

The chemistry and synthesis of 1H-indole-2,3-dione (Isatin) and its derivatives

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ABSTRACT

Isatins are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds. In this, a convenient method has been developed for the conversion of Indoles into Isatins and some heterocyclic derivative were synthesised such as 5-nitro-1H-indole-2,3-dione, 2-methylquinoline-4-carboxylic acid which may be used as raw material for drug synthesis. The general process utilizes the effective method for synthesis of Isatin from Indole is bromination and oxidation with an N-bromosuccinimide-dimethyl sulfoxide reagent. The nitration of Isatin at C-5 takes place by using KNO_3 , conc. H_2SO_4 , 2-methylquinoline-4-carboxylic acid are usually obtained from pfitzinger reaction.

Keyword: Indole; Isatin; NBS-DMSO; Pfitzinger reaction; 5-nitro-1H-indole-2,3-dione; 2-methylquinoline-4-carboxylic acid

1. INTRODUCTION

Isatins (1H-indole-2,3-dione) are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as raw material for drug synthesis^{1-4,8-9}. The general process utilizes the effective method for synthesis of Isatin from Indole is bromination and oxidation with an N-bromosuccinimide- dimethyl sulfoxide reagent. The nitration of Isatin at C-5 takes place by using KNO_3 , con. H_2SO_4 .²⁰⁻²⁵ 2- Methylquinoline-4-carboxylic acid are usually obtained from pfitzinger reaction.

A spiro compound N,N'-(2-oxo-3'H-spiro[indoline-3,2'-[1,3,4]thiadiazole]-3'5'-diyl)diacetamide were synthesise by refluxing Isatin and thiosemicarbazone in ethanol and then on heating with acetic anhydride underwent to cyclization into intermediate that on acetylation of the NH and NH_2 groups afforded the spiro compound. Isatins have also been found in mammalian tissue and their function as a modulator of biochemical processes has been the subject of several discussions¹¹.

The advances in the use of isatins for organic synthesis during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported in this review and in the accompanying supplementary information⁶. Isatin (1H-indole-2,3-dione, Figure 1) was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of

indigo by nitric and chromic acids¹². Isatin (1H-indole-2,3-dione), was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids. The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. Three reviews have been published regarding the chemistry of this compound: the first by Sumpter, in 1954, a second by Popp in 1975 and the third on the utility of isatin as a precursor for the synthesis of other heterocyclic compounds¹⁰. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives. These properties are more fully detailed in the supplementary material. In nature, isatin is found in plants of the genus *Isatis*, in *Calanthe discolor* LINDL. and in *Couroupita guianensis* Aubl., and has also been found as a component of the secretion from the parotid gland of *Bufo* frogs, and in humans as it is a metabolic derivative of adrenaline¹²⁻¹⁵.

Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant *Melochia tomentosa* as well as from fungi: 6-(3'-methylbuten-2'-yl)isatin was isolated from *Streptomyces albus* and 5-(3'-methylbuten-2'-yl)isatin from *Chaetomium globosum*. Isatin has also been found to be a component of coal tar. Isatin (2,3-dioxindole) is an endogenous compound identified in humans, and its effect has been studied in a variety of systems. Biological properties of isatin include a range of actions in the brain and offer protection against certain types of infections. Isatin has anxiogenic, sedative, anticonvulsant activities and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro*¹²⁻¹⁵. A series of p-substituted Isatin semicarbazones have shown anticonvulsant activity in MES, scPTZ and scSTY tests. Various isatin-N-Mannich bases of isatin-3-thiosemicarbazones have shown antiviral and tuberculostatic activity¹⁰⁻¹²⁻¹⁵.

2. MATERIAL AND METHODOLOGY

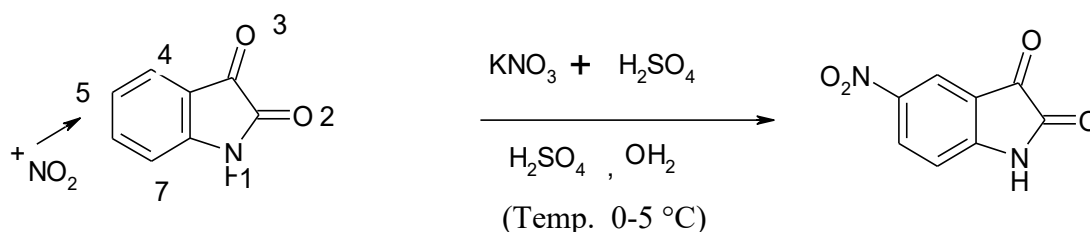
2. 1. Scheme I. Synthesis of 1H-indole-2,3-dione (Isatin)

A mixture of Indole, NBS, And Anhyd. DMSO was taken in clean and dry 3-necked R.B. flask and stirred for 60 °C for 6 hours and then above 80 °C for 16 hours under reduced pressure. After the completion of reaction the mixture was poured into water and extracted by using dichloromethane and extracts is dried over MgSO₄ and purified by silica gel chromatography with DCM as (20×3) eluent M.P. 202 °C.



Scheme I. Synthesis of 1H-indole-2,3-dione (Isatin).

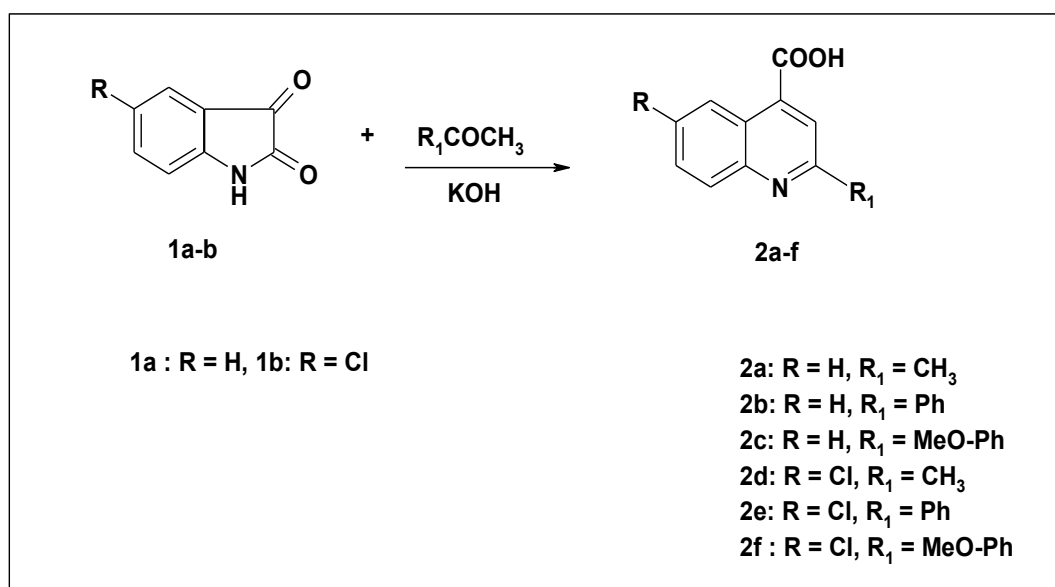
The reaction proceeded by adding a solution of Isatin, con. H₂SO₄ dropwise to a solution of at 0 to 5 °C over a time period of 1 hours, produced 5-nitroisatin. M.P. 249-250 °C.



Scheme II. Synthesis of 5-nitro-1H-indole-2,3-dione.

Scheme III. Synthesis of 2- methylquinoline-4-carboxylic acid

2-methylquinoline-4-carboxylic acids are usually obtained by the Pfitzinger reaction i.e. by heating a mixture of isatin with acetone in the presence of alkali KOH or NaOH. The mixture of isatin with a solution of NaOH stirred and then acetone was added and refluxed for 8 hours and then neutralizes to pH 5-6 and precipitate is washed and then crystallise from methanol. M.P. 239-241 °C .



Scheme III. Synthesis of 2-methylquinoline-4-carboxylic acid.

3. RESULTS

1H-indole-2,3-dione (Isatin): IR (KBr): 3207 cm⁻¹ (-NH), 1743.4 cm⁻¹ and 1691.12 cm⁻¹ (C=O), 1294.83 cm⁻¹ (C-N stretching), 1457.97 cm⁻¹ (C=C), 1097.25 & 1073.06 cm⁻¹ (C-O stretching), below 900 cm⁻¹ benzenoid ring. MS m/z (%) = 147.2(M⁺ 40), 119.0(100), 105.0(2), 90.0(70), 77.0(8), 65.0(40), 52.0(12), 43.0(12) (Fig. 2, 4).

5-nitro-1H-indole-2,3-dione: M/S m/z (%) = 193.0(M⁺ 60) , 119.0(10), 105.0(10), 90.0(40.0), 77.0(10), 65.0(20), 52.0(5.0), 46.0(5) (Fig. 3).

2-methylquinoline-4-carboxylic acid: ¹H NMR δppm- 3.0 (s,3H, CH₃), 2.5(s, 1H, CH), 7.90(d, 1H), 8.10(d , 1H,)8.319-8.347(dd, 1H) , 8.639-8.667(dd, 1H) the peak at 10.90 which were D₂O exchangeable (Fig. 1).

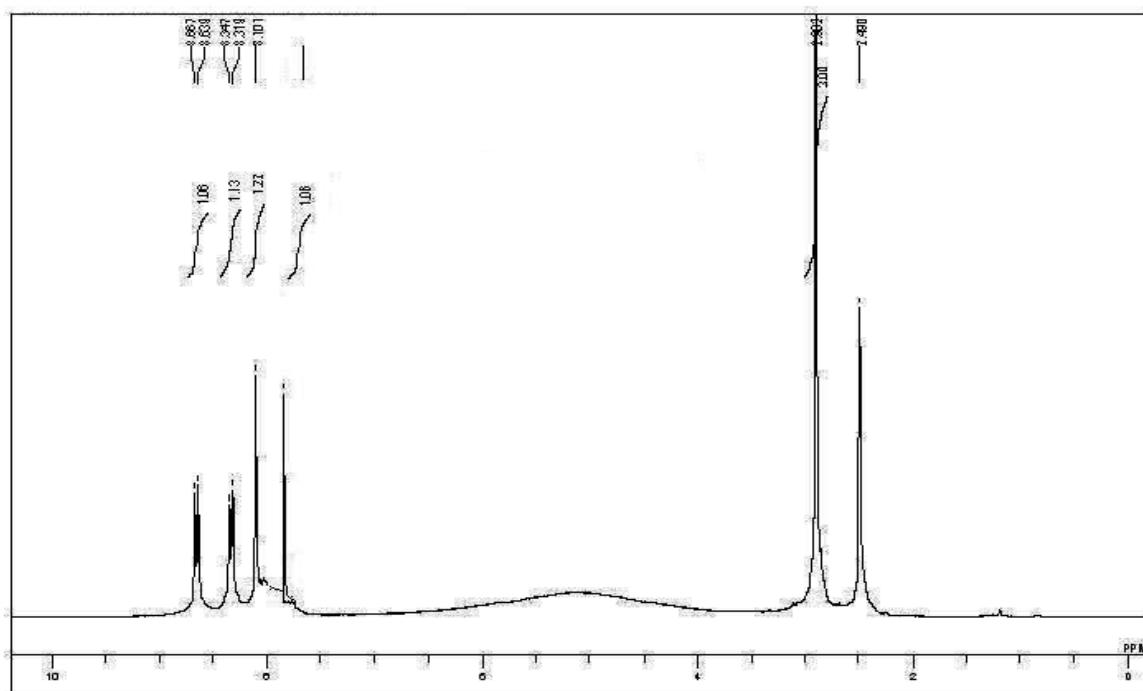


Fig. 1. ¹H NMR of 2-methylquinoline-4-carboxylic acid.

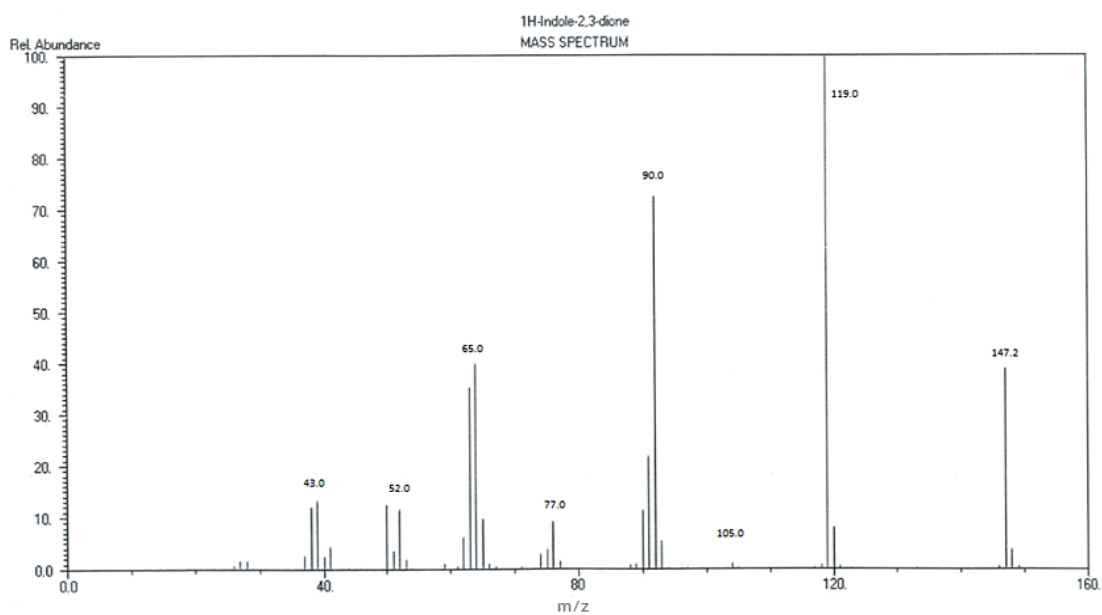


Fig. 2. Mass Spectra of 1H-indole-2,3-dione (Isatin).

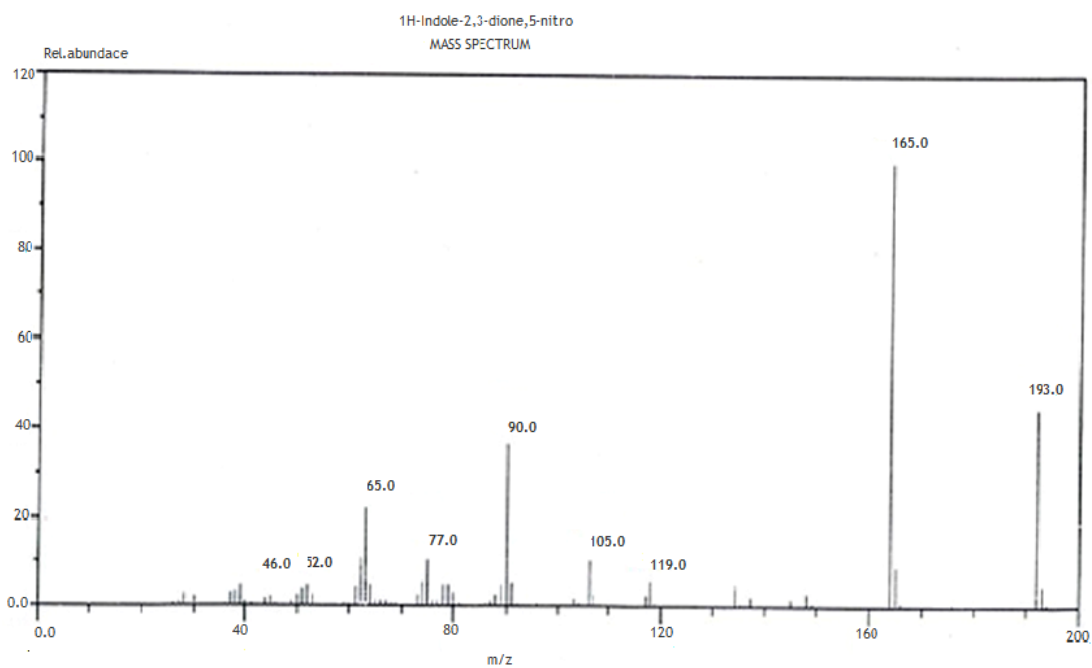


Fig. 3. Mass Spectra of 5-nitro-1H-indole-2,3-dione.

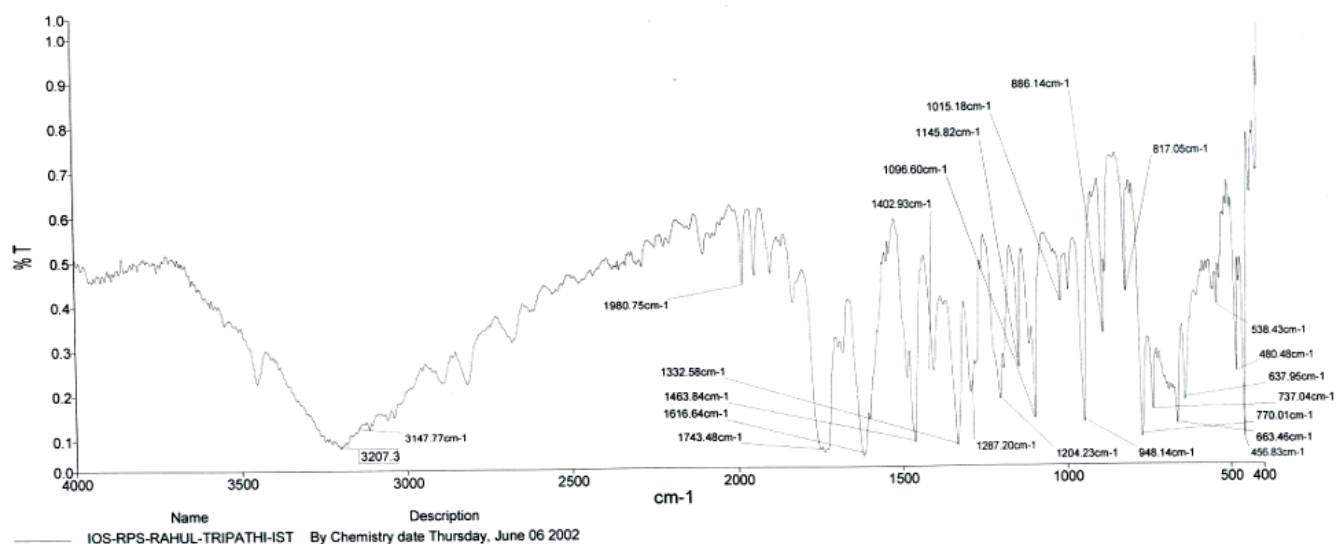


Fig. 4. INFRARED SPECTRA of 1H-indole-2,3-dione.

4. CONCLUSION

We have report the sythesis of 1H-indole-2,3-dione (Isatin), 5-nitro-1H-indole-2,3-dione, 2-methyl-4-quinoline carboxylic acid. They can be further modified for the research purpose. These compound in turn can be used to synthesize various heterocyclic Compound which may have promising biological activity.

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