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Review Article

A Review on Isatin and Its Biological Activities

Chaudhari Anwar[1*], Ugale Vinod Kumar[2], Dule Priya[1], Patil Kunal[1], Pawara Jayashri[1], Garkar Rushikesh[1], Jagtap Vaibhav kumar[1]

[1]NES's Gangamai College of Pharmacy, Nagaon, Dhule, (M.S.)

[2]R.C Patel Institute of Pharmaceutical education and research, Shirpur, Dhule (M.S.)

A B S T R A C T

Isatin, also (1H-indole-2,3-dione) is a natural molecular having a unique indole circle configuration. Erdmann and Laurent separated the phenomenon for the very first moment in 1841. Due to their numerous biological effects, this substance and its offspring have piqued researchers' interest. Isatin is widely recognized for its antibacterial, antiviral, anticonvulsant, anti-inflammatory, as and anti-cancer properties. The ability of this compound to react with an abundance of biological targets, including enzymes and receptors, makes it a useful scaffold for pharmacological design and development. Moreover, the isatin counterparts are under scrutiny regarding the potential use in creating of a heterocyclic a molecule, which are valuable in medicinal chemistry. The current study continues searching for new potential uses in forms of action for the isatin, highlighting its importance in the discipline of medicine and pharmaceutical synthesis.

Keyword: Isatin, Indol, Schiff's base, Mannich base, Analgesic, Anticonvulsant.

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*Address for Correspondence:
Anwar Chaudhari, NES's Gangamai College of Pharmacy, Nagaon, Dhule, (M.S.)

INTRODUCTION

A gland located in the Bufo frog is dedicated for isatin, which (1H-indole-2, 3-Dione), a chemical that exists naturally with an easily understood structure. Erdman and Laurent initially isolated it in 1841 as a byproduct of nitric and chromic acids oxidizing indigo.One of the rare substances that was synthesized prior to its discovery in nature is isatin[1][2].

The Isatis genus of plants, including the species Aubl, Melochia tomentosa, Boronellakoniamboensis, Couroupita guianensis, and Aubl. Plants can also include substituted isatins. For instance, melosatin alkaloids (methoxy phenyl pentylisatins) derived from the tumor-causing plant Melochiatomentosa in the Caribbean and fungi: Five (3'-methylbuten-2'-yl) isatin and six (3'-methylbuten-2'-yl) isatin were recovered from Chaetomiumglobosum and Streptomyces albus, respectively. Isatin has also been found to be a component of coal tar [3 – 10].

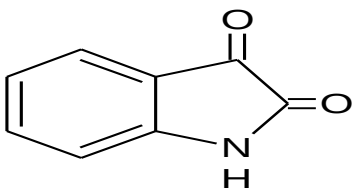


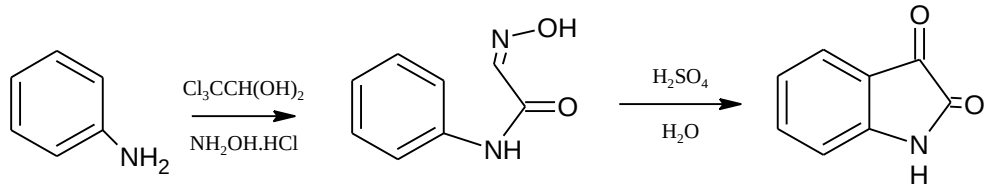
Figure 1: 1H-indole-2, 3-Dione

Isatin is an endogenous compound which is widely distributed in mammalian tissues and body fluids. Isatin readily crosses the blood–brain barrier, suggesting its possible action on the central nervous system (CNS) [11].

SYNTHESIS OF ISATIN

THE SANDMEYER METHODOLOGY

For isatin synthesis, Sandmeyer's method is the most well-known and widely applied. Isonitrosoacetanilide is created when aniline interacts with chloral hydrate 2 1 2 as well as hydroxylamine hydrochloride or aqueous sodium sulfate. Sulfuric acid treatment of this isonitrosoacetanilide is necessary in order to extract isatin with a rate of yield above seventy-five percent. 1. Numerous heterocyclic amines, like 2-aminophenoxathine, and anilines with substituents that may drain electrons, like 2-fluoroaniline, can be produced using this approach. [12] (Figure 2).



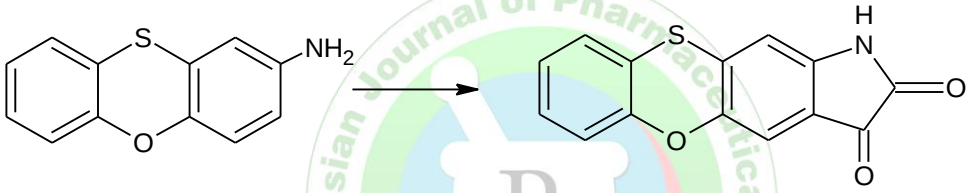


Figure 2: Sandmeyerisatin synthesis

USE OF NITROACETANALIDES

Nitroacetanilides also simply cyclized form isatin-3-oximes that ambient temperatures by concentrated sulfuric acid or trifluoromethane sulfonic acid; the latter provides higher yields. Nitroacetanilides are produced via alkaline hydrolysis of 1-arylamino-1-methylthio-2-nitroethenes.Despite having some similarities to the Sandmeyer methodology, this methodology is not clearly superior to it [13] (Figure 3).

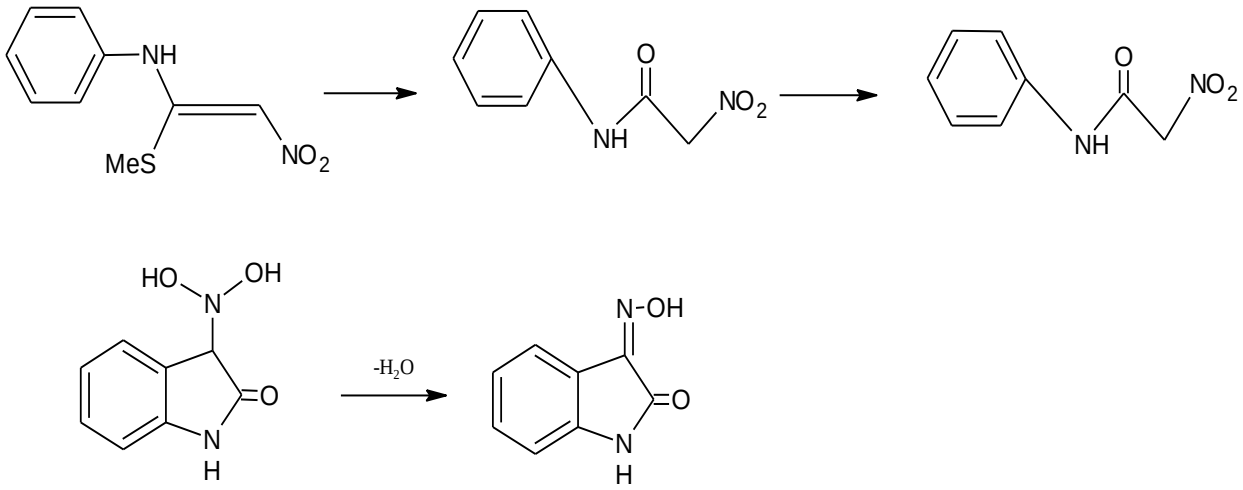


Figure 3: Isatin synthesis from nitroacetanilides

THE STOLLE PROCEDURE

This Stolle method is a basic equivalent for Sandmeyer's process. Using this method, anilines with oxalyl chloride come together to produce a substance called chlorooxalylanilide that can be cyclized in the presence of a Lewis acid, usually BF3 is or alumina chloride.Et2O,

while the equivalent isatin has also been obtained by using TiCl4. The synthesis of 1-aryl and polycyclic isatins from phenoxazine, phenothiazine, dibenzoazepine, and indoline has been accomplished using this technique.As demonstrated by the synthesis of melosatin, .

albeit in very low yield [14–16] (Figure 4), spontaneous cyclization has been observed to generate dimethoxyisatins in the case of dimethoxyanilines in the absence of a Lewis acid.

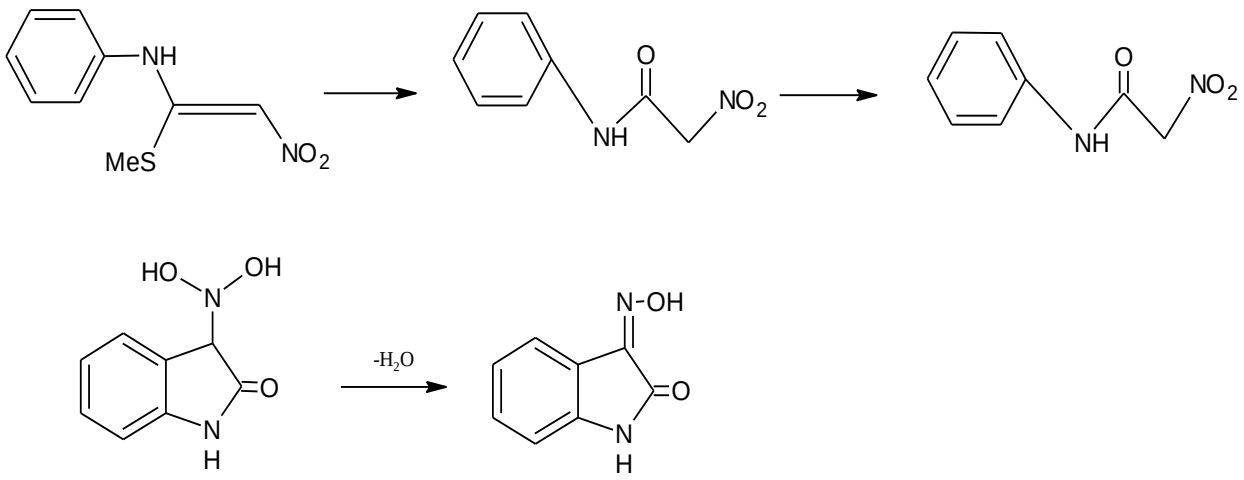


Figure 4: Stolle Isatin synthesis

THE MARTINET ISATIN SYNTHESIS

This Martinet method to stay the manufacture about indole-2,3-diones involves reacting a nitrogenous aromatic mixture using an oxomalonate the ester as well as the retain moisture in a solution of a base resulting in a 3-(3-hydroxy-2-oxindole)carboxylic acidic derivatives, and that is then oxidation decomposed into its equivalent isatin. This approach was used successfully to synthesize 5, 6-dimethoxyisatin with 4-aminoveratrole, despite the consumption of 1, 2, 4-dimethoxyaniline appeared more unsuccessful [17] (Figure 5).

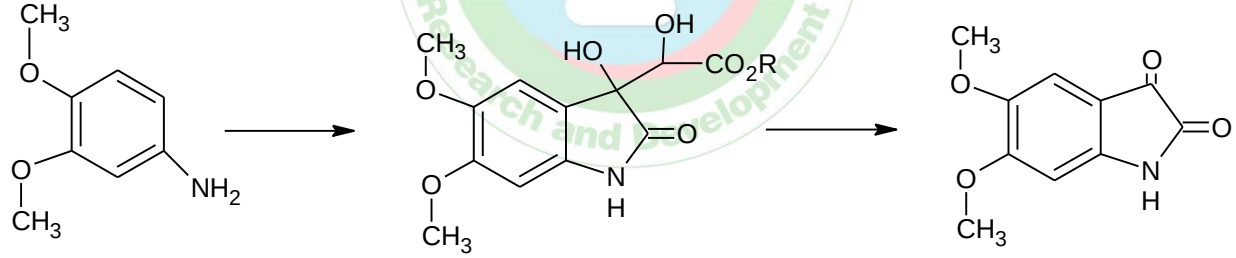


Figure 5: Martinet isatin synthesis

LITERATURE REVIEW

REACTION OF ISATIN

A large number of organic compounds can be synthesized from the isatin series of compounds because they are multifunctional compounds. Due to the presence of some reaction centers in isatin and its derivatives, different types of reactions can be carried out on these compounds. Consequently, keto groups at positions 2 and 3, particularly at positions 3, can be added at the C=O bond and condensed with the release of water. Isatin compounds exhibit the ability to undergo N-alkylation, N-acylation, N-methylene amino (mannich base), and N-sulfonylation through the NH group [18].

N-ALKYLATION

N-alkylated isatins can be prepared using a variety of techniques, including alkyl chlorides, bromides, and iodides, as well as reactive allyl-, benzyl-, and propargyl halides, which are capable of successfully producing them under basic events. Conventional heating at reflux temperatures between 40-100^{o}C is typically used to produce N-alkylated isatins. In general, the N-alkylation of isatin consists of reacting the isatin substrate with a range of bases, including Na_2CO_3, K_2CO_3, Cs_2CO_3, LiH, NaH, CaH_2, TEA, LiOH, NaOEt, and a solvent (DMF, DMA, MPT, MeCN, DMSO, NMP, EtOH, MeOH, Me_2CO). The usage of radiation from microwaves to speed up this process was initially described using K_2CO_3/DMF or NaOEt/EtOH in a standard microwave appliance [19-23] (Figure 6).

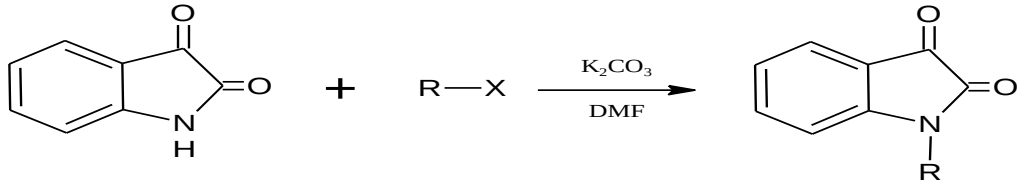


Figure 6: n-Alkylation

N-ARYLATION

The N-Arylisatin can be synthesized from isatin in quantitative yields either by reacting it with Ph3Bi (OAc) 2 and CuO under an inert atmosphere, or by using aryl bromides and cupric oxide [24].

MANNICH BASE REACTION

It is possible to apply the Mannich reaction readily to isatins. In addition to the N-aminomethylisatins (Mannich bases), these products can also be obtained by reacting with an amine or with acetyl chloride in order to produce N-chloromethylisatin, which can be further treated with potassium phthalimide or alcohol to produce N-phthalimidomethyl or N-alkoxymethylisatins. Isatin derivatives, such as isatin-3-hydrazones and isatin-3-thiosemicarbazones [25], may also be used in the Mannich reaction

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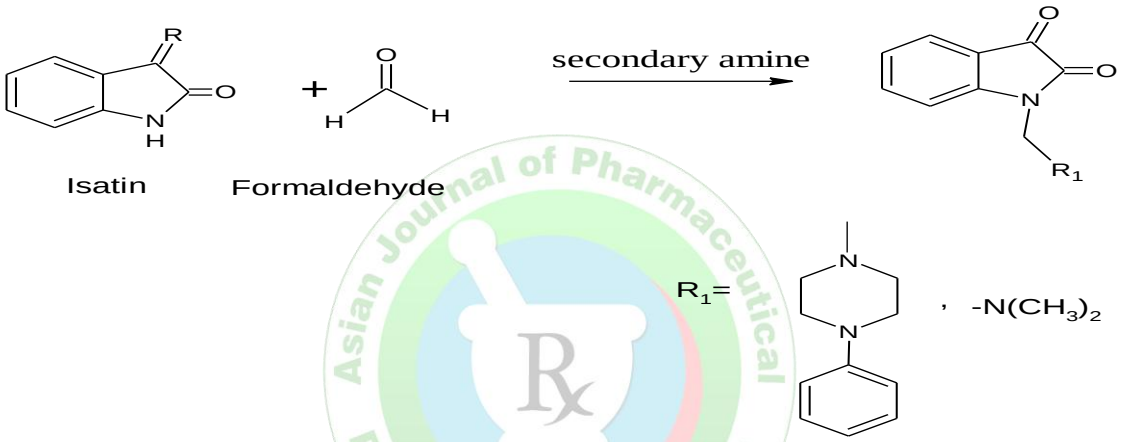


Figure 7: Mannich base reaction

N-ACYLATIONS

N-acylisatins have been synthesized under a variety of conditions using acyl chlorides or anhydrides under reflux using a number of methods. Alternatively, the reaction can be performed without additives or utilizing benzene with perchloric acid, benzene with triethylamine, benzene with pyridine, or chloroform with triethylamine as a catalyst; or by converting isatin to sodium isatide under reflux using NaH in toluene under reflux and subsequent reaction with acyl chlorides. Bisacylisatins can be produced by using acyl chlorides, such as oxalyoctanedioyl or nonanedioyl chlorides. Despite the fact that attempts were made to obtain 2,2-dimethylmalonyl-bis-isatin using 2,2-dimethylmalonyl chloride, the result was an unusual tricyclic compound which was characterized by spectroscopy and X-ray diffraction [26].

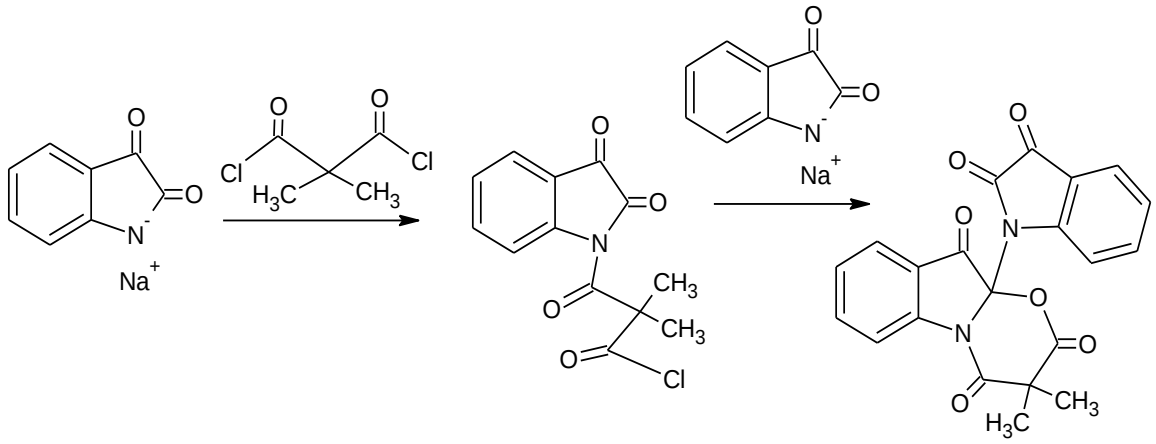


Figure 8: n-acylation

NUCLEOPHILIC ADDITION REACTION

Synthesis of Indoles

It was found that lithium aluminum hydride reduction in pyridine yielded indoles with moderate yields of indoles. This procedure was applied to the synthesis of substituted derivatives by using THF as a solvent under an inert atmosphere, giving greater yields (86-92%). A chemoelective alkylation of isatins at positions 1 or 3 can be achieved by reducing the compounds using metal hydrides [27]. (Figure 9)

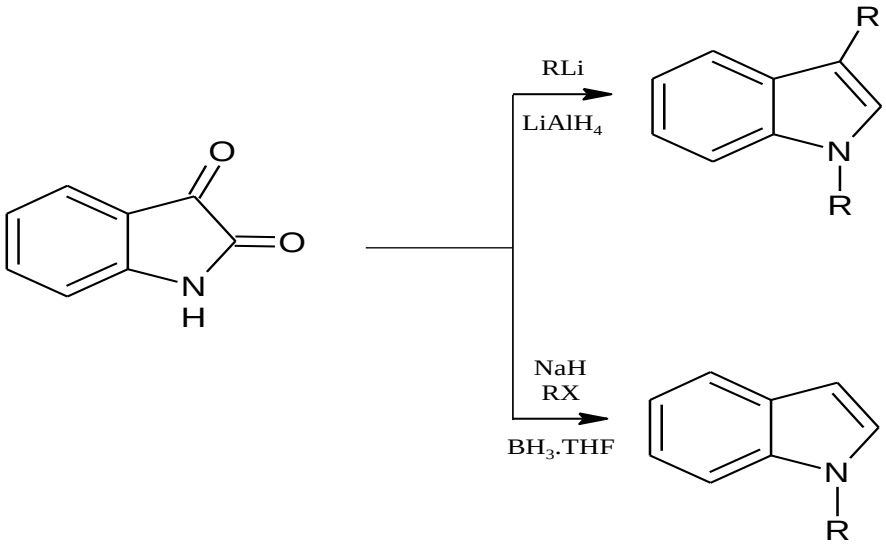


Figure 9: Synthesis of indoles from isatin

Oxidation of the heterocyclic ring

The oxidation of isatin using either hydrogen peroxideor chromic anhydride yields isatoic anhydride [28][29]. (Figure 10)

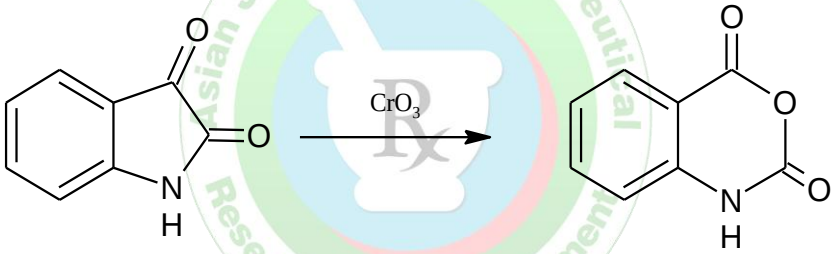


Figure 10: Oxidation of isatin

Nucleophilic attack at positions C-2 or C-3

Nucleophilic attacks on isatins and derivatives are possible at positions C-2 and/or C-3. Chemoselectivity in these reactions is determined by the nucleophile, by the substituents attached to the nucleus of the isatin compound, and especially those attached to the nitrogen atom. Furthermore, the solvent and temperature employed determine the chemoselectivity of these reactions. An additional nucleophilic group can react with the initial products obtained to produce cyclization products. The reactions have been sorted according to the nature of the nucleophile.

Amines and related compounds

Ammonia, hydroxylamine and hydrazine

Isatin works with ammonium hydroxide, or ammonium acetate and generates an assortment of chemical compounds. These consist of isamic ethanol and its amide bonding, isamide. Throughout 1877, they has been disagreement about their structures, which were at last settled in 1976. Isamic acid can be thought of as a dimer derived by the addition/condensation of one copy of amino and two corresponding forms of isatin. This intermediate is lactonized and then converted to isamic acid during an internal abundant assault, after whom the acid is transformed to isamide via another ammonia corresponding reaction. 1-Methylisatin reacts the same way generating N-methylisamichcl. [30]. (Figure 11).

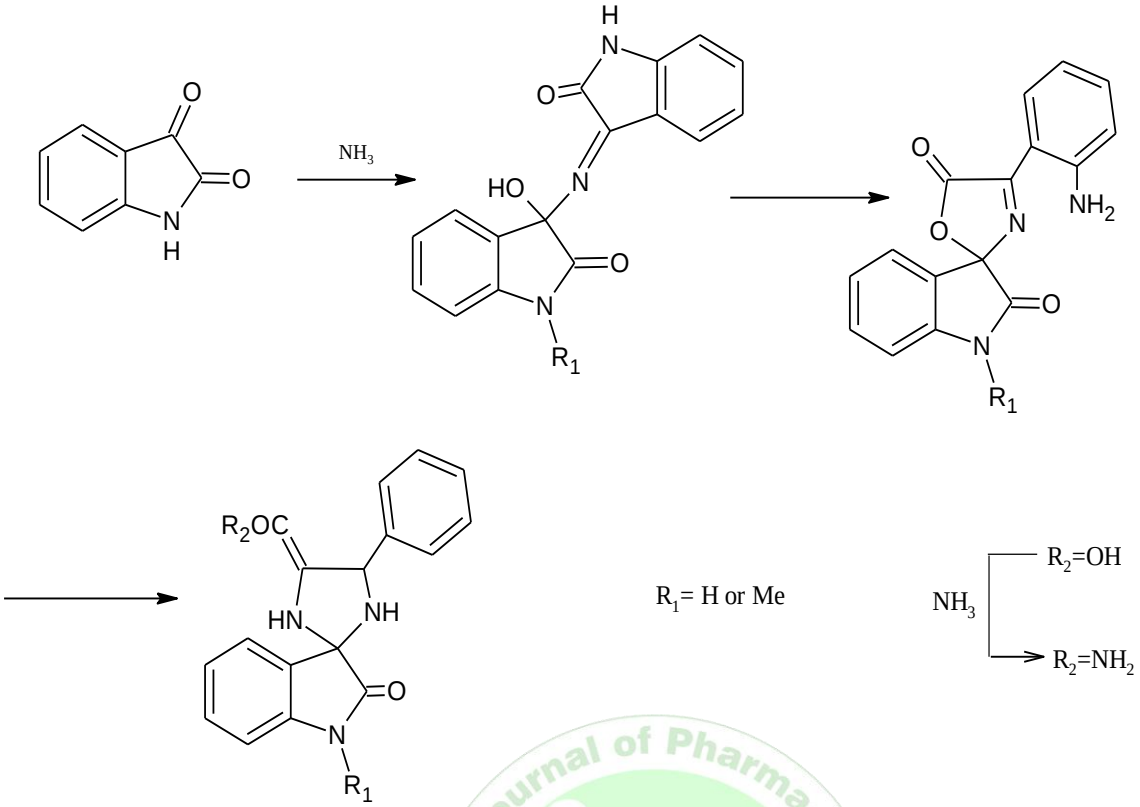


Figure 11: Nucleophilic attack at positions C-3

When 1-acetylisatin is reacted with hydroxylamine hydrochloride, it gives quinazoline-3-oxide through the cyclization of the intermediate hydroxamic acid.

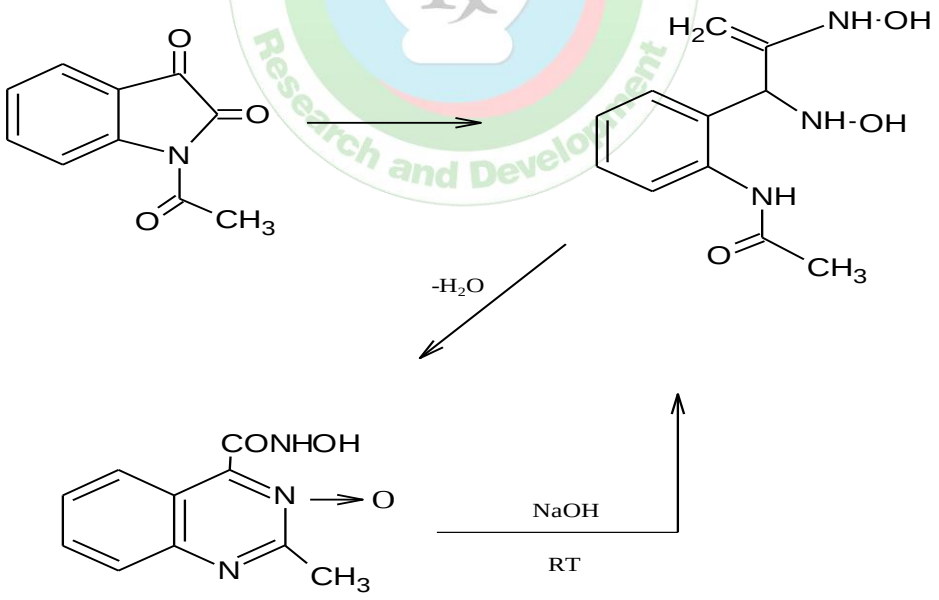


Figure 12: Acetylisatin reacted with hydroxylamine hydrochloride

IIsatin and 1-alkylisatins produce condensation products at the C-3 position when reacted with hydrazine. A reaction involving 1-methylisatin and semicarbazone produced methisazone, a compound used in treating smallpox [31-33], a virus that has now been eradicated.

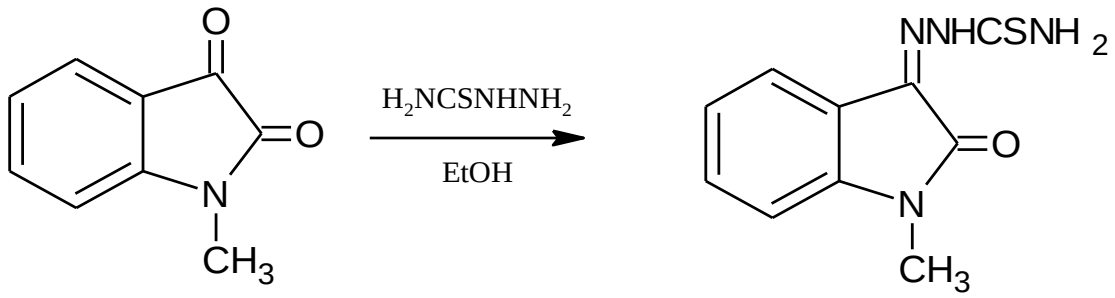
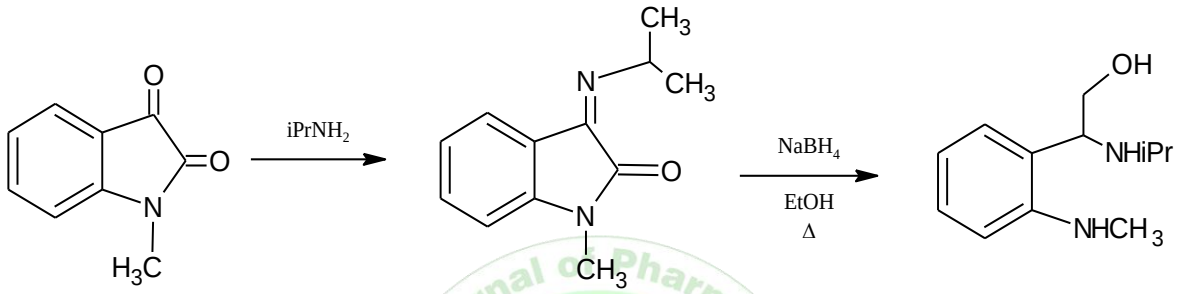


Figure 13: 1-alkylisatins reacted with hydrazine

b) Alkylamines

In a hot ethanol solution, isatin and 1-alkylisatins react with primary alkylamines to yield 3-imines, which upon reduction with sodium borohydride give phenylethanolamine derivatives.



[34].

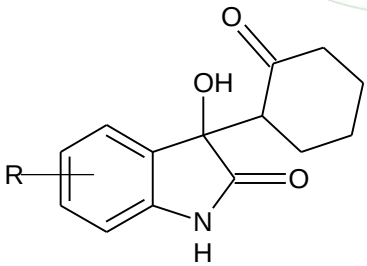
Figure 14: 1-alkylisatins react with primary alkylamines

BIOLOGICAL APPLICAGTIONS OF ISATIN

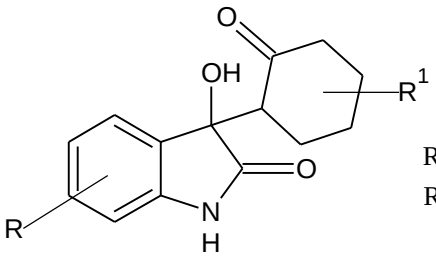
The synthetic versatility of isatin makes it an important raw material for the synthesis of a wide spectrum of bioactive compounds.

ANTICONVULSANT

The anticonvulsant activity of cyclohexane and other cyclic ketone derivatives of isatin is screened (Figure 15). A considerable number of analogs were active in pentylenetetrazole seizure threshold tests. However, no consistent structure-to-activity relationship was observed[35-41].



R=H, 1-$CH_2C_6H_5$, 5-Br, 5-Cl, 5-CH_3, 5-OCH_3, 6-Cl

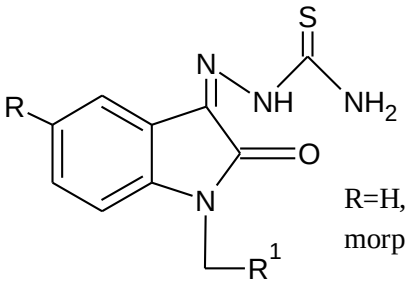


R= Br, NO_2; R^1=CH_3 $COCH_3$
R^2=NO_2, COOH, OCH, Cl, F

Figure 15: Isatin derivatives

ANTIMICROBIAL

Isatin-3-thiosemicarbazone derivatives, Mannich bases of isatin, and other carbonyl compounds have shown antiviral and tuberculostatic activities against viruses, fungal and bacteria. Three compounds in this series were toxic to cancer cells and two compounds were active against poliovirus type II and Gram-positive bacteria, fungi and yeasts. In addition to the structure shown in (Figure 16), it has been reported that isatin N-Mannich bases are also present.[42]

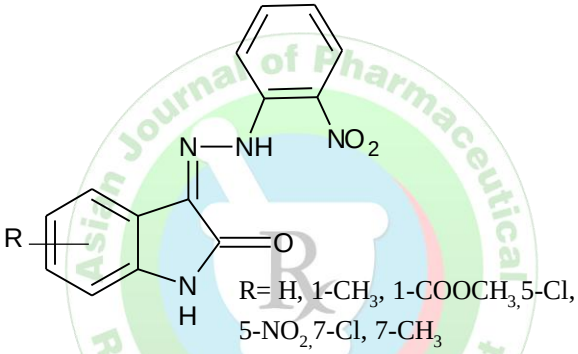


R=H, Br: R^1=Piperidino, morpholino

Figure 16: Schiff's and N-Mannich Bases of Isatin

ANTICANCER

A series of 3-o-nitrophenyl hydrazones of isatin was synthesized by condensing isatin with o-nitrophenyl hydrazine (Figure 17). These compounds were found to be active intramuscularly against Walker carcinoma-256, but were inactive against L-1210 lymphoid leukemia.[43]



R= H, 1-CH_3, 1-$COOCH_3$, 5-Cl, 5-NO_2, 7-Cl, 7-CH_3

Figure 17: Schiff base of isatin

ANTI-HIV ACTIVITIES

Isatin, its 5-chloro and 5-bromo derivatives have been reacted with N-[4-(4'-chlorophenyl)thiazol-2-yl] thiosemicarbazide to form Schiff bases and the N-Mannich bases of these compounds were synthesized by reacting them with formaldehyde and secondary amines and found to anti-HIV activity against replication of HIV-1 (IIIB) in MT-4 cells (Figure 18) [44]

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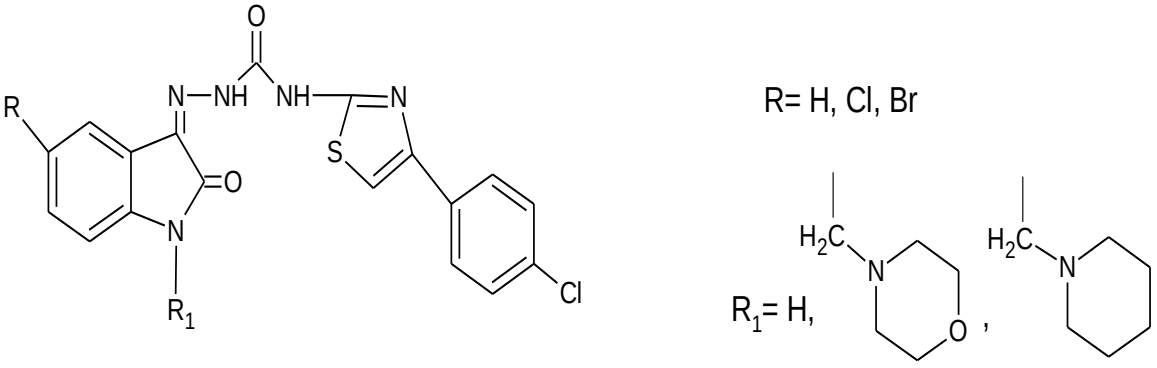

Figure 18: Schiff and mannich base of isatin

ANALGESIC ACTIVITY

The Mannich base of isatin containing Quinazolinone system was synthesized and evaluated for analgesic activity [45] (Figure 19).

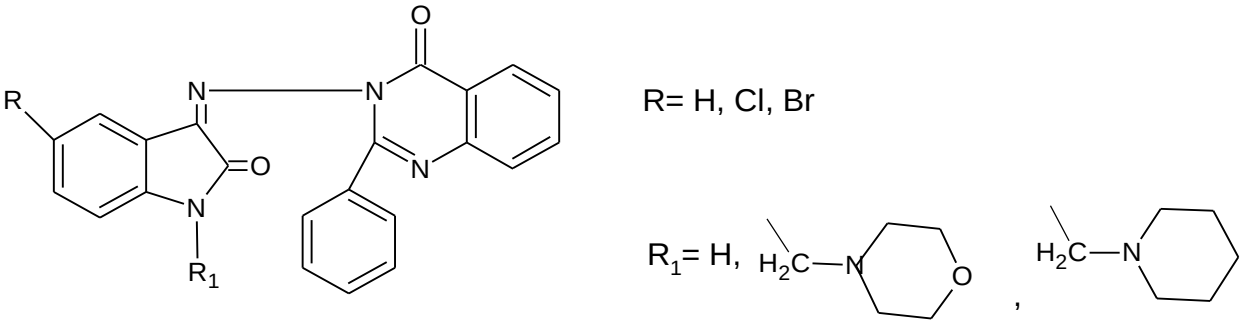

Figure 19: Schiff and mannich base of isatin

CNS DEPRESSANT ACTIVITIES

The anticonvulsant and sedative-hypnotic activities of a series of N-methyl/acetyl 5-substituted isatin-3-semicarbazones were investigated [46] (Figure 20).

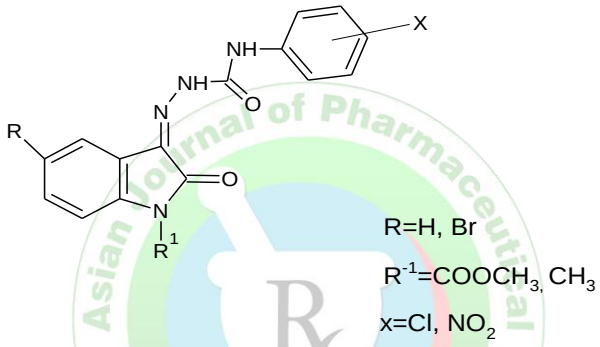

Figure 20: n-alkylation and Schiff base of isatin

ANTI-INFLAMMATORY ACITIVITY

Lian-shun F., reported the synthesis of some novel Schiff's bases of 5-subsituted Isatin (Figure 21) these synthesized compounds were investigated for analgesic (Tailimmersion method) and anti-inflammatory (carrageenan- induced paw edema method) activity [47-48].

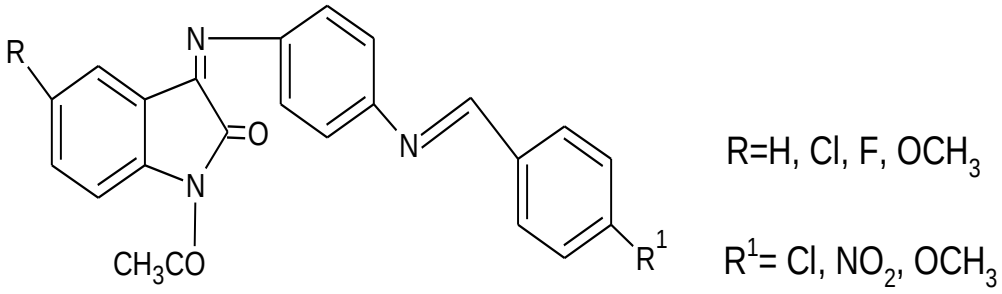

Figure 21: Schiff's bases of 5-subsituted Isatin

APPLICATIONS OF ISATIN

Chemical Synthesis

In the synthesis of organic isatin, which is commonly employed as a beginning substance or intermediaries. It is utilized as a precursor to the manufacture of a few heterocyclic compounds and drugs. [49].

Pharmaceuticals

Isatin, also as well as its derived compounds show interesting biological activity, comprising cancer-fighting, antiviral, antibacterial, as well as soothing features. Researchers are looking into the possibilities of developing medications and finding. [50].

Analytical Chemistry

Isatin can be employed as a reactant in scientific research, which is with spectrophotometric techniques used for identifying various substances. It creates colorful combinations between minerals and different chemical compounds which are detectable and quantitative. [51].

Dyes and Pigments

Isatin, also derivatives serve as precursors in the manufacture for pigments and dyes as they can impart specific shades other features.[52].

Biomedical Research

Isatin is now being studied because a function within various pathways of metabolism in addition to being a potential medicine targeting aware processes in biology.[53].

Photography

Isatin has historically been used in photographs because an element of developing answers, though the use has decreased given the advent of digital photographs. [54].

Coordination Chemistry

Isatin was and its metabolites may serve as compounds in compounds that coordinate with metallic ions, influencing their features as well as sensitivity. [55].

Agrochemicals

Isatin was compounds were investigated for potential use potential agricultural chemicals notably insect repellents including insecticides.[56].

RECENT ADVANCES OF ISATIN DERIVATIVES

Isatin was equivalents gain popularity partly because of their multiple biological functions and potentially therapeutic uses. Major advances in the area are a number of things.

Anticancer Acitivity

Isatin was analogue were recently deeply investigated regarding their possible therapeutic benefits. Enzymes might interfere with several kinds of enzyme who govern the proliferation of cancer tissue cells, which renders them beneficial targets therapy intervention. [57].

Anti-Inflammatory Properities

Many isatin, which molecules exhibit anti-inflammatory capabilities mainly influencing the generation of cytokines via inflammatory pathways. It renders it promising in treatment autoimmune conditions including rheumatoid arthritis. [58].

Antimicrobial Effects

Isatin was derivative display antibacterial abilities over bacteria as well as mushrooms. They collaborate across a selection of procedures, includes altering the cell membranes and affecting important functions.[59].

Neuroprotective Potential

Several kinds compounds isatin, which compounds are currently explored for potentially neuroprotective qualities. Since corticosteroids decrease the effects of oxidative stress and inflammation in the cerebellum, statins may be helpful with issues with neurodegeneration.[60].

Antioxidant Activity

As a result of the antioxidant properties, isatin, which esters may eliminate free radicals and shield tissues from damage from oxidation, which is linked to ageing and various kinds of diseases. [61].

Metal Ion Chelation

Many isatin derivative contain the ability to dissolve ions of metals, which makes them helpful as imaging contrast substances and for the administration for ionic overload diseases. [62].

Drug Delivery Systems

The possible application of isatin, which esters in medication routes is also being studied. In order to enhance the drug's solubility, equilibrium, and targeted absorption to specific tissue types, proteins may get combined with various other substances. [63].

Biological Probes

Although isatin derivatives bind preferably to specified targets, these are employed are biological sensors to investigate an assortment many biological processes of systems. [64].

Structure Activity Relationship Acitivitys

Determining the structure-activity relationships of the protein isatin analogues is the primary aim of current study with the aim to better understand the pharmacologic characteristics as reduce the possibility of adverse reactions. [65].

Synthetic Advances

Improved isatin compounds with better potency, effectiveness, etc absorption are having been created prospective by improvements and the synthesis of organic molecules, widening up the door for putative uses in medicine.[66].

The versatility and promise of isatin, which compounds in the discovery and creation of drugs in several therapeutic areas is shown by these current developments. The ultimate objective of ongoing investigation regarding this topic involves finding novel therapeutic potential as well as enhance the medicines' safe and effective attributes.

CONCLUSION

Isatin is a required molecule having distinctive biological characteristics which enable them to be widely employed for various medicinal and clinical uses, that include antidepressant, analgesics cancer prevention, anti-inflammatory, as along with anti-tubercular. Therefore, this overview was greatly broadened with the goal to identify novel and green ways of isatin, which production whilst simultaneously fixing the associated problems. In addition, since isatin reactions generate an array of novel compounds that have significant biological attributes that can be used in many different kinds of biological and therapeutic

applications, they have been a focus of significant study. Isatin can be forms a significant nucleus which provides novel paths for study in the future under all of these purposes.

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