounds is ascribed to the negative charge on the carboxylic acid group of the lateral chain$^{71}$. 

\[ \text{NH}_2 \text{C}-\text{NH}-(\text{CH}_2)_n-\text{C} = \text{O} \]

XIV

Recently, a number of mono-substituted guanidines (XV) carrying a quaternary amino group have been prepared$^{76}$. 

\[ \text{NH}_2 \text{C}-(\text{CH}_2)_n \overset{\ominus}{\text{N}} \]
None of these monoguanides, has as yet shown any promising activity.

(ii) Diguanides: These may be considered as being made up of two guanidine molecules joined by a chain of methylene groups (XVI). It was found that hypoglycemic action was directly related to the length of the methylene chain. Of the compounds tested, the most active and relatively least toxic were synthalin A (XVI; \( n = 10 \)) and synthalin B (XVI; \( n = 12 \)). These compounds, however, compared unfavourably with insulin and when it was found that their use was responsible for hepatic and renal damage in some patients, their use in the management of diabetes was discontinued.

(iii) Biguanides: In 1929, Slotta and Tschesche\(^{72}\) synthesised various biguanides and described their effect on the blood-sugar of animals. These compounds, however, did not find any clinical application at that time. Thirty years later Ungar, Freedman, and Shapiro\(^{77}\) reported the hypoglycemic activity of Phenoformin (DBI, PEBG) (XVII)
and since then several hundreds of biguanides have been synthesised and tested for their hypoglycemic action on animals.

Chemically the biguanides may be considered to be derived from two molecules of guanidine with the elimination of one molecule of ammonia. Each biguanide molecule thus has only five N-atoms in contrast to the six N-atoms of the diguanide molecule.

According to Shapiro, the active biguanides can be classified in two groups:

(a) **Derivatives of N'-phenylpolymethylene biguanides:** All these compounds exhibit activity; phenethyl biguanide, (XVIII; R = H; n = 2), is one of the most powerful compounds in diabetic therapy. Replacement of the second H at N' by a methyl group results in N'-benzyl-N'-methyl biguanide (XVIII; R = CH₃; n = 1) which is also active. Activity is retained if a methoxyl or a halogen is introduced at the p or m-position of the benzene ring, while the p- or m-methyl derivatives are inactive.
If the phenyl ring is substituted by a pyridine-, thiophene-, or furan ring, the hypoglycemic effect is maintained. On the other hand, indolin-biguanide or

\[
\text{R} \quad \text{NH} \quad \text{NH} \\
\text{C}_6\text{H}_5-\text{(CH}_2\text{)}_n-\text{N}^\prime-\text{C-NH-C-NH}_2
\]

\[\text{XVIII}\]

tetrahydroisoquinoline-biguanide are almost completely inactive.

(b) **Alkylbiguanides**

\[
\text{NH} \quad \text{NH} \\
\text{CH}_3\text{(CH}_2\text{)}_n-\text{NH-C-NH-C-NH}_2
\]

\[\text{XIX}\]

Structure-activity relationships have been studied in this series of compounds with varying length of carbon chain. Thus N'-butyl-, n- and isomyl derivatives are comparable in activity with N'-phenethyl-biguanide. Compounds with six to eight carbon chain lengths are less potent and activity drops to nil when \(n = 10\).

The substitution of both the hydrogens at N' results in erratic effects on the biological activity. Thus N', N'-Dimethyl-biguanide, in doses of 100 mg./kg.
causes hypoglycemic convulsions in rabbit. This substance is now on the market as Glucophage. The corresponding $N^1$, $N^1$-diethylbiguanide ($XX, R = C_2H_5$) is completely inactive. Except for $N^1$, $N^1$-dimethylbiguanide ($XX; R = CH_3$), as a

$$R \quad \text{NH} \quad \text{NH}$$
$$\quad \mid \quad \| \quad \|$$
$$R-N \quad \text{C-NH-C-NH}_2$$

$XX$

general rule, $N^1$-monoalkylbiguanides are more active than the corresponding $N^1$, $N^1$-dialkylbiguanides.

Simultaneous substitution at $N^1$ and $N^5$ results in hypoglycemic compounds if:

(a) not more than three of the four replaceable hydrogens are substituted, and

(b) the alkyl substituents are small (the total number of carbon atoms of all the three alkyl groups do not exceed five).

Thus $N^1$-$n$-propyl-$N^5$, $N^5$-dimethylbiguanide ($XXI$) is a powerful hypoglycemic agent parenterally, but is ineffective orally. In contrast to this, $N^1$, $p$-chlorophenyl-$N^5$-iso-propylbiguanide (paludrine; $XXII$) used in malarial
therapy has only very slight blood-sugar lowering property.

Physical and chemical properties of phenethyl-biguanide (DBI) and related compounds led Shapiro and his coworkers \(^74\) to the conclusion that the phenethyl-biguanide was present \textit{in vivo} in an ionic form, acting as a cation at the pH of the tissue fluids; and that the ion assumed the form of an internal six-membered-hydrogen-bonded ring (XXIII). It was this hydrogen-bonded cyclic cation protonated at the N\(^*\) (and which exists in equilibrium with the dibasic cation at the pH of the gastric juice and stomach contents) which was considered to be the physiologically active form of this biguanide. Further, the biguanides are free from toxic effects on the liver or the kidney. This is best exemplified by paludrine (XXII) which has been used for years in the
Mechanism of action of biguanides

The mechanism of action of biguanides is still not clear. There is overwhelming evidence that Phenoformin and related compounds are effective both in depancreatized and hepatectomized animals and that they produce hypoglycemia in diabetic patients, both adult and juvenile. On the other hand, the blood-sugar level of the normal human subjects is not lowered. PEBG does not stimulate the \( \beta \)-cells nor does it act as an insulinase-inhibitor. This suggests a mode of action quite different from that of the sulfonylureas. Wick and co-workers have shown that in animals the uptake of PEBG results in the following triad of effects - increased glucose uptake, diminished oxygen consumption and increased production of lactic acid. This may be presumed to represent accelerated treatment of malaria without toxic effects on liver or kidney. As stated earlier, however, paludrin possesses only a slight hypoglycemic activity.
anaerobic glycolysis secondary to an inhibition of oxidative metabolism. The snag in this explanation, however, is that with such a chronic inhibition of oxidative metabolism, serious toxic effects would be expected. Large scale clinical trials do not support such expectations. The reason for such a discrepancy may lie in either of the two explanations, i.e. the biguanides in therapeutic doses in vivo, may lower blood sugar by mechanisms other than those adduced from animal experimentations, or the inhibition of oxidative metabolism may be small, periodic, and quickly reversible, so that no deleterious effects are obtained.

(d) Sulfonamides and related compounds: The first of the sulfonamide compounds whose hypoglycemic action was recognized were the sulphanilyl thiadiazoles (XXIV) used by Janbon and coworkers in vivo in 1942 and synthesised earlier by Vonkennel and Kimmig. During the next four years Loubatieres and his group investigated this and closely related compounds in animals. They proposed the theory that these compounds lower blood sugar by stimulating
the release of insulin from the \( \beta \)-cells of the pancreas. Consistent with this view, these compounds were inactive in depancreatized animals. They examined the structure-activity relationship in this series in some detail and came to the following conclusions:

1) The presence of the \( p \)-aminobenzene group was essential for hypoglycemic activity;

ii) \( R \) was an aliphatic side-chain whose structure influenced the degree of hypoglycemic activity. It was maximal for alkyls containing 4 or 5-carbon atoms, less for 3-carbon alkyls and still less for alkyls of greater or smaller size.

The conclusions of Loubatieres and coworkers \(^83\) were confirmed by La Barre and Reuss \(^83\) in Belgium and by Chen \(^84\) in U.S.A.

Recently the synthesis of a number of related compounds has been reported in which the \( p \)-amino group of benzene has been replaced by alkyl groups: viz., 2-(alkylbenzenesulfonamido)-5-alkyl-1,3,4-thiadiazole \(^85\) (XXV; \( X = S \)). Structural analogues of these, like oxadiazoles (XXV; \( X = 0 \)) having substituents ranging from methyl to higher alkyls, alkoxy-, and halogens at different positions of the benzene nucleus in combination with different alkyls and cycloalkyls at the 5-position.
of the heterocyclic ring, have also been reported.\(^86^,87\)

Further, isomeric thiadiazoles like, 1,2, 5-thiadiazole-3, 4-dicarboxamide \(^{88}\)(XXVI) and 5-(aryl-sulfonamido)-3-substituted-1,2,4-thiadiazoles \(^{89}\) have been claimed to be highly effective where liver function has become impaired.\(^90\)

In accordance with the findings\(^90\) that insulin as well as pancreatic islets contain large amounts of sulfur-containing compounds, like cystine, cysteine and glutathione which play an important role in carbohydrate metabolism, sulfonyl derivatives of amino acid such as glycine \(^{91^,92}\), have been investigated.

Another group of compounds of related structure that have received some attention are the arylsulfonyl-semicarbazides \(^{93^,95}\) and corresponding thiosemicarbazides \(^{96}\) having an alkyl chain containing up to 7-carbon atoms, either open or in a cyclic form. These have been claimed to possess varying degrees of hypoglycemic activity.
(e) Sulfonylureas and related compounds:

Sulfonylureas (XXVII; \( R = \text{aryl}, R' = \text{open-chain or cyclic alkyl group} \)) comprise the most important group of compounds used in oral diabetic therapy, and constitute the most widely investigated series.

\[
R - \text{SO}_2 - \text{NH-C-NHR'}
\]

XXVII

Since the accidental discovery of blood-sugar lowering effect of carbutamide, thousands of these sulfonylureas derivatives have been synthesised and tested. The most important of these are given in the Table I:

\[\text{Table I}\]

<table>
<thead>
<tr>
<th>Name</th>
<th>Aryl</th>
<th>( R' )</th>
<th>Hypoglycemic activity</th>
<th>Duration of persistence of detectable amounts in blood</th>
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<td>Carbutamide</td>
<td>( 4-\text{NH}_2\text{C}_6\text{H}_4- \text{C}_4\text{H}_9 )</td>
<td>++</td>
<td>33 hours</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>( 4-\text{CH}_3\text{C}_6\text{H}_4- \text{C}_4\text{H}_9 )</td>
<td>++</td>
<td>4 hours</td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>( 4-\text{Cl-C}_6\text{H}_4- \text{C}_3\text{H}_7 )</td>
<td>+++</td>
<td>35 hours</td>
<td></td>
</tr>
<tr>
<td>Methahexamide</td>
<td>( 3,4-\text{NH}_2\text{(CH}_3\text{)}-\text{C}_6\text{H}_3- )</td>
<td>++++</td>
<td>26 hours</td>
<td></td>
</tr>
</tbody>
</table>
The variation of the substituents at the two positions (XXVII; R and R') determines the degree of hypoglycemic activity, its duration and the extent of toxic side effects. The variations at R and R' thus made are too numerous to be discussed here and sometimes contradictory results have been obtained by different group of workers. Exhaustive reviews on the effect of different substituents at R and R' on the hypoglycemic activity are available. For our purpose, it will suffice to give a summary of the salient points regarding the structure-activity relationships in this series:

1) In contrast to Loubatieres' compounds, the p-NH₂ group is not essential for hypoglycemic activity of the sulfonylureas. Some of these new compounds, e.g., tolbutamide, being devoid of antibacterial property, are actually less toxic than carbutamide. The most potent and longest acting drugs of this series are the halogen-substituted sulfonylureas, of which the chlorpropamide has to date proved clinically the most satisfactory.

2) When the NH₂ group is replaced by -OH, -CH₂OH, -COOH, and -NO₂, hypoglycemic activity is lost entirely.

3) For the desired effect on the blood sugar level, R' must be an alkyl group of a certain size and confer lipophilic properties on the molecule. Methyl group
is inactive, ethyl has some activity, and maximal activity is obtained with a side-chain alkyl group containing 3-6 carbon atoms. Activity diminishes again with greater chain length and is lost completely with alkyls of 12 or more carbon atoms. Aryl substituents at \( R^1 \) generally give toxic compounds, although some, such as metahexamide, have powerful hypoglycemic action.

![Chemical structure](image)

**Mechanism of action of sulfonylureas**

Pioneering work in this field has been done by Loubatieres. As pointed out by \(^{105}\) him the majority of pharmacological substances are not characterised by a simple, specific and exclusive mechanism of action. In addition to a principal action, there probably exist secondary effects which, under certain conditions, overshadow the principal action. The hypoglycemic sulfonamides are no exception to this rule.

The work of Loubatieres \(^{105}\), Chen and Anderson \(^{84}\) and La Barre \(^{83}\) on experimental animals as well as on human beings clearly favours the view that these drugs act by stimulating the \( \beta \)-cells of the islets of Langerhans to release stored insulin and perhaps also to produce more of the hormone. In addition, the sulfonylureas may under
certain conditions affect liver cell-activity either by inhibiting in some manner the output of sugar or by reducing the activity of an insulinate system.

(f) Miscellaneous drugs: It would be pertinent to mention some of the different types of compounds which, though quite different in structure from the known hypoglycemic agents, have been claimed, from time to time, to exhibit hypoglycemic activity. These include Kobayashi's mesoxalic acid, Hultquist's monolodoacetic acid and amide; Tarall's Tris-buffer (Trishydroxymethyl-amino) methane, Pagliaro's C-lipoic acid,

\[
\begin{align*}
\text{XXXVIII} & \quad \text{COOH} \\
\text{XXXIX} & \quad \text{CH}_2\text{OH} \\
\text{XXX} & \quad \text{CH}_2\text{OH} \\
\text{XXXI} & \quad \text{C}_6\text{H}_5
\end{align*}
\]

(XXX); Guarian's nicotinic acid; Berry's nicotine and phenylbutazon (XXXI). These substances have been claimed to have blood-sugar lowering ability but their clinical data are not available.

Based on considerations outlined below, 3-substituted hydantoins and thiohydantoins as well as 8-substituted hydantoin esters were also prepared.
Some of these compounds although promising in preliminary experiments, failed to show consistent activity high enough for clinical use.

Control of diabetes has also been reported either with estrogen alone or in combination with insulin\textsuperscript{121,122}.

**Present work**

The foregoing discussion clearly shows that there are a wide variety of compounds which exhibit hypoglycemic activity in experimental animals as well as in man. Their emergence undoubtedly points to the possibility of a positive chemotherapeutic approach to the problem of diabetes.

In consideration of all these factors, it seemed of interest to study the chemical structures of the known antidiabetic agents with a view to finding out a common moiety in these compounds which may be regarded as the primary function responsible for the hypoglycemic property of the entire molecule. A critical examination of some of the important hypoglycemic agents (Table II) revealed that they all were characterised by the presence of either a urea, a guanidino or a potential thiourea function in the molecule.
This included also the older toxic hypoglycemic agents - guanidine and syntalin. A synthetic programme such as would lead to the preparation of organic compounds of different types, which would contain in their molecular make-up one or more of the aforesaid functions, either free
or potential, was therefore planned.

The various series of compounds that were studied with this plan in view are discussed below:

Suitably substituted 1,2,4-thiadiazoles of the type (XXXII-XXXV) were the first of the series. These are closely related to the 1,3,4-thiadiazoles - the progenitors of the present day sulfonylureas. The tautomeric possibility in the 3-, and 5-amino-1,2,4-thiadiazoles was studied by ultra-violet spectroscopy.

The maximum activity was exhibited by N-(2-pyridyl-), N'-3-(5-phenyl-1,2,4-thiadiazolyl) urea. This led to a study of ureides containing a pyridine nucleus at one end. Thus compounds of the type (XXXII, XXXIII, XXXIV, XXXV) were synthesised.
As mentioned earlier, the sulfonylureas and biguanides exhibit their properties by different modes of action and a combination therapy with the use of Tolbutamide and Phenformin has shown most effective results. A thiadiazole molecule containing guanidinourea moiety (XXXVI) as an internal combination was also prepared.

\[
\begin{align*}
&\text{XXXVI} \\
&\text{R-SO}_2\text{NH-C-NH-C-NH} \\
&\text{NH} \quad \text{O} \\
&\text{R-SO}_2\text{NH-C-NH-C-NH} \\
\end{align*}
\]

Sulfonylimidazolidinones (XXXVII), pyrimidones, (XXXVIII) and uracils (XXXIX) may be regarded as cyclic analogues of the existing effective sulfonylureas and would be expected to present a similar, though more rigid, molecular configuration for interaction at the relevant bio-receptors.
A synthesis of the compounds of the type, XXXVII, XXXVIII, XXXIX, was, therefore, undertaken and a study made of the structure-activity relationships in these series.

In addition, some N-tosylamino acid amides(XL) have also been synthesised with a view to studying the effect of introducing a methylene residue in the urea moiety of hypoglycemic sulfonylureas.

\[
\begin{align*}
R^f & \quad 0 \\
R & -SO_2NH-CH-(CH_2)_n-C-NHR'
\end{align*}
\]

A comparison of the activities, if any, of these compounds, with those of the foregoing sulfonylurea derivatives, would throw light on the function of the urea moiety in the latter type of compounds.

Another line of approach was the study of the effect on blood sugar of separating the urea moiety from the sulfonyl function in the compounds of the type(XLI).

\[
\begin{align*}
R' & \quad 0 \\
R & -SO_2NH\text{CH}_2\text{CH}_2-N-C-NHR'
\end{align*}
\]
Reports from different laboratories have demonstrated the ability of auxin and auxin-like substances to lower the blood sugar level and attempts have been made to correlate the auxin-like activity of the compounds with their hypoglycemic effects. Hypoglycemic and auxin-like activities appear to have somewhat common structural requirements. Most of the hypoglycemics possess urea, thiourea or guanidino moieties, while some ureas, acids and amides have also been noted as potent plant growth regulators. It was, therefore, considered desirable to synthesize indolyl and isoindoliny1 compounds containing urea moieties with a view to examine their ability to affect the blood sugar level. The following types of compounds were accordingly prepared.

![Chemical structures](image)
The structural confirmation of the compounds synthesised, wherever necessary, was substantiated through the study of ultra-violet, infra-red and n.m.r. spectroscopy. For example, in the series of isoindolines, the carbon-hydrogen bonds occurring in 2700-3200 cm\(^{-1}\) region of their infra-red spectra were examined and related to their molecular structures.

Similarly, the reaction product of hydroxylamine and vinylpyridines was assigned a di-adduct structure in contrast to the mono-adduct structure on the basis of infra-red and n.m.r. spectroscopic evidence.
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CHAPTER I

Syntheses of 1, 2, 4-thiadiazoles

and its derivatives
The discovery of the hypoglycemic activity in 2-\(p\)-(aminobenzenesulfonamido)-5- isopropyl- 1,3,4-thiadiazole (IPTD) by Janbon & co-workers\(^1\) was a milestone in the search for oral antidiabetic compounds. A large number of variously substituted 1,3,4-thiadiazoles were prepared (some of the important ones are listed in Table I) and Loubatieres\(^{1}\) pioneering work during 1942-55 on these and the sulfonyleureas has done much to clear our views on the mode of action of these compounds.

Table I

\[
P - H_2N-C_6H_4SO_2NH-C-S-C-R
\]

1. \(R = \text{isopropyl} \ (2254\ RP)\)
2. \(R = n\ - \text{butyl} \ (2263\ RP)\)
3. \(R = \text{isobutyl} \ (2256\ RP)\)
4. \(R = t\ - \text{butyl} \ (2259\ RP)\)
5. \(R = \text{amyl} \ (2261\ RP)\)
Compound number 1 (2254 RP) was the first of a pharmacological and therapeutic group of agents of the sulfonamide variety that were hypoglycemic.

The 1,3,4-thiadiazoles were subsequently superseded by the sulfonylureas but the work done on these compounds by Loubatieres, Chen et al., and Holt has contributed materially towards a better understanding of the nature of diabetes. It has shown, for example, that the disease we call diabetes mellitus is not a single entity. Insulin in a way unites the different forms by being the one means which can normalize the blood sugars of them all.

It was suggested earlier that the activity of the thiadiazoles as well as that of subsequently introduced sulfonylureas and the biguanides was associated with the presence, in their molecules, of urea, thiourea or a guanidino-moieity. To verify the validity of such a hypothesis, various 3-substituted hydantoins, and 6-substituted hydantoin esters were prepared. Preliminary testing of these compounds on rats gave encouraging results. This coupled with the already known activity of 1,3,4-thiadiazoles stimulated the present study of the isomeric 1,2,4-thiadiazoles. Preliminary testing of 3,5-diamino-1,2,4-thiadiazole and 5-amino-3-(p-toluene sulfonylamo)-1,2,4-thiadiazole indicates that these compounds possess interesting hypoglycemic activity and low toxicity (A.K. Roy, personal communication). It was, therefore, considered of
interest to introduce sulfonamido, urea, sulfonylurea and semicarbazide moieties into the 1,2,4-thiadiazole nucleus at suitable positions with a view to test these compounds for hypoglycemic activity. Attempts have also been made to incorporate a sulfonyl guanidine residue into the thiadiazole nucleus in a model compound in order to see the combined effect of both on the blood sugar level. The following types of 1,2,4-thiadiazoles were accordingly prepared:

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\text{III} & \quad \text{IV}
\end{align*}
\]

At the same time it seemed desirable to study the structure of these thiadiazoles before undertaking the present study as these compounds may tautomerize to (Va) or (Vb) under suitable experimental conditions.
Kurzer & Taylor\(^8\) prepared acetyl derivatives of 3-alkoxy-5-substituted amino 1,2,4-thiadiazoles (VI). They suggested that these compounds may have any one of the formulae (VII, a, b and c).

Goerdeler and Bechlers\(^9\), who had also obtained the monoacetyl derivatives under similar conditions, designated these as 5-acetamido compounds (VII b).

An examination of ultraviolet spectra of 3-methyl-5-amino-1,2,4-thiadiazole (I, \(R^1 = H\)), its methyl derivative (VIII), and 3-amino-5-phenyl-1,2,4-thiadiazole (IX) revealed interesting facts: that (I, \(R^1 = H\)) and (IX) bear a close similarity with each other; (I, \(R^1 = H\)) shows strong absorption at \(\lambda_{max} 248\) \(\mu\) (\(\epsilon 7856\)) and (IX) at \(\lambda_{max} 250, 310\), \(\mu\) (\(\epsilon 13838, 3926\)), whereas (VIII) does not show this absorption. It was, therefore, concluded that (I, \(R^1 = H\) and IX) be formulated as (Va) and (VIII) as (Vb). On this analogy, the acetyl derivatives obtained by Kurzer and Goerdeler would be formulated as (VIIa).
U.V. Spectra

3,4-Dimethyl-5-imino-4,5-dihydro-1,2,4-thiadiazole hydroiodide (VIII) was prepared by Pulvermacher's method by methylaing (I, R' = H). Kurzer and Taylor found that (IX) was resistant to methylation with methyl iodide under the above conditions. The present experiments confirm their findings and this is in accord with the theoretical considerations outlined above. Preferential methylation in (IX) would normally be expected to take place at position 2 due
to tautomeric possibilities. However, its proximity to the electronegative sulfur inhibits the entry of the methyl group in this position also.

The chemistry of 1,2,4-thiadiazoles has been probed only recently by Kurzer et al.\textsuperscript{11}, and Goerdeler and co-workers\textsuperscript{12}.

5-Amino-3-methyl-1,2,4-thiadiazole (I, R\textsuperscript{1} = H) has been prepared by the following series of reactions:

\[
\begin{align*}
\text{CH}_3\text{CN} + \text{C}_2\text{H}_5\text{OH} + \text{HCl} & \rightarrow \text{CH}_3\text{C} = \text{NH}.\text{HCl} \\
\text{NH} & \\
\text{CH}_3\text{C} - \text{NH}_2.\text{HCl} & \rightarrow I, \ R\textsuperscript{1} = H
\end{align*}
\]

3-Methyl-5-(p-toluenesulfonamido-) 1,2,4-thiadiazole was synthesized by condensing 5-amino-3-methyl-1,2,4-thiadiazole with appropriate sulfonyl chloride\textsuperscript{13}. The p-nitrobenzoyl derivative (I:R\textsuperscript{1} = p-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}CO-) was prepared by allowing the corresponding amino thiadiazole to react with p-nitrobenzoyl chloride in acetone in presence of pyridine; the 5-(3-phenylureido-) compound (I:R\textsuperscript{1} = C\textsubscript{6}H\textsubscript{5}NHCO-) was obtained in excellent yield by the usual procedure, using phenyl isocyanate in dry acetone.

3-Amino-5-phenyl-1,2,4-thiadiazole\textsuperscript{14} (IX) was obtained through the following sequence of reactions:
For the preparation of compound (II), the intermediate, ethyl N-(5-phenyl-1,2,4-thiadiazol-3-yl) carbamate, (X), which could not be prepared by the condensation of 3-amino-5-phenyl-1,2,4-thiadiazole\textsuperscript{14} with ethyl chloroformate in acetone, chloroform, or dimethyl formamide containing anhydrous potassium carbonate or in absolute alcohol containing sodium ethoxide, was obtained in 75% yield by the condensation of 3-amino-5-phenyl-1,2,4-thiadiazole with an excess of ethyl chloroformate at 120\textdegree{}C. The carbamate, so obtained, was condensed with suitable amines to yield the desired thiadiazole ureas (II). Interestingly enough, the phenylhydrazone, glycine ethyl ester and arylsulfonyl guanidine compared with amines in activity towards the thiadiazole carbamate.

The sulfonylurea derivatives of 5-phenyl-1,2,4-thiadiazole (III) were prepared by the interaction of the appropriate carbamates of sulfonamides\textsuperscript{15,16} and 3-amino-5-phenyl-1,2,4-thiadiazole.

For the synthesis of the compound (IV), the guanidine hydrochloride was tosylated\textsuperscript{17} and the product
was condensed with ethyl-N-(5-phenyl-1,2,4-thiadiazol-3-y1)
carbamate according to the following scheme:

\[
\begin{align*}
\text{NH} \\
\begin{array}{c}
2 \text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl} + \text{H}_2\text{NCNH}_2\cdot\text{HCl} \rightarrow \\
\text{NH} \\
\begin{array}{c}
\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NCHNH}_2 + \text{X} \rightarrow \text{IV}
\end{array}
\end{array}
\end{align*}
\]
EXPERIMENTAL

5-Methyl-3-amino-1,2,4-thiadiazole

This was prepared following exactly the procedure outlined by Goerdeler, m.p. 198-200°C; picrate m.p. 202°C.

3-Amino-5-phenyl-1,2,4-thiadiazole

This was prepared by the procedure used by Kurzer, m.p. 132-34°C.

3,4-Dimethyl-5-imino-4,5-dihydro-1,2,4-thiadiazole-HI

A mixture of 5-amino-3-methyl-1,2,4-thiadiazole (0.5 g) and slight excess of methyl iodide was heated for four hours in a sealed tube at 100°C. The reaction mixture, on cooling, was triturated several times with cold ethanol. The residue, on removal of the solvent, was fractionally crystallized from alcohol to almost colorless needles,
melting at 218°C, in 70% yield. (Found: N, 16.73.
C₄H₈I N₃S requires N, 16.35%)

3-Methyl-5-(p-toluenesulfonylamido)-1,2,4-thiadiazole

p-Toluenesulfonyl chloride (3.3g) was added to a solution of 5-amino-3-methyl-1,2,4-thiadiazole (2 g) in pyridine (10.5 ml) and the mixture kept overnight. Pyridine was then distilled under vacuum and the residue treated cautiously with 10% HCl when a small quantity of a gummy mass separated which was filtered. On further acidification of the filtrate, a precipitate was obtained which on crystallization from ethanol furnished the product, melting at 223-24°C in 63% yield. (Found: N, 15.95. C₁₀H₁₁N₃O₂S₂ requires N, 15.62%).

3-Methyl-5-(p-nitrobenzamido)-1,2,4-thiadiazole

A mixture of 5-amino-3-methyl-1,2,4-thiadiazole (0.9 g), p-nitrobenzoyl chloride (1.5 g), and pyridine (0.7 g) was refluxed in acetone solution for 3 hours. After removal of the solvent at reduced pressure, the residue was treated with 10% HCl and precipitate recrystallized from acetone, m.p. 289°C, in 65% yield. (Found: N, 21.39. C₁₀H₈N₄O₃S requires N, 21.22%).

3-Methyl-5-(3'-phenylureido)-1,2,4-thiadiazole

Phenyl isocyanate (2 g.) was added gradually to
a solution of 5-amino-3-methyl-1,2,4-thiadiazole (2 g.) in minimum quantity of dry acetone and the mixture kept at 40°C for one hour. On dilution with water, the reaction mixture gave a white precipitate which was subsequently crystallized from isopropanol-water, m.p. 250°C, in 80% yield. (Found: N, 23.97. \( \text{C}_5 \text{H}_{13} \text{N}_4 \text{O} \text{S} \) requires N, 23.93%).

**Ethyl N-(5-phenyl-1,2,4-thiadiazol-3-yl) carbamate**

3-Amino-5-phenyl-1,2,4-thiadiazole was mixed intimately with excess of ethyl chloroformate and the mixture heated gradually to 120°C. The temperature was maintained for four hours, followed by removal of the unchanged ethyl chloroformate under reduced pressure. On crystallization from ethanol, the residue gave the product, m.p. 119°C, in 75% yield. (Found: C, 53.22; H, 4.77; N, 16.64. \( \text{C}_{11} \text{H}_{11} \text{N}_3 \text{O} \text{S} \) requires C, 53.02; H, 4.42; N, 16.86%)

**5-Phenyl-3-substituted ureido-1,2,4-thiadiazoles**

In the general preparative procedure, an intimate mixture of the above carbamate, the appropriate amine (1:2.5 molar ratio), and a few drops of pyridine was heated at 120°C for 3 to 4 hours. Pyridine and most of the unchanged amine were subsequently removed under
reduced pressure and the residue was treated with cold dilute hydrochloric acid; the resulting thiadiazole crystallized from ethanol. \( \gamma / \gamma \)-diethylaminopropylureido-derivative was, however, isolated as hydrochloride and crystallized from isopropanol. In the reactions in which 2-, 3-, and 4-aminopyridines were employed, the residue was simply washed with water and recrystallized from ethanol.

The compounds prepared in this series are reported in Table I.

3-(3'-Arylsulfonyleido)-5-phenyl-1,2,4-thiadiazoles

A suspension of 3-amino-5-phenyl-1,2,4-thiadiazole in benzene was treated with an equimolar quantity of the appropriate arylsulfonyl urethanes and the mixture was refluxed to a clear solution. The solvent was removed under vacuum and the residue heated at 120°/4 mm for 4 hours. The residue was purified subsequently by refluxing successively with ethanol, ethyl acetate and chloroform. The final product which usually did not dissolve in any of these solvents, was obtained in a crystalline form.

In the case of p-toluensulfonyl- and benzenesulfonyl- derivatives, the products were finally crystallized from ethyl acetate.
Compounds prepared in this series are reported in Table II.

**p-Toluenesulfonylguanidine**

This was prepared according to Cerkovnikov\(^\text{17}\), m.p. 207-8°C.

\[ 1-(p-\text{Tosylguanidino})-3-(5',\text{phenyl}-1',2',4'-\text{thiadiazol}-3'-yl) \text{urea} \]

A mixture of the thiadiazole carbamate (0.9 g.) and p-toluenesulfonylguanidine (0.8 g.) was refluxed in anhydrous benzene till solution occurs. After removal of the solvent at reduced pressure the residue was gradually heated to 145°C and the melt was subsequently kept at that temperature for four hours under 4 mm. pressure. The residue was taken into alcohol and fractionally recrystallized to give the product melting at 203-5°C, in 58% yield. (Found: C, 49.53; H, 4.29; N, 20.53. \(C_{17}H_{16}N_6O_3S_2\) requires C, 49.04; H, 3.85; N, 20.19%).
<table>
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<th>R'</th>
<th>M.P.</th>
<th>Formula</th>
<th>% Carbon</th>
<th>% Hydrogen</th>
<th>% Nitrogen</th>
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<td>1</td>
<td>112-13°</td>
<td>C₁₃H₁₀ON₄S</td>
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<td>56.52</td>
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<td>59.21</td>
<td>6.54</td>
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<td>60.81</td>
<td>4.45</td>
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<td>189-90°</td>
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<td>171°</td>
<td>C₁₆H₁₄ON₄S</td>
<td>..</td>
<td>..</td>
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</tr>
<tr>
<td>7</td>
<td>155°</td>
<td>C₁₇H₁₆ON₄S</td>
<td>63.33</td>
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<td>C_{16}H_{14}O_{3}N_{4}S_{2}</td>
<td>51.32</td>
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<td>213°</td>
<td>C_{15}H_{10}O_{3}N_{4}Cl_{2}S_{2}</td>
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REFERENCES

CHAPTER II

Syntheses of imidazolidinones, tetrahydro-
pyrimidone, 1, 1,3-substituted
ureas, tosylated amino acid
amides and barbituric acids
In pursuance of our search for hypoglycemic agents among organic compounds containing urea, thiourea or guanidino-moieties\(^1\), l-arylsulfonyl-3-substituted-2-imidazolidinones, corresponding tetra hydropyrimidones and 1-p toluenesulfonyl-3-butyl-dihydouracil have been synthesized. The imidazolidinones and tetrahydropyrimidones (I, II) are cyclic analogues of the hypoglycemic l-alkyl-3-arylsulfonylureas and would, therefore, be expected to present a similar, though more rigid, molecular configuration for interaction with the relevant bioreceptor.

With a view to further examine the structural specificity of these sulfonylureas, a few N-tosylamino acid amides (III) have also been synthesized in order to study the effect of the introduction of methylene residues in the urea moiety of hypoglycemic sulfonyl ureas.

The structural specificity of sulfonylureas has further been explored by the study of such compounds
of type IV:

\[
\begin{align*}
\text{III} & \quad \text{IV} \\
RSO_2NH\text{-}CH\text{-}(CH_2)_nCNHR & \quad RSO_2NHCH_2CH_2N-C-NHCH_2CH_2
\end{align*}
\]

in which the ureido moiety is separated from arylsulfonyl moiety by the introduction of an aminoethyl residue.

In addition, in view of the activity of some of the hydantoins reported earlier, it seemed of interest to study the effect of 1-substituted barbiturates which may be considered as homo-hydantoins. Hypoglycemic activity has been reported for some barbiturates.

**Synthesis of the parent nucleus**

For the synthesis of 1-arylsulfonyl-3-substituted imidazolidinones and tetrahydropyrimidones the following two schemes were considered:

1. Synthesis of the parent nucleus (or suitably substituted nucleus) followed by (a) acylation and (b) alkylation of 1- and 3-positions respectively.

2. By reacting N-\(\omega\)-haloalkyl-1-arylsulfonamide with substituted urethanes.
1. In view of the resemblance of the structure of imidazolidinones with ureas, most of the methods of urea synthesis, which involve the condensation of amine with compounds that under suitable conditions would form isocyanates, have been used for their syntheses. For example, \( \omega \)-alkylenediamine on treatment with phosgene, urea or substituted ureas, give rise to imidazolidinone. Other methods, described for the synthesis of the parent nucleus include the Hofmann rearrangement of benzoyl-\( \beta \)-alanine amide, reaction of ethylene glycol with urea, ethanolamine with urea or ammonia and carbon dioxide, reaction of ethylene diamine at elevated temperatures and pressure with carbon dioxide, diethyl carbonate or carbonyl sulfide, and alternatively, ethylene carbonate with ammonia at autogenous pressures. Imidazolidinones, substituted or unsubstituted, have also been synthesized by reacting ethylene or substituted alkylenediamines with \( \text{H}_2\text{O}_2 \).

(a) **Acylation of the parent nucleus at 1-position**

Imidazolidinones resemble very closely the open-chain ureas in structure and therefore a similarity in chemical behaviour can also be predicted. Unlike carbonyl ureas, sulfonyl ureas have not so far been obtained by the action of appropriate sulphonyl halides on ureas or its simple substituted products. Two
isolated claims of successful condensation of this type have not been substantiated by later work. Acylation of imidazolidinones at 1-position has not been reported until recently (Noriak, A.) where arylsulfonyl chloride has been reacted under mild conditions to give 1-arylsulfonyl-2-imidazolidinone.

Cyclization of 1-arylsulfonyl-3-bromoethylurea with caustic soda has also been reported to yield 1-arylsulfonyl-2-imidazolidinone together with 2-aryl-sulfonamido-2-oxazoline.

Alternative methods considered for the synthesis of the acylated parent nucleus included (i) Hofmann rearrangement of β-arylsulphonamido-propionamide(V) or (ii) the Lossens' rearrangement of the corresponding hydroxamic acid (VI), followed in each case by intramolecular cyclisation.

\[
\begin{align*}
\text{RSO}_2\text{NHCH}_2\text{CH}_2\text{CONH}_2 & \xrightarrow{\text{V}} \text{RSO}_2\text{NHCH}_2\text{CH}_2\text{NH} \xrightarrow{0} \text{RSO}_2\text{N-C-NH} \\
\text{RSO}_2\text{NHCH}_2\text{CH}_2\text{CONHOR} & \xrightarrow{\text{VI}} \text{RSO}_2\text{NHCH}_2\text{CH}_2\text{NCO} \xrightarrow{+} \text{RSO}_2\text{N-C-NH} \\
\end{align*}
\]

These two procedures, however, in our hands did not give the desired products.
(b) Alkylation of the parent nucleus at 3-position

No instance is to date available to bring a substitution at 3-position by reacting 1-arylsulfonyl 2-imidazolidinone with alkylhalides. In urea and sulfonyle urea series, usually both N- and O-alkylation would proceed by the treatment with alkyl halides. A substitution of only aliphatic or araliphatic nature may, however, be effected indirectly by acylating the 1-arylsulfonyl-2-imidazolidinone (VII) with acid halides followed by reducing the carbonyl function under milder conditions by means of LAH. The latter reagent is known to have little effect at carbonyl function of ureas and sulfonyleureas.

\[
\text{VII} + R'COX \rightarrow RSO_2N-C-N-C-R' \rightarrow \text{I}
\]

This scheme, however, was not followed up since another route to these compounds showed more promising results.

2. Synthesis of 1-arylsulfonyl-3-substituted-2-imidazolidinones employing substituted urethanes

Attempts to prepare 1-arylsulfonyl-3-substituted-
2-imidazolidinones (I) by condensing N-β-chloroethyl-aryl sulfonylamide (IX) with alkyl urethanes, did not succeed by the following scheme:

\[
\text{RSO}_2NH + \text{EtO-CO} \rightarrow \text{RSO}_2N-R' + \text{EtOH} \rightarrow \text{I}
\]

A modification of the above scheme as shown below led to an unambiguous synthesis of a variety of 1-aryl sulfonyl-3-substituted (even aryl)-2-imidazolidinones (I) and corresponding tetrahydropyrimidones; (II).

Sodium salt of the aryl sulfonamide (X) was reacted under pressure with polymethylene chlorohydrin, (IX) to give N-η-hydroxyalkylaryl sulfonylamide \(^{42}\), (XII). Latter, on treatment with thionyl chloride, gave the corresponding chloro-derivative \(^{42}\), (XIII) which was converted to N-η-substituted aminoalkylaryl sulfonylamide (XIV) by refluxing with appropriate amines. The diamine thus formed underwent smooth cyclization when treated with

\[
\begin{align*}
R-SO_2NH_2 + \text{Cl-CH}_2-(\text{CH}_2)_n-OH & \rightarrow R-SO_2NHCH_2-(\text{CH}_2)_n-OH \\
\text{X} & \rightarrow \text{XI} & \rightarrow \text{XII}
\end{align*}
\]
phosgene. Presumably, the cyclization proceeded through the intermediate formation of carbamyl chloride, (XV) which ultimately reacted with the labile proton of the sulfonamido function to give the desired product according to the following mechanism.

\[
\begin{align*}
\text{RSO}_2\text{NH} & \quad \text{NHR}^- \quad \xrightarrow{\text{COCl}_2} \quad \text{RSO}_2\text{N} - \text{R'} \quad \xrightarrow{\text{Cl}} \quad \text{HC} - \left[\text{CH}_2\right]_n \quad \xrightarrow{\text{I, II}} \quad \text{IR} - \text{spectrum of these imidazolidinones in chloroform solution clearly indicated a sharp peak at 1710 cm}^{-1}. \\
\end{align*}
\]

This is in accordance with the findings of Randall et al. that in the series of hydantoins, the carbonyl function at -2- position appears between 1710-1760 cm\(^{-1}\). Other peaks were located at 1350 cm\(^{-1}\) and 1163 cm\(^{-1}\) characteristic of \(\text{SO}_2\) function.

Substitution of the ureido moiety at 3-position of the sulfonyl imidazolidinone (VII) had been achieved easily by reacting them with appropriate isocyanates in the presence of pyridine.

\[
\begin{align*}
\text{VII} & \quad \xrightarrow{\text{R'NCO}} \quad \text{RSO}_2\text{N} - \text{C} - \text{N} - \text{C} - \text{NHR}^- \quad \xrightarrow{\text{CH}_2 - \text{CH}_2} \quad \text{XVI}
\end{align*}
\]
The tosylated amino acid amides, (III) were prepared by tosylating the appropriate amino acids according to Marshall\textsuperscript{45} and converting them to the corresponding acid chlorides which on treatment with ammonia solution gave the corresponding amides. The substituted amides were obtained by reacting the amino acid esters with the appropriate amines.

1-Alkyl-2-(β-arylsulfonamido) ethyl-3-phenylureas, (IV) were prepared by reacting the N-β-alkylaminoethylarylsulfonamides, (XIV), with phenyl isocyanate in petroleum ether solution.

These compounds have been assigned the structure (IV) because (i) of their failure to form hydrochlorides, (ii) their solubility in alkali and (iii) the IR which showed $\nu_{\max}$ at 1661 cm$^{-1}$ ($\nu_{\text{N-C-N}}$).
EXPERIMENTAL

N-(β-Hydroxyethyl)p-toluenesulfonamides

p-Tosylamide (1 mole) was added to a solution of sodium (1 mole) in methanol, the alcohol distilled off, and the residue was treated twice with dry benzene. On removal of the solvent, the sodio-derivative was dried in vacuum desiccator over fused calcium chloride. Ethylene chlorohydrin (1.2 moles) was added to the product and the mixture was heated in an autoclave for 6 hours at 120°C. The product was extracted with hot alcohol to give a viscous syrup.

The method was extended to the preparation of N-(β-hydroxyethyl) benzenesulfonamide, N-(β-hydroxyethyl) p-Cl-, F, MeO-, n-Pr-benzenesulfonamides and N-(γ-hydroxy propyl) p-toluenesulfonamide using sealed tubes instead of autoclave.

N-(β-Chloroethyl)-p-toluenesulfonamide

The above substance was treated with thionyl chloride (1.3 moles) and stirred at 15-20°C for 2-3 hours.
Stirring was continued (cooling in ice-water bath) for four hours and the reaction mixture was allowed to stand overnight at room temperature. The residue was then heated at 60-70°C for 2 hours and finally at 100°C for one hour while stirring and poured onto cold water. The granular mass thus obtained was crystallized from ethanol or methanol.

The procedure was extended to include the synthesis of N-(β-chloroethyl)-benzenesulfonamide, N-(β-chloroethyl) p-Cl-, F-, MeO-, and n-Pr- benzenesulfonamides and N-(γ-chloropropyl) -p-toluenesulfonamide.

**N-(β-Alkyl-, aryl-, and arylalkyl-aminoethyl)-arylsulfonamides**

As a general procedure, a mixture of the above N-(β-chloroethyl) arylsulfonamides and an excess of appropriate primary amines was heated at 120°C for four hours. The excess of the amines removed under reduced pressure; the residue treated with concentrated ammonia solution and extracted with ether. The free bases, on removal of the solvent, were obtained as viscous pale-yellow oils, and converted into their hydrochlorides which were crystallized from ethanol-ether or acetone-ether mixtures.

**N-(γ-Alkylaminopropyl)-p-toluenesulfonamide**

This was prepared by the method described above using propylene chlorohydrin in place of ethylene chlorohydrin,
b.p. 230°C/10⁻³ mm (bath temperature) (Found N, 10.37,
C₁₃H₂₀N₂O₂S requires N, 10.41%.

These diamines are described in Table I.

1-Arylsulfonyl-3-alkyl-, aryl- and arylalkyl-2-imidazolidinones

As a general procedure, a solution of phosgene in toluene (1.5 moles; 12%) was added dropwise to stirred mixture of the above amines (1.0 mole), potassium carbonate (1 mole) and ether kept at 0°C. After the addition was complete the mixture was stirred at room temperature for another four hours. The solvents were removed under vacuum, the residue washed repeatedly with water and crystallized from ethanol.

The various imidazolidinones thus obtained are described in Table 2.

1-Arylsulfonyl-3-(substituted and unsubstituted)
phenylcarbamyl-2-imidazolidinones

The appropriate isocyanates were added to a solution of 1-arylsulfonyl-2-imidazolidinones in chloroform pyridine mixture and the mixture heated for 16 hours at 100°C. On removal of the solvents the residue was washed thoroughly with dry ether or crystallized from aqueous acetone, ethanol or acetone-alcohol mixture.

These imidazolidinones are described in Table 2.
1-Alkyl-1-(β-arylsulfonylamidoethyl)-3-phenylureas

A mixture of the above respective amines (1 mole) and phenyl isocyanate (1.2 moles) in petroleum ether was refluxed under stirring for 30 minutes. The solvent was removed under reduced pressure and the products purified either by crystallization from aqueous alcohol or by chromatography over alumina using chloroform as eluent.

These compounds have been described in Table 3.

Tosylamino acid amides

Tosylation of amino acids was done according to Beecham, when p-tosyl chloride (0.1 mole) was added to a solution of amino acid (0.1 mole) in 100 ml. of H₂O containing NaOH (0.2 mole) and the suspension heated to 70-80°C with shaking until a clear solution resulted. After acidification in cold, the product either crystallizes or is taken into ether, washed, and dried over MgSO₄. On removal of the solvent, the residue was crystallized from ethanol-ether and petrol mixture.

The corresponding acid chlorides were prepared by reacting the tosylated amino acids (0.01 mole) in 20-30 ml. of anhydrous ether solution with PCl₅ (0.015 mole) and shaken until all organic material had dissolved. The filtered solution was diluted with 100 ml of petrol
(b.p. 80-100°C) which, on keeping at 0°C for several hours, crystallized.

The tosylated amino acid esters were obtained when the thionyl chloride (1 mole) was added dropwise to an alcoholic solution (absolute ethanol or methanol) of the tosylated amino acids at 0°C and allowed the mixture to stand overnight at room temperature. On removal of the solvent, the ester remained as a viscous oil or crystallizes out.

The corresponding acid amides were prepared by treating the N-tosyl amino acid chlorides with aqueous ammonia or amine or by heating the esters with appropriate amines under reflux at 100°C for 4 hours and are described in Table 4.

**1-p-Toluenesulfonyl-3-butyldihydouracil**

A mixture of β-(p-toluenesulfonamido) propionic acid butylamide (2.2 g), ethyl chloroformate (1 ml), potassium carbonate (1.5 g) and acetone (20 ml) was refluxed for ten hours. Acetone was removed under vacuum and the semi-solid residue was heated at 110°C/5 mm. for six hours, cooled and the resulting 1-p-toluenesulfonyl-3-butyldihydouracil, washed with dilute hydrochloric acid and crystallized from aqueous ethanol, m.p. 95°C. (Found: C, 55.67; H, 7.36; N, 8.99. C₁₅H₂₀N₂O₄ requires C, 55.56; H, 6.17; N, 8.64%).
1-Substituted ureas

These were prepared by the several known methods \(^{47-49}\) by reacting the salts of the appropriate amines with potassium cyanate, or by reacting the free amines with nitrourea in alcohol \(^{50}\).

1-Substituted barbituric acids

These were prepared according to \(\text{stein}^{51}\).

As a general preparatory procedure, a mixture of p-tolylurea (9.38 g) and ethylmalonate (9.5 g), was refluxed for 6 hours at 120-30°C in a solution of Na (1.5 g) in absolute ethanol (38 ml). The reaction mixture, on cooling, was diluted with water (50 ml) and the clear filtrate on acidifying with dil HCl (1:1, 13 ml) gave a massive precipitate. Latter was purified by dissolving in caustic soda solution, (10%) acidifying the clear filtrate with dil HCl and recrystallizing the product from water.

These have been described in Table 5.
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* Lit. 4 m.p. 153°C; the analytical data of the authors are rather beyond the accepted limits.


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CHAPTER III

Syntheses of pyridylalkylureas
In view of the encouraging results obtained during animal experiments on the hypoglycemic activity of the N-(2-pyridyl)-N'-[3-(5-phenyl, 1,2,4-thiadiazolyl)] urea (I), it was considered desirable to assess the pharmacodynamic potentiality, if any, of the pyridine moiety in terms of hypoglycemic action. Accordingly, the following types of simple urea and thiourea derivatives (II, III; \(n = 1\) or \(2\)) having 2- or 4-pyridyl nuclei as substituents were synthesised.

![Chemical structures](image-url)
The following two schemes were formulated for this purpose:

i) First, the pyridylethylolation of suitably substituted urea derivatives with 2- or 4-vinylpyridine:

\[
\text{CH} = \text{CH}_2 + \text{NH}_2 \text{C-NHR} \rightarrow \text{CH}_2\text{CH}_2\text{NHCNHR}
\]

ii) The second scheme involved the pyridylethylolation of ammonia to yield pyridylethylamine which was condensed with the appropriate isocyanate or isothiocyanate giving (II) or (III).

As a preliminary to the first scheme, study of the reaction of 2- and 4-vinylpyridines with phthalhydrazide and hydroxylamine was first undertaken.

The analogous reactions of 2- and 4-vinylpyridines with amides and imides under base-catalysed conditions as well as without the use of any catalyst have been described. For example, the reaction with acetamide and propionamide was catalysed by sodium metal\(^1\), that of phthalimide by Triton\(^2\) B or piperidine\(^3\), and succinimide also by a basic catalyst\(^4\). The reaction of these vinylpyridines with 1,3-benzoxazine-2,4-dione was...
carried out in the absence of any catalyst. In the preliminary experiments using acid catalysed conditions, an attempt was made in the first instance to add phthalhydrazide and hydroxylamine on 2- and 4-vinylpyridines. Phthalhydrazide reacted with both the isomers under acid-catalysed conditions to give excellent yields of monoadduct products (IV), which were further characterised as hydrobromides.

![IV](image)

The reaction of hydroxylamine hydrochloride (hydrochloride ion acting as a catalyst) with 4-vinylpyridine yielded a base, C_{14}H_{17}N_{3}O, whose infra-red spectrum in chloroform showed a band at 3600 cm\(^{-1}\), characteristic of free hydroxyl groups. The base formed a trihydrobromide and a benzoate ester which was isolated as the dihydrobromide. From this date, this base is assigned structure (V, R = H).
chlorides, phenylisocyanate) gave rise to highly coloured gums or amorphous solids, either as the free bases or their salts.

The n.m.r. spectrum of VI (R = H) (60 Mc.) in deuterochloroform (using tetramethylsilane as internal standard) showed five groups of signals: A sharp signal at $\delta = 3.13$ p.p.m. which is attributed to two equivalent C$_2$H$_4$ moieties; a broad signal at $\delta = 7.88$ p.p.m. which is assigned to NOH and signals which are assigned to $\alpha$, $\beta$, and $\gamma$-protons of the pyridine ring. Integral information revealed two $\alpha$-protons, two $\gamma$-protons, four $\beta$-protons, one NOH, and eight CH$_2$ protons.
The addition of hydroxylamine (as the hydrochloride) to 2-vinylpyridine was reported to afford a compound C7H10N2O, m.p. 105.9-106.8 °C, which was formulated as N-(2-(2-pyridyl) ethyl) hydroxylamine, 2-C6H4N-CH2CH2NH2OH. However, repetition of this experiment with or without modification of the procedure always gave a solid, m.p. 105-106.5 °C, which analysed for C14H17N3O, and exhibited a free hydroxyl band in its infrared spectrum (in chloroform solution) and fitted the dipyrkdylethyl hydroxylamine structure (VI, R = H). The base was further characterised by a crystalline dihydrobromide. It is not unusual for dibasic 2-pyridylethyl substituted amines such as 2-C5H4NCH2CH2NHR to form either mono- or dipicrates, and tribasic amines such as N-(dialkyl-amo-no-alkyl)-N-(2-(2-pyridyl)ethyl) anilines to form dipicrates. Attempts to prepare other functional derivatives of V or VI (R = H) with a number of conventional reagents (e.g., acetylchloride, arenesulfonyl
chlorides, phenylisocyanate) gave rise to highly coloured gums or amorphous solids, either as the free bases or their salts.

The n.m.r. spectrum of VI (R = H) (60 Mc.) in deuterochloroform (using tetramethylsilane as internal standard) showed five groups of signals: A sharp signal at $\delta = 3.13$ p.p.m. which is attributed to two equivalent $C_2H_4$ moieties; a broad signal at $\delta = 7.88$ p.p.m. which is assigned to NOH and signals which are assigned to $\zeta$, $\beta$, and $\gamma$-protons of the pyridine ring. Integral information revealed two $\zeta$-protons, two $\gamma$-protons, four $\beta$-protons, one NOH, and eight $CH_2$ protons.
In order to prove conclusively the structure of the above adduct (VI, $R = H$) another route for its synthesis was devised which involved the reaction of 2-vinylpyridine with benzyloxyamine followed by the hydrolysis of the product to give VI ($R = H$). The addition of benzyloxyamine to either 2- or 4-vinylpyridine afforded an excellent yield of the corresponding dipyrindylethyl derivative. As these compounds could not be distilled satisfactorily, they were isolated as salts. Again, the 4-pyrindylethyl derivative, $V\,(R = C_6H_5CH_2)$, crystallized as the trihydrobromide, the isomeric 2-pyrindyl adduct VI ($R = C_6H_5CH_2$) as the dihydrobromide. The hydrolysis of N, N-di-2(4-pyridyl)ethyl benzyloxyamine $V\,(R = C_6H_5CH_2)$, with 48% hydrobromic acid removed the benzyl group to form the hydroxy derivative $V\,(R = H)$ almost quantitatively. A similar hydrolysis of N, N-di 2-(2-pyridyl)ethyl) -benzyloxyamine, VI ($R = C_6H_5CH_2$), under milder conditions furnished the corresponding hydroxylamine, VI ($R = H$), thus affording conclusive proof of structure for the 2-vinylpyridine and hydroxylamine adduct.

All attempts to add 1-substituted ureas, on the above analogy, to 2-, and 4-vinylpyridines under a variety of acid or base catalysed conditions, were, however, unsuccessful. The only products isolated were gums or unchanged ureas.
The second route was more successful. 2- or 4-vinylpyridine was reacted with ammonium chloride\(^1\) to yield the corresponding pyridylethylamine. The latter with the appropriate isocyanate or isothiocyanate reacted smoothly to give (II) or (III) respectively.

With a view to find out if the shortening of the carbon chain length had any effect on activity, N-(2-pyridyl) methyl-N'-p-toluenesulfonylurea was prepared by reacting tosylamide with 2-pyridylacetamide through Hofmann reaction:

\[
\begin{align*}
\text{N} & \quad \text{CH}_2 \cdot \text{C} \cdot \text{NH}_2 + \text{H}_3 \text{C} \cdot \text{C} \cdot \text{SO}_2 \cdot \text{NH}_2 \\
\text{OH} & \quad \text{Br} \\
\text{N} & \quad \text{CH}_2 \cdot \text{NH} \cdot \text{C} \cdot \text{NH} \cdot \text{SO}_2 \cdot \text{C} \cdot \text{CH}_3
\end{align*}
\]
EXPERIMENTAL

For the synthesis of 2-vinylpyridine, the method of Winterfeld\textsuperscript{9} was followed. The required intermediate, β-(2-pyridylethanol) was prepared by reacting paraformaldehyde with α-picoline in an autoclave at 140°C under 50 atmosphere pressure of H\textsubscript{2}. The 2-vinylpyridine was obtained by distilling the above alcohol over KOH.

2- and 4- (2-Aminoethyl) pyridines (VII) were prepared according to Levine\textsuperscript{1} by reacting NH\textsubscript{4}Cl on the respective pyridines and distilling the products, 2- (2-aminoethyl) pyridine and the 4-isomer at 90-93°C/9 mm and 117-120°C/17 mm, respectively.

N-Alkyl (or aryl) N'-β(2-or 4-pyridyl)ethylureas or thio ureas

As a general preparatory procedure, the appropriate isocyanate or isothiocyanate in petroleum ether solution was added gradually to a stirred suspension of 2- or 4- (2-aminoethyl) pyridine in petroleum ether in cold. After 30 minutes at room temperature, the product was filtered, washed with boiling petroleum ether and crystallized.
from aqueous ethanol or from ether-petrol mixture.

**N-Phenyl-N'-(4-pyridyl)ethylurea**

Yield: 90%; m.p. 156°C (Found: N, 17.02

C\textsubscript{14}H\textsubscript{15}N\textsubscript{3}O requires N, 17.42%).

**N-p-Methoxyphenyl)-N'-(4-pyridyl)ethylurea**

Yield: 73%; m.p. 153°C (Found: N, 15.68

C\textsubscript{15}H\textsubscript{17}N\textsubscript{3}O requires N, 15.50%).

**N-β-(4-Pyridyl)ethyl-N'-(n-propylurea**

Waxy solid. Yield 50%; m.p. 54-57°C

(Found: N, 20.49. \textsubscript{11}H\textsubscript{17}N\textsubscript{3}O requires N, 20.29%).

**N-Butyl-N'-(4-pyridyl)ethylthiourea**

Yield: 61%; m.p. 66°C. (Found: N, 17.58

C\textsubscript{12}H\textsubscript{19}N\textsubscript{3}S requires N, 17.72%).

**N-Phenyl-N'-(2-pyridyl)ethylurea**

Yield: 90%; m.p. 123-4°C (Found: N, 17.60

C\textsubscript{14}H\textsubscript{15}N\textsubscript{3}O requires N, 17.42%).

**N-β-(2-Pyridyl)ethyl)-N'-propylurea**

Yield: 53%, viscous oil at room temperature which crystallizes in cold (Found: N, 20.09 C\textsubscript{11}H\textsubscript{17}N\textsubscript{3}O
requires N: 20.29%).

N-p-Methoxyphenyl-N'-'(2-pyridyl)ethylurea

Yield: 60%, m.p. 128°C. (Found: N, 15.67
C_{15}H_{17}N_{3}O_{2} requires N, 15.50%).

N-Phenyl-N'-β-(2-pyridyl)ethylthiourea:

Yield: 65%; m.p. 110-111°C. (Found: N, 16.29
C_{14}H_{15}N_{3}S requires N, 16.34%)

N,N-Di(2-(2-pyridyl)ethyl)hydroxylamine

Redistilled 2-vinylpyridine (21.0 g.; 0.2 mole) was added to a solution of hydroxylamine hydrochloride (7 g.; 0.1 mole) in 50% aqueous acetic acid (50 ml) and the mixture heated at 100°C for 0.25 hr. The solution was cooled to 0°C and sodium carbonate (32 g.; 0.3 mole) was added. The solid was filtered, dried, and freed from admixed inorganic salts by several extractions with acetone. Concentration of the acetone solution afforded the base, 19.9 g. (82% based on 2-vinylpyridine), m.p. 102-105°C. Recrystallization from a mixture (5:3) of benzene and petroleum ether (b.p. 30-60°C) gave light brown needles, m.p. 105-106.5°C. (Found: C, 69.23; H, 6.97; N, 17.27,
C_{14}H_{17}N_{3}O requires C, 69.13; H, 7.06; N, 17.27%).

The dihydrobromide was isolated in almost quantitative yield by passing a stream of hydrogen bromide
gas through an ice-cold ethanol solution of the hydroxylamine. The salt was recrystallized from ethanol-ether (8:5), m.p. 160-161°C. (Found: C, 41.70; H, 4.67; N, 10.12; Br, 39.65, \( \text{C}_{14}\text{H}_{19}\text{N}_3\text{O} \) \( \text{Br}_2 \) requires C, 41.50; H, 4.74; N, 10.37; Br, 39.44%).

\[ \text{N,N-Di(2-(4-pyridyl)ethyl)hydroxylamine} \]

This hydroxylamine was prepared in 70% yield from 4-vinylpyridine by the procedure outlined for 2-vinylpyridine. It crystallized from acetone in colorless needles, m.p. 143-144°C. (Found: C, 69.22; H, 6.93; N, 17.39; \( \text{C}_{14}\text{H}_{17}\text{N}_3\text{O} \) requires C, 69.13; H, 7.06; N, 17.27%).

The trihydrobromide, was crystallized from ethanol-ether and melted at 200-202°C. (Found: C, 34.71; H, 4.20; N, 8.57, \( \text{C}_{14}\text{H}_{20}\text{N}_3\text{O} \) \( \text{Br} \) requires C, 34.59; H, 4.16; N, 8.65%).

A solution of the above hydroxylamine (1.2 g.; 0.005 mole) in chloroform (25 ml) was added in small portions (over a period of 10 min.) to a chloroform solution of benzoyl chloride (3.0 g.; 0.02 mole in 25 ml). After standing at 25°C for 2 hr., the solvents were removed in vacuo and the residue dissolved in 10 ml of ice water. Addition of 20% sodium carbonate solution liberated an oil which was taken up in ether (60 ml in all). The ethereal solution was dried (sodium sulfate) and saturated with hydrogen bromide gas at 0°C. The gum which separated was
dissolved in ethanol. Careful addition of anhydrous ether yielded the **benzoate dihydrobromide** (1.5 g.; 60%); which crystallized from ethanol-ether (2:1), m.p. 158-159°C. (Found: C, 49.37; H, 4.66; N, 8.25; Br, 31.29; \( \text{C}_{21}\text{H}_{23}\text{N}_{3}\text{O}_{2}\text{Br}_{2} \) requires C, 49.52; H, 4.57; N, 8.26; Br, 31.38%).

The infrared spectrum of this compound (in Nujol) showed the C = O stretching frequency of the ester to be at 1740 cm\(^{-1}\).

**Benzylxoyamine hydrochloride**

A mixture of N-benzylxoyphthalimide, made by the method of McKay\(^{10}\), (77 g.; 0.3 mole), concentrated hydrochloric acid (77 ml.) and acetic acid (250 ml.) was heated under reflux for 0.25 hr., and then evaporated almost to dryness in vacuo. Sodium hydroxide solution was added until the solution was strongly basic and the base extracted with ether. The ether solution was dried (sodium sulfate) and then a stream of hydrogen chloride was led through it. The salt (33.8 g.; 71%) was obtained in colorless shining flakes, m.p. 232°C. Lit.\(^{11}\) m.p. 230-35°C.

**N,N-Di 2-(2-pyridyl)ethyl-benzylxoyamine dihydrobromide**

Redistilled 2-vinylpyridine (5.3 g.; 0.05 mole)
and benzyloxyamine hydrochloride (4.0 g.; 0.025 mole) were heated in 50% aqueous acetic acid (12.5 ml) at 100°C for 0.25 hr. The solution was cooled to 0°C, treated with sodium carbonate (9.6 g.; 0.91 mole), and the viscous oil which separated was extracted with ether (150 ml). The ethereal solution was dried (sodium sulfate) and an ice-cold saturated ethanolic hydrogen bromide solution (50 ml) was added. The salt, which separated as a gum, solidified upon standing (11.12 g.; 90%) m.p. 145-150°C and was crystallized from methanol-ether (2:3) in colorless cubes m.p. 157-158°C. (Found: C, 50.83; H, 5.01; N, 8.52; Br, 32.33; C21H25N3O Br2 requires C, 50.80; H, 5.08; N, 8.49; Br, 32.30%).

The hydrochloride or p-toluenesulfonylate could not be obtained crystalline.

N,N-Di(2-(4-pyridyl)ethyl)benzyloxyamine trihydrobromide

This was prepared (83%), m.p. 169-172°C, in a similar fashion from 4-vinylpyridine. It crystallized from methanol-ether (1:1) m.p. 180-180.5°C. (Found: C, 44.16; H, 4.73; N, 7.49; Br, 41.72; C21H26N3O Br3 requires C, 43.80; H, 4.56; N, 7.50; Br, 41.60%).

The tri-p-toluenesulfonylate could be prepared in 66% yield by the above procedure when the gum was treated with p-toluenesulfonic acid instead of hydrogen bromide.
It crystallized from ethanol-ether (4:3), m.p. 149°C.
(Found: C, 59.05; H, 5.85; N, 4.94; S, 11.14; \( \text{C}_{42}\text{H}_{47}\text{N}_{3}\text{S}_{3} \text{O}_{10} \) requires C, 59.33; H, 5.58; N, 4.94; S, 11.32%).

**Hydrolysis of \( \text{N,N-Di(2-(4-pyridyl)ethyl)benzyloxamine trihydrobromide} \)**

A solution of the salt (1.0 g.; 0.0017 mole) in concentrated hydrobromic acid (10 ml. of 48%) and acetic acid (10 ml) were heated under reflux for 40 min. Solvents were then removed in vacuo at 50°C, and the residual yellow gum crystallized from ethanol (10 ml), and anhydrous ether (5 ml). The salt (0.82 g.; 98%) had m.p. 190-195°C, undepressed when mixed with a sample of N, N-di(4-pyridyl) ethyl)hydroxylamine trihydrobromide. Their infrared spectra (Nujol) were also identical. Addition of 20% sodium carbonate solution to this salt afforded the free base (m.p. 142-145°C) which was identical to \( \Psi \) (\( R = H \)).

**Hydrolysis of \( \text{N,N-(2-(2-Pyridyl)ethyl)benzyloxamine hydrobromide} \)**

A solution of the salt (4.0 g.; 0.0081 mole) in 48% hydrobromic acid (50 ml) was boiled for 5 min. only. The solution was chilled immediately to 0°C, made alkaline with 10% sodium hydroxide solution, saturated with sodium sulfate, and the mixture extracted with ether (400 ml). The ethereal solution was dried (sodium sulfate),
the solvent removed, and the residual, black gum, triturated with acetone (2 ml). The crystals (0.7 g.; 36%), which separated on standing overnight at 5°C, had m.p. 104-5°C. Recrystallization from acetone raised the m.p. to 105-107°C, undepressed on admixture of a sample of N,N-di(2-(2-pyridyl)ethyl)hydroxylamine.

N-(2-(2-Pyridyl)ethyl)phthalhydrazide

A solution of 2-vinylpyridine (7.8 g.; 0.074 mole) and phthalhydrazide (6.0 g; 0.037 mole) in 75% aqueous acetic acid (12 ml) was heated at 100°C for 0.5 hr. Dilution of the cold reaction mixture with 150 ml of water afforded the product (7.75 g.; 78% based on phthalhydrazide) which crystallized from acetone as colorless needles, m.p. 156-157°C. (Found: C, 67.64; H, 5.06; N, 15.69; C_{15}H_{13}N_{3}O_{2} requires C, 67.41; H, 4.87; N, 15.73%).

When equimolar proportions of reactants were used, the product was isolated in 31% yield only.

The hydrobromide (prepared with hydrogen bromide gas in ethanol) crystallized from methanol-ether (3:5), m.p. 223-224°C. (Found: N, 12.06; C_{15}H_{14}N_{3}O_{2}Br requires N, 12.09%).

N-(2-(4-Pyridyl)ethyl)phthalhydrazide was prepared in 93% yield from 4-vinylpyridine (0.05 mole) and phthalhydrazide (0.025 mole). It crystallized from ethanol in colorless needles, m.p. 216-217°C. (Found: C, 67.56;
The hydrobromide crystallized from methanol-ether (5:2), m.p. 250°C. (Found: N, 12.01; \( \text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_2\text{Br} \) requires N, 12.09%).

**N-(2-Pyridyl)methyl,N'-p-toluenesulfonylurea**

A mixture of 2-pyridylacetamide (1.5 g.) and p-tosylamide (1.7 g.) was dissolved in 5 ml. of 4N-NaOH and 20 ml. of water. The solution was slowly heated to 60°C and treated dropwise with 0.6 ml. of bromine, maintaining the pH at 7-7.5 by careful addition of NaOH solution. The reaction mixture was then heated to 80-90°C, cooled, filtered and the filtrate, on acidifying with dil HCl, gave 60% of the product, melting at 127°C. (Found N: 13.66% \( \text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3\text{S} \) requires N, 13.78%).
REFERENCE


8. The spectrum was kindly determined by Dr. L.F. Johnson, Varian Associate, Palo Alto, California.


CHAPTER IV

Syntheses of indole, isoindoline and their derivatives
During his researches on enzymatic degradation of insulin, Mirsky made an important observation that liver tissues contained a factor capable of inhibiting the action of the insulin-destroying enzyme, the "insulinase". A systematic examination revealed that auxin and auxin-like substances, indole-3-acetic-, propionic-, and butyric acids; nicotinic and anthranilic acids and tryptophane and its metabolites, on oral or parental administration, induce more or less the same effect: that they are insulinase-inhibitors in vitro and hypoglycemics in vivo. Mirsky and coworkers have, in their later findings, correlated the auxin-like activity of these compounds to their ability to lower the blood sugar. Hypoglycemic and auxin-like activities appear to have a somewhat common structural requirements. Most hypoglycemics possess urea, thiourea, or a guanidino-moieties, while some ureas, amides have also been noted as potent plant-growth regulators. It, therefore, appeared interesting to synthesize some indole derivatives containing a urea moiety with a view to examine their possible use as antidiabetic compounds.

Structural resemblance with indole and its proven
pharmacodynamic potentialities in other fields, prompted us to include the isoindoline nucleus also in compounds under present study. The compounds of the series illustrated by formulae (I to VII) were thus

\[
\text{\textbf{Formula I}}
\]

\[
\text{\textbf{Formula II}}
\]

\[
\text{\textbf{Formula III}}
\]

\[
\text{\textbf{Formula IV}}
\]

\[
\text{\textbf{Formula V}}
\]

\[
\text{\textbf{Formula VI}}
\]

\[
\text{\textbf{Formula VII}}
\]
synthesized. A study of the biological properties of these compounds would clearly show whether (i) the isoindoline nucleus per se had any hypoglycemic property (cf. tryptophane in the indole series) and (ii) whether the isoindoline system could be used as a useful carrier of activity as a substituent in the sulfonylurea molecules \( \text{IV, } R = \text{tosyl, } X = 0 \) (cf. \( R = \text{cyclohexyl and cycloheptyl which are active} \)).

Some more isoindoline compounds \( \text{V, VI, VII} \) containing generally useful substituents (for example in antihistaminics, and anaesthetics) were also synthesized. These are discussed in the sequel.

Out of a variety of methods available for the synthesis of indole \( ^{17-26} \), the one according to Tyson \( ^{27} \) was followed which involved the pyrolysis of potassium salt of 0-formotoluide.

Indole was condensed under forced conditions with appropriate isocyanates in presence of few drops of pyridine to give alkyl or aryl-substituted ureas.

Tryptamine was prepared by LAH reduction of 3,2'-nitrovinyldole \( ^{28} \). The latter was obtained by reacting indole-3-aldehyde with nitromethane in presence of ammonium acetate \( ^{28} \).

A suspension of tryptamine in petroleum ether reacted smoothly with isocyanates and isothiocyanates to give the corresponding urea and thiourea derivatives. The corresponding sulfonyleurea derivative was obtained either by
pyrolyzing the salt of ethyl N-(toluenesulfonyl) carbamate with tryptamine or by refluxing the mixture of both in toluene solution.

Tryptophane was converted into methyl ester and the free base was reacted with the ethyl N-(p-toluenesulfonyl) carbamate in a way similar to that described for tryptamine to give the sulfonylurea.

Several methods are reported in literature for the synthesis of isoindoline but eventually most of them were found to be impracticable. For example, the electrolytic reduction of the phthalimide required special apparatus and careful control of experimental conditions while other methods including LAH reduction of phthalimide suffered from the drawback of very poor yields. Bornstein (1957) reported a two-step synthesis of isoindoline by reacting o-xylene dibromide with p-toluenesulfonamide followed by cleavage of the sulfonamide residue with hydrobromic acid in presence of phenol. Neumeyer's method (1964), involving the preparation of benzylisoindoline and its subsequent-hydrogenolysis to give isoindoline was, however, the method of choice.

N-Benzylphthalimide, prepared by the action of phthalic anhydride on benzylamine, was reduced to N-benzylisoindoline in higher yields by slight modification of Neumeyer procedure. Hydrogenolysis of N-benzylisoindoline over palladium-charcoal gave the isoindoline.
Isoindoline reacted readily in petroleum ether solution with isocyanates and isothiocyanates to give substituted ureas and thioureas. The corresponding sulfonyleurea derivative was obtained in the usual manner.

Attempt was also made to synthesize the isoindoline (XIII) through the application of Hofmann-Löffler reaction according to the following scheme:

\[
\begin{align*}
\text{NHa} & \quad \xrightarrow{\text{Liran}} \quad \text{X} \\
\text{CH}_2 & \quad \text{XII} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2 & \quad \text{LAAH} & \quad \text{CH}_2 & \quad \text{U-V} \\
\text{NH}_2 & \quad \text{III} & \quad \text{XI} & \quad \text{IX} \\
\end{align*}
\]

X was obtained in good yields by LAH reduction of the corresponding cyano compound (IX). N-halogenation was achieved readily by the action of N-chlorosuccinimide on (X) in methylene chloride solution. The (XI) so obtained gave positive tests with KI in chloroform solution which remained unaffected after U-V irradiation. The (XII) did not cyclize by the action of methanolic alkali and instead of XIII, an oily product was obtained which on tosylation gave a compound m.p. 110-112°C. It analysed for C_{15}H_{17}NO_S; \nu_{max}. 3390 \text{ cm}^{-1} (\text{NH}), 1325, 1156 \text{ cm}^{-1} (\text{SO}_2). This was
found to be identical with the tosylated product obtained from X and was therefore assigned the structure $^{37b}$ XV.

During the preparation of 2-(3-aminopropyl) isoindoline (XVIII) from 2-cyanoethylphthalimide (XVII), both cyano and the carbonyl groups get reduced simultaneously in one step by the action of LAH. This base was obtained as an oil which readily absorbed carbon dioxide from the air to form solid carbonate. The salt could, however, be decomposed by the addition of strong alkali.

The corresponding urea or thiourea derivatives of the above amino were easily obtained by reacting it with appropriate isocyanate or isothiocyanate in petroleum ether solution or by the action of amines on ethyl N-$\gamma$-isoindolylpropyl carbamate. The latter was obtained according to the procedure of Marshall $^{38}$ by reacting the 2-(3-aminopropyl) isoindoline with ethyl chloroformate in acetone solution under reflux in presence of potassium carbonate.

The synthesis of 1-[3-(2-isoindolinyI)-propyl] dihydouracil (XX) which may be considered as an isoindoline substituted homo-hydantoin was achieved by the following sequence of reactions.
It was found that 2-(3-aminopropyl) isoindoline, (XVIII) could be added to acrylamide as well as to ethyl acrylate. The addition of 2-(3-aminopropyl)-isoindoline to acrylamide produced the amide of N-(3-isoindolinyl) propyl)-beta-alanine.

On the structural pattern of some of the well-known empirical drugs, a few more isoindoline derivatives were prepared. These were 2-(2-isoindolinyl) ethyl benzhydryl ether (V) and 1,6- bis- (2-isoindolinyl) hexane (VII).

Three esters containing isoindole ring system, the 2-isoindoliny-lethyl 4-aminobenzoate hydrobromide, 2-isoindoliny-lethyl diphenylacetate hydrochloride and 2-isoindoliny-lethyl dl-mandelate hydrochloride were synthesized on the analogy of procaine, trasentine, and eucatropine respectively.
Most of the compounds prepared were found to contain three carbon-hydrogen absorption bands in the 2700-3200 cm\(^{-1}\) region of their infrared spectra. Since there were present in these molecules three distinct types of carbon-hydrogen bonds, it was felt that with the aid of several simple model compounds, analysis of this region of their spectra would be possible. From a study of the spectra of the compounds listed in Table I, it appeared that the three bands were the result of absorption by the carbon-hydrogen bonds of the aromatic ring, the carbon-hydrogen bonds of the heterocyclic ring, and the carbon-hydrogen bonds of the alkyl chain attached to the nitrogen atom.

The bands appearing at 3025-3050 cm\(^{-1}\) result from absorption by aromatic carbon hydrogen bonds. When only a single aromatic ring is present in the compound, the band occurs at 3025 as a shoulder on the stronger peak at 2940 cm\(^{-1}\). However, the addition of a second phenyl group as in 2 phenylisoindoline, 2-phenyl-4- aminoisooindoline, or 1,6-bis(2-isooindoliny1) hexane, increases the intensity of this band and it occurs as a separate peak. The absorption bands at 2940 to 2975 cm\(^{-1}\) were definitely established. These appeared to be due to absorption of the carbon-hydrogen bonds of the alkyl groups connected to the heterocyclic
nitrogen atom. Substitution of a phenyl group for the alkyl group, 2-phenylisoindoline and 2-phenyl-4-aminooisoindoline, resulted in the loss of absorption peaks in this area. Furthermore, the substitution of an ethyl group for the methyl group of 2-methylisoindoline gave rise to a doublet rather than a single peak.

It appeared likely that the absorption bands occurring in the portion of the infrared spectra 2720 and 2800 cm$^{-1}$ might be caused by the absorption of

TABLE I. STUDY OF THE SPECTRA

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-H Bond</th>
<th>C-H Bond</th>
<th>C-H Bond</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aromatic</td>
<td>Hetero</td>
<td>Alkyl</td>
</tr>
<tr>
<td></td>
<td>Ring</td>
<td>cyclic</td>
<td>Chain</td>
</tr>
<tr>
<td>2-Methylisoindoline</td>
<td>3025$^a$</td>
<td>2775</td>
<td>2940</td>
</tr>
<tr>
<td>2-Ethylisoindoline</td>
<td>3025$^a$</td>
<td>2800</td>
<td>2940-2975</td>
</tr>
<tr>
<td>2-Phenylisoindoline</td>
<td>3050</td>
<td>2750</td>
<td>...</td>
</tr>
<tr>
<td>2-Phenyl-3-aminoisoindoline</td>
<td>3040</td>
<td>2720</td>
<td>...</td>
</tr>
<tr>
<td>1,6-Bis-(2-isooindolyl) hexane</td>
<td>3050</td>
<td>2780</td>
<td>2940</td>
</tr>
<tr>
<td>N-Methylphthalimide</td>
<td>3050</td>
<td>...</td>
<td>2975</td>
</tr>
</tbody>
</table>

$^a$ Occurs as a shoulder on the peak at 2940 cm$^{-1}$
carbon-hydrogen bonds of the methylene group of the heterocyclic ring. It was, therefore, desirable to obtain the spectra of an isoindoline ring system which did not contain carbon-hydrogen bonds in that ring. Since it was difficult to obtain a 1,1,3,3 tetra-substituted isoindoline, the spectra of the compounds previously synthesized were compared to the spectra of N-methylphthalimide. While the previously identified peaks at 3050 and 2975 cm\(^{-1}\) were present, the peak at 2720 to 2800 was missing. This indicates that the peak usually occurring in this area is due to absorption of the methylene group of the heterocyclic ring.
Indole was prepared according to Tysen,\textsuperscript{27} b.p. 121°C/5 mm; m.p. 52-53°C.

1-(Phenylcarbamoyl)-indole was prepared according to Henry\textsuperscript{39}, m.p. 135-36°C.

1-(p-Methoxyphenylcarbamoyl)-indole

This was prepared by slight modification of the above procedure by reacting equimolar quantities of indole and p-methoxyphenyl isocyanate in petrol-ether solution in presence of few drops of pyridine, and crystallizing the product from aqueous ethanol. Yield: 85\%, m.p. 221°C. (Found: N, 10.61, C\textsubscript{16}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2} requires N, 10.53%).

In a similar way 1-(n-propylcarbamoyl)-indole was prepared by reacting the indole with n-propylisocyanate and crystallizing the product from aqueous ethanol in cold. Yield. 70\%, m.p. 199. (Found N, 13.71, C\textsubscript{12}H\textsubscript{14}N\textsubscript{2}O requires N, 13.86%).

3-(2'-Nitrovinyl)-indole\textsuperscript{28} was obtained according to Young, m.p. 171-72°C which on reduction with LAH in ether gave tryptamine, m.p. 146°C, hydrochloride, m.p. 249-250°C.
N-β-(3-Indolyl)ethyl, N'-((p-methoxyphenyl) urea

The following procedure illustrates in general the preparation of all the urea derivatives of tryptamine described here. These were crystallized from aqueous ethanol, yield: 70-80%.

To a suspension of tryptamine in ligroin was added with stirring p-methoxyphenyl isocyanate (equimolar quantities) and the mixture was heated for 30 minutes at 100°C. On cooling the product was filtered and washed several times with boiling ligroin. It was finally crystallized from aqueous ethanol. m.p. 88-89. (Found: N, 13.67, C_{18}H_{19}N_{13}O requires N, 13.59%).

N-β-(3-Indolyl)ethyl-N'-n-propylurea

M.p. 106. (Found: N, 06, C_{14}H_{19}N_{3}O requires N, 17.14%).

N-β-(3-Indolyl)ethyl-N'-n-butyl thiourea

M.p. 96°C. (Found: N, 15.40, C_{15}H_{21}N_{3}S requires N, 15.27%) 

N - β -(3-Indolyl)ethyl-N'-p-toluenesulfonylurea

A mixture of tryptamine and ethyl N-(p-toluene-sulfonyl) carbamate (1: 1.2 moles) in benzene was refluxed till a homogenous suspension is obtained. On removal of the
solvent, the residue was heated at 120°/8 mm. pressure
for eight hours, and crystallized from aqueous ethanol.
Yield 76%, m.p. 140°C. (Found: N, 11.84. C_{18}H_{19}N_{3}O_{3}S
requires N, 11.76%).

Isoindoline was prepared according to the
method of Neumeyer 35 by hydrogenolysis of N-benzyliso-
indoline over 5% palladium-charcoal at 50°C under a
pressure of 50 p.s.i. of hydrogen; b.p. 105°C/20 mm.

N-Benzylphthalimide was obtained in good yields
by the action of benzylamine on phthalic anhydride, m.p.115°C.

N-Benzylisoindoline 35 was prepared by LAH reduc-
tion of N-benzylphthalimide (3:1 mole) in ether under
nitrogen atmosphere. Yield 87%; b.p. 135°C/10^-4 mm.

2-(Phenylcarbamoyl)isoindoline

A solution of isoindoline (1.19 g.; 0.01 mole)
in petrol ether was treated with phenylisocyanate (1.31 g.;
0.011 mole) in cold. After standing for two hours at room
temperature, the product was filtered, washed with petroleum
ether and crystallized from aqueous ethanol. Yield 83%; m.p.
231°C. (Found: N, 12.09, C_{15}H_{14}N_{2}O requires N, 11.76%).

Similarly were prepared the following:
2-(p-Methoxyphenylcarbamoyl)isoindoline

Yield 60%; m.p. 178°C. (Found: N, 10.53,
C_{16}H_{16}N_{2}O_{2} requires N, 10.44%).
2-(p-Nitrophenylcarbamoyl)-isoindoline

Yield 65%; m.p. 241°C, (Found: N, 15.11, C\textsubscript{15}H\textsubscript{13}N\textsubscript{3}O\textsubscript{3} requires N, 14.84%).

2-(n-Propylcarbamoyl)-isoindoline

Yield 50%; m.p. 161°C (Found: N, 13.59, C\textsubscript{12}H\textsubscript{16}N\textsubscript{2}O requires N, 13.72%)

2-(n-Butylthiocarbamoyl)-isoindoline

Yield 63%; m.p. 143°C (Found: N, 12.01, C\textsubscript{13}H\textsubscript{18}N\textsubscript{2}S requires N, 11.96%)

2-(p-Toluenesulfonylcarbamoyl) isoindoline

A solution of isoindoline in toluene was gradually added to ethyl N-(p-toluenesulfonyl)carbamate (1:1.2 moles) in toluene solution and the mixture heated under reflux for 3 hours. The product, on removal of the solvent, was crystallized repeatedly from aqueous ethanol. Yield 30%; m.p. 286°C. (Found: N, 8.84, C\textsubscript{16}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3}S requires N, 8.86%).

2-(3-Aminopropyl)isoindoline

2-Cyanoethylphthalimide\textsuperscript{40} (15.0 g, 0.087 mole) was placed in a Soxhlet thimble and extracted into a slurry of 10.6 g of lithium aluminum hydride in 200 ml of anhydrous ether. After the reaction was completed, the reaction mixture
was cooled to 5°C, decomposed first with absolute alcohol, and finally with sufficient water to precipitate the aluminum oxide. The suspension was filtered and the clear filtrate was dried over anhydrous sodium sulfate. The mixture was filtered and the solvent removed by distillation. The resulting oil was distilled under vacuum. The fraction distilling at 94-96°C/0.6 mm. was collected. It weighed 9.8 g. (60%). (Found: C, 74.82; H, 9.34; N, 15.82. \( \text{C}_{11}\text{H}_{16}\text{N}_{2} \) requires C, 74.95; H, 9.15; N, 15.90%).

**N-\( \gamma \)-(2-Isocindolinyl)propyl-N'-phenylurea**

The following is a general preparatory procedure for 2-isocindolylpropylureas and thioureas. Crystallization was invariably done from aqueous ethanol. Yields 65-75%.

To a solution of 2(3-aminopropyl)isoindoline in petroleum ether in cold was added gradually while stirring phenyl isocyanate (1: 1.2 moles) in petroleum ether. After standing for two hours, the product was filtered, washed with petroleum ether and crystallized from aqueous ethanol. Yield 73% m.p. 105-106°C. (Found: N, 14.13. \( \text{C}_{18}\text{H}_{21}\text{N}_{3} \) requires N, 14.23%).

**N-\( \gamma \)-(2-Isocindolinyl)propyl-N'-phenylthiourea**

M.p. 169°C. (Found: N, 13.22. \( \text{C}_{18}\text{H}_{21}\text{N}_{3}\text{S} \) requires N, 13.50%).
\textbf{N-n-Butyl-N'-\(\text{-}\)-(2-isooindoliny1)propylthiourea}

M.p. 91°C, (Found: N, 14.32. \(\text{C}_{16}\text{H}_{25}\text{N}_{3}\text{S}\) requires N, 14.43%).

\textbf{N-Allyl-N'-\(\text{-}\)-(2-isooindoliny1)propylthiourea}

M.p. 97°C. (Found: N, 15.50. \(\text{C}_{15}\text{H}_{21}\text{N}_{3}\text{S}\) requires N, 15.28%).

\textbf{N-\(\text{-}\)-(2-Isooindoliny1)propyl-N'-p-nitrophenylurea}

M.p. 136-37°C. (Found: N, 16.64. \(\text{C}_{18}\text{H}_{20}\text{N}_{4}\text{O}_{3}\) requires N, 16.47%).

\textbf{N-p-Aminophenyl-N'-\(\text{-}\)-(2-isooindoliny1)propylurea}

The corresponding nitro-derivative (5 g.) was reduced over Raney Nickel in tetrahydrofuran solution under initial pressure of 30 lbs. of hydrogen. After the absorption of the theoretical quantity of hydrogen the catalyst was filtered and the filtrate on removal gave a residue which was taken into aqueous alcohol. On keeping overnight in cold, a solid precipitated from the alcoholic solution. This was charcoalied and crystallized from acetone-petrol. Yield 80%; m.p. 126-28°C. (Found: N, 17.92. \(\text{C}_{18}\text{H}_{22}\text{N}_{4}\text{O}\) requires N, 18.06%).

\textbf{Ethyl N-\(\text{-}\)-(2-isooindoliny1)propyl carbonate hydrochloride}

To a boiling solution of 2-(3-aminopropyl)
isoindoline (1.76 g.; 0.01 mole) in acetone was added gradually with stirring ethyl chloroformate (1.62 g.; 0.015 mole) in presence of potassium carbonate (0.1 mole) and the mixture refluxed for 18 hours. The solvent was removed and the residue in ether was dried and hydrogen chloride gas passed in the ethereal solution, yielding the hydrochloride. It was finally crystallized from isopropanol-ether mixture. Yield: 45%; m.p. 122-23°C. (Found: N, 9.57, C_{14}H_{21}Cl N_{2}O_{2} requires N, 9.84%).

N-\(\gamma\)-(2-Isoindoliny1)propyl-N'-p-methoxyphenylurea

A mixture of the above (2.84 g.; 0.01 mole) and p-anisidine (2.48 g.; 0.02 mole) in presence of few drops of pyridine was heated at 120°C for 5 hours. The excess of the amine was then removed under vacuum and the residue crystallized from aqueous alcohol. Yield, 63% m.p. 133-34°C (Found: N, 13.00, C_{19}H_{23}N_{3}O_{2} requires N, 12.92%).

2-(2-Hydroxyethyl)isoindoline

A solution of N-(2-hydroxyethyl)phthalimide in tetrahydrofuran was slowly added to a previously cooled slurry of lithium aluminum hydride in anhydrous ether. After the addition was completed, the cold reaction mixture was decomposed with absolute alcohol. Water was then added until the aluminum oxide was completely precipitated. The resulting suspension was filtered and the clear filtrate
dried over anhydrous sodium sulfate. After the removal of
the ether, the residue was distilled. It boiled at 167-169°C/
15 mm. The distillate weighed 4.6 g. (60%).

von Braun and co-workers prepared 2-(2-
hydroxyethyl)isoindoline by the reaction of ethylene
oxide on isoindoline. They reported the isolation of an
oil boiling at 162-164°C/12 mm.

2-Isoindolinylethyl p-nitrobenzoate

To a stirred solution of 6.5 g. (0.04 mole) of
2-(2-hydroxyethyl)isoindoline in 50 ml. of dry benzene was
added, dropwise, a solution of 7.5 g. (0.04 mole) of
p-nitrobenzoyl chloride in 25 ml. of dry benzene. The reaction
mixture was refluxed for 2 hours and the solvent removed. The
remaining oil was neutralized with 10% sodium hydroxide and
then extracted with benzene. After evaporation of the solvent,
9.3 g. (75%) of yellow crystals was obtained. These were
recrystallized from an alcohol-water mixture. (Found: C, 65.18;
H, 4.96; N, 8.78; \( \text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4 \) requires C, 65.37; H, 5.16;
N, 8.97%)

2-Isoindolinylethyl p-Aminobenzoate Hydrobromide

The reduction of 2-isoindolinylethyl p-nitro-
benzoate to 2-isoindolinylethyl 4-aminobenzoate was carried
out by shaking a solution of 3.0 g. (0.009 mole) of the nitro
compound in 75 ml. of ether with 0.3 g. of Raney nickel
catalyst at 15 pounds of hydrogen pressure. When the theoretical quantity of hydrogen had been absorbed, the hydrogenation was discontinued and the catalyst removed by filtration. The filtrate was treated with anhydrous hydrogen bromide. The precipitated hydrobromide salt was filtered and recrystallized from absolute alcohol by precipitation with anhydrous ether. The pure compound weighed 1.2 g. (42%) and melted at 239-240°C. (Found: C, 56.00; H, 5.26; N, 7.80. \( \text{C}_{17}\text{H}_{19}\text{BrN}_2\text{O}_2 \) requires C, 56.21; H, 5.26; N, 7.70%).

2-(2-Chloroethyl)isoindoline Hydrochloride

To 8.6 g. (0.53 mole) of 2-(2-hydroxyethyl) isoindoline dissolved in 20 ml. of chloroform was added slowly a solution of 8 ml. of thionyl chloride in 15 ml of chloroform. The reaction mixture, after being refluxed for approximately 15 minutes, crystallized. After cooling in ice, the reaction mixture was filtered and the resulting crystalline solid washed with chloroform and then with ether. After recrystallization from absolute alcohol by the addition of a few drops of anhydrous ether, an yield of 10.6 g. (91%) of a white crystalline solid was obtained. It melted at 191-192°C. (Found: C, 55.21; H, 5.87; Cl, 32.43. \( \text{C}_{10}\text{H}_{13}\text{Cl}_2\text{N} \) requires C, 55.06; H, 6.00; Cl, 32.51%).

This compound has been previously reported by Gump, et al. Its preparation and physical constants were
Silver mandelate was prepared by neutralizing 10.0 g. of dl-mandelic acid with dilute ammonium hydroxide and adding a 10% solution of silver nitrate until the precipitation of the silver salt was complete. The silver mandelate was removed by filtration, washed with water, alcohol, and finally ether.

A mixture of 4.2 g. (0.016 mole) of silver mandelate, 3.5 g. (0.20 mole) of 2-(2-chloroethyl) isoindoline hydrochloride, and 20 ml. of dry benzene was refluxed for 8 hours. During this time the solution was protected from light. The resulting silver chloride was removed by filtration. Ether was added to the filtrate to produce a gummy mass which solidified upon standing in the refrigerator overnight. The solvent was decanted and the residue dissolved in absolute alcohol. The hydrochloride precipitated upon the addition of anhydrous hydrogen chloride. After recrystallization from isopropyl alcohol, 3.0 g. (58%) of a white solid melting at 151-152°C was obtained. (Found: C, 64.27; H, 6.09; Cl, 10.28; N, 4.37; C_{18}H_{20}ClNO_3 requires C, 64.75; H, 6.00; Cl, 10.64; N, 4.20%).

2-Isoindolinylethyl Diphenylacetate Hydrochloride

To a stirred solution of 7.0 g. (0.043 mole) of
2-(2-hydroxyethyl) isoindoline in 25 ml of dry benzene was added slowly a solution of 10.0 g (0.043 mole) of diphenylacetyl chloride in 15 ml of dry benzene. The reaction mixture was refluxed on a steam bath for 2 hours. After removal of the solvent on a flash evaporator, the residue was recrystallized from isopropyl alcohol. The pure compound melted at 194-195°C and weighed 15 g (92%). (Found: C, 73.16; H, 6.21; Cl, 9.00; N, 3.70; C₂₄H₂₄ClNO₂ requires C, 73.18; H, 6.14; Cl, 9.02; N, 3.56%).

2-(2-Isocindolinyl)ethyl Benzhydryl Ether Hydrochloride

2-(2-Hydroxyethyl) isoindoline (8.0 g, 0.049 mole) was dissolved in 20 ml of dry benzene. To this solution was added 1.3 g (0.055 mole) of sodium cut in very small pieces. After the mixture was refluxed for 1 hour, a solution of 13.7 g (0.055 mole) of benzhydryl bromide was added and the resulting solution refluxed for 4 hours. The reaction mixture was filtered to remove the precipitated sodium bromide. After evaporation of the solvent in a flash evaporator, the residue was distilled. It boiled at 195°C/0.35 mm. The viscous reddish-brown distillate was dissolved in the least possible amount of benzene and the solution was allowed to stand overnight. A small amount of tetraphenylethane (m.p. 200°C) crystallized and was removed by filtration. An equal volume of ether was added to the filtrate and the resulting solution was saturated with anhydrous hydrogen
chloride. The hydrochloride precipitated and was removed by filtration. After recrystallization from absolute ethanol, 0.7 g. (38%) of a white solid melting at 204-204.5°C was obtained. (Found: C, 75.66; H, 6.72; Cl, 9.86. C_{23}H_{29}ClNO requires C, 75.51; H, 6.56; Cl, 9.71%).

1,6-Hexamethylenediphthalimide

To 10.0 g. (0.085 mole) of 1,6-hexamethylene-diamine in a round bottomed flask was added 25.5 g. (0.17 mole) of phthalic anhydride. After the vigorous reaction had subsided, the mixture was heated for 45 minutes at 100°C, after which the temperature was increased to 160°C for 10 minutes. The solid residue was treated with boiling 50% alcohol and the insoluble precipitate was removed by filtration. After recrystallization from tetrahydrofuran the crystals melted at 178-179°C. It weighed 30.0 g. (97%). (Found: C, 70.13; H, 5.31; N, 7.65. C_{22}H_{20}N_{2}O_{4} requires C, 70.21; H, 5.32; N, 7.44).

1,6-Bis-(2-isoindoliny1)hexane Dihydrochloride

A solution of 6.6 g. (0.018 mole) in 20 ml of tetrahydrofuran was added, dropwise, to a slurry of 4.0 g. of lithium aluminium hydride in 75 ml of anhydrous ether. The reaction mixture was refluxed for 15 minutes and then the reagent was decomposed by the addition of ethanol. Water
was carefully added to precipitate the alumina which was filtered. The clear filtrate was evaporated to dryness and the resulting solid dissolved in benzene and treated with an equivalent of an alcoholic solution of hydrogen chloride. The precipitated hydrochloride, after recrystallization from methanol, melted at 297-298°C. The crystals weighed 3.5 g. (50%). (Found: C, 66.85; H, 7.13; N, 6.81. \( \text{C}_{22}\text{H}_{30}\text{Cl}_{2}\text{N}_{2} \) requires C, 67.17; H, 7.63; N, 7.12%).

2-(2-Bis(2-chloroethyl)aminoethyl)isoindoline Dihydrochloride

To a 100 ml mixture of equal parts alcohol and benzene was added 7.5 g. (0.034 moles) of 2-(2-chloroethyl) isoindoline hydrochloride and 4.6 g. (0.034 mole) of diethanolamine. The resulting solution was refluxed for 4 hours, after which the solvents were removed on a flash evaporator. The residue dissolved in 10 ml of chloroform was added, dropwise, to a solution of 15 ml of thionyl chloride in 15 ml of chloroform. When the addition was completed the mixture was heated under reflux for 20 minutes and then cooled in an ice bath until crystallization was complete. The solid reaction product after filtration and recrystallization from a mixture of equal parts acetone and alcohol weighed 11.0 g. (90%) and melted at 270°C (decompn.). (Found: C, 46.52; H, 6.26; Cl, 39.51; N, 7.85. \( \text{C}_{14}\text{H}_{22}\text{Cl}_{4}\text{N}_{2} \) requires C, 46.66; H, 6.12; Cl, 39.45; N, 7.78%).
N-(3-(2-Isoindolinyl)propyl)-beta-alanine Amide Dihydrochloride

A solution of 1.8 g. (0.01 mole) acrylamide in 20 ml. of absolute ethanol was slowly added to a stirred solution of 2.1 g. (0.02 mole) of 2-(3-aminopropyl)isoindoline in 10 ml. of absolute ethanol. The mixture was allowed to stand for 1 week. After removal of the solvent in a flash evaporator, the dark residue was washed with anhydrous ether and then dissolved in absolute alcohol. The hydrochloride was precipitated by the addition of anhydrous hydrogen chloride. The resulting precipitate was recrystallized from a mixture of equal parts of isopropanol and 95% alcohol. The recrystallization gave 2.7 g. (85%) of a white crystalline precipitate that melted at 173-174°C. (Found: C, 52.43; H, 6.97; Cl, 22.31; N, 12.98. C_{14}H_{23}Cl_{2}N_{3}O requires C, 52.50; H, 7.24; Cl, 22.14; N, 13.13%).

N-(3-(2-Isoindolinyl)propyl)-beta alanine Ethyl Ester

A solution of 5.7 g. (0.057 mole) of ethyl acrylate in 10 ml. of absolute alcohol was added dropwise, with stirring, to a cooled solution of 10.0 g. (0.057 mole) of 2-(3-aminopropyl) isoindoline in 20 ml. of absolute alcohol. The mixture was allowed to stand at room temperature for 4 days, at which time the solvent was removed on a steam bath under vacuum. The residue distilled and a fraction weighing 14.2 g. (90%) and distilling at 156-158°C/0.6 mm. was collected. (Found: C, 69.28;
H, 8.52; N, 10.11, C₁₆H₂₄N₂O₂ requires C, 69.53; H, 8.75; N, 10.15%.

l-(3-(2-Isindoliny1)propyl)dihydouracil

To a stirred solution of 8.8 g. (0.032 mole) of N-(3-(2-isindoliny1)propyl)-beta-alanine ethyl ester in a mixture of 3 ml. of hydrochloric acid and 10 ml. of water was added, dropwise, a solution of 3.4 g. (0.042 mole) of potassium cyanate in 10 ml. of water. The resulting solution was stirred for 1 hour and then allowed to stand overnight at room temperature. During this time a second layer formed. The upper layer was separated and treated with sufficient alcohol to precipitate the potassium cyanate present completely. After filtration of the solid, the filtrate was evaporated to dryness. A solid remained which, after recrystallization from absolute alcohol, gave 2.2 g. (25%) of a white crystalline solid melting at 184-185°C. (Found: C, 65.63; H, 7.29; N, 15.38, C₁₅H₁₉N₃O₂ requires C, 65.91; H, 7.00; N, 15.38%).

N-Phenyl-3-nitrophthalimide

To 3-nitrophthalic anhydride \(^{43}\) (66.0 g, 0.45 mole) was added, dropwise, 42.0 g. (0.45 mole) of redistilled aniline. After the addition was completed and the reaction had subsided, the reaction mixture was heated at 210°C for 20 minutes. The resulting orange liquid solidified on cooling
and was recrystallized from a mixture of equal parts of acetone and ethanol. It yielded a yellow crystalline solid which melted at 136-138°C. The yield was 107.0 g. (82%). (Found: C, 62.43; H, 2.89; N, 10.32; C_{14}H_{8}N_{2}O_{4} requires C, 62.68; H, 3.01; N, 10.52%).

**N-Phenyl-3-aminophthalimide**

N-Phenyl-3-nitrophthalimide (10.0 g, 0.037 mole) dissolved in 100 ml of equal parts tetrahydrofuran and ethanol, was reduced over Raney nickel catalyst in a Parr hydrogenator at 30 pounds of hydrogen pressure. After approximately 8 hours of shaking, the theoretical quantity of hydrogen had been absorbed. The solvent was then removed on a flash evaporator and the solid residue was recrystallized from benzene to yield 7.5 g. (85%) of a white crystalline solid. It melted at 185-187°C. (Found: C, 70.63; H, 4.02; N, 11.88; C_{14}H_{10}N_{2}O_{2} requires C, 70.58; H, 4.23; N, 11.76%).

**2-Phenyl-4-aminoisoindoline**

A solution of 13.0 g. (0.054 mole) of N-phenyl-3-aminophthalimide in 100 ml of tetrahydrofuran was added, dropwise, to a suspension of 6.2 g. of lithium aluminium hydride in 75 ml of tetrahydrofuran. The addition required 45 minutes. The reaction mixture was then refluxed for an additional 10 minutes, cooled in an ice bath, and the excess lithium aluminium hydride decomposed with absolute alcohol.
The alumina was precipitated by the careful addition of water and the reaction mixture was filtered. The filtrate was dried over anhydrous sodium sulfate. After removal of the solvent, a greenish solid remained. After recrystallization from ethanol it weighed 10.0 g. (87%) and melted at 123-124°C. (Found: C, 79.72; H, 6.83; N, 13.55, C\textsubscript{14}H\textsubscript{14}N\textsubscript{2} requires C, 79.96; H, 6.71; N, 13.33%).

\[
N^1-(4-(2-Phenylisoindolynyl))-N^4-acetylsulfanilamide
\]

To a refluxing solution of 2.1 g. (0.010 mole) of 2-phenyl-4-aminooisoindoline and 0.8 g. (0.010 mole) of pyridine in 30 ml. of benzene was added, dropwise, a solution of 2.6 g. (0.011 mole) of 4-acetamidobenzensulfonyl chloride in 20 ml. of equal parts benzene and acetone. After the addition was completed, the resulting solution was refluxed for 10 minutes. Upon cooling, an oil settled to the bottom of the flask. The supernatant liquid was decanted and the oil was washed with ether and finally with cold water. Upon standing it solidified and was recrystallized from 50% isopropanol to give 3.3 g. (81%) of a white crystalline solid. The solid melted at 230-231°C. (Found: C, 64.78; H, 5.55; N, 10.41; S, 7.51, C\textsubscript{22}H\textsubscript{21}N\textsubscript{3}O\textsubscript{3}S requires C, 64.84, H, 5.19; N, 10.31; S, 7.86%).

\[
N^1-(4-2-Phenylisoindolynyl)sulfanilamide
\]

\[
N^1-(4-(2-Phenylisoindolynyl))-N^4-acetylsulfanilamide
\]
(2.8 g, 0.007 mole) was refluxed for 1 hour with a solution of 2 ml. of hydrochloric acid in 4 ml. of water. The reaction mixture was then neutralized with sodium carbonate and the precipitated product collected on a Buchner funnel. After recrystallization from isopropanol to which a few drops of acetone was added, 1.8 g. (69%) of a white crystalline solid was obtained. It melted at 234-236°C. (Found: C, 65.50; H, 5.51; N, 11.22; S, 8.68. \( \text{C}_{20}\text{H}_{19}\text{N}_{3}\text{O}_2\text{S} \) requires C, 65.73; H, 5.25, N, 11.49; S, 8.77%).

2-Methylisoindoline

2-Methylisoindoline was prepared by the lithium aluminum hydride reduction of N-methylphthalimide, following the procedure employed for the preparation of 2-(2-hydroxy-ethyl) isoindoline. It distilled at 85-86°C/15 mm. (lit. 44 b.p. 81-82°C/13 mm.)

2-Ethylisoindoline

The compound was prepared by the lithium aluminum hydride reduction of N-acetylphthalimide, following the procedure of Rabjohn, Drumm, and Elliott. A fraction distilling at 217-220°C was collected (lit. 45 b.p. 219-220°C).

2-Phenylisoindoline

N-Phenylphthalimide was reduced with lithium aluminum
hydride as described by Wittig, Closs and Mindermann. It melted at 168-169°C (lit. 46 b.p. 169-170°C).

Ω-Tolunitrile was prepared according to the methods described in the Organic Synthesis Collective Vol. I, pp 514. It distilled at 94-96°C/20 mm.

Ω-Xylylamine was prepared by LAH (1.2 moles) reduction of Ω-tolunitrile (1 mole) in ether. The fraction distilling at 125°C/105 mm was collected.

N-Chlorosuccinimide was prepared according to Tscherniac.

N-Chloro-Ω-Xylylamine was prepared by following the method of Rushig et al 47, by reacting the amine in methylene chloride solution with N-chlorosuccinimide. The N-chloro-derivative gave a positive test with 5% KI in 5% aqueous acetone.

**Hofmann-Loffler Reaction**

A well-stirred solution of N-chloro-Ω-Xylylamine (5 g) in redistilled trifluoroacetic acid (20 g) was exposed to u-v-lamp in the nitrogen atmosphere at 20°C. After 20 minutes a test portion of the reaction mixture gave a negative test with KI reagent. On removal of the solvent, the residue was refluxed with 4 molar equivalents of KOH in methanol for one hour, concentrated under vacuum, poured on ice and extracted with methylene chloride. The solvent was removed and the residue was tosylated in the usual way, giving the product melting at 110-112°C.
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CHAPTER V

Biological Activity

(Structure-Activity Relationship)
Some selected compounds of each series were screened in the Division of Experimental Medicine of this Institute for their effect on blood sugar at a dose level of 250 mg/kg body weight by administering orally in male Albino rats of C.D.R.I., Colony. In cases where the results were encouraging, the drugs were repeated at 100 and 50 mg/kg body weight as well. Prior to testing, the rats weighing 100-125 g. were starved for 18-24 hours. The blood was taken from the tail and the sugar estimated using Nelson-Somogyi method at 2 and 4 hours interval. Carbutamide was chosen as a reference standard for direct comparison.

**Imidazolidinones and pyrimidine**

From the results of the present study it is obvious that the effect on blood sugar in these imidazolidinones and tetrahydropyrimidones is markedly influenced by the nature of the substituents as well as the size of the ring. The effect of changes at R, R', X (\(^{>}C = 0\) or \(^{>CH_2}\)) and n (1 or 2) is discussed under the following heads:
(a) Structure of the group $R$

![Chemical structure](image)

A number of compounds, where $R = \text{H}^-, \text{CH}_3^-, \text{CH}_3\text{CH}_2\text{CH}_2^-, \text{Cl}^-, \text{F}^-$ and $\text{CH}_3\text{O}^-$, have been studied. The methyl group seems to confer the most favourable hypoglycemic activity; the unsubstituted and the chloro compounds are either inactive or very slightly active, while the methoxy does not bring about any change. $\text{F}$-substitution, on the other hand, evokes hyperglycemia.

(b) Structure of group $R'$

Out of a wide variety of groups as $R'$ ($\text{H}$, ethyl-$\text{n}$-propyl-, iso-propyl-, allyl-, $\text{n}$-butyl-, cyclohexyl-, phenyl-, benzyl-, phenethy1- and substituted carbamoyl-) the allyl group seems to be the most active one for lowering the blood sugar. Lengthening or branching of the chain reduces the activity. Aryl and arylalkyl also reduce the activity. Introduction of a urea moiety at $R'$ also does not increase the activity. When $R' = \text{H}$, the effect, on the other hand, is markedly hyperglycemic.
(c) **Effect of n** (Size of the ring)

The size of the ring also seems to play a significant role in relation to structure and activity in the present series. Bearing the same substituents as in imidazolidinone for maximum activity, the expansion of the ring (tetrahydropyrimidone) brings about hyperglycemia.

(d) **Effect of X**

Another variation in the ring, where $n = 2, X = \gamma C = 0$ (dihydouracil) brings about a fall in the hypoglycemic activity and a tendency to hyperglycemia is observed.

From the above study it may be noted that 1-arylsulfonyl-3-alkyl- and 3-aryalkyl-2-imidazolidinones in general show hypoglycemic action. Amongst the substituents in the benzene ring, the 4-methyl group seems to confer the maximum hypoglycemic activity, while of the groups at 3-position, the allyl has the most favourable effect. Of the compounds tested, 1-(p-methylbenzene- and p-chlorobenzene-) sulfonyl-3-allyl-2-imidazolidinones showed the maximum hypoglycemic activity. The corresponding 3-unsubstituted compounds and also the 3-carbamoyl compounds, on the other hand, exhibited hyperglycemic activity. Any alteration in the size or nature of the ring alters the activity.
The results have been summarised in Table I.

**Tosylamino acid amides**

\[
\text{RSO}_2\text{NHCH} \left( \text{CH}_2 \right)_n \text{CNHR}
\]

None of the tosylamino acid amides or \(N(\beta\text{-arylsulfonamido})\text{ethyl-\(N\text{-alkyl-\(N\text{-phenyl ureas}}\)) tested showed any hypoglycemic activity.

The results have been summarised in Table II.

**Barbituric acids**

1-Aryl barbituric acids in general show hypoglycemic activity under present investigation. The activity reaches its maximum when \(R = o\text{-CH}_3\) and minimum when \(R = p\text{-CH}_3\) or \(o\text{-Cl}\), whereas an aryl group bearing no substitution moderates the activity.

The results have been summarised in Table III.

**Thia diazoles**
In 1,2,4-thiadiazole series, various substituents at 5-position, such as phenyl-, ureido-, substituted aroyl amide and aryl sulfonamides have been studied. Among them, only phenyl substituent was found to confer activity to the parent nucleus. In view of this a number of 5-phenyl-3-substituted thiadiazoles were prepared where the 3-substituent was an alkyl, aryl, arylalkyl or a heterocyclic system or a urea moiety. In general a ureido function at 3-position leads to the active compounds.

Among the sulfonyleurea type of compounds, where \( R' = \text{arylsulfonyl-} \), the only compound having some hypoglycemic activity was \( \text{N-p-toluenesulfonyl-N'-(5'-phenyl 1',2',4'-thiadiazol-3'-yl) urea} \), while those where \( R' = \text{phenylsulfonyl-} \), mono- or doubly substituted chloro benzenesulfonyl- and p-acetamidobenzenesulfonyl groups, are either inactive or very slightly active.

In the series of simple ureas an alkyl or arylalkyl group as \( R' \) usually leads to inactive compounds, while a phenyl group confers a moderate type of activity to the molecule. In order to see the effect on activity of various substituents at the phenyl nucleus, a number of electron accepting or donating groups have been examined and it was found that none of the substituents influence the blood sugar as much as the unsubstituted phenyl group itself.
Interestingly enough, a substituent (R') carrying a basic nitrogen atom either in cyclic or acyclic system generally gives rise to effective compounds. The maximum fall in blood sugar noted among such heterocyclic systems was in the compounds where R' = 2-pyridyl group. Other isomers of pyridine, substituted or unsubstituted, are moderately active. Significant activity was similarly noted in the compound where R' = diethylaminopropyl group.

The results have been summarised in Table IV.

**Pyridylethylureas**

![Pyridylethylureas structure]

In the series of pyridylethylureas no correlation could be established between structure and activity of the compounds under present study as the members so far evaluated exhibit activity of low order only. It was, however, noted that 2-isomers are more effective than the 4-isomers and an alkyl rest favours the hypoglycemic activity in comparison to the corresponding aryl rest. The corresponding thioureas exhibit hyperglycemic effects.

The results have been summarised in Table V.
Isoindolylureas and thioureas

Almost all of the isoindolylureas and thioureas so far studied are devoid of any hypoglycemic activity. The results have been summarised in Table VI.

Indolylureas

Usually these derivatives have been found to exhibit hypoglycemia. Marked effects have been observed in case of tryptophane and tryptamine derivatives. The results have been summarised in Table VII.
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<th>Dose (mg/kg)</th>
<th>Blood sugar in mg/100cc blood</th>
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<th>R'</th>
<th>Fasting</th>
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[↓] FALL IN BLOOD SUGAR
Summary and Conclusion
The correlation of biological activity with chemical constitution in any series of chemotherapeutic agents is made difficult by a number of factors such as solubility, absorption from the host alimentary tract or site of injection, rate and mode of excretion, metabolism and so on. These difficulties are all encountered in the assessment of oral hypoglycemic agents.

Apart from the factors mentioned above, diabetes is not one disease; it is the summation of factors arising out of the faulty metabolism of glucose in an organic system, and is brought about by one or more of such diverse conditions as faulty function of $\beta$- and (or)$\alpha$-cells of the islets of Langerhans, of liver and perhaps more distantly of the adrenal medulla and cortex, the anterior lobe of pituitary or even the thyroid.

The various antidiabetic compounds and insulin have one thing in common; they reduce the blood sugar level. The compounds do not resemble insulin either in structure or in metabolic activity, they are neither as effective nor as safe as insulin clinically. But with their help it may be possible to study in greater details various aspects of the disorders associated with diabetes and eventually to define
the mode of action of insulin itself.

Attempt has, therefore, been made in a limited sense to study the structure-activity relationship in each of the following series of compounds on purely empirical basis.

The present findings are in excellent agreement with our original hypothesis that one or more of urea sulfonylurea or guanidino moieties is essential for conferring hypoglycemic activity to a molecule. This was found true in cases where such moieties are present in open chain structures such as urea and sulfonylurea derivatives incorporating indole, tryptamine or tryptophane as one of the supports. In the case of thiadiazoles, imidazolidinones and barbituric acids, such moieties exist as part of the ring systems. Further confirmation was obtained by the inability of tosylamino acid amides to exhibit any hypoglycemic effect. In these compounds the urea moiety has been interrupted by the introduction of one or more methylene residues which clearly indicates that an unaltered \( \text{N-C-N} \) residue is in some way, associated with hypoglycemic activity.

In the 5-phenyl-1,2,4-thiadiazoles carrying substituted ureido function at 3-position, it was found that those having a basic nitrogen atom either in the cyclic or open chain system (S. Nos. 44, 48) generally gave rise to more active compounds. The maximum fall in
blood sugar, nearly of the order of carbutamide, was noticed where the substituents were the 2-pyridyl ring and $\gamma$-diethylaminopropyl residue as in $N$-(2-pyridyl), $N'^{-}(5'$-phenyl, 1',2',4'-thiadiazol-3'-yl) urea, and $N$-($\gamma$-diethylamino propyl-)$N'^{-}(5'$-phenyl, 1',2',4'-thiadiazol-3'-yl), urea respectively.

1-Arylsulfonyl-3-alkyl- and 3-arylalkyl 2-imidazolidinones in general show hypoglycemic action. A combination of $p$-tolyl at one end and an allyl substituent at 3-position of the imidazolidinone seems to confer the maximum hypoglycemic activity. Thus 1-$p$-tolylsulfonyl-3-allyl-2-imidazolidinone is almost as active as carbutamide. The 3-position when devoid of any substituent gives rise to compounds of marked hyperglycemic nature, as 1-$p$-tolylsulfonyl and 1-$p$-chlorobenzenesulfonyl-2-imidazolinones. The hypoglycemic activity has been observed to fluctuate between the two extremes when 1- and 3-positions bear different kinds of substitutions.

Amongst the barbiturates, owing to the small number of compounds studied it is not possible to draw any conclusions regarding structure-activity relationships. The point of interest was that 1-$O$-methoxyphenylbarbituric acid exhibited activity approaching that of carbutamide.

Encouraging results obtained in the series of indole derivatives stimulated the synthesis of a number of structurally related compounds, e.g. isoindoline derivatives,
in order to study their effect on blood sugar. These compounds, however, did not show any effect on blood sugar.

The product obtained by the condensation of 2-vinylpyridine and hydroxylamine was studied. It was shown to be a di-, rather than a mono- adduct as described in literature. Infrared and n.m.r. studies supported this view which was finally confirmed by synthesis of the compound.

The possibilities of tautomerism in 1,2,4-thiadiazoles of the type:

\[
\begin{align*}
\text{NH}_2 & \quad \text{CH}_3 \\
\text{N} & \quad \text{NH} \\
\text{O} & \quad \text{N} \quad \text{CH}_3
\end{align*}
\]

were studied with the aid of ultra-violet spectroscopy.

The carbon-hydrogen absorption bands present in the infra-red spectra of isoindoline ring systems were related to their chemical structure.

Finally, in the present state of knowledge, it is difficult to pin-point an attack on this complex syndrome condition and to build effective antidiabetic compounds on a specific rationale. The search for new types of antidiabetic compounds must, therefore, continue to progress by empiricism.
If speculation was permitted a suitably substituted urea moiety attached to a group which has generally non toxic but powerful antimycobacterial properties still remains the formula of choice for the synthesis of an ideal oral hypoglycemic agents.