Ain Shams University
Faculty of Science
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Utility of isatin in synthesis of heterocycles of anticipated biological activity

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In

Organic Chemistry

Presented

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DEDICATION

To my distinguished parents:

I do appreciate my God for giving me such wonderfully parents for their continuous support, encouragement, and enlighting my life.

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The author wishes to refer her deep appreciation and gratitude

To

Prof. Dr. Ahmed Said Ahmed Youssef, *Professor of Organic Chemistry, Chemistry Department, Faculty of Science, Ain Shams University.*

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For

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QUALIFICATION

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Summary

Isatin and some of its derivatives are used in this investigation on the hope of getting heterocyclic compounds bearing indolinone moiety to enhance their biological activities.Thus,2 - (2- oxindolin -3 - ylidene) malononitrile (**1a**) or (E,Z)ethyl 2-cyano-2-(2-oxindolin-3-ylidene)acetate (**1b**) or isatin-β-thiosemicarbazone (**1c**) undergo reactions with prototype hydrazine hydrate itself and some of its simple congeners and gave hydrazone derivatives bearing indoline-2-one moiety (**2a-d**). Refluxing of (E,Z) ethyl 2-cyano-2-(2-oxindolin-3-ylidene)acetate (**1b**) with hydroxylamine hydrochloride in ethanol and a catalytic amount of ammonium acetate produced the oxime derivative **3**.Treatment of **1a, b** with *o*-phenylenediamine in acetic acid yielded 5H-indolo[2,3-b]quinoxaline**(4)** in one-pot reaction. On the other hand the reaction of **1a** with *o*-phenylenediamine in ethanol produced di-hydroquinoxaline derivative **5** in good yield. The reaction of hydrazide derivative **6** and isatin **1** in ethanol afforded the hydrazone derivative **7** in a good yield. Refluxing of isatin**1** and imidazolone derivative **8** in

n-butanol produced compound **9** in a good yield. The reaction of isatin **1** with 2-benzamidoacetic acid in acetic anhydride not afforded the expected oxazolone derivative **10**, instead it produced the open adduct **11**. On the other hand the reaction of **1** with p-nitrobenzyl cyanide in the presence of a catalytic amount of triethyl amine gave a mixture of diastereo isomers of **12.**

We aimed to undergo benzoylation or acylation to compounds **1a** and **1b** hoping to prevent the removal of dicyano methylene of orcyanocarboethoxy methylene moieties of compounds **1a 1b** by the action of hydrazines.Heating of **1a** with benzoyl chloride in dry acetone in the presence of anhydrous potassium carbonate as a base yielded an adduct which was proved to be a mixture of two compounds, the 2-(1-benzoyl-2-oxindolin-3-ylidene) malononitrile (**13**) and ethyl 2-(2-benzamidophenyl)-3,3-dicyanoacrylate **(14)**. Compound **14** is formed by ring opening of **13** during its crystallization with ethanol. Heating of compounds **1a** and **1b** in acetic anhydride furnished compounds **15a,b** as a mixture of N-acetyl and O-acetyl derivatives in addition

to ethyl 2-amino-3-cyanoquinoline-4-carboxylate **(16)** in case of the reaction with **1a**. Treating an ethanolic solution of **15a** with hydrazine hydrate yielded the cinnoline derivative **18** in addition to a minor amount of the hydrazone derivative **2a.** Similar treatment of compound **15b** with hydrazine hydrate gave the N-acetyl hydrazone **19** and small amounts of the hydrazone derivative **2a**.The reactions of **15a** and **15b** with phenyl hydrazine furnished (Z)-1-acetyl-3-(2-phenyl hydrazono) indolin-2-one (**20**), beside compound **2b** in minor amount.

The authors utilized hydrazones **2** and **7** in the synthesis of some heterocycles.Thus, refluxing the hydrazone derivative **2a** with acetyl acetone, ethyl acetoacetate, diethyl malonate or malononitrile in pyridine afforded the spiro derivatives **23a, 23b, 25** and **27**, in addition to the fused system **26** in case of its reaction with diethyl malonate. Treating of hydrazone**7** with ethyl acetoacetate in dioxane with a catalytic amount of pipredine; gave the dihydropyrrole derivative **28.** Refluxing of hydrazone **2a** with benzoyl isothiocyanate and/or lauroylisothiocyanate in dry acetonitrile furnished

the thiosemicarbazide derivatives **30a,b** in good yields. Compound **30a** was heated with hydrazine hydrate in the presence of a catalytic amount of pipredine, to give the 1,2,4-triazole derivative **31.**Compound **7**was heated in acetic anhydride on the hope of getting a heterocyclic system bearing indoline moiety. Instead, it furnished a mixture of oxazolone derivative **32** and hydrazone derivative **33**.

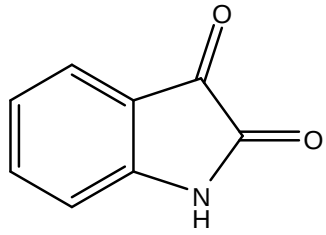
Refluxing of compound **2d** in acetic anhydride gave the N-acetyl derivative **34**.

The chemistry of isatins

1. Introduction

Isatin (1H-indole-2,3-dione) **(1)** is a synthetically versatile substrate, where it can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles, quinolines, and as a raw material for drug synthesis. Isatin has also been found in mammalian tissues, and its function as a modulator of biochemical processes has been the subject of several discussions. The advances in the use of isatin for organic synthesis are reported in this thesis.

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.



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In nature, isatin is found in plants of the genus *Isatis,*[1] in *Calanthe discolor* LINDL.[2] and in

*Couroupitaguianensis*Aubl,[3] and has also been found as a component of the secretion from the parotid gland of *Bufo*frogs,[4] and in humans as it is a metabolic derivative of adrenaline.[5-7] Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxy phenyl pentyl isatins) obtained from the Caribbean tumorigenic plant *Melochiatomentosa*[8-10] as well as from fungi: 6-(3'-methylbuten-2'-yl)isatin was isolated from *Streptomyces albus* [11] and 5-(3'-methylbuten-2'-yl)isatin from *Chaetomium globosum.*[12]Isatin has also been found to be a component of coal tar.[13]

Recently, 6-methoxy-1-methylisatin was isolated from the plant *Boronellakoniambiensislies*. [14] Isatin-3-oximes are useful antiallergic agents with potent and prolonged action. Derivatives of these compounds are also potassium channel openers for treatment of respiratory diseases, convulsions, renal disorders, urinary incontinence and diarrhea.[15,16]

It has been reported that several compounds containing an isatin moiety possess antibacterial, antifungal, anticonvulsant, anti-inflammatory, and anti-