BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY, DHAKA, BANGLADESH

SYNTHESIS OF SOME SPIRO HETEROCYCLIC DERIVATIVES OF SUBSTITUTED ISATINS

A
DISSERTATION SUBMITTED
IN PARTIAL FULFILMENT OF THE REQUIRMENTS FOR THE
DEGREE OF MASTER OF PHILOSOPHY
IN
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THESIS ACCEPTANCE LETTER

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Author

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INTRODUCTION

1. INTRODUCTION

The development of carbon-hetero atom chemistry has been strongly influenced by the need in synthetic organic chemistry and at the same time it has been stimulated and sustained by advances in the field of synthesis. The chemical synthesis of molecules containing carbon-hetero atom nucleus has been a major field of scientific endeavor for over a century.

In addition for the last century, there has heen a continuing and dramatic growth in the power of science of constructing complex heterocyclic molecules, which showed no signs of decreasing interest. Carbon-hetero atom chemistry is an information rich field because of the multitude of known types of reactions as well as the number and diversity of hetero atomic compounds. Tlus richness provides various types of chemical methodology which makes broad way to access synthetic heterocyclic compounds.

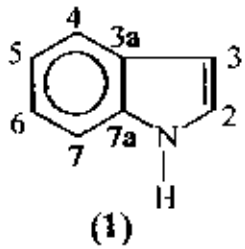
Researches on the chemistry of indole have been focused for attention to chemists since long time, due to their wide spread occurrence in nature and diversified biological activities. Furthermore, those compounds in which indole-3 carbon as in the form of a spiro atom exhibits enhanced bioactivity.

Isatin (2,3 – dioxindole) has long heen known as a pharmacological agent which exerts distinct metabolic and behavioural effect in vitro and in vivo. Very recently its presence has been discovered in body fluids and in tissues. Its distribution is distinct and discontinuous in the brain with highest levels in the hippocampus and cerebellum. Isatin level in the hippocampus is about 0.1μg (0.5μM). It is anxiogenic due to the cause of increase in brain

tissue. At physiological concentration it inhibits atrial natriuretic peptide (ANP) binding in the brain and antagooiscs ANP stimulated particle, guanylate cyclase. It does not affect morc than 50 other neuroregulatory systems at thesc levels. Thus isatin is a new, highly spccialised, endogenous regulator which has a potential role in the control of both stress and the natriuetic peptide system. Still it is unknown about the origin and subsequent metabolism of isatin.

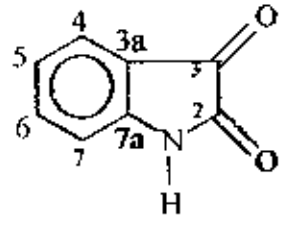
1.1 HISTORICAL BACKGROUND

Both isatin and indole havc identical chemical structure. Indolc comprises a benzene ring fused to thc pyrrole nucleus whcre the numbering of **1** and **2** begins with nitrogen and proceeds around the ring as indicatcd below:



(1)

Indole



(2)

Isatin or Indole -2,3 dione.

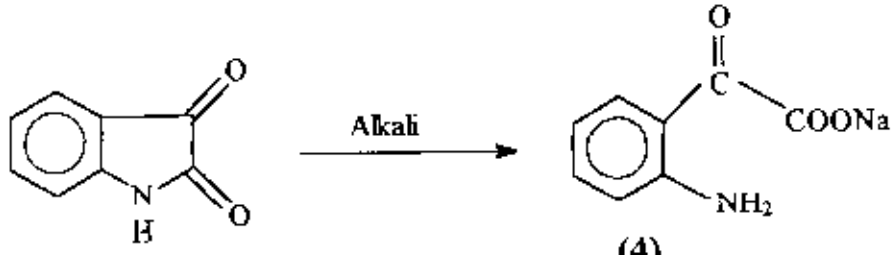
Position **2** and **3** arc often called α and β respectively. Thc orthoquinonc type indole containing two carbonyl groups in the hetero ring is known as isatin. Numbering of isatin is similar to that of indole. As a dioxo indole derivative the chcmical name of isatin is indole 2, 3 –dionc **(2)**

Instead of natural product, Bacyer[1] synthesized isatin in the laboratory from phenyl acetic acid. The success of thc last venture spurrcd onwards the

work on. Indigo **(3)** which was first prepared commercially in 1878 by Baeyer, through different routes according to the **Scheme 1.**

This was the earliest synthesis in organic chemistry and it may be taken as a landmark in the history of chemistry. Nitration of phenyl acetic acid followed by reduction with zinc/hydrochloric acid led to the cyclized product lactam. This lactam on treatment with nitrous acid gave the oxime which on reduction with tin/hydrochloric acid afforded aminolactam. Oxidation of aminolactam with ferric chloride produced isatin **(2).** Isatin was then converted into trans indigo **(3).** Trans indigo was synthesized in another route from aniline as shown in **Scheme 1.**

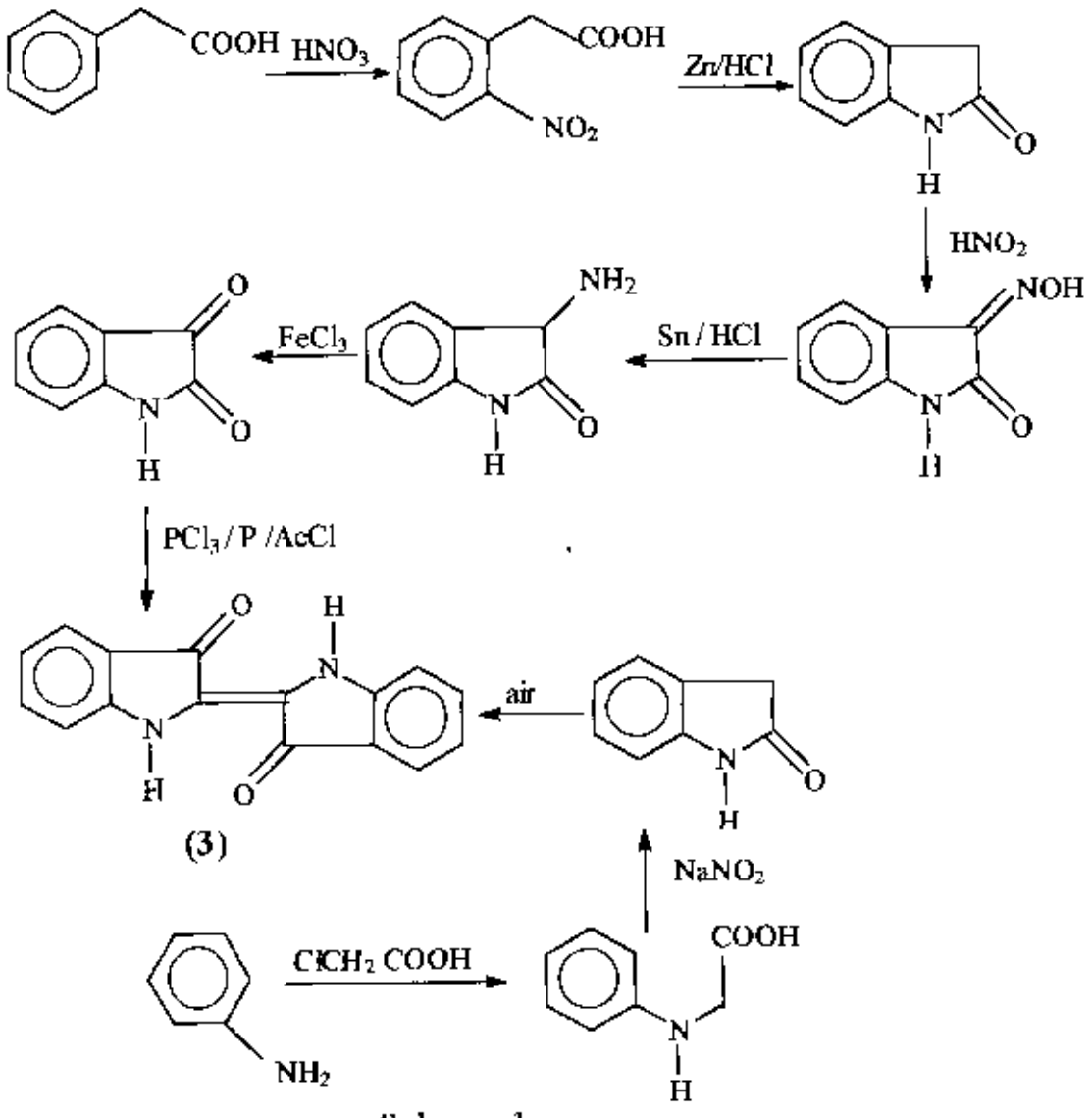
Isatin dissolves in alkali and gives the salt of an acid, isatinic acid **(4).**



(2) **(4)**

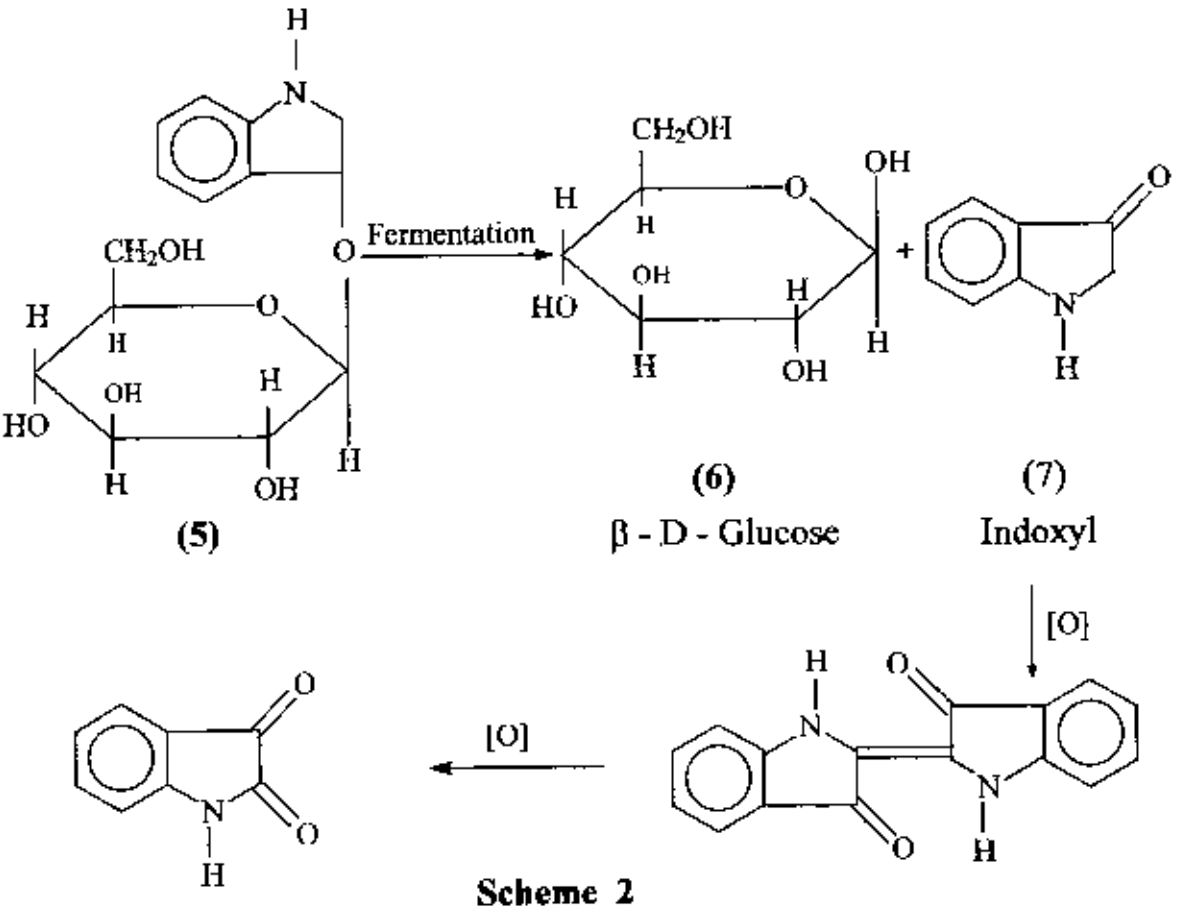
Isatinic Acid (salt)

It was the quick realization that isatinic acid was an *o* - amino phenyl formic acid and its precursor isatin was its lactam (2, 3 - diketo - 2, 3 - dihydro indole).



Scheme 1

Erdmann [2-3] and Leurent [4-5] independently obtained isatin **(2)** from the oxidation of trans indigo in 1840 and 1842 respectively. Trans indigo **(3)** was also obtained by the oxidation of indoxyl **(7)** which was the fermentation product of indican glucoside **(5)**, a dye isolated from the plant ***isatin tinctoria***. The overall reaction steps are shown in the **Scheme 2.**



(5) (6) β - D - Glucose (7) Indoxyl

Scheme 2

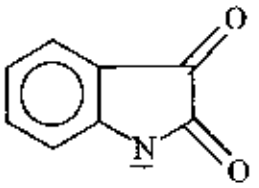
1.2 GENERAL PROPERTIES OF ISATIN

Physical Properties

Isatin is a red shining solid crystal.

Salt formation

Isatin reacts with NaOH or KOH and forms salt. Isatin forms silver salt with alcoholic silver acetate. Isatin also produce perchlorate salt with perchloric acid. Isatin anion can be represented as a hybrid of the two charged species **(8, 9),** with a smaller contributions of the quinoid structure **(10)**.



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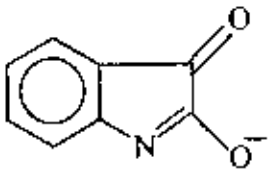

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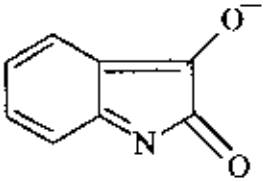


(10)

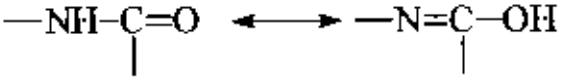
Tautomerism and its evidence

Isatin and dioxindoles show amido – imidol tautomerism. Isatin is a ketonic lactam (**structure 2**)

(2)
Lactam

(2a)
Lactim

This is an example of the amido – imidol tautomerism.



Jullien *et al*[6] showed that dioxindole also exibits the following tautomerism.

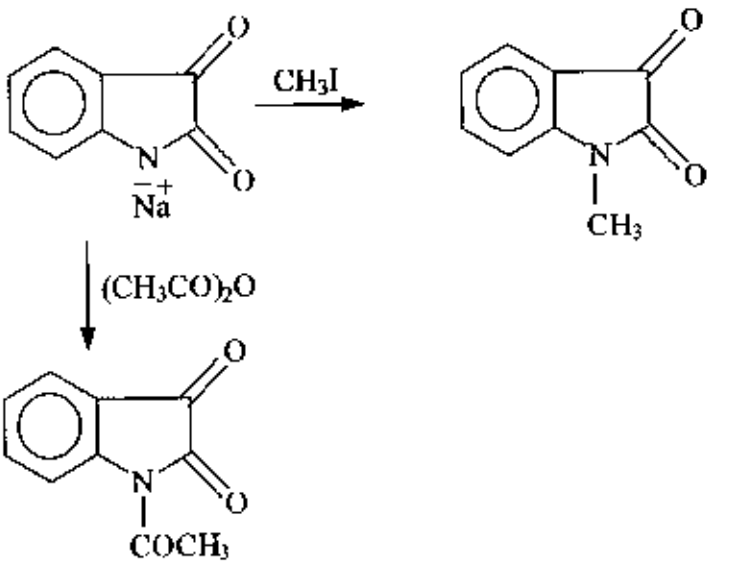
(2)
Lactam

(2a)
Lactim

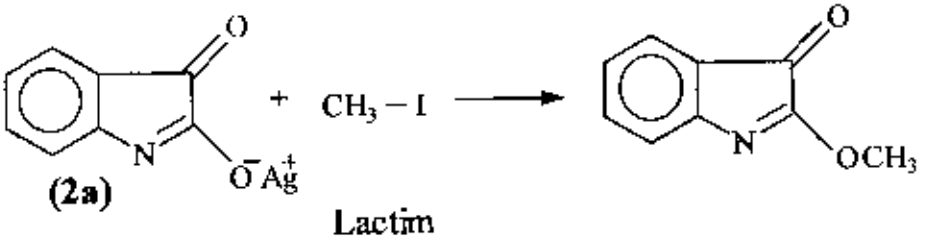
Keto – enol tautomerism of dioxindole.

Evidence of tautomerism

The reactivity of isatin behaves like a lactam towards most of the reagent. As for example,

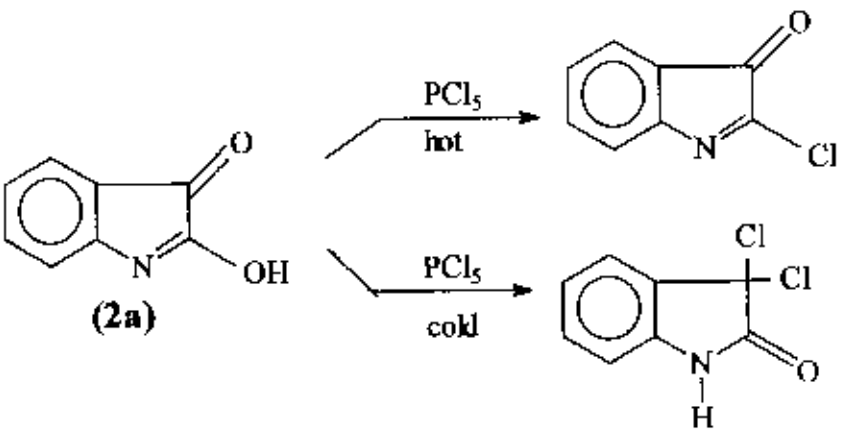


Bnt the silver salt of isatin yields *o* – alkyl derivative which indicates the lactim form **(2a)** of isatin.



(2a) Lactim

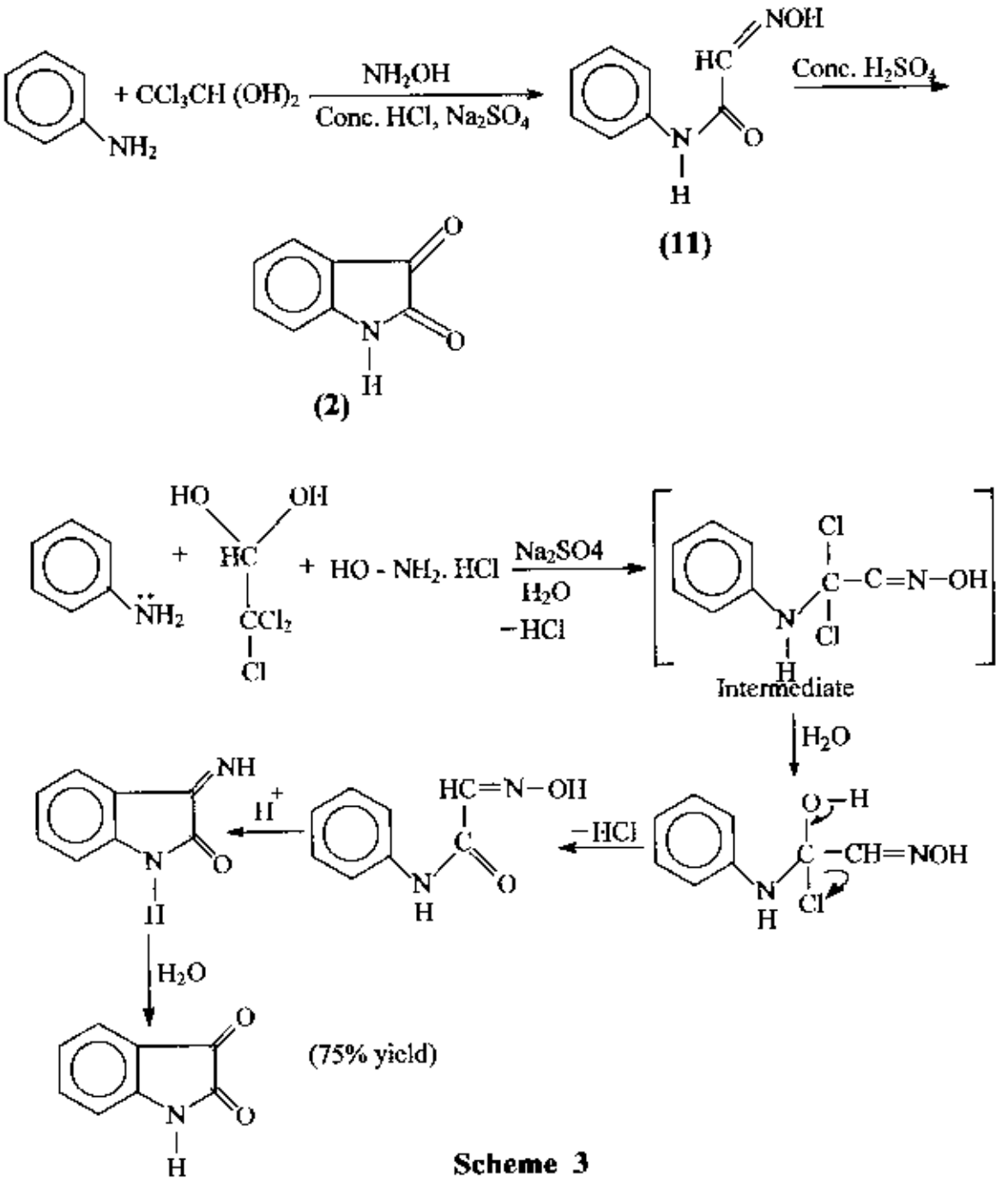
Another evidence of the lactim structure **(2a)** is shown in the following reaction of isatin with PCl_5 in benzene which gave isatin α – chloride at warm condition and 3, 3 – dichloro isatin at cold condition.



1.3 REVIEW OF THE EARLIER RESEARCH WORK OF ISATIN PREPARATION

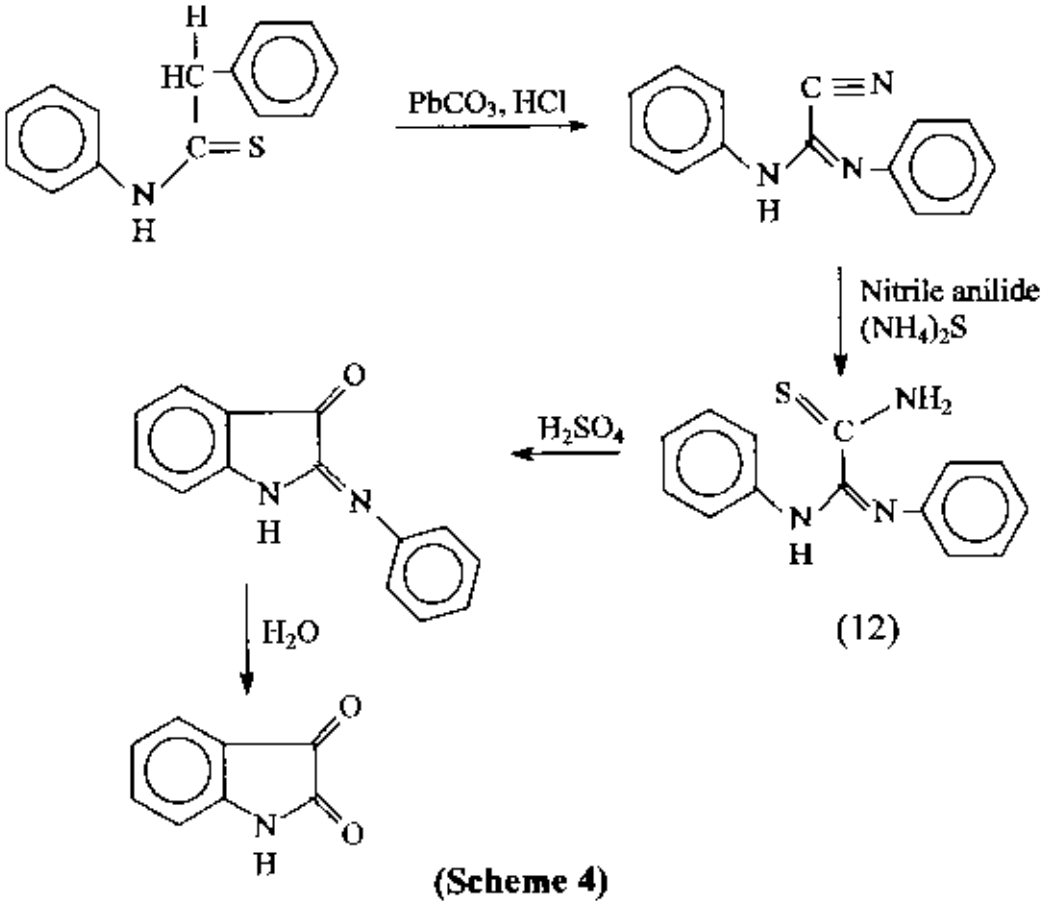
The various methods have been developed for the preparation of isatin and its derivatives. The most important and general method was developed by Sandmeyer[7] in Germany. Besides the Sandmeyer method, other methods have also been developed. A brief compute is given below.

Sandmeyer synthesized isatin from aniline. Treatment of the solution of aniline in concentrated hydrochloric acid with aqueous solution of chloral hydrate and hydroxylamine hydrochloride in presence of sodium sulphate produced crystals of oximino acetanilide **(11)** which on treatment with concentrated sulfuric acid afforded isatin **(2)**. This is shown in **Scheme 3**.



Scheme 3

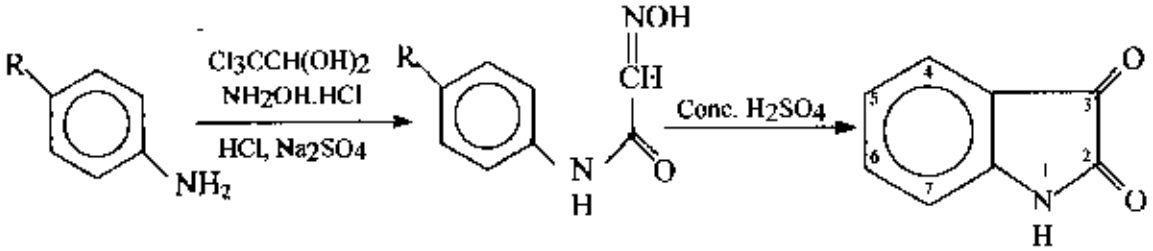
Sandmeyer used thiocarbamide as a starting material to synthesize isatin in his early method. Treatment of thiocarbanilide with lead cabonate and hydrogen cyanide produced nitride anilide which was exposed by ammonium sulphide afforded thioamide **(12)** in good yield. The subsequent cyclization with sulfuric acid followed by hydrolysis, produced isatin **(2)**.



(12)

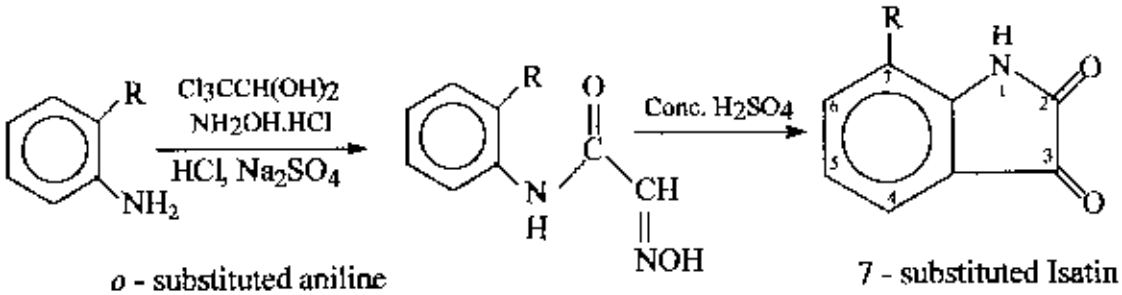
(Scheme 4)

Using sandmeyer method [7] mono – substituted *o*, *m* and *p* – anilines can be converted into their correspondiug isatins. Ortho and para–substituted anilines gave 7– substituted and 5 – substituted isatins respectively whereas the meta – substituted anilines gave two positional isomeric isatins (**a** and **b**) as shown in **Scheme 5.**



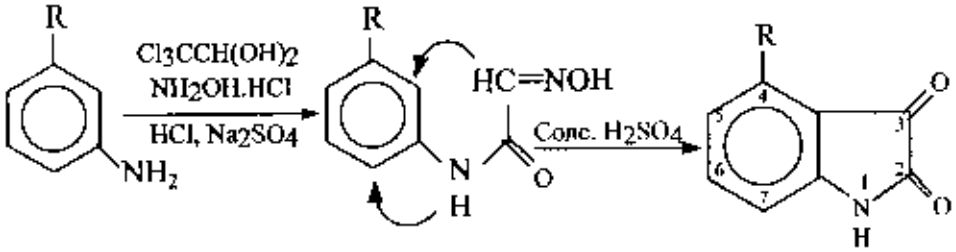
p- substituted Aniline

5 - substituted Isatin



o - substituted aniline

7 - substituted Isatin

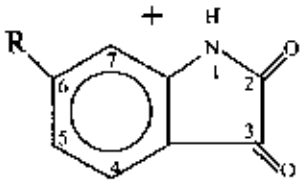


m-substituted aniline

(a)

4- substituted Isatin

+



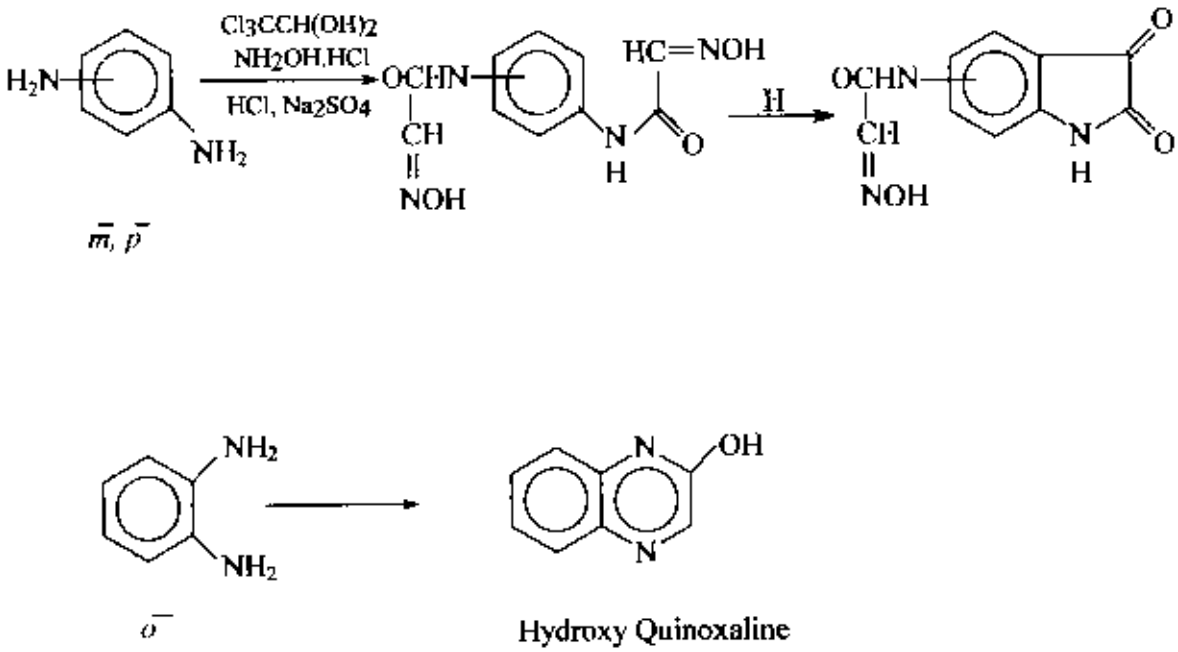
(b)

6-substituted Isatin

Scheme 5

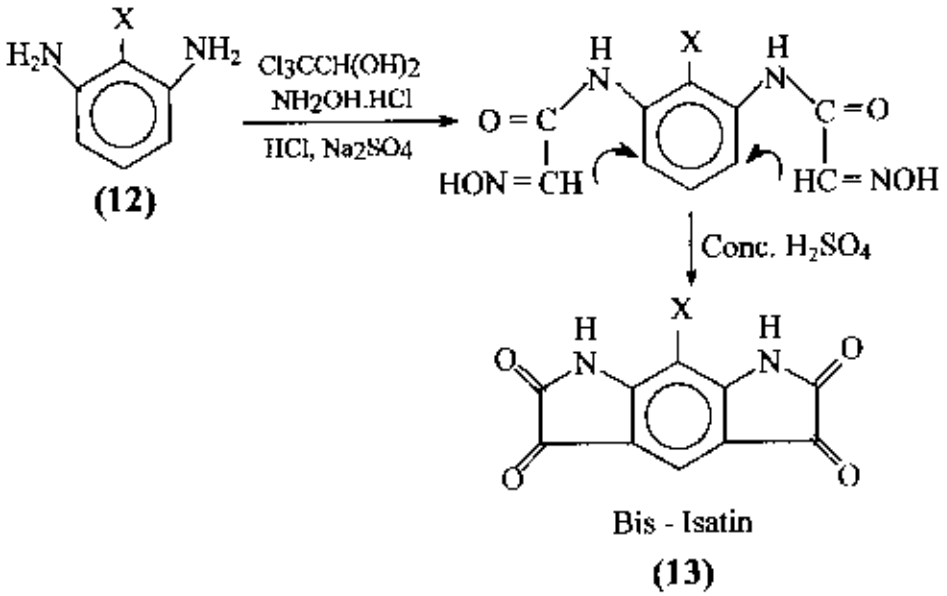
Recently Islam ***et al*** [8] obtained 4 and 6-chloroisatin from *m*-substituted aniline in a ratio of 1:1 and the products were isolated by column chromatography.

Morsh and Schulze [9] used *m* and *p* – phenylenediamines for dicyclization products but only mono cyclization products was obtained whereas *o* – phenylenediamine yielded hydroxyquinoxaline by intramolecular cyclization as shown in the **Scheme 6.**



Scheme 6

Later Z. Allan [10] successfully applied Sandmeyer reaction to produce bis-dioxopyroline benzene **(13)** of good yield.

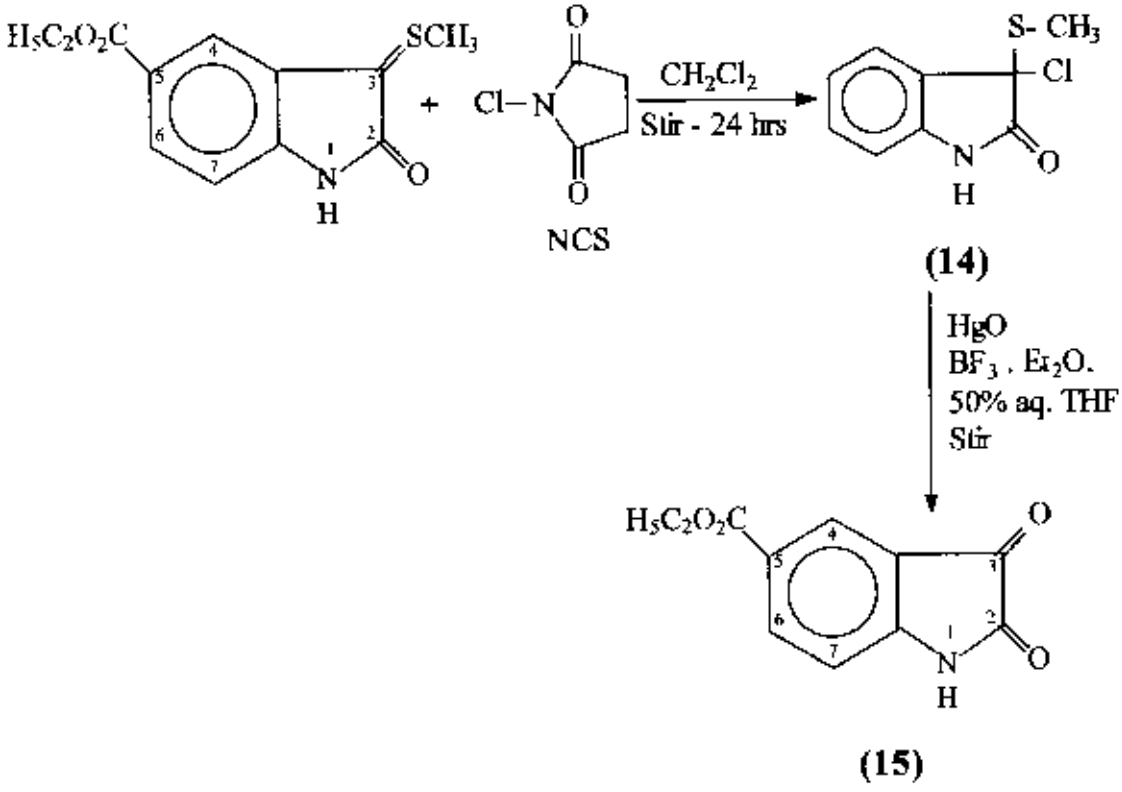


(12)

Bis - Isatin

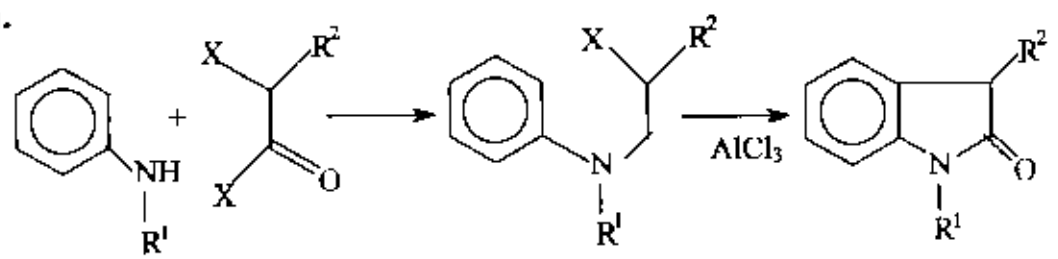
(13)

Isatin **(15)** can be prepared by oxidative halogenations of 3 – alkyl thioxindole with NCS followed by Lewis acid catalyzed hydrolysis of haloginated product **(14)**.



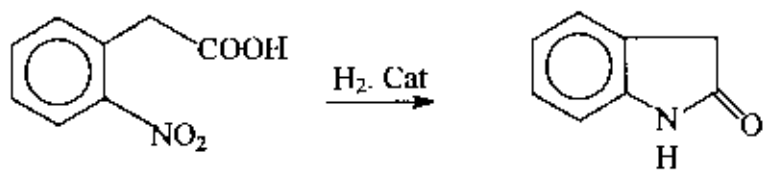
Oxindoles can also be prepared from **(a)** anilides with α-halo carbonyl chloride by means of Friedel-Crafts reaction, **(b)** catalytic hydrogenation of *o*–nitro phenyl acetic acid and **(c)** base catalyzed cyclization of *N*–acetyl phenyl hydrazides.

a.

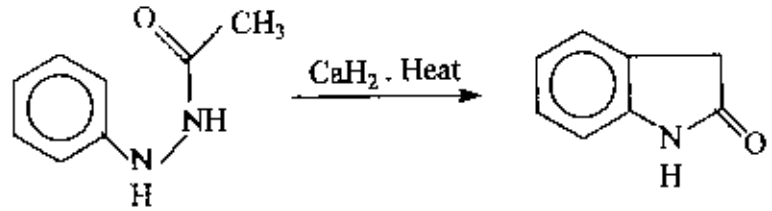


X = Cl, Br

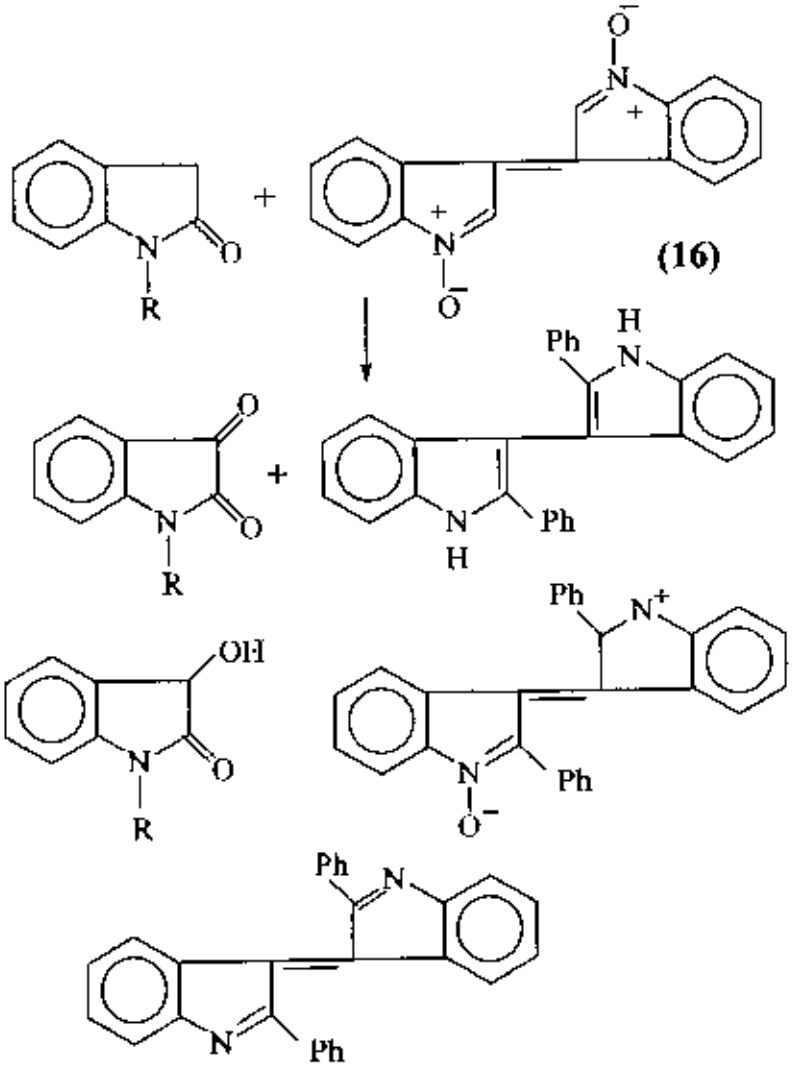
b.



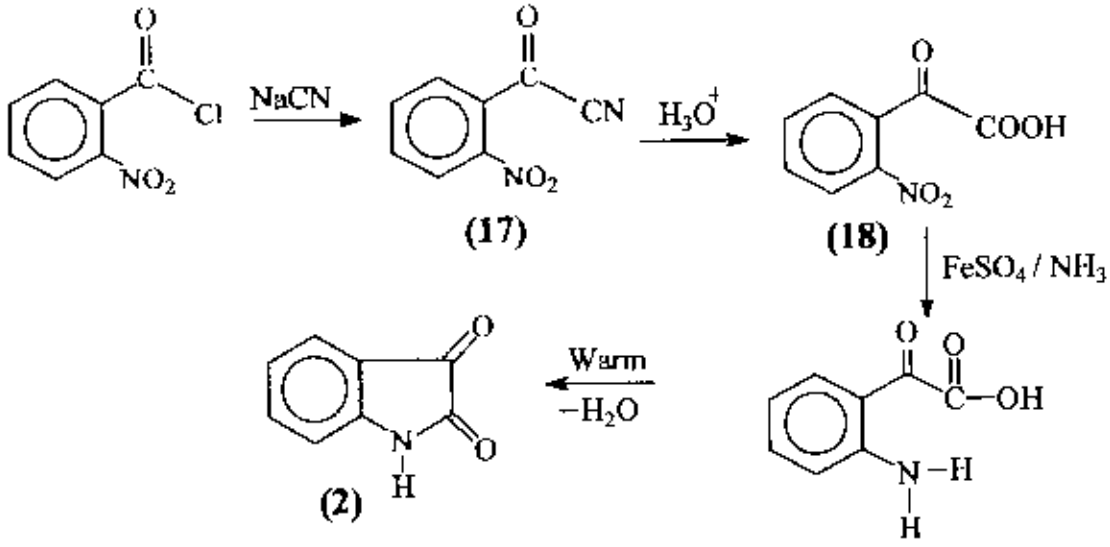
c.



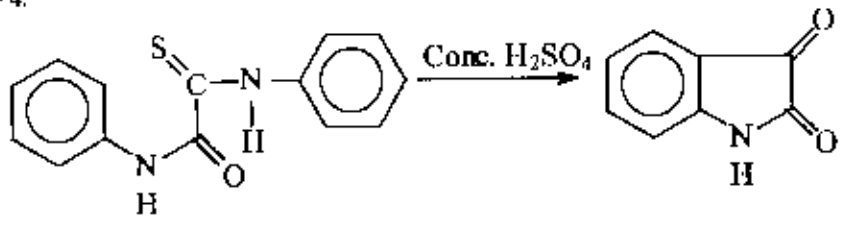
Oxidation of the synthesized oxindoles with indolic binitrone **(16)** afforded isatin as follows:



Claisen-Shadwell [12] reported the multistep synthesis of isatin. The author used *o* – nitro benzoyl chloride and sodium cyanide to obtain substituted products *o* – nitro benzoyl cyanide **(17)**. Acid catalyzed hydrolysis of the compound **(17)** gave *o* – nitro phenylpyruvic acid **(18)**. Mild reduction of **(18)** with ferrous sulfate and ammonia gave *o* – amino pyruvic acid which was dehydrated by warming to obtain the desired product **(2)**.

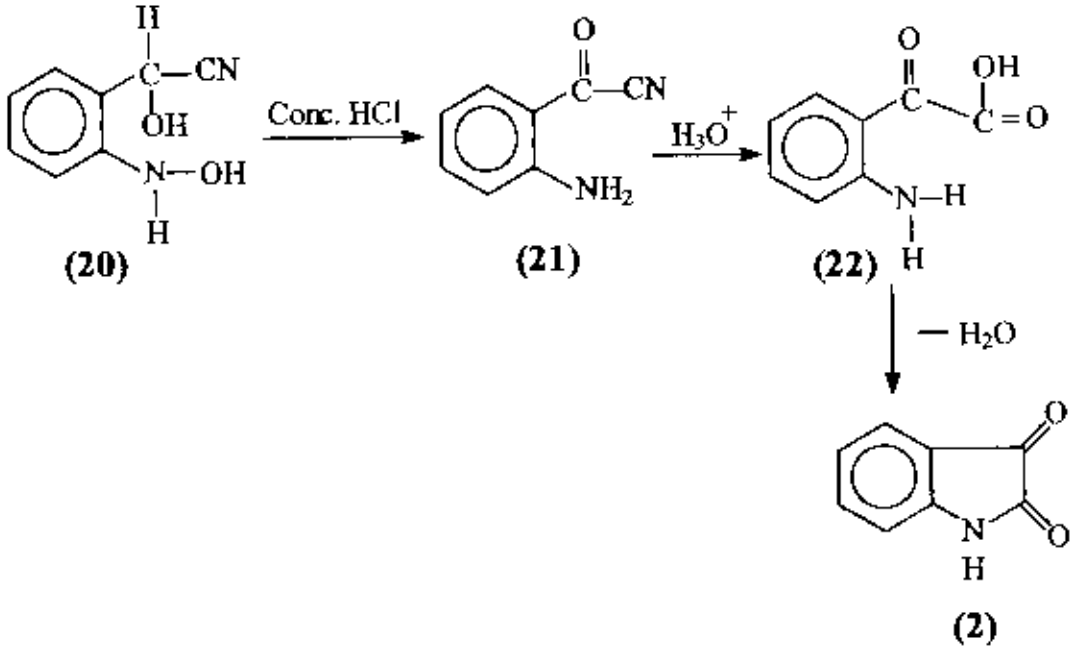


Isatin can also be formed by the treatment of thioxainilde **(19)** with cone. H_2SO_4.



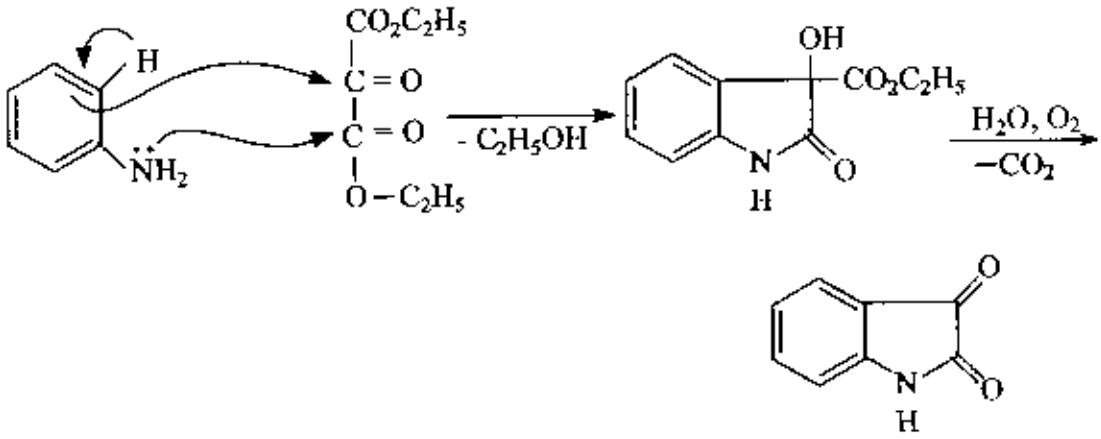
(19)

Heller[13] reported the synthesis of isatin via *o*- aminophenyl pyruvic acid **(22)**. The author synthesized **(21)** from *o*- hydroxyaminocyano mandelate **(20)** and conc. hydrochloric acid which was hydrolyzed to *o*- aminophenyl pyruvic acid **(22)** by acid catalysis. Finally the product **(22)** afforded isatin **(2)** by intermolecular water elimination.



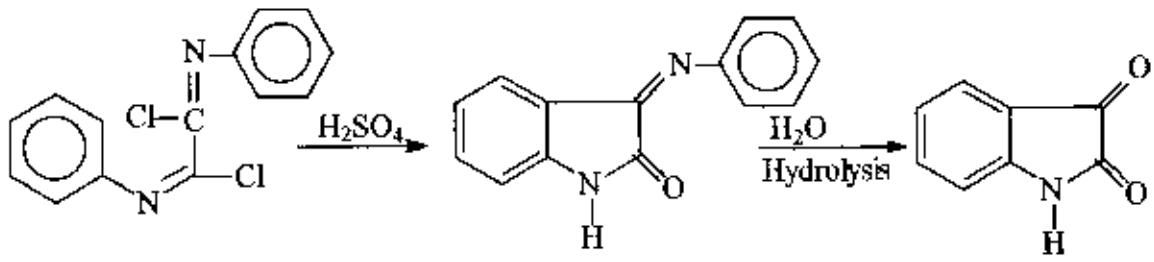
(20) (21) (22) (2)

Martinent *et al* [14] reported the most valuable method for the synthesis of many isatins. The author synthesized dioxoesters by the condensation of anilines with oxamalonic ester which on hydrolysis and subsequent decarboxylation in an open atmospheric air produced isatin.



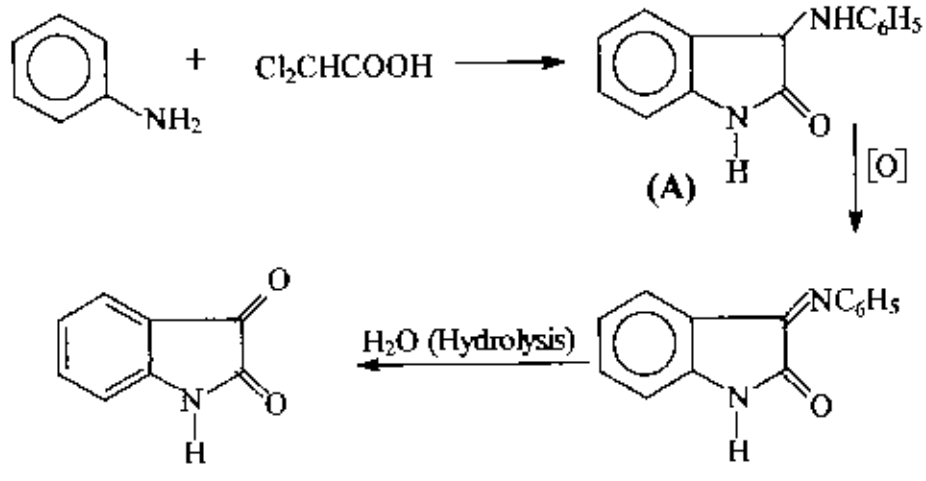
(2)

Both isatin and nuclear substituted isatin have been synthesized by treating substituted imide chlorides of oxalic acid with H_2SO_4 and subsequent hydrolysis.



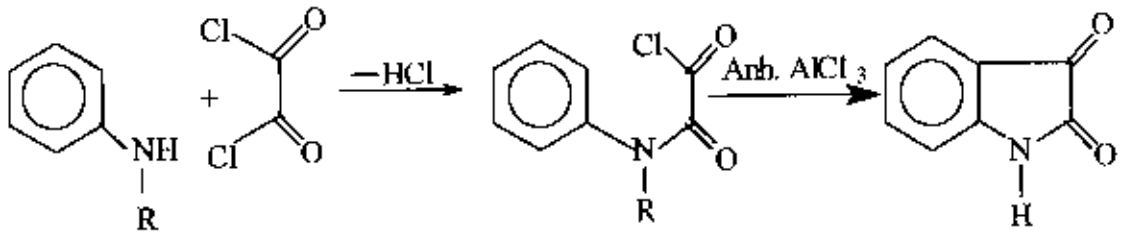
(2)

Treatment of aromatic amine with dichloro acetic acid led to the formation of intermediate **A** which upon oxidation formed **B** and subsequent hydrolysis of **B** yielded isatin.

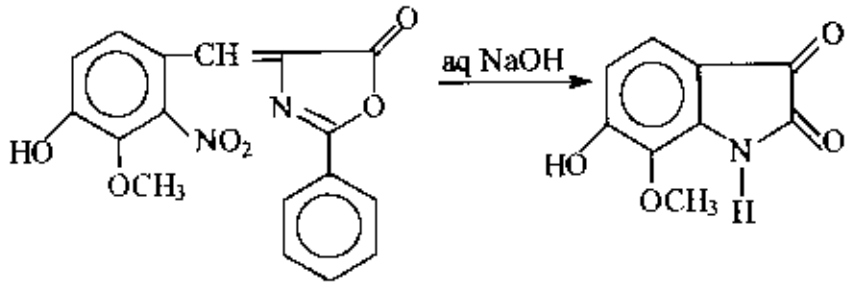


(2) (B)

Sumpter[15] reported an alternative method of isatin synthesis. In this method a mono anilide was formed by aniline with oxalyl chloride.



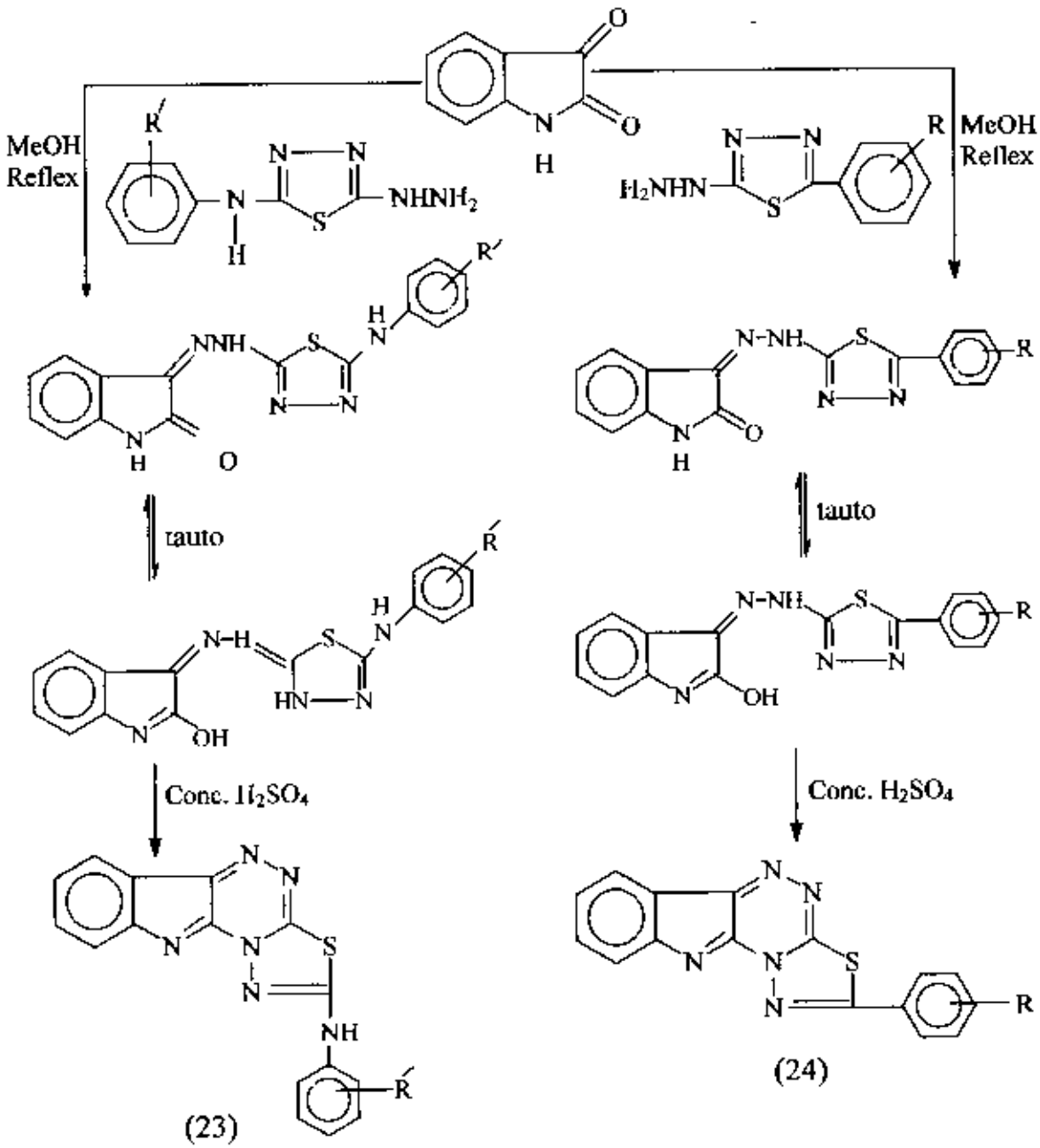
Sumpter *et al*[15] synthesized highly substituted isatin by the treatment of 2-nitro 3 – methyl – 4 – hydroxyl azalactone with aq. sodium hydroxide.



1.4 REVIEW OF THE EARLIER RESEARCH WORK ON SPIRO COMPOUND OF ISATIN

Isatin possesses both an amide and a keto functional groups in a five membered heterocyclic ring fused with an aromatic nucleus. So, usually isatin displays the characteristic reactions of keto group very easily.

Shailendra *et al* [16] very recently synthesized some important 2 – snbstituted – 1, 3, 4 – thiadiazole (2, 3 – e) I, 2, 4 – triazino (5, 6 – b) indoles (**23, 24**) by the reaction of isatin with various hydrazides followed by cyclization with conc. H_2SO_4 .

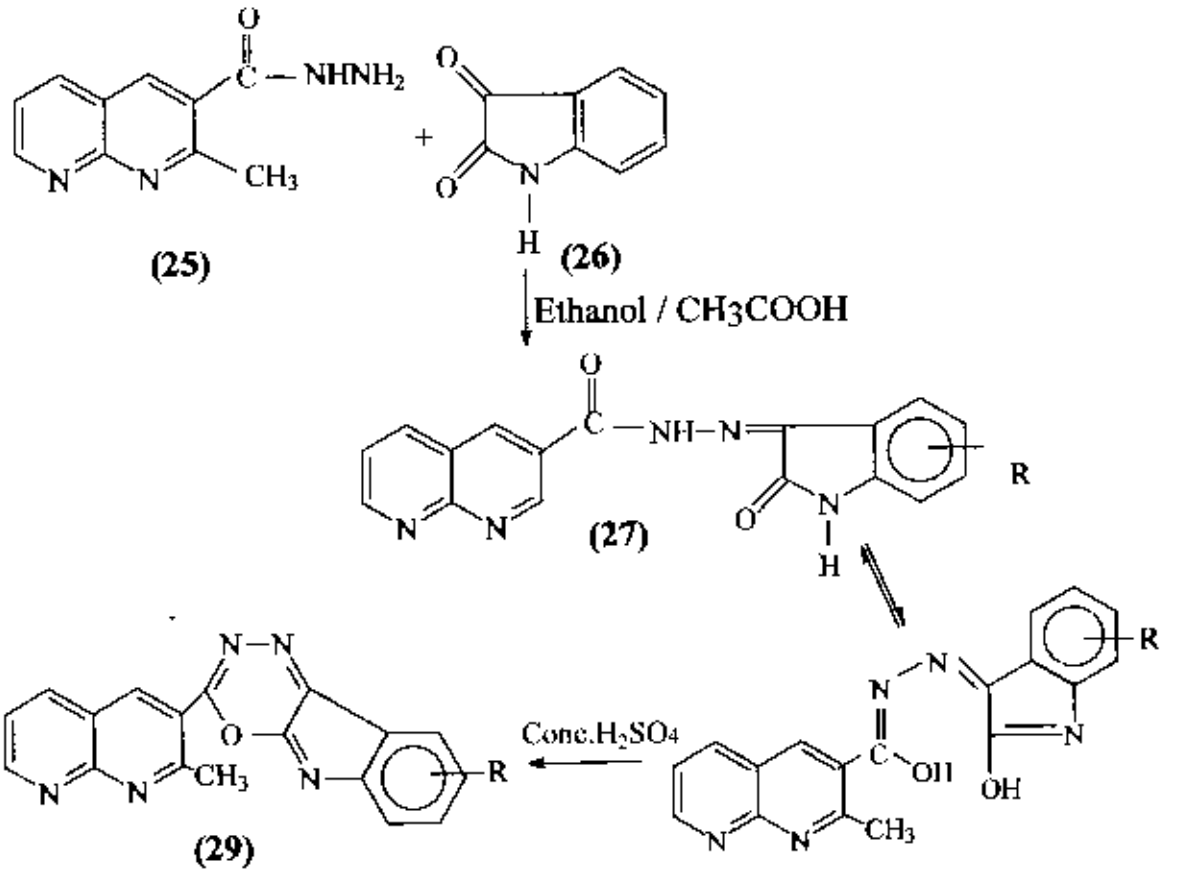


R´=H, 2-Cl, 4-CH_3, 2-OH, 4-NO_2
a b c d e

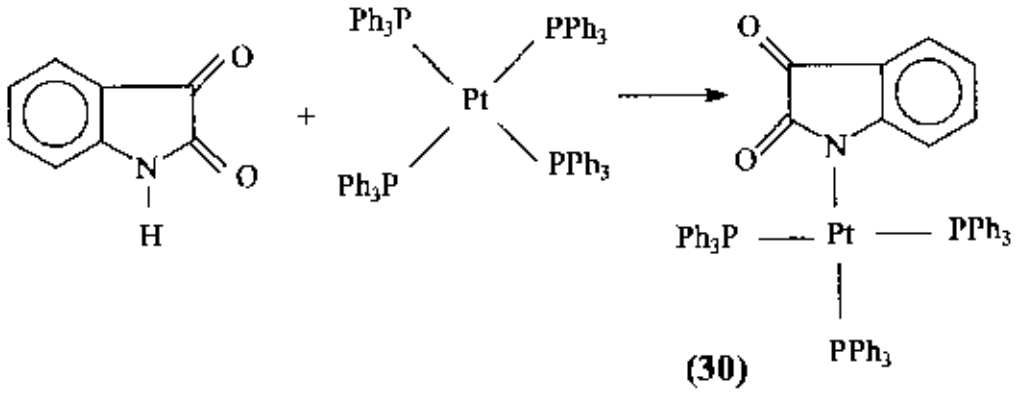
R= 2-Cl 4-CH_3 4-OCH_3 4-NO_2
a b c d

Rani and his group [17] carried out the synthesis of some 3'– (2 – methyl – 1 – 8 – naphthyridine – 3 – carbonylamino) spiro [3H – indole – 3, 2 – thiazolidine] – 2,4 (1H) – diones and 2 – (2 – methyl – 1,8 – naphthyridine 3 – yl) – [1,3,4] oxadiazino (5, 6 – b) indoles as an important bioactive

compounds. Their group followed a simple synthetic technique such as the condensation of 2 – methyl – 1,8 – naphthyridine – 3 carboxylic acid hydrazide **(25)** with different isatin **(26)** gave the corresponding isatin β – (2 – methyl –1, 8 – naphthyridine-3- carbonyl hydrazones **(27)**, which on treatment with mercaptoacetic acid in DMF in the presence of anhydrous zinc chloride afforded the substituted 3 – (2 – methyl – 1, 8 – naphthyridine – 3 – carbonylamino) spiro – [3H-indole – 3, 2 – thiazolidine] – 2, 4 (1H) diones **(28)**. Treatment of compound **(27)** with conc. Sulphuric acid undergoes cyclodehydration to yield the desired 2 – (2 –methyl 1,8 – naphthyridine – 3 – yl) – [1, 3, 4] oxadiazino [5 ,6 – b] indoles **(29)**.

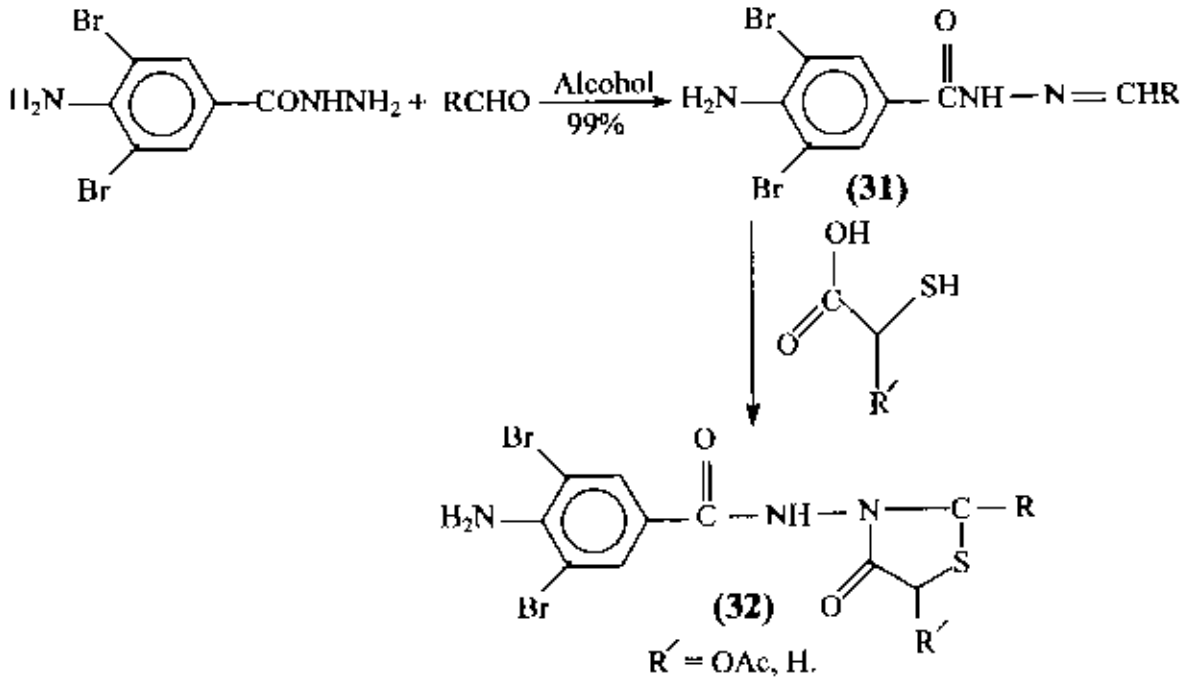


Jain *et al* [18] in 1990 prepared some metal isatin complex. According to Jain when MCl_4 (M = Sn, Ti, Th) was mixed with isatin in a suitable solvent (dry THF, dry ether in N_2 atmosphere) then metal isatin complex was obtained as **(30)**.

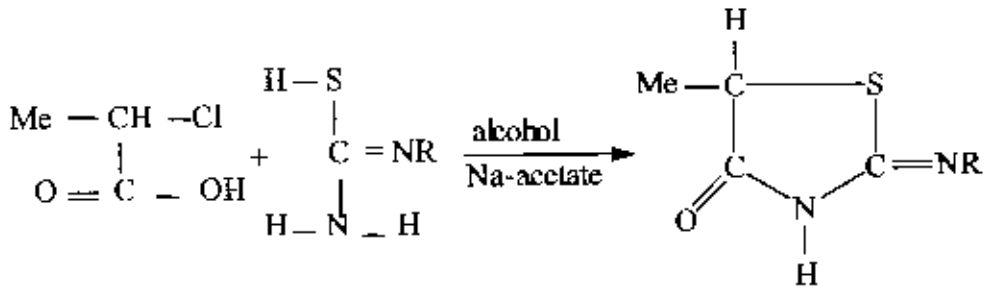


(30)

Thaker and his group [19] investigated on the thiazolidinones as potential antitubercular active compounds. Their group prepared 2 – aryl – 3– (4 – amino – 3, 5 – dibromobenzaimido) 5 – Substituted – 4 thiazolidinones **(31)** by the condensation of mercaptoalkonic acid with azomethins **(32)**.

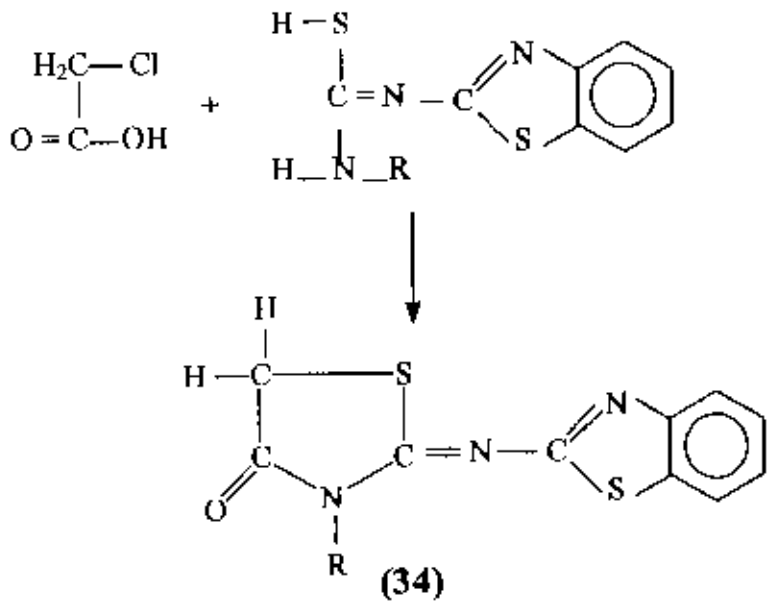


Bhargava *et al* [20] synthesized 2 – arylimino – 5 – methyl – 4 thiazolidinones and 3 – alkyl – 2, 2′– benzothaizolylimino – 4 – thiazolidines 2 – aryl amino – 5 – methyl – 4 – thaizolidinones and 3-alkyl – 2, 2′ – benzothiazolylimino – 4 – thiazolidones and investigated fungicidal activity of their hydrochlorides.



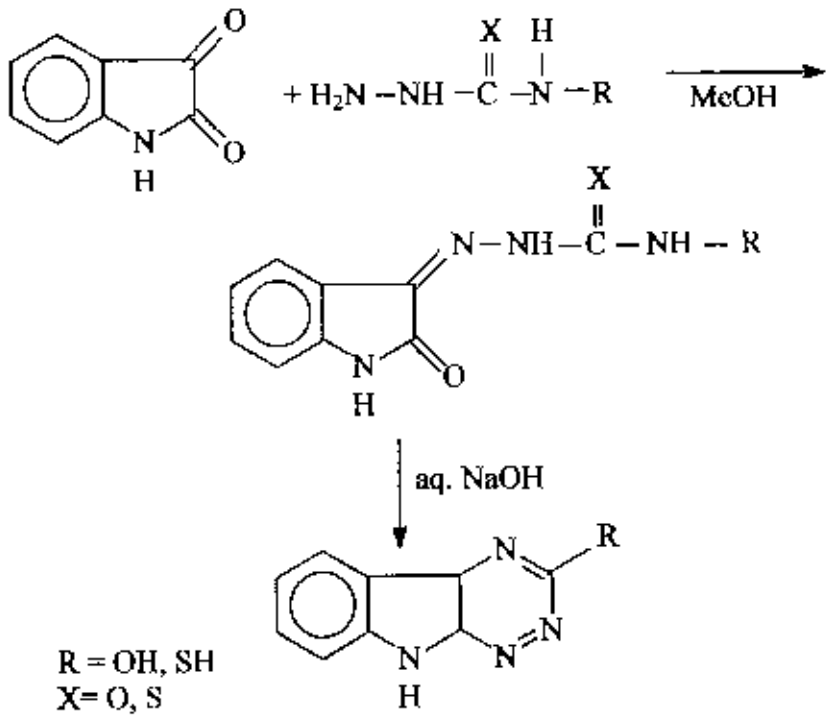
(33)

2- arylimino - 5 methyl - 4 - thiazolidinones



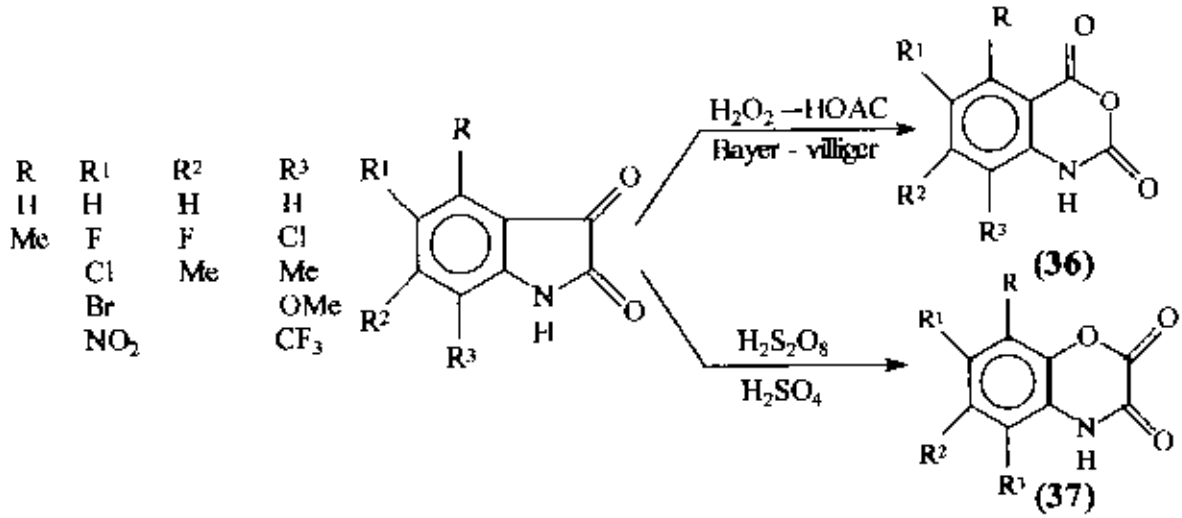
3 - alkyl - 2, 2′ - benzothiazolylimino - 4- thiazolidones.

Ioffe *et al* [21] synthesized thiosemicarbazone by thiosemicarbazide which undergoes a beautiful intracyclization to give the substituted – 1, 2, 4 – triazacarbazoles **(35)** of greater than 75% yield.

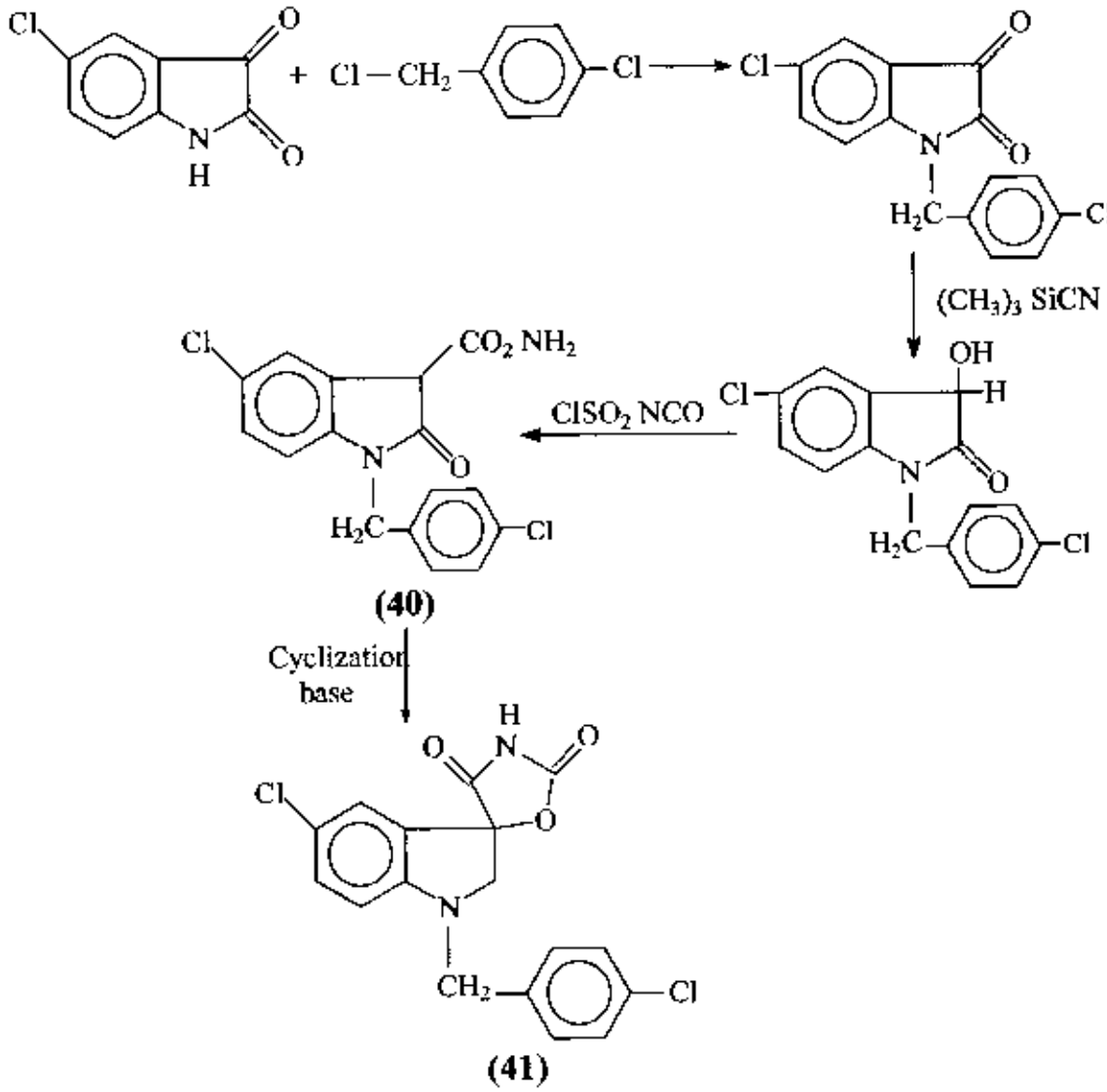


(35)

Bayer villager [22] Oxidation of isatins with H_2O_2 in AcOH gave 70–90% isatonic anhydrides **(36)** whereas oxidation of isatin with disulphuric acid in conc. H_2SO_4 gave benzoxazinediones **(37)** in an excellent yield. Each of the isomeric products **(36)** and **(37)** were uncontaminated by the other isomer.

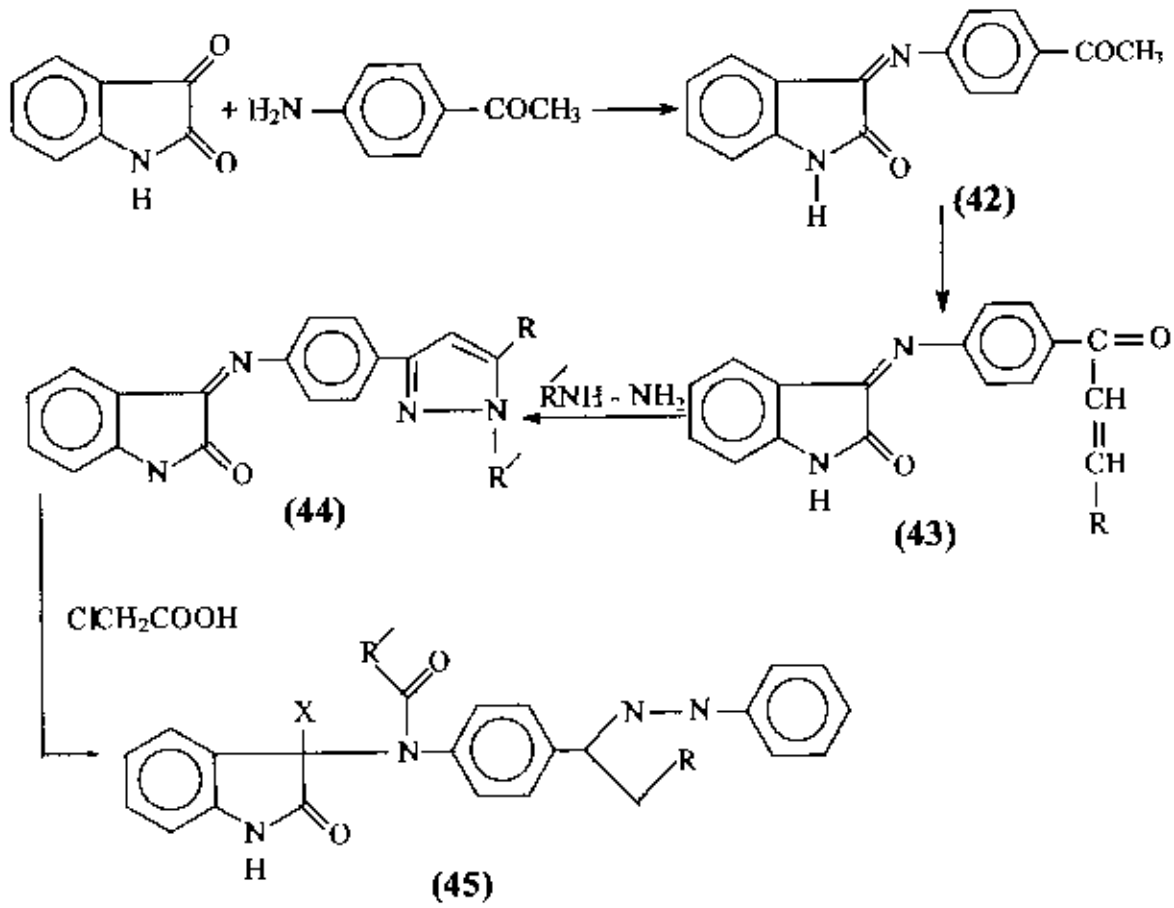


4 – Chloro isatin reacted with *p* – chloro benzyl chloride and gave *N* – substituted isatin **(38)** which was reduced by trimethylcyanosilane followed by hydrolysis gave **(39).** Compound **(39)** reacted with $ClSO_4NCO$ and then cyclocondensation in basic medium yielded the important spiro compound **(40).**



p-Methoxy aniline and isatin gave a Schiff base **(42).** The condensation and elimination of the compound gave **(43),** which reacted with substituted hydrazine and hence the product **(44)** was obtained. Compound

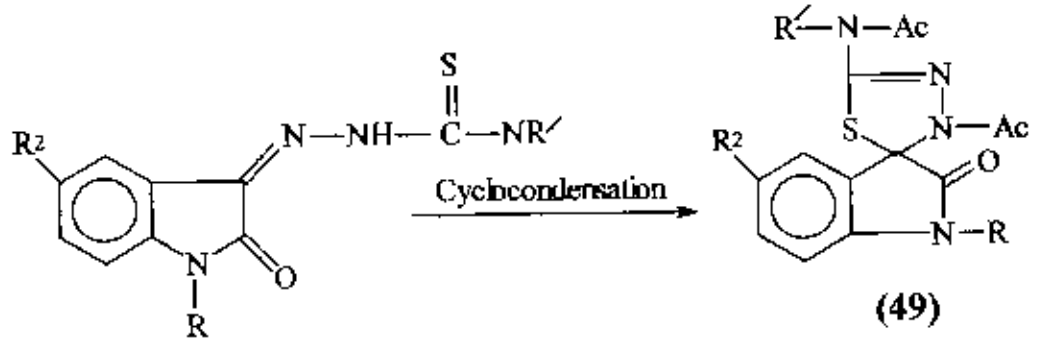
(44) was converted into spiro molecule **(45)** by cyclocondensation with mono–chloro acetic acid or mercapto–acetic acid.



X = Cl: R = Ph, 2 - HOC $_6H_4$, 4-ClC$_6H_4$, 4Me$_2$NC$_6H_4$, 4-NO$_2$C$_6H_4$

Very recently Kumud *et al* [23] synthesized 2′-substututed spiro [indoline –3, 5′ (5H)] [1, 3, 4] oxa/thiadiazolo [3, 2– thiazole] –2′– ones. The molccule has been achieved by cyclocondensation to 3–substituted spiro [indoline –3, 2 – thizolidene] – 2′, 4′ – diones with conc. H_2SO_4.

Cyclocondensation of some isatin – β – thiosemicarbazones with suitable solvent gave the following types of spiro compounds.

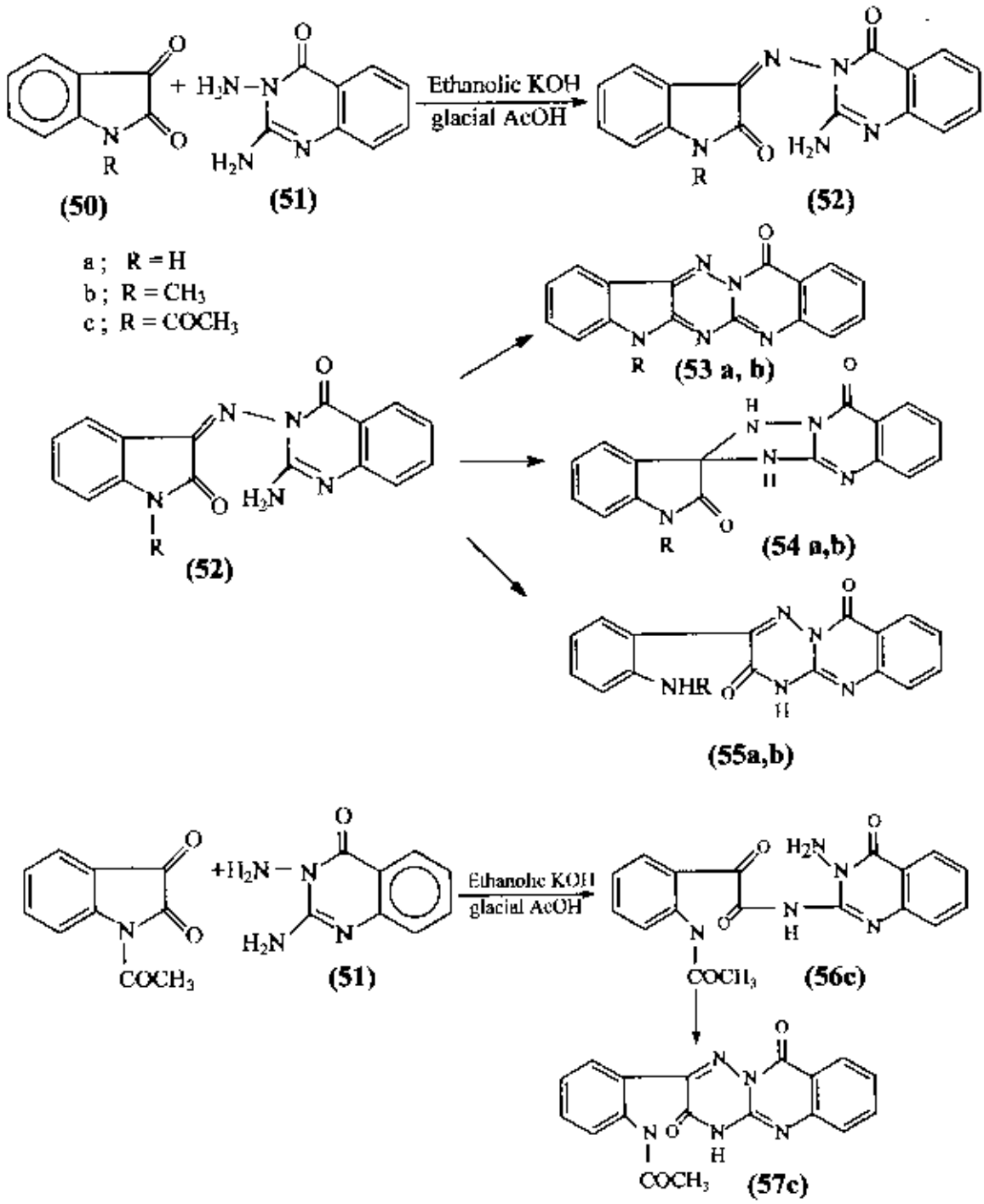


(48) **(49)**

R	R′	R2
Ac	H	H
Me	Ph	Br
H		

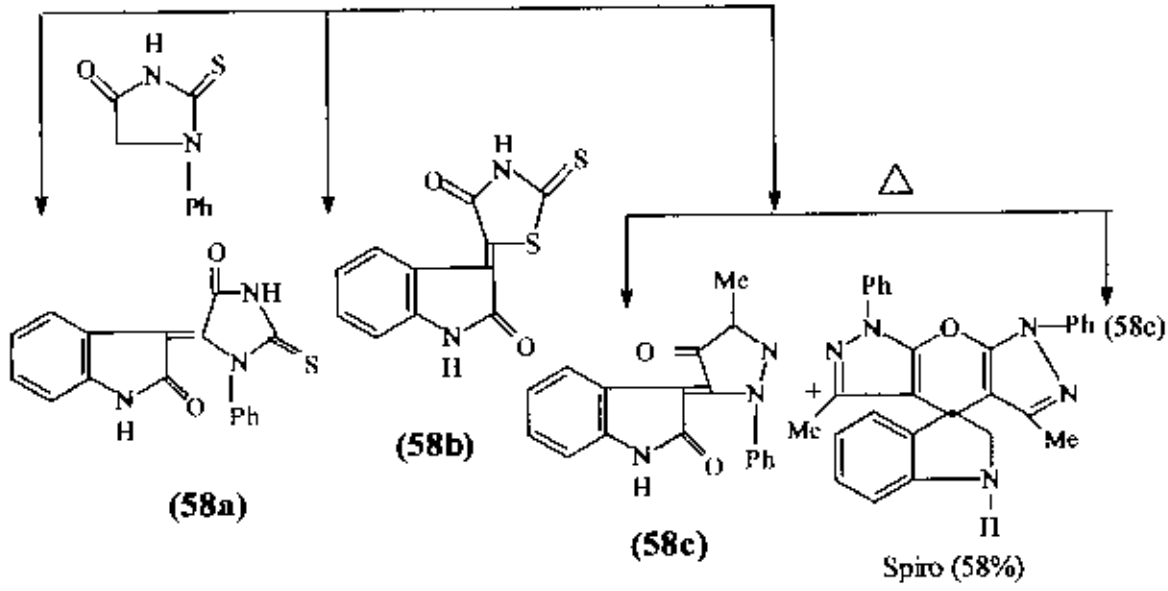
Spiro [indoline - 3, 2′(3H)] [1,3,4] thiadiazoline - 2 - ones

Recently Anshu Dandai [25] synthesized some spiro compounds. Reactions of indole – 2, 3 – dione derivatives (**50** a – c) with 2, 3 – diamino – 4 (3H) – quinazolone **(51)** in presence of catalytic amount of ethanolic KOH and glacial acetic acid have been studied and a number of products obtained *viz.* 3 – [(2 – amino – 4 – quianazolone) – imino] 2H indole – 2 – one 52 a, 3 – (2 –aminophenyl) [1, 2, 4] thiazino [3, 2 – b] quinazolonc –2, 6 – dione (**53a, b**), spiro [3H – indole – 3, 2 ′ (1H) [1, 2, 4] triazolo [5, 50 – b] quinazolone – 2, 9′ (1H, 3′H) dione (54a), indole [2′, 3′: 5, 6′] [1, 2, 4] triazino [3, 2 – b] –quinazolone-14 (7H) – one **(55a)**, *o*-oxamoylacetanilide **(56c)** and N– [2– (3, 4–diyhdro – 3, 10 – dioxo) [1, 2, 4] triazino [3, 2 – b] quinazoline) phenyl] acetamide (**57c**). The ratio of the products obtained was influenced by the solvent used and the substitutent at the indole nitrogen atom.

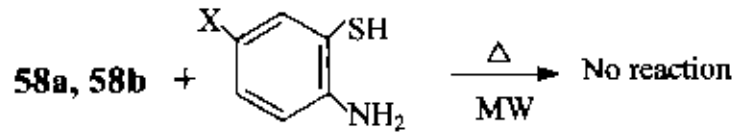


Ansu Dandai [26] and his group described an efficient solvent less method for the exclusive one pot synthesis of novel annealated 1, 5–benzothiazepines possessing a spiro 3H – indoline nucleus. The reaction between substituted *o* – aminothiophenols (**59** a-g) with 3 (imidazolidinyl / thiazolidinyl /

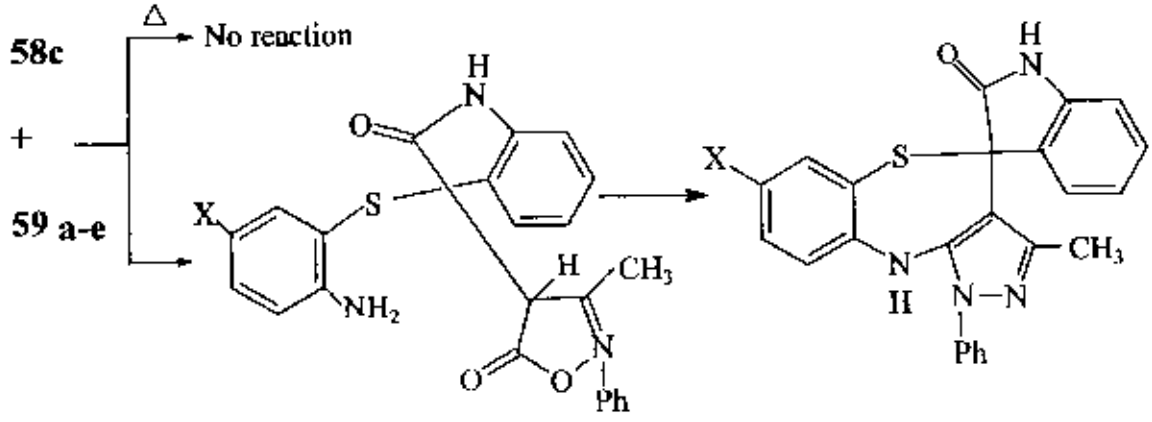
phrozolidinyl) 2H – indol – 2 – ones (**58a – c**) has been investigated under both conventional and non-conventional condition using microwave irradiation to explore the possibility of formation of different novel heterocycles due to the presence of various reaction sites available in these synthons. Exclusive formation of the title compound was satisfactory yield as was achieved under microwave irradiation coupled with various inorganic supports only in case of (**58c**) possessing pyrazole moiety. It was however, reluctant to undergo any reaction under drastic thermal conditions of prolonged reflux using strong acidic/basic catalyst in high boiling solvents for many days, indicating thereby the existence of a very strong specific microwave affect. While, (**58a**) and (**58b**) were found to uncreative in both conditions. All reactions are shown below.



Reaction in case of (**58a**) and (**58b**) did not occur and positive results were obtained only when 1, 3 – dihydro – 3 – (2 – methyl) – 5 – oxo – 4 phenyl parazolidine) – 2H – indole – 2 – one (**58c**) reacted with (**59 a-e**).

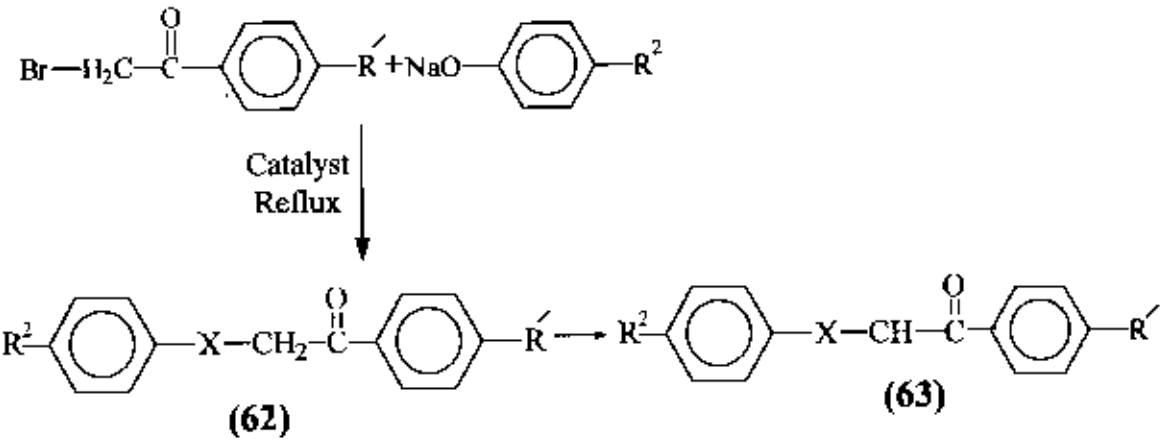


59 a-e

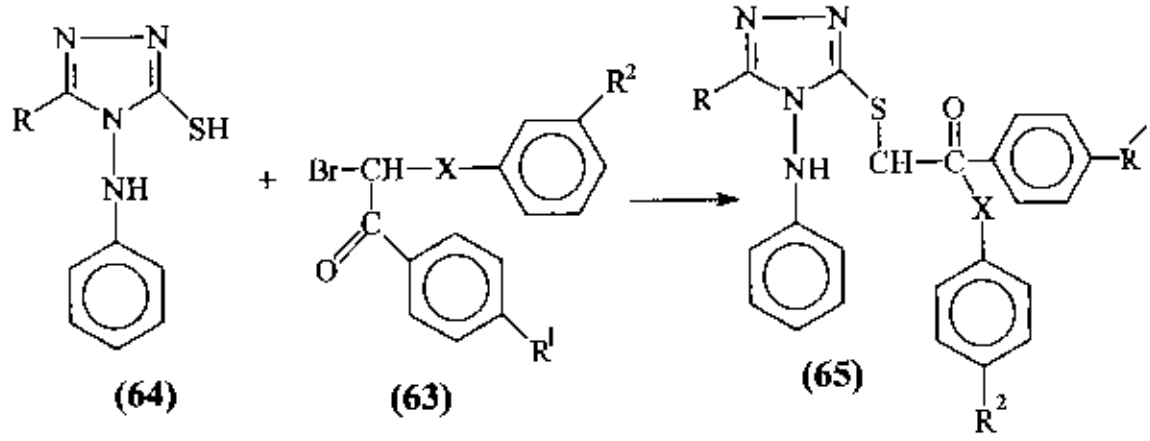


60 a-e **61 a-e**

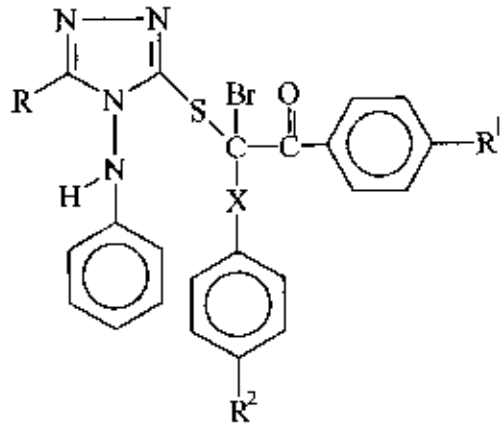
Madhukar and his group[27] synthesized some 3 – substituted 5 – phenyl – 6 substituted benzoyl – 6 – substituted phenoxy / thiophenoxy –1, 2, 4, triazole –(3, 4 – b) [1, 3, 4] thiadiazolines as potential antibacterial active compound. They used very simple synthetic technique and prepared 4 – anilino – 5 – (2′– substituted phenoxy / thiophenoxy) phenacylmercapto 3 – substituted –1, 2, 4 – triazole, (**65**, X = O, S) by the interaction of 4 – anilino – 5 mercapto – 3 – substituted –1, 2, 4 – triazole with 2 – bromo – 2 – substituted phenoxy /thiophenoxy acetophenones (**63**, X = O, S) which upon bromination followed by cyclization afforded 3-substituted – 5 – phenyl – 6 substituted benzoyl – 6 – substituted phenoxy/thiophenoxy – 1, 2, 4, – triazolo [3, 4–b] [1, 3, 4] thiadiazolines (**67**, X =O, S). The whole reactions are given below.

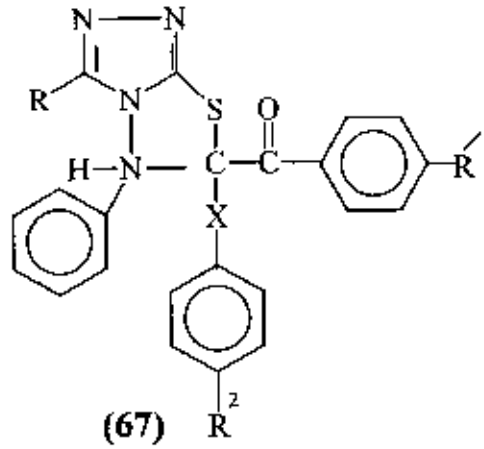


(62) (63)



(64) (63) (65)



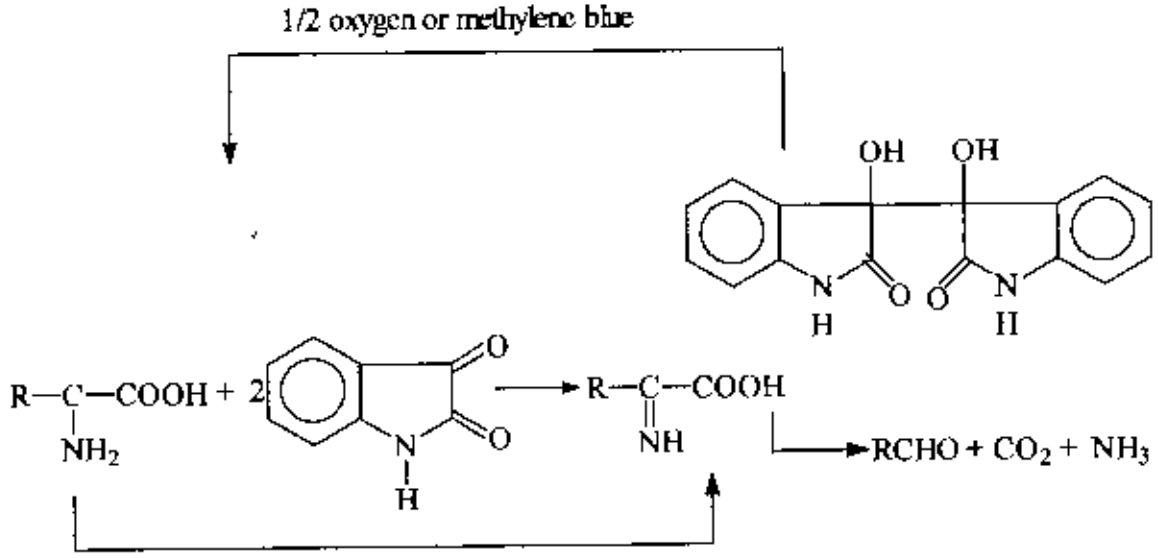


(66) (67)

1.5 ECONOMIC IMPORTANCE OF ISATIN AND ITS DERIVATIVES

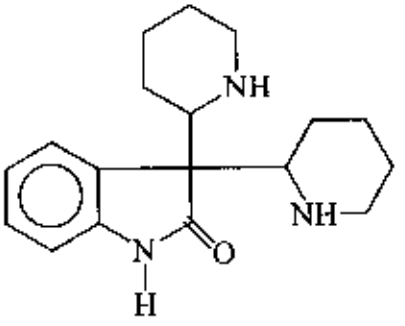
a) Enzyme like molecules

Isatin possesses an important enzyme like activity in the dehydrogenation of amino acids. Thus, heating α – aminophenylacetic acid with isatin in aqueous medium produced benzaldehyde in good yield. In other report potent activity and the following mechanism have been suggested in which either atmospheric oxygen or methylene blue served as the H–acceptor, where isatin being reduced reversibly in intermediate step as isatidine.

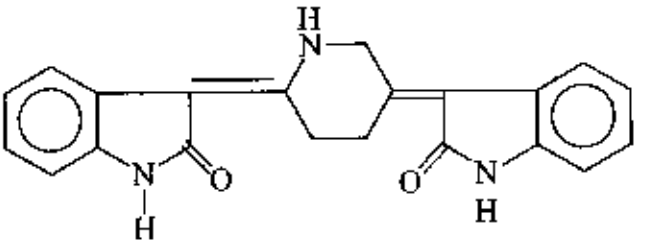


b) As Dyeing Agents

A large uumber of dyes have been synthesized from isatin. The following products **(68, 69)** were prepared from the combination of isatin and piperidine.

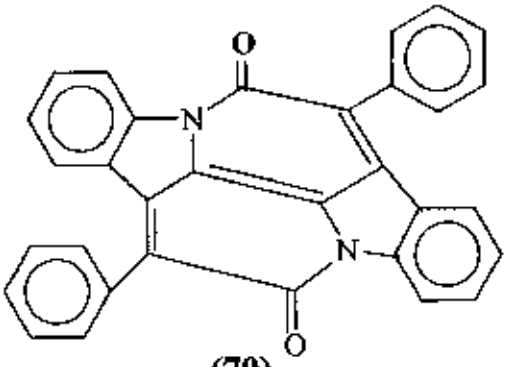


(68)

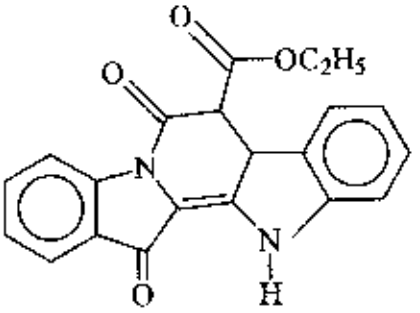


(69)

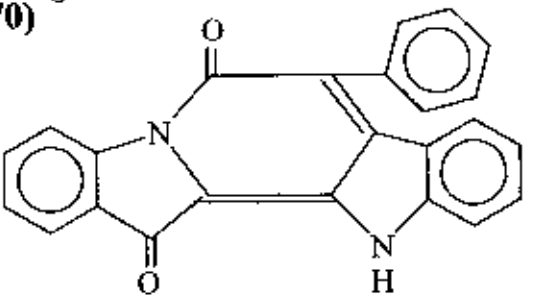
Isatin's precursor indigo can be condensed with phenyl acetyl chloride to Ciba lake red **(70)** and indigo can be condensed with malonic ester to red violet ethyl indigo malonate **(71)**. Ethyl phenyl acetate can be condensed with indigo to dye **(72)**.



(70)

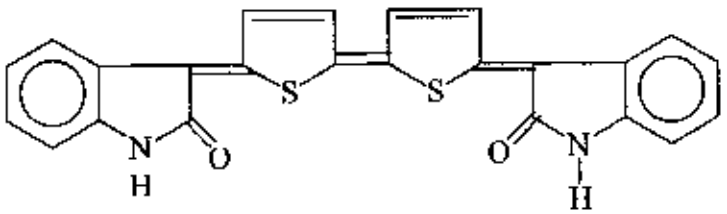


(71)



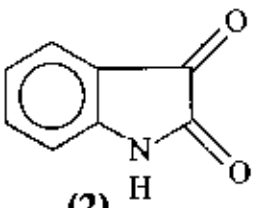
(72)

A familiar blue dye indophnin **(72)** was formed when isatin was treated with conc. H_2SO_4.



(73)

C) Physiological Effect of Isatin



(2)

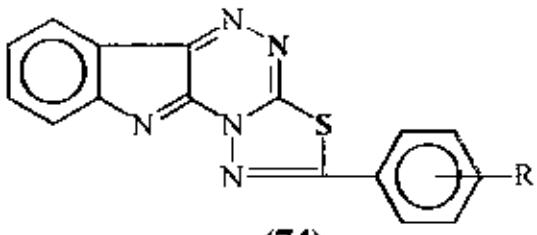
The effect of various doses of isatin (2) on electroencephalogram (EEG) manifestations of vigilance groups of rhythmic discharges and the incidence of epileptic pathology activities were studied in repeated chronic experiments in rat . Isatin (0.1– 6 mg) perfusion caused a dose dependent decrease in the amplitude of ventricular constriction and the CARDIAC output of insitu frog heart. The effect was not blocked by atropine. Isatin had no effect on guineapig or dog heart in doses upto 10 and 100 mg respectively. Isatin had little effect on blood pressure of cats and dogs.

d) As chemotherapeutic and pharmacological Agents

Isatin is well known as biologically active molecule. It has been found to possess fungicidal, bactericidal, herbicidal activities. 1, 3, 4 – thiadiazole ring is associated with broad spectrum of biological activities by virtue of in corporation to N= C= S linkage. A triazino –

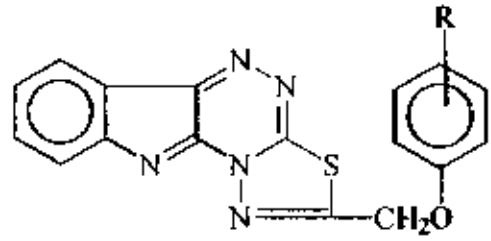
thiadiazole system may be viewed as a cyclic analogue of very important toxophore *i,e,* thiosemicarbazide which often displays diverse biological activities.

(i) On the basis of above discussion Sailendra ***et al*** [16] in 1994 prepared following some important compound **(74-76)** from isatin and heterocyclic aromatic hydrazines. All the compound showed antifungal activity.



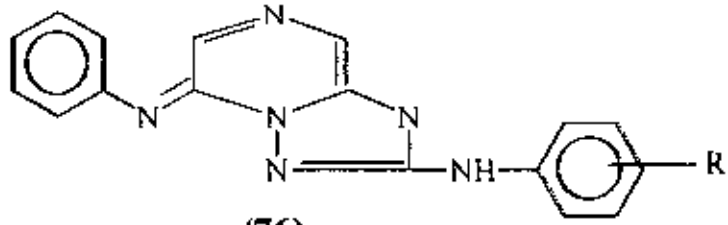
(74)

a. R = H b. R = C-Cl
c. R = 4 -Cl d. R = 3 - CH_3
e. R = 2 -OH f. R = 4 - NO_2



(75)

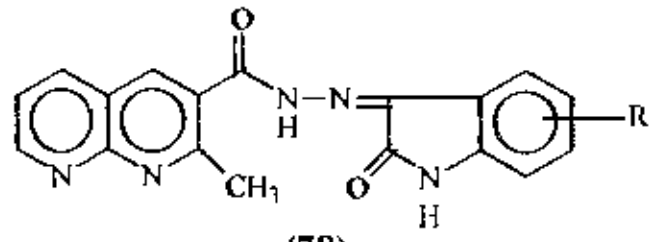
a. R = 4 -Cl
b. R = 4- CH_3 c. R = 3- Cl, 4-CH_3



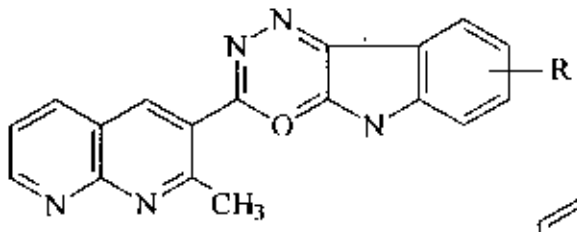
(76)

	a	b	c	d
R	4 - Cl	4 - CH_3	4 - OCH_3	4 - NO_2

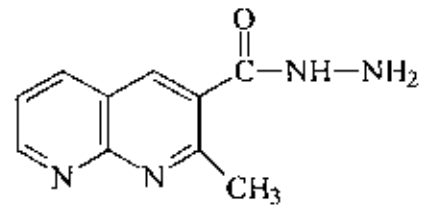
(ii) In 1995 Sudhakar ***et al*** [17] synthesized more important biologically active compounds from isatin and substituted napthyridine as follows **(78-80)**.



(78)



(79)



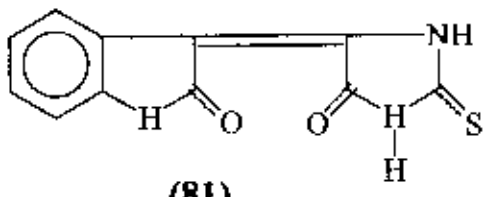
(80)

Recently, much interest has been focused on the synthesis and biological activities of substituted 8 – naphthyridines. Moreover, compounds having 4 – thiazolidinone moiety reported to be useful antimicrobial, antitubercular, and hyponotic agents. Further 1, 2, 3 – oxadiazino and indole derivatives have gained prominence because of their potential pharmaceutical values. Prompted by these observations and contributions of their work on the synthesis of 1, 8 – naphthyridines they reported here in the synthesis of novel spiro heterocyclic, *viz.* spiro [3H-indole – 3, 2 – thiazolidine] – 2, 4′ (1H) – diones and a fused heterocyclic system, [1, 3, 4] oxdiazino [5, 6 –b] indoles confining 8-naphthyridine moiety.

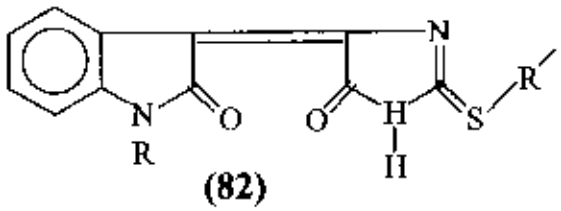
All the title compounds **(78– 80)** were screened against various bacteria and showed moderate antibacterial activity. Other compounds exhibited very weak antibacterial activity.

(iii) As Anticancer Reagent

Following compounds **(81)** and **(82)** have been reported [29] as the suppression of carcinoma (cancer).



(81)

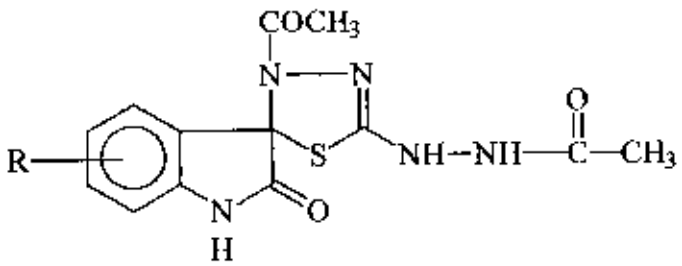


(82)

$R' = CH_3$, CH_2Ph, CH_2CO_2Et

ANTICANCER DRUG

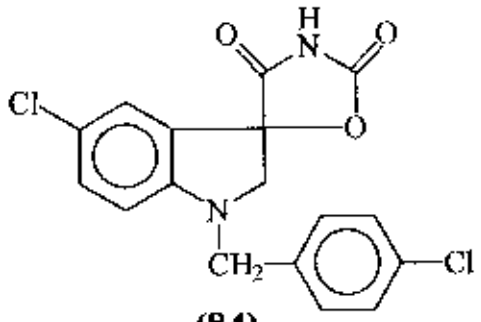
These compounds display immunosuppressive and anticancerous activities. Very recently Islam ***et al*** [24] colaboration with National Cancer Institute (NCI) of U.S.A. observe that acylated 1, 2, 4–thiadiazoline derivatives (83) of isatin shows potential anticancerous activity against a number of cancer cells.



(83)

Anticancer Drug

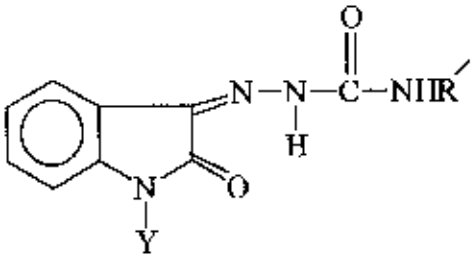
(vi) As antidiabates: The following spiro compound (**84**) can inhibit the enzymatic activity of aldose reductase and hence it is used as antidiabates [30].



(84)

Antidiabates

v) Anti ulcer Agent: Highly *N*–substituted β – thiosemicarbazides [31-32] of the following types compound **(85)** are highly active against ulcer.



n = 0, 1.

(85)

R = Cl, Br, alkyl

NR^2R^3 = Pyrrolidonyl

Y = CH_2, CO

AIM OF THE PROJECT

A comprehensive literature survey and the diverse biological activities associated with isatin derivatives, evoked us to investigate the reaction of mercapto acids with the substituted indole 2,3 – diones (isatin derivatives) under different experimental conditions with a view to obtain some isatin spiro heterocyclic compounds which might have potential biological activities.

Therefore, the aim of the project involves

i) preparation of oximino acetanilide by condensation of chloral hydrate, hydroxylamine hydrochloride and substituted aniline.

ii) cyclization with concentrated sulphuric acid and quantitative hydrolysis to substituted isatin.

iii) formation of hydrazone by the different hydrazine.

iv) synthesis of the desired heterocyclic spiro derivatives with marcapto acetic acid.

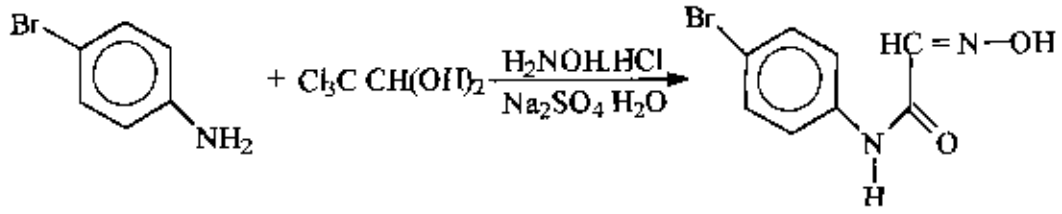
v) all the synthesized compounds will be purified by different chromatographic technique and they will be subjected to both physical and chemical methods of analyses, specially spectroscopic method.

CHAPTER – 2

EXPERIMENTAL

2.1.A. SYNTHESIS OF OXIMINO ACETANILIDE

Reaction involved



Procedure

A mixture of aniline (500 mg, 2.9 m mol), chloral hydrate (519 mg, 3.1 m mol), hydroxyl amine hydrochloride (640 mg, 9.1 m mol) was refluxed in water in presence of sodium sulphate and hydrochloric acid (0.250 ml, 3 m mol) for one and half hour. The progress of the reaction was monitored by TLC (pet.ether: ethyl acetate; 6:4, $R_f = 0.58$). Then the reaction mixture was cooled to room temperature and was filtered with suction pump and washed several times with water to remove excess sodium sulfate. Then the crude product oximino acetanilide was obtained as off-white solid and recrystallized from methanol to yield a fine off-white crystal, m. p. 149–150°C, yield 98%.

^{13}C NMR (CD_3OD, 75 MHz)

S: 118 (C–7), 123 (C– 6, C–8), 133 (C–5, C-9), 139(C–4), 144 (C–1) and 163 (C–2) ppm.

DEPT ^{13}C NMR (CD_3OD, 75 MHz)

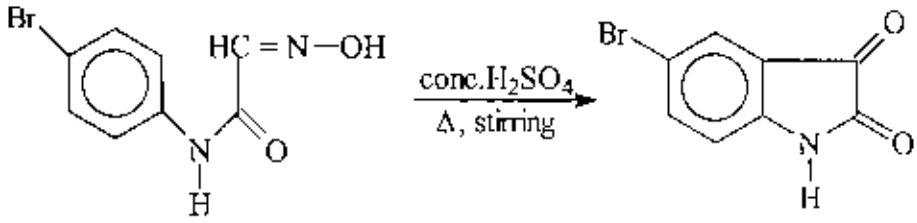
S: 123 (C_6 – H, C_8 – H), 133 (C_5 – H, C_9 – H) and 144(C_1 – H) ppm.

IR spectrum

υ_{max} (KBr) cm^{-1}: 3383 (S, N–H), 3250-3100 (w, O–H) 3066 (C–H, aromatic), 3017 (C–H, N=C–H), 1654 (>c=O), 1648 (>C=N), 1592 (C=C, aromatic), 1539 (C=C, aromatic), 1521 (C=C, aromatic), 1486 (C–N).

2.1.B. SYNTHESIS OF 5 – BROMO ISATIN

Reaction involved



Procedure

Oximino acetanilide (500 mg, 2 m mol) was heated in conc. H_2SO_4 for 1 hour 20 minutes. The progress of the reaction was monitored by TLC (pet. ether: ethyl acetate; 7: 3, $R_f = 0.65$). Then the reaction mixture was cooled to room temperature and poured upon ten to twelve times its volume of cracked ice. After standing for about one and half hour, the product was filtered with suction pump and washed several times with cooled water to remove the sulfuric acid and then dried in the air. The crude product was obtained as yellow orange coloured solid mass which was purified by silica gel column chromatography, using pet. ether and ethyl acetate (9:1) as eluant. After purification a fine yellowish crystal was obtained, m. p. 227 -230°C, yield 80 %.

^1H NMR (300MHz, DMSO – d_6)

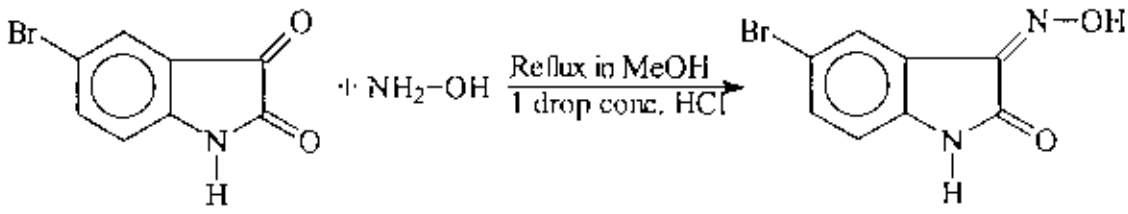
δ : 6.9 (d, 1H, aromatic), 7.6 (s, 1H, aromatic), 7.7 (d, 1H, aromatic), 11.1 (b, 1H, NH).

IR Spectrum

υ_{max} (KBr) cm^{-1}: 3179-3175 (w, N–H), 1748, 1734 (>C=O), 1706, 1700 (N–C(=O)—), 1612 (C=C, aromatic), 1469 (C = C aromatic).

2.2.A. SYNTHESIS OF 5 – BROMO ISATIN – 3 – OXIME.

Reaction involved



Procedure

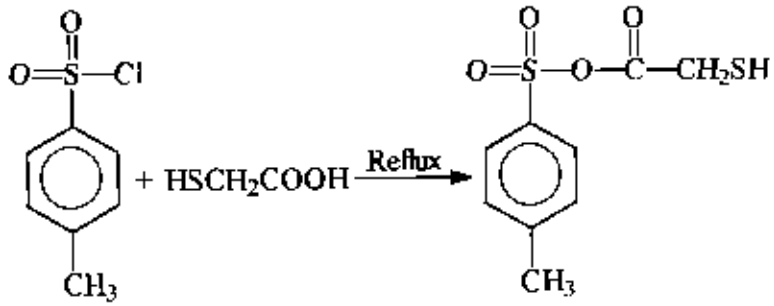
A mixture of 5 – bromoisatin (678 mg, 3 m mol) and hydroxylamine hydrochloride (200 mg, 3 m mol) was refluxed in methanol in presence of a catalytic amount of hydrochloric acid (1 drop) for 3 hours. The progress of the reaction was observed by TLC (pet.ether: ethyl acetate; 7: 3, $R_f = 0.54$). Then the reaction mixture was cooled to room temperature and methanol was removed by rotary evaporator. The resultant semi solid mass was recrystallized several times from ethyl acetate. The desired compound was isolated as a yellowish crystal, m. p. 252-255°C, yield 78%.

IR spectrum

υ_{max} (KBr) cm^{-1}: 3230-3210 (w, O–H), 3050(C–H, aromatic), 1735 (>C=O), 1718 (C=N), 1617 (C=C, aromatic), 1452 (C=C, aromatic), 1441 (C=C, aromatic).

2.2.B. SYNTHESIS OF *p* – TOSYL MERCAPTOACETATE

Reaction involved



Procedure

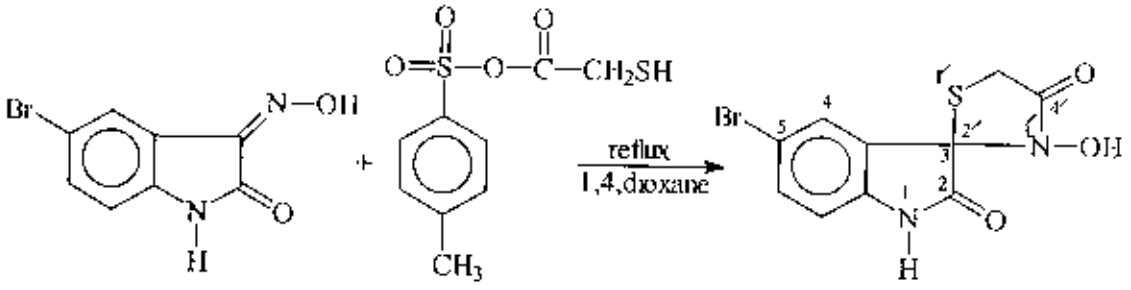
A mixture of mercaptoacetic acid (241 mg, 2.6 m mol) and *p* – toluene sulphonyl chloride (580 mg, 3 m mol) was refluxed in methanol (7 ml). The reaction was monitored by TLC (ethyl acetate : *n* – hexane; 2:8, R_f = 0 40). The reaction mixture was cooled to room temperature. Then the solvent and excess mercaptoacetic acid were removed by rotary evaporator. After evaporation pure violet liquid was obtained, yield 65%.

^{1}H NMR (300 MHz, $CDCl_3$)

δ : 2.2 (m, 1H, S – H), 2.4 (S, 3H, – CH_3), 3.7 (S, 2H, – CH_2 – S), 7.3 (d, 2H, aromatic), 7.8 (d, 2H, aromatic).

2.2.C. SYNTHESIS OF 3′(HYDROXY) SPIRO [5 – BROMO INDOLINE – 3, 2′–THIAZOLIDINE] – 2, 4′ – DIONES

Reaction involved



Procedure

A mixture of 5-bromoisatin-3-oxime (0.482 gm, 2 m mol) and *p* – tosylmercaptoacetate (1.5 gm, 6 m mol) was refluxed in 1.4 dioxane for 2 hours. The progress of the reaction was monitored by T.L.C. (ethyl acetate: pet.ether; 6 : 4, R_f = 0.66). Then 1, 4 – dioxane was removed by rotary evaporator. The crude mass was purified by column chromatography as off – white crystal, m. p. 180-182°C, yield 45%.

^{1}H NMR (300MHz, $CDCl_3$)

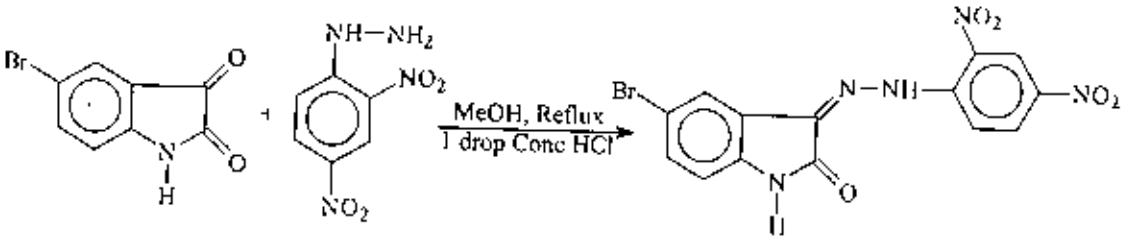
δ: 1.2 (b, 1H, O –H), 2.03 (5, 2H, – C(=O)– CH_2), 6.8 (d, 1H, aromatic), 7.3 (d, 1H, aromatic), 7.4 (s, 1H, aromatic), >10 (1H, N – H).

IR Spectrum

υ_{max} (KBr) cm^{-1}: 3400-3100 (OH, N–H), 1720 (w, C=O), 1600 (C=C, aromatic), 1490 (C=C, aromatic), 1450 (C=C, aromatic).

2.3.A. SYNTHESIS OF 5 – BROMOISATIN – 3 (2, 4 – DINITROPHENYL) – HYDRAZONE.

Reaction involved



Procedure

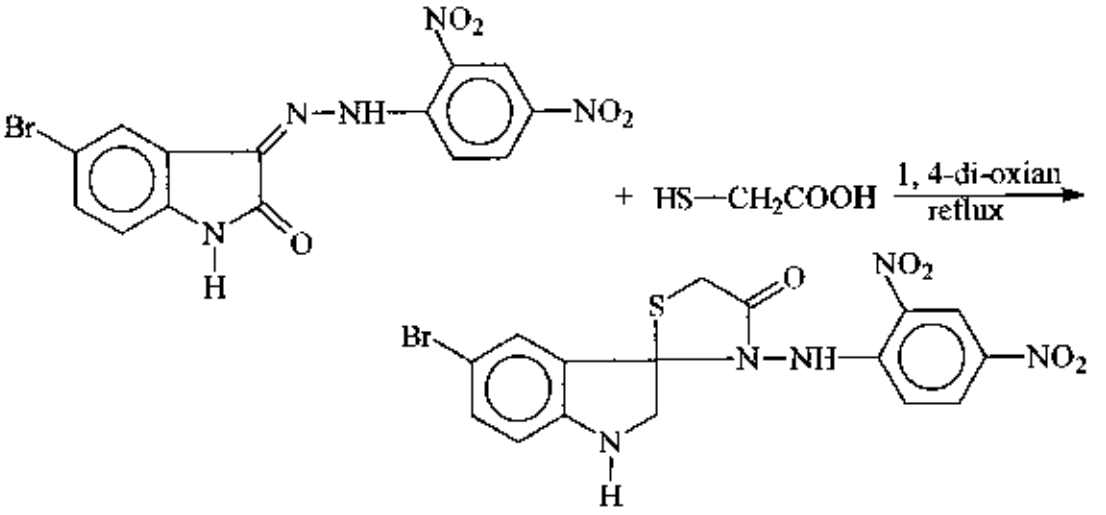
A mixture of 5 – bromoisatin (452 mg, 2 m mol) and 2,4 dinitrophenyl hydrazine (398 mg, 2 m mol) was refluxed in methanol (8 ml) in presence of catalytic amount hydrochloric acid (1 drop) for 4 hours. The progress of the reaction was observed by TLC (ethyl acetate : pet.ether; 5:5, $R_f = 0.82$). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resultant solid mass was recrystallized several times from ethyl acetate. The desired compound was isolated as red colour, m. p. 260-263°C, yield 75%.

IR spectrum

υ_{max} (KBr) cm^{-1} : 3600-3233(w, 2 N-H), 1730(>C=O), 1695 (C=N), 1637, 1612, 1589, 1500 and 1471 (C=C, aromatic).

2.3.B. SYNTHESIS OF 3'(2, 4 – DINITROPHENYL AMINO) SPIRO [5 – BROMO INDOLINE– 3, 2'-THIAZOLIDINE] – 2, 4' – DIONES.

Reaction involved

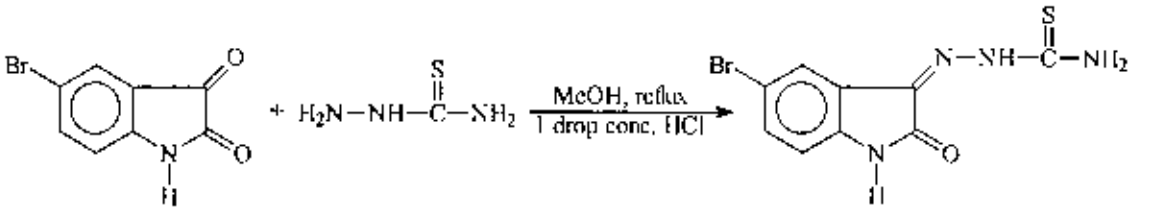


Procedure

A mixture of 5 – bromoisatin- 3 (2,4 – dinitrophenyl) – hydrazone (0.406gm, 1 m mol) and mercaptoacetic acid (184 mg, 2 m mol) was refluxed in 1, 4 – dioxane for 24 hours. The progress of the reaction was monitored by TLC but no product was observed on TLC, only reactant was isolated.

2.4.A. SYNTHESIS OF 5 – BROMOISATIN – 3 – THIOSEMI CARBAZONE

Reaction involved



Procedure

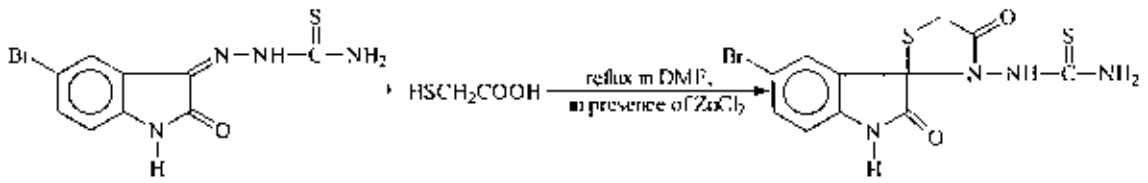
A mixture of 5 – bromoisatin (678 mg, 3 m mol), thiosemicarbazide (273 mg, 3 m mol) and one drop concentrated hydrochloric acid was refluxed in methanol (8 ml) for 6 hours. The progress of the reaction was monitored by TLC (ethyl acetate : pet.ether ; 4:6, R_f = 0.57). Then the reaction mixture was cooled to room temperature and methanol was removed by rotary eveporator. The resultant solid mass was recrystallized several times from ethyl acetate and a yellow crystal was obtained, m. p. 258-260°C, yield 90%.

IR spectrum

υ_{max} (KBr) cm^{-1} : 3414-3161(w, 2 N – H, 1 NH_2), 1696(>C=O), 1684(C=N), 1607, 1491, 1459 (C = C, aromatic), 1444(C = S).

2.4.B. SYNTHESIS OF 3' (THIOUREIDO) SPIRO [5 – BROMOINDOLINE – 3, 2' – THIAZOLIDINE] – 2, 4' – DIONES.

Reaction involved



Procedure

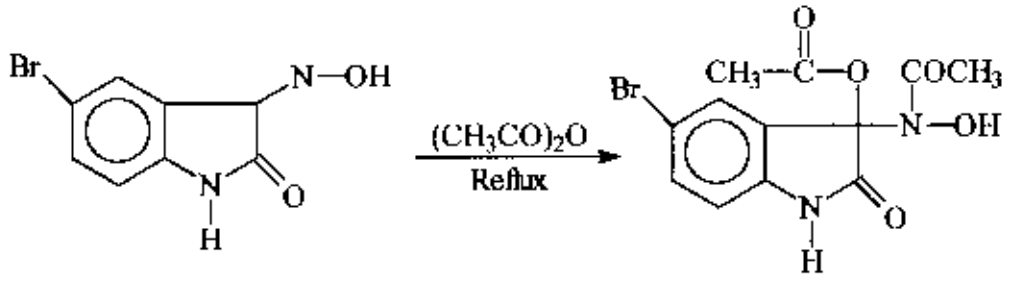
A mixture of 5-bromoisatin – 3 – thiosemicarbazone (598 mg, 2 m mol) and mercaptoacetic acid (552 mg, 6 m mol) was refluxed in DMF (8 ml) for 8 hours in presence of catalytic amount of zinc chloride. The progress of the reaction was monitored by TLC (ethyl acetate : pet.ether ; 4:6, R_f = 0.57). The reaction mixture was then cooled to room temperature and DMF was removed by adding water and subsequent extraction with chloroform. The crude solid mass was purified by column chromatography as greyish crystal, m. p. 210-212°C, yield 85%.

^{1}H NMR (300 MHz, $CDCl_3$)

δ : 2.2 (s, 2H, – $COCH_2$ –), 2.8 (b, 2H, NH_2), 7.0 (d, 1H, aromatic), 7.4 (d, 1H , aromatic), 7.8 (1H, aromatic), 8.8 (1H, N-H), 11.2 (1H, N-H).

2.5.B. SYNTHESIS OF 3(*N*- HYDROXY – *N* – ACETYL) AMINO – 3 – ACETOXY – 5 – BROMOINDOLE

Reaction involved



Procedure

A mixture of 5 – bromoisatiu – 3 – oxime (482 mg, 8 m mol) was refluxed in acetic anhydride (7 ml) for 3 hours. The progress of the reaction was monitored by TLC (ethyl acetate: pet.ether ; 7:3, R_f = 0.54). The reaction mixture was cooled to room temperature and acetic anhydride was removed by adding water and subsequent extraction with chloroform. The crude solid then purified by column chromatography. The desired compound isolated as a white solid crystal. m. p. 135°C, yield 58%.

IR spectrum

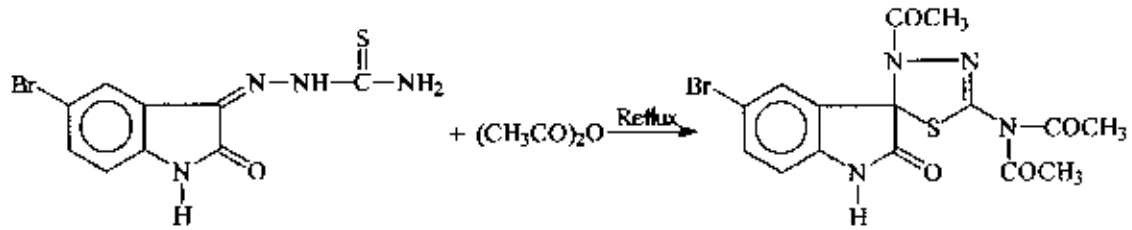
υ_{max} (KBr) cm^{-1} : 3425-3375 (w, 0-H), 3240– 3190 (w, N-H), 1734(>C=O), 1718 (>C=O), 1616 (C=C, aromatic) and 1451(C=C, aromatic).

^{1}H NMR (300 MHz, DMSO- d_6)

δ : 2.49 (s, 3H, – $COCH_3$) , 2.5 (s, 3H, – $OCOCH_3$) , 6.8 (d, 1H, aromatic), 7.5 (d, 1H, aromatic), 8.0 (s, 1H, aromatic), 10.9-10.8 (b, 1H, N-H).

2.6. B. SYNTHESIS OF 2′ (DIACETYLAMINO) – 4′ – *N* – ACETYL – SPIRO – [Δ^2 – (1′, 3′, 4′) – THIADIAZOLIDINE (5′, 3) – 5 – BROMOINDOLINE].

Reaction involved



Procedure

5 – Bromo isatin – 3 – thiosemicarbazone (398 mg, 2 m mol) was refluxed in acetic anhydride (7 ml) for 2 hours. The progress of the reaction was monitored by TLC (pet.ether : ethyl acetate ; 6 : 4, $R_f = 0.56$). The reaction mixture was then cooled to room temperature and extra acetic anhydride was removed by adding water and subsequent extraction several times with chloroform. The resultant solid mass was purified by column chromatography. The desired compound was isolated as a white crystal, m. p. 158 – 160°C, yield 62%.

^{1}H-NMR (300 MHz, $CDCl_3$)

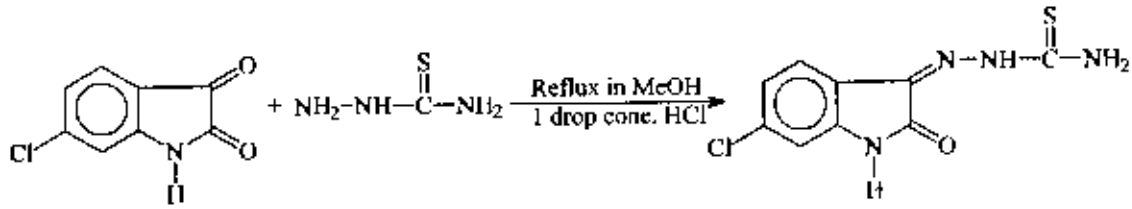
δ : 1.5 (S, 6H, –$COCH_3$), 2.21 (S, 3H, –$COCH_3$) 7.4 (d, 1H, aromatic), 8.6 (2H , aromatic), >10 (1H, N – H).

IR spectrum

υ_{max} (KBr) cm^{-1}: 3400 (w, N-H), 1766 (>C=O), 1718 (>C=O), 1710 (>C=O), 1616 (C=N), 1466 (C=C, aromatic), 1407 (C=C, aromatic).

2.7.A. SYNTHESIS OF 6 – CHLOROISATIN – 3 – THIOSEMICARBAZONE

Reaction involved

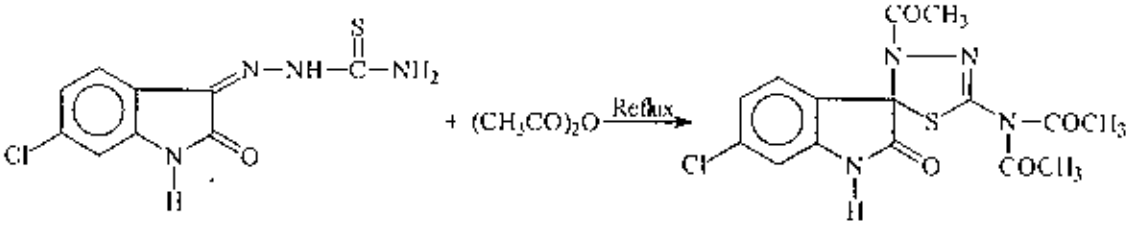


Procedure

A mixture of 6 – chloroisatin (363 mg, 2 m mol) and thiosemicarbazide (182 mg, 2 m mol) was refluxed in methanol in presence of catalytic amount of hydrochlroric acid (1 drop) for 6 hours. The progress of the reaction was observed by TLC (pet.ether : ethyl acetate; 6 : 4, R_f = 0.63). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resultant solid was recrystallized several times from ethyl acetate. The desired compound was isolated as a yellow crystal, m. p. 218-220, yield 85%.

2.7.B. SYNTHESIS OF 2′ (DIACETYLAMINO) – 4′ – *N* – ACETYL – SPIRO – |Δ^2 – (1′, 3′, 4′) – THIADIAZOLIDINE (5′, 3) – 6 – CHLOROINDOLINE|.

Reaction involved



Procedure

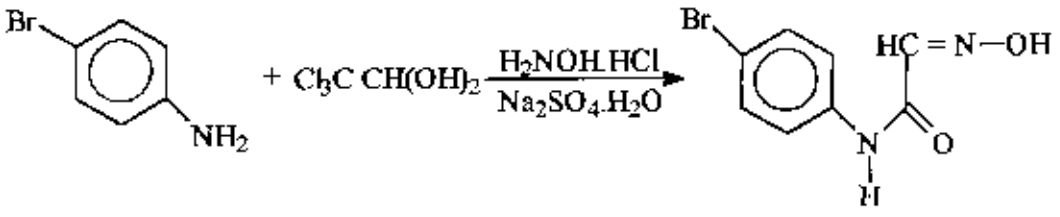
A mixture of 6-chloroisatin – 3 - thiosemicarbazone (255 mg, 1 m mol) was refluxed in acetic anhydride (7 ml) for 4 hours. The progress of the reaction was monitored by TLC (ethyl acetate : pet.ether; 4:6, R_f = 0.66). Then the reaction mixture was cooled to room temperature and excess acetic anhydride was removed by adding water and subsequent extraction with ethyl acetate. The resultant solid mass was purified by column chromatography. The desired compound was isolated as a graphite crystal m. p. 165-167°C, yield 57%.

CHAPTER – 3

RESULT & DISCUSSION

2.1.A. SYNTHESIS AND CHARACTERIZATION OF OXIMINO ACETANILIDE

A mixture of aniline (500 mg, 2.9 m mol), chloral hydrate (519 mg, 3.1 m mol), hydroxyl amine hydrochloride (640 mg, 9.1 m mol) was refluxed in water in presence of sodium sulphate and hydrochloric acid (0.250 cc, 3 m mol) for one and half hour. The progress of the reaction was monitored by TLC (pet ether: ethyl acetate; 6:4, $R_f = 0.58$). Then the reaction mixture was cooled to room temperature and was filtered with suction pump and subsequently washed with water several times to remove excess sodium sufate. Then the crude residue was obtained as off-white solid and recrystallized from methanol to yield a fine off–white crystal, m. p. 149 – 150°C, yield 98%.



The infrared spectrum (**Fig: 1**) showed a sharp absorption band at 3383 cm^{-1} was indicative for non-hydrogen bonded N–H stretching. The wide band ranging from 3250-3100 cm^{-1} was for O-H moiety. The band at 3066 cm^{-1} and 3017 cm^{-1} were suggestive for aromatic C–H stretching and immino C–H stretching respectively. The band at 1654 cm^{-1} and 1648 cm^{-1} were distinctive for C=O and C=N moieties respectively. The characteristic bands at 1592, 1539 and 1521 cm^{-1} were ascribable for aromatic C=C bonds.

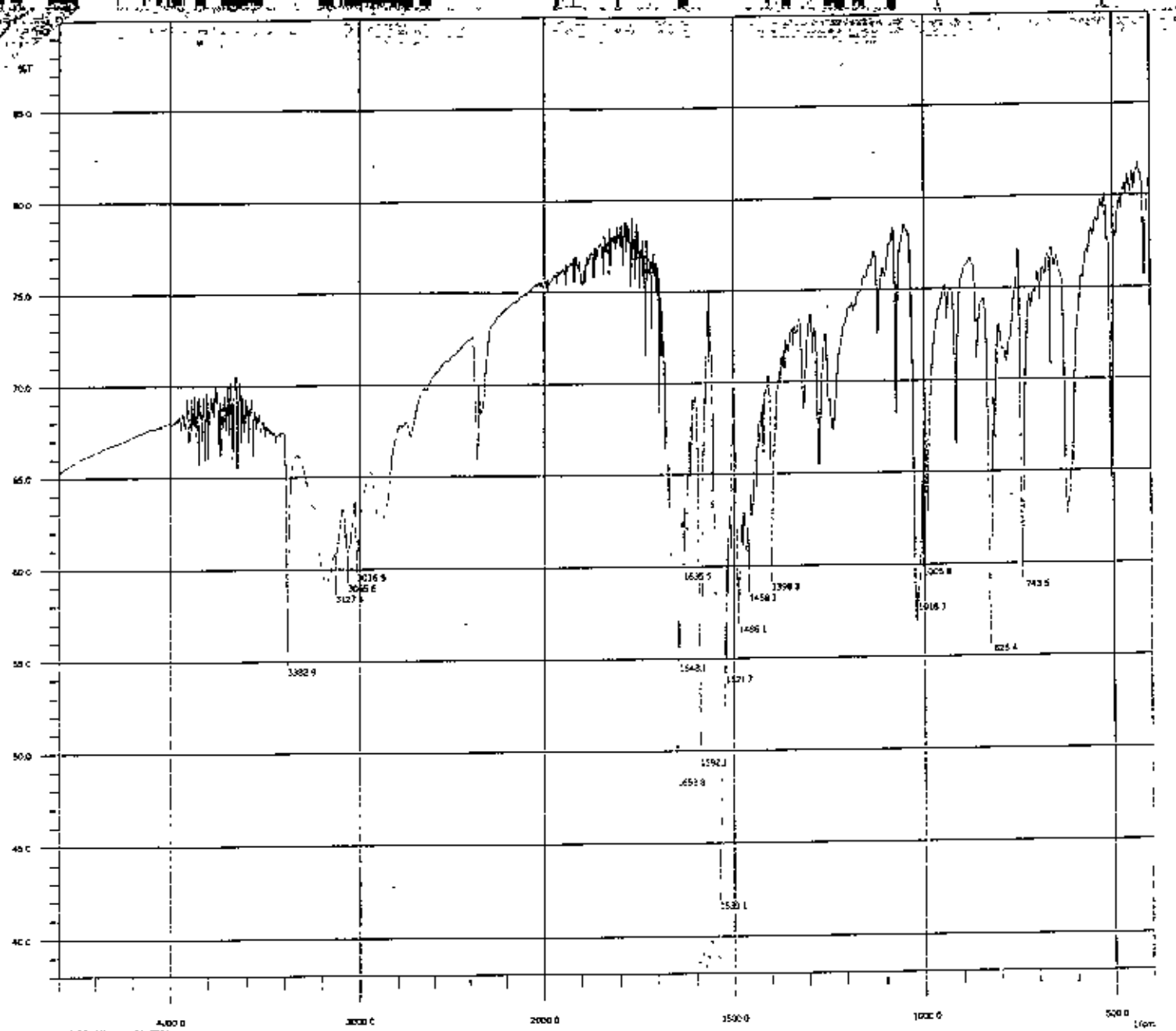


Fig 1: IR spectrum of Oximino acetanilide.

Threshold: 62, Noise: 2, No Range Selection

No	Pos. (1/cm)	Inten. (%T)
1	743.5	59.703
2	828.4	56.230
3	1005.8	60.449
4	1018.3	58.562
5	1398.3	59.725
6	1458.1	59.682
7	1486.1	57.443
8	1521.7	54.748
9	1539.1	42.510
10	1592.1	50.253
11	1635.5	60.354
12	1648.1	55.376
13	1653.8	49.180
14	3016.5	60.426
15	3065.6	60.883
16	3127.4	60.826
17	3382.9	55.309

INA, June 01, 2004

The ^{13}C NMR spectrum (CD_3 OD, 75 MHz, **Fig: 2**) showed six peaks at different chemical shift values which were suggestive for six different types of carbons. Amongst them two carbon were identical at 123 ppm and 133 ppm for (C–6, C–8) and (C–5, C–9) respectively. The characteristic peak at 163 ppm was for carbonyl carbon and 144 ppm for imino carbon.

The DEPT ^{13}C NMR (CD_3 OD, 75 MHz, **Fig: 3**) showed only three different types of peaks at different chemical shift values which were assignable for three different types of carbon bearing odd number of proton. The peaks at 144, 133 and 123 ppm were for C_1, (C_5, C_9) and (C_6, C_8) respectively.

Therefore, IR, ^{13}C NMR and DEPT ^{13}C NMR spectrum expressed harmony for the structure of the product as oximinoacetanilide.

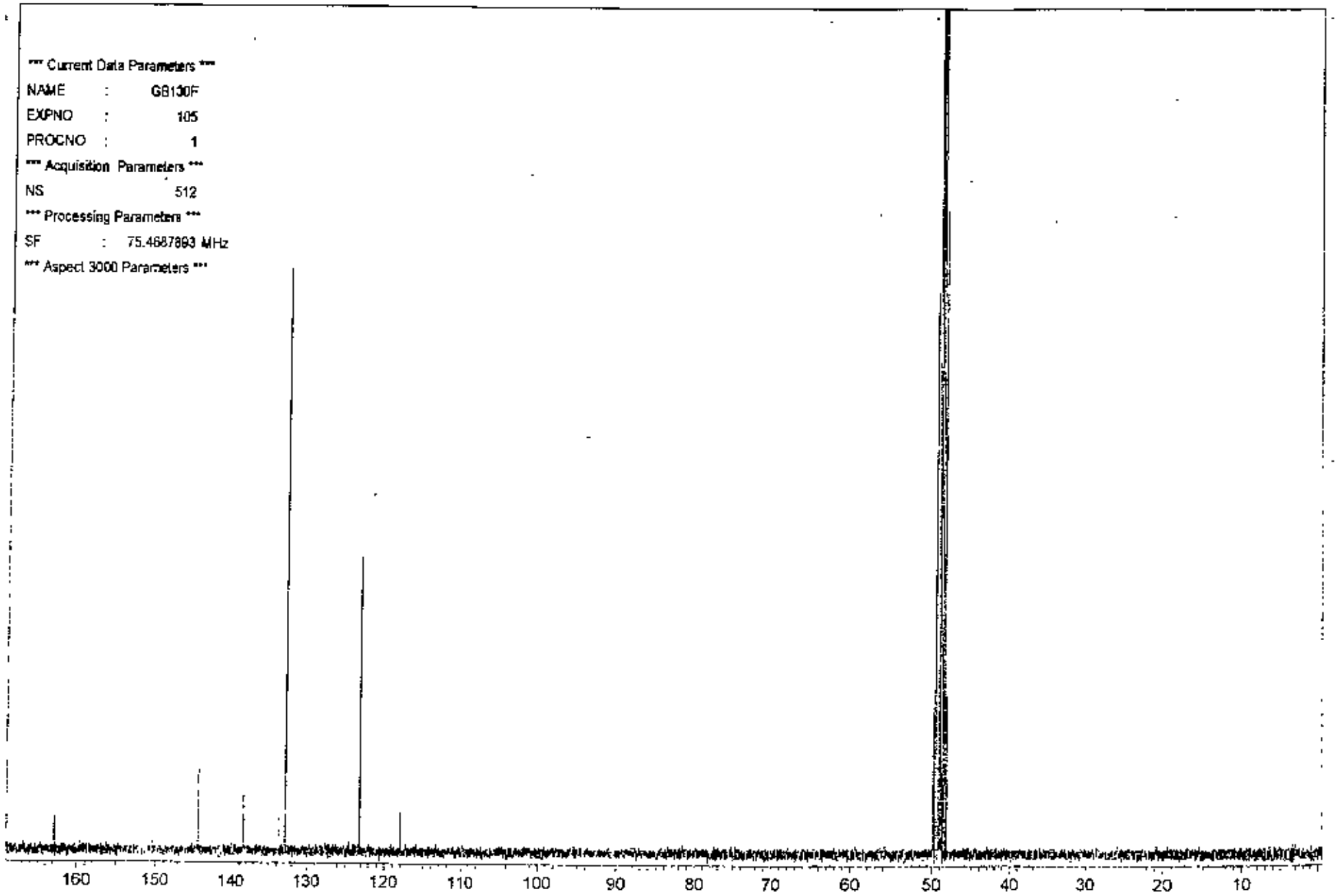


Fig 2: ^{13}C NMR spectrum of Oximino acetanilide.

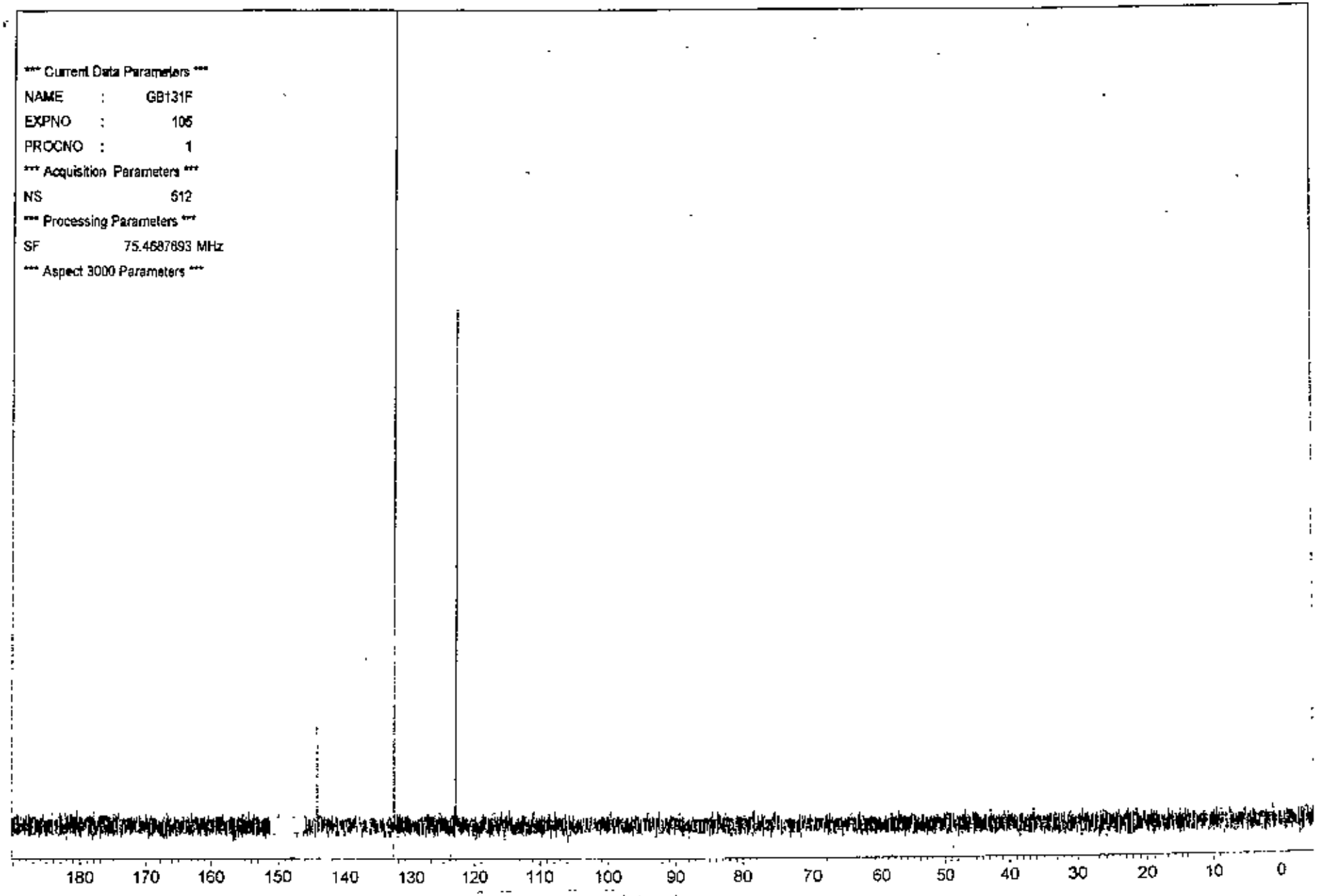
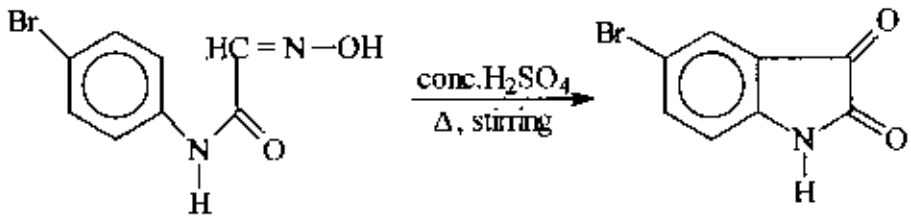


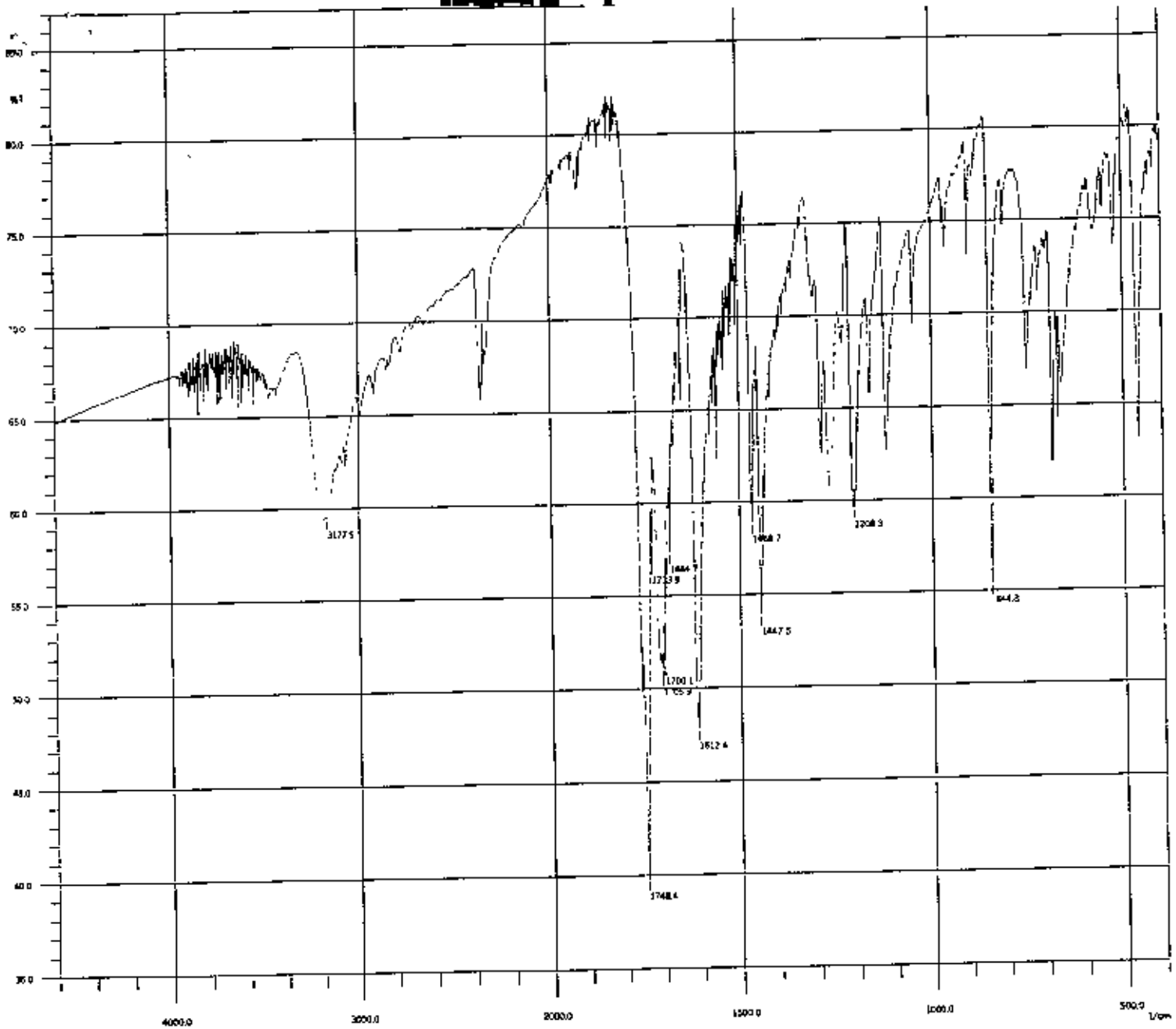
Fig 3: DEPT ^{13}C NMR Oximino acetanilide$_3$

2.1.B. SYNTHESIS AND CHARACTERIZATION OF 5 - BROMO ISATIN

Oximino acetanilide (500 mg, 2 m mol) was heated at 80°C in presence of conc. H_2SO_4 for 1 hour 20 minutes. The progress of the reaction was monitored by TLC (pet. ether: ethyl acetate; 7: 3, R_f = 0.65). Then the reaction mixture was cooled to room temperature and poured upon ten to twelve times its volume of cracked ice. After standing for about one and half hour, the product was filtered with suction pump and washed several times with cooled water to remove sulfuric acid and then dried in the desiccator. The crude product was obtained as yellow orange coloured solid mass which was purified by silica gel column chromatography using pet.ether and ethyl acetate (9:1) as eluant. After purification a fine yellowish crystal was obtained, m. p. 230°C, yield 80 %.



Its infrared spectrum (**Fig: 4**) showed wide absorption band ranging from 3179- 3175 cm^{-1} for N–H group. The characteristic bands at 1748 and 1734 cm^{-1} were for two isomeric carbonyl groups. The bands at 1706 and 1700 cm^{-1} were observed for two isomeric – NCO – moieties. The characteristic bands at 1612, 1469 and 1447 cm^{-1} were assignable for aromatic C=C stretching.



Selection

No.	Pos. (1/cm)	Intens. (%T)
1	844.8	55.375
2	1208.3	59.577
3	1447.5	53.873
4	1468.7	58.884
5	1612.4	47.801
6	1684.7	57.308
7	1700.1	51.289
8	1705.9	51.054
9	1733.9	57.851
10	1748.4	39.775
11	3177.5	59.458

Isatin, June 25, 2004

Fig 4: IR spectrum of 5-bromo isatin.

The ^1H NMR spectrum (300 MHz, DMSO – d_6, **Fig: 5** and **Fig: 6**) showed strong doublets at δ 6.9 and δ 7.7 integrating one proton each were assignable for aromatic proton at C–6 as C–7 respectively. The singlet at δ 7.6 integrating one proton was suggestive for aromatic proton at C– 4. The broad absorption band at δ 11.1 integrating one proton was attributable for N–H moiety.

Therefore, IR and ^1H NMR data confirmed the structure of the product as 5 – bromoisatin.

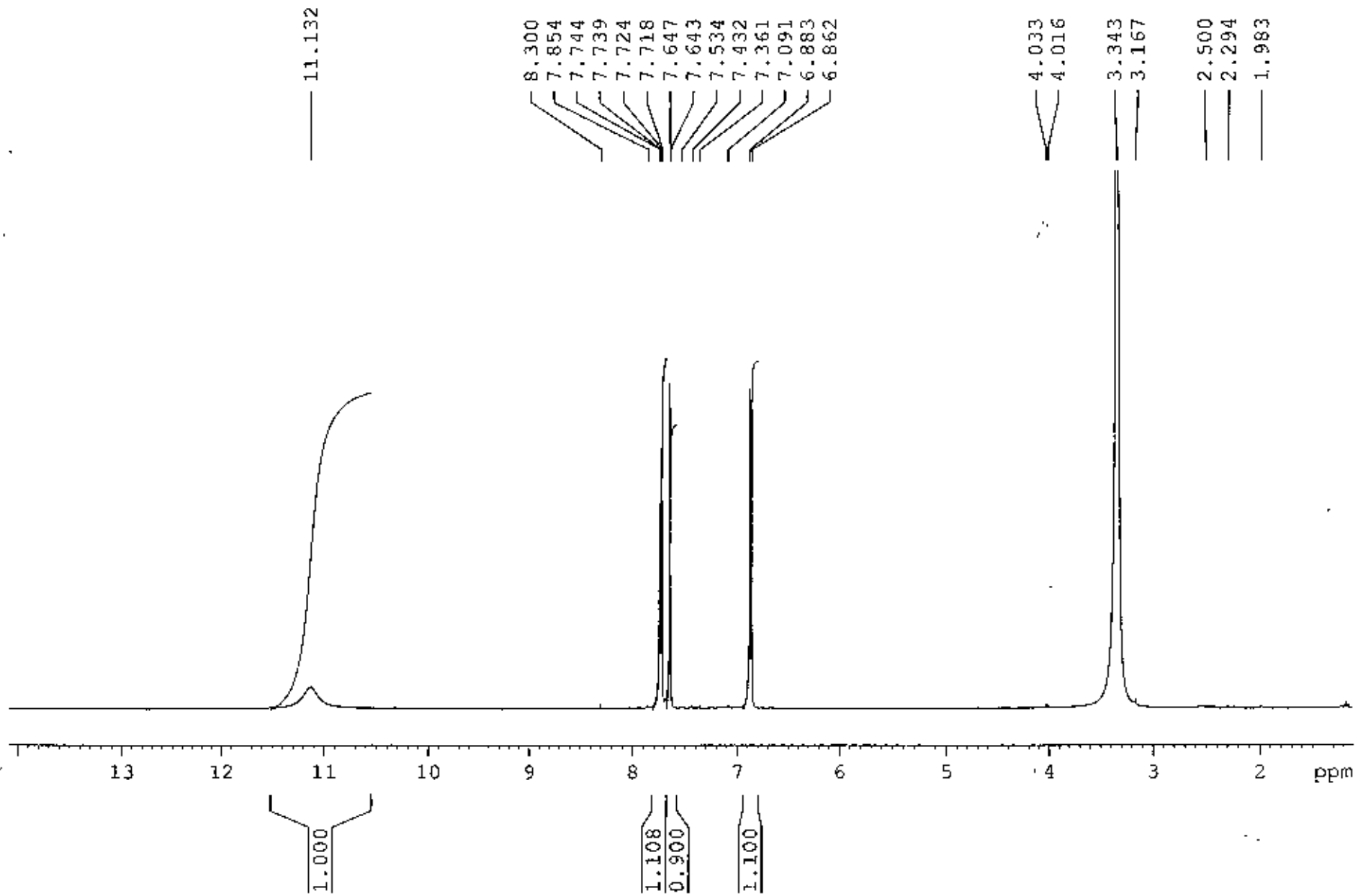


Fig 5: ^{1}H NMR spectrum of 5-bromo isatin.

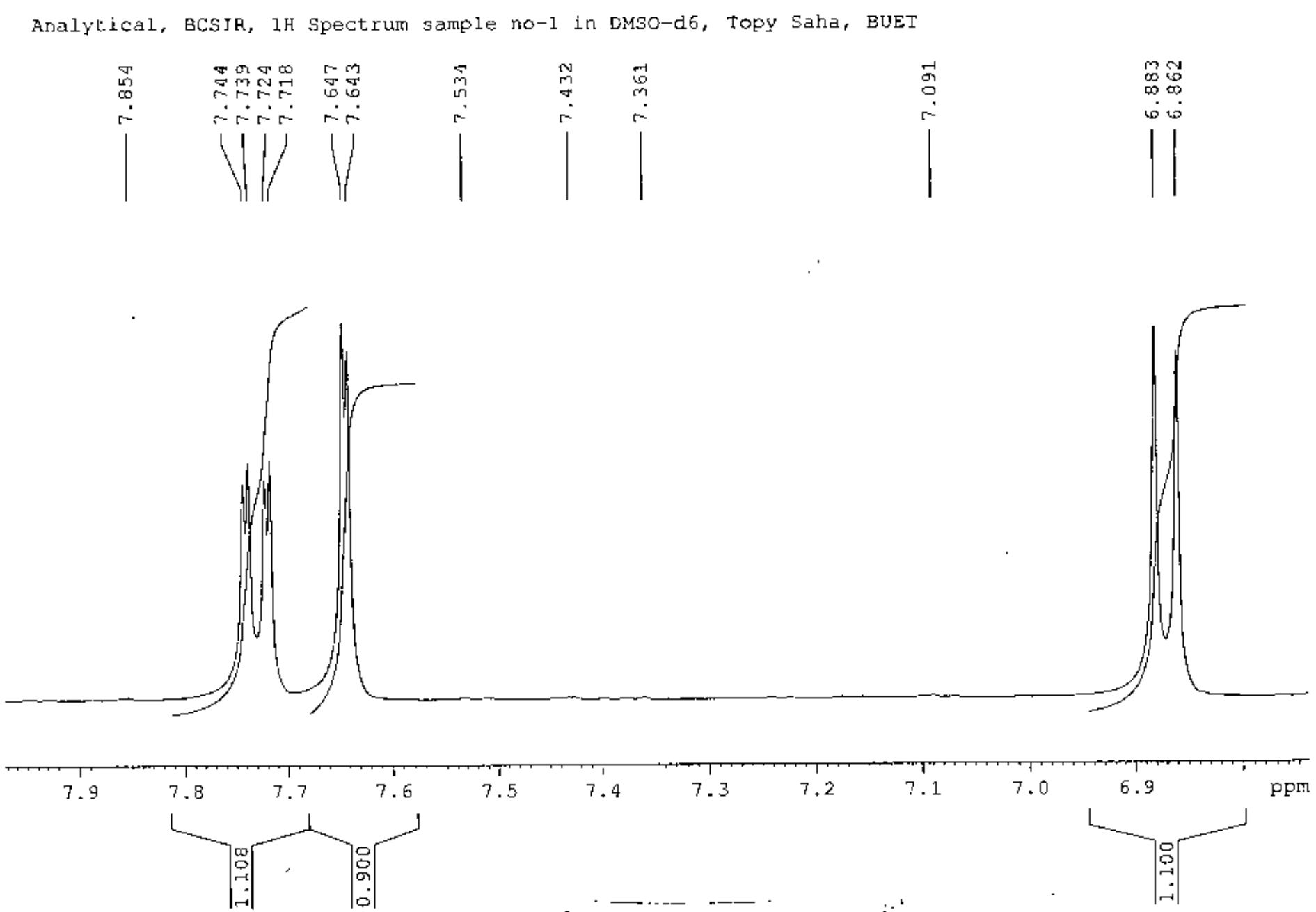
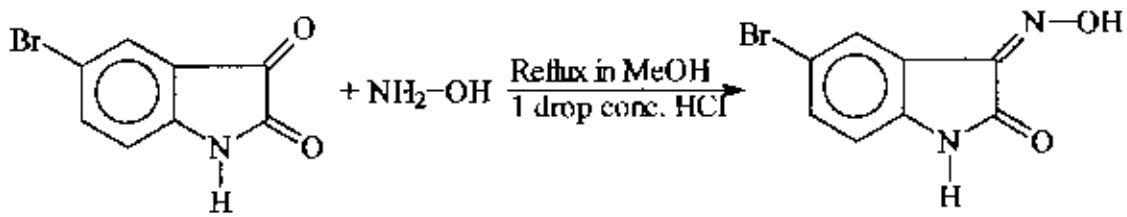


Fig 6: ^{1}H spectrum of 5-bromo isatin.

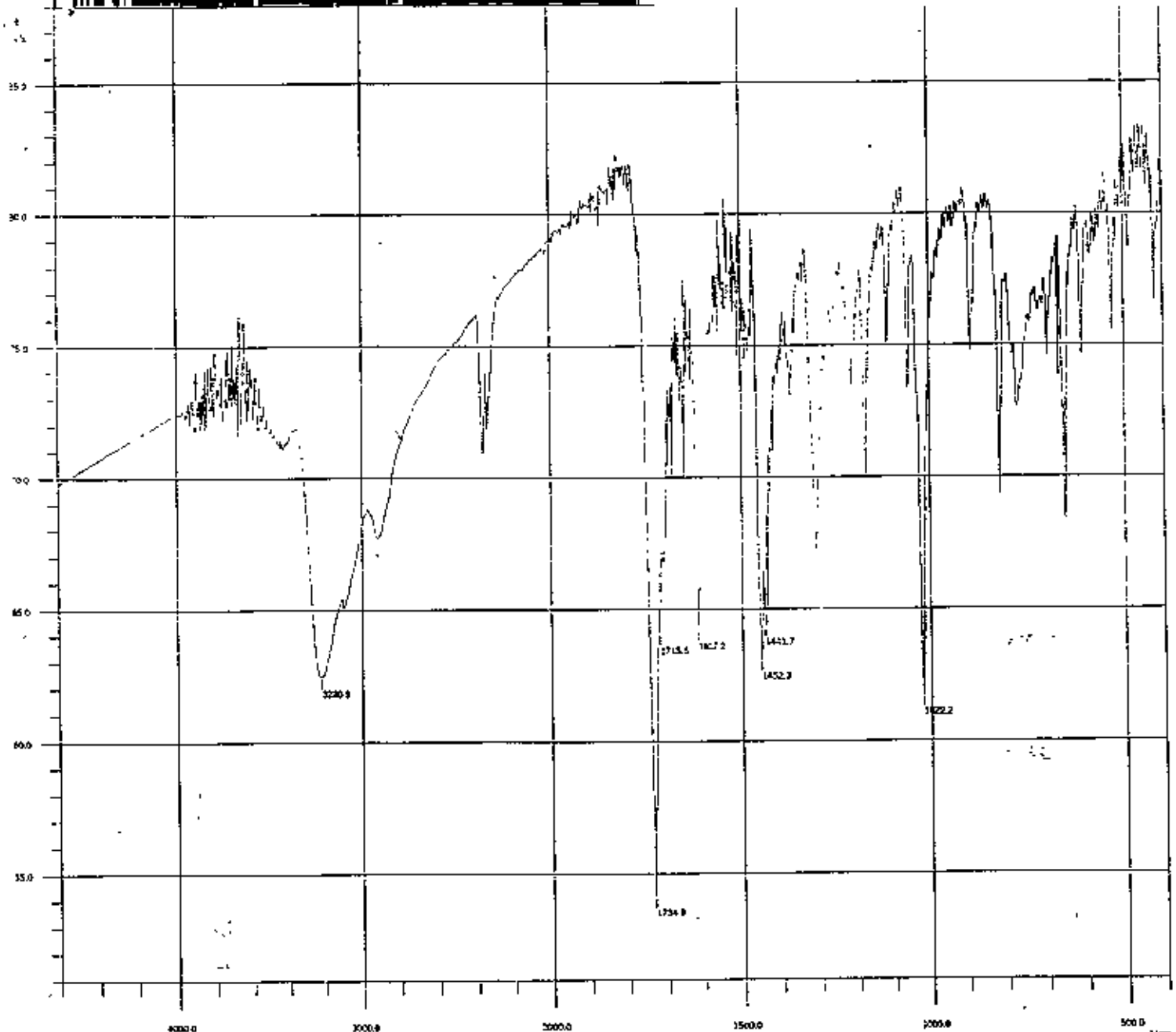
2.2.A. SYNTHESIS AND CHARACTERIZATION OF 5-BROMO ISATIN – 3 – OXIME

A mixture of 5 – bromoisatin (678 mg, 3 m mol) and hydroxylamine hydrochloride (200 mg, 3 m mol) was refluxed in methanol in presence of a catalytic amount of hydrochloric acid (1 drop) for 3 hours. The progress of the reaction was observed by TLC (pet ether: ethyl acetate; 7: 3, R_f = 0.54). Then the reaction mixture was cooled to room temperature and methanol was removed by rotary evaporator. The resultant semi solid mass was recrystallized several times from ethyl acetate as a yellow crystal, m. p. 255°C, yield 78%.



The infrared spectrum (**Fig 7**) showed wide absorption band ranging from 3230-3210 cm^{-1} was ascribable for imino hydroxyl group. The band at 3050 cm^{-1} was indicative for aromatic C–H stretching. Absorption at 1718 cm^{-1}, reletively higher frequency was assignable for C=N moiety. The characteristic band at 1617, 1452 and 1441 cm^{-1} were suggestive for aromatic C=C moieties.

Therefore, the IR spectrum indicated the structure as 5– bromoisatin – 3– oxime.



Threshold, 65, Peak 2, No Range Selection

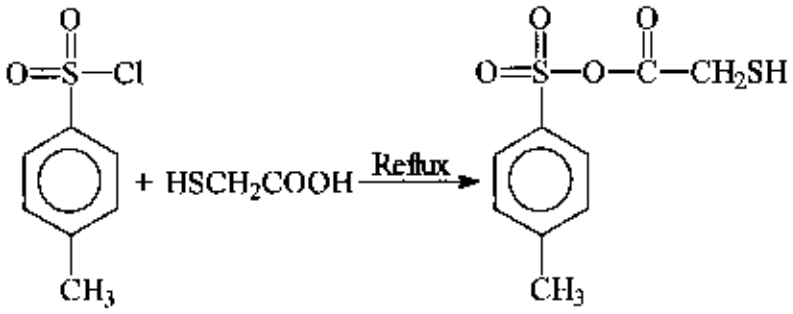
No.	Pos (1/cm)	Inten. (%T)
1	1022.2	61.714
2	1441.7	64.380
3	1452.3	63.106
4	1617.2	64.211
5	1718.5	64.046
6	1734.9	54.151
7	3220.9	62.450

zone-1, July 20, 2004

Fig 7: IR spectrum of 5-bromo isatin – 3 – oxime.

2.2.B. SYNTHESIS AND CHARACTERIZATION OF *p* – TOSYL MERCAPTOACETATE

A mixture of mercaptoacetic acid (241 mg, 2.6 m mol) and *p* – toluene sulphonyl chloride (580 mg, 3 m mol) was refluxed in methanol (7 ml). The reaction mixture was monitored by TLC (ethyl acetate : *n* – hexane; 2:8, R_f = 0.40). The reaction mixture was cooled to room temperature. Then the solvent and excess mercaptoacetic acid were removed by rotary evaporator. After evaporation pure violet liquid was obtained, yield 65%.



The ^{1}H NMR spectrum (**Fig: 8**) clearly indicated ten protons. The multiplet at δ 2.2 integrating one proton was suggestive for thiol moiety. The singlet at δ 2.4 integrating three proton was indicative for methyl group. Another singlet at δ 3.7 integrating two proton were ascribable for – CH_2 moiety to the neighbouring thiol group. The doublet at δ 7.3 was assignable for two identical aromatic proton. Another doublet at δ 7.8 integrating two protons were attributable for two identical aromatic proton.

Therefore, the ^{1}H NMR spectrum strongly suggested the structure of the product as *p*-tosylmercaptoacetate.

Analytical, BCSIR, A1406. 1H spectrum TS4 in CDCl3, Topy Saha< BUET

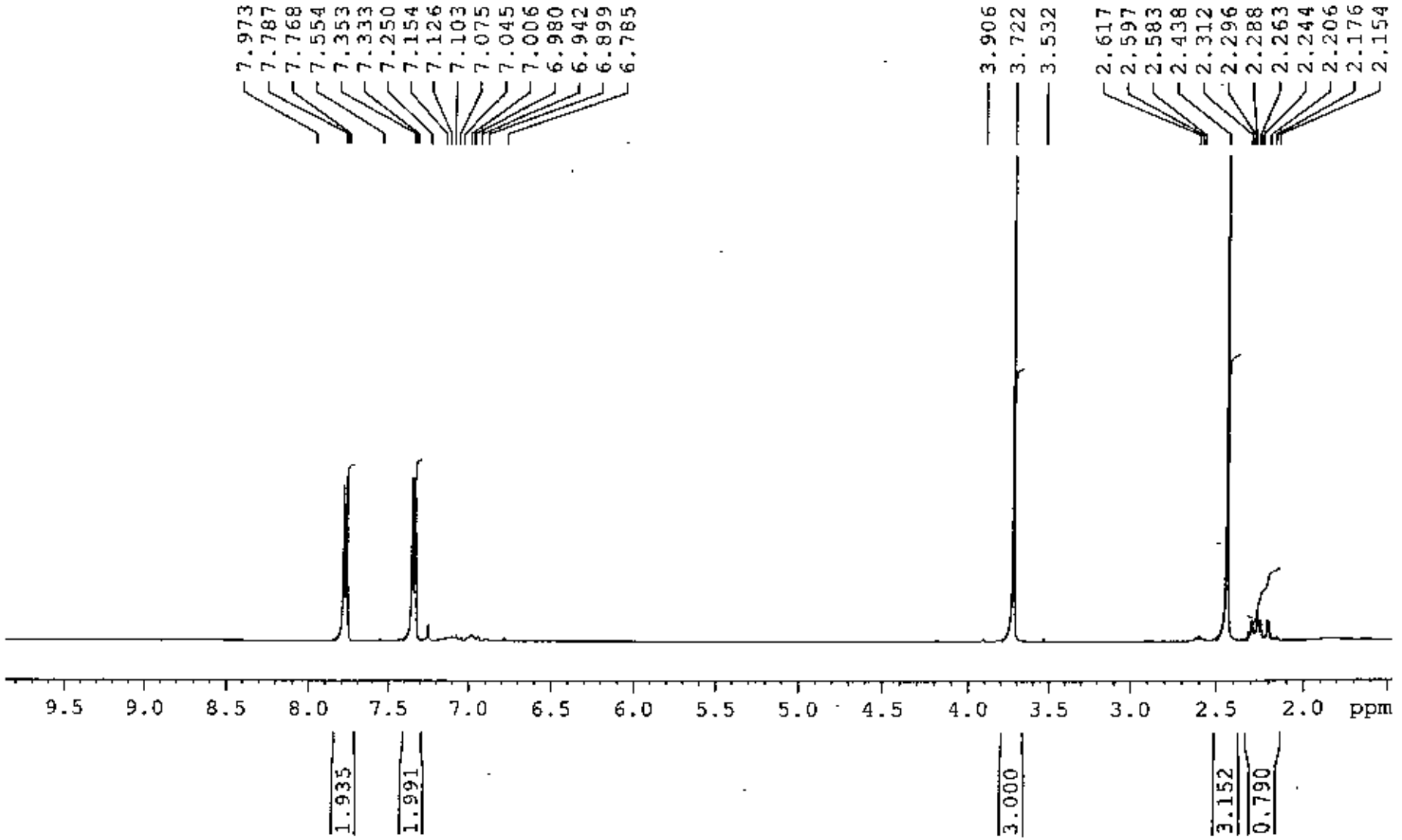
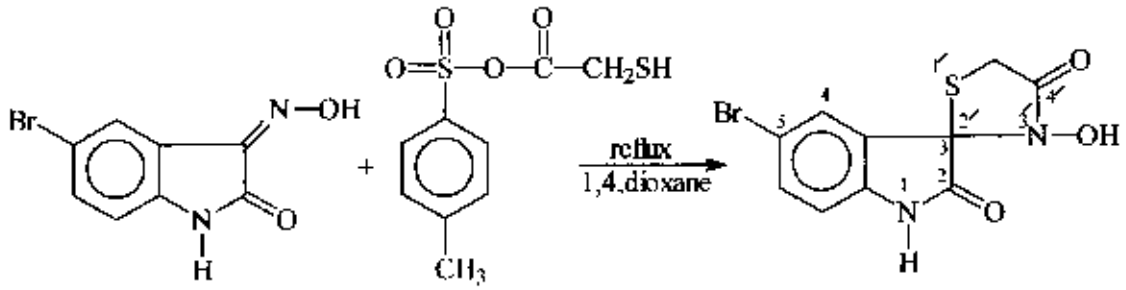


Fig 8: ^{1}H NMR spectrum *p* -tosyl mercaptoacetate.

2.2.C. SYNTHESIS AND CHARACTERIZATION OF 3'(HYDROXY) SPIRO [5 - BROMO INDOLINE – 3, 2'- THIAZOLIDINE] – 2, 4' – DIONES

A mixture of 5 – bromoisatin – 3 – oxime (0.482 gm, 2 m mol) and *p* – tosylmercaptoacetate (1.5 gm, 6 m mol) was refluxed in 1.4 dioxane for 2 hours. The progress of the reaction was monitored by T.L.C. (ethyl acetate : pet.ether ; 6:4, R_f = 0.66). Then 1, 4 – dioxane was removed by rotary evaporator. The crude mass was purified by column chromatography as off-white crystal, m. p. 180°C, yield 45%.



The IR spectra (**Fig: 9**) showed broad absorption band ranging at 3400–3200 cm^{-1} were assignable for two overlapping O–H and N–H groups. The wide band at 1720 cm^{-1} was demonstrative for carbonyl moiety. The characteristic absorption bands at 1600, 1490 and 1450 cm^{-1} were ascribable for aromatic C=C bonds .

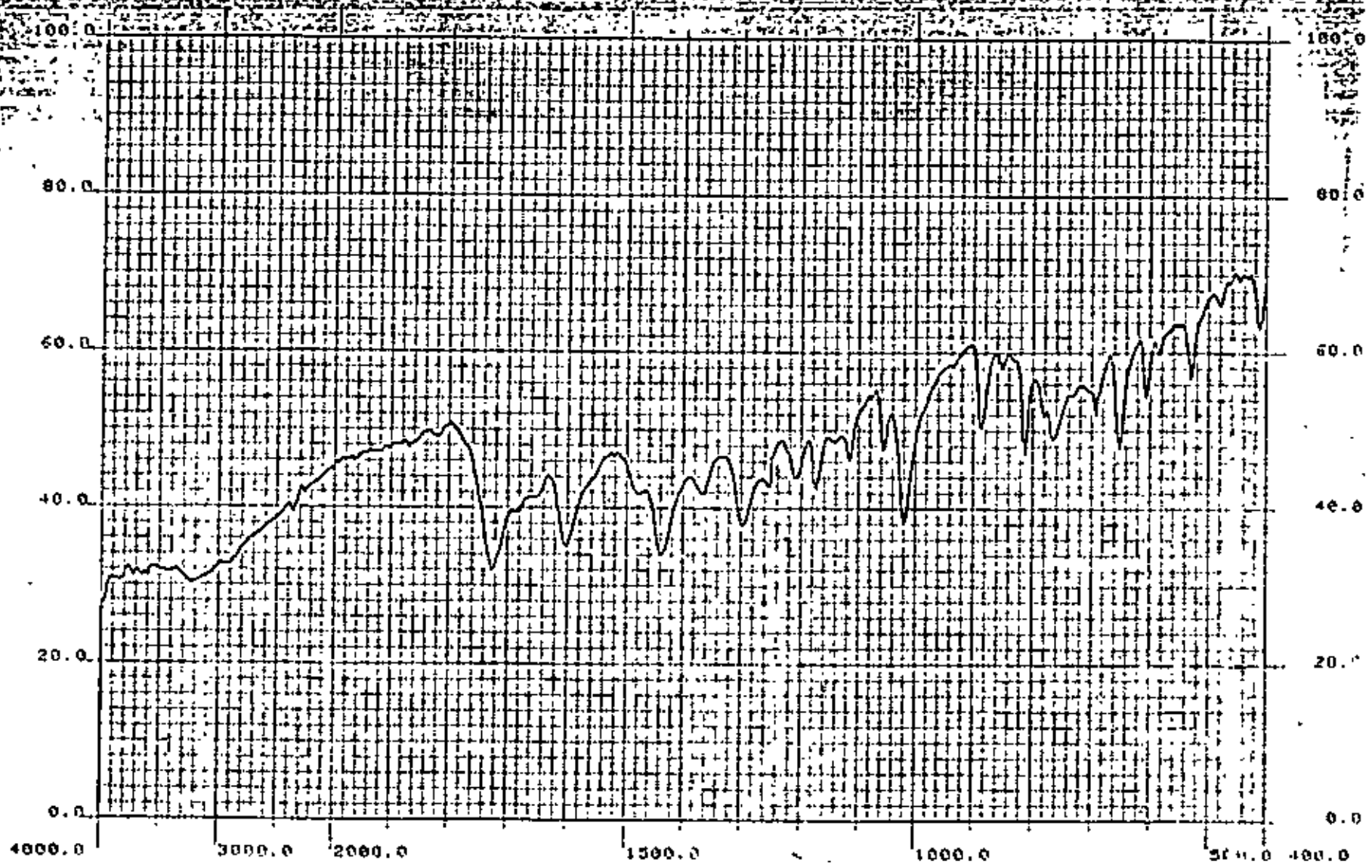


Fig 9: IR spectrum of 3'(hydroxy) spiro [5 – bromoindoline – 3, 2'– thiazolidine] – 2, 4' – diones.

The ^1H NMR spectrum (300 MHz, $CDCl_3$, **Fig: 10**) showed six bands for six proton except N–H proton. Probably it was in the down field. The broad band at δ 1.2 was attributable for O–H moiety. The singlet at δ 2.03 integrating two protons was assigned for – $COCH_3$. The two doublets at δ 6.8 and 7.3 were ascribable for two protons. The singlet at δ 7.4 integrating one proton was assigned for non coupled aromatic proton. The N–H proton was not observed. Probably it was in the out of range of the field.

Therefore, IR and ^1H NMR spectra expressed harmony for the structure of the product as 3′(hydroxy) spiro [5– bromo indoline – 3, 2′ – thiazolidine] – 2, 4′ – diones.

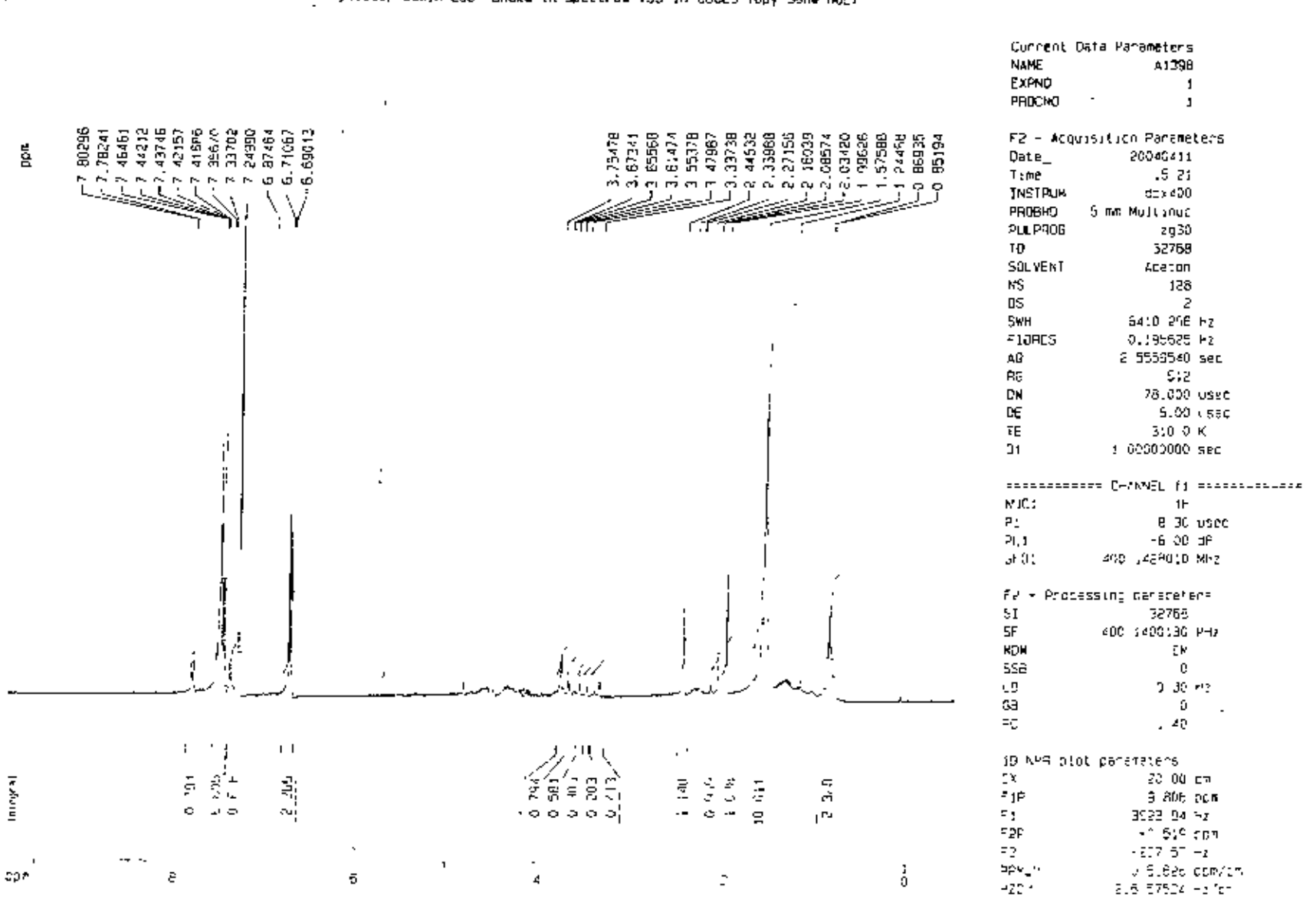
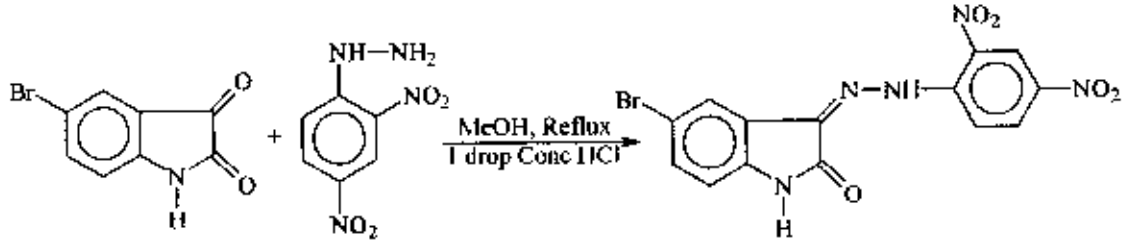


Fig 10: ^{1}H NMR spectrum of 3′(hydroxy) spiro [5 – bromoindoline – 3, 2′– thiazolidine] – 2, 4′ – diones.

2.3.A. SYNTHESIS AND CHARACTERIZATION OF 5 – BROMOISATIN – 3 (2, 4– DINITROPHENYL) – HYDRAZONE

A mixture of 5 – bromoisatin (452 mg, 2 m mol) and 2,4 dinitro phenyl hydrazine (398 mg, 2 m mol) was refluxed in methanol (8 ml) in presence of catalytic amount hydrochloric acid (1 drop) for 4 hours. The progress of the reaction was observed by TLC (ethyl acetate : pet.ether; 5:5, $R_f = 0.82$). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resultant solid mass was recrystallized several times from ethyl acetate. The desired compound was isolated as red colour, m. p. 260°, yield 75%.



The infrared absorption (**Fig: 11**) showed wide absorption band ranging from 3600-3233 cm^{-1} was indicative for two N – H group. The characteristic absorption frequency was found at 1730 for >C=O moiety. The band at 1695 cm^{-1} was ascribable for C=N moiety bearing neighboring electronegative functionalities. The other characteristic bands at 1637, 1612, 1589, 1500 and 1471 cm^{-1} were distinctive for aromatic C=C stretching.

Therefore, the IR spectrum suggested the structure as 5 – bromoisatin – 3 (2, 4 – dimitrophenyl) – hydrazone.

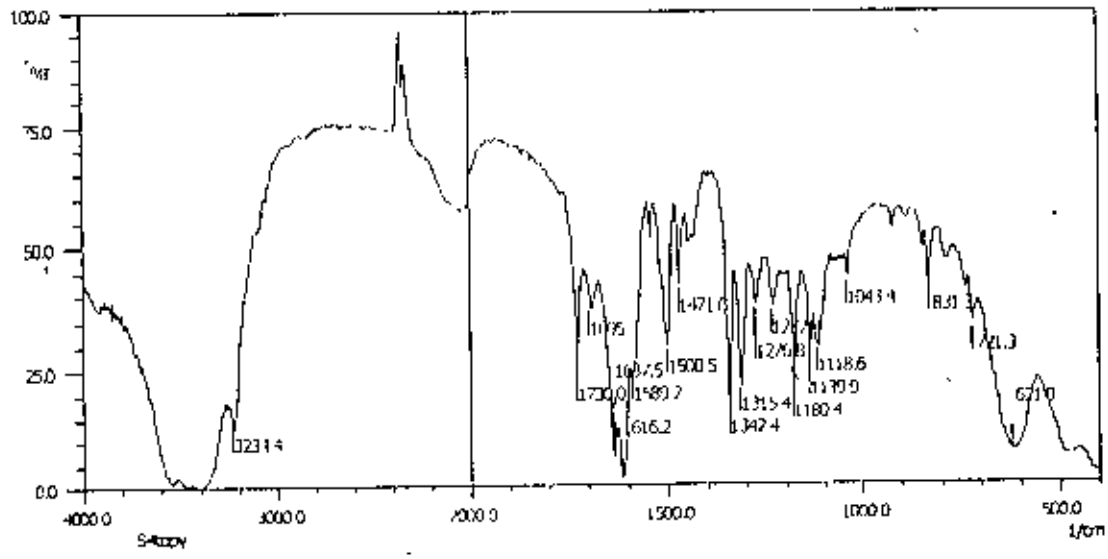
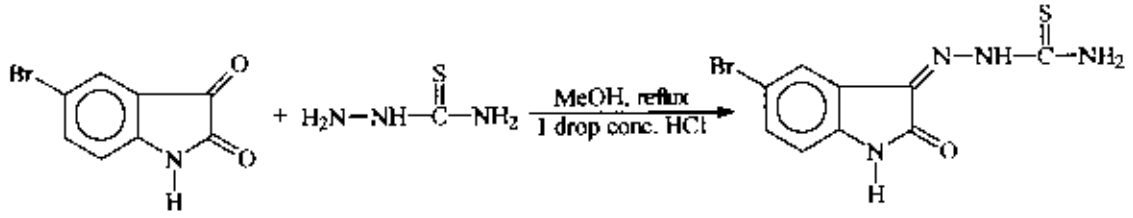


Fig 11: IR spectrum of 5 – bromoisatin – 3 (2, 4 – dinitrophenyl) – hydrazone

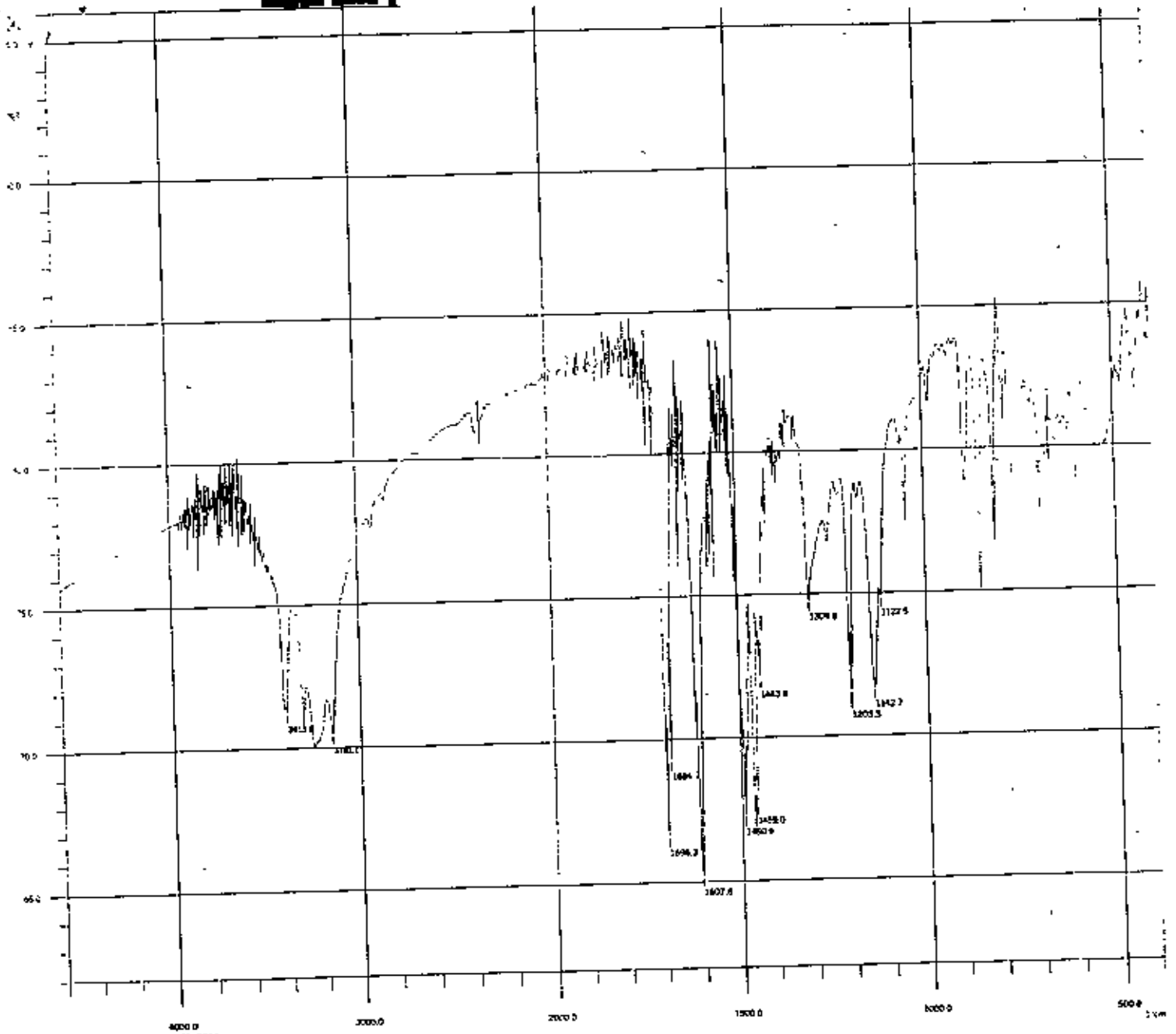
2.4.A. SYNTHESIS AND CHARACTERIZATION OF 5 – BROMOISATIN – 3 – THIOSEMICARBAZONE

A mixture of 5 – bromoisatin (678 mg, 3 m mol), thiosemicarbazide (273 mg, 3 m mol) and one drop concentrated hydrochloric acid was refluxed in methanol (8 ml) for 6 hours. The progress of the reaction was monitored by TLC (ethyl acetate : pet.ether ; 4:6, R_f = 0.57). Then the reaction mixture was cooled to room temperature and methanol was removed by rotary eveporator. The resultant solid mass was recrystallized several times from ethyl acetate and a yellow crystal was obtained, m. p. 258°C, yield 90%.



The infrared spectrum (**Fig: 12**) showed wide intensified band ranging from 3414 –3161 cm^{-1} were distinctive for two N–H and one NH_2 moieties. The sharp band at 1696 cm^{-1} was suggestive for C=O stretching. The band at 1684 cm^{-1} was indicative for C=N moiety. The characteristic bands at 1607, 1491 and 1459 cm^{-1} were assignable for aromatic C=C bonds. The relatively lower intensified band at 1444 cm^{-1} was characterized for C=S group.

Therefore, the IR spectrum indicated the structure of the product as 5 – bromoisatin – 3 – thiosemicarbazone.



Selection

No.	Pos. (1/cm)	Inten. (%T)
1	1122.5	74.882
2	1142.7	71.674
3	1203.5	71.571
4	1309.6	74.753
5	1443.6	72.081
6	1459.0	67.662
7	1490.9	67.311
8	1607.6	65.212
9	1684.7	69.285
10	1696.3	66.616
11	3161.1	70.481
12	3413.8	71.246

zone-2, July 20, 2004

Fig 12: IR spectrum of 5–bromoisatin– 3–thiosemicarbazone

2.4.B. SYNTHESIS AND CHARACTERIZATION OF 3′ (THIOUREIDO) SPIRO [5 – BROMOINDOLINE - 3, 2′ – THIAZOLIDINE] – 2, 4′- DIONES

A mixture of 5-bromoisatin – 3 – thiosemicarbazone (598 mg, 2 m mol) and mercaptoacetic acid (552 mg, 6 m mol) was refluxed in DMF (8 ml) for 8 hours in presence of catalytic amount of zinc chloride. The progress of the reaction was monitored by TLC (ethyl acetate: pet.ether ; 4:6, R_f = 0.57). The reaction mixture was then cooled to room temperature and DMF was removed by adding water and subsequent extraction with chloroform. The crude solid mass was purified by colnmn chromatography as greyish crystal, m. p. 210°C, yield 85%.

The ^{1}H NMR spectrum (**Fig: 13**) showed singlet at δ 2.2 was distinctive for two protons of – $COCH_2$ moicty. The broad band at δ 2.8 was indicative for two protons of NH_2 gronp. The doublet at δ 7.0 and 7.4 were assigned for aromatic protons. The another peak at 7.8 was assignable for aromatic proton. Thc singlet at δ 8.8 was distinctive for one N-H proton of –NHCS–. The another proton of Ph–NHCO – was detectable at δ 11.2. The product was not completely pure though its ^{1}H NMR spectrum suggested the structure as 3′ (thioureido) spiro [5 – bromoindolin – 3, 2′ – thiazolidine] – 2 , 4′ – diones.

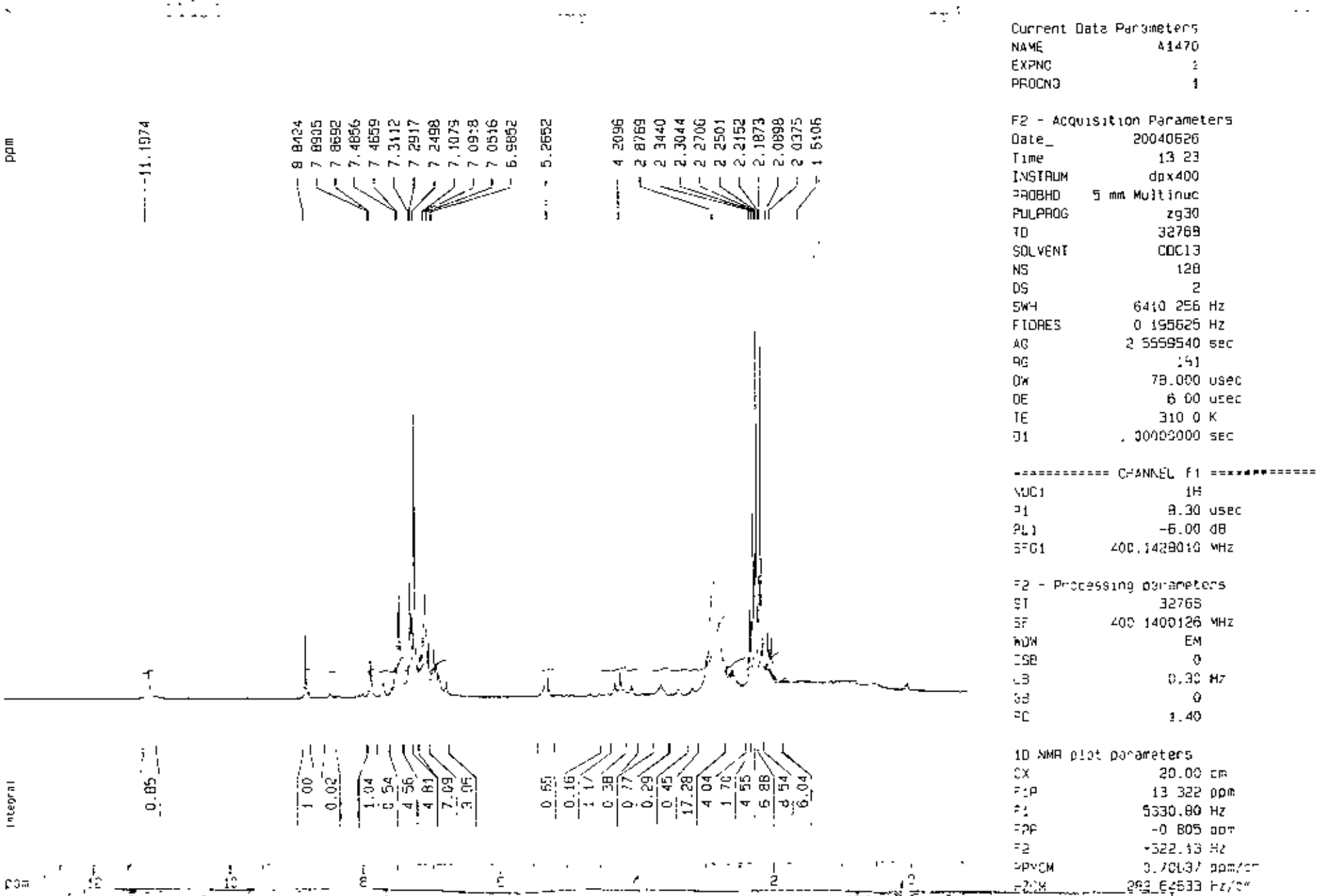
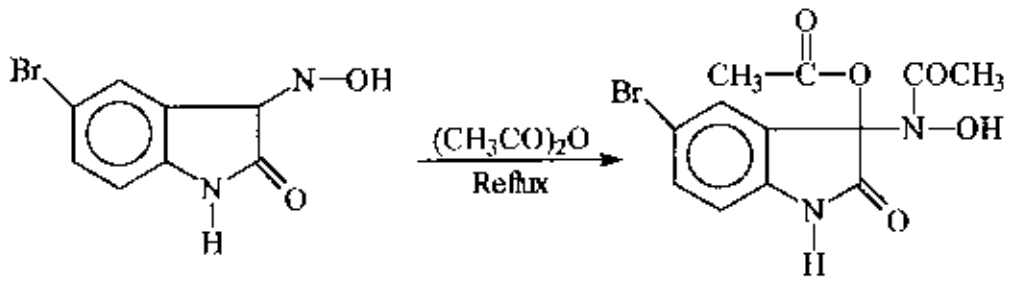


Fig 13: ^1H NMR spectrum of 3′ (thioureido) spiro [5′– bromoindoline-3, 2′– thiazolidine] – 2, 4′– diones.

2.5.B. SYNTHESIS OF 3(*N*- HYDROXY – *N* – ACETYL) AMINO – 3 – ACETOXY – 5 – BROMOINDOLE

A mixture of 5 – bromoisatin – 3 – oxime (482 mg, 8 m mol) was refluxed in acetic anhydride (7 ml) for 3 hours. The progress of the reaction was monitored by TLC (ethyl acetate: pet.ether ; 7:3, R_f = 0.54). The reaction mixture was cooled to room temperature and acetic anhydride was removed by adding water and subsequent extraction with chloroform. The crude solid then purified by column chromatography. The desired compound isolated as a white solid crystal. m. p. 135°C, yield 58%.



The IR spectrum (**Fig: 14**) showed wide absorption band ranging from 3425–3375 cm^{-1} was distinctive for O–H group. The wide band at 3240–3190 cm^{-1} was assigned for N–H moiety. The five membered ring carbonyl absorption was at 1734 cm^{-1}. The other carbonyl absorption band at 1718 cm^{-1} was ascribable for acetyl functionality. The characteristic aromatic C=C absorptions were assignable at 1616 and 1451 cm^{-1}.

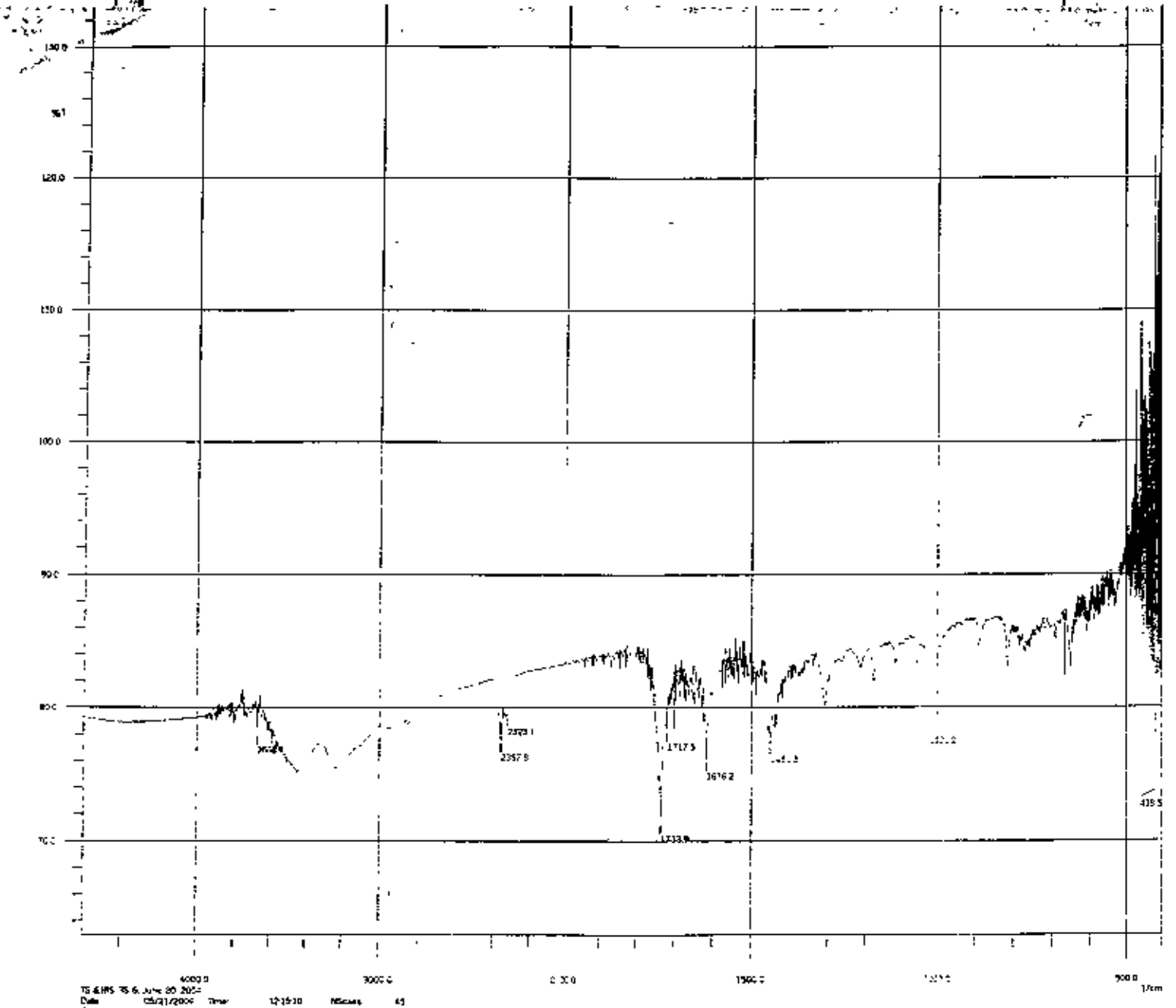


Fig 14: IR spectrum of 3 (*N* – hydroxy – *N* – acetyl) amino (3 – acetoxy) – 5– bromoindole.

^{1}H NMR spectrum (**Fig: 15, Fig: 16**) showed strong singlet integrating three protons at δ 2.49 was assigned for methyl proton of acetyl group. The other singlet for three protons at δ 2.5 was distinctive for methyl proton of cetoxy moiety. The doublets at δ 6.8 and δ 7.5 were ascribable for protons of aromatic ring. The singlet at δ 8.0 integrating one proton was demonstrative for aromatic ring. The broad band at δ 10.9 – 10.8 integrating one protou was indicative for N–H moiety. The O–H proton was not detectable in the spectrum.

Therefore, IR and ^{1}H NMR spectrum expressed harmony for the structure of the product as 3 (*N* –hydroxy – *N* – acetyl) amino – 3 – acetoxy – 5 – bromoindole.

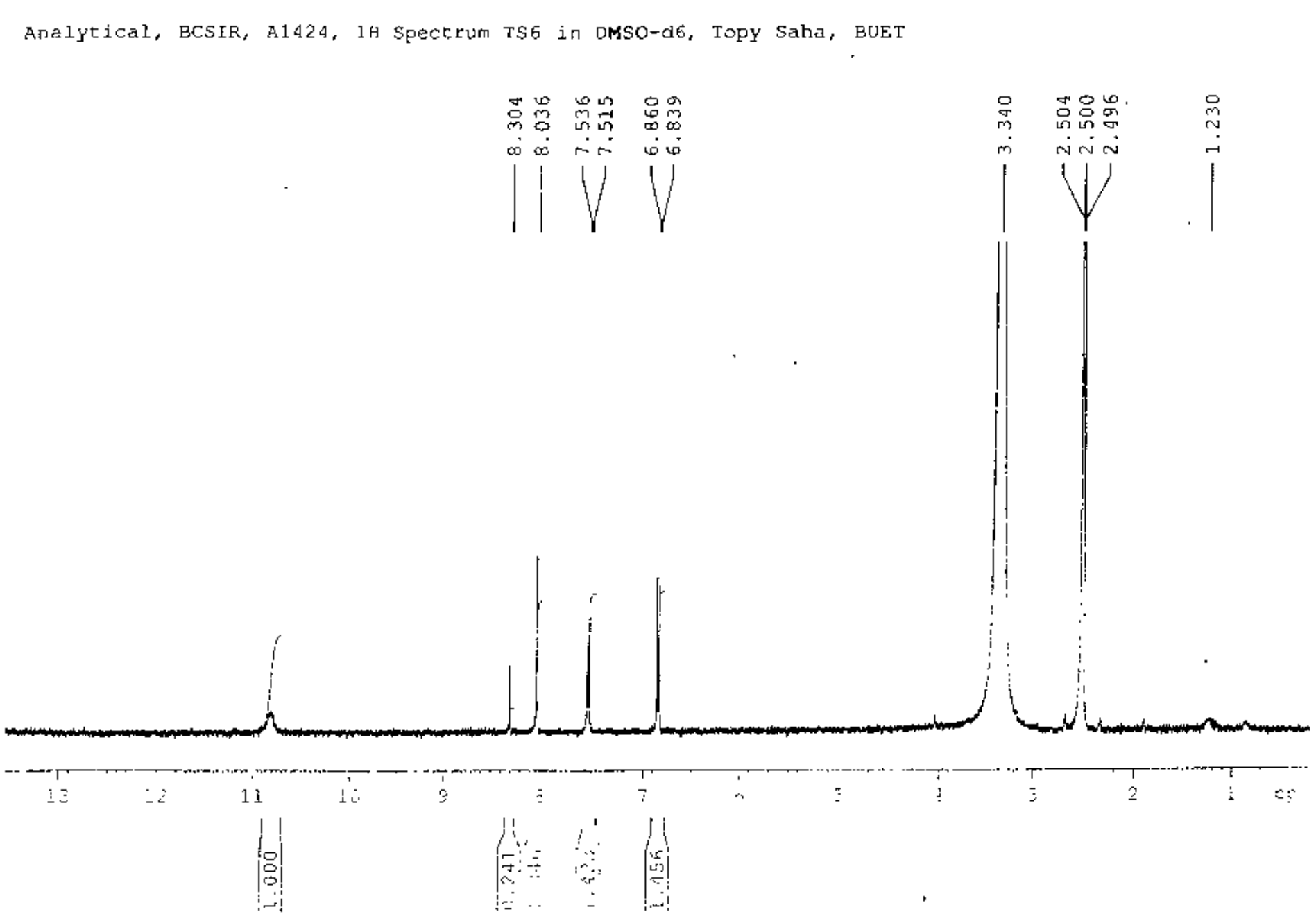


Fig 15: ^{1}H NMR of 3 (*N* – hydroxy – *N* – acetyl) amino (3 – acetoxy) – 5– bromoindole.

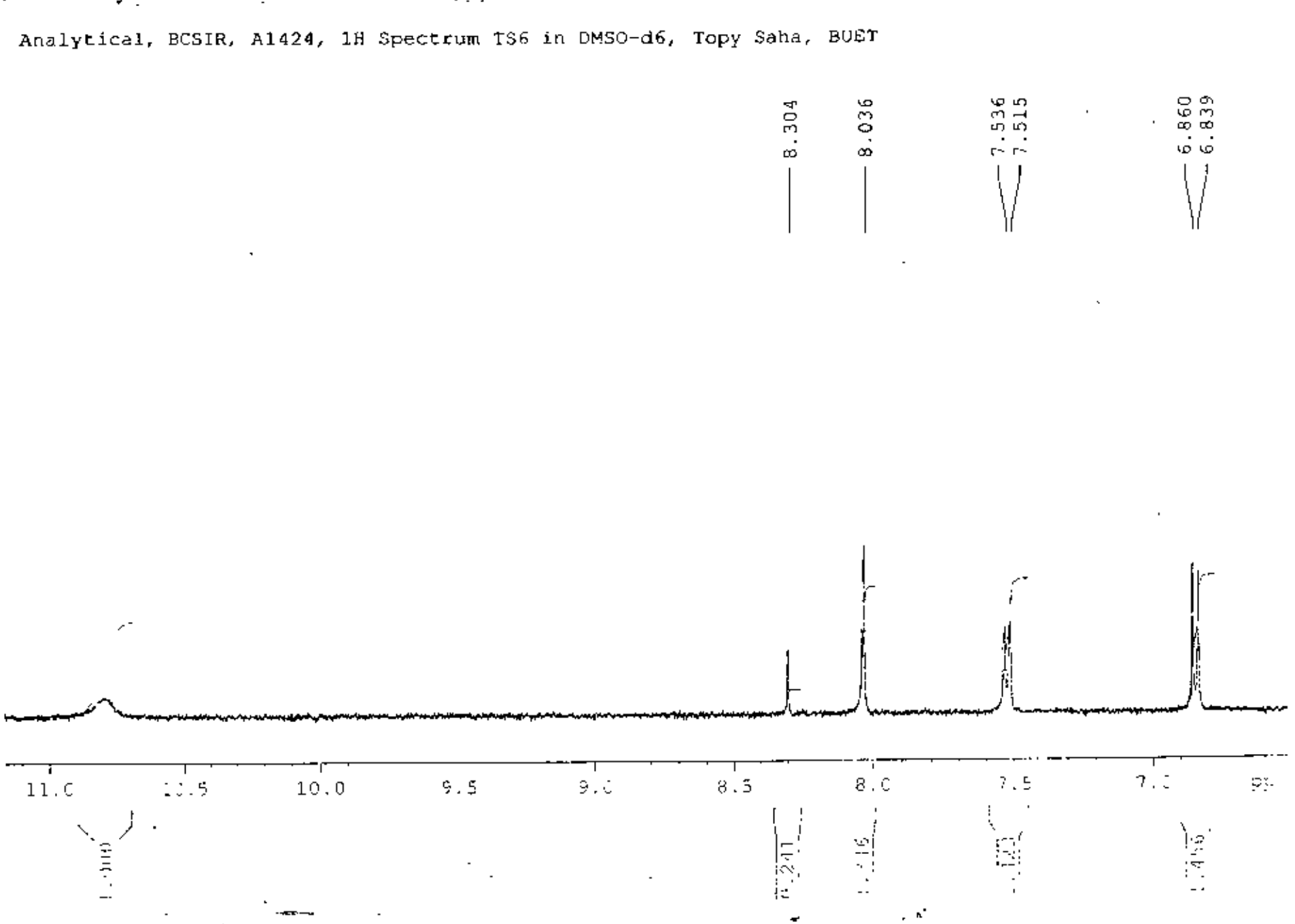
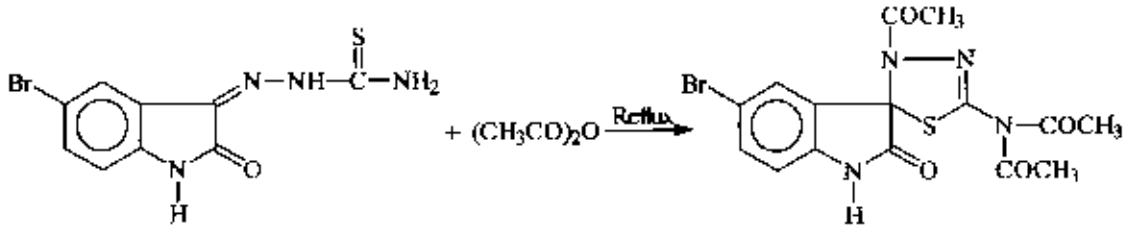


Fig 16: ^{1}H NMR of 3 (*N* – hydroxy – *N* – acetyl) amino (3 – acetoxy) – 5– bromoindole.

2.6.B. SYNTHESIS AND CHARACTERIZATION OF 2′ (DIACETYLAMINO) - 4′ – *N* – ACETYL - SPIRO [Δ^2 – (1, 3, 4) – THIADIAZOLINE – 5′, 3 – 5 – BROMOINDOLINE]

5 – Bromo isatin – 3 – thiosemicarbazone compound (0.398 gm, 2 m mol) was refluxed in acetic anhydride (7 ml) for 2 hours. The progress of the reaction was monitored by TLC (pet.ether : ethyl acetate ; 6 : 4, $R_f = 0.56$). The reaction mixture was then cooled to room temperature and extra acetic anhydride was removed by adding water and subsequent extraction with chloroform several times. The resultant solid mass was purified by column chromatography. The desired compound was isolated as a white crystal, m. p. 158 – 160°C, yield 62%.



The IR spectrum (**Fig: 17**) showed wide absorption band at 3400 cm^{-1} was ascribable for N–H moiety. The characteristic carbonyl frequency of the cyclopentanone ring was assignable at 1766 cm^{-1}. The bands at 1718 and 1710 cm^{-1} were assignable for carbonyl groups of acetyl moieties. The weak band at 1616 cm^{-1} was indicative for C=N groups. The characteristic absorption bands at 1466, 1407 and 1397 cm^{-1} were distinctive for aromatic C=C bonds.

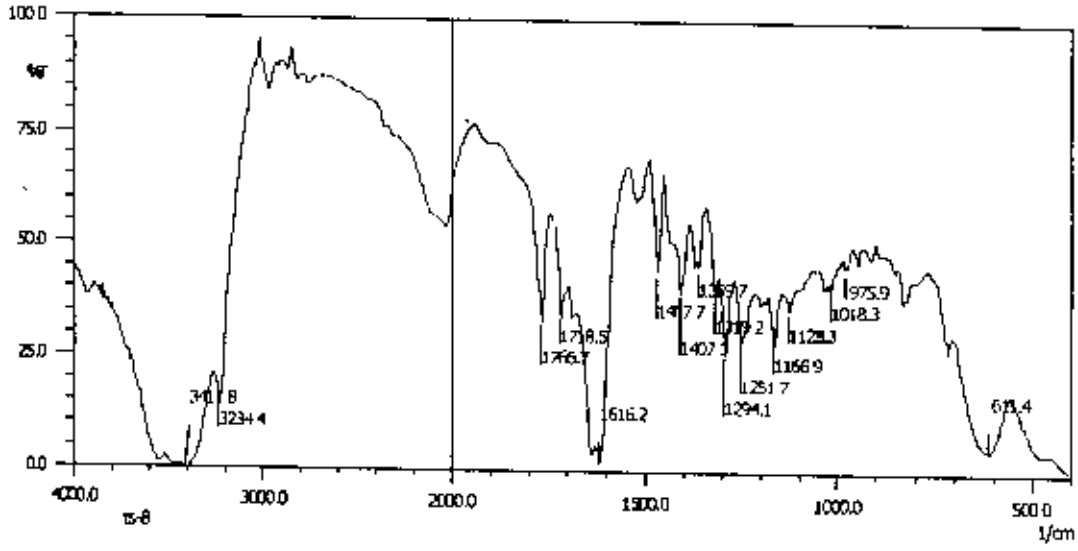
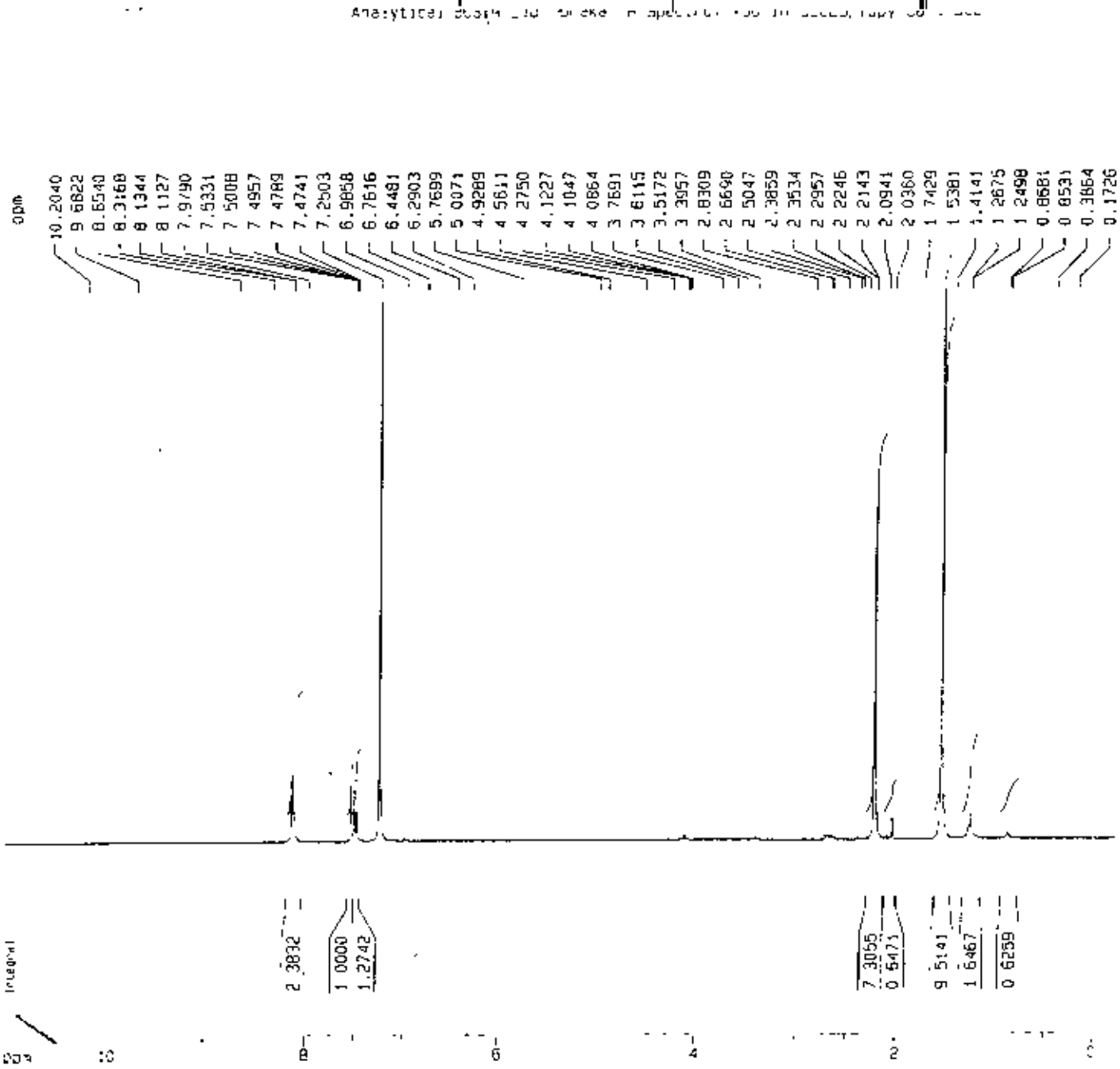


Fig 17: IR spectrum of [2′(diacetylamino) – 4′ – *N* – acetyl - spiro –Δ^2 – (1, 3, 4) - thiadiazoline (5′, 3) – 5 – bromoindoline].

The ^{1}H NMR spectrum (**Fig 18**) showed strong singlet at δ 1.5 integrating six protons was indicative for two $-COCH_3$ moieties. The singlet at δ 2.2 integrating three protons was ascribable for $-COCH_3$. The doublet at δ 7.4 integrating one proton was demonstrative for aromatic proton. The band at δ 8.6 integrating two protons was distinctive for aromatic ring moiety. The N – H proton was not possible to detect because probably it was out of range of the spectrum.

Therefore, IR spectrum and ^{1}H NMR spectrum expressed correlations with the structure as spiro 2′ (diacetylamino) – 4′ – *N* (acetyl) [Δ^2 – (1, 3, 4) thiadiazoline – 5′, 3 – 5 – bromoindoline].



Current Data Parameters

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EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	724.1
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

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P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1400124 MHz
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GB	0
PC	1.40

1D NMR plot parameters

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F1P	11.075 ppm
F1	4431.67 Hz
F2P	-0.230 ppm
F2	-92.03 Hz
PPMCM	0.56525 ppm/cm
HZCM	226.18468 Hz/cm

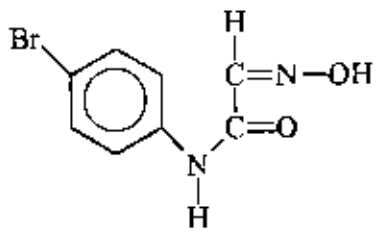
Fig 18: ^{1}H NMR spectrum of [2′(diacetylamino) – 4′ – *N* – acetyl - spiro –Δ^2 –(1, 3, 4) - thiadiazoline (5′, 3) – 5 – bromoindoline].

CHAPTER – 4

SUMMARY

T-1. OXIMINO ACETANILIDE.

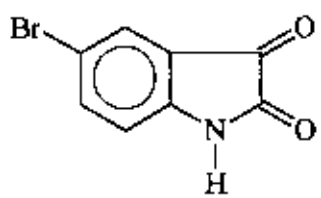
Oximino acetanilide was synthesized with high yields from the corresponding aromatic anilines (500 mg, 2.9 m mol) with chloral hydrate (0.640 gm, 9.1 m ml) and hydroxylamine hydrochloride (640 mg, 9.1 m mol)



98%

T-2. 5- BROMO ISATIN.

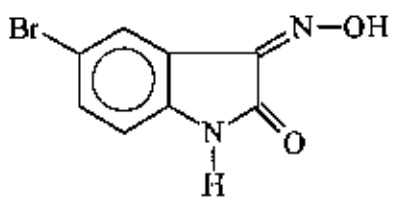
5-Bromo isatin was synthesized by heating of oximino acetanilide (0.500 gm, 2 m ml) in conc. sulfuric acid at 80°C.



80%

T-3 5- BROMO ISATIN – 3 – OXIME.

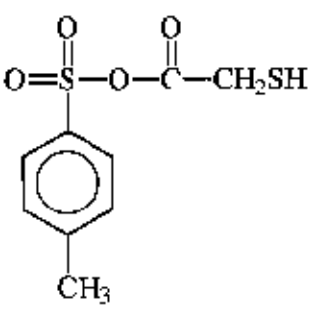
Refluxing a mixture of isatin (678 mg, 3 m mol) and hydroxylamine hydrochloride (200 mg, 3 m mol) in methanol in presence of catalytic amount of hydrochloric acid produced 5– bromoisatin – 3 – oxime of good yield.



78%

T- 4. *p* – TOSYL MERCAPTOACETATE

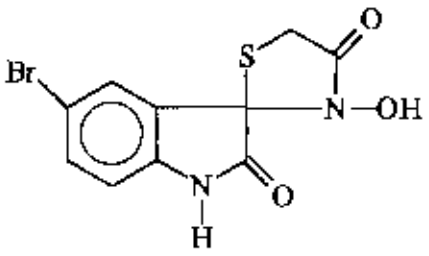
Refluxing a mixture of mercaptoacetic acid (241 mg, 2.6 m mol) and *p*– toluene sulphonyl chloride (580 mg, 3 m mol) in methanol produced *p* – tosyl mercaptoacetate of 65% yield.



65%

T-5 3'(HYDROXY) SPIRO [5– BROMO INDOLINE – 3, 2' THIAZOLIDINE] – 2, 4' – DIONES.

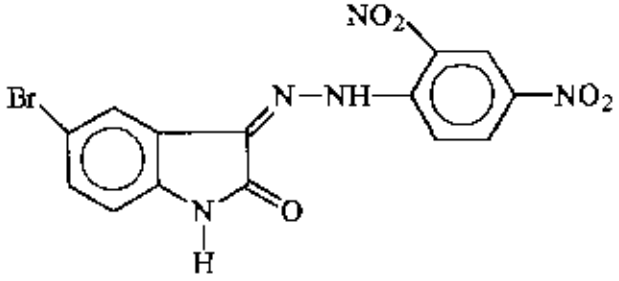
Refluxing a mixture of 5– bromoisatin –3 – oxime (482 mg, 2 m mol) and *p*-tosylmercaptoacetate (1.5 gm. 5 m mol) in 1, 4 – dioxane produced 3 (hydroxy) spiro [5 – bromo indoline –3, 2'– thiazolidine] – 2, 4' – diones of 35% yield.



35%

T-6 5- BROMOISATIN – 3 (2, 4 – DINITRO PHENYL) – HYDRAZONE.

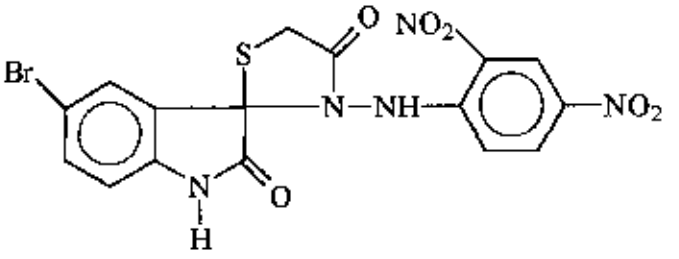
Acid catalyzed condensation of 5–bromoisatin (425 mg, 2 m mol) and 2, 4 – dinitrophenyl hydrazine (398 mg, 2 m mol) in methanol in presence of catalytic amount of hydrochloric acid produced 5 – bromoisatin –3 (2, 4– dinitro phenyl) – hydrazone of good yield.



75%

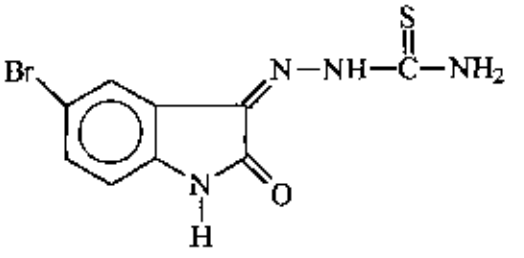
T-7. 3′(2, 4 – DINITROPHENYLAMINO) SPIRO [5 – BROMOINDOLINE – 3, 2′ – THIAZOLIDINE] – 2, 4′ – DIONES.

3′ (2,4- Dinitrophenylamino) spiro [5- bromoindoline – 3,′2 – thiazolidine] – 2, 4′ – diones was attempted to synthesize by refluxing of 5 – bromoisatin – 3 (2, 4– dinitrophynyl) – hydrazone (406 mg, 1 m mol) and mercaptoacetic acid (184 mg, 2 m mol) but it was not possible to detect any desired product.



T-8. 5 – BROMOISATIN – 3 – THIOSEMICARBAZONE.

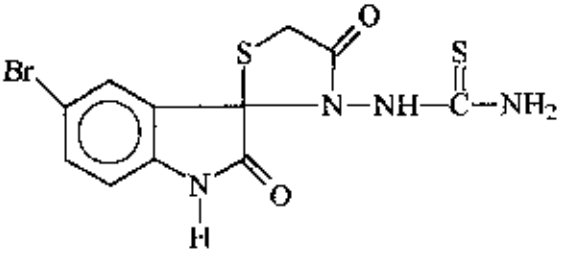
Acid catalyzed condensation of 5 – bromoisatin (678 mg, 3 m mol) and thiosemicarbazide (273 mg, 3 m mol) gave 5 – bromoisatin – 3 – thiosemicarbazone of high yield.



90%

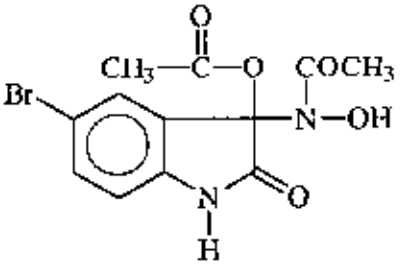
T-9. 3′ (THIOUREIDO) SPIRO [5– BROMOINDOLINE – 3, 2 – THIAZOLIDINE] –2, 4′– DIONES.

Refluxing of 5 – bromoisatin – 3 – thiosemicarbazone (598 mg, 2 m mol) and mercapto acetic acid (0.522 gm, 6 m mol) in DMF in presence of zinc chloride produced '3(thiou reido) spiro [5 – bromoindoline – 3, 2 – thiazolidine] – 2, 4′ – diones of relatively poor yield.



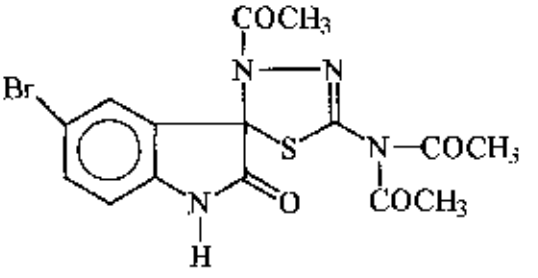
T.10. 3 (*N* – HYDROXY – *N* – ACETYL) AMINO – 3 – ACETOXY – 5 – BROMOINDOL.

5 – Bromoisatin – 3 – oxime (482 mg, 8 m mol) was refluxed in acetic anhydride (7 ml) and produced 3(*N* – hydroxyl – *N* – acetyl)amino – 3 – acetoxy – 5 – bromoindol.



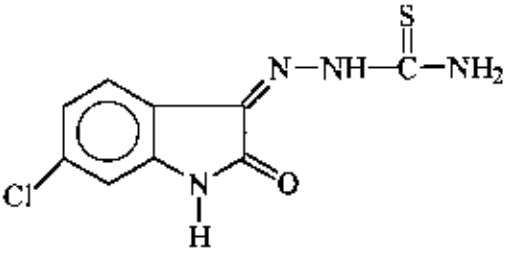
T- 11. 2′ DIACETYLAMINO – 4′ – *N* – ACETYL SPIRO [Δ^2 –1, 3, 4– THIADIAZOLINE (5′, 3) – 5 – BROMOINDOLINE.

Refluxing of 5– bromoisatin – 3 – thiosemicarbazone (398 mg, 2 m ml) in acetic anhydride produced 2′ – diacetylamino – 4′– *N* – acetyl spiro (Δ^2 – 1, 3, 4 – thiadiazoline (5′ , 3) – 5 – bromo – indoline].



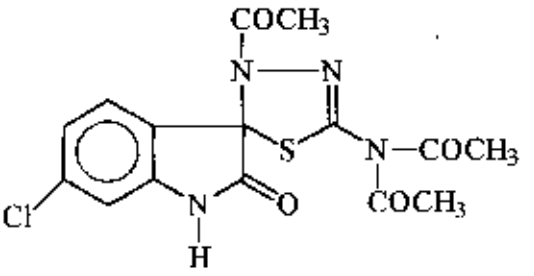
T-12. 6-CHLOROISATIN – 3 –THIOSEMICARBAZONE

A mixture of 6 – chloroisatin (363 mg, 2 m mol) and thiosemicarbazone (182 mg, 2 m mol) was refluxed in methanol in presence of catalytic amount of hydrochloric acid and produced 6 – chloroisatin – 3 – thiosemicarbazone.



T-13. 2′ DIACETYLAMINO – 4′ – N ACETYL SPIRO | Δ^2 –1, 3, 4 – THIADIAZOLINE (5′, 3) – 6 – CHLOROINDOLINE.

6 – Chloroisatin – 3 – thiosemicarbazone (255mg, 1m mol) was refluxed in acetic anhydride(6 ml) and produced 2′– (diacetylamino) – 4′– *N* – acetyl spiro [Δ^2 – 1, 3, 4 – thiadiazoline – (5′, 3) – 6 – chloroindoline].



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