The chemistry of isatins: a review from 1975 to 1999

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Isatina (1H-indol-2,3-diona) é um composto de grande versatilidade sintética, podendo ser utilizado na obtenção de diversos sistemas heterocíclicos, como derivados indólicos e quinolínicos, o que a torna uma importante matéria-prima na síntese de fármacos. Isatina também tem sido detectada em tecidos de mamíferos, o que tem despertado o interesse em seu estudo como modulador em diversos processos bioquímicos. Os avanços na aplicação de isatinas em síntese orgânica, bem como na compreensão de seus efeitos biológicos e farmacológicos, nos últimos vinte e cinco anos encontram-se relatados nesta revisão e seus respectivos materiais suplementares.

Isatin (1H-indole-2,3-dione) is a synthetically versatile substrate, where it can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and 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 during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported in this review and in the accompanying supplementary information.

Keywords: isatin, heterocyclic synthesis, drug synthesis, metal complexes

1. Introduction

Isatin (1H-indole-2,3-dione, Figure 1) was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids.

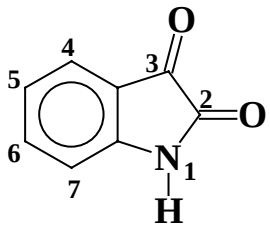


Figure 1

The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. Three reviews have been published regarding the chemistry of this compound: the first by Sumpter, in 1954[1], a second by Popp in 1975[2], and the third on the utility of isatin as a precursor for the synthesis of other heterocyclic compounds[3]. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives. These properties are more fully detailed in the supplementary material.

In nature, isatin is found in plants of the genus *Isatis*[4], in *Calanthe discolor* LINDL.[5] and in *Couroupita guianensis* Aubl.[6], and has also been foundas a component of the secretion from the parotid gland of *Bufo* frogs[7], and in humans as it is a metabolic derivative of adrenaline[8-10]. Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant *Melochia tomentosa*[11-13] as well as from fungi: 6-(3'-methylbuten-2'-yl)isatin was isolated from *Streptomyces albus*[14] and 5-(3'-methylbuten-2'-yl)isatin from *Chaetomium globosum*[15]. Isatin has also been found to be a component of coal tar[16].

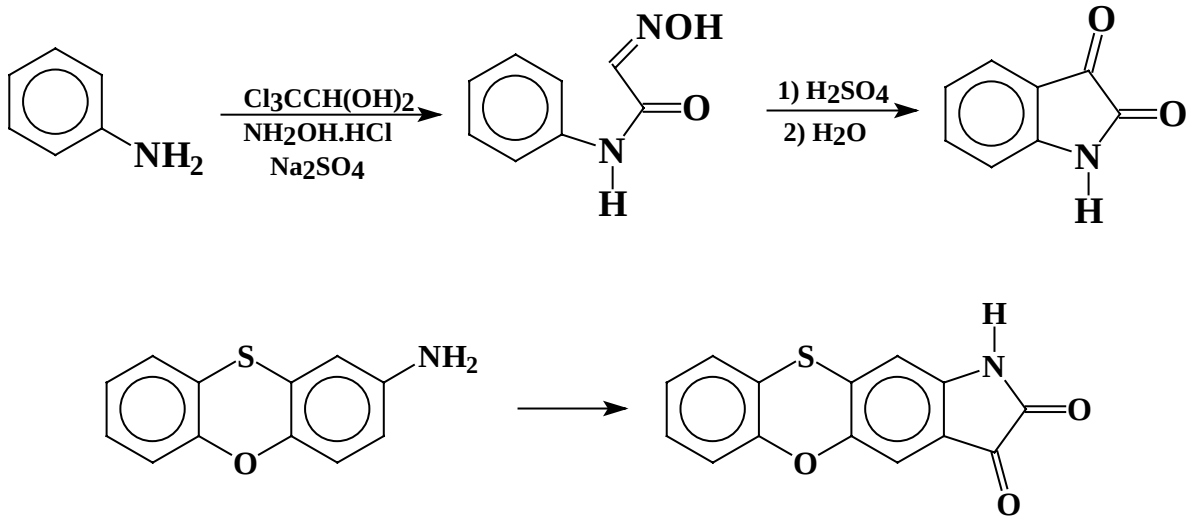
This review aims to document the publications concerning isatin, its synthesis, chemical reactivity and pharmacological properties during the period from 1975 to 1999. The biological and pharmacological data obtained from the scientific literature are summarized in

Supplementary Material 1. A graphical survey of the application of isatin in the synthesis of other heterocyclic systems is presented in Supplementary Material 2 and Supplementary Material 3 is a summary of metal complexes and some organometallic derivatives of isatin. These supplementary materials are available at www.sbq.org.br. The databases used for the preparation of this review were Chemical Abstracts, MEDLINE (www.healthgate.com), Beilstein (chemweb.com), Web of Science ISIS (webofscience.fapesp.br) and the IBM intellectual property network (www.patents.ibm.com).

2. Synthesis of isatins

2.1 The Sandmeyer methodology

The method developed by Sandmeyer is the oldest and the most frequently used for the synthesis of isatin. It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield[17]. The method applies well to anilines with electron-withdrawing substituents, such as 2-fluoroaniline[18], and to some heterocyclic amines, such as 2-aminophenoxathine[19] (Scheme 1).

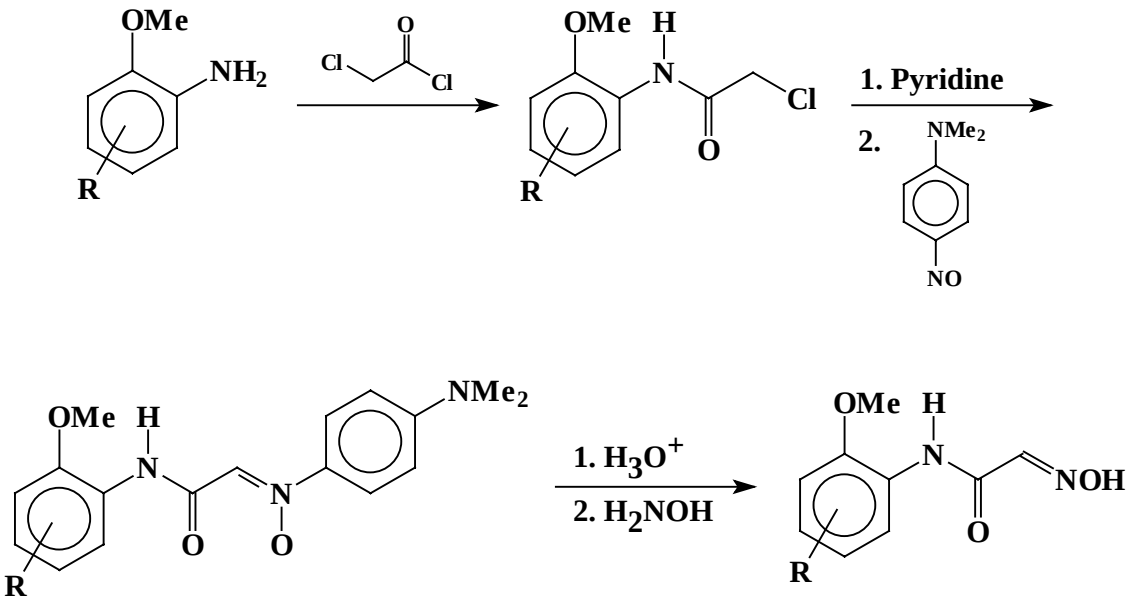


Scheme 1

This method has some economic advantages, as the reagents are cheap and readily available, and the yields are usually high. Recently, the Sandmeyer methodology has been modified by the incorporation of ethanol as a co-solvent[20]. This modification proved to be particularly useful in cases where the aniline derivative was insoluble in the conventional reaction matrix. Application of the modified Sandmeyer methodology allowed the synthesis of 4,6-dibromoisatin, a key intermediate for the synthesis of the marine natural product convolutamydine A, in 85% yield, thus representing a greater than 700% improvement in yield over the existing published procedure. The use of microwave irradiation during both stages of the Sandmeyer procedure has been investigated, and this modified procedure was also employed for the synthesis of convolutamydine A[21].

In addition to the use of H_2SO_4 for the cyclization step, isonitrosoacetanilides can be heated in $BF_3.Et_2O$ at 90 ^oC. After cooling the reaction mixture, addition of water allows isolation of the respective isatins. This methodology has proved to be particularly effective for the preparation of benzo-oxygenated isatin derivatives[22,23]

The Sandmeyer synthesis has been described as being unapplicable to ortho-hydroxy or *ortho*-alkoxyanilines. Therefore an alternative procedure for the synthesis of the isonitrosoacetanilides was reported[24,25] (Scheme 2).

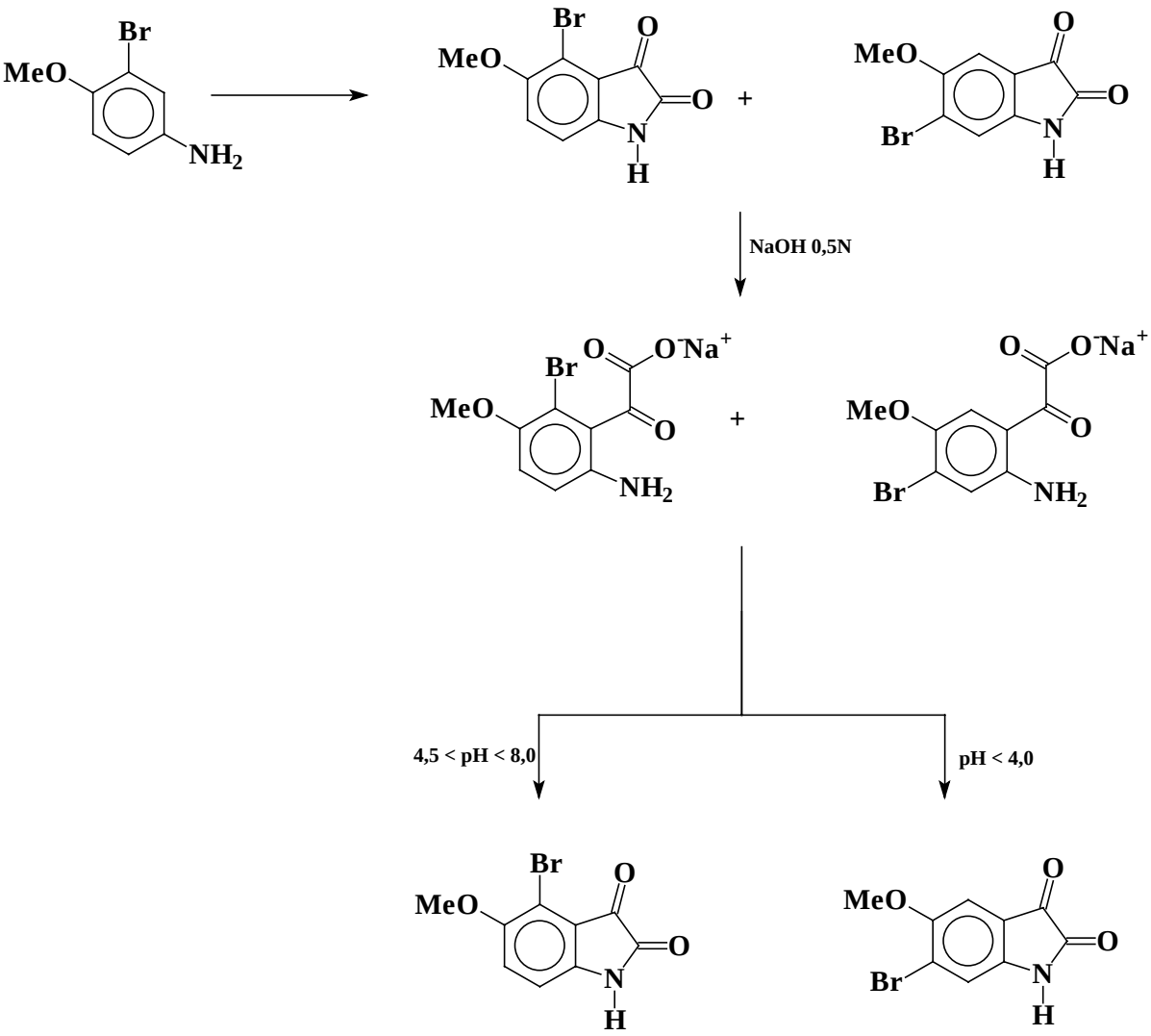


Scheme 2

On the other hand, there are some disadvantages, for instance those listed below.

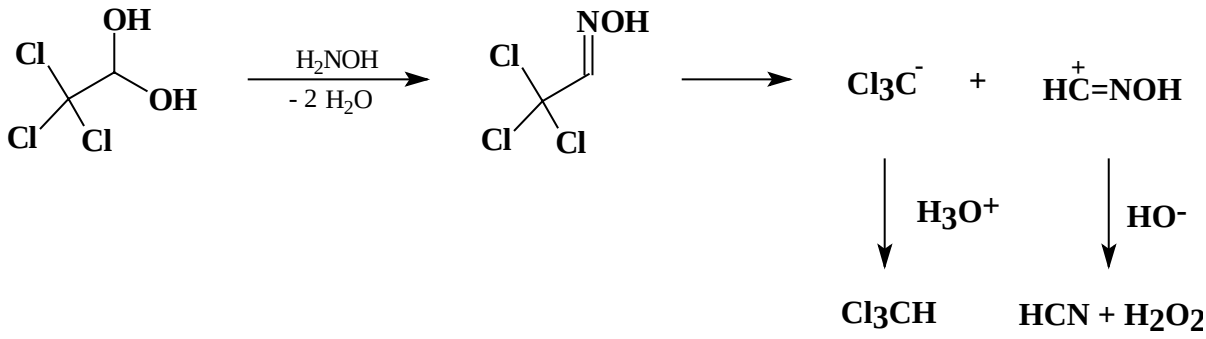
a) The use of *N*-alkylanilines furnishes the corresponding *N*-alkylisatins in low yield. For example, *N*-methylisatin is obtained in 22% overall yield[26].

b) *Meta*-substituted anilines lead to two isomers (4-and 6-substituted isatins), *e.g.*, 3-bromo-4-methoxyaniline yields 4-bromo-5-methoxyisatin (27%) e 6-bromo-5-methoxyisatin (63%). These isomers can be separated by conversion to the corresponding sodium isatinates using 0.5N NaOH. Subsequent controlled acidification of the reaction medium leads to cyclisation of the two isomers at different pH values, regenerating the corresponding isatins, which precipitate from the reaction medium[27] (Scheme 3).



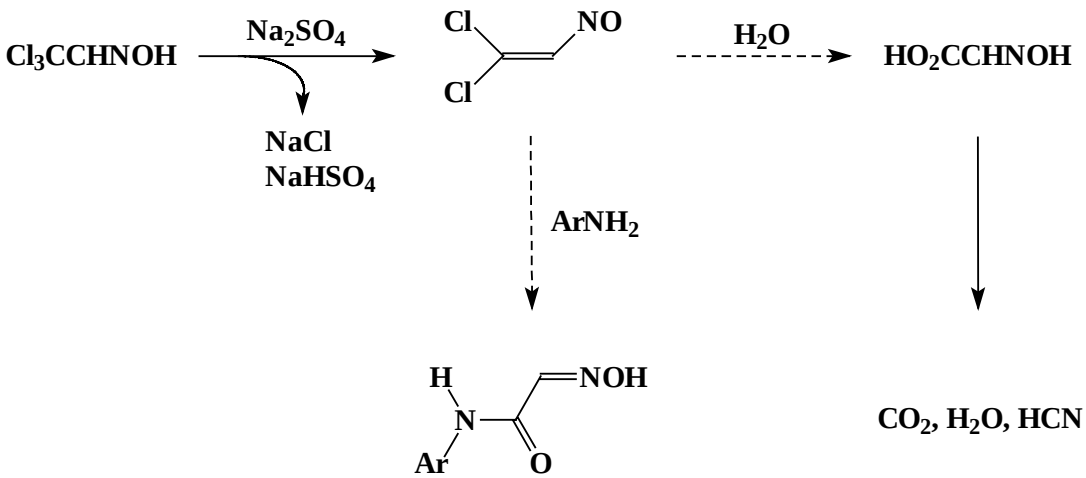
Scheme 3

c) The formation of HCN during the reaction has been detected by the formation of Prussian blue on addition of ferrous sulfate and NaOH[28]. The measured concentration of HCN in the mother liquors from the preparation of the isonitrosoacetanilides was found to be 100 to 200 ppm[29]. The mechanism informally proposed for the formation of HCN is described below (Scheme 4).



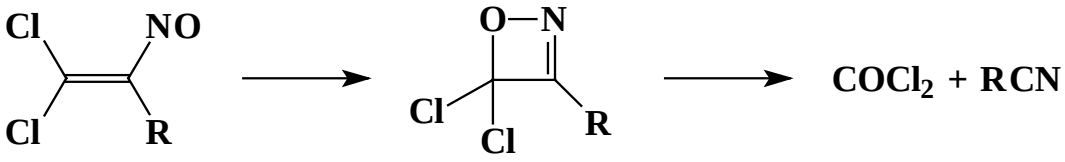
Scheme 4

An alternative explanation for the formation of HCN can be arrived at by consideration of the mechanism of formation of the intermediate isonitrosoacetanilides. It has been previously postulated, although never unambiguously demonstrated, that an intermediate dichloronitrosoalkene is initially formed by elimination of HCl from clhoraloxime during the Sandmeyer isonitrosoacetanilide synthesis. This nitrosoalkene is subsequently attacked by the aniline to give an addition product that yieldS the isonitrosoacetanilide via a subsequent hydrolysis reaction[30,31]. However, competitive addition of water and aniline to the nitrosoalkene would lead to formation of the glyoxalic acid oxime and the isonitrosoacetanilide respectively. Under the conditions of the reaction, refluxing aqueous Na_2SO_4, it could be expected that the glyoxalic acid oxime would decarboxylatively decompose with the concomitant formation of water and HCN (Scheme 5).



Scheme 5

A futher possibility exists. It has been shown that nitrosoalkenes decompose, with formation of HCN, via the formation of an oxazete and retro-cyclisation[31] (Scheme 6).

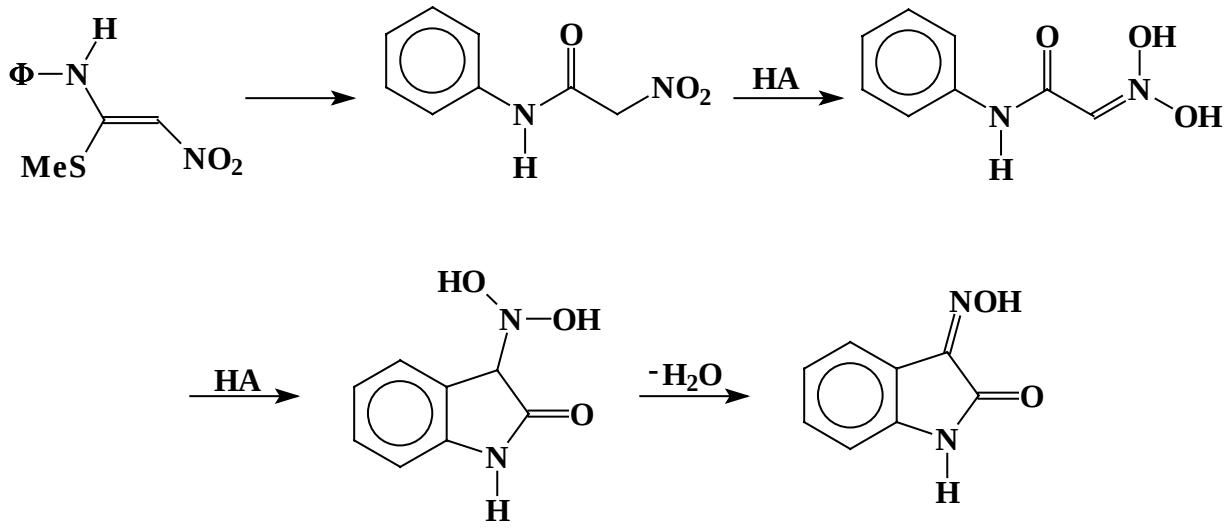


Scheme 6

Whatever the mechanism for formation of HCN during the Sandmeyer isonitrosoacetanilide synthesis, it is resasonable to recommend that appropriate precautions be taken during the preparation of these compounds.

2.2 Use of nitroacetanilides

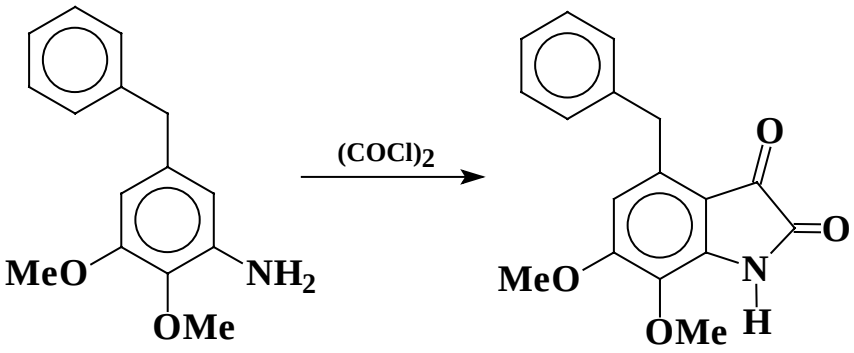
Nitroacetanilides, obtained by alkaline hydrolysis of 1-arylamino-1-methylthio-2-nitroethenes, are readily cyclised to isatin-3-oximes by the use of concentrated sulfuric acid or trifluoromethanesulfonic acid at room temperature; the latter giving somewhat higher yields[32]. Although this methodology is related to the Sandmeyer methodology, it has no obvious benefit over the latter (Scheme 7).



Scheme 7

2.3 The Stolle procedure

The most important alternative to Sandmeyer's procedure is the method of Stolle. In this method anilines are reacted with oxalyl chloride to form an intermediate chlorooxalylanilide which can be cyclized in the presence of a Lewis acid, usually aluminum chloride or $BF_3.Et_2O$[33], although $TiCl_4$[34] has also been used to give the corresponding isatin. This method has been used for the synthesis of 1-aryl[35,36] and polycyclic isatins derived from phenoxazine, phenothiazine and dibenzoazepine[37] as well as indoline[38]. In the case of dimethoxyanilines, spontaneous cyclization to yield dimethoxyisatins in the absence of a Lewis acid has been observed, as exemplified in the synthesis of melosatin A[12], albeit in very low yield (Scheme 8).



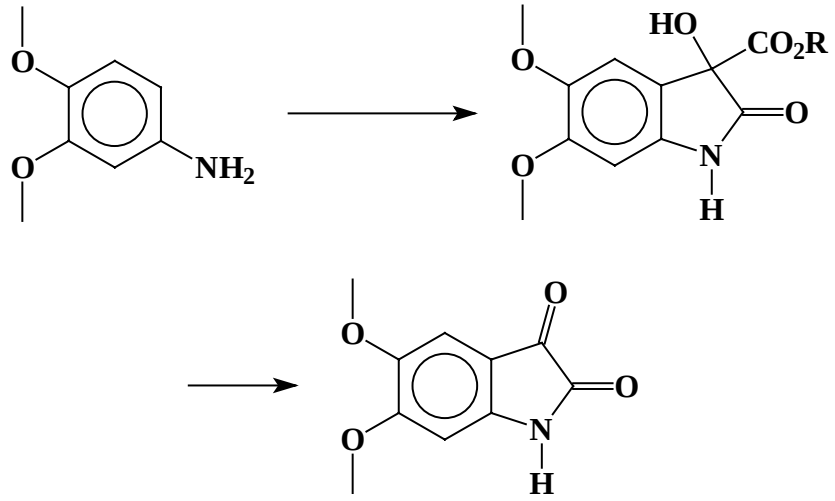
Melosatin A

Scheme 8

Methoxyisatins can be converted to the corresponding phenolic compounds by the action of pyridinium hydrobromide perbromide. This seems to be the best method for obtaining these derivatives, as aminophenols are not useful substrates for the synthesis of isatins[39].

2.4 The Martinet isatin synthesis

The Martinet procedure for the synthesis of indole-2,3-diones involves the reaction of an aminoaromatic compound and either an oxomalonate ester or its hydrate in the presence of an acid to yield a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative which after oxidative decarboxylation yields the respective isatin. This method was applied with success for the synthesis of 5,6-dimethoxyisatin from 4-aminoveratrole whereas the use of 2,4-dimethoxyaniline was less successful[40] (Scheme 9).



Scheme 9

The Martinet procedure is readily applied to napthylamines, thus yielding benzoisatin derivatives[41].

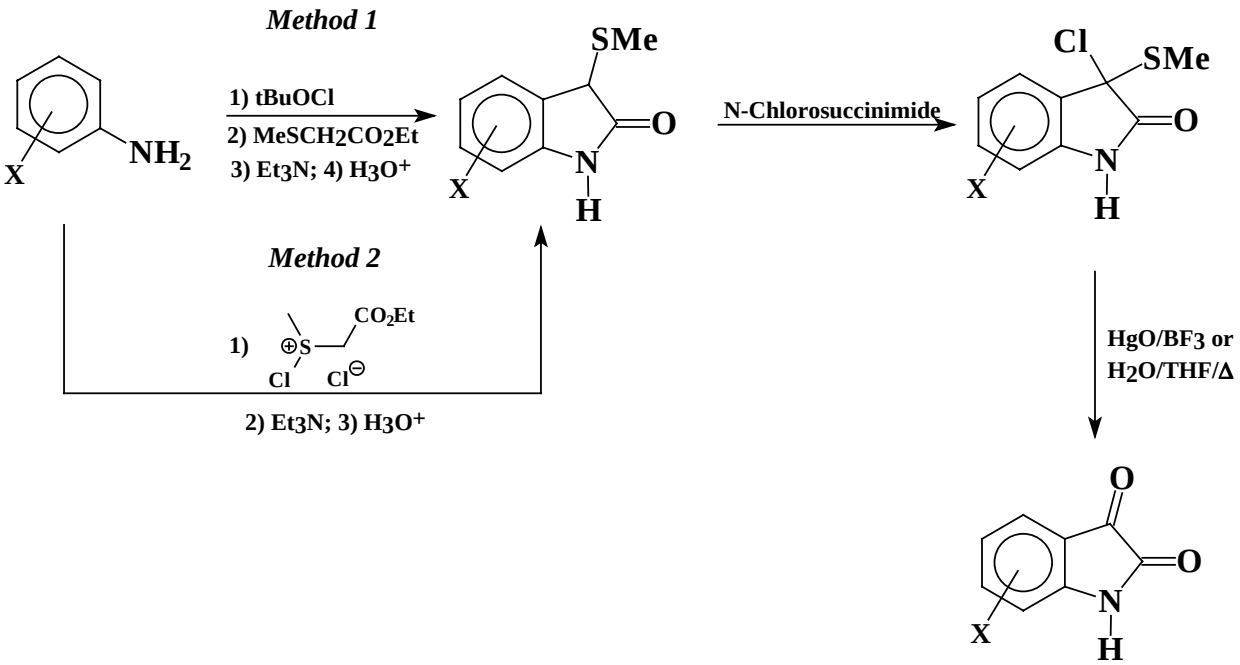
2.5 The Gassman procedure

A fundamentally different and general procedure developed by Gassman is another option for the synthesis of isatins[42,43]. This methodology consists in the formation and subsequent oxidation of an intermediate 3-methylthio-2-oxindole[44-46] to give the corresponding substituted isatins in 40-81% yield.

Two complementary methods for the synthesis of the 3-methylthio-2-oxindoles were developed, and the methodology of choice is dependent upon the eletronic effect of substituents bonded to the aromatic ring. When electron withdrawing groups are present, the

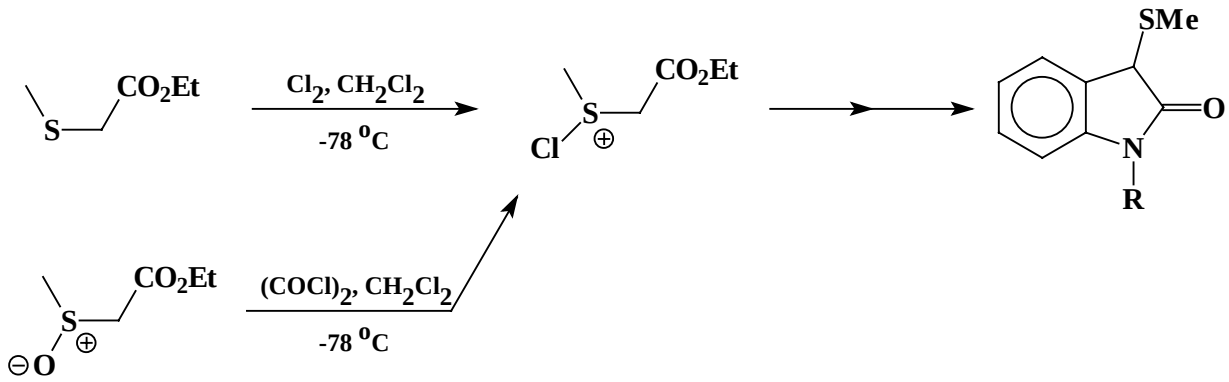
oxindole derivative can be synthesized via a *N*-chloroaniline intermediate, which further reacts with a methylthioacetate ester to furnish an azasulfonium salt (Method 1, Scheme 10). In the case of electron donating groups that destabilize the *N*-chloro intermediate, and thus give diminished yields of the azasulfonium salt, a second method of generetion of this salt, by reaction of the chlorosulfonium salt with an appropriate aniline (Method 2, Scheme 10), gives better yields of the 3-methylthio-2-oxindoles.

Various methodologies have been devised for the conversion of these oxindoles to isatins. Reaction with *N*-chlorosuccinimide generates the unstable 3-chloro-3-methylthio-2-oxindoles, which were hydrolysed to isatins in the presence of red mercuric oxide and $BF_3.Et_2O$ in aqueous THF. Hydrolysis in the absence of these reagents gave a mixture of the isatn and the 3,3-dimethylthio-2-oxindole ketal[42]. Air oxidation of methylthio-oxindoles in the presence of a base in aqueous methanol also resulted in formation of the respective isatin, although over oxidation, generating anthranilic acid derivatives, was a problem and generated anthranilic acid derivatives [47] (Scheme 10).



Scheme 10

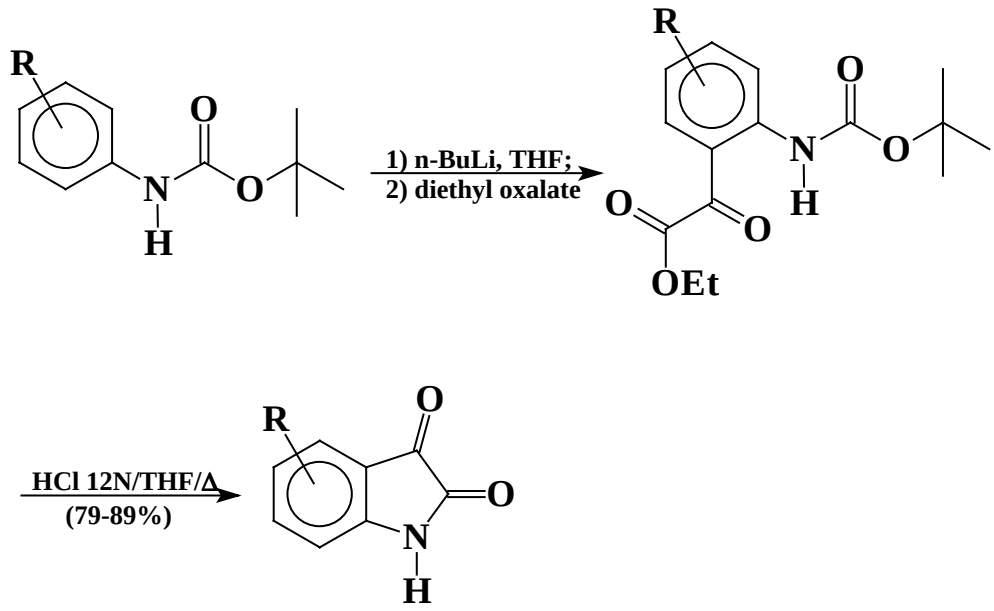
Recently Wright and co-workers have described a modified Gassman oxindole synthesis. They point out the problem associated with the preparation of the chlorosulfonium salt (reagent for Method 2) from chlorine gas and ethyl methylthioacetate, and demonstrated a modified procedure that makes use of a sulfoxide as a synthetic equivalent of a sulfenyl halide[48] (Scheme 11). The Gassman procedure can also be applied to *N*-alkylanilines[43].



Scheme 11

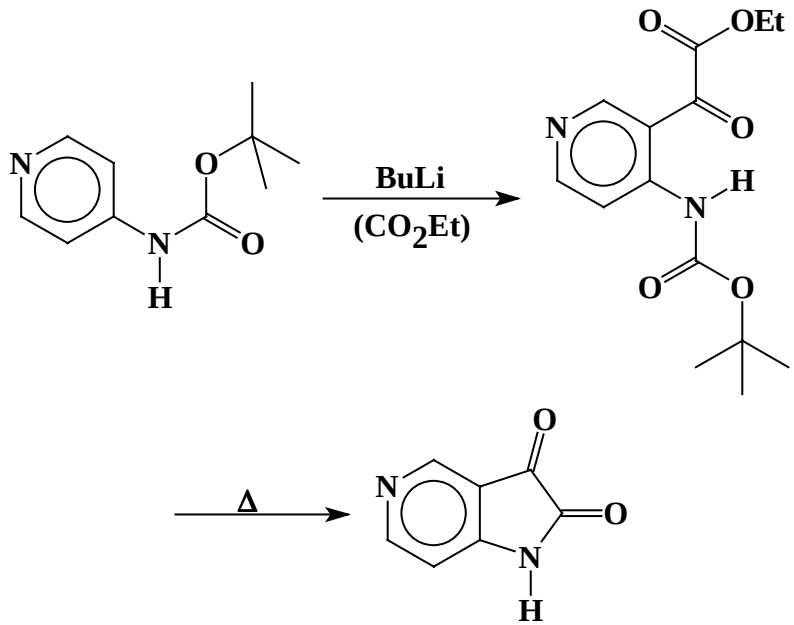
2.6 Metalation of anilide derivatives

A more recent method for the synthesis of isatins is based upon the directed *ortho*-metalation (D*o*M) of *N*-pivaloyl- and *N*-(*t*-butoxycarbonyl)-anilines. The corresponding dianions are treated with diethyl oxalate and the isatins are obtained after deprotection and cyclisation of the intermediate α-ketoesters. This method has the advantage of being regioselective for the synthesis of 4-substituted isatins from *meta*-substituted anilines where the substituent is a metalation directing group (*e.g.* OMe) [49] (Scheme 12).



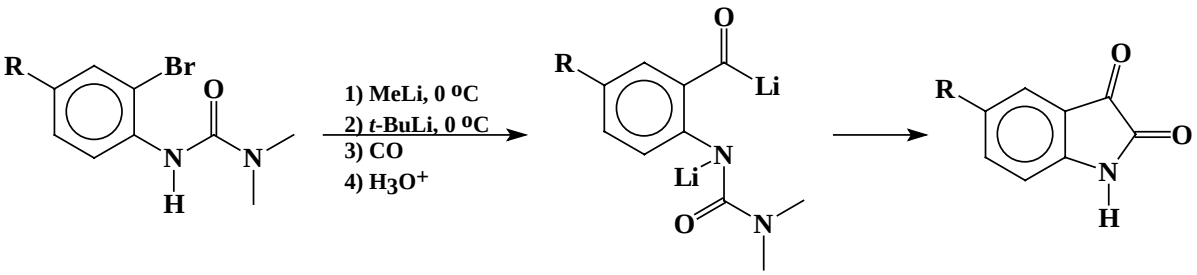
Scheme 12

The synthesis of 5-azaisatin was realized by *ortho*-lithiation of the 4-aminopyridine *t*-butylcarbamate followed by reaction with an excess of diethyl oxalate. Heating the glyoxylic ester under vaccum gave 5-azaisatin[50] (Scheme 13).



Scheme 13

Recently, a metal-halogen exchange method was described for the synthesis of isatins by lithiation of *ortho*-bromophenylureas, carbonylation and subsequent intramolecular cyclisation to give the desired products in 71-79% yield[51] (Scheme 14).



Scheme 14

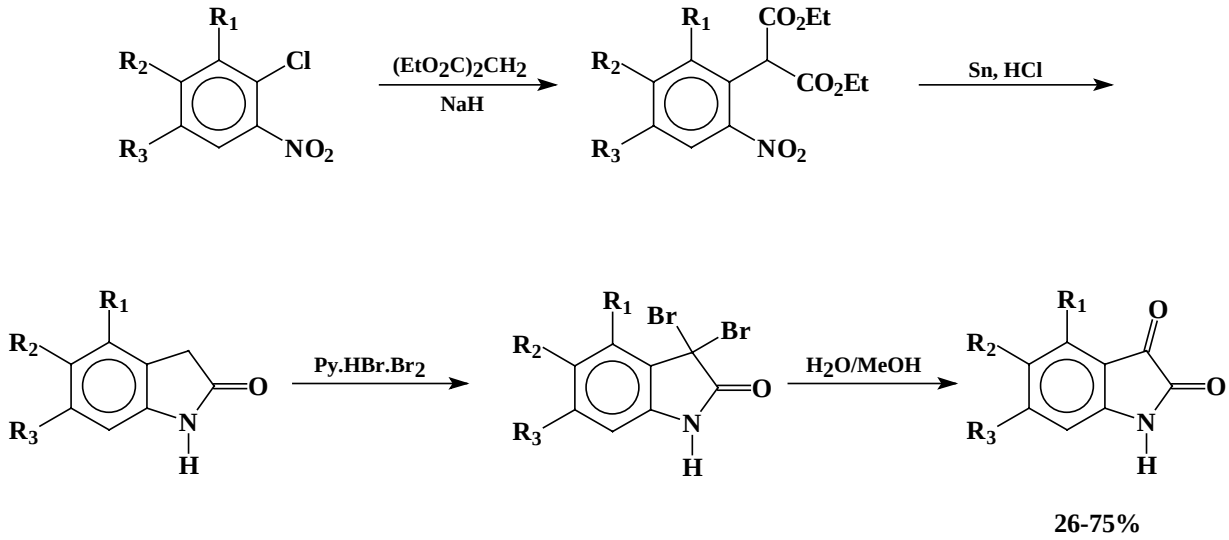
2.7 Miscellaneous procedures

These previously discussed methodologies are the most general and/or most commonly employed procedures for the synthesis of isatins. Other methodologies have been employed, but they are less general and some of them lead to the desired product in low yield.

Parrick and co-workers developed a synthetic methodology for isatins from indoles, using *N*-bromosuccinimide to promote their oxidation to yield 3,3-dibromooxindoles which were subsequently hydrolysed to the desired isatins[52,53]. By using this method it was possible to obtain 7-azaisatin from 7-azaindole, although in low yield. This isatin is more readily obtained by oxidation of the indolic compound using chromic anhydride in acetic acid[54] and this methodology can also be applied to the oxidation of 5-azaindole to yield 5-azaisatin[55].

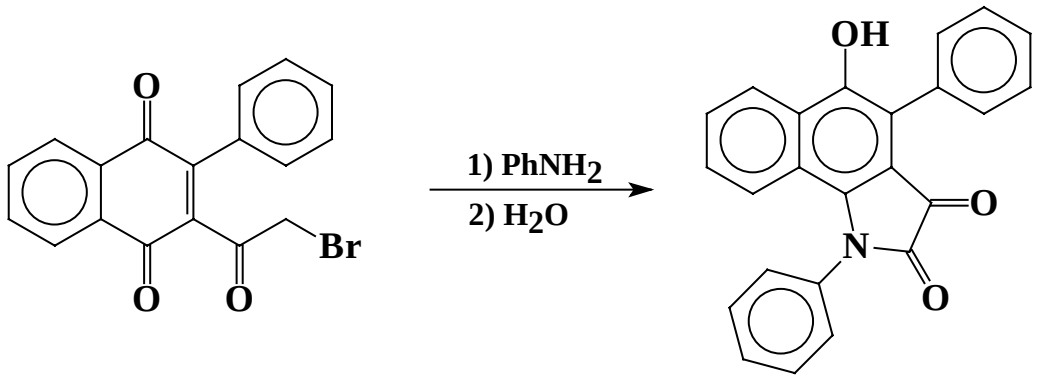
In an alternative methodology, 4- and 6-substituted-2-oxindoles, obtained from *o*-nitroarylmalonates, were converted to 3,3-dibromooxindoles by reaction with pyridinium perbromide. These intermediates were hydrolyzed to the corresponding isatins. This method, although limited to substrates with moderate to strongly electron withdrawing groups

(otherwise bromination of the aromatic ring occurs), suits well for the regioselective synthesis of 4- and 6-substituted isatins, such as 6-benzoylisatin[56] (Scheme 15).



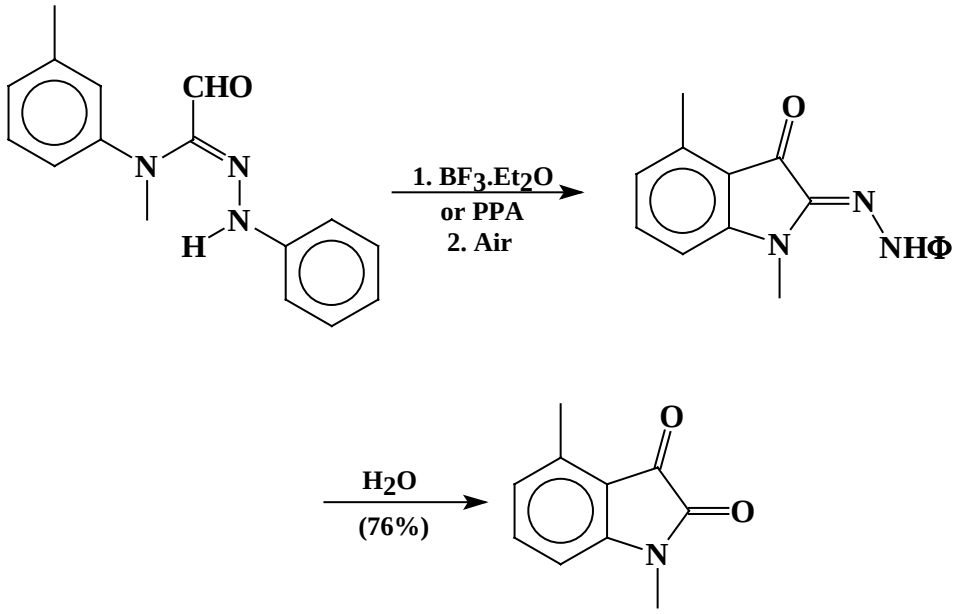
Scheme 15

Nitrones and dichloroketene react to furnish 3,3-dichlorooxindoles, which upon hydrolysis, lead to the desired isatins[57]. *N*-Aryl-benzoisatins can also be obtained from napthoquinones and anilines as a result of oxidation of the cyclic anils [58] (Scheme 16).



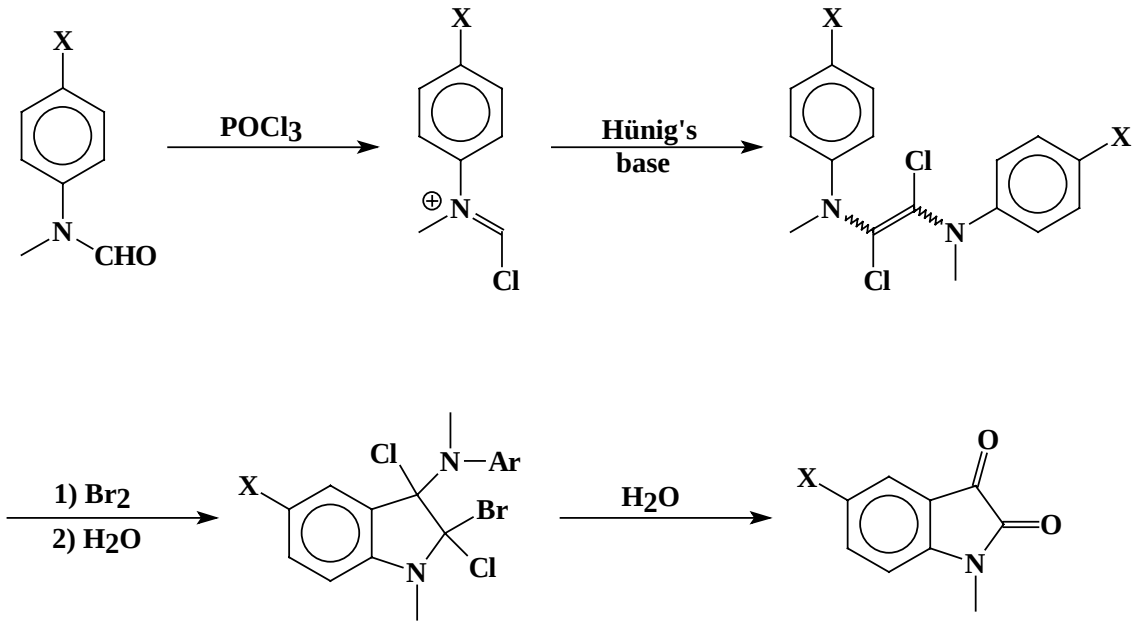
Scheme 16

1,4-Dimethylisatin can be obtained from air oxidation and hydrolysis of the cyclocondensation product of aryliminoacylhydrazones[59] (Scheme 17).



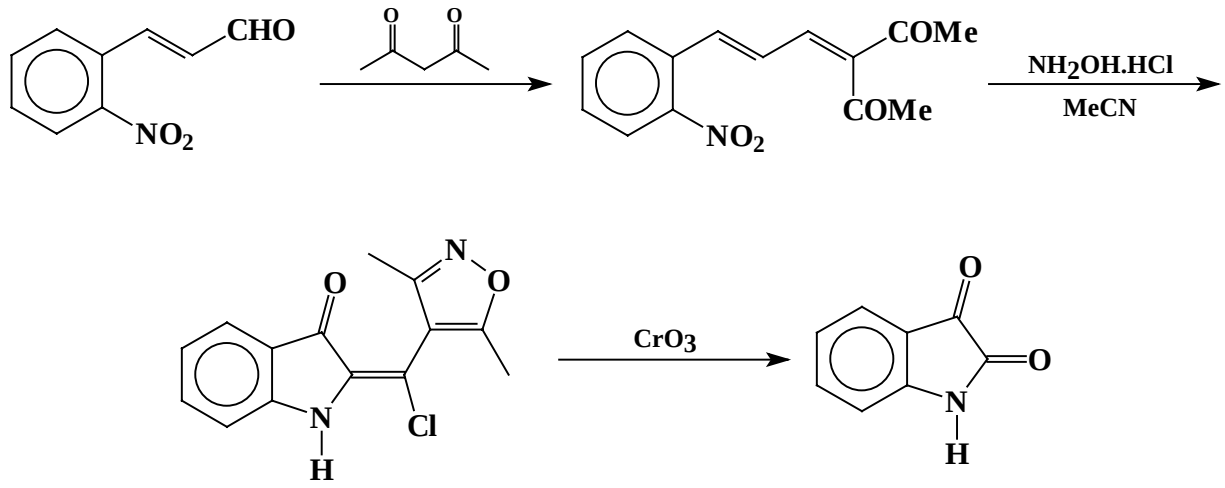
Scheme 17

Meth-Cohn and co-workers have observed that the treatment of 1,2-bis (*N*-methylanilino)-1,2-dichloroethanes, obtained by the dimerisation of the Vilsmeier reagents prepared from *N*-methylformanilides in $POCl_3$ using a tertiary amine, with an eletrophilic species yielded isatins in 11 to 79% after hydrolysis. The best yields were observed when bromine was used as the electrophilic species[60] (Scheme 18).



Scheme 18

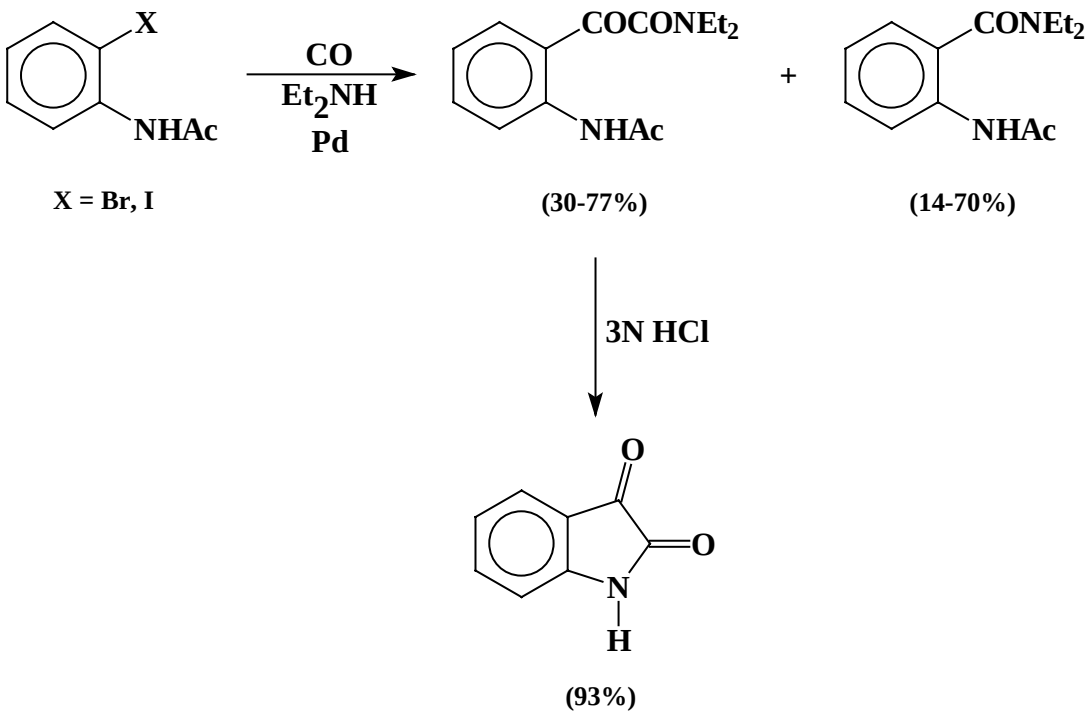
Isatin is formed from 2-nitrocinnamaldehyde through the sequence shown below[61] (Scheme 19):



Scheme 19

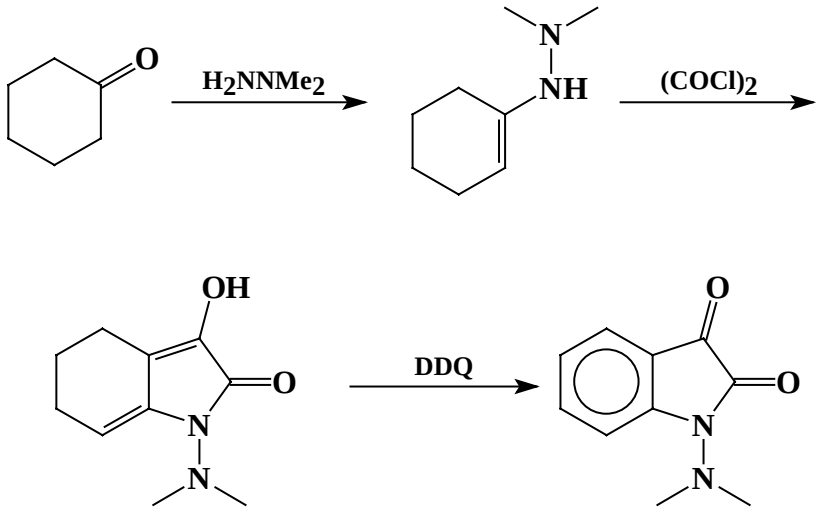
1-Napthylamine, when reacted with 1,2,4-triazin-5-ones in acetic acid, gives benzo[e]indole-2,3-dione in 71 to 81% yields, but both aniline and 1-methylaniline fail to furnish the corresponding isatins[62].

A *de novo* isatin synthesis based upon a palladium catalysed double carbonylation of *ortho*-haloacetanilides in the presence of Et_2NH to yield the corresponding glyoxylic acid amide was reported by Yamamoto and co-workers[63]. Hydrolysis of this amide yielded the respective isatin (Scheme 20).



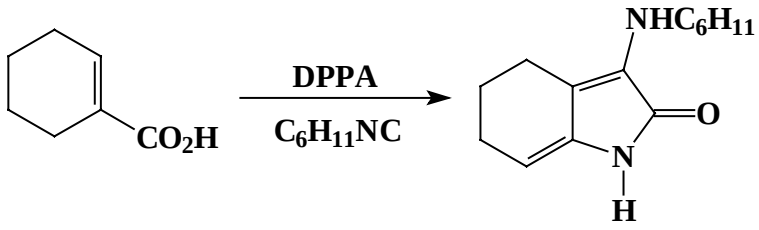
Scheme 20

1-(Dialkylimino)isatins can be prepared from cyclohexanone in three steps, the last involving DDQ oxidative aromatization[64] (Scheme 21).



Scheme 21

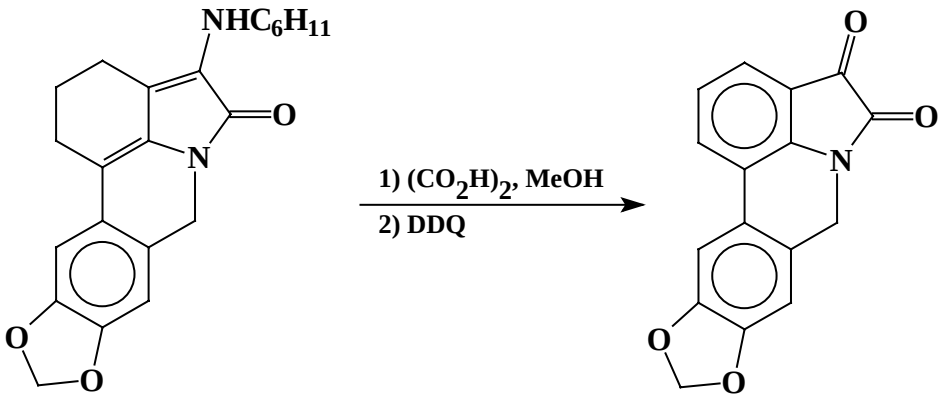
Rigby has developed a different approach for the construction of the hydroindolone intermediates[65]. These compounds were prepared by [1+4] cycloaddition of vinyl isocyanates and isocyanides (Scheme 22).



(84%)

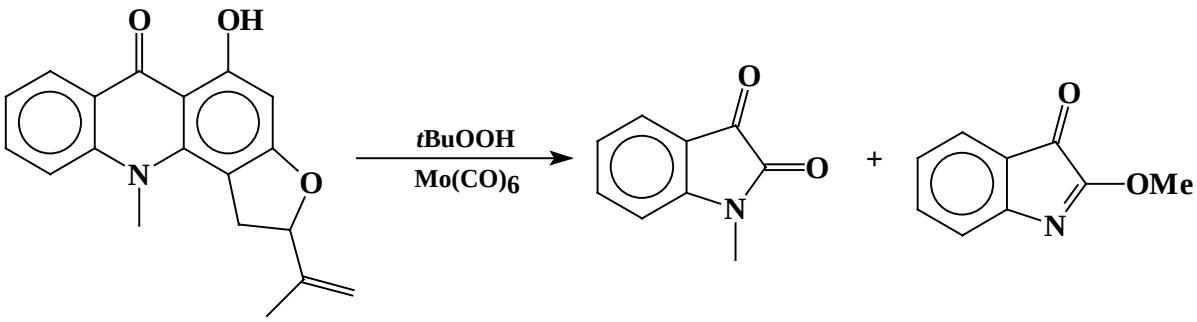
Scheme 22

The resultant dienamides can be hydrolysed and subsequently oxidised by DDQ to yield isatin derivatives[66] (Scheme 23).



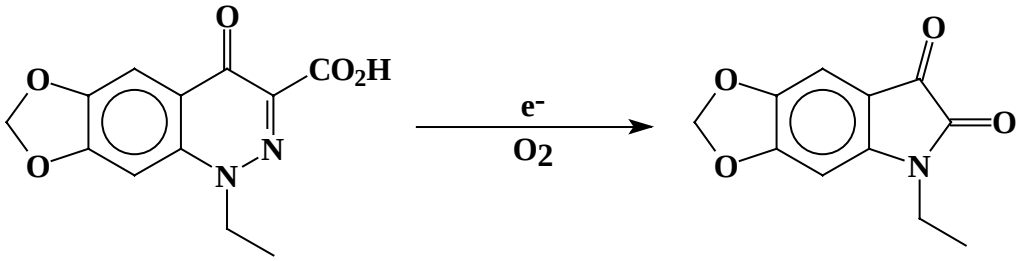
Scheme 23

The formation of isatins has been reported during decomposition studies of the structure or reactivity of natural products. In this manner, the attempted epoxidation of rutacridone led to *N*-methylisatin[67] (Scheme 24).



Scheme 24

Isatins are also formed during the photo-oxidation of 5,6-dihydroindoles[68], from the oxidation of indoles with thallium (III) trinitrate[69] and by electrochemical oxidation of indigo carmine[70]. 1-Ethyl-5,6-methylenedioxyisatin is obtained in the electrochemical reduction of cinoxacin, an antibacterial agent, in 92% yield[71] (Scheme 25).



Scheme 25

3. Reactivity of isatin and derivatives towards electrophiles

3.1 *N*-alkylation

Many methods have been devised for the *N*-alkylation of isatins. These derivatives are commonly synthesized from the reaction of the sodium salt of isatin with alkyl halides or sulphates[72,73]. Various methods for the preparation of this salt have been reported, and include the reaction of isatin with sodium hydride, either in toluene under reflux[74] or in DMF[75]. Other methods include the use of potassium carbonate in DMF[76,77] or in acetone[78]. In the latter case an aldol reaction of the solvent also occurs with the C-3 carbonyl of the isatin derivative.

Heating in *ortho*-dichlorobenzene results in a retro-aldol reaction and the obtention of the *N*-alkylated isatin. More recently the use of CaH_2 in DMF has been reported[79] and this method was used for the synthesis of both mono and bis-*N*-alkylisatins. These latter compounds have been previously prepared using dihaloalkanes and NaH in dioxane[80] or DMF[81] or by the use of LiH[82]. Some of these alkylation methodologies were evaluated for the synthesis of isatins bearing a glycosidic residue linked to the *N*-1 position [83].

An alternative method for preparing 1-alkylisatins consists in the reaction of isatin and alkyl halides in a benzene-chloroform/50% aq. KOH biphasic system, employing tetrabutylammonium hydrogensulfate as the phase transfer catalyst[84].

N-Propargylisatins, obtained from isatin and propargyl halides[79,85], can be converted to *N*-acetonylisatins through hydration with Hg(II) salts in acidic media[86].

The synthesis of 1-methylisatin by the method of Stolle, using tris(methylphenylamino) methane instead of *N*-methylaniline, leads to the desired product in low yields[87].

The reaction of isatin with vinyl acetate in the presence of Na_2PdCl_4 yields 1-vinylisatin[88].

On the other hand, O-alkylation at position 2 has been reported, along with the *N*-alkyl product, using γ-butyrolactone[89] or allyl bromide[90] as alkylating agents and the sodium salt of isatin. O-Methylisatin is described as the product of the reaction of methyl iodide with the silver salt of isatin, which can be prepared from isatin and silver acetate[91]. The alkoxy group has been reported to be displaced by nucleophiles such as hydrazines[92].

3.2 *N*-arylation

N-Arylisatin can be obtained from isatin in quantitative yields by reaction with $Ph_3Bi(OAc)_2$ and Cu^0 under an inert atmosphere[93] or from aryl bromides and cupric oxide[94].

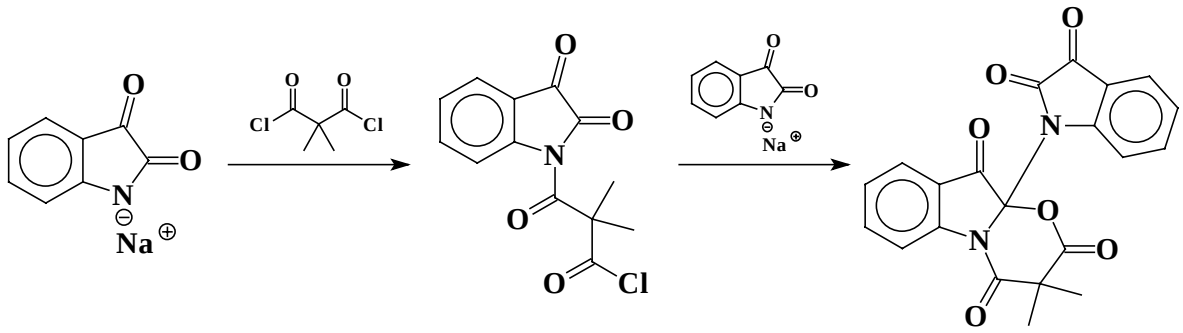
3.3 *N*-methyleneamino derivatives

The Mannich reaction is readily applied to isatins. The products of this reaction, the *N*-aminomethylisatins (Mannich bases), can also be obtained from the *N*-hydroxymethyl derivatives by reaction with an amine[95] or by reaction with acetyl chloride to yield *N*-chloromethylisatin which can be further treated with potassium phthalimide or alcohols to give the corresponding *N*-phthalimidomethyl or *N*-alkoxymethyl isatins[96]. The Mannich reaction can also be performed with isatin derivatives, such as isatin-3-hydrazones[97] and isatin-3-thiosemicarbazones[98].

3.4 *N*-acylation and *N*-sulfonylation

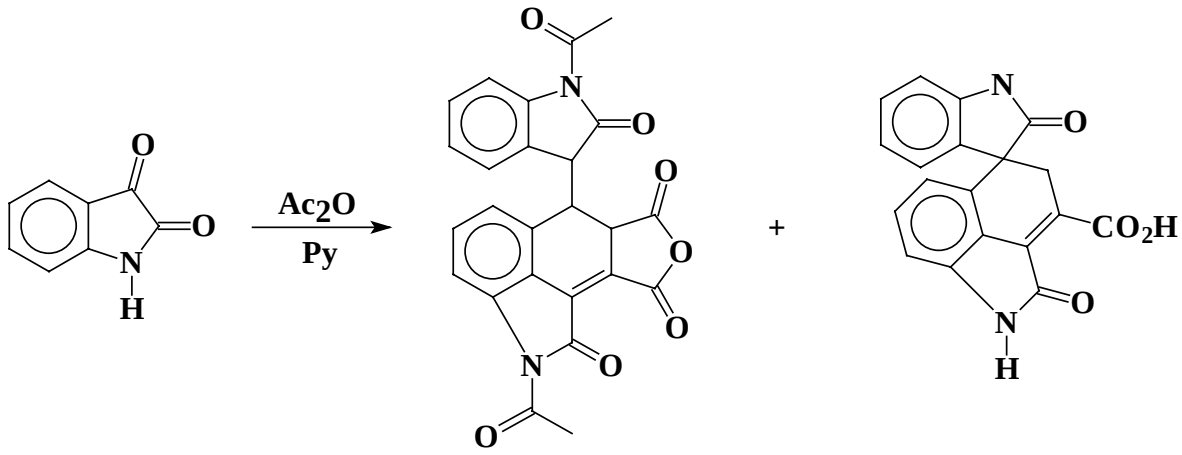
The synthesis of *N*-acylisatins under a variety of conditions has been described using acyl chlorides or anhydrides under reflux, either alone[99] or using perchloric acid in benzene, triethylamine in benzene[100], pyridine in benzene[101], or triethylamine in chloroform[102,103] as catalysts; or by conversion of isatin to sodium isatide using NaH in toluene under reflux and subsequent reaction with acyl chlorides[77].

The use of diacyl chlorides, e.g. oxalyl chloride[104], octanedioyl or nonanedioyl chlorides[105], yields bis-acylisatins. Attempts to use 2,2-dimethylmalonyl chloride to furnish 2,2-dimethylmalonyl-bis-isatin failed, and led instead to an unusual tricyclic compound which was characterized by spectroscopic methods and by X-ray diffraction[106] (Scheme 26).



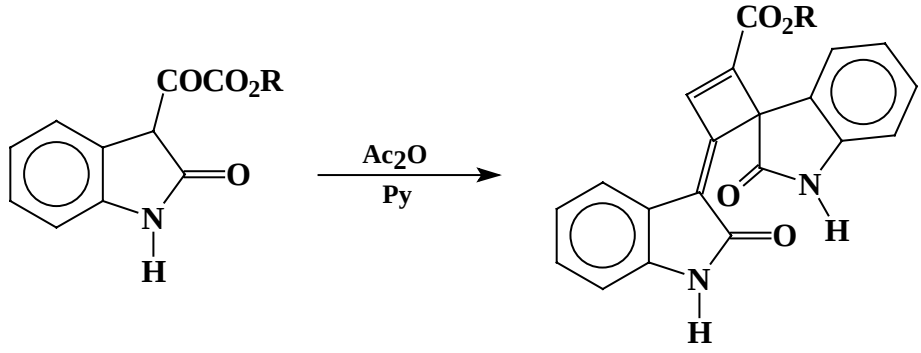
Scheme 26

Other complex products have been obtained from the reaction of isatin and acetic anhydride in the presence of pyridine[107] (Scheme 27).



Scheme 27

Similarly, dimers may be formed in the acetylation of indolylglyoxalates with acetic anhydride in pyridine[108] (Scheme 28).



Scheme 28

N-Sulfonylisatins are obtained from the reaction of isatin and sulfonyl chlorides by applying the same methodologies as used for obtaining 1-acylisatins. For example, 1-tosylisatin is formed in 71-74% yield by mixing tosyl chloride with isatin in the presence of Et_3N or with the sodium salt of isatin[109].

3.5 *N*-Haloderivatives

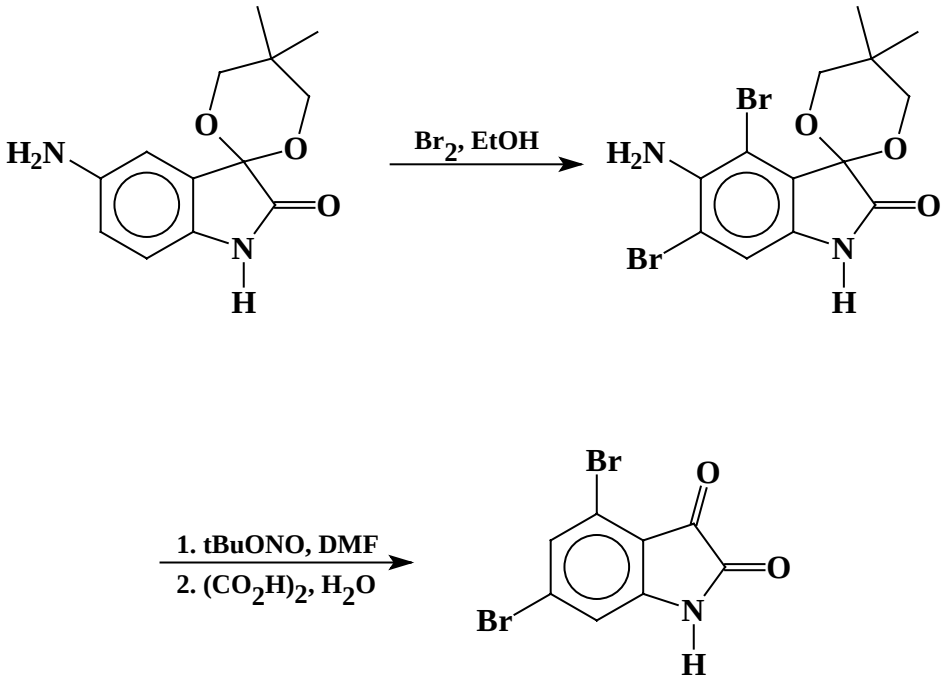
The treatment of isatin with sodium hypochlorite in acetic acid leads to 1-chloroisatin, an effective mild oxidizing agent for the conversion of alcohols to aldehydes and ketones[110] and of indoles to 3-chloroindoles without formation of by-products[111]. *N*-[phenyliodine(III)] bisisatin can be obtained from the sodium salt of isatin and phenyliodine (III) bistrifluoroacetate in 85% yield. This compound is a member of a group of iodine(III)imides, which possess mild oxidizing properties[112].

3.6 Reactivity of the aromatic nucleus

Although isatins with substituents attached to the aromatic ring are usually obtained from the corresponding functionalized anilines, they can be synthesized by electrophilic aromatic substitution. Nitration of isatin using the sulfonitric mixture yields 5-nitroisatin[113]. Precise temperature control is needed[114], otherwise a mixture of nitrated products are formed[115].

The bromination of isatin in alcohols gives 5,7-dibromo-3,3-dialkoxyoxindoles in an acid catalyzed ketalization of the halogenated isatin[116]. Monobromination at position 5 can be achieved, at least on a microscale, with the use of *N*-bromoacetamide in acetic acid medium[117]. 5-Bromoisatins can suffer arylation by the use of aryl or heteroarylboronic acids via a palladium-catalyzed Suzuki cross-coupling reaction[118]. Recently, 4,6-dibromoisatin, a

key intermediate in the synthesis of convolutamidine A, was prepared by bromination in ethanol of a 5-aminoisatin derivative[119] (Scheme 29).



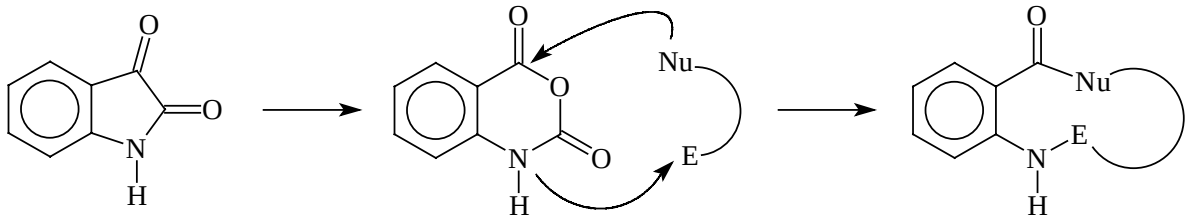
Scheme 29

4. Application of isatin**s in organic synthesis**

Many synthetic methodologies have been described for the conversion of isatins to other heterocyclic systems. This chemistry can be generalised as one of the following strategies:

a. Partial or total reduction of the heterocyclic ring, leading to indoles and derivatives;

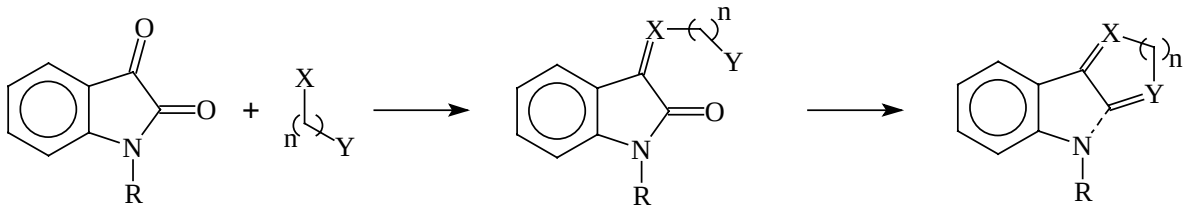
b. Oxidation of the heterocyclic ring. For example, conversion of isatin to isatoic anhydride, with subsequent conversion to other heterocyclic systems (Scheme 30);



Isatoic anhydride

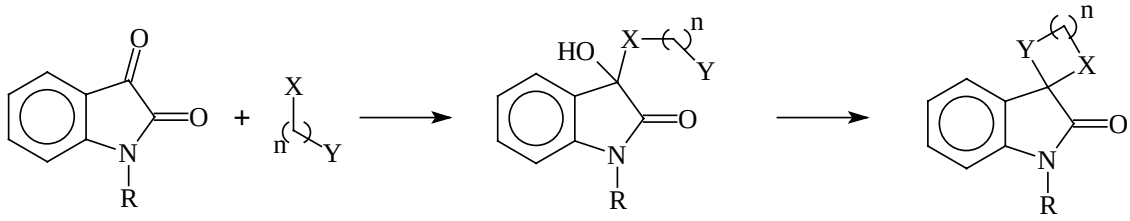
Scheme 30

c. Nucleophilic addition at position C-3, which may be further followed by a cyclization process, with or without N_1-C_2 bond cleavage (Scheme 31);



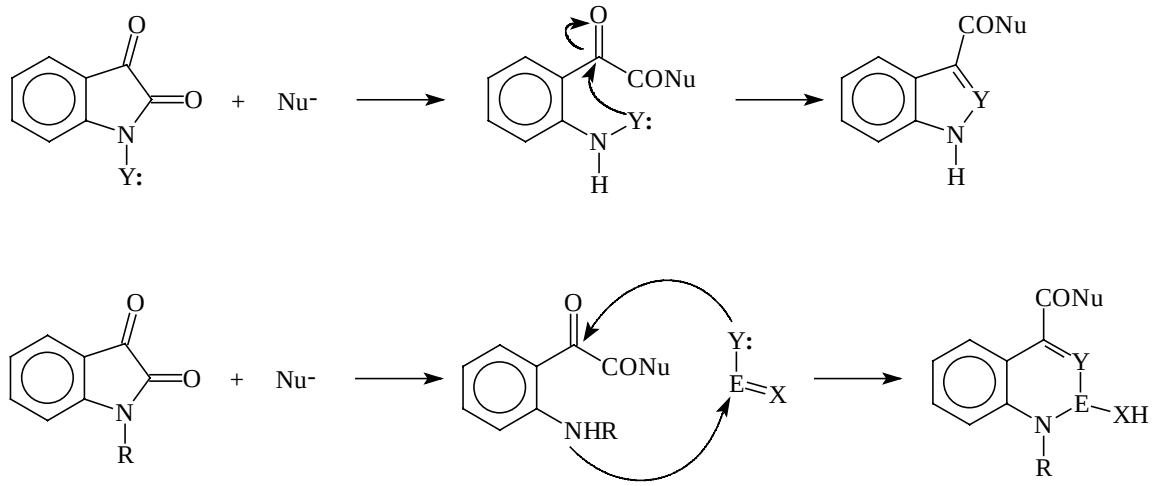
Scheme 31

or by a *spiro*annelation at position C-3 (Scheme 32):



Scheme 32

d. Nucleophilic substitution at position C-2, leading to the opening of the heterocyclic ring. This process may be followed by an intramolecular or by an intermolecular *exo-trig* cyclization (Scheme 33).



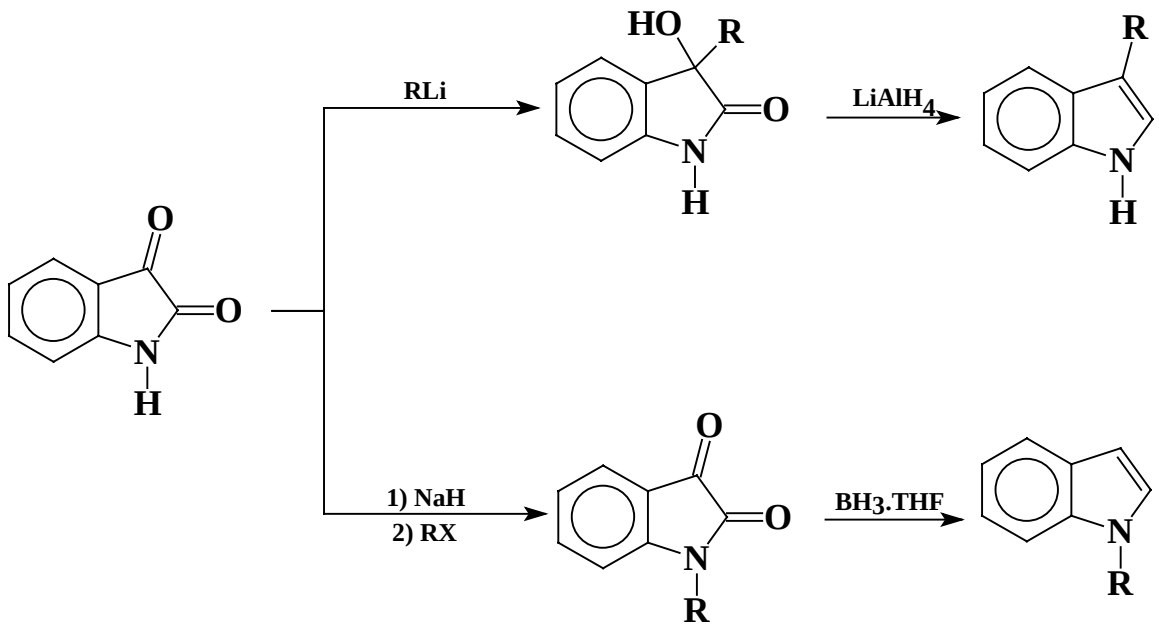
Scheme 33

4.1 - Reduction of the heterocyclic ring

4.1.1- Synthesis of indoles

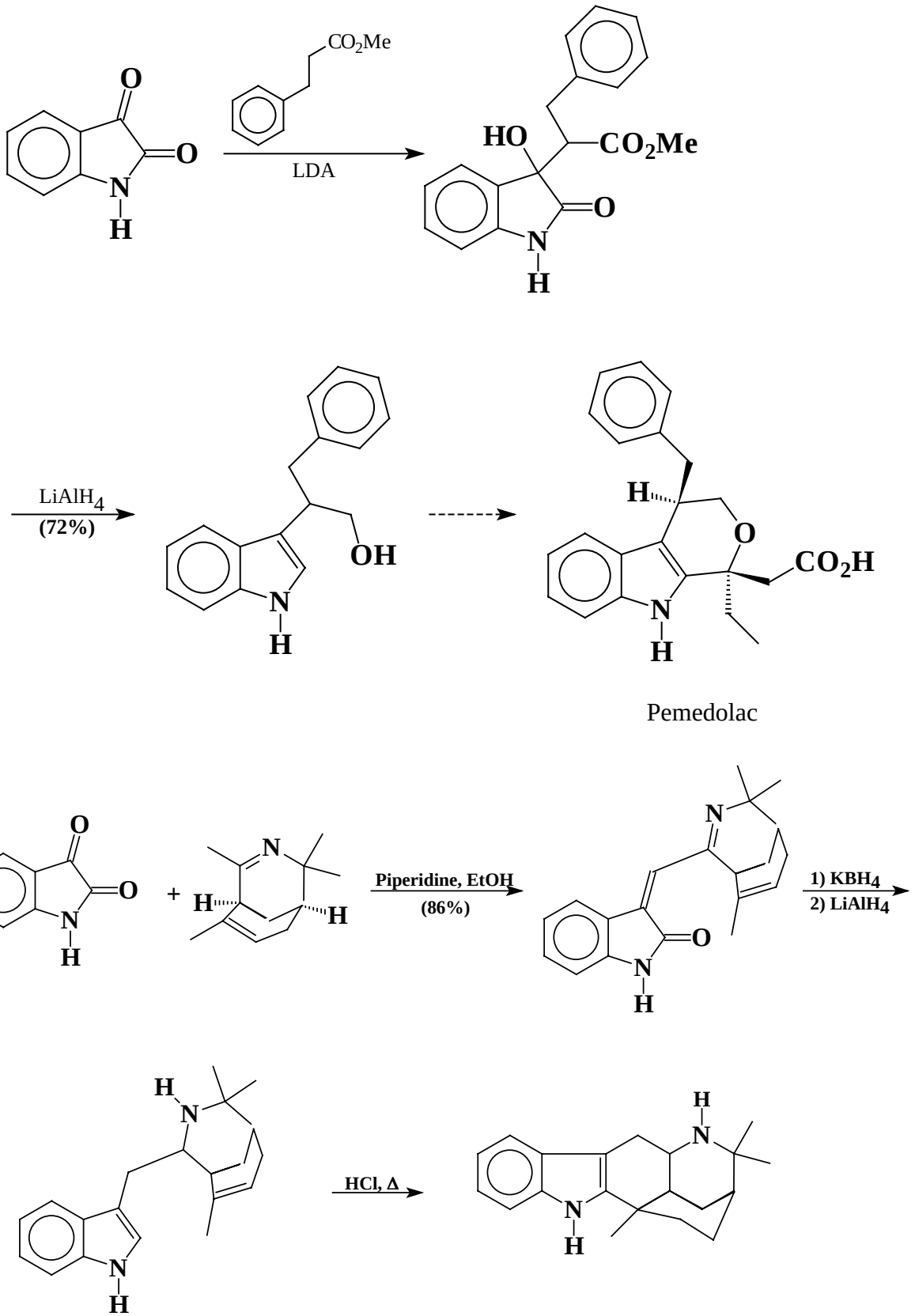
The reduction of isatins with lithium aluminum hydride in pyridine gave indoles in moderate yields. However, the use of THF as a solvent under an inert atmosphere gave greater yields (86-92%) and this procedure was applied to the synthesis of substituted ellipticine derivatives[120].

Isatins can be chemoselectively alkylated at positions 1 or 3. Subsequent reduction of these compounds using metal hydrides leads to 1- or 3-alkylindoles[121] (Scheme 34).



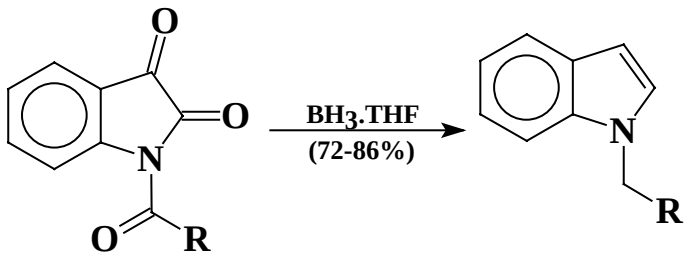
Scheme 34

The analgesic drug pemedolac[122-124], analogues of etodolac[125,126] and the synthesis of the alkaloids hobartine and aristoteline[127] were initiated by the C-3 alkylation of isatins to yield dioxindoles that were then reduced to the corresponding indoles by the use of lithium aluminum hydride (Scheme 34).



Scheme 34

In a similar manner, 1-acylisatins can be reduced to 1-alkylindoles by BH_3.THF in high yields[99] (Scheme 35).



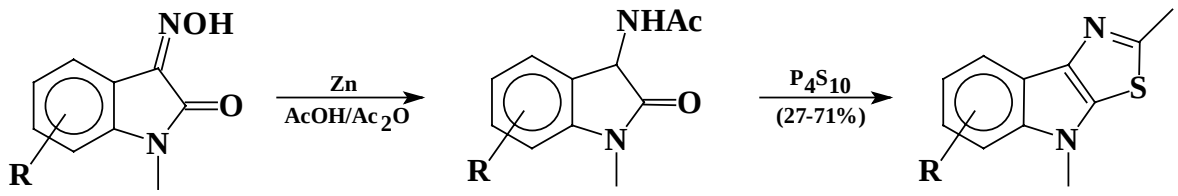
Scheme 35

As part of the synthetic methodology for the synthesis of the cytotoxic marine alkaloid, dragmacidin, 6,7-dibromo-4-methoxyisatin was reduced to the corresponding indole in 33% yield using a commercial solution of 1M BH_3.THF[128].

Wierenga and co-workers investigated the use of BH_3.THF and the dimethylsulfide complex for the reduction of 3-methyl-3-thiomethyl-2-oxindoles and 3-alkyl-3-hydroxy-2-oxindoles. The resulting indoles were obtained in excellent yields[129].

Isatins are readily converted to 3-fluoroindoles in a two step process involving firstly the reaction of an isatin derivative with DAST (diethylaminosulfur trifluoride) to yield the 3,3-difluoro-2-oxindole derivative and secondly reduction of the difluorooxindole using BH_3.THF to give the respective 3-fluoroindole. The reaction course was shown to proceed by formation of the 3,3-difluoroindolines, which subsequently eliminated HF. The presence of electron withdrawing groups on the aromatic nucleus retarded elimination of HF resulting in the obtention of 3,3-difluoroindolines as the major product[130].

Isatins have been used for the synthesis of fused indole derivatives. The reduction of 1-methylisatin-3-oximes, by Zn in acidic media, leads to an acetamidooxindole, which upon reaction with P_4S_{10} gives indolothiazoles in moderate to good yields[131] (Scheme 36).



Scheme 36

4.1.2 - Synthesis of oxindoles and dioxindoles

The products of partial reduction of isatin, dioxindole and oxindole, have been widely used in organic synthesis, especially in the development of new drugs. Some natural products also belong to these classes of compounds, for instance dioxibrassinin[132]. There is also a medical interest, as dioxindole has been isolated from the urine of a schizophrenic patient and from suspected drug abusers[133].

Dioxindoles can be obtained from isatins by reduction of, or by carbanion addition to the C-3 ketone functionality. Amongst the methods for the reduction of isatin to dioxindoles are the use of Zn/$HgCl_2$ in refluxing benzene[72] and Fe/HCl in aqueous ethanol[134], as well as eletrochemical[135] and photochemical[75] reduction. *N*-Methylisatin can be reduced to the corresponding dioxindole in quantitative yield by reaction with potassium tetracarbonylhydridoferrate ($KHFe(CO)_4$)[136].

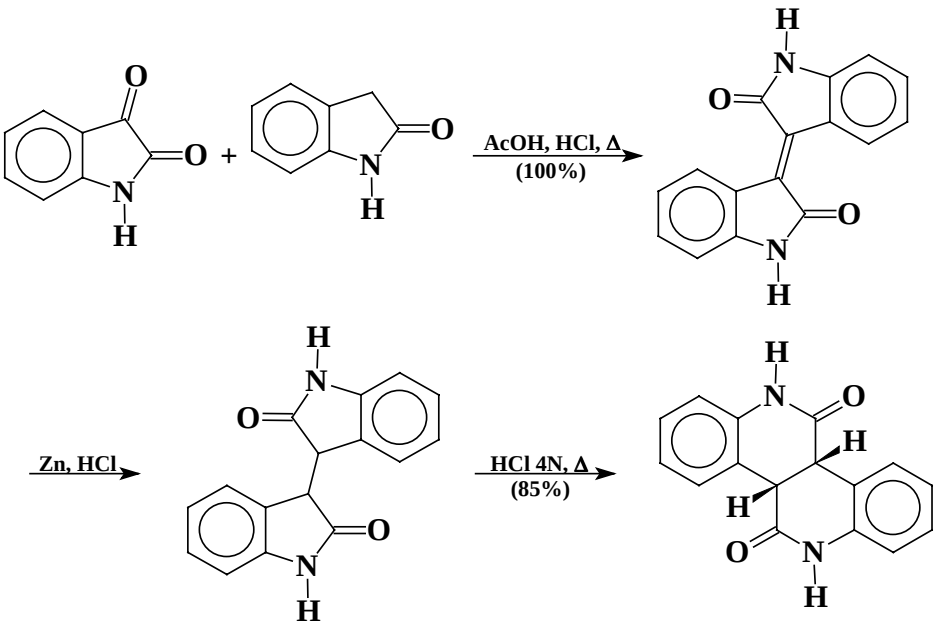
Oxindoles can be prepared by the reduction of dioxindoles or isatins: by using red phosphorous and iodic acid[134]; by reduction of isatin with H_2S in a pyridine/co-solvent mixture[1137]; by reduction of the isatin-3-ethylene thioketal with Raney nickel[138] or by the Wolf-Kishner reaction[139-142], where the use of lower molecular weight alcohols as solvent, such as EtOH or *i*PrOH, lead to high yields of the desired product[143]. It has however been found that isatin could be reduced to the corresponding oxindoles in high yields (76-92%) by the use of hydrazine hydrate as the solvent in the absence of any additional base[144,145].

A chromatographic method for the quality control of oxindoles, frequently used as raw materials for pharmaceutical products, using normal phase HPLC has been developed[146].

Indigo, isoindigo and indirubin are natural pigments bearing the oxindole motif and have considerable economical importance. As a consequence synthetic methodologies have been developed for the obtention of these pigments and analogues: indigo and monothioindigo can be obtained from the reaction of isatin with P_4S_{10}[147]; isoindigos have been prepared by an acid catalyzed reaction of isatin and oxindole derivatives[148,149] and from the reaction of *N*-methylisatoic anhydride or *N*-methylisatin with sodium phosphonates[150,151]; isoindigos and thioisoindigos can be prepared from the condensation of isatin promoted by Lawesson's reagent[152]; indirrubins, which are described as effective antileukemic agents, can be prepared from isatin and indican, a compound extracted in high yields from *Baphicacanthus cusia*[153], or from isatin and *N*-methyl-O-acetylindoxyl[149,154] and from isatin and 3-hydroxyindole[155]; pyrrolo-indigo compounds can be prepared by the condensation of isatin with pyrrolin-4-ones[156]; and thionaphthene indigo dyes (Thioindigo Scarlet) are obtained from hydroxythionaphthenes and isatin in acidic media[157].

In a reverse sense, isatin has been identified as one of the products of the oxidation of indigo by nitric acid and light. This process may be involved in the fading of indigo in museum collection objects[158] and denim jeans[159,160]. The same conversion can be realized by ozonolysis[161], acidic bromate[162] or by a chemiluminescent autoxidation of indigo[163]. *N*-Methylisatin is also obtained in the photooxidation of *N*-methylindole-3-acetic acid[164].

Isoindigo, obtained from isatin and oxindole, is converted diastereoselectively into diazacrisenodiones by reduction with Zn/AcOH, and subsequent acid-catalyzed rearrangement[148] (Scheme 37).

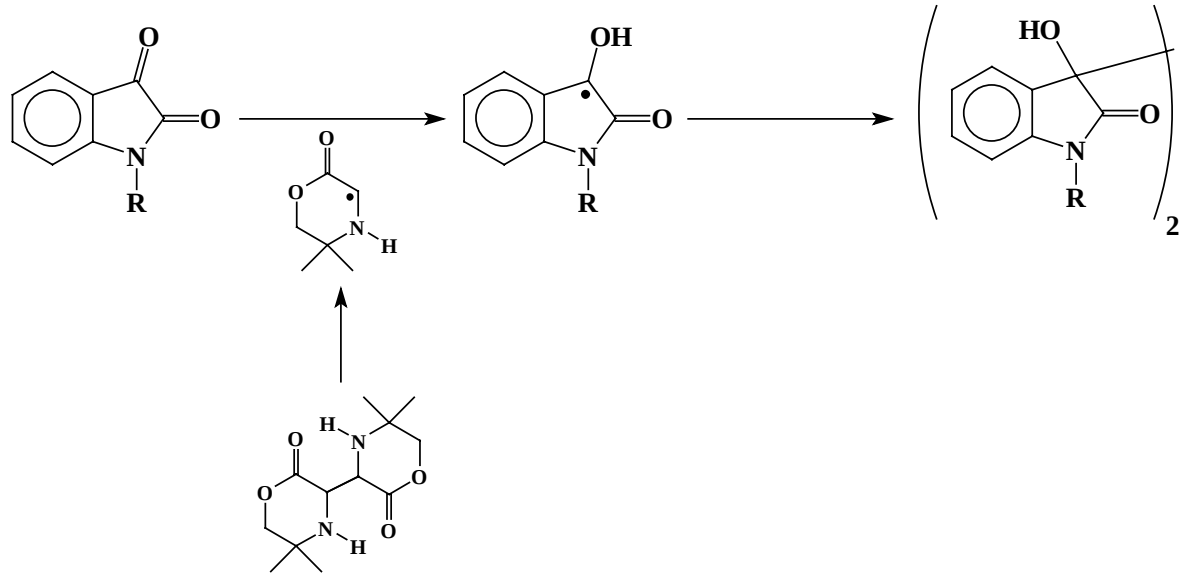


Scheme 37

Isatin oximes have also been reduced to 3-aminooxindoles by use of $SnCl_2$/HCl[165] or by electrochemical means[166,167]. 3-Aminooxindoles have also been obtained by reduction of isatin-3-imines and isatin-3-hydrazones by hydrogenation and converted into ureido derivatives for study as antiulcer agents[168-171]. 3-Formyloxindoles are prepared from the Vilsmeyer-Haack reaction of oxindole[172], while 3-acyloxindoles, useful as analgesic and anti-inflammatory compounds, are obtained by reaction of oxindole with isocyanates[160,173,174,175], acyl chlorides[176], or with esters[177]. Oxindoles[178] and 1-aryloxindoles[179,180] can suffer nucleophilic heterocyclic ring opening with hydroxides, leading to phenylacetic acid derivatives which also possess anti-inflammatory activity. Phenylacetic acids are also reported to be formed during the Wolff-Kishner reduction of 1-naphthylisatins[181]. A unique procedure for the synthesis of these acids is also described in a French patent, where diclofenac is claimed to be obtained during the reduction of an isatin-3-sulfonylhydrazone by sodium borohydride at 60-70 ^{o}C[182]. Oxindoles have also been employed in the synthesis of polyimides for use in coatings and laminates for printed circuits[183].

4.1.3 - Reduction involving free radicals

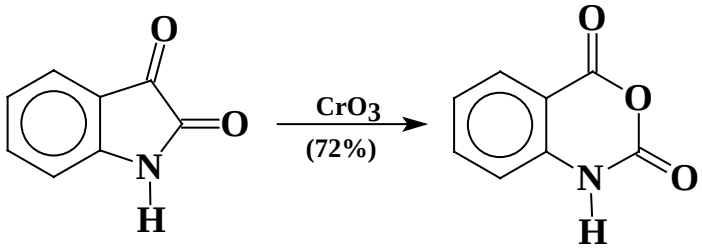
Isatin and 1-methylisatin can be reduced by merostabilized free radicals to isatide and N,N'-dimethylisatide through the intermediate dioxindolyl radicals[184] (Scheme 38):



Scheme 38

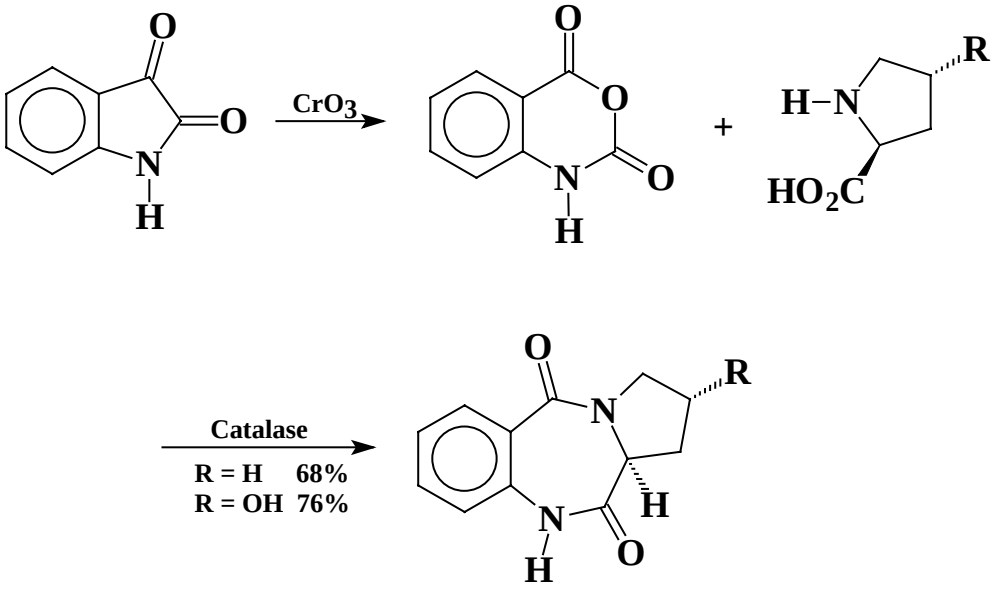
4.2 - Oxidation of the heterocyclic ring

The oxidation of isatin using either hydrogen peroxide[185,186] or chromic anhydride yields isatoic anhydride[187] (Scheme 39):



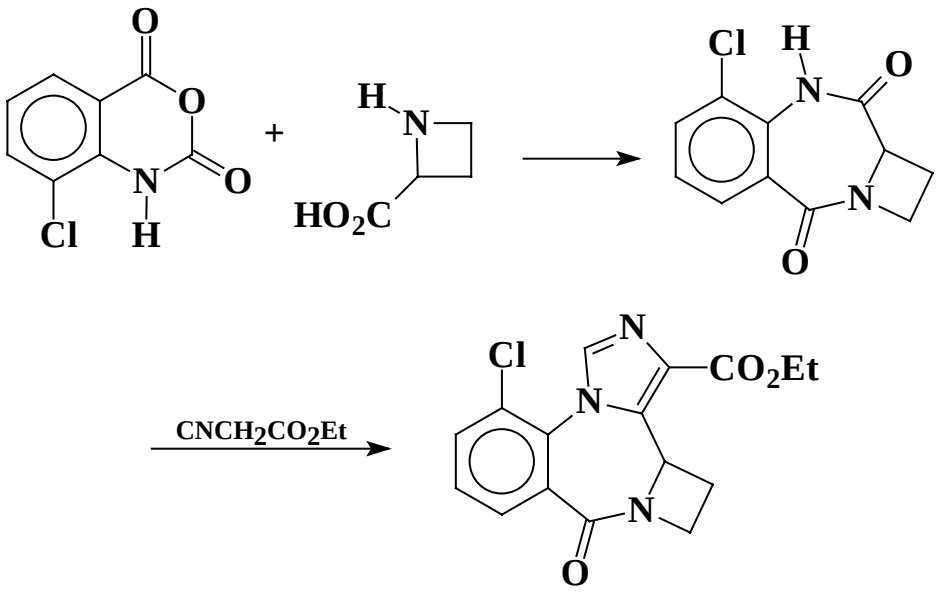
Scheme 39

Isatoic anhydride can be condensed with proline in polar aprotic solvents at high temperature, or in a reaction catalyzed by the enzyme catalase, to yield a pyrrolo[1,4]benzodiazepine ring, a structural pattern found in some antineoplasic antibiotics[188] (Scheme 40).



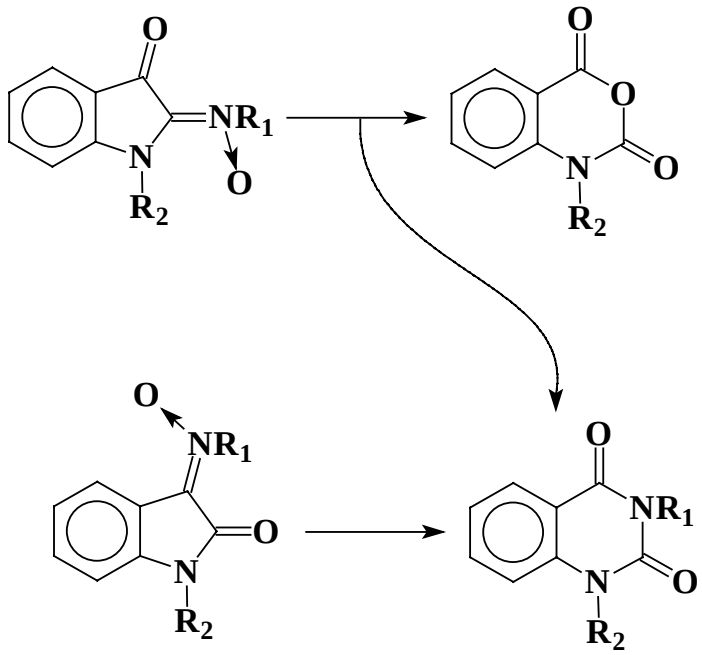
Scheme 40

6-Chloroisatoic anhydride can also be converted into benzodiazepinones by cyclocondensation with 2-azetidinecarboxylic acid, which reacts with ethyl isocyanoacetate, to give imidazo[1,5-a]-[1,4]benzodiazepinones[189- 192] (Scheme 41).



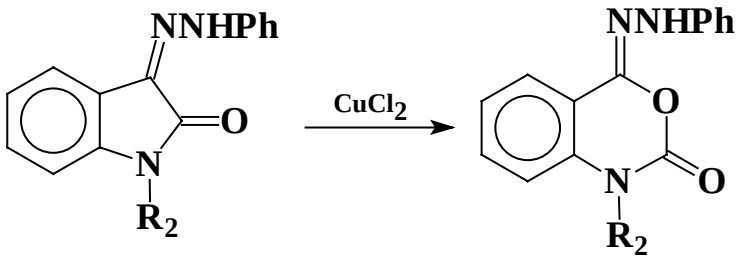
Scheme 41

Isatin-2-iminooxides lead to isatoic acid derivatives and quinazolinediones by photolysis, while isatin-3-iminooxides are reported to furnish only quinazolinediones. In both cases some isatin is also obtained[193] (Scheme 42).



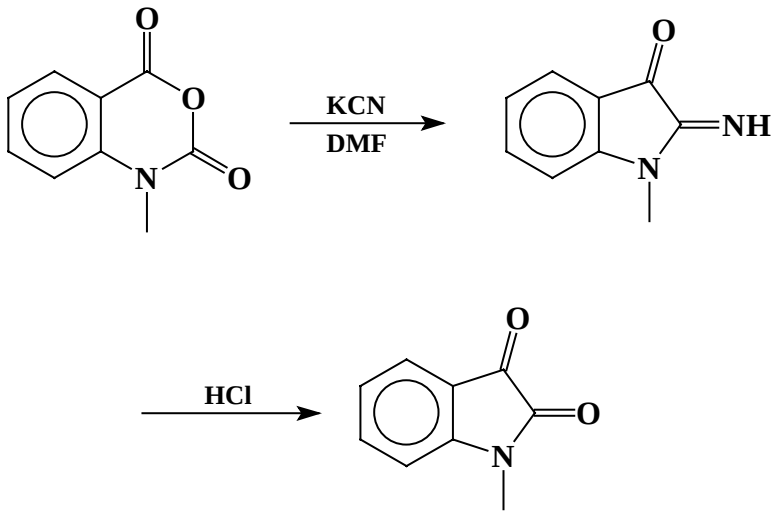
Scheme 42

In a related reaction, isatin-3-phenylhydrazone yields 1,3-benzazoxane-2-one-4-hydrazone upon treatment, under reflux, with an ethanolic solution of cupric chloride[194] (Scheme 43).



Scheme 43

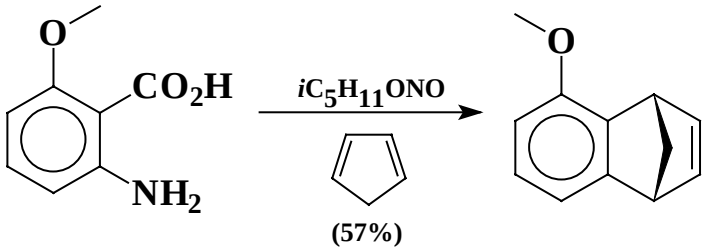
Isatoic anhydrides can be converted to isatins by treatment with cyanide and further hydrolysis of the 2-imino derivatives in acidic media[195] (Scheme 44).



Scheme 44

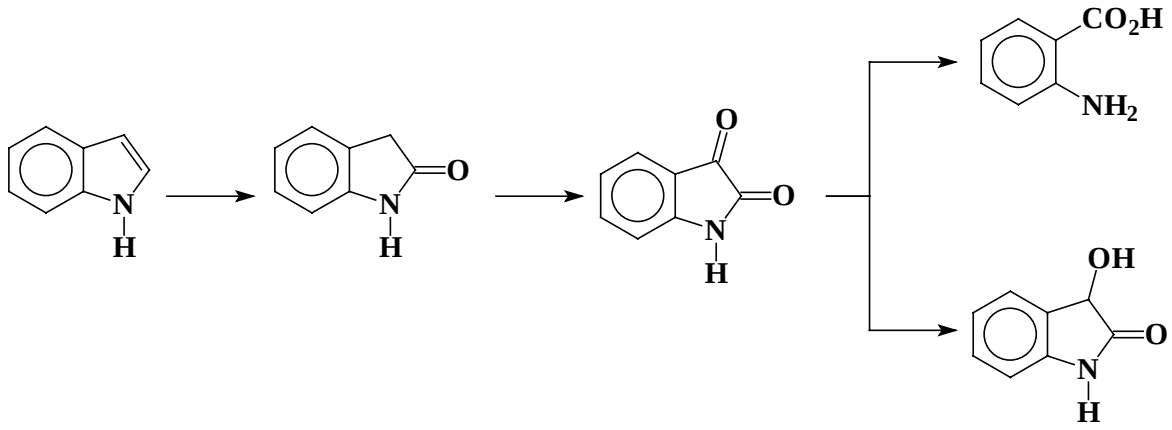
Anthranilates can be prepared from isatins by reaction of hydrogen peroxide in an alkaline solution[24,196], or by the use of chloroamine-T or dichloroamine-T[197] or by hydrolysis of isatoic anhydride with an aqueous alkaline solution[198] and may also be formed through oxidation of indigo carmine by hypohalides in alkaline medium[199]. Anthranilic acid is also formed in the photolysis of isatin to isatoic anhydride, which is subsequently hydrolysed[200]. Anthranilic acid hydrazides are synthesized from isatoic acid and hydrazines[201].

The economic importance of anthranilates resides in their well-estabilished anti-inflammatory activity. Thus, many derivatives have been synthesized with the objective of discovering new pharmacological agents such as immunosupressants[202], fungicides[203] and agents for the prevention of nerve cell damage[204]. Anthranilic acid has also been used in the synthesis of polycyclic aromatic hydrocarbons, such as dicyclooctabiphenylenes[205], phenanthrenequinones[206], fluorenones[207], benzonorbornadienes[208], toluenes[209], naphthalenes and anthracenes[210] and benzyne-furan adducts[211]. Most of these syntheses are based upon the formation of benzyne after diazotization of anthranilic acid and the subsequent addition to a diene. This methodology has been used in the synthesis of odorous compounds[212] and for the synthesis of podocarpic acid[213] (Scheme 45).



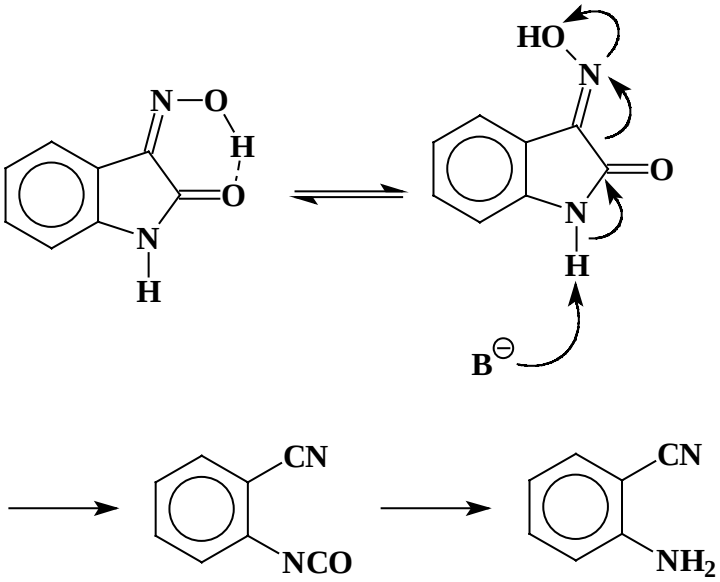
Scheme 45

Anthranilate, as well as isatin, isatoic anhydride, dioxindole and oxindole have been found to be products of microbial oxidation of indoles, as shown in the sequence below[214,215] (Scheme 46). Similar pathways are found in the degradation of indole-3-acetic acids[216].



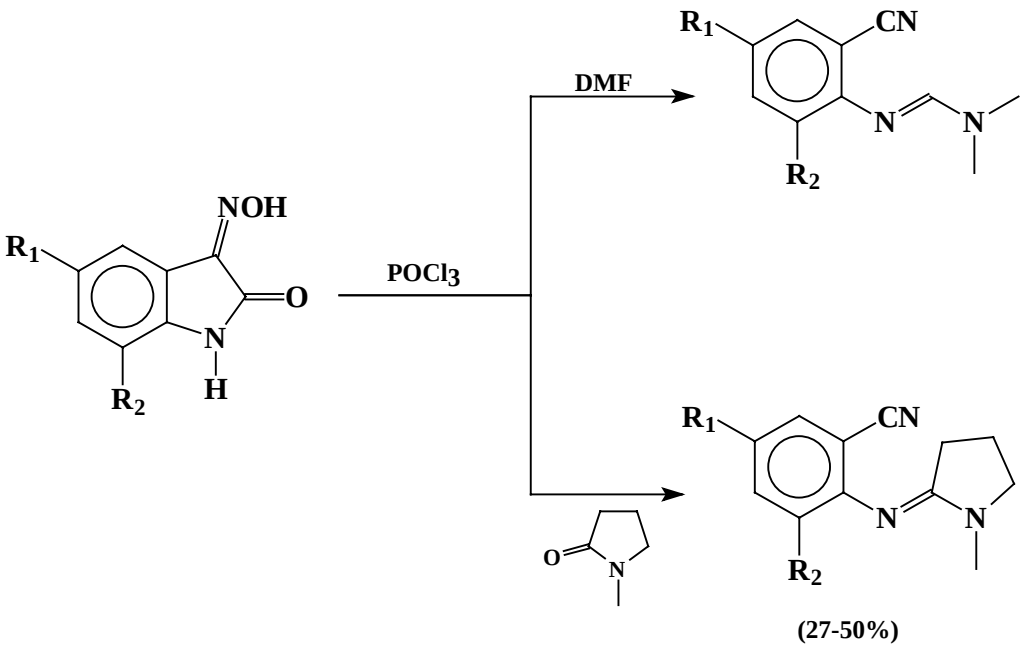
Scheme 46

The treatment of isatin-3-oximes or their O-sulfonates with bases, such as sodium methoxide in refluxing diethyleneglycol[217] or NaOH and $CuSO_4$[218] leads to 2-cyanoanilines. Under Beckmann rearrangement conditions, O-tosyl oximes furnish the cyanoanilines[219], while the parent oxime gives the intermediate 2-cyanophenylisocyanate[220]. When the O-acetyl oximes are reacted with sodium azide, cyanoanilines are also produced[221]. Campbell[217] proposed a mechanism where the E-isomer of the oxime suffers elimination, forming a 2-cyanoisocyanate, which upon hydrolysis and decarboxylation gives 2-cyanoaniline (Scheme 47).



Scheme 47

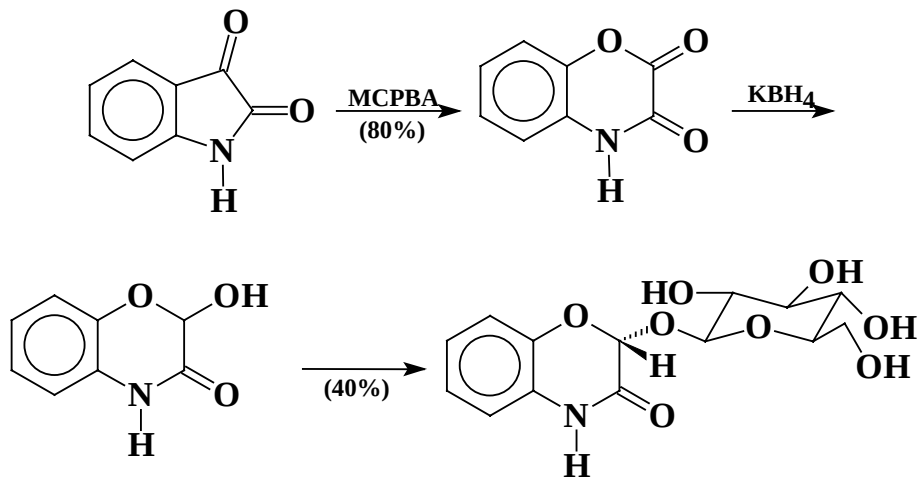
Isatin-3-oximes are also decomposed to benzonitrile derivatives under Vilsmeier-Haack conditions, furnishing formamidines[222] (Scheme 48).



Scheme 48

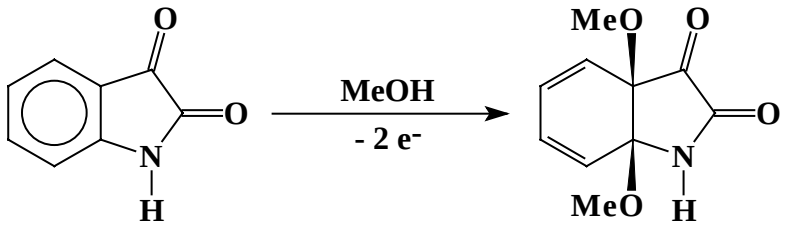
These methods have been applied to the efficient synthesis of substituted cyanoanilines such as 2-cyano-4-nitroaniline[223].

The oxidation of isatin with *meta*chloroperbenzoic acid yields 1,4-benzoxazine-2,3 (4H)-dione, which was subsequently converted to blepharin, a glycoside obtained from *Blepharis edulis* Pers. whose seeds are used in rejuvenescent therapy in Ayurvedic medicine[224]. This oxidation can also be performed with potassium persulfate in sulfuric acid[225,226] (Scheme 49).



Scheme 49

Isatin undergoes anodic methoxylation in acidic medium when using platinum electrodes in a unique fashion that results in the dimethoxylation of isatin at positions C-3a and C-7a[227] (Scheme 50).



Scheme 50

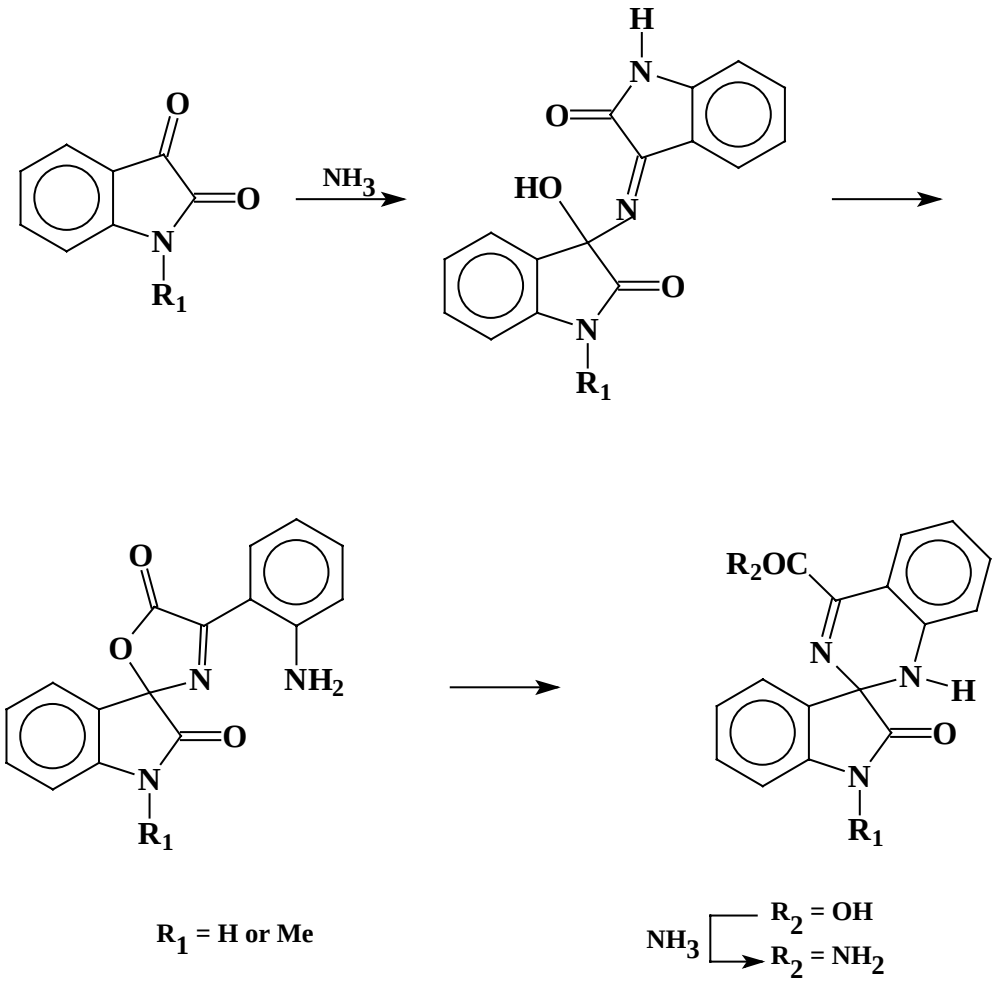
4.3 - Nucleophilic attack at positions C-2 or C-3

Isatins and derivatives can suffer nucleophilic attack at positions C-2 and/or C-3. The chemoselectivity of these reactions depends on the nature of the nucleophile, on the nature of the substituents attached to the isatin nucleus, and especially of those bonded to the nitrogen atom, as well as upon the solvent and temperature employed. The initial products obtained can suffer further reaction in the presence of a second nucleophilic group to give cyclization products. For didactic reasons, these reactions have been sorted by the nature of the nucleophile.

4.3.1 - Amines and related compounds

a) Ammonia, hydroxylamine and hydrazine

Isatin reacts with ammonium hydroxide or ammonium acetate to furnish a mixture of compounds. Amongst them are isamic acid and its corresponding amide, isamide. Since 1877 there had been a discussion as to their structure, which in 1976 was finally elucidated, by Sir John Cornforth on the basis of chemical and spectroscopic data[228]. Isamic acid can be regarded as a dimer formed by the addition/condensation of one equivalent of ammonia with two equivalents of isatin. This intermediate suffers lactonization and subsequent conversion to isamic acid by an internal nucleophilic attack, where upon the acid is converted to isamide by reaction with a second equivalent of ammonia. 1-Methylisatin reacts similarly, furnishing *N*-methylisamic acid (Scheme 51).

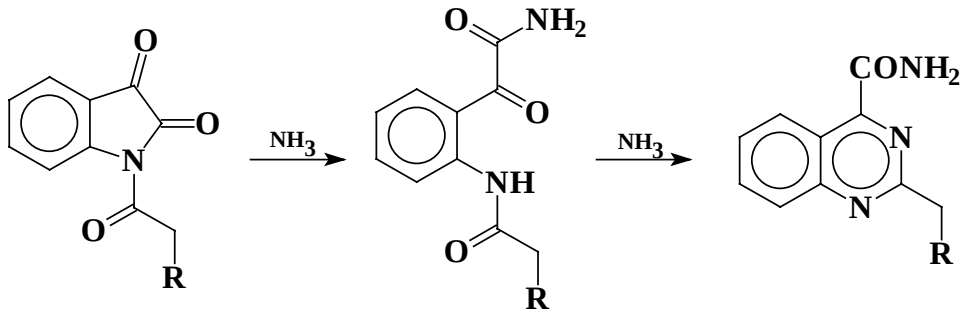


Scheme 51

Isatin and 1-alkylisatins react with hydroxylamine or O-methyl hydroxylamine hydrochloride under aqueous alkaline conditions to furnish the corresponding 3-oximes, which have been studied as monoamine oxidase inhibitors[229,230]. Isatin oximes can be acylated simultaneously at the heterocyclic ring nitrogen and at the oxime oxygen by reaction with anhydrides or acid chlorides[231].

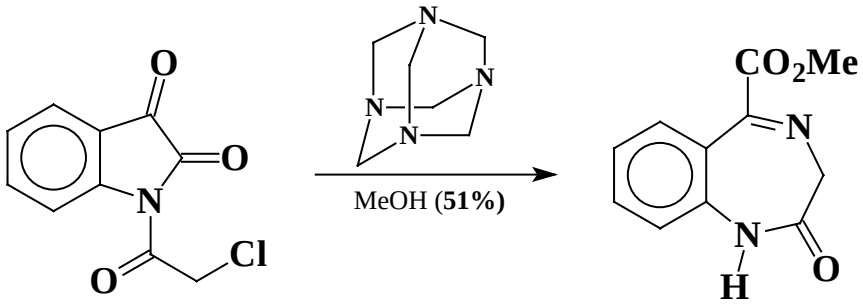
While these products are derived from the nucleophilic attack at the C-3 carbonyl, the reaction of *N*-acylisatins with the respective nucleophiles results in opening of the heterocyclic ring. The reaction of *N*-acetylisatin[232] and *N*-chloroacetylisatin[233] with ammonia yields products resulting from nucleophilic attack at the C-2 carbonyl that leads to

heterocyclic ring cleavage. The benzoylformamides obtained in these cases further react with a second equivalent of ammonia to produce quinazoline derivatives (Scheme 52).



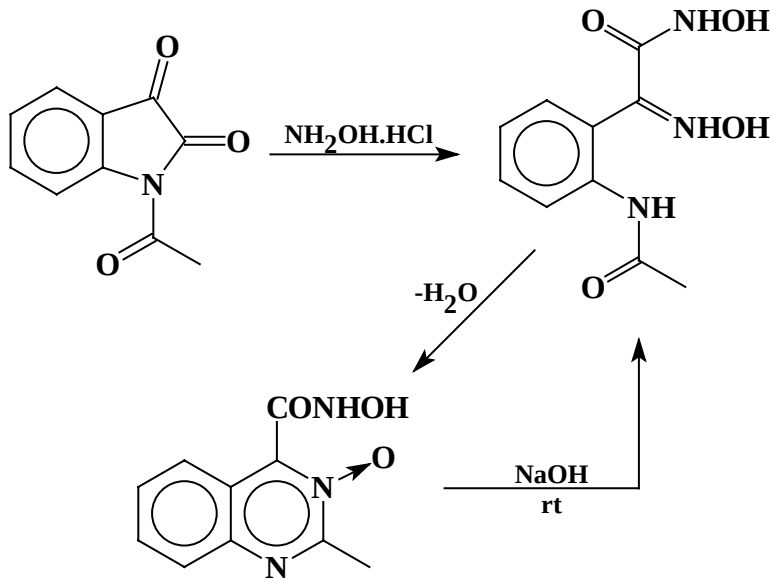
Scheme 52

Compounds bearing the 1,4-benzodiazepine moiety have potential use as anxiolytic agents. One of the methods for the synthesis of this heterocyclic system involves the reaction of 1-α-chloroacetylisatin with hexamethylenetetramine in methanol[233], thus yielding the 1,4-benzodiazepine-5-carboxylic ester via solvolysis of the *N*-acylisatin and the *in-situ* nucleophilic substitution of chloride, generating the glycine amide that subsequently undergoes cyclo-condensation (Scheme 53).



Scheme 53

In a similar fashion, 1-acetylisatin, when reacted with hydroxylamine hydrochloride furnishes quinazoline-3-oxide through cyclization of the intermediate hydroxamic acid[234]. This intermediate hydroxamic acid can be isolated by treatment of the quinazoline oxide with alkali[235] (Scheme 54).

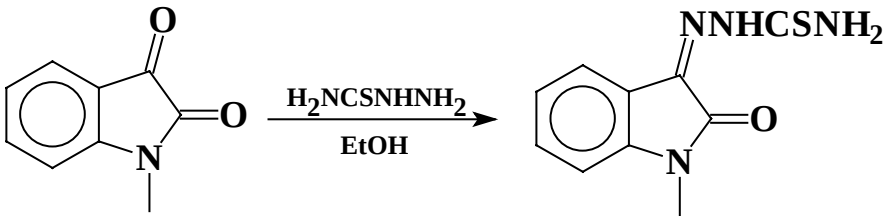


Scheme 54

The reaction of oxalyl*bis*isatin with O-methyl hydroxylamine hydrochloride yields the hydroxamic acid, with no further cyclization to a quinazoline occuring to yield quinazolines [104].

Isatin and 1-alkylisatins furnish condensation products at the C-3 position when reacted with hydrazine[236], alkyl and arylhydrazines[237,238,239], heteroarylhydrazines derived from pyrimidine[240], pyrazine[241], thiazole[242], 1,2,4-triazine[243], quinazoline[244,245], benzimidazole[246,247], benzothiazole[248,249], phthalazine[250] and triazines[251,252], acylhydrazides of oxalic[253], benzoic[254], phenoxyacetic[255] and oxanilic acids[256], arylsulfonylhydrazides[257], guanylhydrazones[258], semicarbazines[259] and thiosemicarbazides[260,261,262].

The reaction of 1-methylisatin and semicarbazone yielded methisazone, a compound that found use in the treatment of variola, a viral disease that has now been eradicated [263] (Scheme 55).

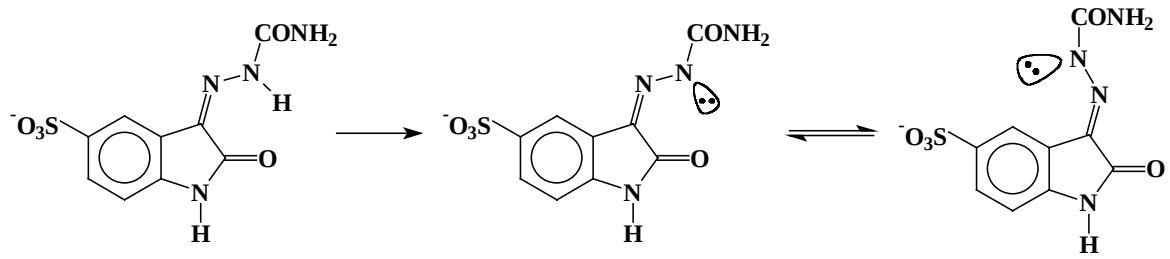


Methisazone

Scheme 55

Isatin-3-imines also react with hydrazine derivatives such as heteroarylhydrazines[264], thiosemicarbazides[265] and acylhydrazides[266], resulting in a substitution reaction at the C-3 position. Substitution reactions are also described to occur when O-methylisatin is treated with thiosemicarbazines, furnishing isatin-2-thiosemicarbazones[91].

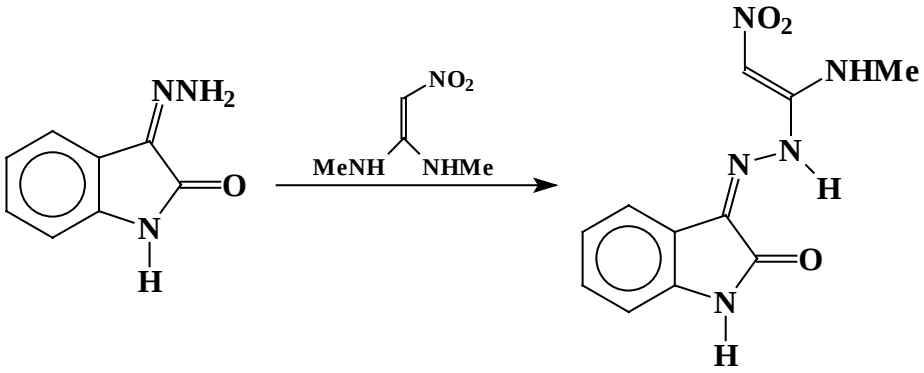
The stereochemistry of isatin-3-thiosemicarbazone-5-sulfonate was studied in aqueous solution, and in acidic pH the *Z* isomer was determined to be the most stable, but after deprotonation, the corresponding anion slowly converts to the *E* isomeric anion[267] (Scheme 56).



***Z* isomer** ***Z* anion** ***E* anion**

Scheme 56

Isatin hydrazones and thiosemicarbazones can also be used as substrates for the Mannich reaction, leading to functionalization at *N*-1[268,269]. Isatin-3-hydrazone reacts with 1,1-dimethylamino-2-nitroethene to give a transamination product[270] (Scheme 57).



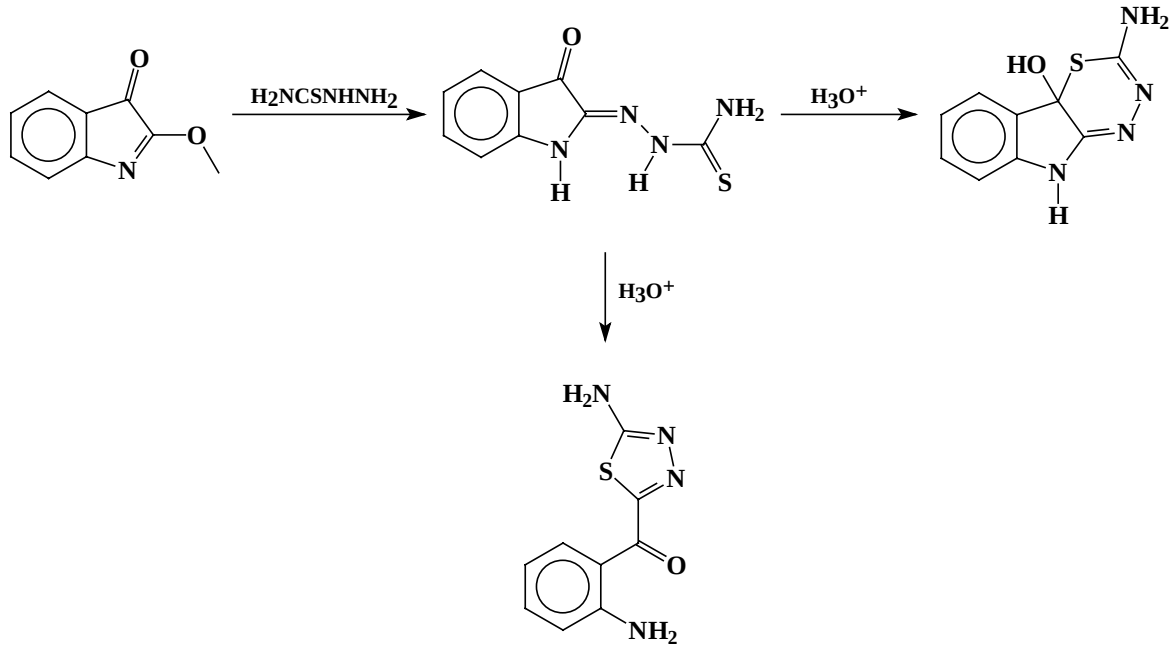
Scheme 57

The reactions of 1-acyl or 1-arylsulfonylisatins with hydrazines, thiohydrazides and thiosemicarbazine derivatives are dependent on the nature of the nucleophile and on the reaction conditions. These reactions can lead to products of nucleophilic attack at C-2 and/or C-3. 2-Hydrazinopyridine and quinoline in aq. PrOH/AcOH[271], bis-thiazolidinehydrazones in refluxing AcOH[272] and thiocarbohydrazine in aqueous EtOH[273,261] react with 1-acetylisatin to furnish solely the products of attack at the C-3 ketone group. The same occurs with the use of *N*-acetylhydrazide hydrochloride in dioxane, while the reaction of the free base in EtOH leads to the product resulting from attack at the C-2 position, giving a ring opened derivative, together with a small quantity of 1-acetylisatin-3-acetylhydrazone[274]. 1-(4-Nitrobenzoyl)-isatin reacts with guanidine in the presence of sodium ethoxide to yield the ring opened product[275].

The results described by Tomchin are far more complex than those described above. It has been stated that 1-acetylisatin reacts with thiosemicarbazide to furnish the corresponding isatin-3-thiosemicarbazone, together with a small portion of the ring opened product that results from attack at C-2. The yield of the latter product increases as the solvent is changed from ethanol to dimethylacetamide and to AcOH, whilst none of the ring opened product is obtained using dioxane. On the other hand, when the same solvents were used in the reaction of 1-butyrylisatin with thiosemicarbazides, the only product formed was the corresponding 3-

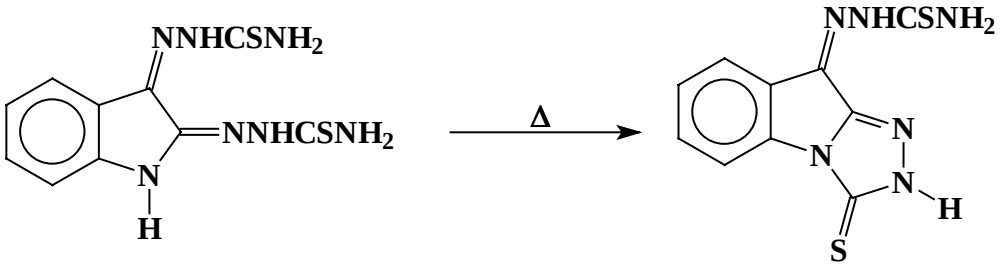
thiosemicarbazone. A further conflicting result is that of 1-tosylisatin which behaves similarly to 1-acetylisatin in its reaction with thiosemicarbazides, but when using dioxane as the solvent the major product is that due to ring opening[109]. The reaction of 1-acetyl-5-bromoisatin with thiosemicarbazine in EtOH yielded only the corresponding 3-thiosemicarbazone, while in acetic acid a mixture of products resulting from attack at C-2 and C-3 was observed, the former being favored[276]. Both products were also formed in the reaction of 1-acetylisatin with thioacylhydrazides in AcOH[277].

Tomchin and coworkers also described that *O*-methylisatin reacts with thiosemicarbazine to furnish isatin-2-thiosemicarbazone, which can undergo a cyclization reaction under acidic conditions to furnish a thiadiazanoindole derivative[92]; the kinetics of the reaction were subsequently determined[278]. Later, Tomchin also described that isatin-2-thiosemicarbazones suffer a cleavage reaction of the five member ring, and the intermediate formed recyclizes to a thiadiazole derivative[279] (Scheme 58).



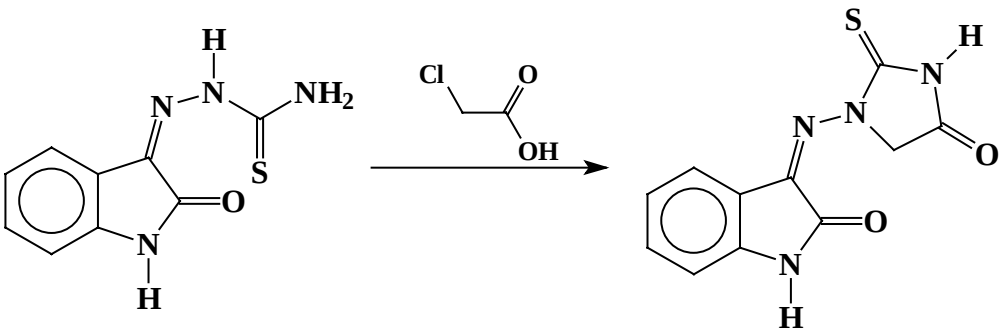
Scheme 58

Isatin-2,3-thiosemicarbazone is said to be produced only from isatin-2-thiosemicarbazone and thiosemicarbazine; direct reaction of isatin with an excess of thiosemicarbazine gives only the C-3 substituted oxindole. The isatin-2,3-thiosemicarbazone cyclizes to a thiotriazinoindole derivative when heated[280] (Scheme 59).



Scheme 59

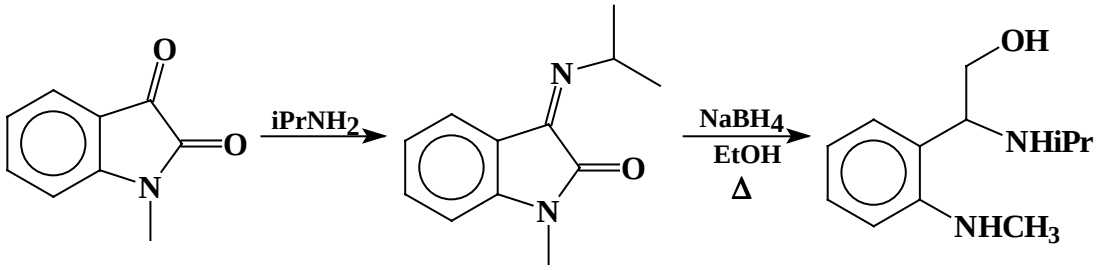
Isatin-3-thiosemicarbazones are useful substrates for the synthesis of other 3-substituted oxindoles. For example, they can be converted to thiohydantoin or thiazolidine derivatives by reaction with chloroacetic acid[281] (Scheme 60).



Scheme 60

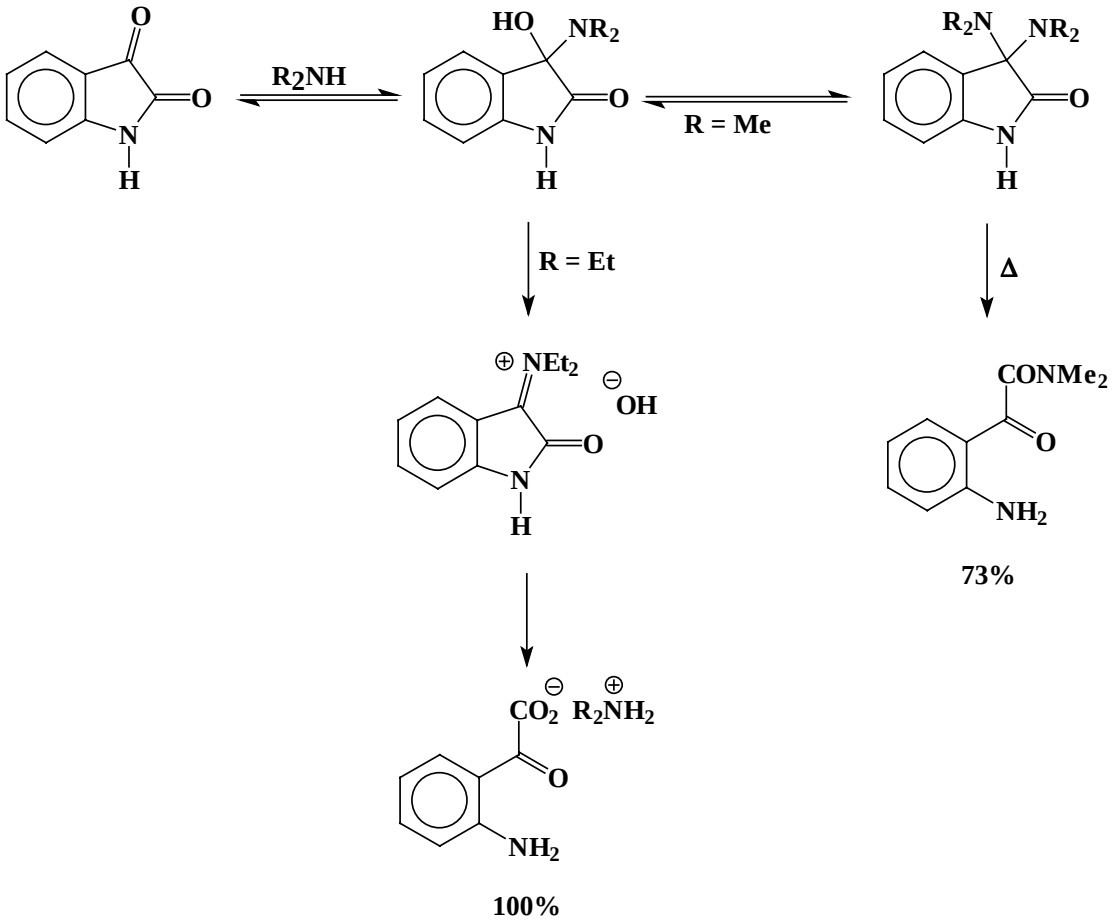
b) Alkylamines

The reaction of isatin and 1-alkylisatins with primary alkylamines yields the corresponding 3-imines, which upon reduction with sodium borohydride in hot ethanol yield phenylethanolamine derivatives[282] (Scheme 61).



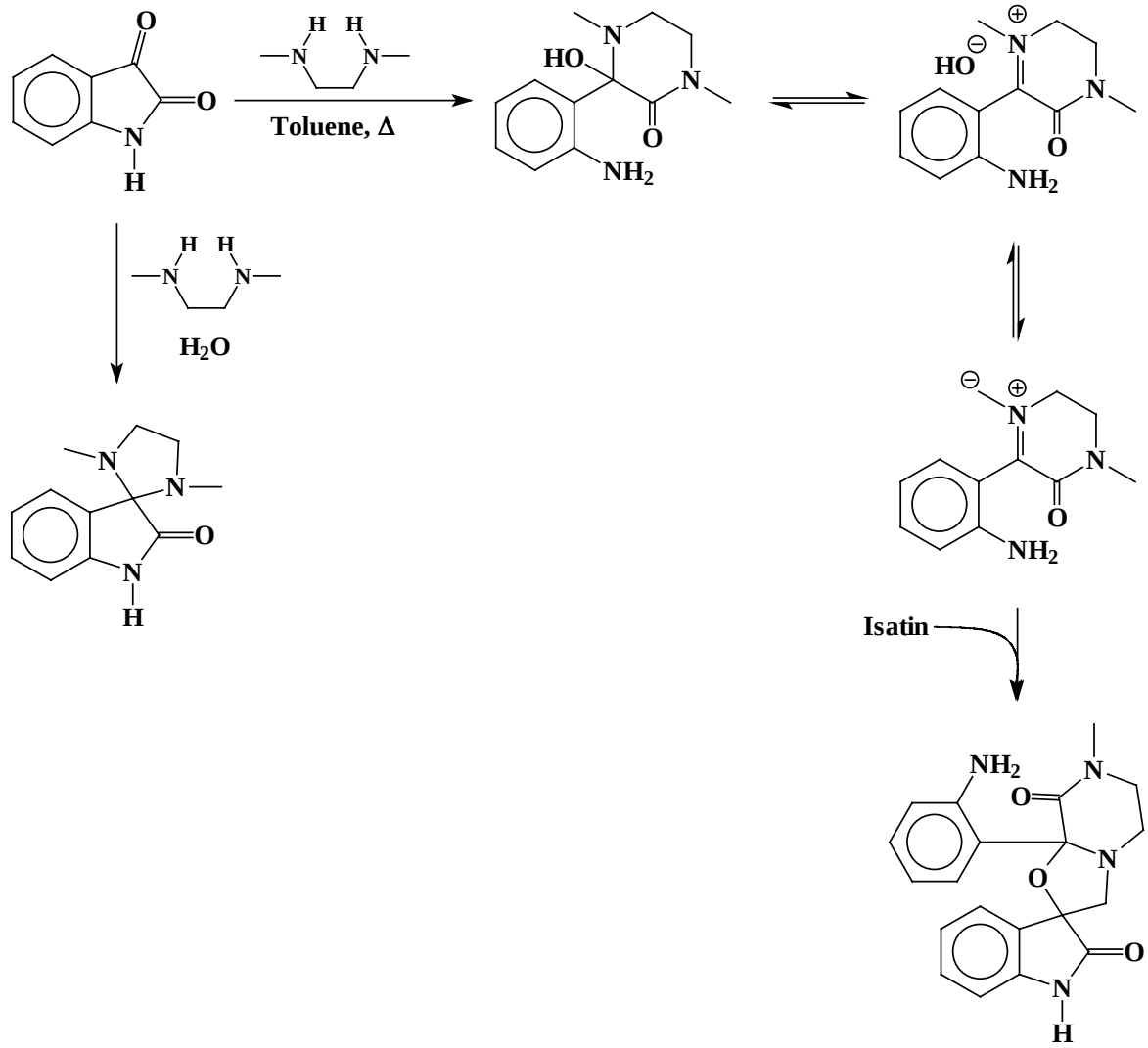
Scheme 61

Secondary alkylamines react with isatin to give a 1:1 adduct, as a result of the nucleophilic attack of the amine at position C-3. In the case of dimethylamine a second equivalent of amine adds, leading to a 1:2 adduct as the kinetic product; upon heating the ring opened glyoxamide is formed. Diethylamine and higher non-cyclic amines only give the 1:1 adduct, probably due to steric hindrance, which decompose to dialkylamonium benzoylformates[283] (Scheme 62).



Scheme 62

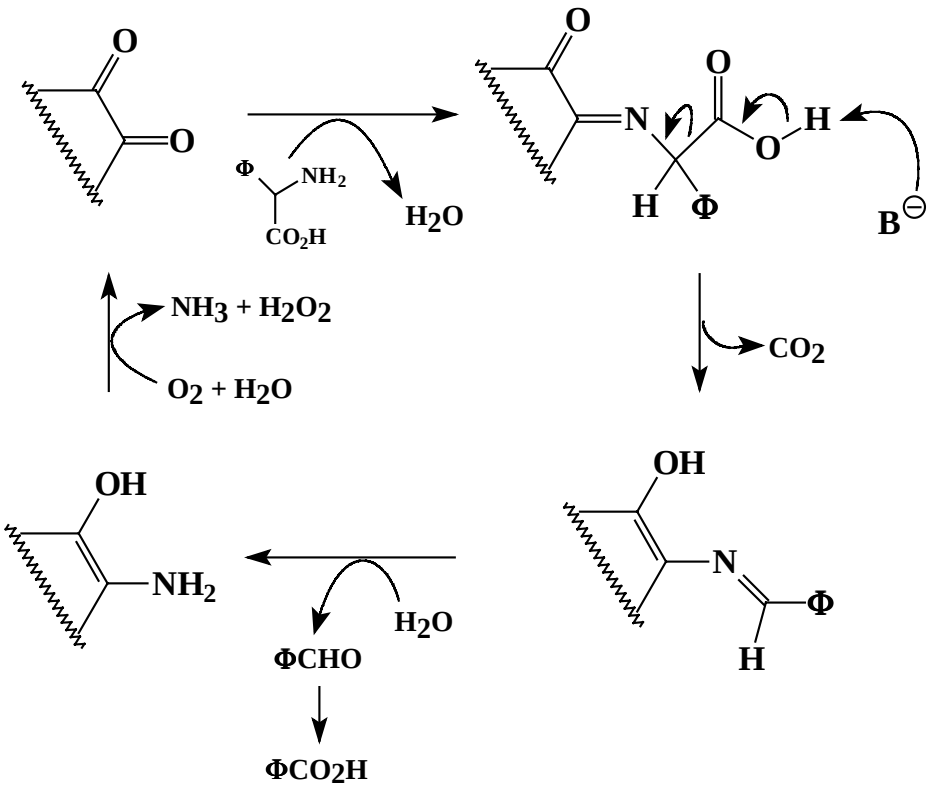
On the other hand, the reaction of isatin with N,N-dimethylethylenediamine in water yields the spiro-diazolaneoxindole whereas the corresponding condensation reaction performed by azeotropic distillation in toluene yielded the unusual 2:1 adduct as the result of the addition of an unstable azomethine ylide to isatin[283] (Scheme 63).



Scheme 63

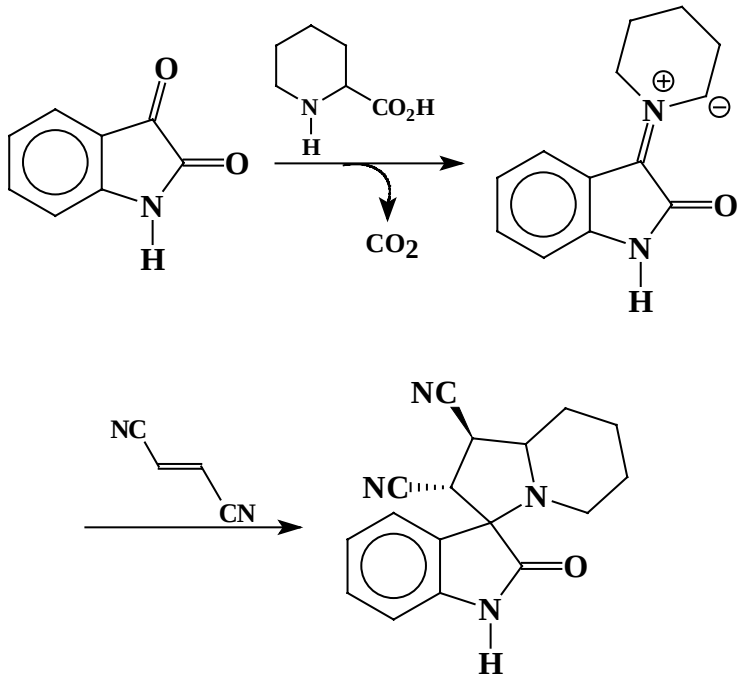
The decarboxylation of α-aminoacids catalyzed by isatin in aqueous media has been studied as a model for the enzymatic decarboxylation of these compounds. As a result, phenylglycine yields benzaldehyde and benzoic acid as products, but the efficiency of isatin is far lower than that of methoxatin (PQQ), the coenzyme of several alcohol and amine

dehydrogenases. The redox cycle for methoxatin is proposed to proceed as below[284] (Scheme 64):



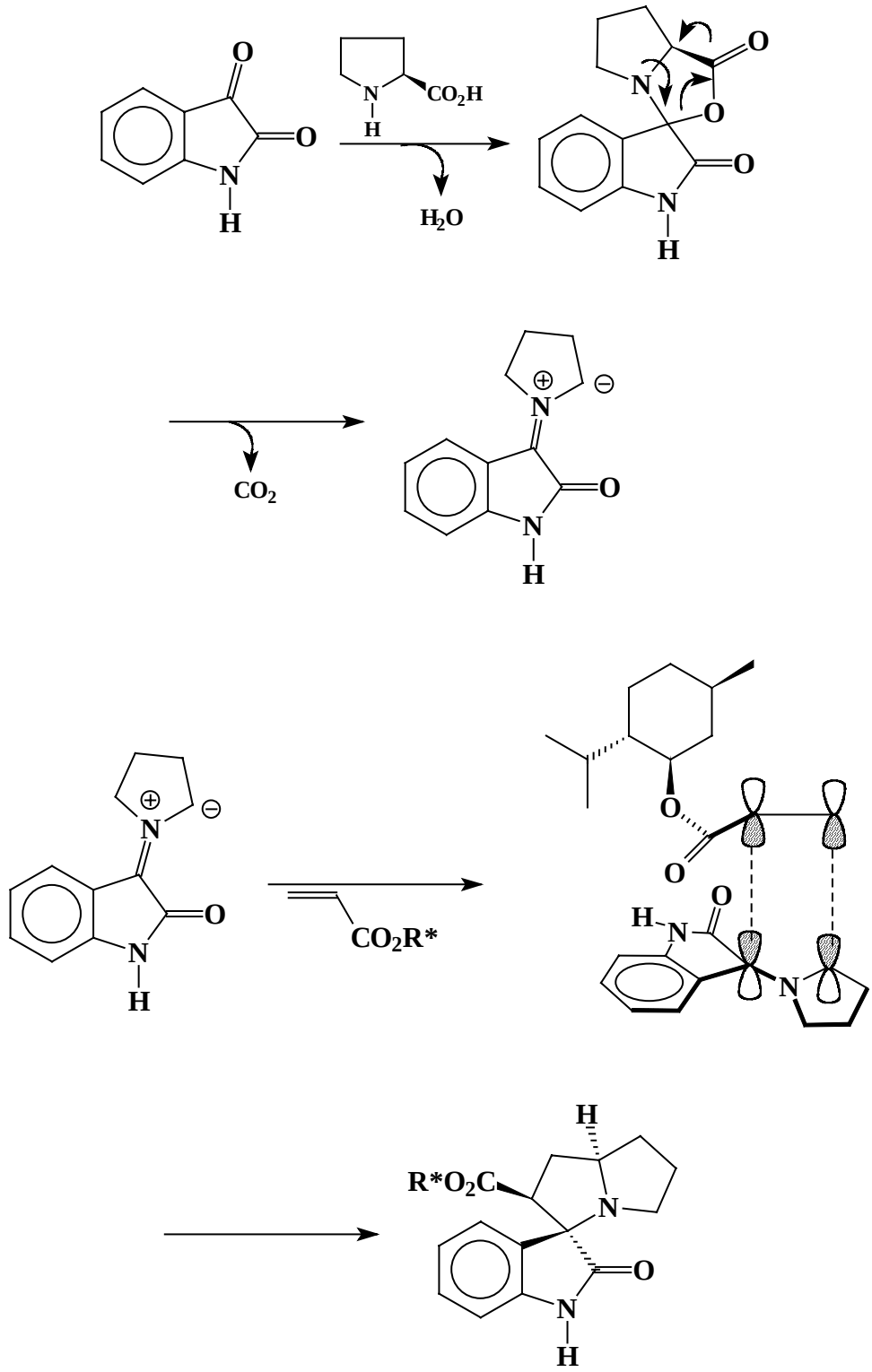
Scheme 64

Pipecolic acid, a cyclic aminoacid, when reacted with isatin, suffers decarboxylation, furnishing an azomethine ylide, which reacts with dipolarophiles, such as fumaronitrile, to yield a *spiro* derivative[285] (Scheme 65).



Scheme 65

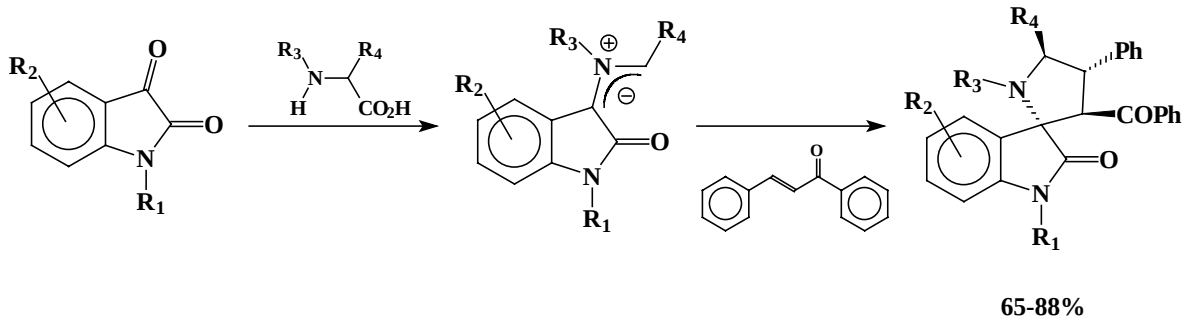
Proline and isatin also furnish an azomethine ylide, which reacts regio- and stereo-selectively with acrylates, such as (1R, 2S, 5R)-menthyl acrylate, to yield a mixture of diastereoisomers. The structure of the major diastereoisomer was determined by X-ray crystallography and the following transition state was proposed for its formation[286] (Scheme 66):



Scheme 66

Similar processes can be found in the reactions of isatin with pyrrolidine or benzylamine and methyl acrylate[287,288], with sarcosine or glycine and oxoindolin-3-ylidene

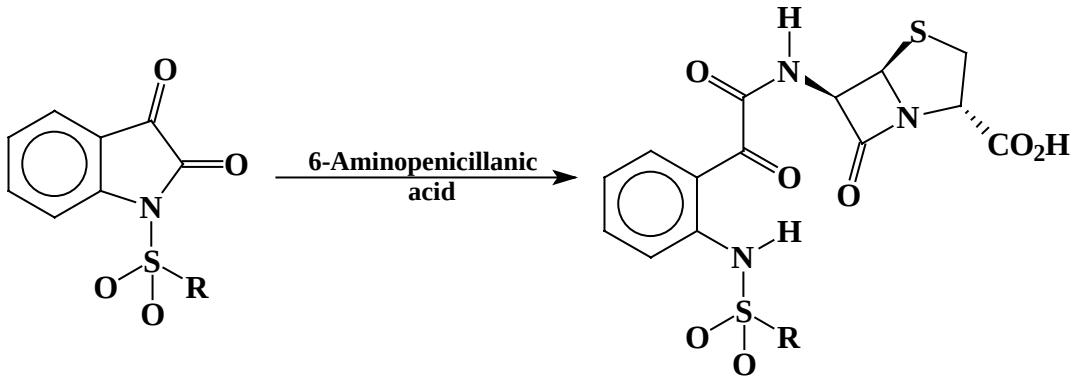
acetophenones[289] and with phenylglycine and acenaphthylene[290]. The reaction of an unstable azomethine ylide and a chiral oxoindolin-3-ylidene acetate ester resulted in an asymmetric synthesis of the oxindole alkaloid Horsfiline[291]. This reaction has also been employed in the construction of a molecular library of *spiro*[pyrrolidine-2,3'-oxindoles] from isatin, aminoacids and chalcones[292,293] (Scheme 67).

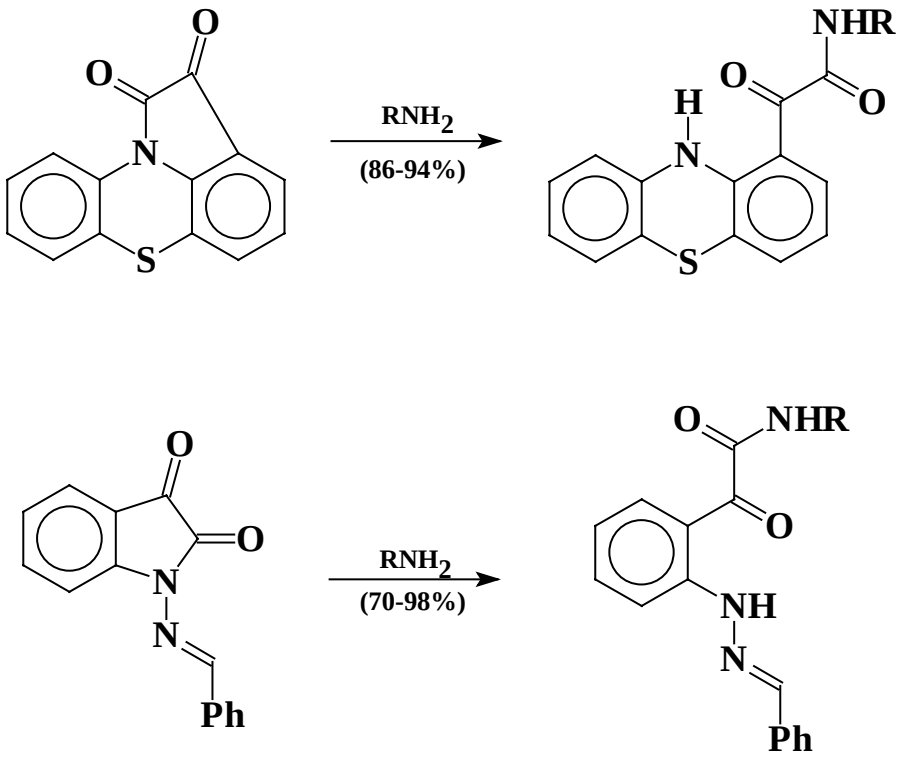


Scheme 67

Alkylamines and 1-acylisatins lead to 2'-acylamidobenzoylformamides due to opening of the heterocyclic ring[294,295], which can be reduced to mandelic acid derivatives with $NaBH_4$ or $LiAlH_4$[296]. Under acidic conditions, the 2'-acylamidobenzoylformamides regenerate isatin[63].

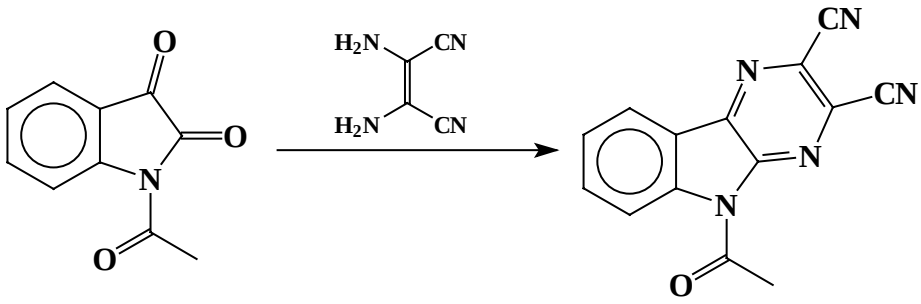
Products arising from the opening of the heterocyclic ring are also obtained with 1-alkylsulfonylisatins[297], 1,2-dioxo-1,2-dihydropyrrolophenothiazine[298] and 1-iminobenzylideneisatin[299] (Scheme 68).





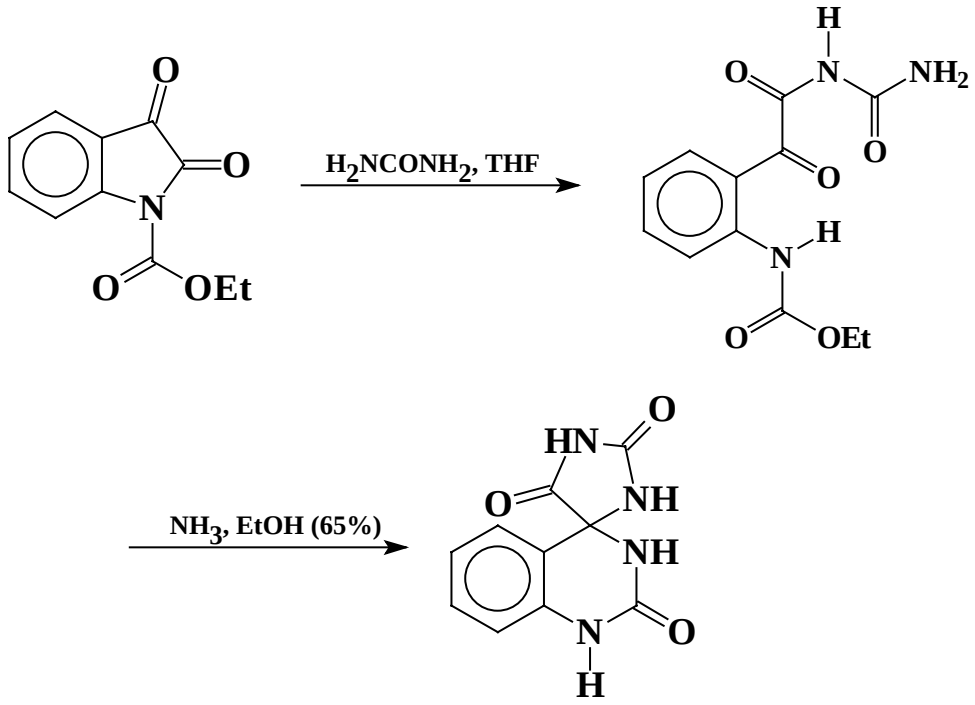
Scheme 68

In contrast the reaction of *N*-acetylisatin with diaminomaleonitrile has been reported to produce a pyrazinoindole[300] (Scheme 69).

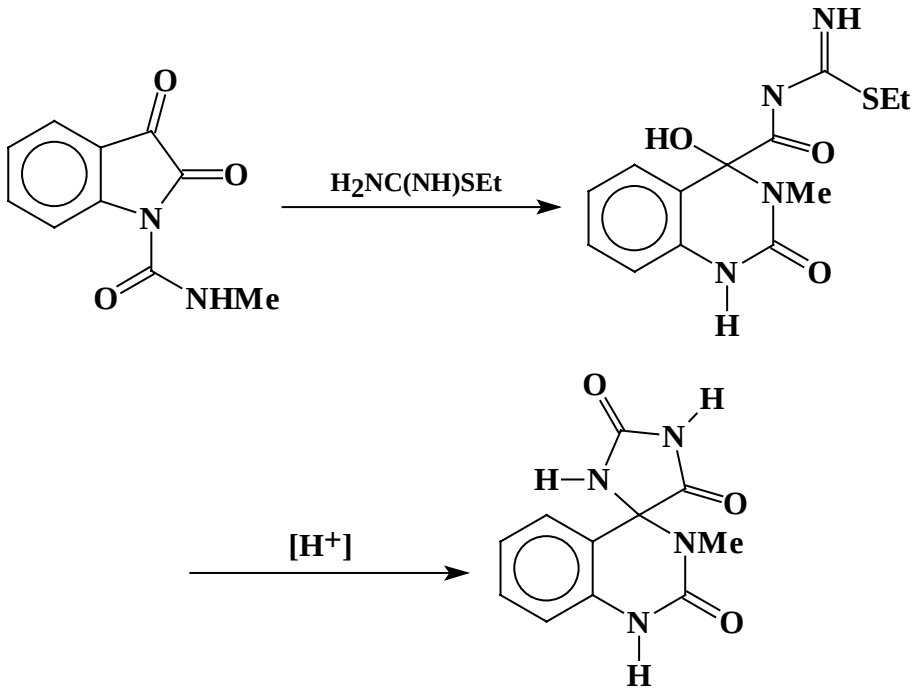


Scheme 69

Isatin-1-ethylcarbamate and urea yield a ring-opened product, which after treatment with ammonia yields a *spiro* hydantoinquinazolone[301] (Scheme 70). Similarly, 1-carboxamidoisatins furnish quinazolones upon treatment with thiourea derivatives[302] (Scheme 71).



Scheme 70



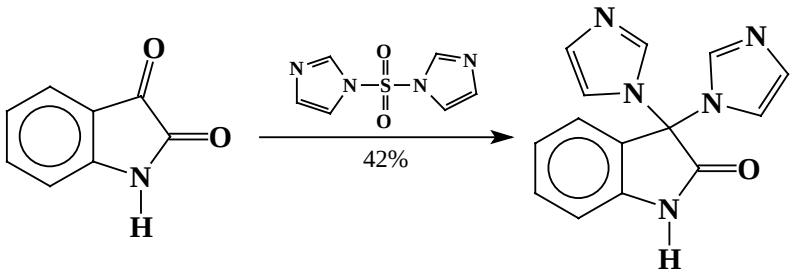
Scheme 71

c)Anilines and heterocyclic amines

As with alkylamines, isatin[303,304], 1-alkylisatins[305], 1-hydroxyisatin[306] and 1,2-dioxo-1,2-dihydropyrrolophenothiazine[298] lead to the corresponding 3-imines when treated with

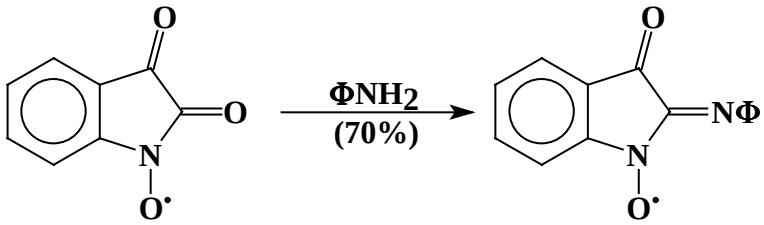
anilines or heteroarylamines[307]. These imines can be acylated[308] or they may participate in the Mannich reaction and thus yielding *N*-1 substitution products[309,310], although exchange of the imino group can also occur[311].

Upon reaction with N,N'-thionyldiimidazole, isatin and 1-methylisatin furnish the substitution product resulting from the addition of two imidazole groups at position C-3. These compounds where found to possess antimycotic activity[312] (Scheme 72).



Scheme 72

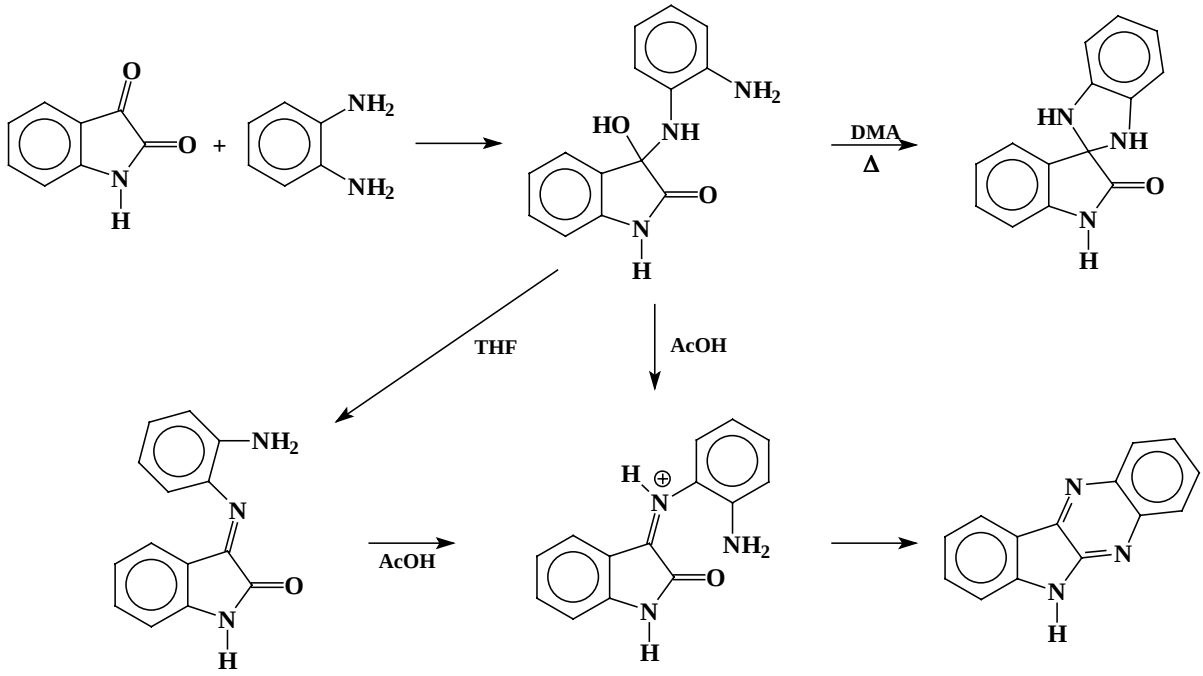
Isatinyl-N-oxide, obtained from 1-hydroxyisatin, yields the corresponding 2-imino derivative when reacted with anilines or with aliphatic amines[313] (Scheme 73).



Scheme 73

The reaction of isatins with *ortho*-phenylenediamines gives indophenazines, 3-iminoisatins and/or *spiro*benzimidazolines, the proportion between them being affected mostly by the solvent polarity. Indophenazines were obtained in yields of 89% by treating isatins and *ortho*-phenylenediamines in acetic acid[314-317]; isatin-3-imines were obtained when using THF, benzene (90% yield) or MeOH (50% yield), together with indophenazines. Isatin-3-imines are converted to the corresponding indophenazines by treatment with AcOH[318].

These imines have been studied as hair dyes[319]. The use of the polar aprotic solvent N,N-dimethylacetamide, and high temperatures yields *spiro*benzimidazoles in high yields[320]. A summary of these reactions is depicted in Scheme 74.

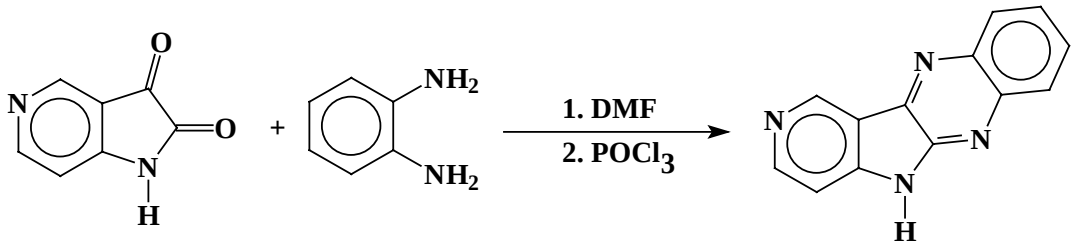


Scheme 74

These findings can be rationalised by consideration of a common intermediate. An intermediate carbinolamine could undergo either a nucleophilic substitution reaction, probably through an ionisation step facilitated by the high temperature and by assistance from the nitrogen lone pair to form the *spiro* compound in dimethylacetamide, or the intermediate may suffer dehydration in apolar solvents to form the corresponding isatin-3-imine. This imine can undergo facile *syn-anti* isomerisation upon protonation in acetic acid and thus yields the indoloquinoxaline derivative[321].

A number of indophenazines have been applied to the synthesis of photoconductor polymers[322].

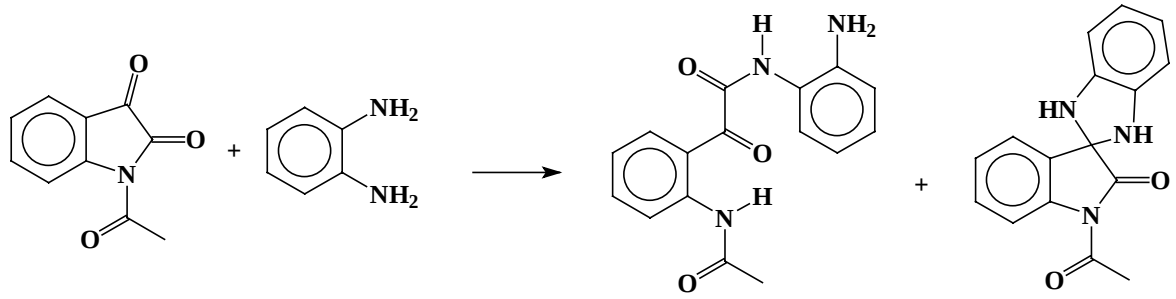
Reaction of 5-azaisatin with *o*-phenylenediamine yielded a pyridopyrroloquinoxaline[50] (Scheme 75).



Scheme 75

Other diamines, such as 2,3-diamino-4(3H)-quinazolone[323] and 2,3-diaminobenzoic acid[324], behave similarly to *ortho*-phenylenediamine when reacted with isatin.

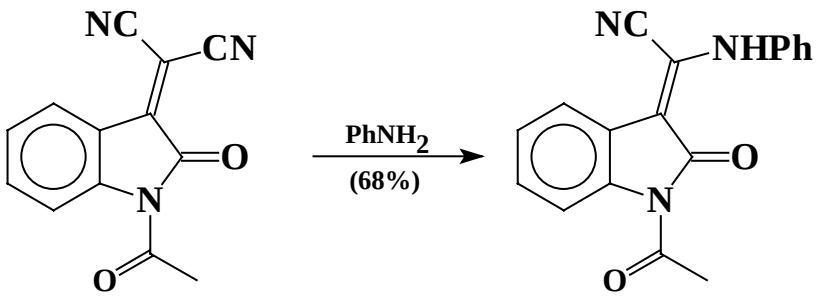
When the reaction is carried out with 1-acylisatins, ring opened products are formed using benzene, acetic acid or ethanol as the solvent[325-329]. However, it has been reported that with the latter two solvents a *spiro* benzimidazole derivative is also formed[330]. The formation of ring opened products has also been reported to occur when using alkyldiamines[331] (Scheme 76).



Scheme 76

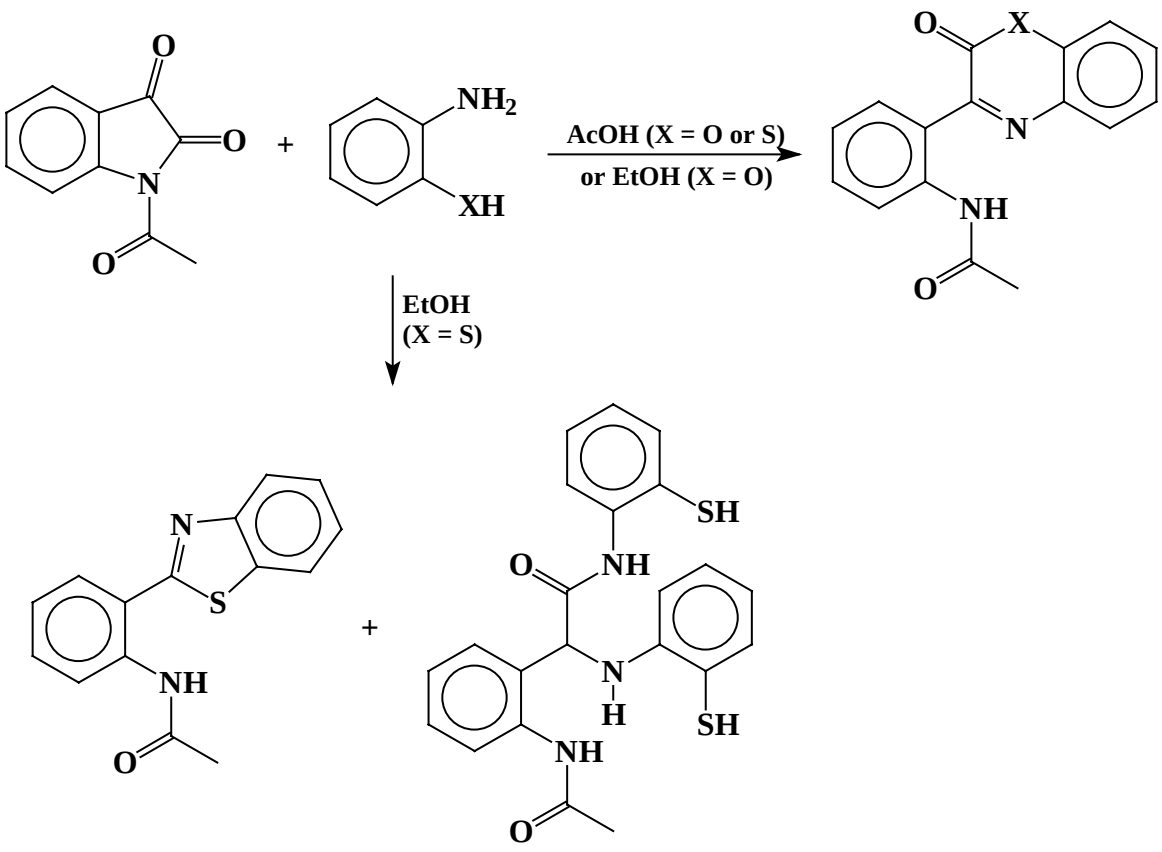
Likewise, the reactions of 1-acylisatins and anilines[296] or *N*-methylanilines[332] led to ring opened products, but one report states that 4-arylthio and 4-arylsulfonylanilines react with 1-acetylisatin to furnish 3-imines[333].

1-Acetyl-3-dicyanomethyleneisatin undergoes a substitution reaction with aniline, in nonpolar solvents, leading to a cyanoenamine[334] (Scheme 77).



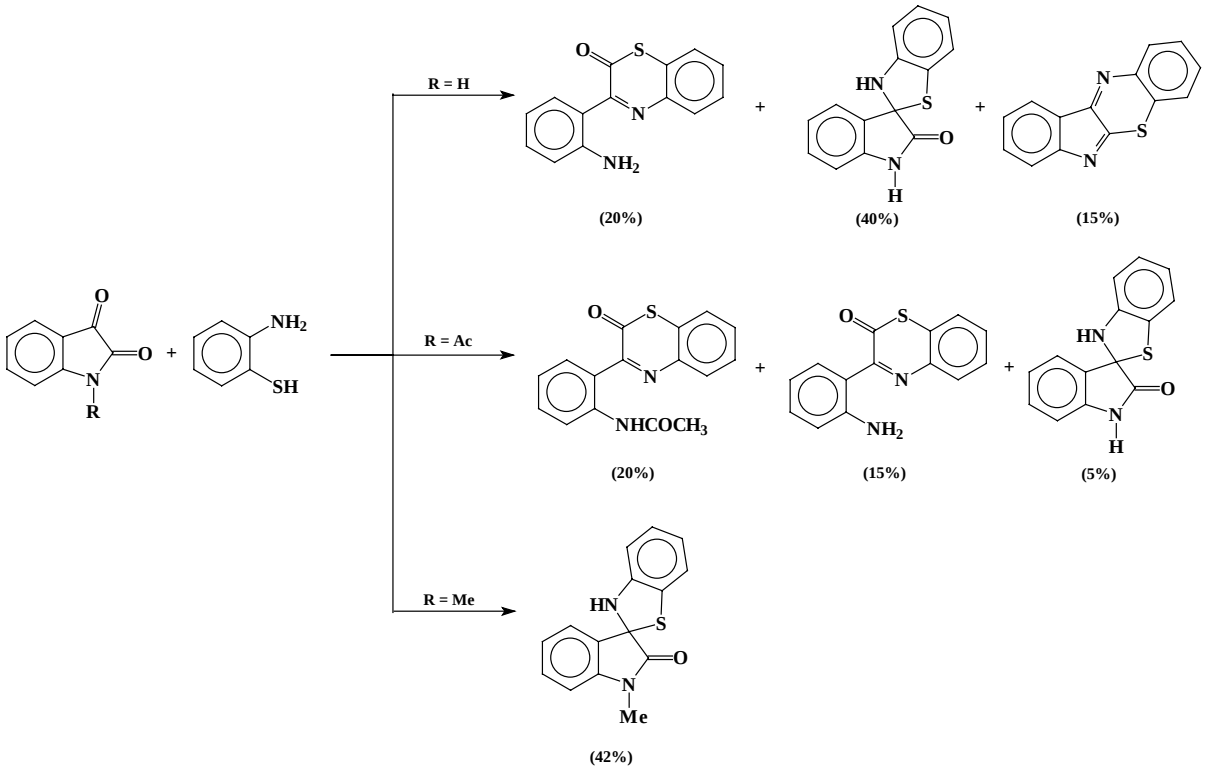
Scheme 77

The reactivity of isatin derivatives towards *ortho*-aminophenol and *ortho*-aminothiophenol has been the subject of a number of reports and some of the products obtained are quite intriguing. The first report attests that 1-acetylisatin reacts with *o*-aminophenol to furnish a ring opened product in ethanol as well as in AcOH. The same result occurred with *o*-aminothiophenol in acetic acid, whilst in ethanol two different products were formed in a disproportionation reaction, as can be inferred from the change of the oxidation state of what was the 1-acetylisatin C-3 ketone group. The structures were assigned based upon spectroscopic data and, for the benzothiazole derivative, on comparison with a sample obtained by a different route[335] (Scheme 78).



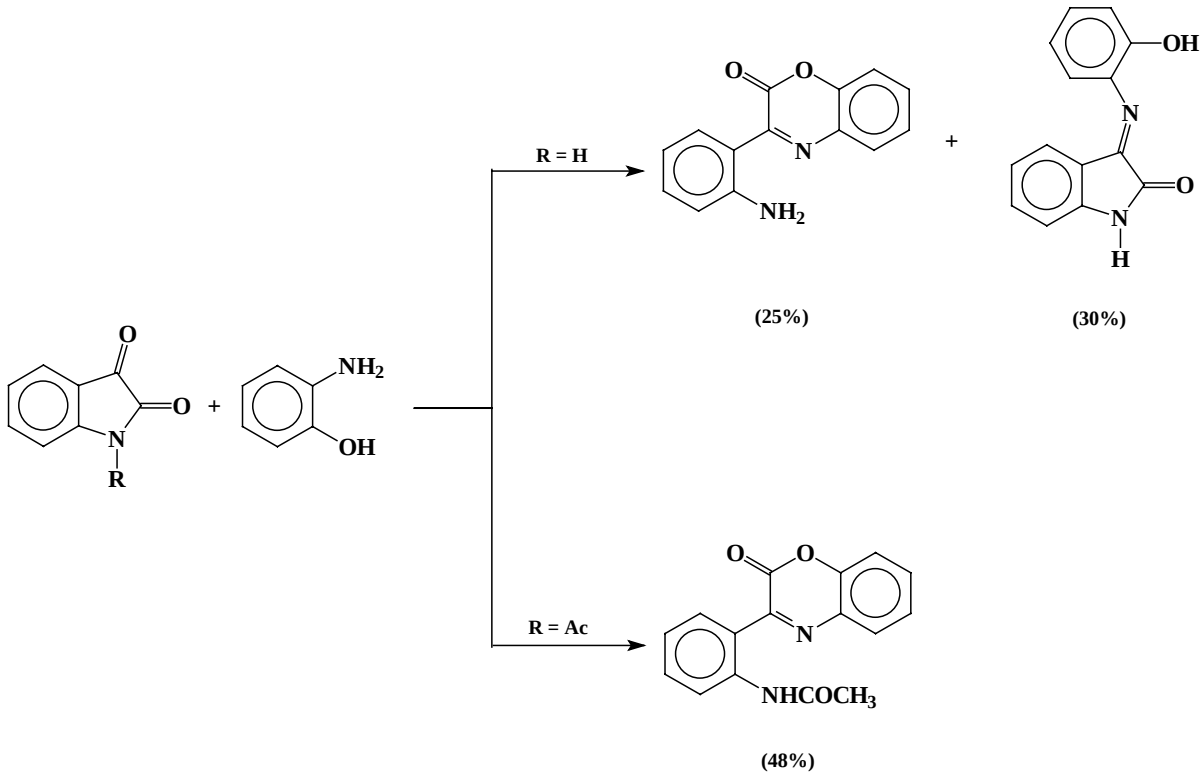
Scheme 78

Subsequent reports[336- 338] on the reactivity of isatins towards *o*-aminothiophenol reported that isatin furnishes a benzothiazinone (18%), due to attack at the C-2 position, and a *spiro*benzothiazole (10%), due to attack at C-3, when the reaction is carried out in dry xylene in the presence of anhydrous $ZnCl_2$ at room temperature. If the same reaction is carried out under reflux, the products formed are the benzothiazinone (20%), the *spiro* benzothiazole (40%) and an indolobenzothiazide (15%). 1-Acetylisatin, under the same reaction conditions furnishes, at room temperature, the corresponding ring opened product (20%), which can suffer deacetylation (15%), whereas under reflux these products (40 and 30%, respectively) are accompanied with the *spiro* compound (5%). 1-Methylisatin reacts only at reflux furnishing solely the *spiro* compound (42%) (Scheme 79).



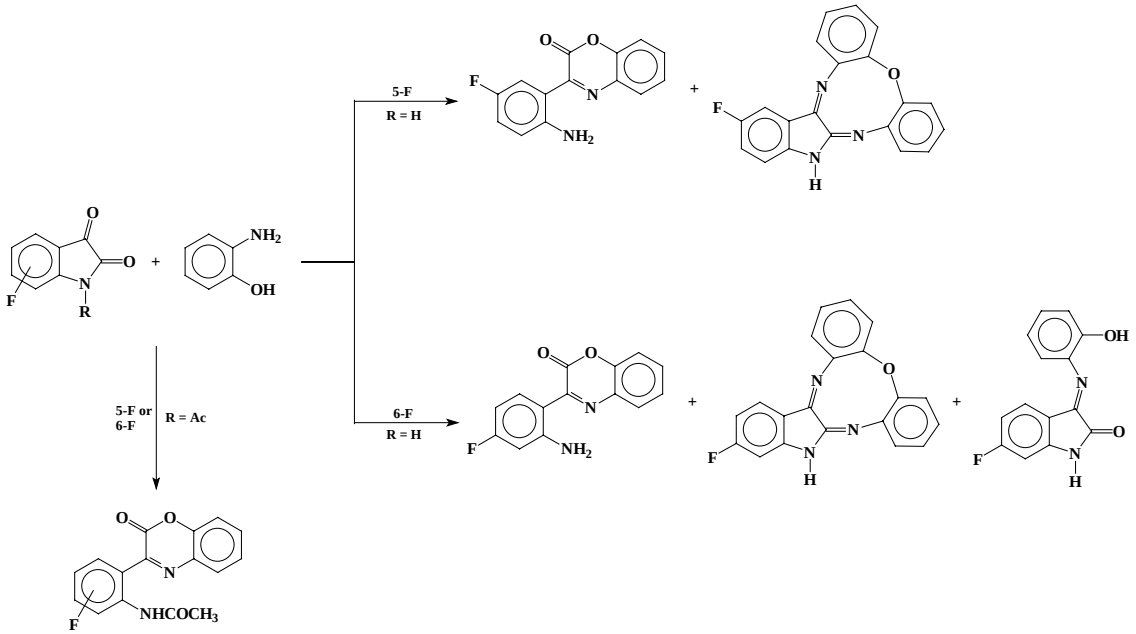
Scheme 79

The reactions of these compounds with *o*-aminophenol occur only at reflux. In the case of isatin, the formation of a ring opened product (25%) occurs along with the 3-imino derivative (30%), whilst 1-acetylisatin furnishes solely a ring opened product (48%). Characterisation of the products was based upon their mass, IR, ^{1}H and ^{13}C NMR spectra (Scheme 80).



Scheme 80

The reaction of 5-fluoroisatin with *o*-aminophenol under the same conditions as the previous study was reported to result in the formation of a heterocyclic ring opened product and a nine membered ring compound. The isomeric 6-fluoroisatin was reported to furnish, apart from these two products, the corresponding 3-imine. The acetylated fluoroisatins behave similarly to 1-acetylisatin, giving rise to the ring opened product[339] (Scheme 81).

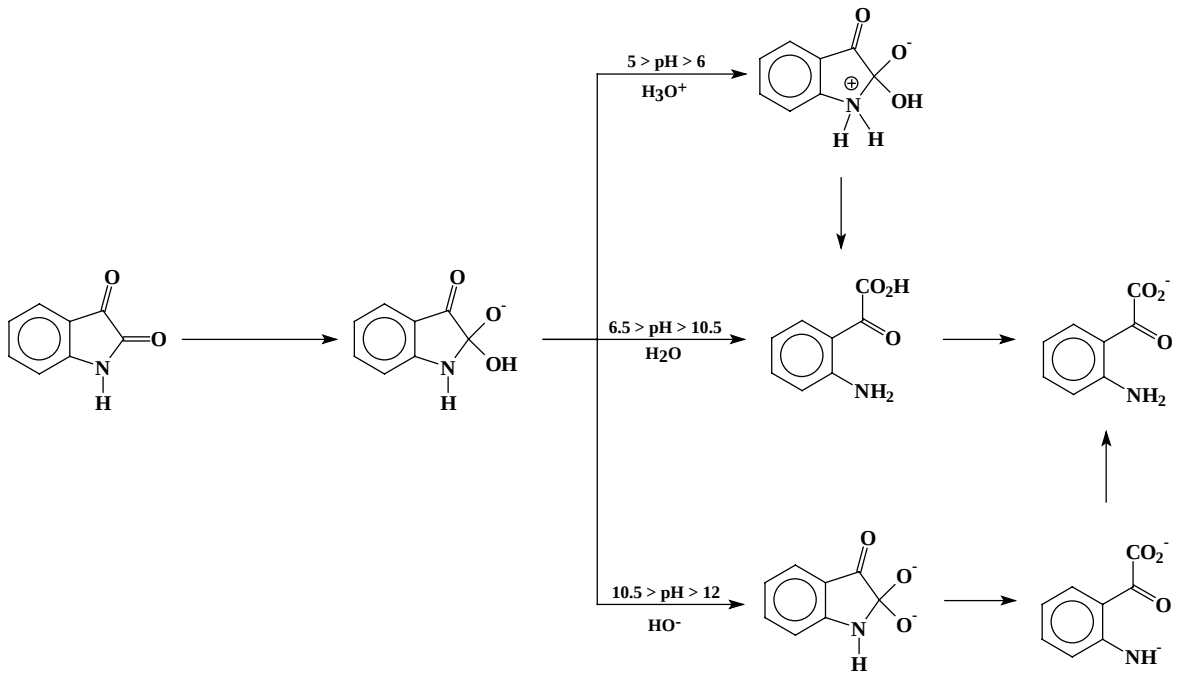


Scheme 81

3.3.1.2 - Oxygen, sulfur and phosphorous nucleophiles

Isatin[340] and 1-arylisatins[341,342,343] suffer hydrolysis in alkaline solutions, leading to isatinates. Kinetic studies have shown that this is a thermodynamically favored process, which also occurs under physiological conditions, implying that some, or all, of the biological and pharmacological activities described for isatins are indeed due to their isatinates[344,345].

The pH profile for the hydrolysis of isatin has shown that at pH < 3, isatin is the predominant species, and at pH > 6, the ring opened isatinate is the major component. At pH values between 5 and 6, the rate of hydrolysis is first-order in hydroxide concentration or inversely proportional to the concentration of the hydronium ion, but from pH 6.5 to 10.5 it is pH independent. This result reveals the existence of a complex behaviour for the hydrolysis of isatin, with different rate limiting steps depending upon the pH of the solution. [346]. A similar profile has been observed for 1-methylisatin[347] (Scheme 82).



Scheme 82

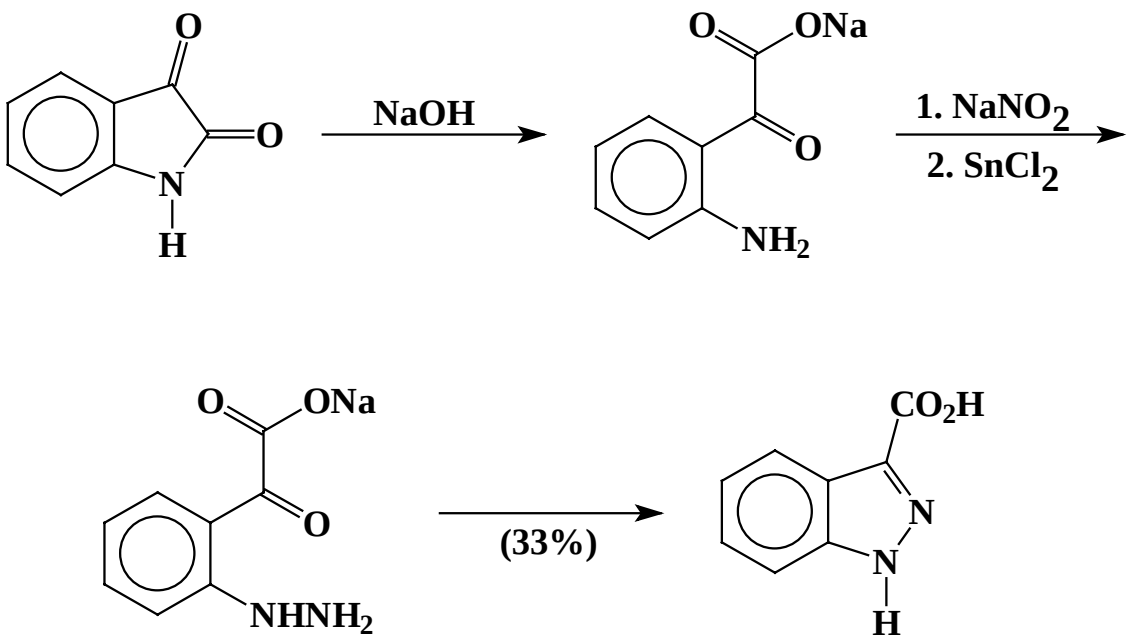
It was also observed that in the presence of ethanol and ethylene glycol the rate of hydrolysis decreases[348]. The effects of other solvents[349], as well as the photophysics[350] of the hydrolysis reaction of isatin have also been studied.

Isatinates can be electrochemically reduced to mandelates at different pH values using mercury electrodes[351].

The isatinates can be converted to the corresponding oximes, which possess pharmacological interest as anti-inflammatory agents[352].

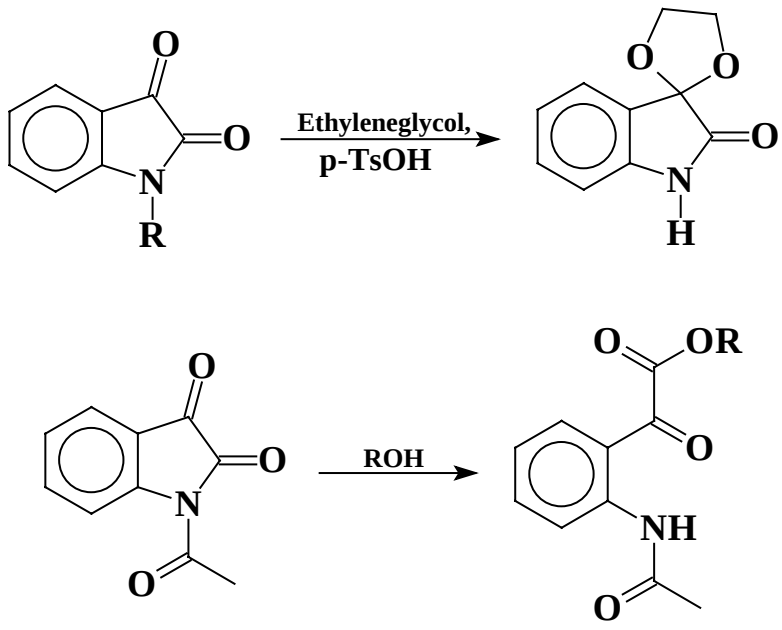
Isatin-3-imines are hydrolyzed to isatin and the corresponding amine. A ring opened intermediate is proposed to be involved in the process as it was detected by polarography[353].

The alkaline hydrolysis of isatin is the first step of a method for the construction of the indazolic ring system[354]. This method has been applied to the synthesis of serotonin antagonists[355] (Scheme 83).



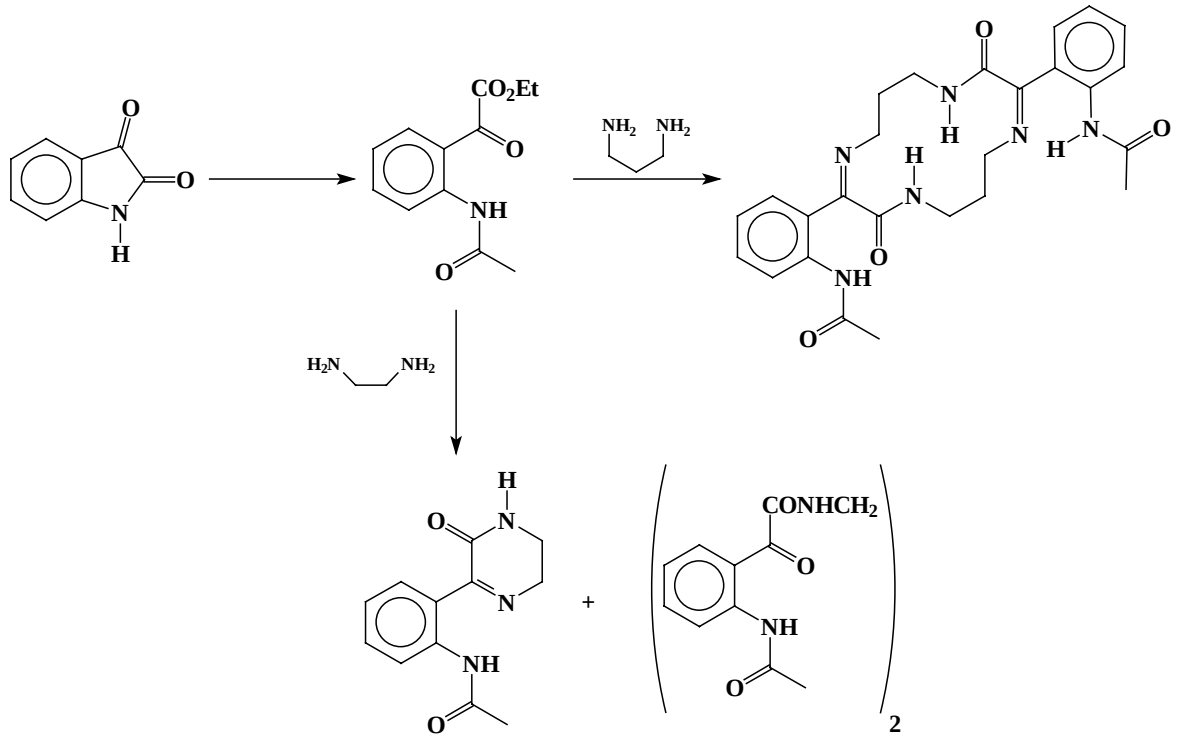
Scheme 83

Isatin-3-ketals are obtained by reaction with diols under homogeneous[356] or heterogeneous acid catalysis, employing the strongly acidic resin Dowex 50X-X2[357] or by transacetalation with trimethyl orthoformate[358]. 1-Acetylisatin reacts with alcohols in neutral media to furnish ring opened products[228] (Scheme 84).



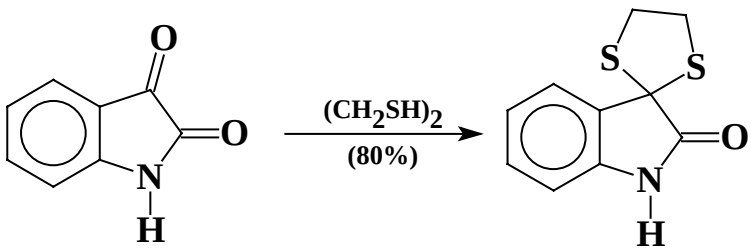
Scheme 84

Bergman and Vallberg used the ethyl glyoxalate obtained by solvolysis of *N*-acetylisatin in refluxing ethanol to reinvestigate the reactions of *N*-acetylisatin with ethylenediamine and propane-1,3-diamine. The investigations were extended to a number of other diamines and the resulting dihydropyrazinones could be transformed to the corresponding pyrazidoindoles[359] (Scheme 85).



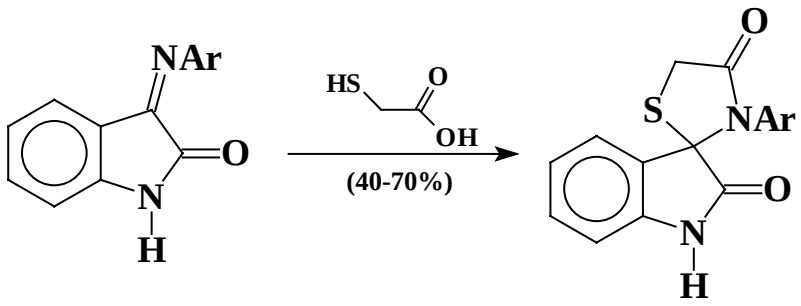
Scheme 85

The reactions of isatins[360,159] and 1-alkylisatins[361] with thiols yield substitution products at position C-3, such as isatin-3-thioketals and 3-alkylthiooxindoles[362] (Scheme 86).



Scheme 86

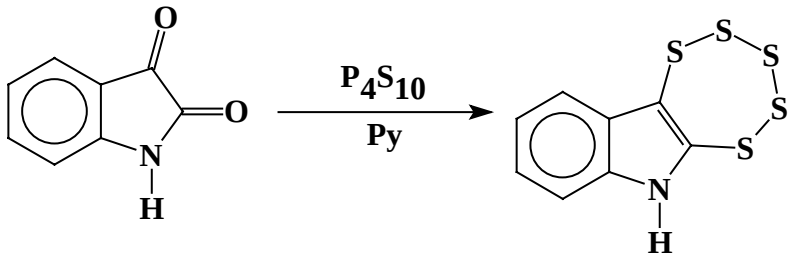
Isatin-3-*N*-arylimines react with mercaptoacetic acid to yield *spiro*thiazolinones[363] (Scheme 87). These can be further acylated or submitted to a Mannich reaction, thus giving products substituted at the oxindole nitrogen atom[364].



Scheme 87

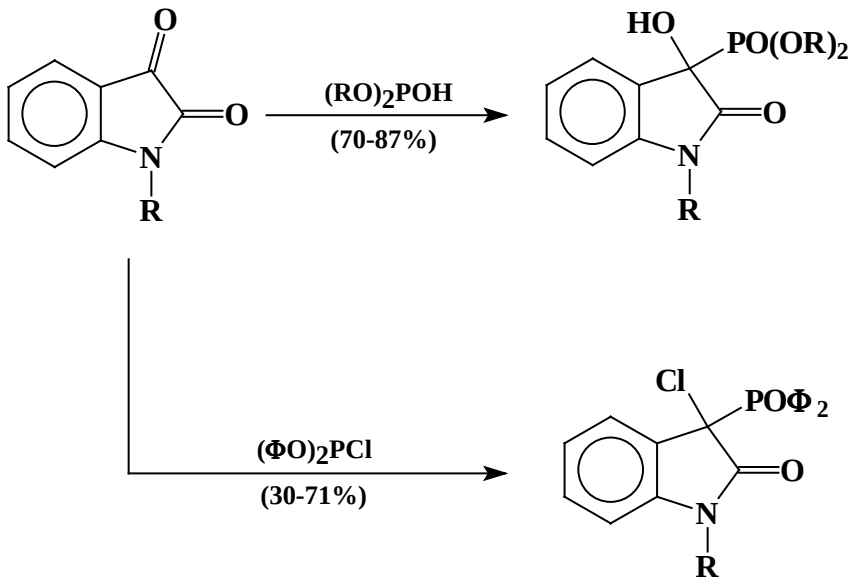
The addition of thiols to isatin anils to yield the respective thioazoketals is general[365].

The reaction of isatin with P_4S_{10} in pyridine resulted in the obtention of pentathiepino[6,7-b]indole[136] (Scheme 88).



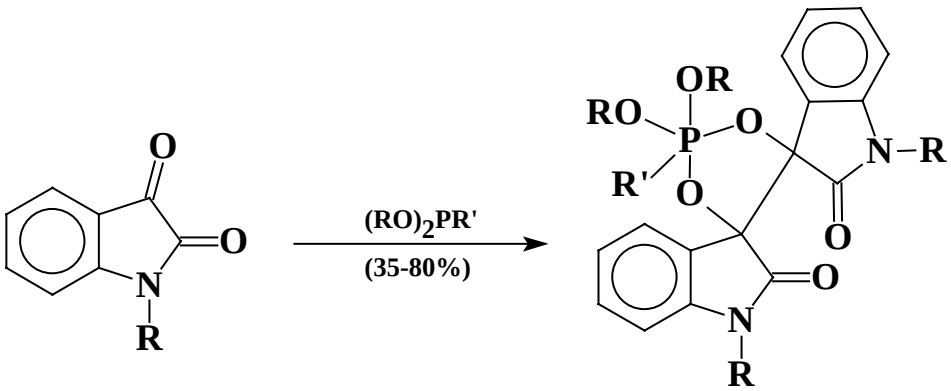
Scheme 88

Dialkylphosphites add to isatin and 1-substituted derivatives at position C-3 generating dioxindolophosphonates[366]. Isatin-3-oximes react in a similar manner[367]. The use of chlorophosphines generates 3-(3-clorooxindolyl) phosphine oxides[368] (Scheme 89).

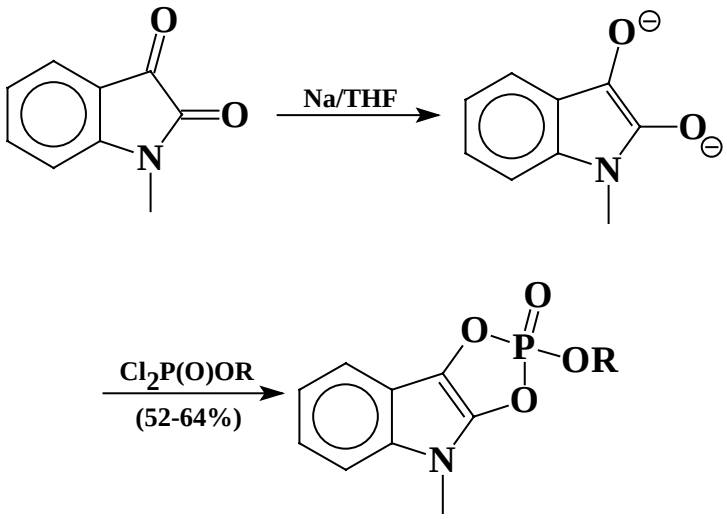


Scheme 89

On the other hand, cyclic dioxaphospholanes[369], phosphites[370] and trialkyl phosphites[371,372] react with isatins to yield dimeric *spiro* phospholanes (Scheme 90). Cyclic indolic phosphates were obtained when 1-methylisatin was reduced with sodium in THF to yield a dianion that subsequently reacted with alkyl phosphorodichloridates[373] (Scheme 91).



Scheme 90



Scheme 91

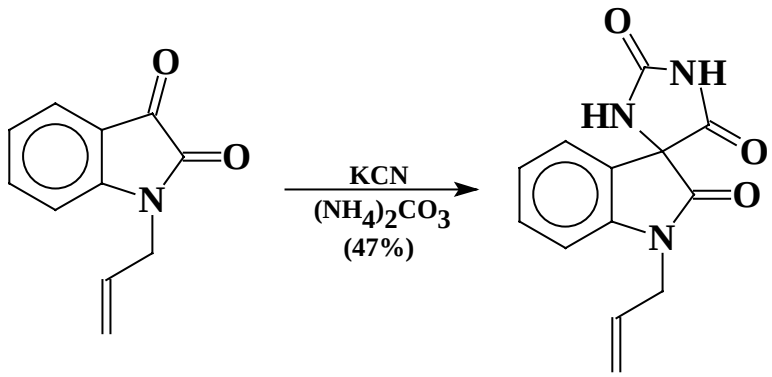
Isatin-3-*N*,*N*-dimethylhydrazone when reacted with diethyl phosphonate, furnishes isatin-*N*-ethyl-*N*,*N*-dimethyl hydrazonium ethyl phosphonate[374].

The reaction of isatin with triphenylphosphine was believed to furnish indirrubin[375], but a reinvestigation of this reaction has shown that the products formed are 3-triphenylphosphoranylideneoxindole and isoindigo[376].

4.3.3 - Carbon nucleophiles

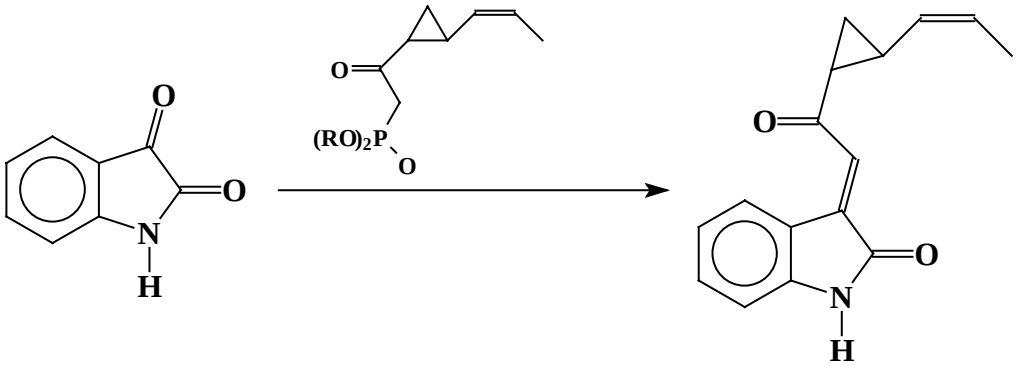
Carbon nucleophiles add to isatin and derivatives at position C-3 in most cases, and the products formed have been submitted to further transformations giving rise to a variety of heterocyclic systems.

Potassium cyanide and ammonium carbonate react with 1-alkyl[377] or 1-alkenylisatins[363] generating *spiro*hydantoins. These compounds are inhibitors of the enzyme aldose reductase, and have potential use as hypoglycemic agents (Scheme 92).



Scheme 92

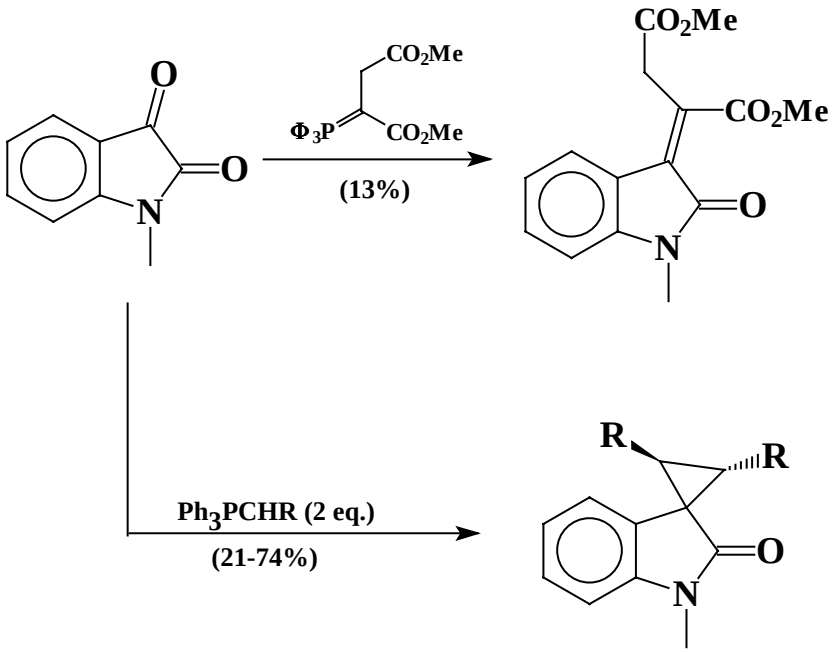
Isatins can be used as the electrophilic component in the Wittig-Horner reaction with phosphonates and furnish products resulting from attack at position C-3[378,379]. Other α-carboxyphosphonates[380] and α-carboxyphosphites[381] have also been studied and yield 3-methyleneoxindoles in moderate yields (Scheme 93).



Scheme 93

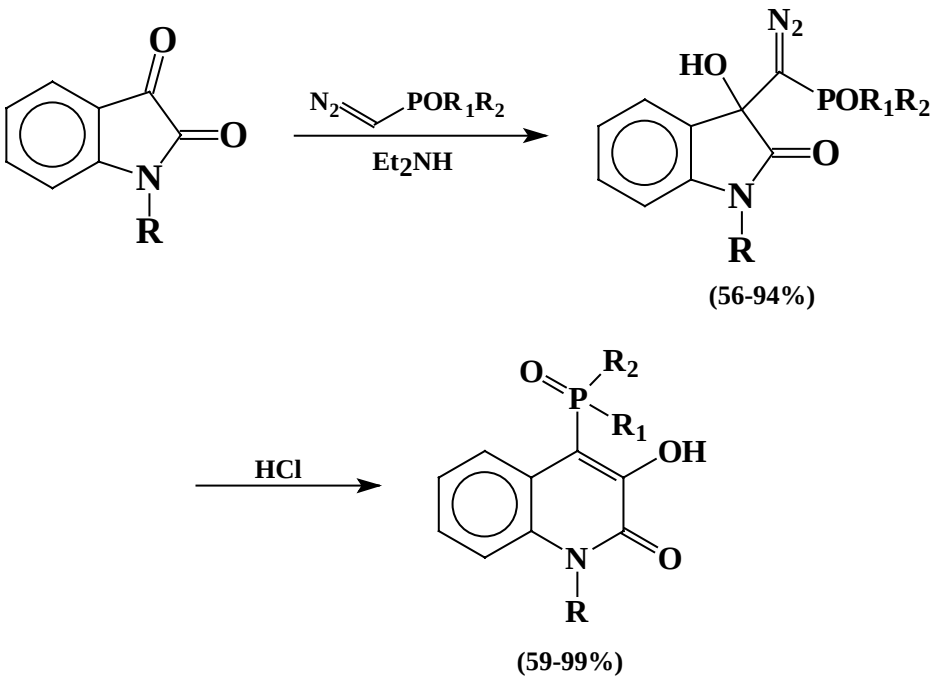
1-Alkyl and 1-acylisatin react with equimolar quantities of a succinyl triphenylphosphorylidene to give dimethyl 2-oxoindolin-3-ylidenesuccinate derivatives in low yields[382] (Scheme 94). Dimers of this product are obtained from the reaction of isatin-3-(4-chlorophenyl)imine with DMAD in the presence of cupric acetate[383].

When the Wittig reaction is carried out with two equivalents of the Wittig reagent, 3-*spiro*-cyclopropanes are formed[384] (Scheme 94).



Scheme 94

α-Diazophosphorous derivatives also attack at the C-3 position of the isatin ring to give dioxindoles[385,386] which upon treatment with acid yield the ring expanded quinolones (Scheme 95).

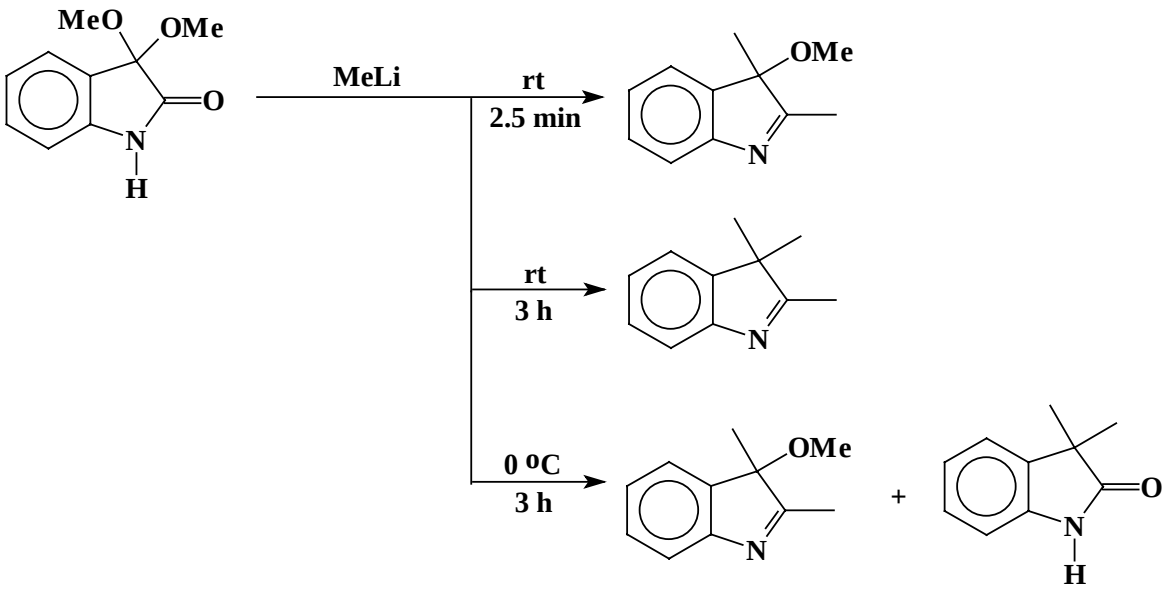


Scheme 95

3-Alkyldioxindoles and their dehydration products, 3-methyleneoxindoles, are formed in the reactions of isatins with organoboron compounds, such as triallylboron[387]; organomagnesium reagents[388,389]; organozinc reagents[390,391] ; organolithium reagents[392,393], such as methyllithium[154]. These compounds are also obtained in aldolic and related condensations with acetone[394] or its oxime[395]; aromatic[396,397] and heteroaromatic methylketones[398,399]; cyclic alkylketones[400]; acetates[401]; propionates[402]; acetoacetates[403]; cyanoacetates[404]; nitroalkanes[405]; benzodiazepinones[406]; imidazolinones[407]; indoles[408]; 2-methylquinolines[409]; pyrazinones[410]; thiazolidinediones[411-415] and xanthinones[416]

In the reaction of isatins with some cyclic ketones, such as 4-hydroxy-2H-benzopyran-2-one[417], the initial dioxindole formed reacts with a second equivalent of the ketone yielding a 3,3-disubstituted oxindole.

The addition of methyl lithium to isatin-3,3-dimethylketal (3,3-dimethoxyoxindole) at room temperature for 2.5 min lead to an indolenine derivative through addition at C-2 and substitution of one methoxy group at C-3. By extending the reaction time to 3 hours, the second methoxy group was also substituted, furnishing 2,3,3-trimethylindolenine. This same product was obtained when the reaction was carried out at 0 ^{o}C, together with 3,3-dimethyloxindole[418] (Scheme 96).

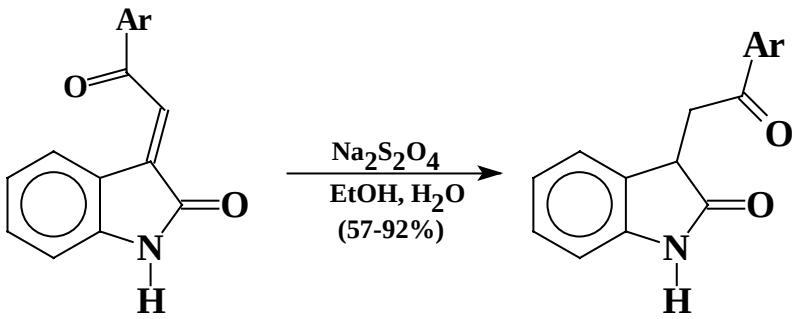


Scheme 96

Isatins fail to yield Knoevenagel condensation products with malonic acid[419]. However, malonic acid can be condensed with isatin in a mixture of ethanol and pyridine, in which the initial condensation product suffers decarboxylation, furnishing an acetic acid derivative. This can be converted to the acid chloride and submitted to a Friedel-Crafts acylation reaction, yielding acetophenone derivatives[420]. Alternatively the oxoindolinylidene acetic acid derivative can be treated with an arene in the presence of $AlCl_3$ to yield *spiro*[indoline-3,3'-indan]-2,1-dione derivatives[421].

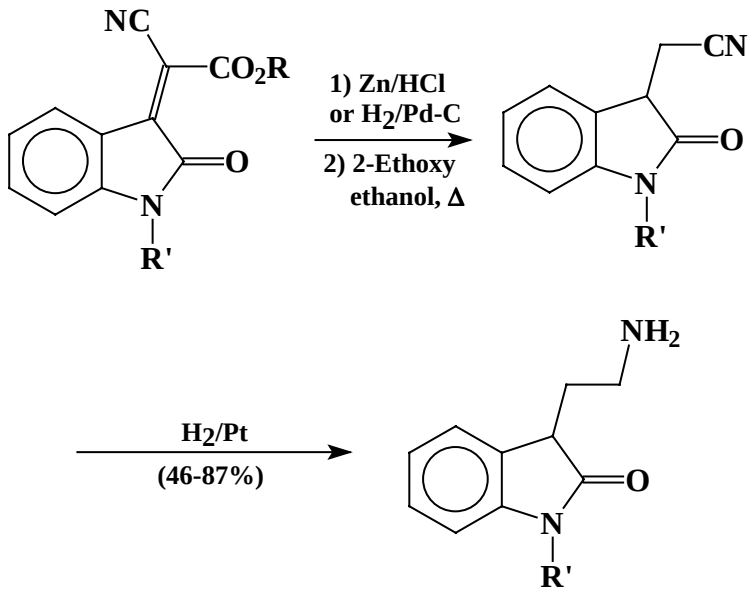
Microwave irradiation has been used for promoting the reaction of isatin with malononitrile to give 3-dicyanomethyleneoxindole and gives better results in comparison to the usual method[422]. The dielectric properties of this condensation product have been studied[423].

The dehydration of the dioxindoles can be achieved by treatment with a mixture of HCl and AcOH[424,425]. The 3-methyleneoxindoles can be selectively reduced at the carbon-carbon double bond using $Na_2S_2O_4$ in aqueous ethanol[426,427] (Scheme 97).



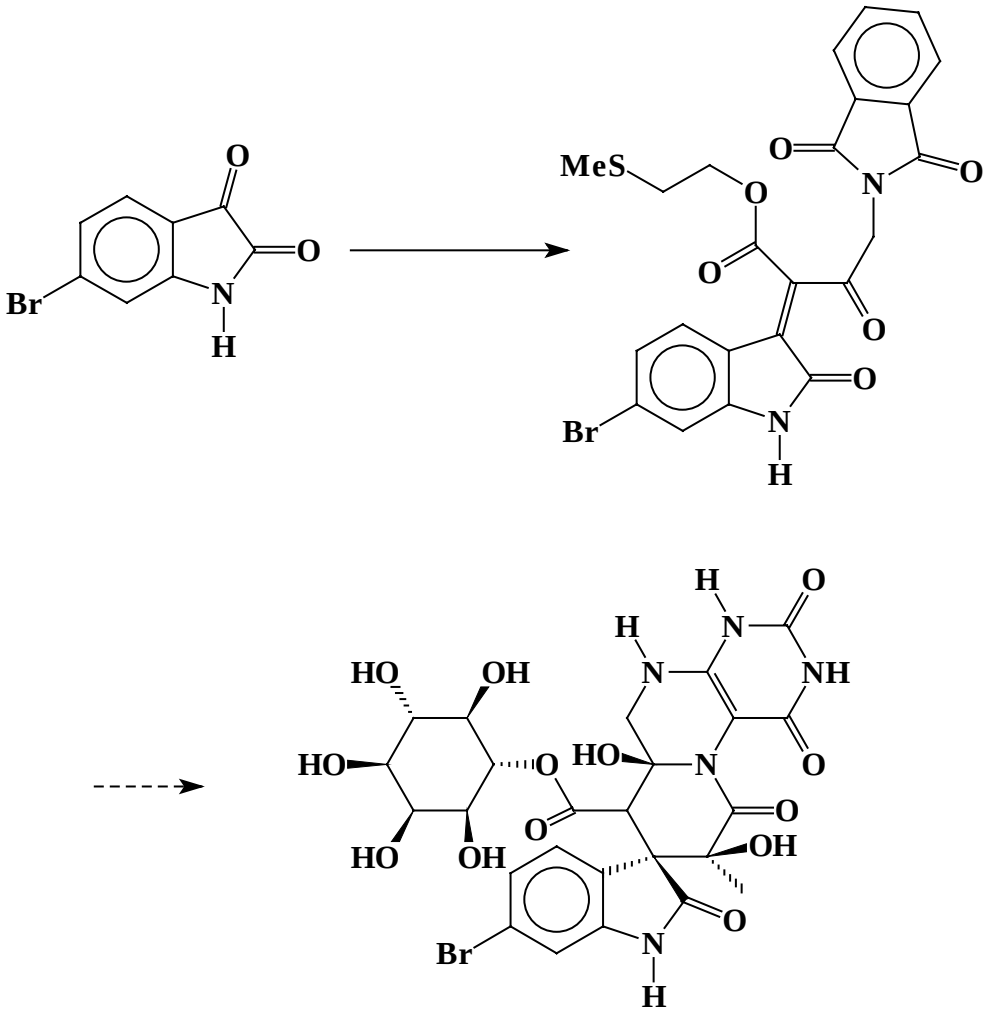
Scheme 97

The condensation products from the reactions of isatins with cyanoacetates can be reduced at the carbon-carbon double bond with Zn dust in HCl or by hydrogenation with Pd/C. Subsequent decarboxylation can be achieved by refluxing in 2-ethoxyethanol. Further reduction of the nitrile yields an ethylamine oxindole[428] (Scheme 98).



Scheme 98

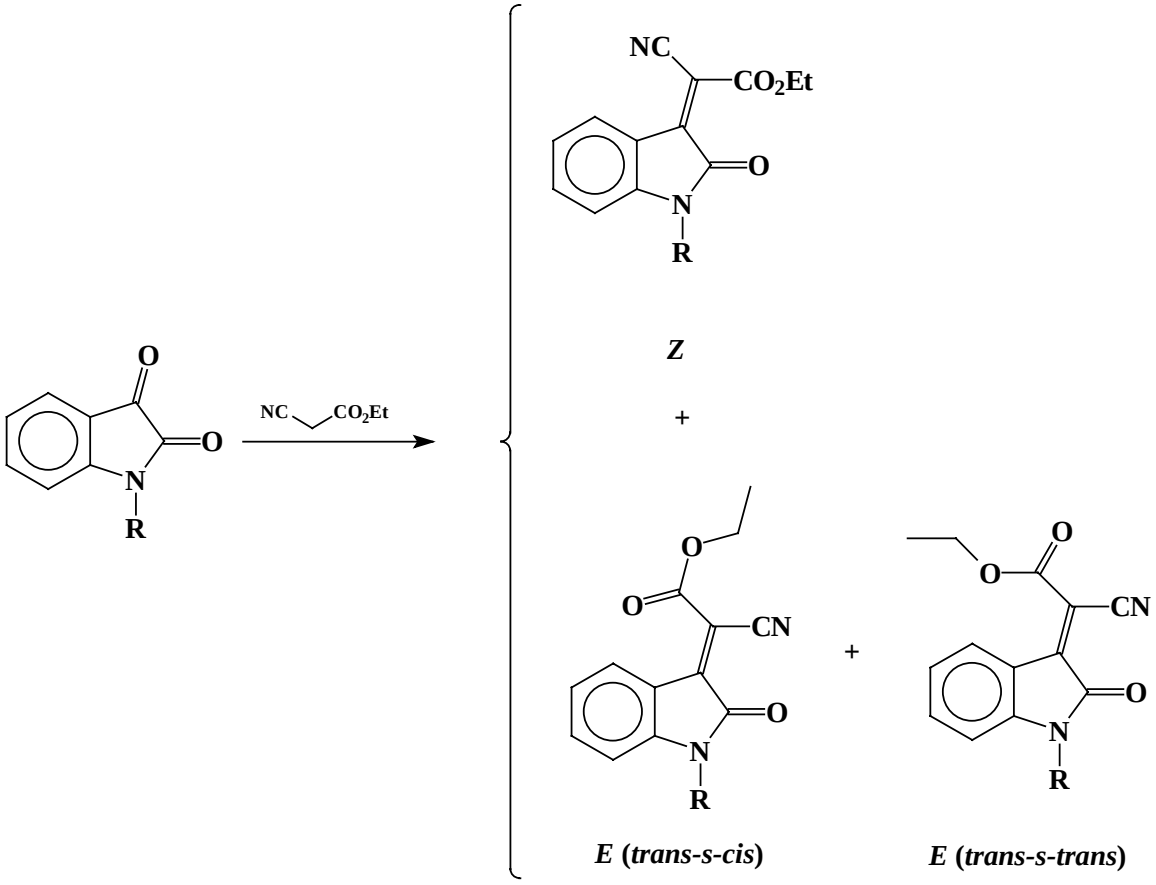
The total synthesis of the marine natural products surugatoxin[429-432] and neosurugatoxin[435,436] began with a Knovenagel condensation employing 6-bromoisatin (Scheme 99).



Surugatoxin

Scheme 99

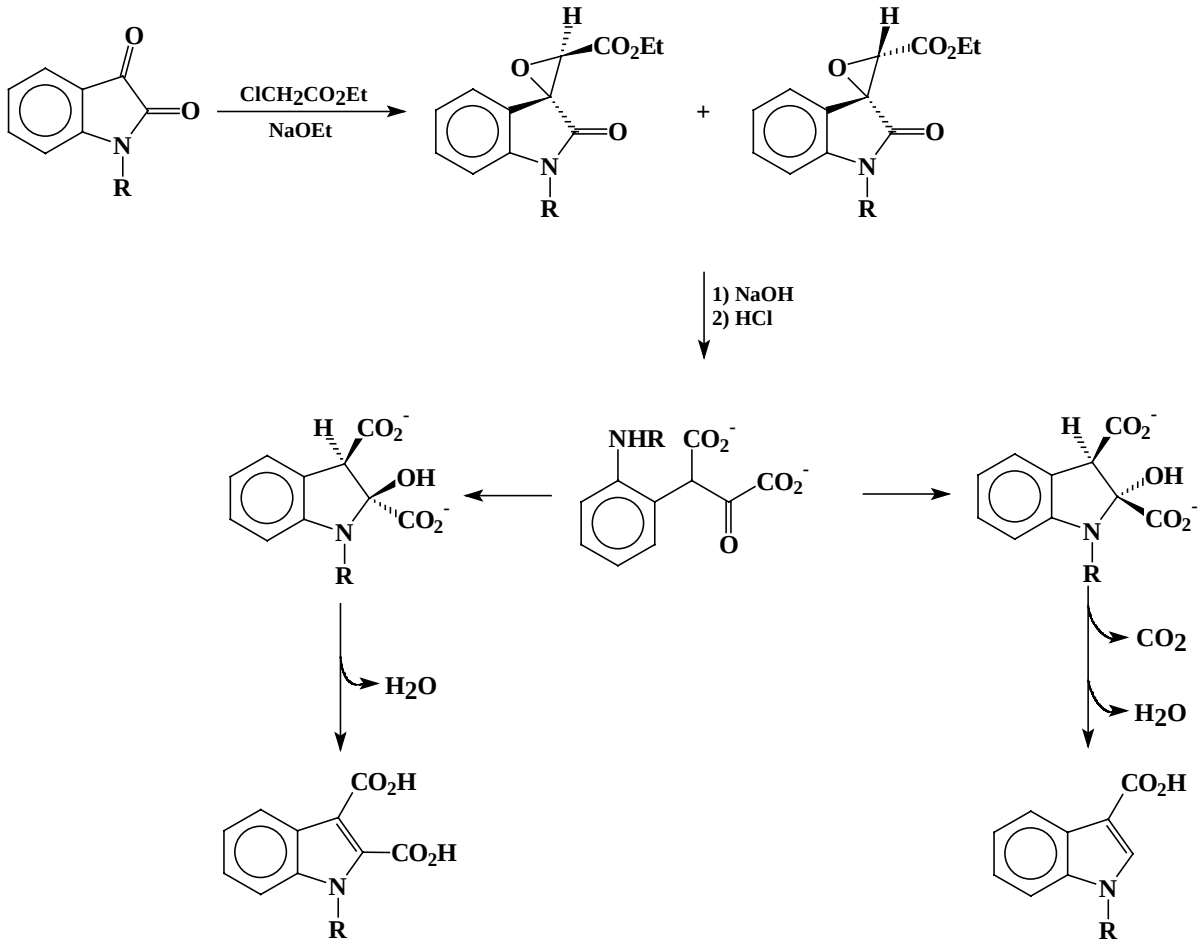
An important issue with respect to the Knovenagel condensation is that a mixture of isomeric disubstituted 3-methyleneoxindoles can be obtained. ^{1}H NMR measurements, including nOe experiments, and quantum chemical calculations have also shown that 3-[cyano(ethoxycarbonyl)methylene]-2-oxindoles, which are obtained from the reaction of isatin or from 1-methylisatin with ethyl cyanoacetate, exist as a mixture of the *E* and *Z* isomers, and that the *E* isomer exists in an equilibrium between two conformers, *trans*-*s*-*cis* and *trans*-*s*-*trans*[437] (Scheme 100).



Scheme 100

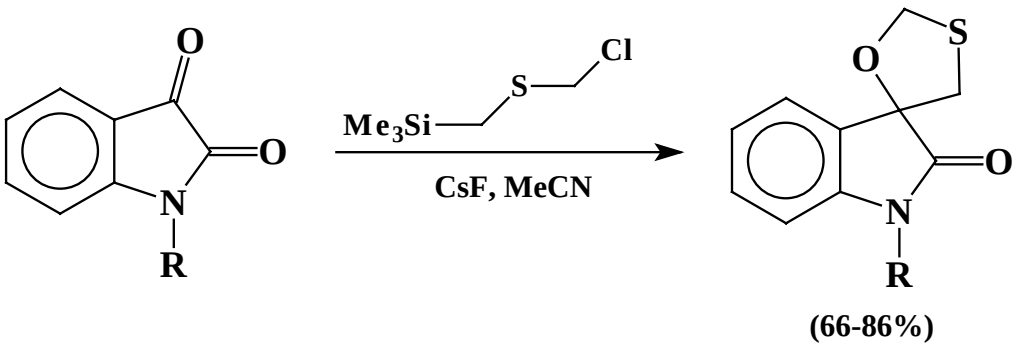
D.R. Long and co-workers have studied monosubstituted 3-methyleneoxindoles and for most of them only the *E* isomer could be detected. 2-Oxoindolin-3-ylideneacetonitrile exists as a separable E,Z-pair, but the Z-isomer slowly isomerises when dissolved in dimethylsulfoxide[438].

The Darzens reaction of isatin with ethyl chloroacetate yields glycidic esters. Alkaline hydrolysis of the glycidic esters yields indole-2,3-dicarboxylic and indole-3-carboxylic acids in a 6:1 proportion. The isolation of two isomeric glycidic esters, and the fact that both produce the indolecarboxylic acids in the same proportion led to a mechanistic proposal for the formation of the later through a common intermediate[439] (Scheme 101).



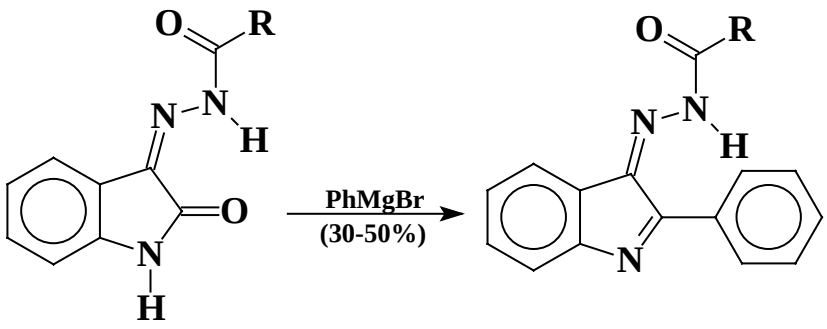
Scheme 101

Masked carbanions, such as silanes, also react with isatins at position 3 and this methodology has been applied to the synthesis of 1,3-oxathiolanes[440,441] (Scheme 102).



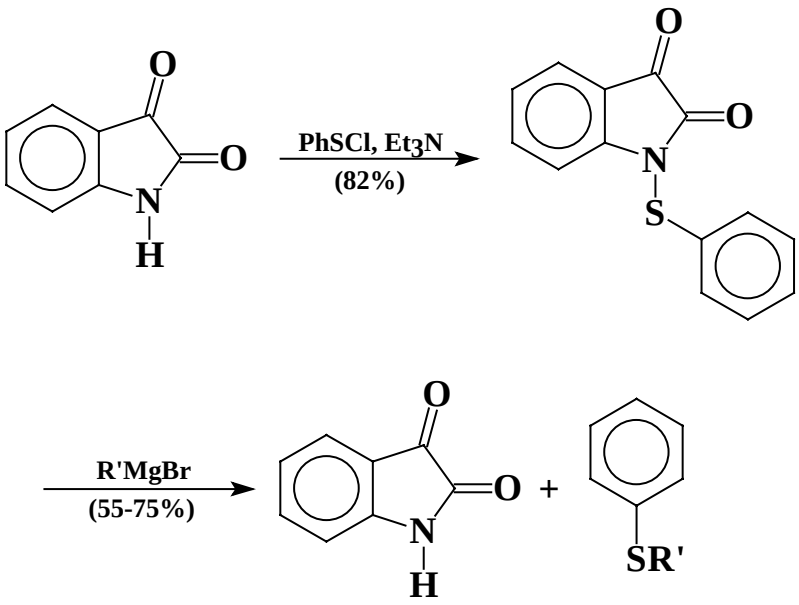
Scheme 102

The reactions of some isatin derivatives with organometallic reagents follow reaction patterns that differ from those of isatin. Addition of phenylmagnesium bromide to isatin-3-acylhydrazones gave a product resulting from nucleophilic attack at C-2[442] (Scheme 103).



Scheme 103

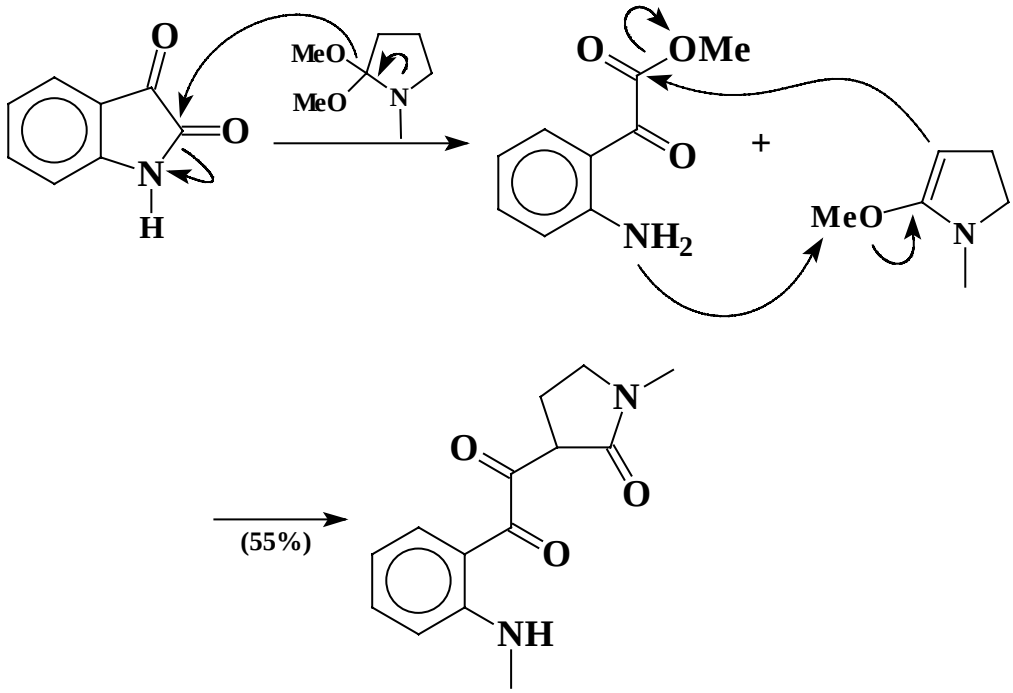
On the other hand, addition of Grignard or organolithium reagents to 1-(arylthio)isatins led to cleavage of the *N*-S bond and formation of the respective sulfides[443] (Scheme 104).



Scheme 104

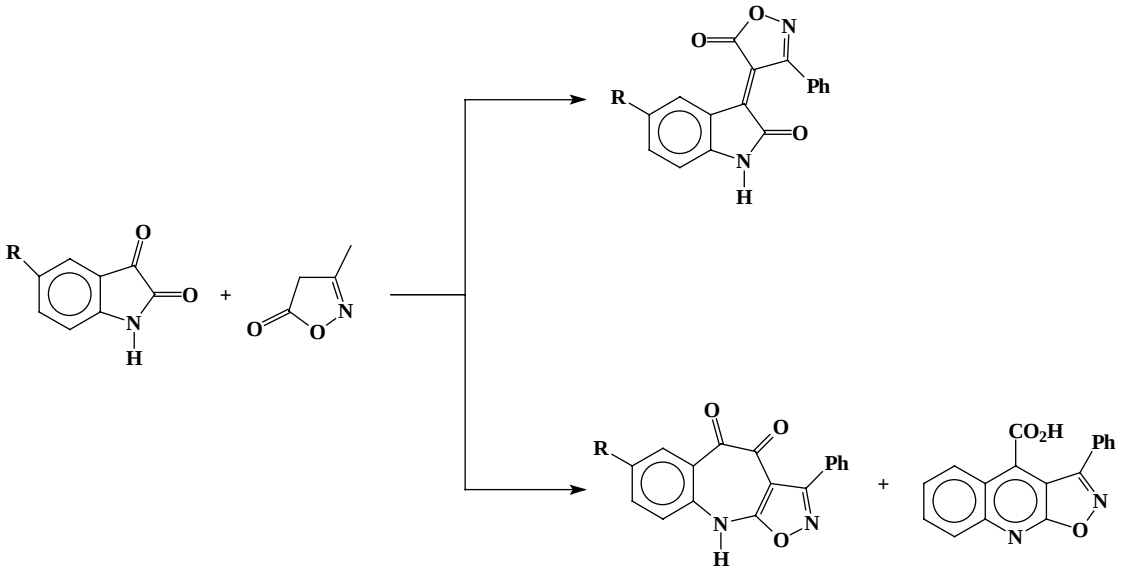
2,2-Dimethoxy-1-methylpyrrolidine adds to isatin in a unique manner furnishing an α-diketone through an intermediate α-ketoester[444] and the proposed mechanism is shown in

Scheme 105. When the reaction was performed with the lactam acetal, 2,2-dimethoxytetrahydroazepine, the product obtained was 1-methylisatin[444,445].



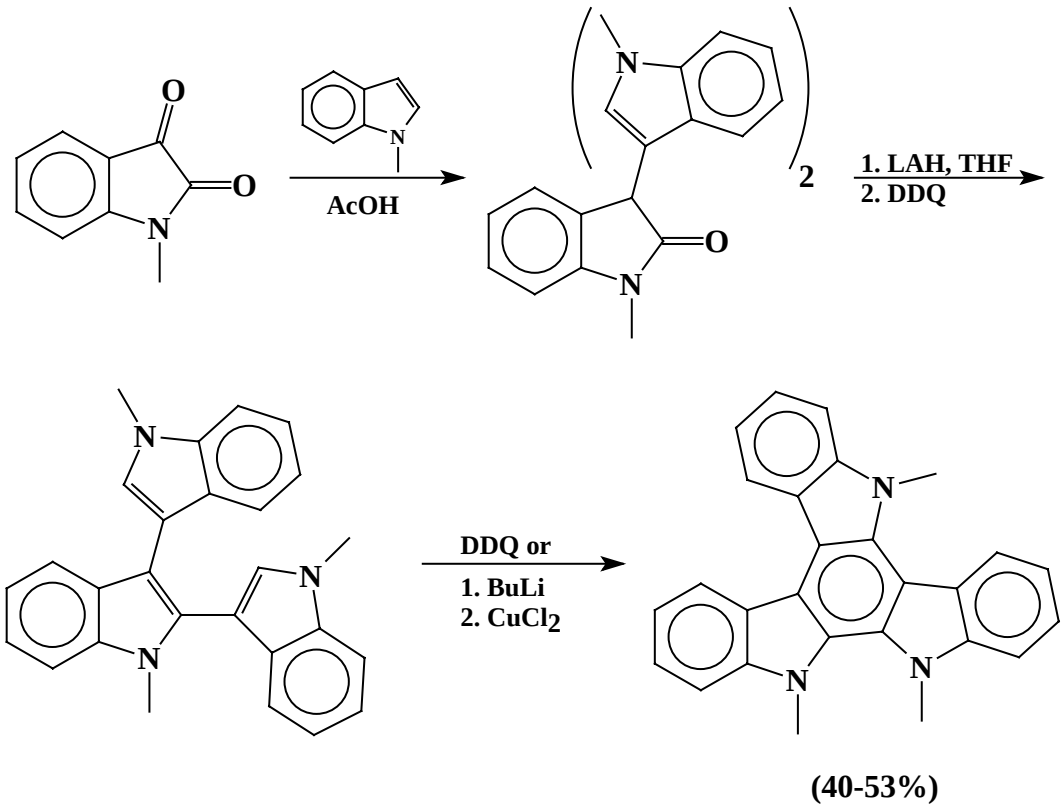
Scheme 105

Different reaction pathways can be observed in the reaction of isatins with carbanions under photochemical or thermal conditions. Thus, the reaction of isatin and isoxazolone under thermal conditions led to addition at position C-3, whilst under UV irradiation cleavage of the isatinic N_1-C_2 bond occured yielding isatic acid, which subsequently condensed with isoxazolone[446] (Scheme 106).



Scheme 106

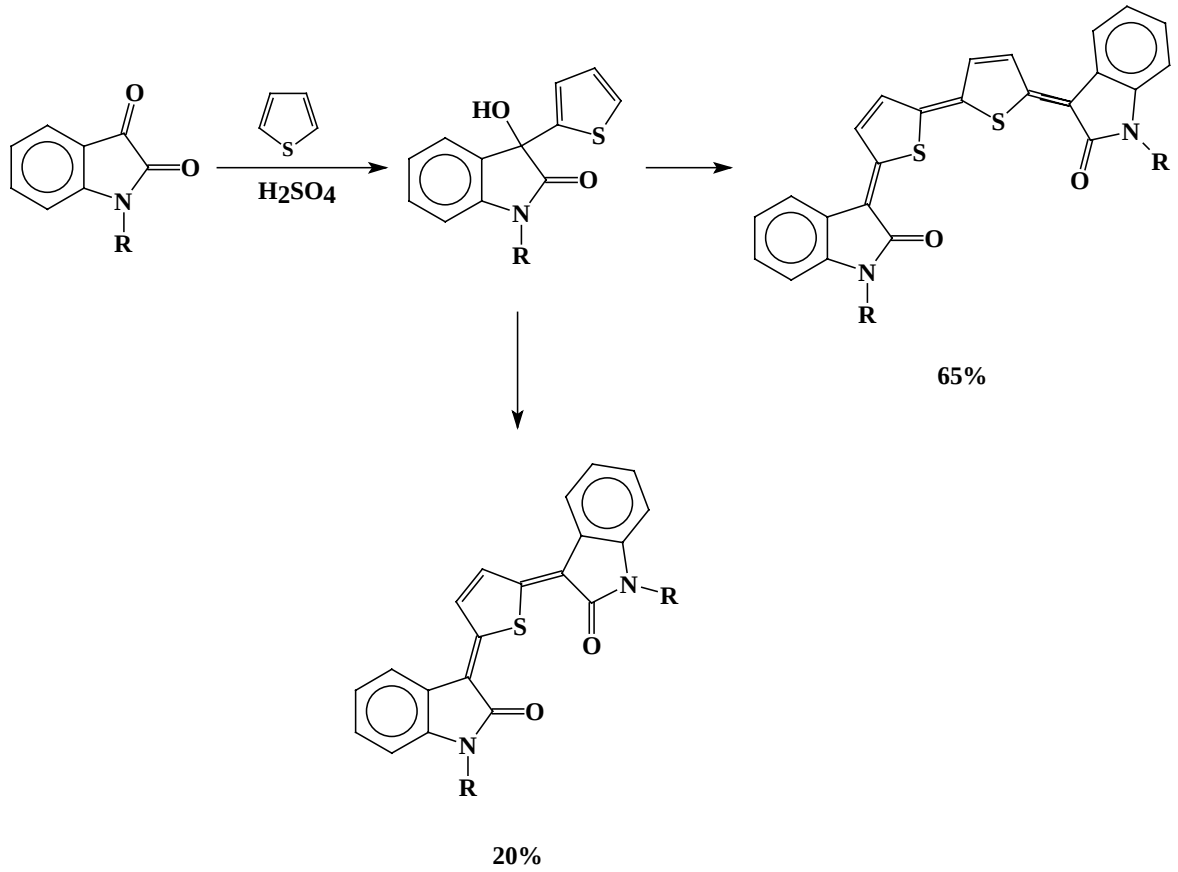
The condensation of 1-methylisatin with 1-methylindole in an acidic medium led to a 3,3-*bis*indolyloxindole, which after reduction to an indoline and oxidative rearrangement with DDQ, furnished a *tris*-indolobenzene[447] (Scheme 107).



Scheme 107

The reactions of isatin and thiophene or 2,2'-bithiophene proceed similarly to those of indoles. However, in these cases mixtures of oligomeric products were obtained[448]. This reaction has been applied to the synthesis of electrically conducting polymers[449].

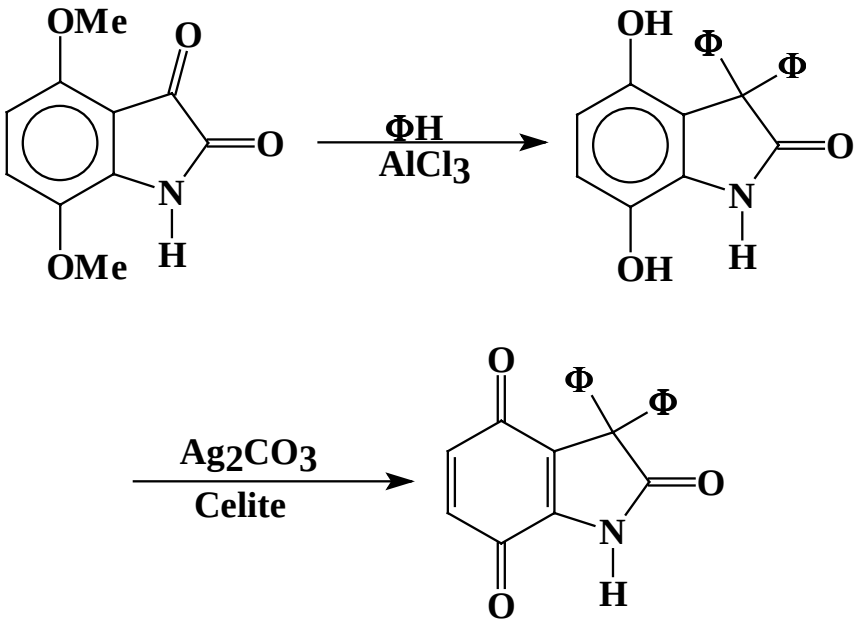
Under acidic catalysis, isatin condenses with thiophene or pyrrole to give indophenine dyes. These compounds are formed as a mixture of geometric isomers[450], and may possess one or two thiophene units; the latter being the major product[451] (Scheme 108).



Scheme 108

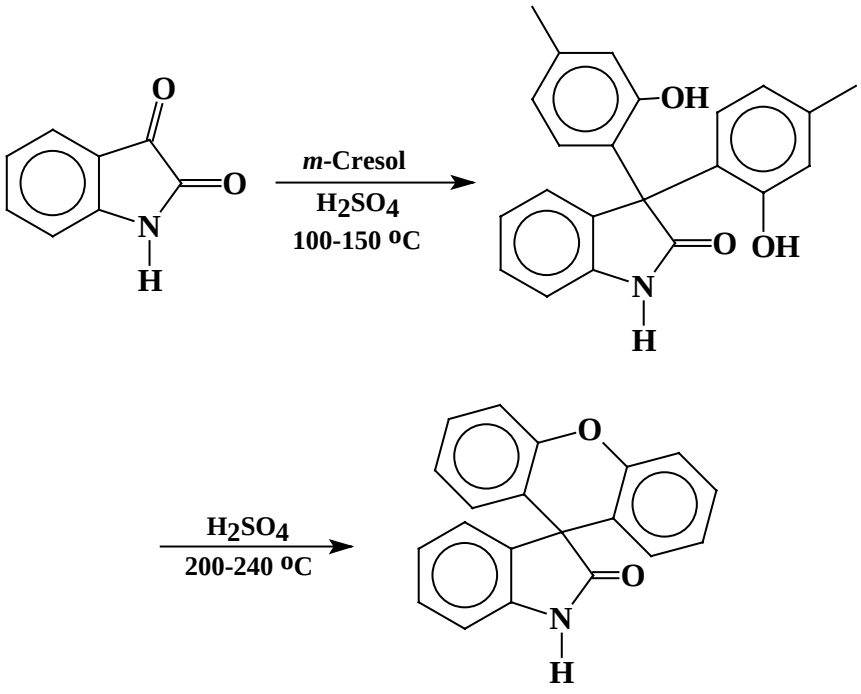
Isatin reacts with benzene and phenol under typical Friedel-Crafts conditions[452,453]. The corresponding 3,3-diaryloxindoles are obtained in high yields[454] and their laxative properties have been studied[455]. Very high yields, up to 99%, are obtained when this reaction is performed using a combination of trifluromethanesulfonic and trifluoroacetic acids; this methodology enabled the preparation of libraries of 3,3-diaryloxindoles by using mixtures of aromatic compounds[456].

Dimethoxyisatins can be converted into 3,3-diaryloxindole quinones in two steps, by Friedel-Crafts reaction and subsequent oxidation with silver carbonate[457] (Scheme 109).



Scheme 109

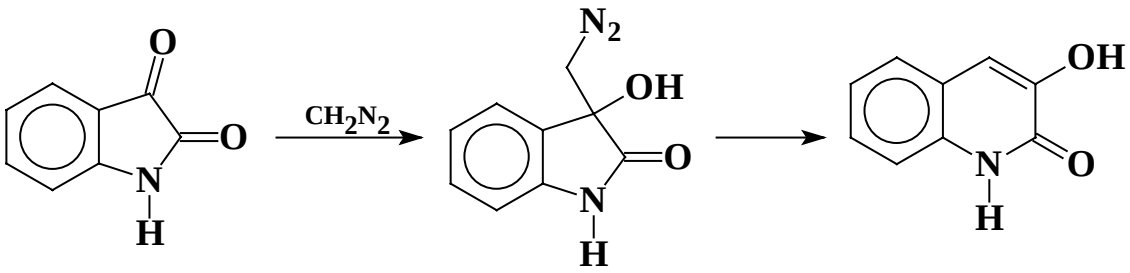
When isatins are used in the Friedel-Crafts alkylation of *m*-cresol in an acidic medium at high temperature, the adduct formed suffers dehydration, furnishing a *spiro* dibenzopyran derivative[458] (Scheme 110).



Scheme 110

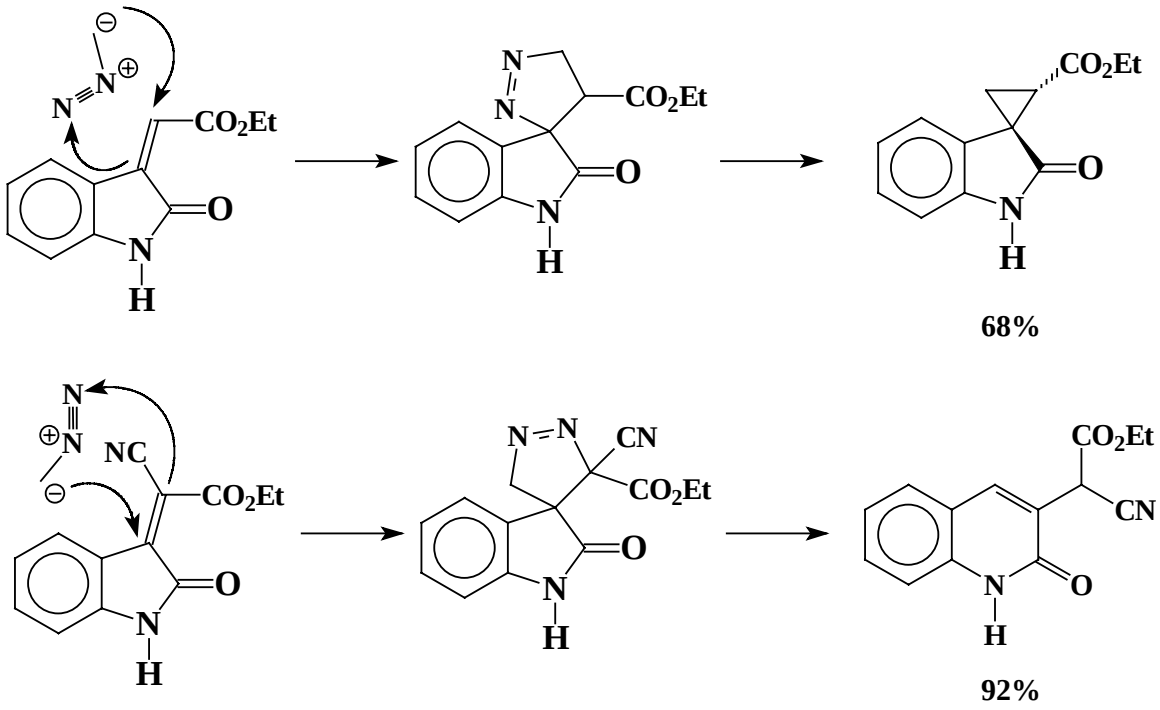
3,3-Diaryloxindoles have been used as precursors for the synthesis of thermoplastic carbonates[459].

Diazoalkanes, such as diazomethane[460] and diazoarylalkanes[461,462] add to isatin at the C-3 position, leading to a carbinol that suffers a ring expansion to give the corresponding quinolone[463] (Scheme 111).



Scheme 111

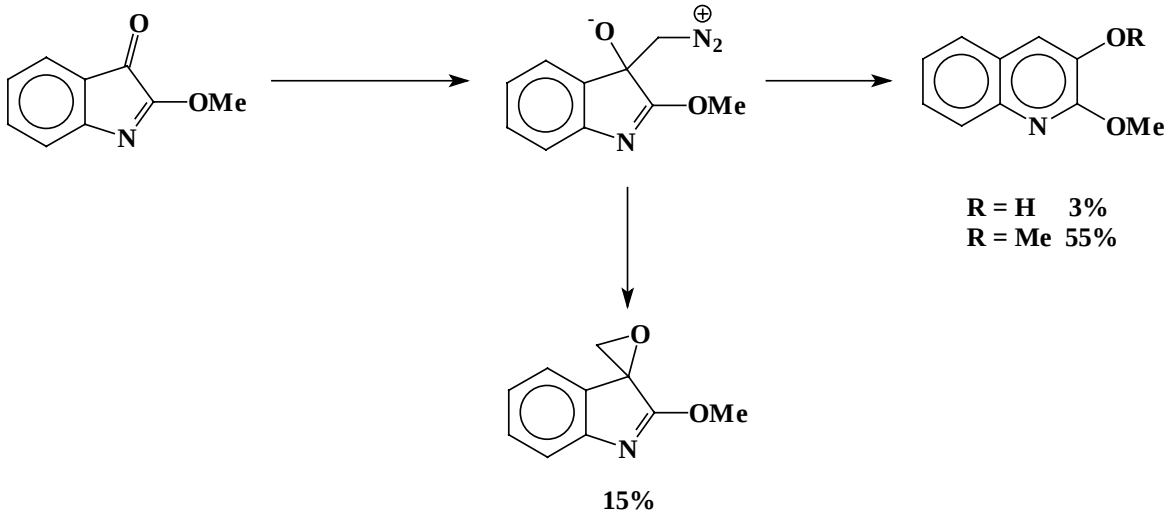
Oxindolylacrylates react with diazomethane in a regioselective manner, depending on the substituent attached to the carbon atom α to the ester carbonyl group. In non-substituted acrylates, the 1,3-dipolar cycloaddition occurs furnishing a pyrazoline which, upon heating, losses N_2 to give a *spiro* cyclopropane derivative[464,465]. If α-cyanoacrylates are used, the cyano group reverses the polarization of the C-C double bond, and the diazomethane addition involves initial C-C bond formation β to the ester. The adduct loses N_2, furnishing a quinolone[465] (Scheme 112).



Scheme 112

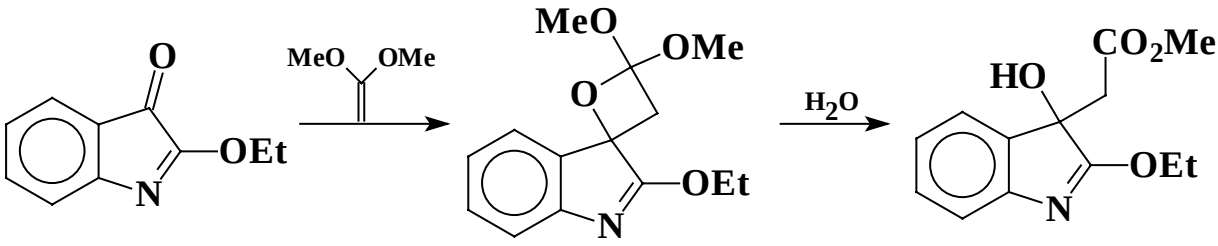
The same reaction when carried out in the presence of triethylamine gives a furoquinoline derivative[466].

The O-methylether of isatin reacts with diazomethane to furnish a quinoline derivative as the major product, together with a *spiro*oxirane derivative[467] (Scheme 113).



Scheme 113

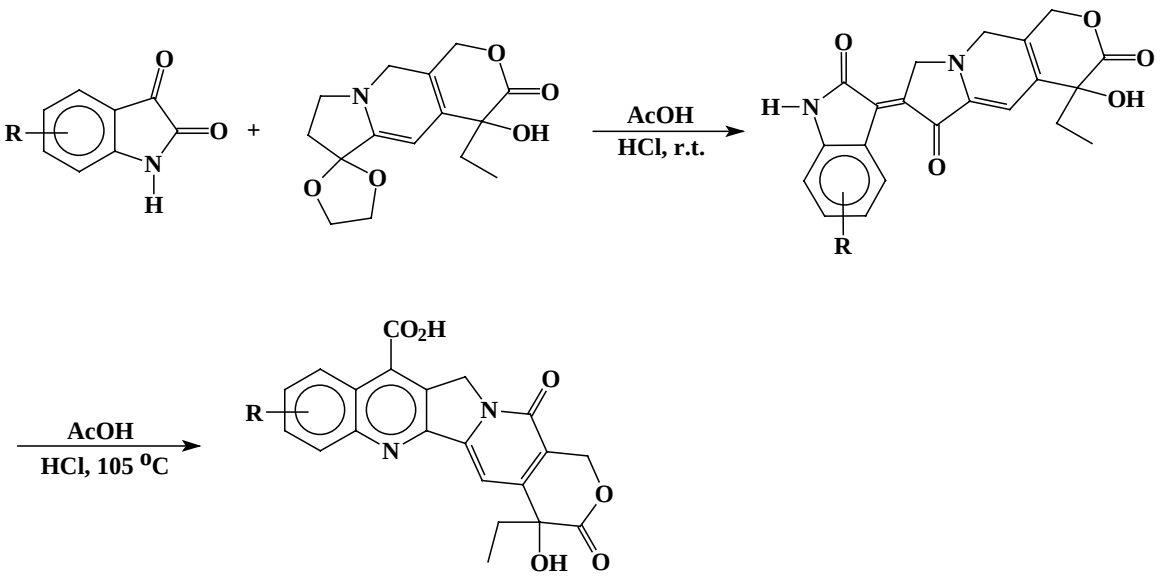
2-Ethoxy-3-indolone suffers a thermal [2+2] cycloaddition with 1,1-dimethoxyethene, leading to an oxetane that is hydrolyzed to an indoleninylacetate in 40% yield[468] (Scheme 114).



Scheme 114

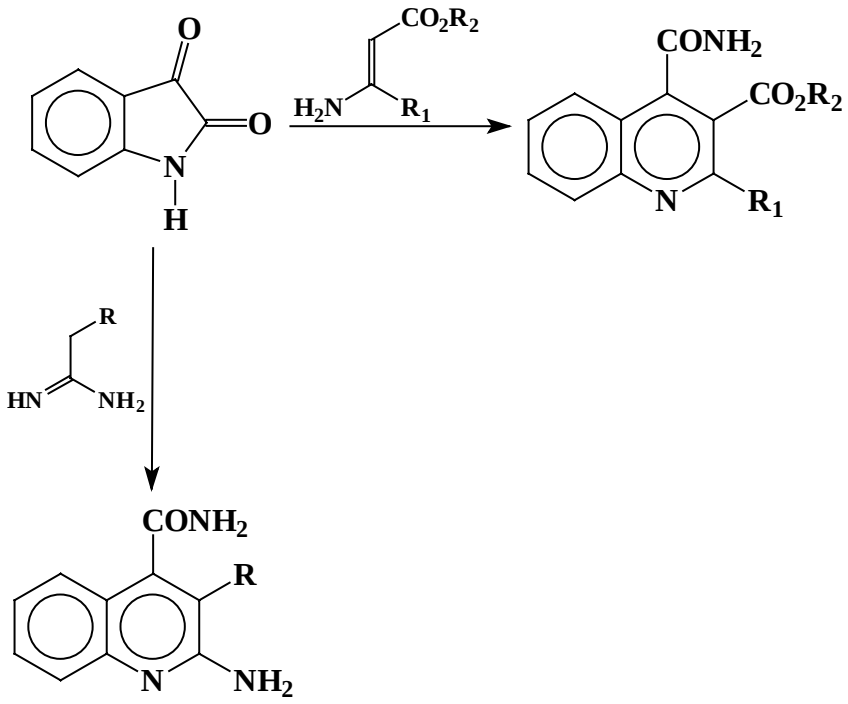
2-Oxoindolin-3-ylidene derivatives, which are prepared by Knoevenagel condensations of reactive methylene compounds with isatin, can readily undergo a variety of cyclization reactions with ethyl vinyl ether or with enamines giving rise to a variety of heterocyclic systems[469,470]. These compounds also readily undergo Diels-Alder reactions with cyclopentadiene giving a mixture of two diastereoisomers[471] and with unsymmetrical butadienes[472,473] or with isoprene[474]. 2-Oxoindolin-3-ylidene derivatives undergo cycloaddition with phenylnitrile oxide to yield the corresponding oxazoles[464].

Isatinates, obtained from the alkaline hydrolysis of isatin derivatives, are the precursors of the quinoline-4-carboxylic acids. These compounds are prepared by the Pfitzinger reaction from isatins in the presence of enolizable keto compounds in strongly alkaline medium, such as 8N KOH. In these solutions, isatinates condense with the keto compound and subsequently cyclize to the quinoline products. Recently, a modified procedure has been described, using acidic conditions[22]. This methodology was subsequently applied to a concise manner for the preparation of derivatives of camptothecin, a topoisomerase I inhibitor[23] (Scheme 115).



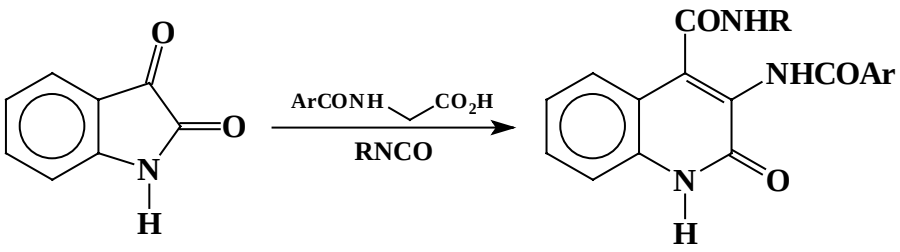
Scheme 115

The Pftzinger reaction has been carried out with aliphatic ketones[475], including acetone[476], acetophenones and homologues[477,478], chalcones[479], and α-acyloxyacetophenones, leading in the last case to 3-hydroxyquinoline-4-carboxylic acids[480]; heteroaromatic ketones, such as 2-acetylphenothiazine[481], acid chlorides[482] and anhydrides[483], furnishing 2-hydroxy-4-quinoline carboxylic acids; hydrazides[484]; enaminones, furnishing 4-carboxamido-quinoline-3-carboxylates, and with imidines, leading to 2-aminoquinoline-4-carboxamides[485] (Scheme 116);



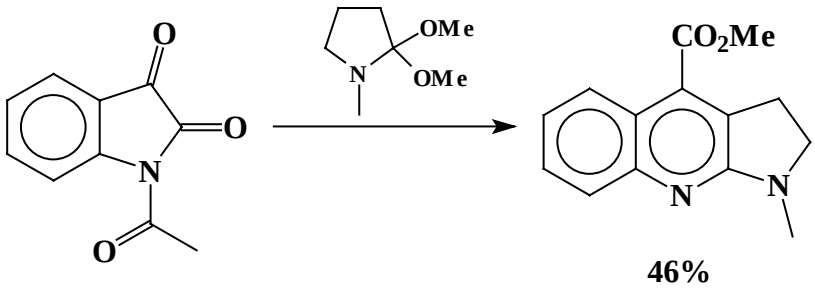
Scheme 116

acylaminoacids and isocyanates to yield 3-acylamino-2-oxo-1,2-dihydroquinoline-4-carboxamides[486] (Scheme 117);



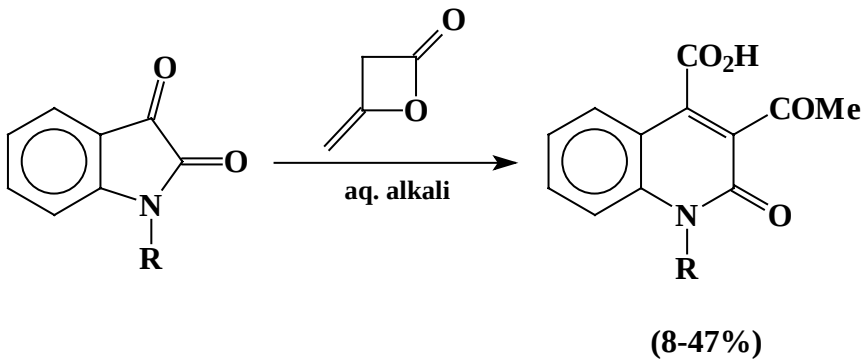
Scheme 117

lactam acetals to furnish dihydropyrroloquinolines[444] (Scheme 118);



Scheme 118

and diketene to yield 2-quinolones[487] (Scheme 119).

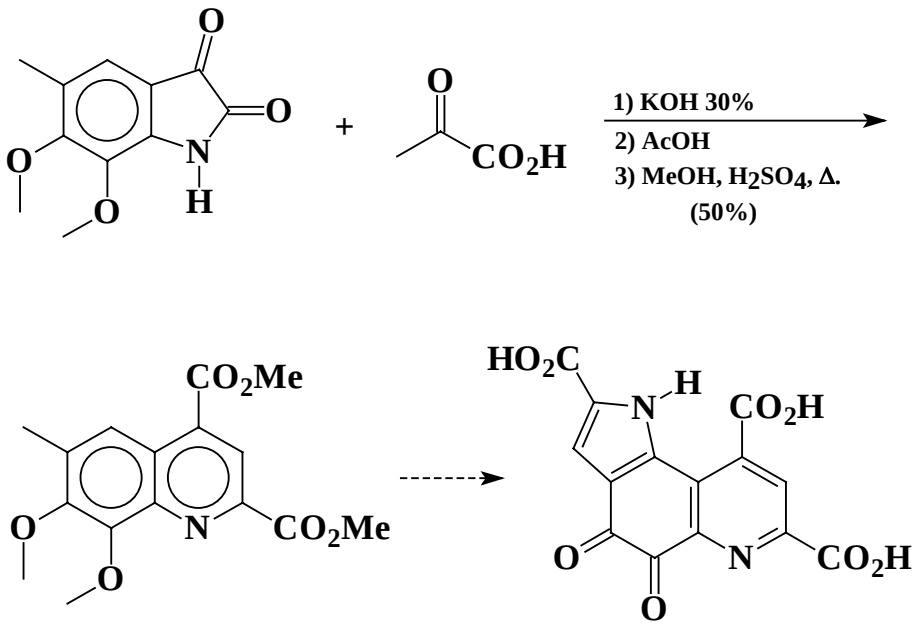


(8-47%)

Scheme 119

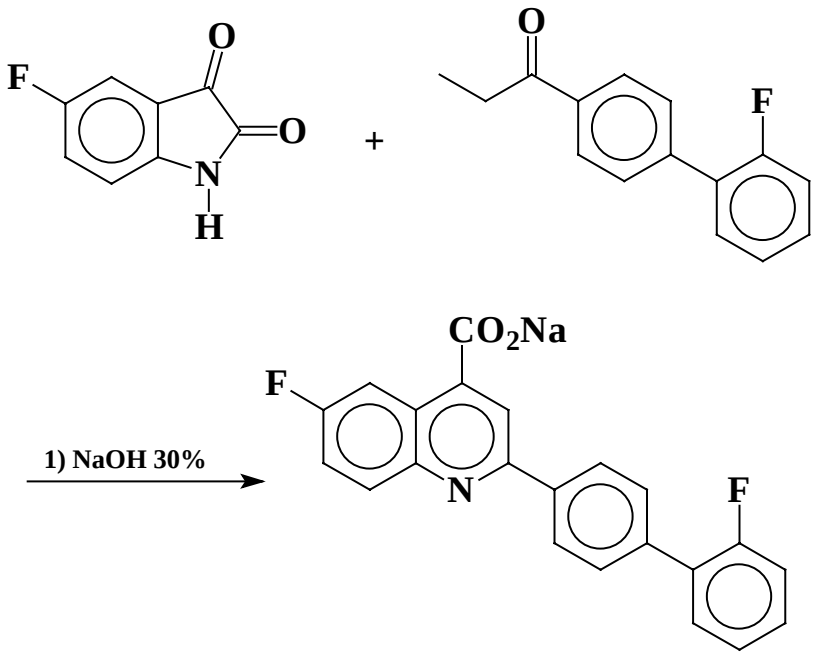
The use of ammonium hydroxide as base furnishes 4-quinolinecarboxamides[488], which when subjected to Hoffmann degradation conditions produce 4-aminoquinolines[489]. 4-Cyanoquinolines are produced when the corresponding acids are treated with 4-toluenesulfonamide and $POCl_3$[490].

The Pfitzinger reaction has been used in the synthesis of methoxatine, a coenzyme of the bacterial enzyme alcohol dehydrogenase[491,492] (Scheme 120) and of DuP 785, an anticancer agent[493] (Scheme 121).



Methoxatine

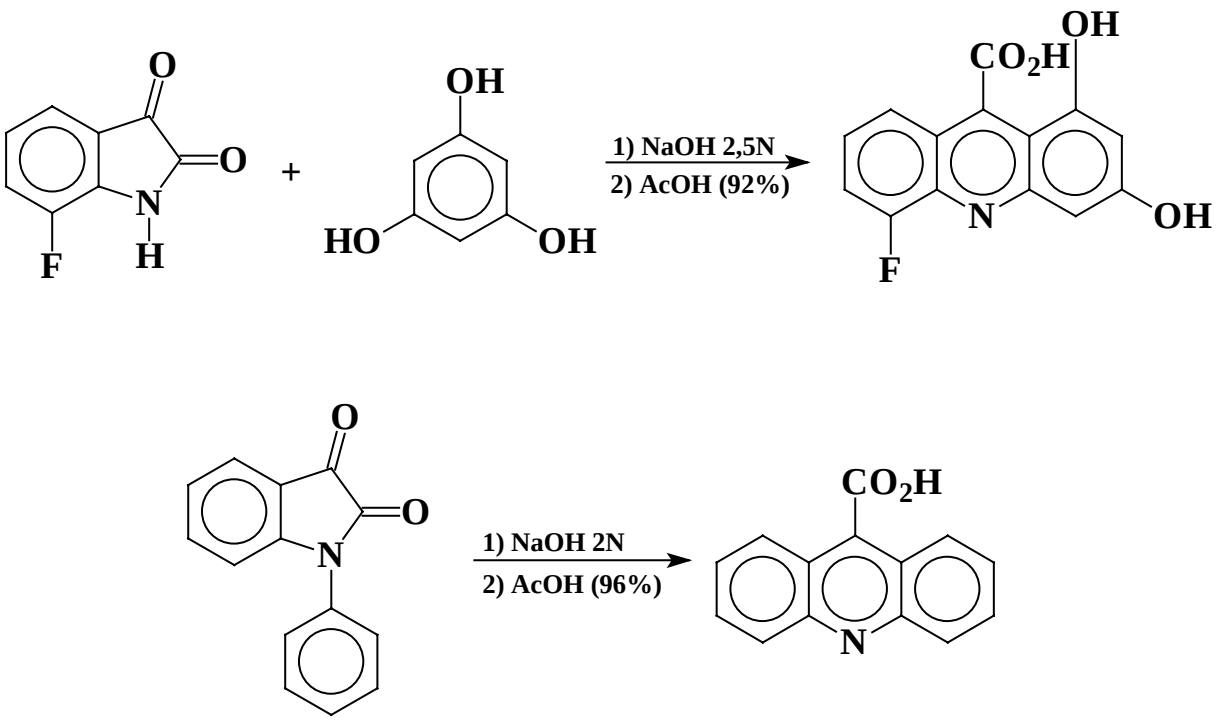
Scheme 120



DuP 785

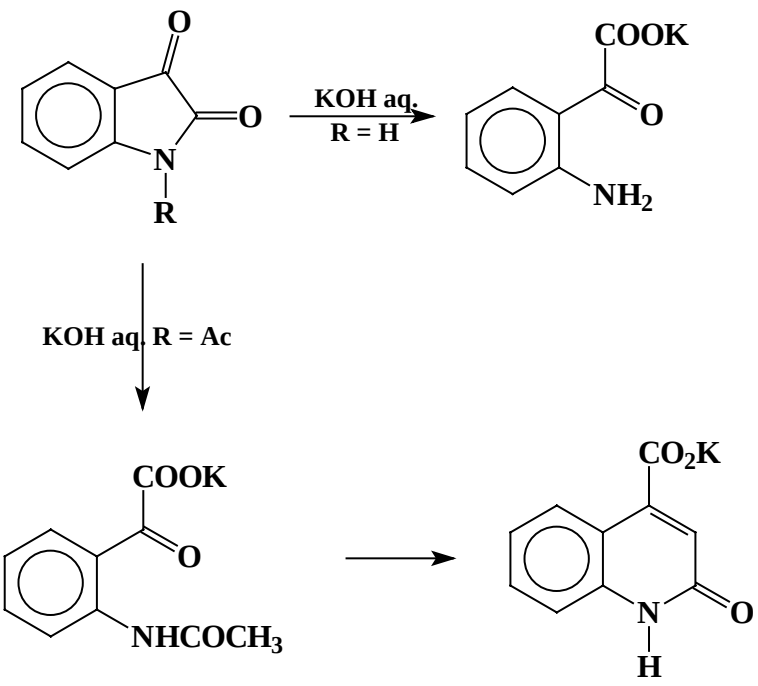
Scheme 121

In a similar manner, the use of phenols[494] or dihydronaphthalenones[495] yield acridines, which are also obtained from the treatment of *N*-phenylisatin with aqueous sodium hydroxide[496] (Scheme 122).



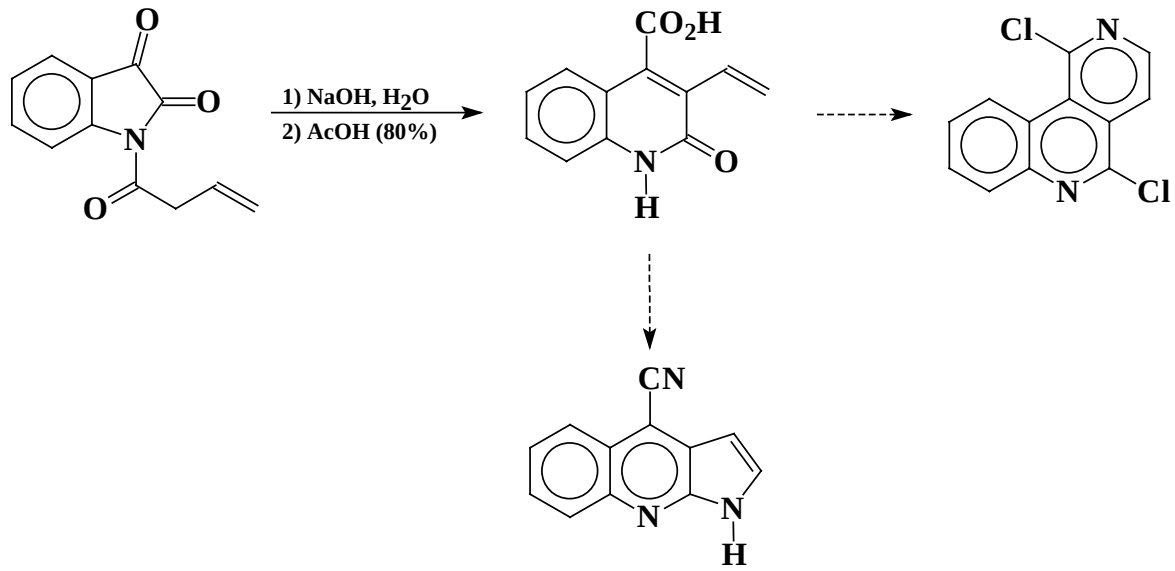
Scheme 122

1-Acylisatin, bearing at least one hydrogen atom at the α position of the acyl group, also furnishes an isatinate, but it reacts with a second equivalent of hydroxide, leading to 3,4-disubstituted -2-quinolones. This heterocyclic system is also formed by treatment of 1-acylisatins with alkoxide solutions[497] (Scheme 123).



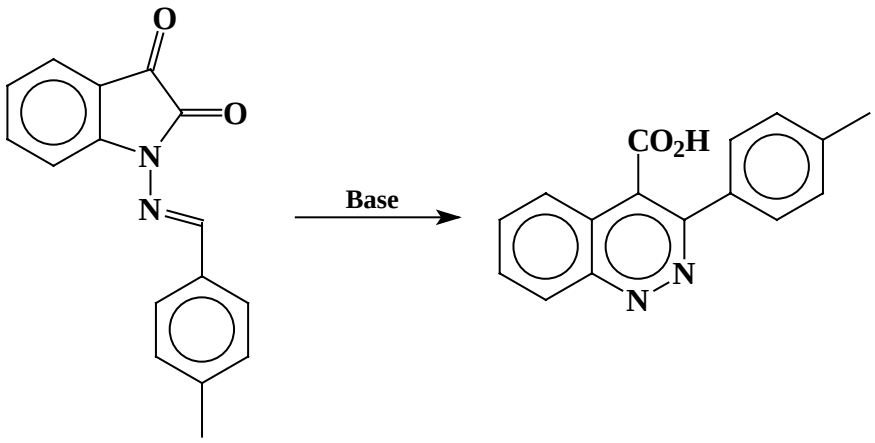
Scheme 123

The use of N-acylisatins for the construction of quinolones has been applied to the synthesis of pyridoquinolines[498] and pyrroloquinolines[499] (Scheme 124).



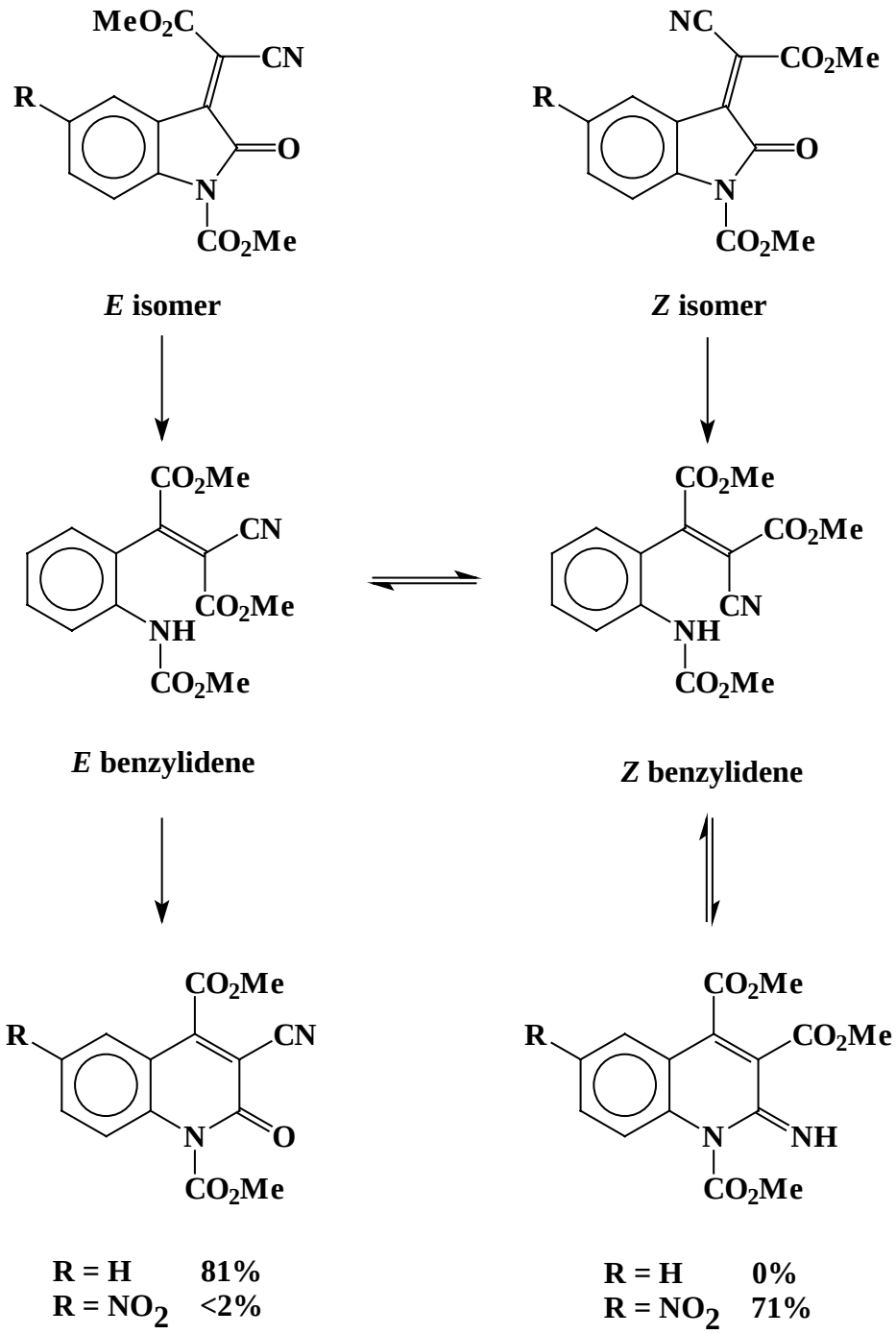
Scheme 124

In a similar procedure, 1-iminobenzylideneisatins furnish cinnoline derivatives[500] (Scheme 125):



Scheme 125

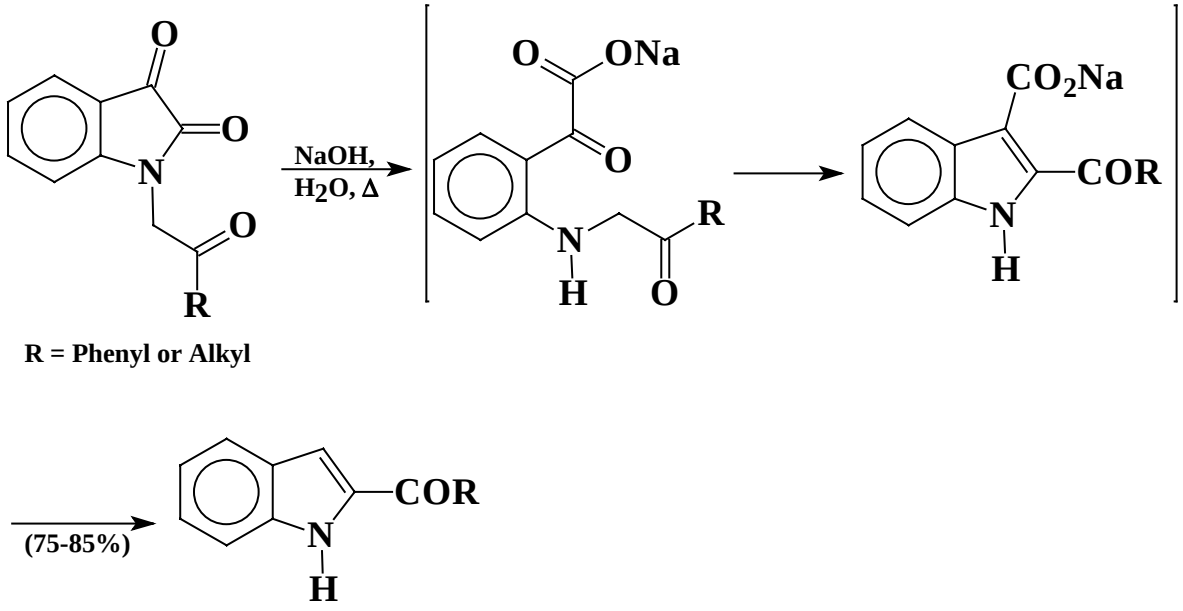
3-Dicyanomethyleneoxindoles undergo base catalysed alcoholysis to yield the respective 2-aminoquinolines[501]. 3-Methyleneoxindoles also suffer ring expansion to quinolones. Mechanistic studies, based on ^{1}H NMR data, show that isomeric methyleneoxindoles lead to the same products through a nucleophilic ring opening step and a subsequent *Z*-*E* interconversion step of the benzylidene intermediates. Due to steric repulsions the *Z* isomer is more stable, but as the cyclization step from the *E* isomer is irreversible the equilibrium is shifted towards this isomer. The presence of electron-withdrawing groups bonded to the aromatic nucleus shifts the equilibrium in the direction of the *Z* isomer due to a decrease in the nucleophilicity of the carbamoyl nitrogen atom, and thus favors the cyclization product that results from the *Z* isomer[502] (Scheme 126).



Scheme 126

When the alkaline hydrolysis is performed with *N*-phenacyl[503] or *N*-acetonylisatins[504,505], 2-substituted indoles are obtained after spontaneous decarboxylation of the resultant 2-acylindole-3-carboxylic acid . The mechanism of this reaction probably involves a ring opening reaction, followed by cyclization through a Knovenagel-like condensation[506], but a very complex mechanism has also been proposed[507]. This methodology

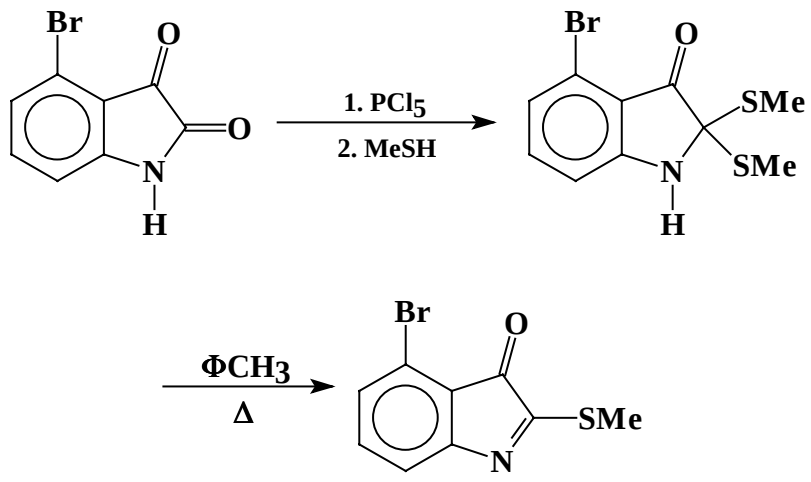
has many advantages over others previously described for the obtention of these indolic derivatives, due to the readily available raw materials (Scheme 127).



Scheme 127

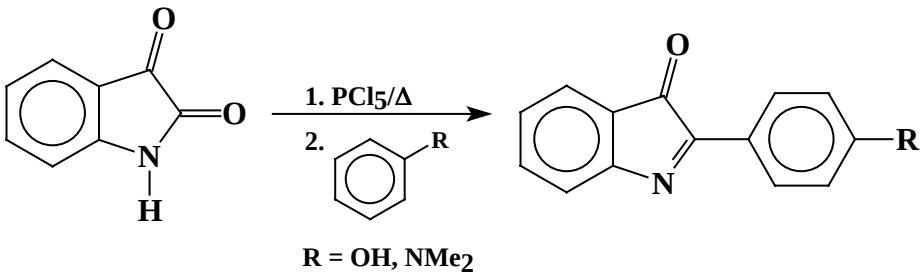
4.3. 4 - Halogen nucleophiles

The reaction of isatin with phosphorous pentachloride led to 3,3-dichlorooxindole when the reaction was carried out in benzene at room temperature. This intermediate has been used in the synthesis of oxindoles substituted at position 3 by reaction with a diverse range of nucleophiles such as KSCN, amines and thiols[508]. When the reaction was performed with boiling benzene, a red crystalline product was obtained. This compound was originally characterized as 2-chloro-3H-indol-3-one based not on spectral data but on its reactivity. For example, 4-bromoisatin, after reaction with PCl_5 in toluene under reflux for eight hours was treated with methanethiol to furnish the corresponding 2,2-thioketal, which was decomposed to 4-bromo-2-methylthio-indolin-3-one[509] (Scheme 128).



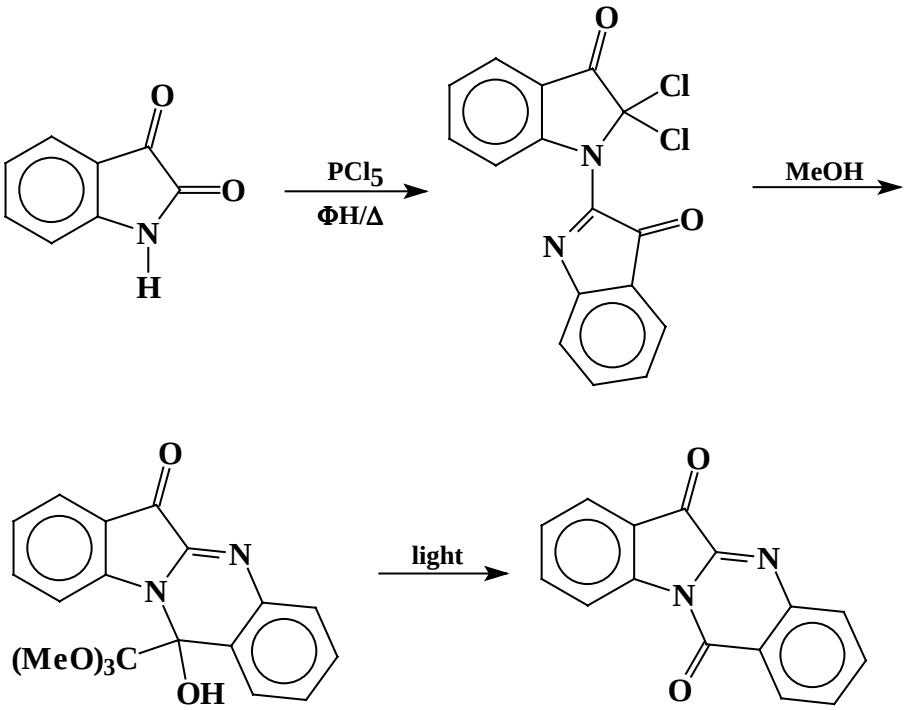
Scheme 128

The putative 2-chloro-3H-indol-3-one was also reacted with phenols[510] and N,N-dimethylaniline[511] to give dyestuffs (Scheme 129).



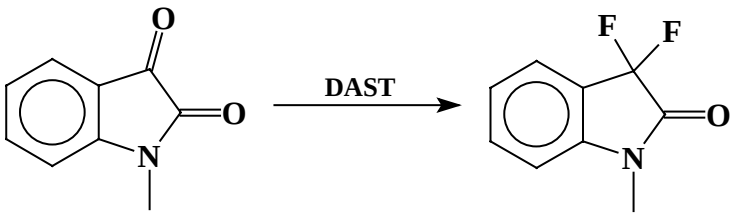
Scheme 129

On the other hand, the reaction of this chloride with anilines always led to isatin-3-imines. In an attempt to rationalize these contradictory results, it was proposed that 2-chloro-3H-indol-3-one was the substrate but that this compound, which reacts with nucleophiles at the C-2 position, readily hydrolyzed in solvents containing water, thus yielding isatin and products resulting from attack at C-3[512]. Sir John Cornforth revisited the chemistry of this compound recently, and elucidated the structure as being 2-(2,2-dichloro-2,3-dihydro-3-oxoindol-1-yl)-3H-indol-3-one based upon ^{1}H, ^{13}C n.m.r. and X-ray crystallographic analysis. The same authors used this compound to synthesize an indoloquinazoline structurally related to the alkaloid tryptanthrin[513] (Scheme 130).



Scheme 130

1-Methylisatin reacts with diethylaminosulfur trifluoride (DAST) to furnish 1-methyl-3,3-difluorooxindol in 95% yield[514]. This methodology has been subsequently modified and extended to the synthesis of numerous other 3,3-difluorooxindole derivatives[130,515] (Scheme 131).

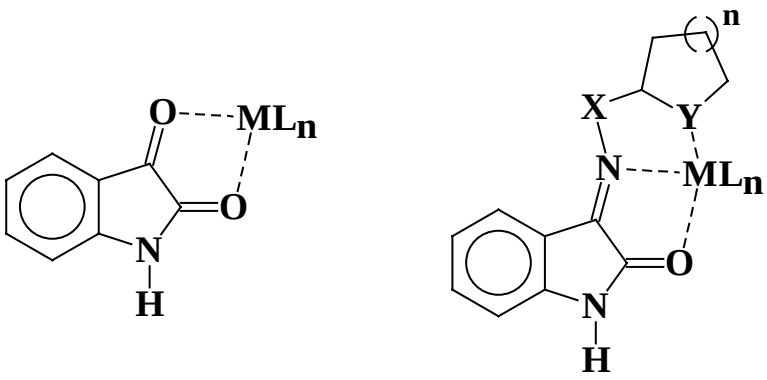


Scheme 131

5 - Metal complexes

Isatin, due to its *cis* α-dicarbonyl moiety, is a potentially good substrate for the synthesis of metal complexes, either alone or with other ligands. Their derivatives, mostly those substituted at C-3, such as isatin-3-hydrazones and isatin-3-imines bearing an extra heteroaromatic ring are also generally employed as ligands. In this manner, Schiff bases

formed from isatin and amino silica gel are useful sorbents for divalent cations and for Fe (III)[516] (Scheme 132).



Scheme 131

Due to its ability to bind ferric ions, isatin-3-thiosemicarbazone can be used to form magneto-polymer composites with poly (vinyl chloride)[517].

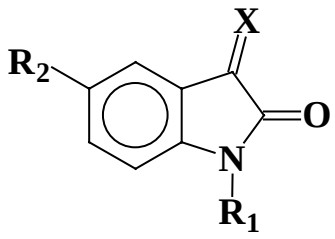
An extensive list of metal complexes can be found in the Supplementary Material 3.

6. Crystallographic and spectral analysis

6.1 - Crystallographic data

The crystallographic data for isatin reveals that it is almost planar, with a bond length between the two carbonyls of 1.55 Å. This large value was attributed to lone pair electron repulsion between the two oxygen atoms[518,519], though this interpretation was subsequently refuted by comparison of bond lengths of *cis* and *trans* 1,2-diketones where no systematic or substantial difference between the bond lengths was observed[520]. A similar bond length was observed for 1-acetylisatin[521], 1-α-chloroacetylisatin[522], diethyl (2,3-dihydro-2-oxo-3-indolylidene)propanedioate[523], 1,1'-oxalylbisisatin[524] and 1-methylisatin[525], as well as in derivatives where C-3 is tetrahedral, such as 3,3-dichloro-1H-indol-2(3H)-one[526] and 5'-bromospiro-[1,3-dioxolano-2,3-indolin]-2'-one[527], as well as in 3-methyleneoxindoles[528] (Table 1) and in products obtained by nucleophilic ring opening of 1-acetylisatin, where the 1,2-dicarbonyl system assumes a *s-trans* conformation[529]. The crystal structure of 2-methoxyisonitrosoacetanilide, an intermediate in the Sandmeyer procedure for the synthesis of 7-methoxyisatin has also been determined[530].

Table 1



X	R_1	R_2	C_2-C_3
O	H	H	1.55
O	Ac	H	1.538
O	Me	H	1.545
Cl, Cl	H	H	1.556
OCH_2CH_2O	H	Br	1.539
$CHCH=C(CH_3)_2$	H	H	1.508

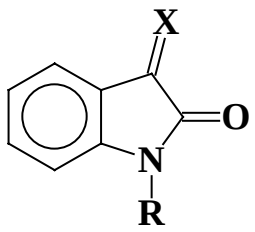
6.2 - Infrared spectroscopy

The infrared spectrum of isatin shows two strong bands at 1740 and 1620 cm^{-1} corresponding to the carbonyl stretching vibrations. A broad band occurs at 3190 cm^{-1} due to the *N*-H stretching, and it is accompanied by many sub-bands, all of which are moved to a lower frequency on deuteration, which also affects several bands in the region of 1400-1100 cm^{-1}, associated with *N*-H in-plane bending[531,532]. Although the νC=O values are not modified by *N*-alkylation, *N*-acetylation leads to a hypsochromic shift of the lactam absorption of about 50-70 cm^{-1}, while the ketone band shifts to 1750 cm^{-1}, as a consequence of the extension of conjugation of the nitrogen lone pair with the acetyl group[100]. On the other hand, 3-methyleneoxindoles show a bathochromic shift for the lactam band of around 20 to 30 cm^{-1}, this shift being greater when there are groups at the C-3 position, such as OH, which can form a hydrogen bond with the lactam carbonyl. In this case, νC=O appears at 1660 cm^{-1} [438]. 3,3-Difluorooxindoles reveal a hypsochromic shift of about 20 cm^{-1} in comparison to the respective isatin[514].

6.3 - ^{1}H NMR spectroscopy

The ^{1}H NMR spectrum of isatin shows the signals of the aromatic nucleus signals at 6.86 (doublet), 7.00 (triplet), 7.47 (doublet) and 7.53 (triplet) ppm (DMSO-d_6), corresponding to H-7, H-5, H-4 and H-6 respectively. While *N*-alkylation does not alter this pattern, *N*-acetylation leads to a downfield shift of all the signals, but most significantly of H-7 due to the anisotropic effect of the carbonyl group. In a similar fashion, 3-methyleneoxindoles bearing cyano groups reveal a downfield shift of H-4 by about 0.6-1.0 ppm, with no significant effect over the other signals[533,534] (Table 2).

Table 2[533]



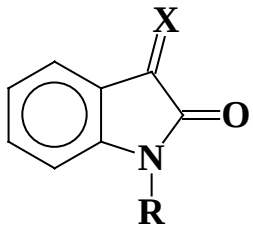
X	R	H-4	H-5	H-6	H-7	CH_3CO	Solvent
O	H	7.50d	7.07t	7.60t	6.92d	-	DMSO-d_6
O	Me	7.59d	7.12t	7.61t	6.91t	-	DMSO-d_6
O	Ac	7.27d	7.33t	7.70t	8.38d	2.73s	DMSO-d_6
$C(CN)_2$	H	7.87d	7.12t	7.59t	6.94d	-	DMSO-d_6

6.4 - ^{13}C NMR spectroscopy

The ^{13}C NMR spectrum of isatin was the object of controversy in the literature. Different proposals for assignment of the signals have been published[42,535,536,537]. This question was resolved by the obtention of the HETCOR spectrum, which revealed that the assignment proposed by Galasso, based on quantum mechanical calculations using the

CNDO/S wave functions, was correct[536]. This result allowed the correction of the assignments of the spectra of 1-acetylisatin[538,539,540] and of 1-methylisatin and 3-dicyanomethyleneoxindole[512,502]. Again, acetylation of *N*-1 implies an important change in the pattern of the spectra, with a deshielding effect over C-7[538] (Table 3).

Table 3

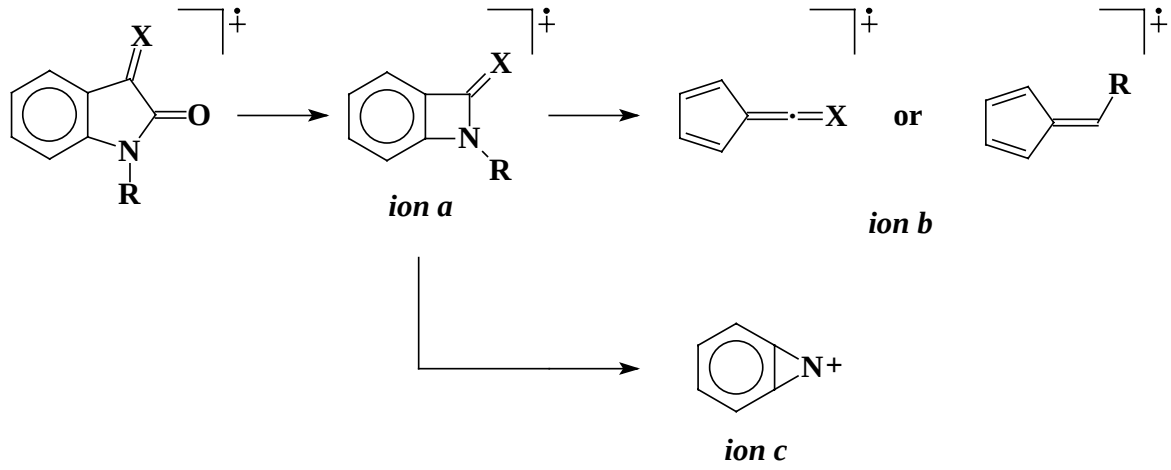


X	O	O	O	$C(CN)_2$
R	H	Ac	Me	H
C-2	159.6	157.8	158.1	163.6
C-3	184.6	180.1	183.2	146.4
C-3a	118.0	119.1	117.2	137.8
C-4	124.8	126.1	125.0	122.9
C-5	123.0	125.2	123.7	118.5
C-6	138.6	138.6	138.4	125.7
C-7	112.4	118.1	109.9	111.6
C-7a	150.9	148.5	151.3	150.4
Reference	536	538	512	512

6.5 - Mass spectrometry

The electron-impact mass spectra of isatin[542], 1-alkylisatins[543] and derivatives, such as hydrazones[544], usually show an intense molecular ion peak. In the case of 3,3-dissubstituted oxindoles[545], the base peak corresponds to the loss of the substituents at C-3. A peak corresponding to the loss of CO (ion *a*) can also be observed, whose intensity decreases with

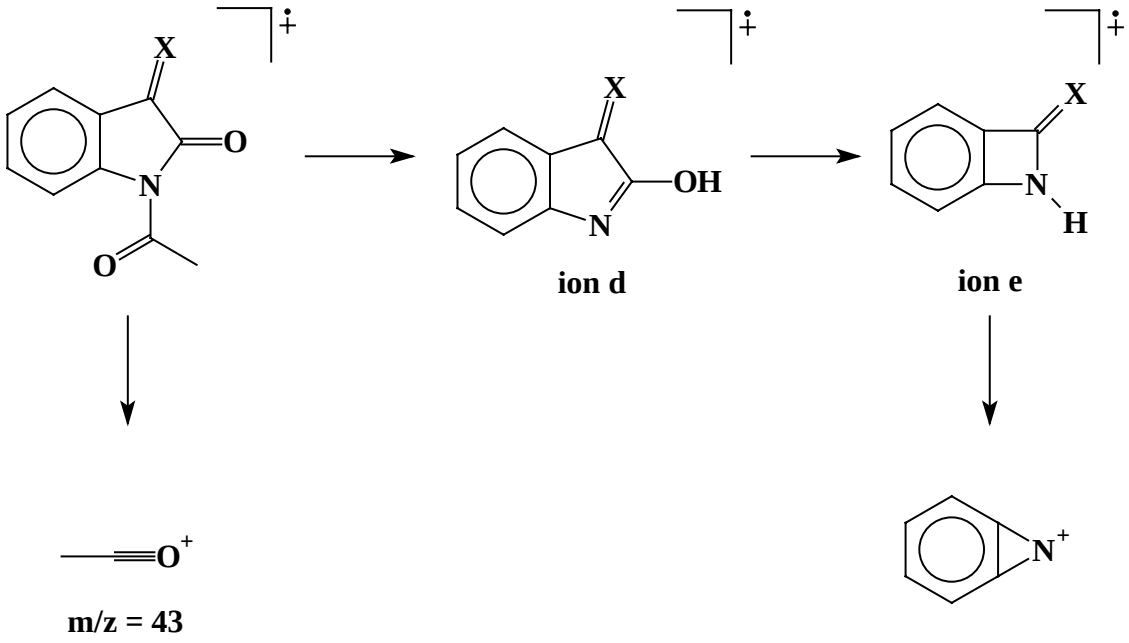
the increase in size of the alkyl chain of 1-alkylisatins[546]. Ion *a* usually looses HCN, leading to a fulvene ion (ion *b*). An arene aziridine is also observed (ion *c*), which arises from a second loss of CO[547-549]. The ions *b* and *c* are also observed in the gas-phase pyrolysis of isatin[550]. In a general manner, the mass spectra of 3-substituted isatins show a sequential loss of neutral molecules[551] (Scheme 133).



Scheme 133

A different pattern is observed in the mass spectra of isatin-3-oximes, where a peak corresponding to the loss of CO is not found; this is attributed to a Beckmann rearrangement of the molecular ion leading to a heterocyclic ring opened ion[552].

In the case of the acetylated derivatives, the molecular ion is usually of low intensity. The fragmentation pattern includes loss of ketene (ion d) and of CO (ion e) (Scheme 134).



Scheme 134

66 - ^{14}N NQR

The ^{14}N nuclear quadrupole resonance of isatins and derivatives have been thoroughly studied as this method can furnish important information with respect to the electronic distribution around the nitrogen atom. The results obtained confirmed the existence of H bonds between isatin molecules in the solid state[553], and showed a linear relationship between the depletion of charge of the C-N bonds and the electron withdrawing character of the substituents attached to the aromatic nucleus, as represented by the inductive Taft parameter[554]. The results also revealed that the lone pair of electrons of the nitrogen atom is involved in conjugation with the aromatic ring[555].

6.7 - Further spectroscopic data

The eletronic absoption spectra of isatin[556,557,558], isatin-3-arylhydrazones[559], isatin and 1-methylisatin anion radicals[560] were studied and correlated with theoretical calculations with

good results. The electron spin resonance spectra of the isatin anion radical was also recorded and revealed that the monoanion radical exists in equilibrium with the dianion radical in the solvents employed[560]. DSC thermograms of some alkylisatins were also recorded[561].

7. Technological applications

7.1 - Organic analytical chemistry

Isatin is known to be a colour reagent for the aminoacid proline, forming a blue derivative[562]. This property has been exploited for the determination of the level of this aminoacid in pollens[563,564,565,566] and other vegetal materials[567] using paper chromatography, or for the detection of polymer bound compounds possessing proline residues[568]. It has also been used in a colourimetric screening test for human serum hyperprolinemia[569], in a colourimetric assay of HIV-1 proteinase[570] and for the estimation of the age of bones in crime investigations[571].

As isatin produces a fluorogenic derivative when reacted with tryptophan, it has been used for the detection of this aminoacid by thin layer chromatography[572,573]. It is also useful for the detection of 3,4-dehydroproline, which is oxidized by isatin and further reacted with *p*-dimethylaminobenzaldehyde to give a coloured derivative[574].

In a similar manner, isatin-3-hydrazone has been studied for the colourimetric determination of steroids[575,576], including deoxycorticosterone[577]. A further application of isatin in steroid analysis is its use as a coloured marker in the Sephadex LH-20 chromatographic separation of steroidal blood components[580,581].

1-Chloromethylisatin has been used as a derivatizing agent for alcohols[582], small chain[583] and fatty carboxylic acids[584], amines, including indole[585], and compounds containing acidic C-H bonds[586] for their analysis by RP-HPLC or TLC.

Isatin has been used in the determination of the enzymatic activity of ketopantoyl-lactone reductase[587-590] and other fungal carbonyl reductases[591-594], as it is a substrate of these enzymes that is reduced to a dioxindole in a reaction that can be monitored by colourimetry. Ketopantoyl-lactone reductase, also named as isatin hydrolase, can be used to remove unwanted isatin from the broth of the microbial production of indigo[595,596].

Isatin serves as a substrate for the biosynthesis of violacein, a trypanocide agent, by *Chromobacterium violaceum*[597].

7.2 - Pigments and dyes

Isatins, associated with other amino heterocycles, can be used for hair dyes[598-616], while azo*bis*isatins have been thoroughly studied as dyes for plastic materials[617]. 3-Methyleneoxindoles derived from isatins bearing a benzimidazole ring[618], as well as thioindigoid thiazolidines[619], have also been used for dyeing synthetic and natural fibers (Figure 2).

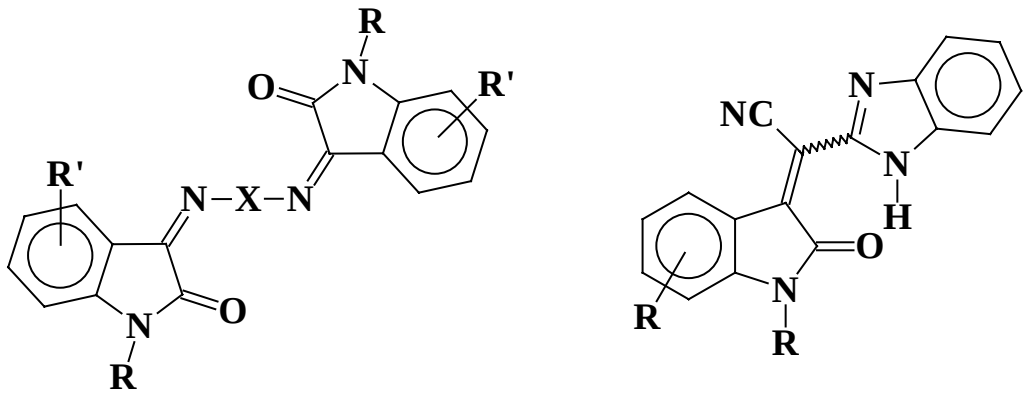


Figure 2

7.3 - Miscellaneous applications

Isatins and derivatives have been used in the development of colour photographic recording materials[620-622], of blood coagulation promoters[623-626], of liquid crystal components for display devices[627-629] and in the inhibition of corrosion of aluminum[630] and Fe-Ni alloys[631] and of iron[632].

Isatin can be used as a photosensitizer, together with a photoinitiator, for methacrylate[633,634] and epoxysilicone[635] polymerization. It is also used for the synthesis of branched polycarbonate resins, improving the moldability of this polymer[636].

The reaction of isatin with thiophene in an acidic medium, containing ferrous ion, gives rise to an intense violet color, due to the formation of indophenine dyes. Due to this phenomenon, it was proposed that isatin could be used as a revealing agent for the presence of thiophene in water-soluble organic solvents where it is used as a denaturating agent[637].

The lithium and thallium (I) salts of isatin-3-oxime (isatin oximates) were employed in the development of ion-selective electrodes for these cations[638]. Transition metal complexes of isatin derivatives can also be employed as catalysts for the oxidative self-coupling of alkylphenols[639,640].

8. Pharmacological activity

Isatin and derivatives display diverse pharmacological activities. A summary of these activities can be found in the Supplementary Material 1 and a review on the biological properties of isatin was published some years ago[641]. The detection of isatin in mammalian tissues, formed probably from heme-protein bound trypthophan in an iron catalyzed oxidation reaction[642], led to the development of a HRGC-MS technique for its detection in biological samples[10].

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References.

1.Sumpter, W.C. *Chem. Rev* . **1954**, *34*, 407.

2.Popp, F.D. *Adv. Heterocycl. Chem.* **1975**,*18*, 1.

3.Shvekhgeimer, M.G.A. *Chem. Heterocycl. Compd. (Engl. Transl.).* **1996**, *32*, 249.

4.Guo, Y.; Chen, F. *Zhongcaoyao* **1986,** *17*, 8.

5.Yoshikawa, M.; Murakami, T.; Kishi, A.; Sakurama, T.; Matsuda, H.; Nomura, M.; Matsuda, H.; Kubo, M. *Chem. Pharm. Bull.* **1998,** *46*, 886.

6.Bergman, J.; Lindström, J.O.; Tilstam, U. *Tetrahedron* **1985,** *41*, 2879.

7.Wei, L.; Wang, Q.; Liu, X. *Yaowu Fenxi Zazhi* **1982,** *2*, 288.

8.Ischia, M.; Palumbo, A.; Prota, G. *Tetrahedron* **1988,** *44*, 6441.

9.Palumbo, A.; Ischia, M.; Misuraca, G.; Prota, G. *Biochim. Biophys. Acta* **1989,** *990*, 297.

10.Halket, J.M.; Watkins, P.J.; Przyborowska, A.; Goodwin, B.L.; Clow, A.; Glover, V.; Sandler, M. *J. Chromatogr*. **1991,** *562*, 279.

11.Kapadia, G.J.; Shukla, Y.N.; Chowdhury, B.K.; Basan, S.P.; Fales, H.M.; Sokoloski, E.A. *J. Chem. Soc. Chem. Commun.* **1977,** .535.

12.Kapadia, G.J.; Shukla, Y.N.; Basak, S.P.; Sokoloski, E.A.; Fales, H.M. *Tetrahedron* **1980,** *36*, 2441.

13.Kapadia, G.J.; Shukla, Y.N. *Planta Med.* **1993,** *59*, 568.

14. Grafe, U.; Radics, L. *J. Antibiotics* **1986,** *39*, 162; Graefe, U.; Schade, W.; Fleck, W. *Ger (East) DD 241,749 24 Dec 1986 (CA 107:216174k)* **1986,** 5 pp.

15.Breinholt, J.; Demuth, H.; Heide, M.; Jensen, G.W.; Moller, I.L.; Nielsen, R.I.; Olsen, C.E.; Rosendahl, C.N. *Acta Chem. Scand.* **1996,** *50*, 443.

16.Yan, Y.; Li, G.; Wang, F.; Mao, W. *Huadong Huagong Xueyuan Xuebao* **1992,** *18*, 192.

17.Alam, M.; Younas, M.; Zafar, M.A.; Naeem *Pak. J. Sci. Ind. Res* **1989,** *32*, 246.

18.Smolders, R.R.; Waefelaer, A.; Francart, D. *Ing. Chim. (Brussels)* **1982,** *64*, 5.

19.Loloiu, G.; Loloiu, T.; Maior, O. *Khim. Geterosilk. Soedin.* **1998,** 396.

20.Garden, S.J.; Torres, J.C.; Ferriera, A.A.; Silva, R.B.; Pinto, A.C. *Tetrahedron Lett.* **1997,** *38*, 1501.

21.Jnaneswara, G.K.; Bedekar, A.V.; Deshpande, V.H. *Synth. Commun.* **1999,** 29, .3627.

22.Lackey, K.; Sternbach, D.D. *Synthesis* **1993,** 993.

23.Lackey, K.; Besterman, J.M.; Fletcher, W.; Leitner, P.; Morton, B.; Sternbach, D.D. *J. Med. Chem.* **1995,** 38, 906.

24.Prinz, W.; Kayle, A.; Levy, P.R. *J. Chem. Res. (S),* **1978,** 116.

25.Prinz, W.; Kayle, A.; Levy, P.R. *J. Chem. Res. (M),* **1978,** 1347.

26.Joshi, K.C.; Jain, R.; Dandia, A.; Sharma, K.; Baweja, S. *Chem. Ind. (London)* **1989,** 569.

27.Varma, R.S.; Singh, A.P. *Indian J. Chem. Sect. B* **1990,** 29B, 578.

28.Goodwin, B. *Chem. Brit.***1988,** 336.

29.Gandy, R.; Hill, M.G. *Chem. Brit.* **1988,** 336.

30.Gilchrist, T.L. *Chem. Soc. Rev.* **1983,** 53.

31.Francotte, E.; Merenyi, R.; Vandenbulcke-Coyette, B.; Viehe, H.G. *Helv. Chim, Acta* **1981,** *64*, 1208.

32.Kearney, T.; Harris, P.A.; Jackson, A.; Joule, J.A. *Synthesis* **1992**, 769.

33.Loloiu, G.; Maior, O. *Rev. Roum. Chim.* **1997**, 42, 67.

34.Fukuda, Y.; Itoh, Y.; Nakatani, K.; Terashima, S. *Tetrahedron* **1994** 50, 2793.

35.Hashiba, I.; Ando, Y.; Kawakami, I.; Sakota, R.; Nagano, K.; Mori, T. *Jpn. Kokai Tokkyo Koho 79 73,771 13 Jun 1979 (CA 91:193174v)* **1979,** 6 pp.

36.Bryant III, W.M.; Huhn, G.F.; Jensen, J.H.; Pierce, M.E. *Synth. Commun.* **1993**, 23, 1617.

37.Lopes, W.A.; Silva, G.A.; Sequeira, L.C.; Pereira, A.L.; Pinto, A.C. *J. Braz. Chem. Soc.* **1993**, 4, 34.

38.Welstead Jr.; W.J.; Moran, H.W.; Stauffer, H.F.; Turnbull, L.B.; Sancilio, L.F. *J. Med. Chem.* **1979**, 22, 1074.

39.Ijaz, A.S.; Alam, M.; Ahmad, B. *Indian J. Chem. Sect. B* **1994**, 33B, 288.

40.Taylor, A. *J. Chem. Res.* **1980,** 347.

41.Rice, K.C.; Boone, B.J.; Rubin, A.B.; Rauls, T.J. *J. Med. Chem.* **1976**, *19*, 887.

42.Gassman, P.G.; Cue Jr.; B.W.; Luh, T.Y. *J. Org. Chem.* **1977,** 42, 1344.

43.Gassman, P.G.; Cue, B.W. *Ger. Offen. 2,815,609 26 Oct 1978 (CA 90:54821v)* **1978,** 26 pp.; Gassman, P.G.; Cue, B.W. *US 4188325, 12 Feb 1980*, **1980,** 9 pp.

44.Gassman, P.G .*Ger. Offen. 3,000,338 24 Jul 1980 (CA 93:204455g)*, **1980,** 20 pp.

45.Gassman, P.G. *US 4186132, 29 Jan 1980*, **1980B,** 8 pp.

46.Gassman, P.G. *US 4252723, 24 Feb 1981*, **1981,** 5 pp.

47.Gassman, P.G.; Halweg, K.M. *J. Org. Chem.***1979,** *44*, 628.

48.Wright, S.W.; McClure, L.D.; Hageman, D.L. *Tetrahedron Lett.***1996,** *37*, 4631.

49.Hewawasam, P.; Meanwell, N. *Tetrahedron Lett.* **1994,** *35*, 7303.

50.Rivalle, C.; Bisogni, E. *J. Heterocyclic Chem.* **1997,** *34*, 441.

51.Smith, K.; El-Hiti, G.A.; Hawes, AC *Synlett* **1999,** 945.

52.Parrick, J.; Yahya, A.; Jin, Y. *Tetrahedron Lett*, **1984,** *25*, 3099.

53.Parrick, J.; Yahya, A.; Ijaz, A.S.; Yizun, J. *J. Chem. Soc. Perkin Trans. I* **1989,** 2009.

54.Valentine, J.J.; Nakanishi, S.; Hageman, D.L.; Snider, R.M.; Spencer, R.W.; Vinick, F.J. *Bioorg. Med. Chem. Lett.* **1992,** *2*, 333.

55.Robinson, R.P.; Donahue, K.M. *J. Org. Chem.* **1991,** *56*, 4805.

56.Kraynack, E.A.; Dalgard, J.E.; Gaeta, F.C.A. *Tetrahedron Lett.* **1998,** *39*, 7679.

57.Baker, A.D.; Wong, D.; Lo, S.; Bloch, M.; Horozoglu, G.; Goldman, N.L.; Engel, R.; Riotta, D.C. *Tetrahedron Lett.* **1978,** 215.

58.Lokmane, E.; Larina, L.; Mazeika, I.; Freimanis, J. *Latv. P.S.R. Zinat. Akad. Vestis, Kim. Ser.* **1980,** 699.

59.Benincori, T.; Fusco, R.; Sannicolo, F. *Gazz. Chim. Ital.* **1990,** *120*, 635.

60.Cheng, Y.; Goon, S.; Meth-Cohn, O *J.Chem. Soc. Perkin Trans. I.* **1998,** 1619.

61.Kurihara, T.; Nasu, K.; Mizuhara, Y.; Hayashi, K. *Chem. Pharm. Bull.* **1982,** *30*, 2742.

62.Chupakhin, O.N.; Rusinov, V.L.; Beresnev, D.G.; Neunhoeffer, H. *J. Heterocycl. Chem.* **1997,** *34*, 573.

63.Ozawa, F.; Yanagihara, H.; Yamamoto, A. *J. Org. Chem.* **1986,** *51*, 415.

64.Bergman, J. *Tetrahedron Lett.***1989,** *30*, 1837.

65.Rigby, J.H.; Qabar, M. *J. Am. Chem. Soc.* **1991,** *113*, 8975.

66.Rigby, J.H.; Mateo, M.E. *Tetrahedron* **1996,** *52*, 10569.

67.Reisch, J.; Schiwek, K. *Acta Pharm. Turc*.**1993,** *35*, 39.

68.Ischia, M.; Prota, G. *Gazz. Chim. Ital.* **1986,** *116*, 407.

69.Ohnuma, T.; Kasuya, H.; Kimura, Y.; Ban, Y. *Heterocycles.***1982,** *17*, 377.

70.Beggiato, G.; Casalboremiceli, G.; Geri, A.; Pietropaolo, D. *Ann. Chim.* **1993,** *83*, 355.

71.Dinner, A.; Rickard, E. *J. Heterocycl. Chem.* **1978,** *15*, 333.

72.Arsenijevic, L.; Bogavac, M.; Pavlov, S.; Arsenijevic, V. *Arh. Farm.***1985,** *35*, 39.

73.Boar, B.R.; Cross, A.J. *PCT Int. Appl. WO 93 12,085 24 Jun 1993 (CA 119:225964t)* **1993,** 70 pp.

74.Muchowski, J.M.; Nelson, P.H. *Tetrahedron Lett.* **1980,** *21*, 4585.

75.Tatsugi, J.; Ikuma, K.; Izawa, Y. *Heterocycles* **1996,** *43*, 7.

76.Radul, O.M.; Zhungietu, G.I.; Rekhter, M.A.; Bukhanyuk, S.M. *Khim. Geterotsikl. Soedin.* **1980,** 1562.

77.Radul, O.M.; Zhungietu, G.I.; Rekhter, M.A.; Bukhanyuk, S.M. *Khim. Geterotsikl. Soedin.* **1983,** 353.

78.Majumdar, K.C.; Kundu, A.K.; Chatterjee, P. *J. Chem. Res.* **1996,** 460.

79.Garden, S.J.; Torres, J. C.; da Silva, L. E.; Pinto, A. C. *Synth. Commun.***1998,** *28,* 1679.

80.Black, D.S.C.; Brockway, D.J.; Moss, G.I. *Aust. J. Chem.* **1986,** *39,* 1231.

81.Li, Q.; Yang, J.; Fan, W. *Huaxue Tongbao* **1991,** 35.

82.Dormidontova, N.P. *Nauka-Farm. Prakt.* **1984,** 63.

83.Hamada, K.; Tanaka, S.; Suzukamo, T.; Morisada, S.; Fukui, M.; Kadota, K.; Okuda, T. *Jpn. Kokai Tokkyo Koho JP 60,246,395 06 Dec 1985 (CA 106:84990r)* **1985,** 11 pp.

84.Joshi, K.C.; Pathak, V.N.; Gupta, R. *Indian J. Heterocycl. Chem.* **1992,** *2,* 15.

85.Haga, T.; Nagano, H.; Enomoto, M.; Morita, K.; Sato, M. *Jpn. Kokai Tokkyo Koho JP 63,313,770 21 Dec 1988 (CA 111:133986h)* **1988**.

86.Rekhter, M.A.; Zorin, L.M.; Zhungietu, G.I. *U.S.S.R. 642,306 15 Jan 1979 (CA 90:186787y)* **1979**.

87.Schonberg, A.; Singer, E.; Stephan, W. *Chem. Ber.***1987,** *120,* 1581.

88.Bayer, E.; Geckeler, K. *Angew. Chem.* **1979,** *91,* 568.

89.Aliev, N.A.; Ahmad-Hasan, E.I.; Abdusamatov, A. *Deposited Doc. VINITI 215-78 (CA 91:157670v)* **1978,** 16 pp.

90.Khuseinov, K. *Dokl. Akad. Nauk Tadzh. SSR.* **1976,** *19,* 30.

91.Tomchin, A.B.; Shirokii, G.A.; Dmitrukha, V.S. *Khim. Geterotsikl. Soedin.* **1976,** 83.

92.Tomchin, A.B.; Shirokii, G.A. *Zh. Org. Khim.* **1977,** *13,* 404.

93.Dombrowski, J.E.; Mattingly, P.G. *Eur. Pat. Appl. EP 369,344 23 May 1990 (CA 113:211829s)* **1990,** 11 pp.

94.Coppola, G.M. *J. Heterocycl. Chem.***1987,** *24,* 1249.

95.Jancevska, M.; Stojceva, B. *Glas. Hem. Tehnol. Makedonija.* **1975,** *2* , 53.

96.Zawadowka, I. *Acta Pol. Pharm.* **1975,** *32*, 33.

97.Varma, R.S.; Chauhan, S.; Prasad, C.R. *Indian J. Chem. Sect. B* **1985,** *24B*, 280.

98.Gupta, R.P.; Narayana, N.L. *Pharm. Acta Helv.* **1997,** *72*, 43.

99.Pinto, A.C.; Silva, F.S.Q.; Silva, R.B. *Tetrahedron Lett.* **1994,** *35*, 8923.

100.Tomchin, A.B.; Fradkina, S.P.; Krylova, I.M.; Khromenkova, Z.A. *Zh. Org. Khim.* **1986,** *22*, 2409.

101.Black, D.S.C.; Bowyer, M.C.; Catalano, M.M.; Ivory, A.J.; Keller, P.A.; Kumar, N.; Nugent, S.J. *Tetrahedron* **1994,** *50*, 10497.

102.Nishigashi, S.; Sakae, M.; Takamatsu, S. *Jpn. Kokai Tokkyo Koho 61 91,163 09 May 1986 (CA 105: 208604v)* **1986**.

103.Nishigashi, S.; Sakae, M.; Takamatsu, S. *Jpn. Kokai Tokkyo Koho 61 91,168 09 May 1986 (CA 106: 4861m)* **1986,** 2 pp.

104.Black, D.S.C.; Moss, G.I. *Aust. J. Chem.* **1987,** *40*, 129.

105.Collino, F.; Volpe, S. *Boll. Chim. Farm.* **1982,** *121*, 408.

106.Black, D.S.C.; Chaichit, N.; Gatehouse, B.M.; Moss, G.I. *Aust. J. Chem.* **1987,** *40*, 1745.

107.Kondo, Y.; Mitadera, Y.; Nozoe, S. *Yakugaku Zasshi* **1985,** *105*, 724.

108.Ballantine, J.A.; Alam, M.; Fishlock, G.W. *J. Chem. Soc. Perkin Trans. I.* **1977,** 1781.

109.Tomchin, A.B.; Krilova, I.M. *Zh. Org. Khim.* **1986,** *22*, 2420.

110.Berti, C.; Greci, L. *Synth. Commun.* **1981,** *11*, 681.

111.Berti, C.; Greci, L.; Andruzzi, R.; Trazza, A. *J. Org. Chem.* **1982,** *47*, 4895.

112.Papadopoulou, M.; Varvoglis, A. *J. Chem. Res.***1983,** 66.

113.Tomchin, A.B.; Tumanova, I.V. *Zh. Org. Khim.* **1990,** *26*, 1327.

114.Daisley, R.W.; Shah, V.K *J. Pharm. Sci.* **1984,** *73*, 407.

115.Mazhilis, L.I.; Terent'ev, P.B.; Bolotin, V.A. *Chem. Heterocycl. Compd. (Engl. Transl.).* **1989,** *25*, 50.

116.Gasparic, J.; Vontor, T.; Lycka, A.; Snobl, D.*Collect. Czech. Chem. Commun.***1990,** *55*, 2963.

117.Gopal, M.; Srivastava, G.; Pande, U.C.; Tiwari, R.D. *Microchim. Acta.* **1977,** 215.

118.Martinez, F.; Naarmann, H. *Synth. Met.* **1990,** *39*, 195.

119.Jnaneswara, G.K.; Deshpande, V.H. *J. Chem. Res. (S).* **1999,** 632.

120.Hewlins, M.J.E.; Jacson, A.H.; Oliveira-Campos, A.M.; Shannon, P.V.R. *J. Chem. Soc. Perkin Trans. 1.* **1981,** 2906.

121.Menicagli, R.; Malanga, C.; Lardicci, L. *Chim. Ind. (Milan).* **1977,** *59*, 652.

122.Katz, A.H.; Demerson, C.A.; Humber, L.G. *U.S. US 4,670,462 02 Jun 1987 (CA 107:96704j)* **1987,** 13 pp.

123.Katz, A.H.; Demerson, C.A.; Humber, L.G. *Eur. Pat. Appl. EP 238,226 23 Sep 1987 (CA 109:6494e)* **1987,** 32 pp.

124.Katz, A.H.; Demerson, C.A.; Shaw, C.C.; Asselin, A.A.; Humber, L.G.; Conway, K.M.; Gavin, G.; Guinosso, C.; Jensen, N.P.; Mobilio, D.; Noureldin, R.; Schmid, J.; Shah, U.; Engen, D.V.; Chau, T.T.; Weichman, B.M. *J. Med. Chem.* **1988,** *31*, 1244.

125.Demerson, C.A.; Humber, L.G.; Philipp, A.H.; Martel, R.R. *J. Med. Chem.***1976,** *19*, 391.

126.Soll, R.M.; Guinosso, C.; Asselin, A. *J. Org. Chem.***1988,** *53*, 2844.

127.Mirand, C.; Massiot, G.; Lévy, J. *J. Org. Chem.***1982,** *47*, 4169.

128.Jiang, B.; Smallheer, J.M.; Amaral-Ly, G.; Wuonola, M.A. *J. Org. Chem.***1994,** *59*, 6823.

129.Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett.* **1983,** *24*, 2437.

130.Torres, J.C.; Garden, S.J.; Pinto, A.C.; da Silva, F.S.Q.; Boechat, N. *Tetrahedron* **1999,** *55*, 1881.

131.Dzyubenko, V.G.; Abramenko, P.I. *Zh. Vses. Khim. O-va. Im. D.I. Mendeleeva* **1986,** *31*, 229.

132.Monde, K.; Sasaki, K.; Shirata, A.; Takasugi, M. *Phytochemistry* **1991,** *30*, 2915.

133.Albrecht, C.F.; Chorn, D.J.; Wessels, P.L. *Life Sci.* **1989,** *45*, 1119.

134.Hashiba, I.; Ando, Y.; Kawakami, I.; Sakota, R.; Nagano, K.; Mori, T. *Jpn. Kokai Tokkyo Koho 79 70,265 05 Jun 1979 (CA 91:175191u)* **1979,** 6 pp.

135.Khattab, M.A.; Ghoneim, M.M. *J. Indian Chem. Soc.* **1983,** *60*, 643.

136.Brunet, J.J.; Chauvin, R.; Kindela, F.; Neibecker, D. *Tetrahedron Lett.* **1994,** *35*, 8801.

137.Ono, Y.; Nishimura, F.; Tamaki, K.; Fujii, K. *Jpn. Kokai Tokkyo Koho 79 151,963 29 Nov 1979 (CA 93:8016a)* **1979,** 3 pp.

138.Wenkert, E.; Bringi, N.V.; Choulett, H.E. *Acta Chem. Scand.* **1982,** *36B*, 348.

139.Kadin, S.B. *U.S. US 4,730,004 08 Mar 1988 (CA 110:23729y)* **1988,** 9 pp.

140.Holmes, R.E.; Jourdan, G.P. *U.S. Publ. Pat. Appl. B 427,946 23 Mar 1976 (CA 85:46381h)* **1976,** 7 pp.

141.Zhong, T. *Huaxue Tongbao* **1986,** 35.

142.Kuo, L.H.; Hsu, J.P.; Chen, C.T. *US 5973165, 26 Oct 1999* **1999,** 4 pp.

143.Igarashi, R.; Nakamura, A. *Jpn. Kokai Tokkyo Koho JP 07,196,610, 01 Aug 1995* **1995,** 4 pp.

144.Crestini, C.; Saladino, R. *Synth. Commun.* **1994,** *24*, 2835.

145.Soriano, D.S. *J.Chem. Educ.* **1993,** *70*, 332.

146.Colgan, S.T.; Pollard, E.B. *J. Chromatogr. Sci.* **1991,** *29*, 433.

147.Bergman, J.; Stalhandske, C. *Tetrahedron Lett.* **1994,** *35*, 5279.

148.Papageorgiou, C.; Borer, X. *Helv. Chim. Acta.* **1988,** *71*, 1079.

149.Isukura, S.K.K. *Jpn. Kokai Tokkyo Koho 61 07,254 13 Jan 1986 (CA 105:24186c)* **1986,** 4 pp.

150.Minami, T.; Matsumoto, M.; Agawa, T. *J. Chem. Soc. Chem. Commun.* **1976,** 1053.

151.Minami, T.; Matsuzaki, N.; Ohshiro, Y.; Agawa, T. *J. Chem. Soc. Perkin Trans. 1* **1980,** 1731.

152.El-Kateb, A.A.; Hennawy, I.T.; Shabana, R.; Osman, F.H. *Phosph. Sulf.* **1984,** *20*, 329.

153.Sichuan Institute of Tradicional Chinese Medicine *Zhongcaoyao* **1981,** *12*, 499.

154.Wu, K.; Zhang, M.; Fang, Z.; Huang, L. *Yaoxue Xuebao* **1985,** *20*, 821.

155.Gu, Y.C.; Li, G.L.; Yang, Y.P.; Fu, J.P.; Li, C.Z. *Yaoxue Xuebao* **1989,** *24*, 629.

156.Pfeiffer, G.; Bauer, H. *Liebigs Ann. Chem.* **1980,** 564.

157.Banerji, K.D.; Mazumder, A.K.D.; Guha, S.K. *J. Indian Chem. Soc.* **1976,** *53*, 923.

158.Grosjean, D. Salmon, L.G.; Cass, G.R. *Environ. Sci. Technol.* **1992,** *26*, 952.

159.Rucker, J.W.; Freeman, H.S.; Hsu, W.N. *Text. Chem. Color.* **1992,** *24*, 66.

160.Reidies, A.H.; Jensen, D.; Guisti, M. *Text. Chem. Color.* **1992,** *24*, 26.

161.Matsui, M.; Morita, Shibata, K.; Takase, Y. *Nippon Kagaku Kaishi*. **1982,** 1268.

162. Jonnalagadda, S.B.; Simoyi, R.; Muthakia, G.K. *J. Chem. Soc. Perkin Trans. II* **1988,** 1111.

163.Nikokavouras, J.; Vassilopoulos, G. *Monatsh. Chem.* **1981,** *112*, 1239.

164.Amat-Guerri, F.; López-González, M.M.C.; Maretinez-Utrilla, R. *Tetrahedron Lett.* **1983,** *24*, 3749.

165.Labouta, I.M.; Salama, H.M.; Eshba, N.H.; El-Chrbini, E. *Acta Pharm. Jugosl.* **1988,** 189.

166.Ghandour, M.A.; Issa, I.M.; Mahmoud, M.R.; Aboudoma, R.A. *J. Indian Chem. Soc.* **1976,** *53*, 258.

167.Hudak, A.; Kosturiak, A.; Hanudel, A.; Meluch, P. *Collect. Chech. Chem. Commun.* **1993,** *58*, 1803.

168.Kobayashi, M.; Kitazawa, M.; Akaha, M.; Tsukamoto, T.; Yamamoto, R.; Nakano, Y. *Jpn. Kokai Tokkyo Koho JP 62,228,072 06 Oct 1987 (CA 109:6418h)* **1987,** 20 pp.

169.Kobayashi, M.; Kitazawa, M.; Akaha, M.; Tsukamoto, T.; Yamamoto, R.; Nakano, Y. *Jpn. Kokai Tokkyo Koho JP 62,234,080 20 Dec 1985 (CA 109:37740m)* **1987**.

170.Kobayashi, M.; Kitazawa, M.; Akaha, M.; Tsukamoto, T.; Yamamoto, R.; Nakano, Y. *Jpn. Kokai Tokkyo Koho 63 156,771 29 Jun 1988 (CA 109:230803n)* **1988,** 15 pp.

171.Kobayashi, M.; Kitazawa, M.; Akaha, M.; Tsukamoto, T.; Yamamoto, R.; Nakano, Y. *Jpn. Kokai Tokkyo Koho 63 156,772 29 Jun 1988 (CA 110:135081n)* **1988,** 30 pp.

172.Hardtmann, G.E. *U.S. 3,923,996 02 Dec 1975 (CA 84:59190z)* **1975,** 6 pp.

173.Kadin, S.B. *U.S. US 4,556,672 03 Dec 1985 (CA 105:24187d)* **1985,** 7 pp.

174.Kadin, S.B. *U.S. US 4,569,942 11 Feb 1986 (CA 105:42644e)* **1986,** 20 pp.

175.Kadin, S.B. *U.S. US 4,725,616 16 Feb 1988 (CA 110:23728x)* **1988,** 30 pp.

176.Kadin, S.B. *U.S. US 4,721,712 26 Jan 1988 (CA 109:210892u)* **1988,** 19 pp.

177. Kadin, S.B. *Eur. Pat. Appl. EP 175,551 26 Mar 1986 (CA 105:133745e)* **1986,** 46 pp.

178.Walsh, D.A.; Moran, H.W.; Shamblee, D.A.; Welstead Jr.; W.J.; Nolan, J.C.; Sancilio, L.F.; Graff, G. *J. Med. Chem.* **1990,** *33,* 2296.

179.Hashiba, I.; Ando, Y.; Kawakami, I.; Sakota, R.; Nagano, K.; Mori, T. *Jpn. Kokai Tokkyo Koho 79 63,042 21 Mayn 1979 (CA 91:193006s)* **1979,** 8 pp.

180.Hu, Z.; Ma, P.; Yao, W. *Zhongguo Yiyao Gongye Zazhi.* **1992,** *23,* 199.

181.Nohara, F.; Fujinawa, T.; Ogawa, K.; Fujimura, H. *Japan. Kokai 77 68,160 06 Jun 1977 (CA 87:151890n)* **1977,** 10 pp.

182.Alcar, S. *Fr. Demande 2,449,674 19 Sep 1980 (CA 95:115066e)* **1980,** 11 pp.

183.Darmory, F.P.; DiBenedetto, M. *US 4,016,173 05 Apr 1977 (CA 87:24139z)* **1977,** 4 pp.

184.Bennett, W.B.; Wharry, D.L.; Koch, T.H. *J. Am. Chem. Soc.* **1980,** *102,* 2345.

185.Czuba, W.; Sedzik-Hibner, D. *Pol. J. Chem.* **1989,** *63,* 113.

186.Reissenweber, G. *US 4316020, 16 Feb 1982* **1982,** 3 pp.

187.Reissenweber, G.; Mangold, D. *Angew. Chem.* **1980,** *92,* 196.

188.Kamal, A. *J. Org. Chem.* **1991,** *56,* 2237.

189.Hunkeler, W.; Kyburz, E. *Eur. Pat. Appl. EP 59,389 08 Sep. 1982 (CA 98:53951r)* **1982,** 46 pp.

190.Hunkeler, W.; Kyburz, E. *Eur. Pat. Appl. EP 59,390 08 Sep. 1982 (CA 98:53949w)* **1982,** 57 pp.

191.Hunkeler, W.; Kyburz, E. *Eur. Pat. Appl. EP 59,391 08 Sep. 1982 (CA 98:53950q)* **1982,** 72 pp.

192.Hunkeler, W.; Kyburz, E. *Eur. Pat. Appl. EP 100,906 22 Feb 1984 (CA 101:7217p)* **1984**.

193.Aurich, H.G.; Grigo, U. *Chem. Ber.* **1976,** *109*, 200.

194.Ashry, E.S.H.E.; Kilany, Y.E. *Indian J. Chem. Sect. B Sect. B* **1978,** *16B*, 1036.

195.Coppola, G.M. *US 4,212,804 15 Jul 1980 (CA 94:15565c)* **1980,** 4 pp.

196.Reissenweber, G.; Mangold, D. *US 4310677, 12 Jan 1982* **1982,** 4 pp.

197.Gowda, N.M.M.; Mahadevappa, D.S. *Curr. Sci.* **1975,** *44*, 757.

198.Hegarty, A.F.; Ahern, E.P.; Frost, L.N.; Hegarty, C.N. *J. Chem. Soc. Perkin Trans. II* **1990,** 1935.

199.Puttaswamy, Mahadevappa, D.S.; Gowda, N.M.M. *Int. J. Chem. Kinet.* **1991,** *23*, 27.

200.Haucke, G.; Seidel, B.; Graness, A. *J. Photochem.* **1987,** *37*, 139.

201.Fulop, F.; Pihlaja, K. *Org. Prep. Proced. Int.* **1991,** *23*, 377.

202.Krantz, A.; Young, J.M. *US 4,873,232 10 Oct 1989 (CA 112:157888z)* **1989.**

203.Richards, I.C.; Wright, B.J.; Parsons, J.H.; Baillie, A.C. *Eur. Pat. Appl. EP 360,417 28 Mar 1990 (CA 113:97199j)* **1990,** 12 pp.

204.Todd, W.P.; Carpenter, B.K.; Schwarcz, R. *Prep. Biochem.* **1989,** *19*, 155.

205.Wilcox Jr.; C.F.; Farley, E.N. *J. Am. Chem. Soc.* **1984,** *106*, 7195.

206.Fritsch, R.; Hartmann, E.; Andert, D.; Mannschreck, A. *Chem. Ber.* **1992,** *125*, 849.

207.Sannicolo, F. *Gazz. Chim. Ital.* **1985,** *115*, 91.

208.Snow, R.A.; Cottrell, D.M.; Paquette, L.A. *J. Am. Chem. Soc.* **1977,** *99*, 3734.

209.Nielsen, A.T.; Henry, R.A.; Norris, W.P.; Atkins, R.L.; Moore, D.W.; Lepie, A.H.; Coon, C.L.; Spanggord, R.J.; Son, D.V.H. *J. Org. Chem.* **1979,** *44*, 2499.

210.Hart, H.; Ruge, B. *Tetrahedron Lett.* **1977,** *36*, 3143.

211.Newman, M.S.; Kannan, R. *J. Org. Chem.* **1976,** *41*, 3356.

212.Cerveny, L.; Marhoul, A.; Winklerova, P. *Seifen, Oele, Fette, Wachse.* **1992,** *118*, 816.

213.Cambie, R.C.; Higgs, P.I.; Rutledge, P.S.; Woodgate, P.D. *Aust. J. Chem.* **1994,** *47*, 1483.

214.Madsen, E.L.; Bollag, J.M. *Arch. Microbiol.* **1989,** *151*, 71.

215.Gu, J.D.; Berry, D.F. *Appl. Environ. Microbiol.* **1991,** *57*, 2622.

216.Jensen, J.B.; Egsgaard, H.; Vanonckelen, H.; Jochimsen, B.U. *J. Bacteriol.* **1995,** *177*, 5762.

217.Campbell Jr.; J.B.; Davenport, T.V. *Synth. Commun.* **1989,** *19*, 2255.

218.Christidis, Y.; Schouteeten, A. *Brit. UK Pat. Appl. GB 2,096,611 20 Oct 1982 (CA 98:143142g)* **1982,** 5 pp.

219.Zaitseva, E.L.; Flerova, A.N.; Gitina, R.M.; Kurkovskaya, L.N.; Teleshov, E.N.; Pravednikon, A.N.; Botvinnik, E.S.; Shmagina, N.N.; Gefter, E.L. *Zh. Org. Khim.* **1976,** *12*, 1987.

220.Sicker, D.; Fiebig, F.; Mann, G. *Ger (East) DD 263,756 11 Jan 1989 (CA 111:194321j)* **1989,** .3 pp.

221.Ranganathan, D.; Bamezai, S.; Ramachandran, P.V. *Heterocycles* **1985,** *23*, 623.

222.Purnaprajna, V.; Seshadri, S. *Indian J. Chem. Sect. B Sect. B* **1977,** *15B*, 335.

223.Saidac, S.; Gheorghe, P.; Savulescu, A.; Zaharia, M. *Rev. Chim. (Bucharest)* **1982,** *33*, 816.

224.Sahu, A.; Chatterjee, A. *Indian J. Chem. Sect. B* **1990,** *29B*, 603.

225.Reissenweber, G.; Mangold, D. *US 4297491, 27 Oct 1981* **1981,** 3 pp.

226.Reissenweber, G.; Niess, R. *Ger. Offen. DE 3,323,975 12 Jan 1984 (CA 100:174428u)* **1984,** 9 pp.

227.Niedzwiecka-Kornas, A.; Bojarska, E.; Kaminski, J.; Kazimierczuk, Z. *Z. Naturforsch.* **1998,** *53B*, 620.

228.Cornforth, J.W. *J. Chem. Soc. Perkin Trans. I.* **1976,** 2004.

229.Watjen, F.; Drejer,J.; Jensen, L.H. *Eur. Pat. Appl. EP 432,648 19 Jun 1991 (CA 115:183089w)* **1991**.

230.Johnson, G. *US 5,192,792 07 Dec 1990 (CA 119:95330v)* **1993**, 15 pp.

231.El Ashry, E.S.H *Sci. Pharm.* **1979,** *47*, 5.

232.Bergman, J.; Engelhardt, P.; Kiss, A.I.; Lindström, J.O.; Wärnmark, K. *Studies in Org. Chemistry: Chemistry of Heterocyclic Compounds* **1988,** *35*, 1.

233.Ogata, M.; Matsumoto, H. *Chem. Ind.* **1976,** 1067.

234.Ranganathan, S.; Ranganathan, D.; Ramachandran, P.V.; Mahanty, M.K.; Bamezai, S.; *Tetrahedron* **1981,** *37*, 4171.

235.Bergman, J.; Carlsson, R.; Lindström, J.O. *Tetrahedron Lett.* **1976,** *40*, 3611.

236.Molloy, B.B *U.S. 3,882,236 06 May 1075* **1975,** 5 pp.

237.Snavely, F.A.; Un, S. *J. Org. Chem.* **1981,** *46*, 2764.

238.Joshi, K.C.; Pathak, V.N.; Jain, S.K. *Pharmazie.* **1980,** *35*, 677.

239.Vostrova, L.N.; Grenaderova, M.V.; Bondar, E.E.; Sozinova, E.K.; Petrenko, N.F.; Fel'dman, S.V. *Ukr. Khim. Zh. (Russ. Ed.).* **1991,** *57*, 542.

240.Ivaschenko, A.V.; Zaitsev, B.E.; Krikunova, S.V.; Poponova, R.V. *Chem. Heterocycl. Compd. (Engl. Transl.).* **1980,** *16*, 1279.

241.Schilt, A.A.; Quinn, P.C.; Johnson, C.L. *Talanta* **1979,** *26*, 373.

242.Agarwal, S.; Pande, A.; Saxena, V.K.; Chowdhury, S.R. *Acta Pharm. Jugosl.* **1985,** *35*, 31.

243.Hamid, H.A.; Shoukry, M.; ElAshry, E. S. H. *Heterocycl. Commun.* **1997,** 79.

244.Sengupta, A.K.; Anand, S.; Pandey, A.K. *J. Indian Chem. Soc.* **1987,** *64*, 643.

245.Dziomko, V.M.; Stopnikova, M.N.; Shmelev, L.V.; Raybokobylko, Y.S.; Adamova, G.M.; Poponova, R.V. *Chem. Heterocycl. Compd.* **1980,** *16*, 1073.

246.Provstyanoi, M.V.; Logachev, E.V.; Kochergin, P.M.; Beilis, Y.I. *Izv. Vyssh. Uchebn. Zadev.; Khim. Khim. Tekhnol.* **1976,** *19*, 708.

247.Sharma, K.; Jain, R. *Rev. Roum. Chim.* **1993,** *38*, 1457.

248.Varma, R.S.; Gupta, P. *J. Indian Chem. Soc.* **1989,** *66*, 325.

249.Varma, R.S.; Singh, A.P. *J. Indian Chem. Soc.* **1990,** *67*, 518.

250.Kassem, E.M.M.; Kamel, M.M.; Makhlouf, A.A.; Omar, M.T. *Pharmazie* **1989,** *44*, 62.

251.Ram, V.J.; Pandey, H.K. *Arch. Pharm.* **1980,** *313*, 465.

252.Zaher, H.A.; Abdel-Rahman, M.; Abdel-Halim, A.M. *Indian J. Chem. Sect. B* **1987,** *26B*, 110.

253.Chernykh, V.P. *Ukr. Khim. Zh. (Russ. Ed.).* **1976,** *42*, 512.

254.Varma, R.S.; Gupta, P. *J. Indian Chem. Soc.* **1988,** *65*, 802.

255.Singh, V.A.; Varma, R.S. *J. Indian Chem. Soc.* **1988,** *65*, 139.

256.Bolotov, V.V.; Nambelbai, A.; Drogovoz, S.M.; Vereitinova, V.P. *Khim. Farm. Zh.* **1986,** *20*, 1463.

257.Agarwal, S.; Pande, A.; Saxena, V.K.; Chowdhury, S.R. *Indian Drugs* **1985,** *22* , 633.

258.Holzer, W.; Györgydeák, Z. *J. Heterocycl. Chem.* **1996,** *33*, 675.

259.Kobayashi, M, Kitazawa, M.; Akaha, M.; Tsukamoto, T.; Yamamoto, R.; Nakano, Y. *Jpn. Kokai Tokkyo Koho JP 62,294,654 22 Dec 1987 (CA 109:73323m)* **1987**.

260.Varma, R.S.; Singh, A.P. *J. Indian Chem. Soc.* **1991,** *68*, 469.

261.Badawy, M.A.; Abdel-Hady, S.A. *Arch. Pharm.* **1991,** *324*, 349.

262.Varma, R.S.; Garg, P.K. *Fresenius' Z. Anal. Chem.* **1981,** *307*, 416.

263.Foye, W.O.; Lemke, T.L.; Williams, D.A. *Principles of Medicinal Chemistry,* Williams; Wilkins, 4 ed.; Media, **1995,** 856.

264.Varma, R.S.; Singh, A.P. *Indian J. Chem. Sect. B* **1988,** *27B*, 482.

265.Varma, R.S.; Garg, P.K *J. Indian Chem. Soc.* **1981,** *58*, 980.

266.Varma, R.S. *J. Indian Chem. Soc.* **1978,** *55*, 1052.

267.Stuenzi, H. *Aust. J. Chem.* **1981,** *34*, 373.

268.Varma, R.S.; Khan, I.A. *J. Indian Chem. Soc.* **1981,** *58*, 811.

269.Agarwal, R.; Misra, S.; Satsangi, R.K.; Tiwari, S.S. *Arch. Pharm.* **1982,** *315*, 142.

270.Strakov, A.; Trapkov, V.; Lukashova, M.; Kozlovskaya, T.; Yerzinkyan, K.; Kacens, J.; Petrova, M.; Tonkih, N. *Latv. Kim. Z.* **1992,** 98.

271.Martynovskii, A.A.; Brazhko, O.A.; Samura, B.A.; Panasenko, O.I.; Romanenko, N.I.; Krasnykh, O.A.; Golub, B.A.; Buluakh, V.G. *Farm. Zh. (Kiev)* **1991,** 69.

272.Salama, H.M.; Vladzimirska, H.V.; Turkevich, N.M.; Stebljuk, P.N. *Pharmazie* **1979,** *34*, 720.

273.Joshi, K.C.; Jain, R.; Dandia, A.; Sharma, V. *J. Heterocycl. Chem.* **1986,** *23*, 97.

274.Nardi, D.; Tajana, A.; Portioli, F.; Bonola, G. *Farmaco* **1982,** *37*, 815.

275.Tomchin, A.B.; Marysheva, V.V. *Zh. Org. Khim.* **1993,** *29*, 444.

276.Tomchin, A.B. *Zh. Org. Khim.* **1990,** *26*, 860.

277.Tomchin, A.B. *Zh. Org. Khim.* **1987,** *23*, 1305.

278.Tomchin, A.B.; Shirokii, G A. *Zh. Org. Khim.* **1979,** *15*, 855.

279.Tomchin, A.B. *J. Org. Chem. USSR (Engl. Transl.).* **1989,** *25*, 760.

280.Tomchin, A.B.; Dmitrukha, V.S.; Pelkis, P.S. *Zh. Org.Khim.***1977,** *13*, 878.

281.Mahmoud, A.M.; Abdel-Rahman, A.E.; El-Naggar, G.M.; El-Sherief, H.A. *Indian J. Chem. Sect. B* **1984,** *23B*, 379.

282.Ashby, J.; Ramage, E.M. *J. Heterocycl. Chem.* **1978,** *15*, 1501.

283.Bergman, J.; Stalhandske, C.; Vallberg, H. *Acta Chem. Scand.* **1997,** *51*, 753.

284.Itoh, S.; Kato, N.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1984,** *25*, 4753.

285.Grigg, R.; Aly, M.F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc.; Chem. Commun.* **1984,** 182.

286.Coulter, T.; Grigg, R.; Malone, J.F.; Sridharan, V. *Tetrahedron Lett.* **1991,** *32*, 5417.

287.Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc. Chem. Commun.* **1986,** 602.

288.Ardill, H.; Dorrity, M,J.R.; Grigg, R.; Leon-Ling, M.S.; Malone, J.F.; Sridharan, V.; Thianpatanagui, S. *Tetrahedron* **1990,** *46*, 6433.

289.Casaschi, A.; Desimoni, G.; Faita, G.; Invernizzi, A.G.; Grunanger, P. *Heterocycles* **1994,** *37*, 1673.

290.Grigg, R.; Thianpatanagul, S. *J. Chem. Soc.; Chem. Commun.* **1984,** 180.

291.Palmisano, G.; Annuziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996,** *7*, 1.

292.Fokas, D.; Ryan, W.J.; Casebier, D.S.; Coffen, DL *Tetrahedron Lett.* **1998,** *39*, 2235.

293.Fokas, D.; Coffen, D.L.; Ryan, W.J. *WO 9912904 18 Mar 1999* **1999,** 55 pp.

294.Petersen, S. *Ger. Offen. 2,408,477 04 Sep 1975* **1975,** 24 pp.

295.Petersen, S. *Ger. Offen. 2,408,478 04 Sep 1975 (CA 84:4943s)* **1975,** 31 pp.

296.Franke, A. *Liebigs Ann. Chem.* **1982,** 794-804.

297.Petersen, S. *Ger. Offen. 2,431,842 22 Jan 1976 (CA 84:135643s)* **1976,** 28 pp.

298.Pinto, A.C.; Hollins, R.A. *J. Heterocycl. Chem.* **1977,** *14*, 677.

299.Petersen, S.; Heitzer, H. *Liebigs Ann. Chem.* **1978,** 280.

300.Rothkopf, H.W.; Wöhrle, D.; Müller, R.; Koβmehl, G. *Chem. Ber.* **1975,** *108*, 875.

301.Yamada, Y.; Matsuoka, Y. *Eur. Pat. Appl. EP 269,378 01 Jun 1988 (CA 109:149559r)* **1988,** 10 pp.

302.Yamada, Y.; Matsuoka, Y.; Matsumoto, M. *Eur. Pat. Appl. EP 204,534 10 Dec 1986 (CA 106:176417n)* **1986**, 52 pp.

303.Enileeva, Z. Sh.; Golovyashkina, L.F. *Dokl. Akad. Nauk Uzb. SSR.* **1976,** 45.

304.Abdel-Rahman, R.M.; Abdel-Halim, A.M.; Ibrahim, S.S.; Mohamed, E.A. *J. Chem. Soc. Pak.* **1987,** *9*, 523.

305.Haensel, W. *Arch. Pharm.* **1976,** *309*, 893.

306.Marchetti, L.; Greci, L.; Poloni, M. *Gazz. Chim. Ital.* **1977,** *107*, 7.

307.Haensel, W. *Justus Liebigs Ann. Chem.* **1976,** 1380.

308.Kallmayer, H.J. *Arch. Pharm.* **1975,** *308*, 743.

309.Varma, R.S.; Khan, I.A. *J. Indian Chem. Soc.* **1979,** *56*, 1038.

310.Varma, R.S.; Gupta, P. *J. Indian Chem. Soc.* **1989,** *66*, 349.

311.Varma, R.S.; Khan, I.A. *Natl. Acad. Sci. Lett. (India)* **1979,** *2*, 137.

312.Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem.* **1981,** *16*, 373.

313.Aurich, H.G.; Weiss, W. *Tetrahedron* **1976,** *32*, 159.

314.Singh, V.A.; Varma, R.S.; Dwivedi, S.D.; Verma, H.N. *Indian Drugs* **1985,** *22*, 582.

315.Bergman, J.O.E.; Aokerfeldt, S.G. *PCT Int. Appl. WO 87 04,436 30 Jul 1987 (CA 108:37866m)* **1987,** 30 pp.

316.Banerji, K.D.; Mazumdar, A.K.D.; Kumar, K.; Guha, S.K. *J. Indian Chem. Soc.* **1979,** *56*, 396.

317.Drushlyak, A.G.; Ivashchenko, A.V.; Titov, V.V. *Khim. Geterotsikl. Soedin.* **1984,** 1544.

318.Hafez, T.S. *Phosph. Sulf. Silicon.* **1991,** *61*, 341.

319.Anderson, J.S.; Schultz, T.M. *Eur. Pat. Appl. EP 359,465 21 Mar 1990 (CA 113:217781s)* **1990,** 9 pp.

320.Niume, K.; Toda, F.; Uno, K.; Hasegawa, M.; Iwakura, Y. *J. Polymer Sci. Polymer Chem. Ed.* **1983,** *21* ,615.

321.Niume, K.; Kurosawa, S.; Toda, F.; Hasegawa, M.; Iwakura, Y. *Bull. Chem. Soc. Jpn.* **1982,** *55*, 2293.

322.Ricoh, Co Ltd. *Jpn. Kokai Tokkyo Koho JP 59 18,696 28 Apr 1984 (CA 102: 87586s)* **1984**.

323.Joshi, K.C.; Dandia, A.; Khanna, S. *Indian J. Chem. Sect. B* **1992,** *31B*, 105.

324.Deady, L.W.; Kaye, A.J. *Aust. J. Chem.* **1997,** *50*, 473.

325.Ivaschchenko, A.V. e Agafonova, I.F. *Khim. Geterotsikl. Soedin.* **1981,** 249.

326.Ivaschenko, A.V.; Drushlyak, A.G.; Titov, V.V. *Khim. Geterotsikl. Soedin.* **1984,** *5*, 667.

327.Ivaschchenko, A.V. e Dziomko, V.M. *Uspekhi Khim.* **1977,** *46*, 228.

328.Drushlyak, A.G.; Ivashchenko, A.V.; Titov, V.V. *Khim. Geterotsikl. Soedin.* **1984,** 1399.

329. Sarkis, G.Y.; Al-Badri, H.T. *J. Heterocycl. Chem.* **1980**, *17*, 813.

330.Joshi, K.C.; Chand, P.; Dandia, A. *Indian J. Chem. Sect. B* **1984,** *23B*, 743.

331. Joshi, B.S.; Likhate, M.A.; Viswanathan, N. *Indian J. Chem. Sect. B* **1984,** *23B*, 114.

332.Capuano, L.; Benz, K. *Chem. Ber.* **1977,** *110*, 3849.

333.El-Ezbawy, S.R.; Wahab, A.M.A.A. *Phosph. Sulf . Silicon.* **1989,** *44*, 285.

334.Younes, M.I. *Liebigs Ann. Chem.* **1990,** 703.

335.Viswanathan, N.; Joshi, B.S.; Likhate, M.A. *Proc. Indian Acad. Sci. (Chem. Sci.)* **1984,** *93*, 589.

336.Joshi, K.C.; Dandia, A.; Khanna, S. *Indian J. Chem. Sect. B* **1990,** *29B*, 824.

337.Dandia, A.; Khanna, S.; Joshi, K.C. *J. Indian Chem. Soc.* **1990,** *67*, 824.

338.Jackson, A.H.; Johnston, D.N.; Shannon, P.V.R. *J.Chem. Soc. Chem. Commun.* **1975,** 911.

339.Dandia, A.; Khanna, S.; Joshi, K.C. *Indian J. Chem. Sect. B* **1991,** *30B*, 469.

340.Hesson, D.P. *U.S. 4,639,454 27 Jan 1987* **1987,** 9 pp.

341.Sone, T.; Iizuka, K.; Kobayashi, M.; Sako, K.; Suzuki, N.; Wakabayashi, M. *Japan. Kokai 77,142,038 26 Nov 1977 (CA 89:42820k)* **1977,** 7 pp.

342.Sone, T.; Iizuka, K.; Kobayashi, M.; Sako, K.; Suzuki, N.; Wakabayashi, M. *Japan. Kokai 77, 142,040 26 Nov 1977 (CA 88:152258)* **1977,** 8 pp.

343.Sone, T.; Sako, K.; Kobayashi, M.; Iizuka, K.; Suzuki, N.; Wakabayashi, M. *Japan. Kokai 78, 02,450 11 Jan 1978 (CA 89:42823p)* **1978**.

344.Maysinger, D.; Birus, M.; Movrin, M. *Pharmazie* **1982,** *37*, 779.

345.Stünzi, H. *Aust. J. Chem.* **1981,** *34*, 365.

346.Casey, L.A.; Galt, R.; Page, M.I. *J.Chem. Soc. Perkin Trans. II* **1993,** 23.

347.Mirrlees, M.S.; Taylor, P.J. *Drug Des. Discov.* **1994,** *11*, 223.

348.El-Nader, H.M.A.; Moussa, M.N.H. *Chem. Pharm. Bull.* **1996,** *44*, 1641.

349.Ismail, A.M.; Zaghloul, A.A. *Int. J. Chem. Kinet.* **1998,** *30*, 463.

350.Berci-Filho, P.; Quina, F.H.; Gehlen, M.H.; Politi, M.J.; Neumann, M.G.; Barros, T.C. *J. Photochem. Photobiol. A.* **1995,** *92*, 155.

351.Chi, Y.; Chen, H.Q.; Chen, G.N. *Anal. Chim. Acta* **1997,** *354*, 365.

352.Connor, D.T.; Flynn, D.L. *PCT Int. Appl. WO 89 03,818 05 May 1989 (CA 111:194317n)* **1989,** 75 pp.

353.Zacharova-Kalavska, D.; Kosturiak, A. *Collect. Czech. Chem. Commun.* **1975,** *40*, 1504.

354.Baiocchi, L.; Giannangeli, G. *Tetrahedron Lett.* **1988,** *24*, 3651.

355.Harada, H.; Morie, T.; Hirokawa, Y.; Terauchi, H.; Fujiwara, I.; Yoshida, N.; Kato, S. *Chem. Pharm. Bull.* **1995,** *43*, 1912.

356. Joshi, K.C.; Jain, R.; Chand, P.; Sharma, V. *Indian J. Chem. Sect. B* **1984,** *23B*, 386

357.Perez, A. L.; Ciccio, J.F. *Ing. Cienc. Quim.* **1991,** *13*, 20.

358.Rajopadhye, M.; Popp, F.D. *J. Med. Chem.* **1988,** *31*, 1001.

359.Bergman, J.; Vallberg, H. *Acta Chem. Scand.* **1997,** *51*, 742.

360.Sakai, S.; Aimi, N.; Kubo, A.; Kitagawa, M.; Hanasawa, M.; Katano, K.; Yamaguchi, K.; Haginiwa, J. *Chem. Pharm. Bull.* **1975,** *23*, 2805.

361.Kaupp, G.; Matties, D. *Chem. Ber.* **1987,** *120*, 1897.

362.Webber, S.E.; Tikhe, J.; Worland, S.T.; Fuhrman, S.A.; Hendrickson, T.F.; Mattews, D.A.; Love, R.A.; Patick, A.K.; Meador, J.W.; Ferre, R.A.; Brown, E.L.; DeLisle, D.M.; Ford, C.E.; Binford, S.L. *J. Med. Chem.* **1996,** *39*, 5072.

363.Otomasu, H.; Ohmiya, S. *Japan. Kokai 75,137,976 01 Nov 1975 (CA 85:21357s)* **1975**.

364.Joshi, K.C.; Pardasani, R.T.; Dandia, A.; Bhagat, S. *Heterocycles* **1981,** *16*, 1555.

365.Abd-El-Rahman, N.M. *Phosph. Sulfur, Silicon Relat. Elem.* **1991,** *63*, 87.

366.Sidky, M.M.; Abdou, W.M.; El-Kateb, A.A.; Osman, F.H.; Abdel-Rahman, N.M. *Egypt. J. Chem.* **1984,** *27*, 817.

367.Mahran, M.R.H.; Khidre, M.D.; Abdou, W.M. *Phosp. Sulf. Silicon Relat. Elem.* **1995,** *101*, 17.

368.Razumov, A.I.; Gurevich, P.A.; Nurtdinov, S.K.; Muslimov, S.A.; Tyl'nova, L.M. *Zh. Obshch. Khim.* **1977,** *47*, 1421.

369.Riisalu, H.; Vasilev, V.V.; Ionin, B.I. *Zh. Obshch. Khim.* **1984,** *54*, 563.

370.Riisalu, H.; Vasilev, V.V.; Ionin, B.I. *Zh. Obshch. Khim.* **1985,** *55*, 2237.

371.Sharma, D.; Bansal, R.K. *J. Indian Chem. Soc.* **1990,** *67*, 29.

372.Gurevich, P.A.; Akhmetova, G.Z.; Gubaidullin, A.T.; Moskva, V.V.; Litvinov, I.A. *Rus. J. Gen. Chem.* **1998,** *68*, 1501.

373.Singh, M.S.; Mishra, G.; Mehrotra, K.N. *Phosph.; Sulf.; Silicon.* **1991,** *63*, 177.

374.Ryapisova, L.V.; Kashevarova, L.B.; Shaikhiev, I.G.; Fridland, S.V. *Rus. J. Gen. Chem.* **1997,** *67*, 1948.

375.Boulos, L.S.; El-Kateb, A.A. *Chem. Ind.* **1983,** 864.

376.Lathourakis, G.E.; Litinas, K.E. *J. Chem. Soc. Perkin Trans. I.* **1996,** 491.

377.Brittain, D.R.; Brown, D.; Wood, R. *UK Pat Appl. GB 2,119,797 23 Nov 1983 (CA 100:174828z)* **1983,** 9 pp.

377.Falsone, G.; Cateni, F.; El-Alali, A.; Papaioannou, A.; Ravalico, L.; Furlani, A. *Pharm. Pharmacol. Lett.* **1992,** *2*, 104.

378.Falsone, G.; Cateni, F.; Denardo, M.M.; Darai, M.M. *Z. Naturforsch.***1993,** *48b*, 1391.

380.Razumov, A.I.; Yarmukhametova, D.K.; Kudryavtsev, B.V.; Gurevich, P.A.; Musiimov, S.A. *Zh. Obshch. Khim.* **1978,** *48*, 228.

381.Razumov, A.I.; Gurevich, P.A.; Muslimov, S.A.; Usacheva, V.G. *Zh. Obshch. Khim.* **1976,** *46*, 2381.

382.Coda, A.C.; Desimoni, G.; Quadrelli, P.; Riguetti, P.P.; Tacconi, G. *Gazz. Chim. Ital.* **1987,** *117*, 301.

383.Coda, A.C.; Desimoni, G.; Invernizzi, A.G.; Quadrelli, P.; Riguetti, P.P.; Tacconi, G. *Tetrahedron* **1987,** *43*, 2843.

384.Eberle, M.K.; Kahle, G.G.; Shapiro, M.J. *J. Org. Chem.* **1982,** *47*, 2210.

385.Felcht, U.; Regitz, M. *Chem. Ber.* **1975,** 2040.

386.Disteldorf, W.; Regitz, M. *Liebigs Ann. Chem.* **1976,** 225.

387.Mikhailovski, A.G.; Ignatenko, A.V.; Bubnov, Y.N. *Chem. Heterocycl. Compd. (NY)* **1998,** *34*, 785.

388.Irvine, J.L. *U.S. 4,020,179 26 Apr 1977 (CA 87:23042a)* **1977,** .3 pp.

389.Isshiki, K.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H.; Tatsuta, K. *J. Antibiotics* **1987,** *40*, 1202.

390.Bogavac, M.; Arsenijevic, L.; Pavlov, S.; Arsenijevic, V. *Arh. Farm.* **1985,** *35*, 99.

391.Kornet, M.J.; Thio, A.P.; Thorstenson, J.H. *J. Pharm. Sci.* **1977,** *66*, 1022.

392.Dallacker, F.; Sanders, G. *Chem.-Ztg.* **1986,** *110*, 405.

393.Kaiser, E.M.; Knutson, P.L. *Synthesis* **1978,** 148.

394.Khan, M.T.J.; Ashraf, M.; Alam, M.; Lone, K.P. *Acta Physiol. Pharmacol. Latinoam.* **1986,** *36*, 391.

395.Gevorkyan, K.A.; Papayan, G.L.; Chshmarityan, S.G.; Paronikyan, R.G.; Akopyan, N.E.; Engoyan, A.P. *Khim. Farm. Zh.* **1987,** *21*, 167.

396.Joshi, K.C.; Jain, R.; Garg, S. *Pharmazie* **1985,** *40*, 21.

397.Metwally, S.A.M.; Younes, M.I.; Abbas, H.H. *Acta Chim. Hung.* **1989,** *126*, 591.

398.Khalil, Z.H.; Abdel-Rahman, A.E. *J. Indian Chem. Soc.* **1977,** *54*, 904.

399.Popp, F.D. *J. Heterocycl. Chem.* **1982,** *19*, 589.

400.Popp, F.D.; Parson, R.; Donigan, B.E. *J. Heterocycl. Chem.* **1980,** *17*, 1329.

401.Dilber, S.; Saban, M.; Gelineo, A.; Arsenijevic, L.; Bogavac, M.; Pavlov, S. *Pharmazie* **1990,** *45*, 800.

402.Dilber, S.; Saban, M.; Jelaca, J.; Gelineo, A.; Arsenijevic, L.; Bogavac, M. *Pharmazie* **1989,** *44*, 649.

403.Hashizume, K.; Nagano, H.; Kakoi, H.; Tanino, H.; Okada, K.; Inoue, S. *Yakugaku Zasshi.* **1985,** *105*, 357.

404.Joshi, K.C.; Jain, R.; Nishith, S. *Heterocycles* **1990,** *31*, 31.

405.Otomasu, H.; Yoshida, K.; Natori, K. *Chem. Pharm. Bull.* **1975,** *23*, 1436.

406.Bogatskii, A.V.; Andronati, S.A.; Zhilina, Z.I.; Kobzareva, ºV.; Sharbatyan, P.A.; Ivanova, R.Y.; Chumachenko, T.K. *Zh. Obshch. Khim.* **1975,** *45*, 396.

407.Chazeau, V.; Cussac, M.; Boucherle, A. *Eur. J. Med. Chem.* **1992,** *27*, 615.

408.Zhungietu, G.I.; Sinyavskaya, L.P. *Khim. Geterotsikl. Soedin.* **1976,** 204.

409.Varma, R.S.; Gupta, P. *J. Indian Chem. Soc.* **1989,** *66*, 804.

410.Kleyer, D.L.; Haltiwanger, R.C.; Koch, T.H. *J. Org. Chem.* **1983,** *48*, 147.

411.Eshba, N.H.; Salama, H.M. *Pharmazie* **1985,** *40*, 320.

412.Rida, S.M.; Salama, H.M.; Labouta, I.M.; Ghany, Y.S.A. *Pharmazie* **1985,** *40*, 727.

413.Lakhan, R.; Bhargava, P.N.; Prasad, S. *J. Indian Chem. Soc.* **1982,** *59*, 804.

414.Vladzimirskaya, E.V.; Kirichenko, B.M. *Farm. Zh. (Kiev)* **1975,** *30*, 41.

415.Vladzimirskaya, E.V.; Zdorenko, V.A. *Farm. Zh. (Kiev)* **1977,** 37.

416.Nosachenko, V.I.; Kochergin, P.M.; Steblyuk, P.N. *Khim. Geterotsilk. Soedin.* **1976,** 1132.

417. Jain, S.C.; Bhagat, S.; Rajwanshi, V.K.; Babu, B.R.; Sinha, J. *Indian J. Chem. Sect. B* **1997,** *36B*, 633.

418. Wenkert, E.; Hudlicky, T. *Synth. Commun.* **1977,** *7*, 541.

419. Ragoussis, N. *Tetrahedron Lett.* **1987,** *28*, 93.

420.AlThebeiti, M.S. *Heteroatom Chem.* **1994,** *5*, 571.

421.Al-Thebeiti, M.S.; El-Zohry, M.F. *Heterocycles* **1995,** *41*, 2475.

422.Dandia, A.; Taneja, H.; Gupta, R.; Paul, S. *Synth. Commun.* **1999,** *29*, 2323.

423.Khalil, S.M.; Hassaan, A.M.A. *Acta Phys. Pol. A.* **1993,** *83*, 477.

424.Popp, F.D.; Donigan, B.E. *J. Pharm. Sci.* **1979,** *68*, 519.

425.Popp, F.D.; Pajouhesh, H. *J. Pharm. Sci.* **1982,** *71*, 1052.

426.Joshi, K.C.; Patni, R.; Chand, P.; Sharma, V.; Bhattacharya, S.K.; Rao, Y.V. *Pharmazie* **1984,** *39*, 153.

427.Beccalli, E.M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1993,** *49*, 4741.

428.Daisley, R.W.; Walker, J. *Eur. J. Med. Chem.* **1979,** *14*, 47.

429.Okada, K.; Tanino, H.; Hashizume, K.; Mizuno, M.; Kakoi, H.; Inoue, S. *Tetrahedron Lett.* **1984,** *25*, 4403.

430.Okada, K.; Hashizume, K.; Nagano, H.; Kakoi, H.; Tanino, H.; Inoue, S. *Yakugaku Zasshi* **1985,** *105*, 368.

431.Inoue, S.; Okada, K.; Tanino, H.; Hashizume, K.; Kakoi, H. *Tetrahedron Lett.* **1984,** *25*, 4407.

432.Hashizume, K.; Nagano, H.; Kakoi, H.; Tanino, H.; Okada, K.; Inoue, S. *Yakugaku Zasshi* **1985,** *105*, 352.

435.Inoue, S.; Okada, K.; Tanino, H.; Kakoi, H. *Tetrahedron Lett.* **1986,** *27*, 5225.

436.Inoue, S.; Okada, K.; Tanino, H.; Hashizume, K.; Kakoi, H. *Tetrahedron* **1994,** *50*, 2729.

437.Junek, H.; Dworczak, R.; Sterk, H.; Fabian, W. *Liebigs Ann. Chem.* **1989,** 1065.

438.Long, D.R.; Richards, C.G.; Ross, M.S.F. *J. Heterocycl. Chem.* **1978,** *15*, 633.

439.Baiocchi, L.; Giannangeli, G. *J. Heterocycl. Chem.* **1988,** *25*, 1905.

440.Hosomi, A. *Eur. Pat. Appl. EP 307,000 15 Mar 1989 (CA 111:134130m)* **1989,** 7 pp.

441.Hosomi, A.; Hayashi, S.; Hoashi, K.; kohra, S.; Tominaga, Y. *J. Chem. Soc. Chem. Commun.* **1987,** 1442.

442.Berdinskii, I.S.; Mashivets, A.; Orlova, L.D. *Zh. Org. Khim.* **1985,** *21*, 895.

443.Furukawa, M.; Suda, T.; Hayashi, S. *Chem. Pharm. Bull.* **1976,** *24*, 1708.

444.Singh, J.; Sardana, Anand, N. *Indian J. Chem. Sect. B* **1989,** *28B*, 1031.

445.Singh, J.; Nigam, M.B.; Sardana, V.; Jain, P.C.; Anand, N. *Indian J. Chem. Sect. B* **1981,** *20B*, 596.

446.Pardasani, R.T.; Pardasani, P.; Muktawat, S.; Ghosh, R.; Mukherjee, T. *J. Heterocycl. Chem.* **1999,** *36*, 189.

447.Bergman, J.; Eklund, N. *Tetrahedron* **1980,** *36*, 1445.

448.Martinez, F.; Naarmann, H. *Angew. Makromol. Chem.* **1990,** *178*, 1.

449.Kallitsis, J.K.; Martinez, F.; Naarmann, H. *Synth. Met.* **1993,** *55*, 773.

450.Pindur, U. *Arch. Pharm.* **1981,** *314*, 337.

451.Tormos, G.V.; Belmore, K.A.; Cava, M.P. *J. Am. Chem. Soc.* **1993,** *115*, 11512.

452.Garrido, F.; Ibanez, J.; Gonalons, E.; Giraldez, A. *Eur. J. Med. Chem.* **1975,** *10*, 143.

453.Ibanez-Catalan, J.; Forn, M.P.; Osso, F.J. *Ann. Quim.* **1976,** *72*, 571.

454.Song, H.N.; Lee, H.J.; Kim, H.R.; Ryu, E.K.; Kim, J.N. *Synth. Commun.* **1999,** *29*, 3303.

455.Pujol, A.H.; Rabassa, S.B. *Ger. Offen. 2,521,966 27 Nov 1975 (CA 84:59188e)* **1975**.

456.Klumpp, D.A.; Yeung, K.Y.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.* **1998,** *63*, 4481.

457.Ijaz, A.S.; Parrick, J.; Yahya, A. *J. Chem. Res.* **1990,** 116.

458.Wexler, H.; Barboiu, V. *Rev. Roum. Chim.* **1976,** *21*, 127.

459.Idel, K.J.; Freitag, D.; Nouvertne, G. *Ger. Offen. 2,500,092 08 Jul 1976* **1976,** 25 pp.

460.Johnsen, B.A; Undheim, K *Acta Chem. Scand.* **1984,** *38B*, 109.

461.Moderhack, D.; Goos, K.H. *Chem. Ber.***1987,** *120*, 921.

462.Moderhack, D.; Preu, L. *J. Chem. Soc.; Chem. Commun.* **1988,** 1144.

463.Mohammed, A.K.; Bekheit, M.M.; Fouda, A.S. *Bull. Soc. Chim. Fr* . **1985,** 331.

464.Franke, A. *Justus Liebigs Ann. Chem.* **1978,** 717.

465.Bennet, G.B.; Mason, R.B.; Shapiro, M.J. *J. Org. Chem.* **1978,** *43*, 4383.

466.Abdel-Latif, F.F.; Regalia, H.A.A.; Gohar, A.K.M.N.; Mohamed, Y.S. *Indian J. Chem. Sect. B Sect. B.* **1985,** *24B*, 775.

467.Kennewell,P.D.; Miller, D.J.; Scrowston, R.N.; Westwood, R. *J. Chem. Res. (S)* **1995,** 396.

468.Koch, T.H.; Olesen, J.; Foy, J. *J. Org. Chem.* **1975,** *40*, 117.

469.Righetti, P.P.; Gamba, A.; Tacconi, G.; Desimoni, G. *Tetrahedron* **1981,** *37*, 1779.

470.Tacconi, G.; Invernizzi, A.G.; Desimoni, G. *J. Chem. Soc. Perkin I* **1976,** 1872.

471.Okada, K.; Sakuma, H.; Inoue, S. *Chem. Lett.* **1979,** 131.

472.Okada, K.; Sakuma, H.; Kondo, M.; Inoue, S. *Chem. Lett.* **1979,** 213.

473.Okada, K.; Kondo, M.; Tanino, H.; Kakoi, H.; Inoue, S. *Heterocycles* **1992,** 589.

474.Richards, C.G.; Thurston, D.E. *Tetrahedron* **1983,** *39*, 1817.

475.Scipchandler, M.T.; Mattingly, P.G. *Heterocycles* **1990,** *31*, 555.

476.Brasyunas, V.B.; Andreyanova, T.A.; Safonova, T.S.; Solov'eva, N.P.; Turchin, K.F.; Sheinker, Y.N. *Chem. Heterocycl. Compd. (Engl. Transl.).* **1988,** *24*, 670.

477.Atwell, G.J.; Baguley, B.C.; Denny, W.A. *J. Med. Chem.* **1989,** *32*, 396.

478.Bass, Y.; Morgan, R.J.; Donovan, R.J.; Baker, A.D. *Synth. Commun.* **1997,** *27*, 2165.

479.Lasikova, A.; Vegh, D. *Chem. Pap. - Chem. Zvesti.* **1997,** *51*, 408.

480.Kerke, J.S.; Sunthankar, S.V. *Indian J. Chem. Sect. B* **1976,** *14B*, 1013.

481.Sparatore, F.; Savelli, F.; Cordella, G. *Farmaco* **1980,** *35*, 735.

482.Baldwin, M.A.; Langley, G.J. *J. Labelled Compd. Radiopharm* **1985,** *22*, 1233.

483.Chaudhuri, N.K.; Servando, O.; Sung, M.S. *J. Labelled Compd. Radiopharm.* **1985,** *22*, 117.

484.Holla, D.C.; Seshadri, S. *Bull. Chem. Soc. Jpn.* **1984,** *57*, 2984.

485.Meyer, H. *Liebigs Ann. Chem.* **1981,** 1545.

486.Jain, A.; Mukerjee, A.K. *Indian J. Chem. Sect. B* **1987,** *26B*, 1102.

487.Radul, O.M.; Bukhanyuk, S.M.; Rekhter, M.A.; Zhungietu, G.I.; Ivanova, I.P. *Khim. Geterotsikl. Soedin.* **1982,** 1427.

488.Weiβenfels, M.; Ulrici, B.; Kaubisch, S. *Z. Chem.* **1978,** *18*, 138.

489.Bielavsky, J. *Collect. Czech. Chem. Commun.* **1977,** *42*, 2802.

490.Hamana, M.; Takeo, S.; Noda, H. *Chem. Pharm. Bull.* **1977,** *25*, 1256.

491.Gainor, J.A.; Weinreb, S.M. *J. Org. Chem.* **1981,** *46*, 4317.

492.Gainor, J.A.; Weinreb, S.M. *J. Org. Chem.* **1982,** *47*, 2833.

493.Chen, S.F.; Papp, L.M.; Ardecky, R.J.; Rao, G.V.; Hesson, D.P.; Forbes, M.; Dexter, D.L. *Biochem. Pharmacol.* **1990,** *40*, 709.

494.Smolders, R.R.; Waefelaer, A.; Coomans, R.; Francart, D.; Hanuise, J.; Voglet, N. *Bull. Soc. Chim. Belg.* **1982,** *91*, 33.

495.Behrens, C.H. *US 4,918,077 17 Apr 1990 (CA 113:115114j)* **1990,** 10 pp.

496.Allais, A.; Guillaume, J.; Poittevin, A.; Nedelec, L.; Chifflot, L.; Peterfalvi, M.; Hunt, P. *Eur. J. Med. Chem.* **1982,** *17*, 371.

497.Nishigashi, S.; Sakae, M.; Takamatsu, S. *Jpn. Kokai Tokkyo Koho 61 91,162 09 May 1986 (CA 105: 208605v)* **1986,** 2 pp.

498.Rajamanickam, P.; Shanmugan, P. *Synthesis* **1985,** 541.

499.Mohan, P.S.; Rajamanickam, P.; Ayyasamy, A.; Prasad, K.J.R.; Shanmugam, P. *Indian J. Chem. Sect. B* **1989,** *28B*, 270.

500.Zey, R.L.; Jones, D.E.; Lemmer, R.R.; Morrill, J.A.; Novak, A.J. *Abstr. Pap. Amer. Chem. Soc.* **1998,** *216*, U590.

501.Capuano, L.; Diehl, V. *Chem. Ber.* **1976,** *109*, 723.

502.Morales-Rios, M.S.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1991,** *29*, 893; Morales-Rios, M.S.; Martinez-Galero, M.L.-C.; Joseph-Nathan, P. *J. Org. Chem.* **1995,** *60*, 6194.

503.Zhungieto, G.I.; Gorgos, V.I.; Rekhter, M.A.; Korpan, A.I. *Izv. Akad. Nauk Mold. SSR, Ser. Biol. Khim. Nauk.* **1980,** 61.

504.Zhungieto, G.I.; Zorin, L.M.; Rekhter, M.A. *Izv. Akad. Nauk Mold. SSR, Ser. Biol. Khim. Nauk.* **1981,** 57.

505.Jackson, A.H.; Prasitpan, N.; Shannon, P.V.R.; Tinker, A.C. *J. Chem. Soc. Perkin Trans. I.* **1987,** 2543.

506.Black, D.S.C.; Wong, L.C.H. *J. Chem. Soc. Chem. Commun.* **1980,** 200.

507.Rekhter, M.A. *Khim. Geterotsikl. Soedin.* **1993,** *29*, 642.

508.Katrizky, A.R.; Fan, W.Q.; Koziol, A.E.; Palenik, G.J. *J. Heterocycl. Chem.* **1989,** *26*, 821.

509.Baker, J.T.; Duke, C.C. *Aust. J. Chem.* **1976,** *29*, 1023.

510.Begley, W.J.; Grimshaw, J. *J. Chem. Soc. Perkin Trans. I.* **1975,** 1840.

511.Adam, J.M.; Winkler, T. *Helv. Chim. Acta* **1984,** *67*, 2186.

512.Katrizky, A.R.; Fan, W.Q.; Liang, D.S.; Li, Q.L. *J. Heterocycl. Chem.* **1989,** *26*, 1541.

513.Cornforth, J.W.; Hitchcock, P.B.; Rozos, P. *J. Chem. Soc. Perkin Trans. I* **1996,** 2787.

514.Middleton, W.J.; Bingham, E.M. *J. Org. Chem.* **1980,** *45*, 2883.

515.Boechat, N; Pinto, A.C. *US 6034266* 07 March 2000, **2000**, 9 pp.

516.Soliman, E.M. *Anal. Lett.* **1998,** *31*, 299.

517.Kosturiak, A.; Polavka, J.; Valko, L.; Slama, J.; Gruskova, A.; Miglierini, M. *J. Magn. Magn. Mater.* **1996,** *153*, 184.

518.Palenik, G.J.; Koziol, A.E.; Katritzky, A.R.; Fan, W.Q. *J. Chem. Soc.; Chem. Commun.* **1990,** 715.

519.Frolova, N.A.; Kravtsov, V.K.; Biyushkin, V.N.; Chumakov, Y.M.; Belkova, O.N.; Malinovskii, T.I. *Zh. Strukt. Khim.* **1988,** *29*, 155.

520.Rathna, A.; Chandrasekhar, J. *J. Chem. Soc. Perkin Trans. II* **1991,** 1661.

521.Zukerman-Schpector, J.; Castellano, E.E.; Pinto, A.C.; Silva, J.F.M.; Barcellos, M.T.F.C. *Acta Cryst.* **1992,** *C48*, 760.

522.Zukerman-Schpector , J.; Pinto, A.C.; Silva, J.F.M.; Barcellos, M.T.F.C. *Acta Cryst.* **1995,** *C51*, 675.

523.Zukerman-Schpector, J.; Pinto, A.C.; Silva, J.F.M.; Barcellos, M.T.F. Pires, S.S.; Fraiz Jr.; S.V. *Acta Cryst.* **1994,** *C50*, 945.

524.Black, D.S.C.; Chaichit, N.; Gatehouse, B.M.; Moss, G.I. *Aust. J. Chem.* **1987,** *40*, 1745.

525.Miehe, G.; Süsse, P.; Kupcik, V.; Egert, E.; Nieger, M.; Kunz, G.; Gerke, R.; Knieriem, B.; Niemeyer, M.; Lüttke, W. *Angew. Chem. Int. Ed. Engl.* **1991,** *30*, 964.

526.Zukerman-Schpector, J.; Pinto, A.C.; Silva, J.F.M.; Barcellos, M.T.F.C. *Acta Cryst.* **1993,** *C49*, 173.

527.De, A. *Acta Cryst.* **1992,** *C48*, 660.

528.Baba, K.; Kozawa, M.; Hata, K.; Ishida, T.; Inoue, M. *Chem. Pharm. Bull.* **1981,** 2182.

529.Zukerman-Schpector, J.; Pinto, A.C.; Silva, J.F.M.; Silva, R.B. *Acta Cryst.* **1994,** *C50*, 87.

530.Plana, F.; Briansó, J.L.; Miravitlles, C.; Solans, X.; Font-Altaba, M. *Acta Cryst.* **1976,** *B 32*, 2660.

531.Bigotto, A.; Galasso, V. *Spectr. Acta* **1979,** *35A*, 725.

532.Petrov, I.; Grupce, O.; Stafilov, T. *J. Mol. Struct.* **1986,** *142*, 275.

533.Laatsch, H.; Thomson, R.H.; Cox, P.J. *J. Chem. Soc. Perkin Trans. II* **1984,** 1331.

534.Baron, M.L.; Martin, L.L.; Era, I.D.; Simmonds, P.M.; Woolcock, M.L. *Aust. J. Chem.* **1990,** *43*, 741.

535.Albright, T.A.; Freeman, W.J. *Org. Magn. Res.* **1977,** *9*, 75.

536.Galasso, V.; Pellizer, G.; Pappalardo, G.C. *Org. Magn. Res.* **1977,** *9*, 401.

537.Winkler, T.; Ferrini, P.G.; Haas, G. *Org. Magn. Res.* **1979,** *12*, 101.

538.Ballantine, J.A. *J. Chem. Soc. Perkin Trans. I* **1979,** 1182.

539.Angell, E.C.; Black, D.S.C.; Kumar, N. *Magn. Res. Chem.* **1992,** *30*, 1.

540.Panasenko, A.A.; Caprosh, A.F.; Radul, O.M.; Rekhter, M.A. *Russ. Chem. Bl.* **1994,** *43*, 60.

542.Augusti, R.; Dias, A.D.; Fortes, I.C.P. *Quimica Nova* **1998,** *21*, 655.

543.Barbuch, R.J.; Peet, N. P.; Coutant, J. E. *Org. Mass Spectr.* **1986,** *21*, 521.

544.Varma, R.S.; Singh, A.P.; Singh, S.P. *Org. Mass Spectr.* **1992,** *27*, 17.

545.Zhungietu, G.I.; Chmykhova, N.I.; Gorgos, V.I.; Rekhter, M.A.; Kharinton, K.S. *Khim. Geterotsikl. Soedin.* **1977,** 642.

546.Khariton, K.S.; Zhungietu, G.I.; Rekhter, M.A.; Oloi, B.T.; Chmykhova, N.I. *Khim. Geterotsikl. Soedin.* **1975,** 957.

547.Peet, N.P.; Barbuch, R.J. *Org. Mass Spectr.* **1984,** *19*, 171.

548.Zhungietu, G.I.; Chmykhova, N.I.; Gorgos, V.I.; Rekhter, M.A.; Kharinton, K.S.; Oloi, B.T.; Dormidontova, N.P. *Khim. Geterotsikl. Soedin.* **1977,** 639.

549.Maquestiau, A.; Beugnies, D.; Flammang, R.; Freiermuth, B.; Wentrup, C. *Org. Mass Spectr.* **1990,** *25*, 197.

550.Thétaz, C.; Wentrup, C. *J. Am. Chem. Soc.* **1975,** *98*, 1258.

551.Ijaz, A.S.; Alam, M. *Arab. J. Sci. Eng.* **1992,** *17*, 481.

552.Terentev, P.B.; Mazhilis, L.I.; Kalandarishvili, A.G.; Stankyavichus, A.P. *Khim. Geterotsikl. Soedin.* **1986,** 1052.

553.Palmer, M.H.; Blake, A.J.; Gould, R.O. *Chem. Phys.* **1987,** *115*, 219.

554.Bray, P.J.; Mulkern, R.V.; Greenbaum, S.G. *Magn. Res. Chem.* **1985,** *23*, 801.

555.Hiyama, Y.; Maruizumi, T.; Niki, E. *Bull. Chem. Soc. Japan.* **1979,** *52*, 2752.

556.Galasso, V. *Gazz. Chim. Ital.* **1976,** *106*, 571.

557.Galasso, V.; Colonna, F.P..; Distefano, G. *J. Electron Spectrosc. Relat. Fenom.* **1977,** *10*, 227.

558.Alam, M.; Mohammad, A. *Proc. Pak. Acad. Sci.* **1987,** *24*, 337.

559.Dessouki, H.A.; Shalabi, A.S.; Killa, H.M.; Zaki, M. *Spectr. Acta.* **1988,** *44a*, 849.

560.Ciurea, L.; Sahini, V.E.; Volanschi, E.*Rev. Roum. Chim.* **1975,** *20*, 1029.

561.Kuhnert-Brandstatter, M.; Reidmann, M. .*Mikrochim. Acta* **1989,** 173.

562.Elliott, R.J.; Gardner, D.L. *Anal. Biochem.* **1976,** *70*, 268.

563.Palfi, G.; Palfi, Z. *Maydica* **1982,** *27*, 107.

564.Palfi, G.; Gulyas, S.; Szollosi, I. *Acta Biol.* **1987,** *33*, 25.

565.Gulyas, S.; Palfi, G. *Sov Plant Physiol-Engl Tr.* **1986,** *33*, 472.

566.Kapyla, M. *Grana* **1991,** *30*, 1992.

567.Eriksen, A.B. *Medd. Nor. Inst. Skogforsk.* **1976,** *32*, 389.

568.Shah, A.; Rahman, S.S.; deBiasi, V.; Camilleri, P. *Anal. Commun.* **1997,** *34*, 325.

569.Yamaguchi, Y. *Clin. Chem.* **1978,** *12*, 2178.

570.Broadhurst, A.V.; Roberts N.A.; Ritchie A.J.; Handa B.K.; Kay C. *Anal. Biochem.* **1991,** *193*, 280.

571.Bonte, W.; Johansson, J.; Garbe, G.; Berg, S. *Arch. Kriminol.* **1976,** *158*, 163.

572.Trigoso, C.I.; Ibanez, N.; Stockert, J.C. *J. Histochem. Cytochem.* **1993,** *41*, 1557.

573.Datta, S.; Datta, S.C. *J. Chromatogr.* **1979,** *170*, 228.

574.Panikkar, B.; Kuttan, R. *Indian J. Biochem. Biophys.* **1989,** *26*, 126.

575.Dochinets, D.I.; Zorya, B.P.; Petrenko, V.V.; Klyuev, N.A. *Ukr. Khim. Zh. (Russ. Ed.)* **1989,** *55*, 389.

576.Dochinets, D.I.; Petrenko, V.V.; Zorya, B.P. *Zh. Anat. Khim.* **1989,** *44*, 510.

577.Dochinets, D.I.; Petrenko, V.V.; Kubrak, E.A. *Khim. Prir. Soedin.* **1988,** 305.

580.Sybulski, S.; Maughan, G.B. *Am. J. Obstet. Gynecol.* **1975,** *121*, 32.

581.Kachel, C.D.; Mendelsohn, F.A. *J. Steroid Biochem.* **1979,** *5*, 563.

582.Wendelin, W.; Knotz, F.; Schramm, H.W. *Monatsh. Chem.* **1975,** *106*, 159.

583.Gubitz, G.; Wendelin, W. *Anal. Chem.* **1979,** *51*, 1690.

584.Gubitz, G. *J. Chromatogr.* **1980,** *187*, 208.

585.Zhungietu, G.I.; Sinyavskaya, L.P.; Filipenko, T.Y. *Khim. Geterotsikl. Soedin.* **1977,** 217.

586.Lindner, W.; Santi, W. *J. Chromatogr.* **1979,** *176*, 55.

587.Kataoka, M.; Doi, Y.; Sim, T.S.; Shimizu, S.; Yamada, H. *Arch. Bioch. Biophys.* **1992,** *294*, 469.

588.Hata, H.; Shimizu, S.; Hattori, S.; Yamada, H. *Biochim. Biophys. Acta.***1989,** *990*, 175.

589.Julliard, J.H. *Bot. Acta* **1994,** *107*, 191.

590.Yamada, H.; Shimizu, A.; Hata, H. *JP 61134339* **1986,** 1 pp.

591.Shimizu, S.; Hattori, S.; Hata, H.; Yamada, H. *Eur. J. Biochem.* **1988,** *174*, 37.

592.Tabushi, I.; Kugimiya, S.; Mizutani, T. *J. Am. Chem. Soc.* **1983,** *105*, 1658.

593.Hata, H.; Shimizu, S.; Hattori, S.; Yamada, H. *J. Org. Chem.* **1990,** *55*, 4377.

594.Nassenstein, A.; Hemberger, J.; Schwartz, H.; Kula, M.R. *J. Biotechnol.* **1992,** *26*, 183.

595.Weyler, W.; Dodge, T.C.; Lauff, J.J.; Wendt, D.J. *WO 9719175, 29 May 1997* **1997,** 54 pp.

596.Weyler, W.; Dodge, T.C.; Lauff, J.J.; Wendt, D.J. *US 5866396* **1999,** 5 pp.

597.Duran, N.; Antonio, R.V.; Haun, M.; Pilli, R.A. *World J. Microbiol. Biotechnol.* **1994,** *10*, 686.

598.Hoeffkes, H.; Buettner, R.; Moeller, H. *Ger. Offen. DE 4,211,450 07 Oct 1993 (CA 119:278349c)* **1992,** 5 pp.

599.Lang, G.; Cotteret, J. *Eur. Pat. Appl. EP 497,697* **1992,** 15 pp.

600. Lang, G.; Cotteret, J. *Eur. Pat. Appl. EP 502,783* **1992,** 14 pp.

601. Lang, G.; Cotteret, J. *US 5190564* **1993,** 7 pp.

602.Lang, G.; Cotteret, J. *US 5261926* **1993,** 7 pp.

603.Lang, G.; Cotteret, J. *US 5279616* **1994,** 7 pp.

604.Lang, G.; Cotteret, J. *US 5340366* **1994,** 6 pp.

605.Lang, G.; Cotteret, J. *Eur. Pat. Appl. EP 502,784* **1995,** 15 pp.

606.Moeller, H.; Hoffkes, H. *WO 9424988* **1994,** 36 pp.

607.Moeller, H.; Hoffkes, H. *WO 9424989* **1994,** 31 pp.

608.Moeller, H.; Hoffkes, H. *WO 9524886* **1995,** 34 pp.

609.Moeller, H.; Hoffkes, H. *EP 695162* **1996**.

610.Moeller, H.; Hoffkes, H. *EP 695163* **1996**.

611.Moeller, H.; Hoffkes, H. *US 5611817* **1997**.

612.Moeller, H.; Hoffkes, H. *US 5616150* **1997,** 7 pp.

613.Moeller, H.; Hoffkes, H. *US 5743919* **1998,** .9 pp.

614.Moeller, H.; Hoffkes, H. *WO 9847472, 29 Oct 1998* **1998,** 39 pp.

615.Rosenbaum, G.; Cotteret, J. *US 4750908* **1988,** 6 pp.

616.Anderson, J.S.; Schultz, T.M. *US 4921503* **1990,** 6 pp.

617.Mueller, W. *Swiss 580,673 15 Oct 1976 (CA 86:6388e)* **1976,** 7 pp.

618.Merlo, F.; Bornengo, G. *Eur. Pat. Appl. 3,565 22 Aug 1979 (CA 92:7839p)* **1979,** 9 pp.

619.Upadhyay, R.K. Agarwal, N.; Mishra, G. *J. Indian Chem. Soc.***1995,** *72*, 849.

620.Kueffner, K.; Marx, P.; Laessig, W. *Ger. Offen. DE 3,217,877 17 Nov 1983*, **1983,** 53 pp.

621.Abolin, A.G.; Balabanov, E.I.; Bespalov, B.P.; Bukin, Y.I.; Rumyantsev, B.M.; Titov, V.V.; Yudina, G.I. *Zh. Nauch. Prikl. Fotogr.* **1981,** *26*, 182.

622.Sugai, A. *JP 9040644, 10 Feb 1997* **1997**.

623.Anraku, H. *Eur. Pat. Appl. EP 241,314 14 Oct 1987* **1987,** 45 pp.

624.Anraku, H. *JP 62240616* **1987,** 1 pp.

625.Anraku, H. *Jpn. Kokai Tokkyo Koho JP 63 82,361 13 Apr 1988* **1988,** 7 pp.

626.Anraku, H. *US 5413786* **1995,** 12 pp.

627.Ozutsumi, M.; Ohnishi, Y.; Miyazawa, Y.; Gonda, M. *Japan Kokai 75 57,084 19 May 1975* **1975,** 6 pp.

628.Ivashchenko, A.V.; Lazareva, V.T.; Rumyantsev, V.G. *Chem. Heterocycl. Compd. (Engl. Transl.).* **1982,** *18*, 190.

629.Yamamiya, S.; Abe, Y.; Nishikatsu, H.; Sasaki, S. *JP 4023869* **1992,** 1 pp.

630.Singh, D.D.N.; Singh, M.M.; Chaudhary, R.S.; Agarwal, C.V. *J. Appl. Electrochem.* **1980,** *10*, 587.

631.Kawana, T.; Hirano, A.; Matsuda, T.; Kimura, H.; Yatagai, H. *JP 61082325*, **1986,** 1 pp.

632.Mohamed, Y.S.; Gohar, A.E.M.N.; Abdel-Latif, F.F.; Badr, M.Z.A. *Pharmazie* **1991,** *40*, 312.

633.Kumar, S.P.; Banerjee, A.N. .*Eur. Polym. J.* **1993,** *29*, 889.

634.Som, P.K.; Banerjee, A.N. *Eur. Polym. J.* **1993,** *29*, 889.

635.Hara, F. *US 5739174*, **1998,** 4 pp.

636.Kubo, R. *JP 3281567* **1991,** 1 pp.

637.Papa, S.S. *Eur. Pat. Appl. EP 424,886 02 May 1991 (CA 115:31583q)* **1991**.

638.Jansons, E.; Puke, K.; Cedere, D. *Latv. Kim. Z.* **1992,** 680.

639.Rutledge, T.F. *US 4,100,203 11 Jul 1978 (CA 90:71895q)* **1978,** 13 pp.

640.Rutledge, T.F. *US 4,100,205 11 Jul 1978 (CA 90:103608s)* **1978,** 16 pp.

641.Glover, V.; Bhattacharya, S.K.; Sandler, M. *Indian J. Exp. Biol.* **1991,** *29*, 1.

642.Ghosal, S.; Bhattacharya, S.K.; Muruganandam, A.V.; Satyan, K.S. *Biog. Amines* **1997,** *13*, 91.