PART-III

REVIEW OF LITERATURE
CHEMISTRY AND BIOLOGICAL ACTIVITY OF SUCCINIMIDES:

Succinimide, the 2,5-pyrrolidinedione and its derivatives had been known for their anti-epileptic activity, particularly against petitmal type of epilepsy. During the last five decades succinimides have been studied for their vast variety of biological activities. Succinimide molecule is a part of many active molecules possessing activities such as CNS depressant, analgesic, antitumour, cytotoxic, anorectic, nerve induction blocking, antispasmodic, bacteriostatic, muscle relaxant, and hypotensive. Miller et al., Davis et al., Clemson et al., have studied extensively the succinimide derivatives for their anticonvulsant activity. A study of the structure activity relationship of the active compounds showed that substitution at C5 position of succinimides was essential for antiepileptic activity. Close and Spielman and Spinks and Waring have stated that among the drugs used for the petittal epilepsy, imido-alkylation is mandatory.

Kornet et al., demonstrated the synthesis of succinimide derivatives in which the alkylating groups have been attached to the imide nitrogen or the third position of the ring. The alkylating groups used were α-halo acetyl, α-halo acetamido, maleiamyl, and maleimido and were prepared as potential long acting anticonvulsants. None of the compounds showed activity against maximal electroshock seizures (MES) and maximal metrazole seizures (MMS). The same authors have studied the effect of alkylating groups attached to the C-2 position of the ring or to the para position of the 2-phenyl substituent. Several number of these derivatives exhibited activity against maximal metrazole seizures as compared to the phensuximide.

Crider et al synthesized some (R, S), -2-amino-N-substituted succinimides (1) and evaluated them for anticonvulsant activity against maximal electroshock seizures and maximal metrazole seizures. The (R, S)-N-benzyl-2-(methane sulfamido)succinimide was the most active compound against both MES and MMS.
Komet synthesized N-amino succinimides (2) by the condensation of hydrazines with succinic anhydride in glacial acetic acid. The compounds were evaluated for MES and ScMet seizure threshold for anticonvulsant activity and rotarod test for neurotoxicity in mice. The lowest dose at which several of the compounds exhibited activity was 300mg/Kg.

Acetyl -D (R) and -L (S)-N-(Para substituted phenyl) succinimides (3, 4) were synthesized by Witiak et al and subjected to the neurotoxic doses (TD50), anticonvulsant potencies (MES and MMS), protective indices and effect of minimal seizure threshold were compared with similar values concomitantly determined for clinically useful anticonvulsants. Those analogs, which contained an acetamido group and chiral center α to one of the imide carbonyl groups exhibits stereo-selective biological activity. The magnitude of the activity difference between isomers was found to be a function of the substituent on the phenyl ring.
Owoyale et al. \textsuperscript{59} studied the effect of N-ethyl succinimido oxyacetate and N-methyl succinimido oxyacetate (5, 6) on electrically and chemically induced seizures in young chicks. The tested compounds yielded moderate results.

Goehring et al. \textsuperscript{60} synthesized some new 2-benzyl succinimides (7, 8) as potential anticonvulsants. Primary screening of these compounds indicated that succinimides containing lipophilic electron withdrawing substituents were most effective in controlling seizures induced by MES and ScMet. All the other compounds showed activity against ScMet-induced seizures equal to that of their 2-phenyl succinimide analogs and somewhat more effective in MES. In Quantitative testing, when administered intraperitoneally in mice, the compounds demonstrated anticonvulsant activity superior to that of ethosuximide by the MES and ScMet assays. However, they also exhibited greater neurotoxicity than ethosuximide in rotarod test.
Clemson et al. studied the effect of substitution in the C-2 position of Phensuximide (9, 10) against MES and pentylene tetrazole induced convulsions but none of them showed great deal of activity when compared with the activity of parent compound.

Edward et al. synthesized several manich bases of 2-phenyl succinimides (11-13) and screened for anticonvulsant activity. All the compounds were evaluated by MES and ScMet threshold tests. In the ScMet threshold test the displayed compounds exhibited an activity pattern equivalent to that of the standard compound Phensuximide and also provided full protection at a dose level of 300mg/Kg.

Das et al. synthesized different N-substituted derivatives of succinimides (14) using manich reaction and amidomethylation reaction. Anticonvulsant activity of these compounds was studied against MES and metrazole seizures. None of the compounds showed activity against Metrazole-induced seizures. Some of the effective N-substituted succinimides produced sedation, potentiated barbiturate hypnosis and inhibited forced locomotion.
Argay and Seres et al. reported the activity of 1-morpholino methyl-3-phenyl pyrrolidin-2, 5-dione as an effective anticonvulsant under the name perlepsyn (Hungarian patent No: 151425, 1962).

Taira et al. reported anti-fungal (fungicidal) activity of succinimide derivatives (15) and Malamas et al. (1994) observed the aldose reductase inhibition of succinimide derivatives.

Hadfield et al. synthesized succinimides (16), phthalimide and isatin derivatives with suitable elements of molecular recognition, as regarding biological activity, these derivatives mimicked the action of β-lactum antibiotics.

Grontas et al. studied the effect of succinimide derivatives (17) for their mechanism-based inhibition of human leukocyte elastase, Cathepsin-G and proteinase-3.
The study conducted by Andrej et al. in connection with the inhibition of 5-HT$_{1A}$ receptors resulted in the identification of several succinimide derivatives (18, 19) with interesting biological activity. The compounds I and II exhibited anxiolytic activity in some animal models.

![Compound 18](image)

**I** Postsynaptic 5HT$_{1A}$ receptor antagonist

![Compound 19](image)

**II** Full 5HT$_{1A}$ receptor antagonist

The research work carried out by Aquereque et al. on bioactivity-guided purification resulted in the isolation of four new antibiotics (20-23). Out of them two were succinimide derivatives and the other two were maleiamide derivatives. All the four isolated compounds exhibited marked anti-bacterial and anti-fungal activities.

![Compound 20](image)

(20)

![Compound 21](image)

(21)
Didier and Loret synthesized a triphenylene compound (24) that had the succinimide probe turned out to hit on Tat (HIV I) and discovered the Tat HIV I inhibiting activity. In this, the succinimide was connected to the triphenylene ring through an aliphatic chain of 5 carbon atoms

Khadikar and Bhayade synthesized a series of succinimide derivatives and evaluated for their hypotensive activity on cats and dogs. Among the derivatives 1-[3-(4-(2-methylphenyl)-1-piperazinyl)-2-hydroxypropyl]-2,5-pyrrolidinedione (25) showed potent activity
MANNICH REACTION, MANNICH BASES AND ITS BIOLOGICAL ACTIVITY

Mannich was the first to recognize the reaction as a general one and a detailed investigation was begun in 1917. According to the work carried out by the researchers, the mannich reaction consists of the condensation of ammonia or a primary amine or a secondary amine usually as the hydrochloride salt, an aldehyde, and a compound capable of supplying one or more active hydrogen atoms. This reaction is useful in adding one carbon atom in a reaction in making many drug molecules. A reaction between a compound containing reactive hydrogen atom, formaldehyde and a secondary amine became a general reaction by the name of Mannich. There are two types of mannich reaction, the C-type, involving the active hydrogen of carbon and N-type, involving the active hydrogen of nitrogen of organic compounds.

Mechanism of mannich reaction:

The steps involved in the reaction are: formation of imine salt and the electrophilic addition of this imine salt to the carbon or nitrogen containing active hydrogen atom.

Step-I

\[
\begin{align*}
\text{imine salt} & \quad \text{H}_2\text{C} = \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{O} \quad \text{CH}_2 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{O} \quad \text{CH}_2 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{O} \quad \text{CH}_2 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\end{align*}
\]
According to Hellmann and opitz, the course of condensation might be expected to follow one of the following sequences.\textsuperscript{69}

I) Reaction of the labile hydrogen compound with formaldehyde to yield the hydroxy methyl derivative which then condenses with amine to produce a mannich base.

II) Addition of amine to formaldehyde to form an N-hydroxy methyl or related derivative which then reacts with labile hydrogen compound to produce a mannich base.

In a series of comprehensive studies they proved that, N-hydroxy methylamine, N-methoxy methylamine and methylene diamine could be formed in the course of manich reaction, depending upon the conditions employed. Since highest yields were obtained when one of these materials was added to a mixture of excess of aqueous acid and the acidic or labile hydrogen compound, a method which gives the highest concentration of the amino methyl carbonium ion, it was concluded that this ion was the active aminomethylating agent.

The reverse order of the addition i.e., adding acid to a mixture of the reactants, does not offer favorable pH conditions until the addition is essentially complete. It was also found that a pH as low as 1.0 is successful in some cases if the proper order of addition is used. Owing to the opinion by these researchers manich reaction is an aminomethylation occurs under acidic conditions. They have got 62% yields using antipyrin, formaldehyde, piperidine and equimolar quantities of hydrogen chloride.
According to Stewart and Bradley\textsuperscript{[69] (c ref)} the maximum concentration of the amino methyl carbonium ion occurs on addition of N-hydroxy methylamine, N-alkoxy methylamine or methylene diamine to aqueous acid.

According to the work by Hellmann and opitz\textsuperscript{[69] (c ref)} with antipyrin mannich base with piperidine, N-hydroxy methylamine, when added to a solution of antipyrin and excess of acid (10\% excess, pH 2.5), gave a 71\% yield of mannich base, while the same ingredients gave only 56\% of mannich base along with methylene bis (4-antipyrin) when the acid was added to the mixture of antipyrin and N-hydroxy methyl piperidine mixture. Use of N-methoxy methyl piperidine gave, on addition to a mixture of antipyrin and excess of acid (6\% excess, pH 3.0) gave an 87\% yield of mannich base. When the acid was present to the extent of 40\% excess (pH 1.0) the reaction still gave a 77\% yield of mannich base. They also found that with similar conditions but reversing the order of addition completely inhibited the mannich reaction.

**Selection of conditions for mannich reaction:**

Formaldehyde for use in the mannich reaction may be provided by aqueous formalin, trioxymethylene or paraformaldehyde. Unfortunately selection of one of these forms is not as simple as it may appear.

Aqueous formalin (37-40\%) is a generally satisfactory source of formaldehyde for mannich reactions that form stable products and have very favorable equilibria positions. It must be remembered that the water present can both serve as a solvent and lead to reversal of mannich reaction in basic media. Aqueous formaldehyde may also be used for acidic media condensations, again providing some reversibility difficulties in certain cases.

Trioxymethylene (Trioxane) is a cyclic trimer of formaldehyde and it is a true acetal and can yield formaldehyde only in the presence of acid even in nonaqueous solvent systems. Studies have shown that trioxymethylene can provide formaldehyde in aqueous acid solution at a uniform
rate. The third form of formaldehyde is linear polymer called paraformaldehyde, more properly called polyoxymethylene and may exist in α, β, and γ paraformaldehyde.

Choice of solvent frequently is of greater importance. The common solvents for the manich reaction include water, acetic acid, ethanol, isoamyl alcohol, and toluene. The first four are possessed of varying degrees of polarity and thus faster the formation of ionic species to different degrees. Water, acetic acid, and isoamyl alcohol have more elevated boiling points than does ethanol, and their use therefore speed up an otherwise slow approach to equilibria. The higher temperature also can hasten the elimination of amine from the manich base product and thus complicate the process. Acetic acid as a medium can suppress the ionization of acidic compounds and thus alter its reactivity. Toluene on the other hand tends to act uniformly to suppress all ion formation.

**Biological activity of manich bases**

Mannich bases of different chemical classes of compounds have shown variety of biological activities such as anticonvulsant, antimalarial, antiviral, antifungal, antibacterial, analgesic and anti-inflammatory activities. Mannich bases derived from chalcones and related compound found to possess anticancer activity. The anticancer activity of manich bases is supposed to be due to formation of enones, which add to the cellular thiol containing groups
Some Mannich bases have been patented for anticancer and antifungal activity. 2-dimethyl aminomethyl benzosuberone methiodide displayed significant potency against murine p388 cells as well as wide range of human tumor cell lines. It displayed nearly 40 fold greater cytotoxicity towards leukemic cell lines compared to human tumor cell lines. The quaternary ammonium salts were more active than the corresponding tertiary bases.71

![Structure of 2-dimethyl aminomethyl benzosuberone methiodide](image)

In a study bis mannich bases of 1,2-cyclopentane dione have shown strong antitumor activity. Mannich bases of phenolic compounds have been evaluated against bacillus anthracis, Corynebacterium pyogenes and found to possess activity against these bacteria. Mannich bases of substituted thiazoles were synthesized and they were found to be highly active against gram-positive bacteria at 5\(\mu\)g/ml concentration. N-mannich bases of isatin showed antimicrobial activity against acid fast, gram-positive, and gram-negative bacteria, yeast and fungi.

Amodiaquine, a mannich base derivative is a clinically useful antimalarial drug and the amodiaquine analog showed comparable activity with chloroquine.

![Amodiaquine](image)
Mannich bases of 7-chloro quinolines were evaluated for antimalarial activity and one compound among them showed significant antimalarial activity.

\[ \text{HO} \cdot \text{N} / \]

Mannich bases of 2-(N-aryl aminomethyl)-5(E)-pentylidine cyclopentanone and their structural isomers displayed significant anti-inflammatory activity. Some man nich bases of N-methyl piperazine derivatives exhibited antidepressant activity along with muscle relaxant activity.

Mannich reactions have been used for the synthesis of various class of drugs which includes Fluoxetine, an antidepressant drug, benzoquinamide, an antipsychotic drug, Ranitidine, a H\textsubscript{2} receptor antagonist, Triprolidine, a H\textsubscript{1} receptor antagonist, Trihexyl phenidyl hydrochloride, an antispasmodic drug.

\[ \text{H}^3 \text{C} - \text{N} \quad \text{V} \]
\[ \text{NH} \]
\[ \text{'CH} \quad \text{CH}, \]
\[ \text{S} \quad \text{\^N} \quad \text{\^0} \]
\[ \text{Ranitidine} \quad (31) \]

(30)

(32)

(33)
Bhawsar et al.\textsuperscript{72} synthesized 8-[(6'-substituted-1',3'-benzothiazol-2'-yl) aminomethyl] substituted hydroxy coumarins (34) by the mannich reaction on substituted hydroxy coumarins with 2-amino benzothiazoles. Their antimicrobial activity has been screened against \textit{Alternaria brassicicola}, \textit{Fusarium udum}, \textit{Staphylococcus aureus} and \textit{E.coli}.

![Chemical structure of compound 34](image)

Gadre et al.\textsuperscript{73} synthesized various mannich bases of 4-[2-(furyl)vinyl]-7-hydroxy coumarins (35) have been synthesized by the mannich reaction of above compound with different amino acids, substituted phenyl piperazines and other secondary amines. These compounds have been tested for their antibacterial activity.

![Chemical structures of compounds 35 and 36](image)

Devki et al.\textsuperscript{74} have prepared mannich bases of from 7-hydroxy coumarins and tested for their antimicrobial activity. Pattanaik et al.\textsuperscript{75} have synthesized mannich bases of thiazolo benzimidazoles (36) with different secondary amines, phthalimide, morpholine, piperidine and quinazolin-4-ones. The compounds were evaluated for fungicidal activity against \textit{curvularia} species and the mannich bases of quinazolone are more active than other compounds.

Balakrishna et al.\textsuperscript{76} prepared Schiff bases by the condensation of 3-substituted-4-amino-5-mercapto-1, 2, 4,- triazoles with 5-nitro thiophen aldehyde were treated with \textit{n}-methyl piperazine.
and formaldehyde to give corresponding mannich bases (37) and screened for their antibacterial
and antifungal activities.

Sridhar et al. studied anticonvulsant activity of hydrazones, schiff and mannich bases of
isatin (38) by maximal electroshock (MES) and Metrazole induced convulsions (MET) at 30, 100,
and 300mg/kg dose levels. Neurotoxicity of the compounds was also assessed at the same dose
levels. Eight compounds of the series exhibited significant anticonvulsant activity at 30mg/kg.
The displayed compound was found to be the most potent compound of the series with 87%
protection at 100mg/kg and an ED50 of 53.61mg/kg. All the compounds exhibited lesser
neurotoxicity compared to Phenytoin.

Niharika et al. prepared several appropriately substituted 4-(dialkylaminoalkyl)-
substituted–stryl-alkyl ketones or acetophenones (39) and subjected to mannich reaction to yield
the compounds. Spermicidal activity of the compounds was evaluated. Several compounds
exhibited spermicidal activity at 0.005% and 01% concentration. A few compounds also inhibited
the interaction between recombinant HIV env and CD4.

R5 and R6 - piperidiny1, morpholinyl, 4-methyl piperazinyl.
Malinka et al\textsuperscript{79} reported 2H- 4, 6-dimethyl-2-[(4'-phenyl piperazin-1-yl)methyl]-3-oxo-2, 3-dihydro isothiazolo[5,4-b]pyridine (40) exhibited high anorectic action in animal models as a result of stimulation of serotonergic system.

\[
\begin{align*}
\text{(40)}
\end{align*}
\]

Sridhar et al\textsuperscript{80} synthesized Schiff bases and hydrazones of substituted isatins by reacting isatin (41) and aromatic primary amines/hydrazines. Anew series of the corresponding mannich bases were synthesized by reacting them with formaldehyde and diphenylamine. The compounds were screened for antibacterial activity against seven gram-negative and seven gram-positive pathological strains by the paper disc diffusion method. The minimum inhibitory concentrations of the active compounds were determined. Mannich bases exhibited greater activity than the corresponding schiff bases.

\[
\begin{align*}
\text{(41)}
\end{align*}
\]

Shivarama holla et al\textsuperscript{81} synthesized mannich bases of 3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurylidine] amino-5-mercapto-1,2,4-triazoles (42) and tested for their antibacterial, antifungal and herbicidal properties.
Incigul et al\textsuperscript{82} studied cytotoxic activity of mono and bis mannich bases derived from acetophenone (43) against Renca and Jurkat cells and found conversion of mono mannich bases to bis mannich bases remarkably increased the cytotoxicity in most cases.

\begin{center}
\includegraphics[width=0.2\textwidth]{image1.png}
\end{center}

(43)

Pandeya et al\textsuperscript{83} synthesized mannich bases of norfloxacin (44) by reacting them with formaldehyde and several isatin derivatives and investigated for in vitro antibacterial activity by agar dilution method against 28 pathogenic bacteria, eight pathogenic fungi and anti HIV activity against replication of HIV-I (III B) in MT4 cells.

\begin{center}
\includegraphics[width=0.2\textwidth]{image2.png}
\end{center}

(44)

Maria et al\textsuperscript{84} designed mannich bases obtained by aminoalkylation of $3H$-pyrrolo[3,2-f] quinoline (45) and prepared as potential vasorelaxing agents.
Pandeya et al\textsuperscript{85} synthesized manich bases of isatin derivatives with 3-amino-2-methyl mercaptoquinazolin-4 (3H)-one (46) and investigated antimicrobial activity by agar dilution method against 26 pathogenic bacteria, 8 pathogenic fungi and anti-HIV activity against replication of HIV-I (III B) in MT-4 cells.

Pandeya et al\textsuperscript{85} synthesized manich bases of isatin derivatives with N-[4-(4'-chlorophenyl)thiazol-2-yl] thiosemicarbazide (47) and evaluated antimicrobial activity by agar dilution method against 26 pathogenic bacteria, 8 pathogenic fungi and anti-HIV activity against replication of HIV-I (III B) in MT-4 cells.