

# Review on Chemistry of Natural and Synthetic Indolizines with their Chemical and Pharmacological Properties

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## ABSTRACT

This review emphasizes chemistry of synthetic indolizine analogs including chemical reactions in addition to natural indolizidine alkaloids and their physical and pharmacological properties. Synthetic indolizine analogs for various pharmacological properties such as central nervous system depressant, analgesic and anti-inflammatory, anticancer, antibacterial, antioxidant, larvicidal, and anti-HIV are reported along with their chemical reactions.

**Key words:** Analgesic and anti-inflammatory, antibacterial, anticancer, antioxidant, central nervous system depressant, indolizidine alkaloids, indolizine, larvicidal and anti-HIV

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## INTRODUCTION

The history of indolizine goes back to 1890 when the Italian chemist Angeli<sup>[1]</sup> reported the preparation of the imine-anhydride (1) of pyrrolypyruvic acid and suggested the name pyrindole for the completely unsaturated parent base (2). Twenty-two years later, in 1912, Scholtz<sup>[1]</sup> reported the first synthesis of compound (2). He treated 2-methylpyridine with acetic anhydride at 200–220°C to give what he called “picolide,” acid hydrolysis of which afforded a colorless crystalline solid (subsequently identified as compound<sup>[2]</sup>) which had weakly basic properties. In view of this observation, it was speculated that this compound could not be a true derivative of pyridine. Furthermore, this new compound gave reactions characteristic of pyrroles and indoles and had the same empirical formula (C<sub>8</sub>H<sub>7</sub>N) as indole and isoindole. In light of these observations, Scholtz ascribed the pyrrolopyridine structure (2) to his new compound and named it pyrrocoline but later adopted the name pyrindole as suggested by Angeli.<sup>[1]</sup> The validity of Scholtz’s formulation was confirmed by Diels and Alder,<sup>[1]</sup> who established the presence of four double bonds by catalytic reduction of pyrrocoline to a derivative (3), which on treatment with cyanogen bromide gave a product shown to be identical in all aspects with (±) coniine (4) [Figure 1] previously prepared by Loffler *et al.* At present, the compound previously known as pyrrocoline or pyrindole is known as indolizine with the following numbering (2a).

## Indolizidines as natural products

Indolizidines [Figure 2] are commonly distributed in nature, especially in plants. Their structures can be described either as analogs of the aromatic bicyclic indolizine or as azabicyclo[4.3.0]nonanes.<sup>[2]</sup>

The indolizidine alkaloids exhibit a wide range of pharmacological properties<sup>[3,4]</sup> and have been the focus of various synthetic studies.<sup>[5-15]</sup> Most of the naturally occurring indolizidines have been isolated from species of the genus *Dendrobates* (poison-arrow frogs), *Dendrobium* (orchids), *Leguminosae* family (plants),

*Monomorium* (ants), and *Tylophora*. Among them, the lipophilic pumiliotoxins and hydrophilic polyhydroxy indolizidines are the two most important classes of compounds.

## Pumiliotoxins

A large variety of structurally distinctive and pharmacologically active compounds are isolated from amphibians. The distinctive source is the skin secretions of certain brightly colored frogs native to the rain forests of Western Colombia and Panama. Likely, since pre-Columbian times, these frogs have been employed by the Noanama and Embera Indians to prepare poison blow darts.<sup>[16,17]</sup> The first description of darts envenomed with skin secretions of poison frogs dated from 1825 and described the use of a single frog to charge at least twenty blow darts. The chemistry and pharmacology of “poison dart” frogs of the family *Dendrobatidae* were pioneered by Witkop, Daly *et al.*<sup>[18,19]</sup> To date, more than 300 organic compounds have been isolated from this amphibian family, the vast majority of which are unique to dendrobatid frogs.<sup>[20]</sup> The pumiliotoxin A and allopumiliotoxin classes of dendrobatid alkaloids are a group of ~40 alkylidene indolizidine alkaloids that display particularly significant pharmacological activities.<sup>[21,22]</sup> Pumiliotoxins A and B were the second and third dendrobatid alkaloids to be isolated and were

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initially obtained in 1967 from skin of the Panamanian poison frog *Dendrobates pumilio*.<sup>[23]</sup> Elucidation of the structure of these alkaloids was complicated by their instability in acid, likely due to their allylic hydroxyl group. The structure of these toxins remained unknown until 1980 when a simpler alkaloid, pumiliotoxin 251D, was isolated as the major alkaloid component of skin extracts of the Ecuadorian poison frog, *Dendrobates tricolor* (*Epipedobates tricolor*). Single-crystal X-ray analysis of pumiliotoxin 251D hydrochloride finally provided the key for revealing the constitution of the pumiliotoxin A alkaloids.<sup>[24]</sup>

The pumiliotoxin alkaloids are characterized by the bicyclic 8-hydroxy-8-methyl-6-alkylidene-indolizines ring system [Figure 3]. The allopumiliotoxins contains an additional hydroxy group at C-7. Besides these two main classes, another bicyclic alkaloid, namely, homopumiliotoxin 223G, has been isolated in small quantities from the Panamanian poison frog *D. pumilio* and its structure analyzed.<sup>[25-27]</sup> In this compound, the indolizines moiety is replaced by quinilidizine ring.

Due to the great number of pumiliotoxins, only a few have been given a common name. Pumiliotoxins A and B are relatively toxic and a subcutaneous dose of pumiliotoxin B of 20 µg can cause death in mice. Recent studies show that pumiliotoxin B binds to a unique modulatory site on the voltage-dependent sodium channel and enhances sodium influx.<sup>[28,29]</sup> This ion flow stimulates phosphoinositide breakdown, which is believed to be ultimately expressed as cardiotoxic and myotonic activities. Structure–activity studies of natural alkaloids and synthetic analogs have shown that the structure of the side chain is critical for these pharmacological activities.<sup>[28-33]</sup> The intriguing pharmacological properties and the low availability of the compounds from their natural sources have led to the development of numerous syntheses of the pumiliotoxins. Important synthetic contributions have been made by the groups of Franklin and Overman<sup>[34]</sup> and Trost and Scanlan,<sup>[35]</sup> which have synthesized key members of the class of pumiliotoxins. When contemplating the design of a total synthesis strategy for the pumiliotoxin

alkaloids, attention is immediately drawn to the (Z)-alkylidene side chain. This unit presents particular problems since stereocontrolled synthesis of exocyclic alkenes is difficult to achieve. The prospects for the selective generation of the (Z)-side chain by a Wittig type functionalization of a suitable precursor indolizidine ketone are low. Therefore, the majority of synthetic approaches have focused on the selective generation of an acyclic configurational stable alkene fragment that was used in a cyclization to generate the pumiliotoxin framework.

## CHEMISTRY OF INDOLIZINES

Generally, there are three major approaches to indolizine synthesis, *viz.*, (1) condensation reactions; (2) 1,3-dipolar cycloadditions; and (3) 1,5-dipolar cycloadditions.

### Synthesis of indolizines by condensation reactions

#### Synthesis of indolizines by reactions of 2-methylpyridine and its derivatives with acetic anhydride (Scholtz's reaction)

Scholtz's synthesis<sup>[1]</sup> of the first indolizine simply involved treating 2-methylpyridine with acetic anhydride at very high temperature to yield a crystalline compound, which he called "picolide" and which, on hydrolysis, afforded the indolizine (2) [Scheme 1]. The principal difficulty Scholtz faced was in elucidating the structure of "picolide" and in rationalizing its formation. The presence of one carbonyl group in "picolide" was clearly established by the formation of oxime, hydrazone, and semicarbazone derivatives. However, it did not give any reaction typical of aldehydes. Furthermore, "picolide" was found to possess only feeble basic properties. Taking into account the above observations, Scholtz and Fraude<sup>[1]</sup> speculated that the nitrogen was acylated and proposed the most suitable structure for "picolide" to be 1-acetyl-2-methyl-4-ketopyrriodocoline (5). If "picolide" was to have the above-mentioned structure, it would be necessary for it to undergo a complicated initial cleavage, followed by ring closure to a five-membered pyrrole in order to explain satisfactorily the formation of indolizine (2) upon its hydrolysis. Moreover, this structure did not explain the observed formation of "picolide" from the reaction of one mole of propionic anhydride with 2-methylpyridine, and consequently, it was suggested that "picolide" be assigned structure (6) [Scheme 2]. However, Tshitschibabin and Stepanow<sup>[1]</sup> doubted the validity of Scholtz's conclusions and, in 1929, they reinvestigated the synthesis and formulated "picolide" as 1,3-diacetylindolizine (11) [Scheme 3]; since 1929, the Scholtz reaction has gained widespread popularity and has been adopted as a general route to indolizines.

#### Synthesis of indolizines by ring closure of the pyridinium salts (Tshitschibabin reaction)

A novel approach to the synthesis of 2-substituted indolizines was developed, in 1927, by Tshitschibabin.<sup>[36]</sup> They speculated the existence of tautomerism in  $\alpha$  and  $\beta$ -alkylated pyridines and suggested that if, for instance, 2-methylpyridine (12) and an  $\alpha$ -halogenoketone were reacted in the presence of an alkali, 2-methylpyridine could react as the aromatic system (12) or as its tautomer (13), reaction in the latter form (13) would then present good possibilities for ring closure, analogous to that observed for compound (14) [Scheme 4]. Speculative as this was, it led to the successful synthesis of 2-substituted indolizines (17) through cyclization of quaternary pyridinium salts (16) [Scheme 5]. This approach was fully exploited and several 2-alkyl- and 2-aryl-indolizines were synthesized. Krohnke *et al.*<sup>[1]</sup> demonstrated that quaternary compounds would react with bases of suitable strength to afford "enol-betaines" which then undergo "acid cleavage" losing an acyl group. In view of this observation, these authors suggested formation of an "enol-betaines" as an intermediate in the

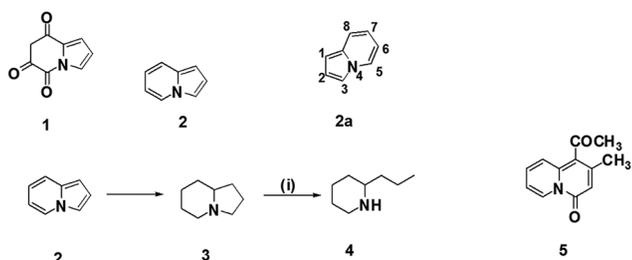


Figure 1: Reagents (i) cyanogen bromide

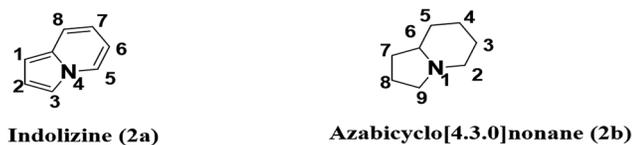


Figure 2: The bicyclic core of indolizidine alkaloids (2b)

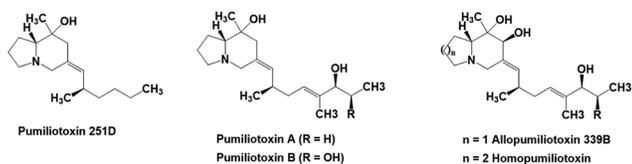
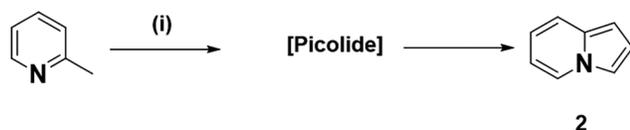


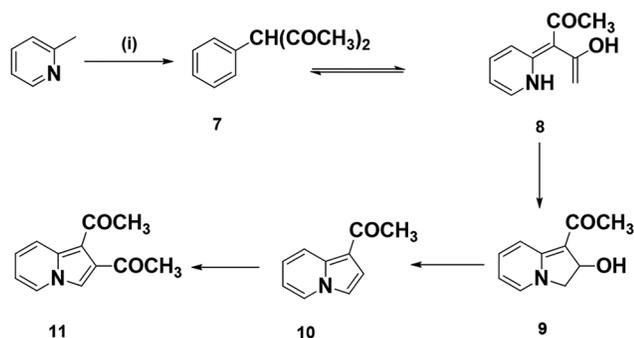
Figure 3: Representative pumiliotoxin and allopumiliotoxin alkaloids

Tshitschibabin reaction, ring closure of which would afford an indolizine [Scheme 5]. However, before long, certain drawbacks become apparent. When  $\alpha$ -halogenated aldehydes were used, the quaternary salts were not very easily formed and did not always cyclize to form the required indolizines. In 1965, Hurst *et al.*<sup>[37]</sup> observed that the Tshitschibabin reaction of ethyl 2-quinolylacetate with phenacyl bromide afforded 2-ethoxycarbonylmethylene-1-phenacyl-1,2-dihydroquinoline (18) which, upon treatment with sodium bicarbonate, did not undergo ring closure as expected. Nevertheless, when treated with boiling acetic anhydride, compound (18) underwent an intramolecular aldol-type condensation to afford the benzindolizine (19).<sup>[38]</sup>

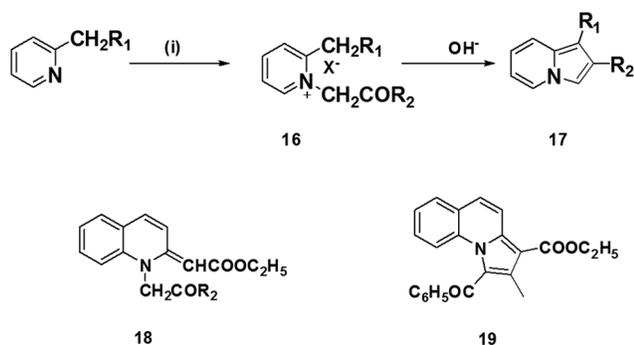
This modified Tshitschibabin indolizine synthesis was successfully extended to the synthesis of the indolizines (25), (27), and (28) from the intramolecular aldol-type condensation of the corresponding acyl methines (24) [Scheme 6].<sup>[39]</sup> In 1946, Borrows *et al.*<sup>[40,41]</sup> attempted the synthesis of acyl and alkoxy carbonyl indolizines from  $\alpha$ -halogeno- $\beta$ -diketones and  $\alpha$ -halogeno- $\beta$ -ketoesters using Tshitschibabin method. However, they could not form the quaternary salt, and the attempt failed almost two decades later, Bragg and Wibberley<sup>[42]</sup> successfully synthesized ethyl 3-acetyl-2-methylindolizine-1-carboxylate and diethyl 2-methylindolizine-1, 3-dicarboxylate from ethyl chloroacetate and 3-chloro-pentane-2,4-dione, using a method which did not require isolation of the quaternary salt. Bragg and Wibberley also synthesized alkyl and aryl indolizine-1-carboxylates from  $\alpha$ -halogenoketones and ethyl 2-pyridylacetate.<sup>[42]</sup> When they treated



Scheme 1: Reagents (i)  $(\text{CH}_3\text{CO})_2\text{O}$



Scheme 3: Reagents (i)  $(\text{CH}_3\text{CO})_2\text{O}$

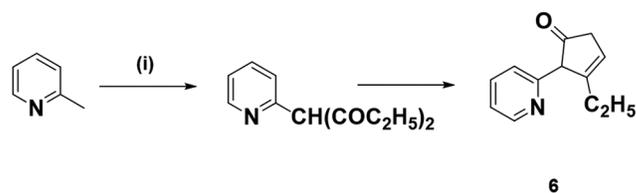


Scheme 5: Reagents (i)  $\text{R}_2\text{COCH}_2\text{X}$

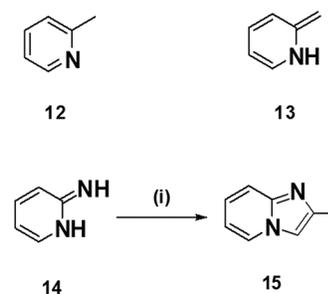
phenacyl bromide with ethyl 2-pyridylacetate (29), ethyl 2-pyridylacetate hydrogen bromide (30), instead of the quaternary salt was formed from which the ethyl-2-phenylindolizine (31) crystallized [Scheme 7]. From the above results, the authors suggested that a part of the ester was behaving as a base, removing hydrogen bromide and leading to ring closure. This approach opened new doors to indolizine synthesis.

### Synthesis of indolizines by ring closure of 3-(2-pyridyl)-1-propanols and their analogs

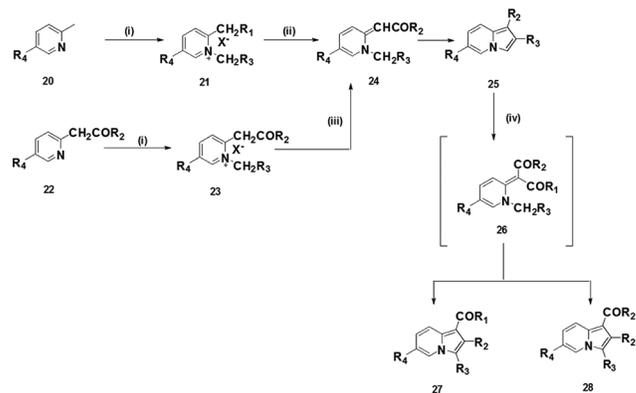
In 1955, Roberts *et al.*<sup>[43]</sup> treated 3-(2-quinolyl)-1,2-propanediol (32) with hydrobromic acid and subjected the product (33) to steam distillation from alkali to afford 5,6-benzindolizine (34) in very high yield [Scheme 8]. This remarkable success caught the interest of chemists worldwide. A year later, two German chemists<sup>[37]</sup> successfully extended this novel approach to the synthesis of the highly substituted indolizines (37) and (38) from the unsaturated alcohols (35) and (36) [Scheme 9]. During the next 2 years, Barrett and Chambers<sup>[44]</sup> reinvestigated Boekelheide's method and conclusively established the ability of amino groups to act as good leaving groups. When they refluxed 3-amino-1-aryl-1-(2-pyridyl)-alkan-1-ols (39) with acetic anhydride, compounds (40) formed, which cyclized with the elimination of the amino and acetoxy groups to afford the 1-aryl indolizines (41)



Scheme 2: Reagents (i)  $(\text{C}_2\text{H}_5\text{CO})_2\text{O}$



Scheme 4: Reagents (i)  $\text{Br}_2\text{CH}_2\text{COCH}_3$



Scheme 6: Reagents (i)  $\text{R}_3\text{CH}_2\text{X}$ ; (ii)  $\text{R}_2\text{COCl}/\text{NaOH}$ ; (iii)  $\text{NaOH}$ ; (iv)  $\text{R}_1(\text{COO})_2/\text{Heat}$

[Scheme 10]. This approach was used to synthesize several indolizines including some aza indolizines in high yield.<sup>[45,46]</sup> Before 1957, many chemists such as Scholtz,<sup>[1]</sup> Borrow and Holland,<sup>[47]</sup> and Diels and Alder, to mention a few, had reported the synthesis of the parent indolizine (2) but never in satisfactory yield. Boekelheide and Windgassen subsequently synthesized the parent indolizine with an overall yield of 35% from 2-(3-hydroxypropyl)-pyridine-n-oxide (42) [Scheme 11], not long after, Boekelheide and Windgassen, bettered this yield.<sup>[48]</sup> They found that pyrolysis of easily available 3-(2-pyridyl)-1-propanol (44) at 280°C in the presence of palladium-carbon afforded indolizine (2) in 50% yield [Scheme 12].

Boekelheide and Windgassen<sup>[48]</sup> also developed methods for synthesizing indolizines with no substituents on the five-membered ring. For example, they treated 6-methylpyridine-2-carboxaldehyde (45) with vinyl magnesium bromide to give (in 68% yield) the vinyl alcohol (46, R = H), which was acetylated and the resulting acetate was then subjected to pyrolysis at 450°C to afford the five-methyl indolizine (45) [Scheme 13].

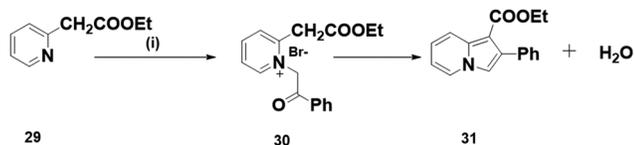
### Synthesis of indolizines by condensation reactions of heterocyclic nitrogen compounds with acetylenic and olefinic compounds

This approach was first introduced by Diels *et al.* in 1932. They isolated indolizines (50) and (51) from the intermolecular condensation of pyridine with acetylene dicarboxylate (48) [Scheme 14]. This

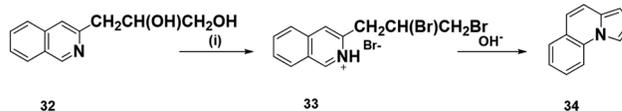
approach used the interest of Wiley and Knabeschuh,<sup>[49]</sup> and, in 1953, they synthesized the indolizine derivative (52) in 29% yield, from 3-methylpyridine and acetylene dicarboxylate [Scheme 15]. Seven years later, Acheson and Plunkett<sup>[50]</sup> tried the same reaction under different conditions, without much success. They only managed to synthesize the indolizine (53) in 6% yield [Scheme 16]. Of particular relevance is a report published in 1968 by Acheson and Robinson,<sup>[51]</sup> in which they related the basicities of pyridines to their reactivity toward dimethyl acetylene dicarboxylate. It was found that when pyridine (pKa value 5.2) was used in the reaction, a quinolizine derivative (54) was formed [Scheme 17]. However, when 4-cyano pyridine was used which has a much lower pKa value (1.90), trimethyl 7-cyano-1, 2,3-indolizine tricarboxylate (55) was synthesized [Scheme 17]. When pyridines with pKa values lower than 1.45 were used, no reaction took place at all. In 1966, Acheson *et al.*<sup>[52]</sup> synthesized dimethyl dibenzo indolizine-2,3-dicarboxylates (58) from the condensation reaction of phenanthridine 5-oxide (56) and dimethyl acetylenedicarboxylate. Compound (57) was the intermediate which, on sublimation, cyclized to (58) from which the first parent heterocycle (59) (R = H) was prepared, although derivatives of this novel heterocycle were known from 1962 [Scheme 18].

### Synthesis of indolizines using miscellaneous condensation reactions

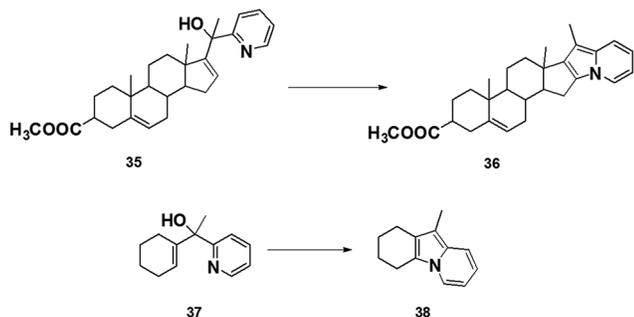
Michael condensation of compounds of the type (60) with  $\alpha\beta$ -unsaturated compounds provides another general route to indolizine



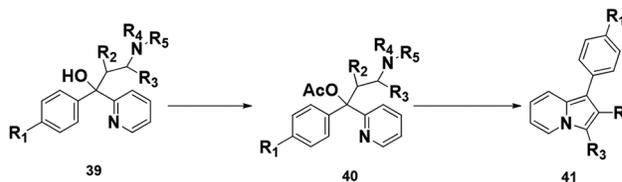
Scheme 7: Reagents (i) phenacyl bromide



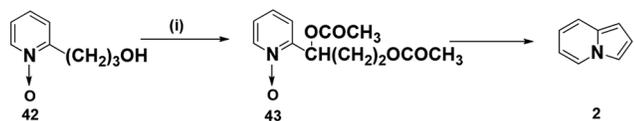
Scheme 8: Reagents (i) hydrogen bromide



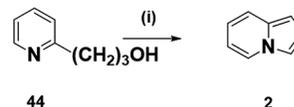
Scheme 9: Conversion of compound 36–38



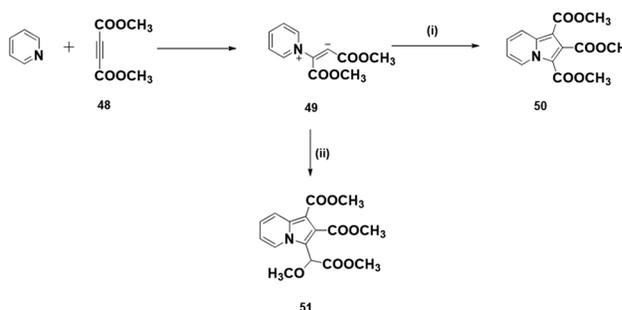
Scheme 10: Reagents (i)  $(\text{CH}_3\text{CO})_2\text{O}/\text{Heat}$



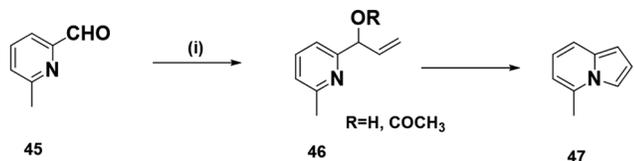
Scheme 11: Reagents (i)  $(\text{CH}_3\text{CO})_2/\text{Heat}$



Scheme 12: Reagents (i) Pd/C, 280°C



Scheme 14: Reagents (i)  $\text{Et}_2\text{O}$  (ii) MeOH

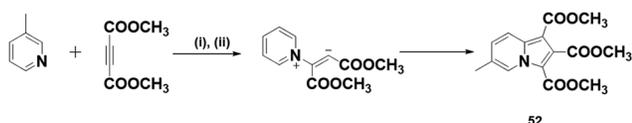


Scheme 13: Reagents (i)  $\text{MgBr}$

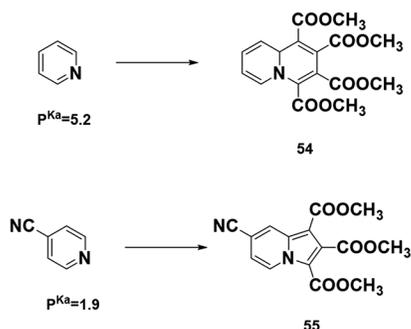
synthesis. This method was introduced as early as 1953 by Boekelheide and Godfrey.<sup>[53]</sup> The authors observed that when acrylonitrile was used, the corresponding 3-substituted 2-amino carbonyl benzindolizine (61) was formed [Scheme 19]. On the other hand, when 2-vinylpyridine or ethyl acrylate was used, ketones of the type (62) were formed which, on heating or treatment with 100% phosphoric acid, underwent ring closure to afford the corresponding benzindolizines (63) and (64), respectively [Scheme 19]. Of particular interest was a paper published in 1969 by two German chemists.<sup>[37]</sup> They reported one of the most powerful methods for the synthesis of parent indolizine (2). Condensation reaction of 2-pyridyllithium (65) with 2-chloromethyloxirane afforded first the 2-hydroxy-2,3-dihydro-1*H*-indoliziniumchloride (66) which, on treatment with 30% sodium hydroxide, gave the parent indolizine (2) [Scheme 20].

### Synthesis of indolizines by 1,3-dipolar cycloaddition

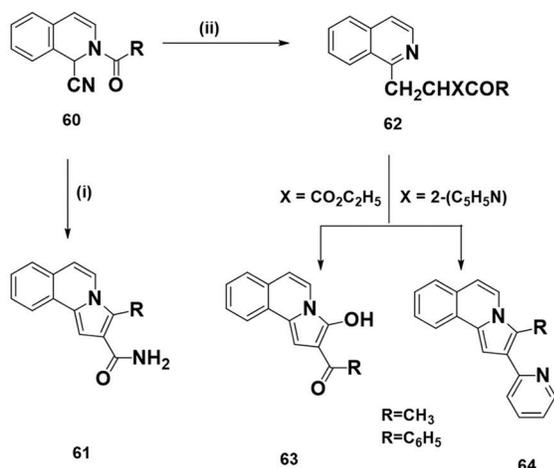
1,3-Dipolar cycloadditions are among the most widely-used reactions in the synthesis of heterocyclic compounds, particularly 5-membered ring compounds. It has been established that pyridinium ylides (67),



**Scheme 15:** Reaction conditions (i)  $-78^{\circ}\text{C}/1\text{h}$ ; (ii)  $-20^{\circ}\text{C}/72\text{h}/\text{Et}_2\text{O}$



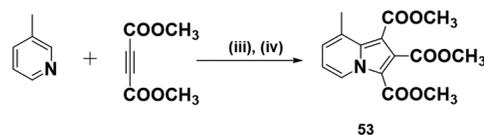
**Scheme 17:** Compounds (54) and (55) were obtained using pyridine and 4-cyano pyridine, respectively



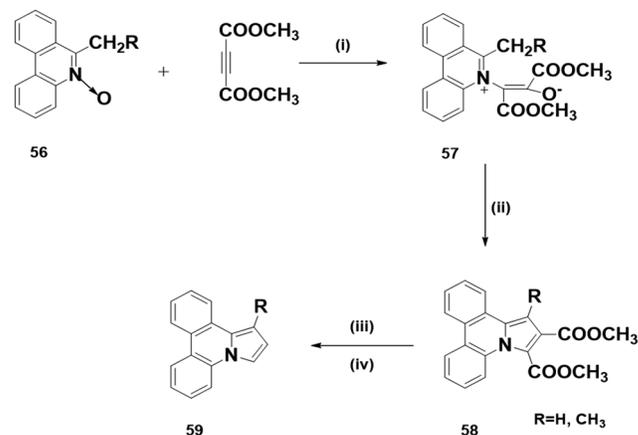
**Scheme 19:** Reagents (i) CH<sub>2</sub>CHCN/C<sub>6</sub>H<sub>5</sub>/Li; (ii) CH<sub>2</sub>CHX/C<sub>6</sub>H<sub>5</sub>/Li, X = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, 2-(C<sub>6</sub>H<sub>5</sub>N)

even in the absence of a dehydrogenation catalyst, combine with dimethyl acetylenedicarboxylate, diethyl acetylene dicarboxylate methyl propynoate, ethyl propynoate, and dicyano acetylene, to mention a few, to form the indolizines (68) [Scheme 21].<sup>[54-59]</sup> However, when the dipolarophile is an ethinic compound, the reaction often does not yield the indolizine directly but the tetrahydro indolizines (69) and the dihydro indolizines (70) and (71) are isolated, subsequent dehydrogenation in the presence of a catalyst such as palladium on carbon, chloranil, or 1, 4-benzoquinone affords the respective indolizines. The relative rates of addition of the ylides (67) to the dipolarophile were found to be dependent on the substituents X1 and X2 [Scheme 21]. A desirable feature of indolizine synthesis by 1,3-dipolar cycloaddition is that the procedures are generally simple and require only two steps. In 1961, Boekelheide and Fahrenholtz<sup>[54]</sup> used this approach for the first time, to synthesize the indolizine (73) from 1-phenacylpyridinium methylyde (72) under dehydrogenating conditions [Scheme 22]. Not long after, Huisgen *et al.*<sup>[60]</sup> used this synthetic principle, to develop indolizine derivatives (75) from the reaction of the azomethine (74) and dimethyl fumarate (DMF) [Scheme 23]. Of particular interest, there was a paper published in 1973;<sup>[37]</sup> they found that diphenylthiirene-S, S-dioxide behaved like acetylenic compounds and reacted with pyridinium methylyde to afford, in 34% yield, the indolizine (76) [Scheme 24].

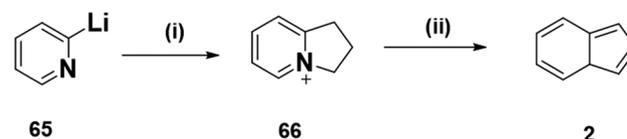
In the same year, research done on *N*-allylpyridinium ylides (77) by two Japanese research groups<sup>[61-63]</sup> established that, in some cases, *N*-allylpyridinium ylides behaves not only as 1,3-dipoles which may cyclo add to another *N*-allylpyridinium ylide to afford



**Scheme 16:** Reaction conditions (iii) Stir/r.t./15h/Et<sub>2</sub>O; (iv) 100°C/2M HNO<sub>3</sub>



**Scheme 18:** Reaction conditions (i) C<sub>6</sub>H<sub>6</sub>, r.t.; (ii) 200°C/0.5–0.05 torr sublimation; (iii) OH; (iv) NaOH/CaCO<sub>3</sub>

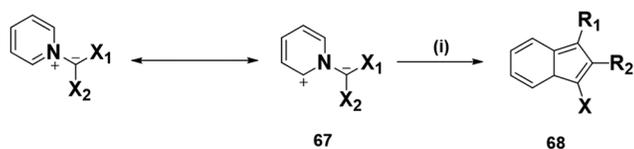


**Scheme 20:** Reagents (i)  $\text{O}-\text{CH}_2\text{Cl}$  (ii) NaOH

the indolizine (78) but also as 1,5-dipoles, which undergo ring closure to give the indolizines (79) [Scheme 25]. The preparation of 3-azaindolizines (81) can be readily achieved by 1,3-dipolar cycloaddition of the *N*-iminopyridinium ylide (80) with acetylenic or ethenic compounds [Scheme 26].

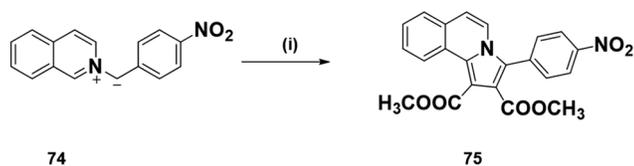
### Synthesis of indolizines by 1,5-dipolar cyclization

1,5-Dipolar cyclization is one of the most versatile routes to heterocyclic molecules. Because of its utility and inherently broad scope, this synthetic approach is of considerable importance and Huisgen *et al.* studied this approach in detail. In 1962, Krohnke and Zecher successfully extended this approach to the synthesis of the aza indolizine (85) from phenacylisquinolinium bromide (82) through

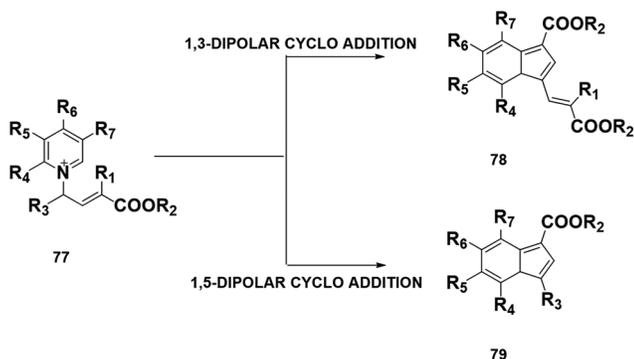


$X_1$  &  $X_2$  = H, alkyl, aryl, acyl, alkoxy carbonyl and cyano

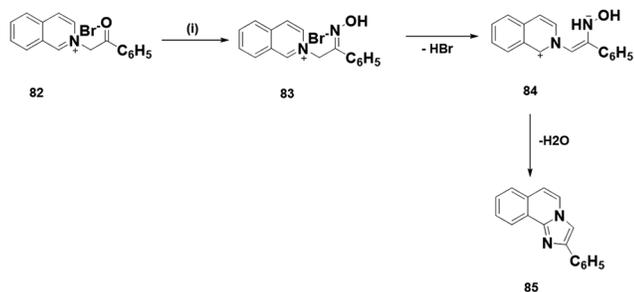
**Scheme 21:** Reagents (i)  $R_1 \equiv R_2$



**Scheme 23:** Reagents (i) diethyl fumarate and chloranil or xylene



**Scheme 25:** *N*-Allylpyridinium ylide transformation



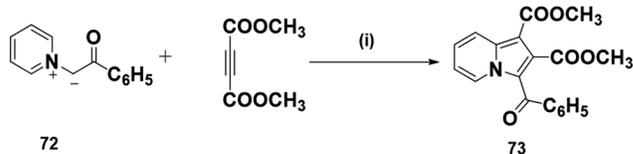
**Scheme 27:** Reagents and conditions (i)  $NH_2OH/HCl/H_2O$ ,  $130^\circ C/24h$ ; (ii) base

the 1,5-dipolar intermediate (84) [Scheme 27]. The authors also reported the synthesis of several benzindolizines (87) [Scheme 28] by simply treating the *N*-picrylmethylcycloimmonium ylides (86) with a base.

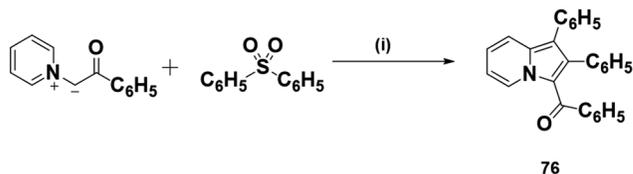
## STRUCTURE AND PHYSICAL AND CHEMICAL PROPERTIES OF INDOLIZINES

### Structure of indolizines

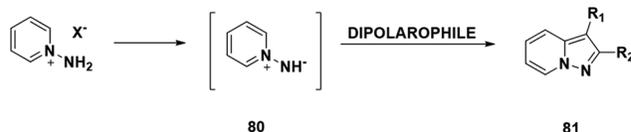
Following an early argument that any resonance stabilization in indolizines is simply due to the presence of the pyrrole ring, the parent indolizine was first considered to be the best represented structure (88). However, the resonance energy (RE) calculated for indolizine was found to be 0.29 kcal/mol, which is larger than the total RE of pyrrole (0.23 kcal/mol). Furthermore, NMR studies have conclusively established delocalization throughout both rings. Therefore, indolizine is now considered to be best represented by a resonance hybrid to which the canonical structures (88), (89), and (90) contribute. X-ray analysis has shown the crystal structure of the bis-indolizine (91) to be nearly planar and the observed bond lengths to correlate well with the Huckel molecular orbital (HMO) bond orders. HMO calculations give the decreasing order of the electron density as:  $3 > 1 > 5 > 8a > 5 > 2 > 7 > 6$  on the ring carbons.<sup>[64]</sup>



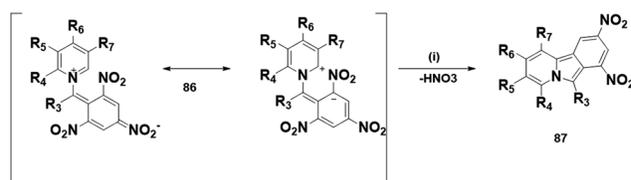
**Scheme 22:** Reaction condition (i) Pd/C, toluene



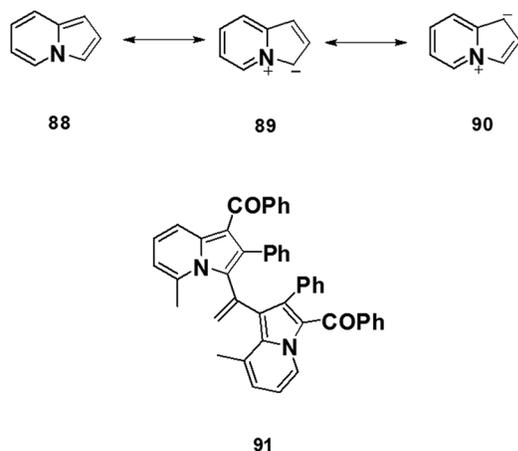
**Scheme 24:** Reagents (i)  $C_6H_6$ ,  $r$ ,  $t$



**Scheme 26:** The preparation of 3-azaindolizines (81) from 1,3-dipolar cycloaddition of the *N*-iminopyridinium ylide (80) with acetylenic or ethenic compounds



**Scheme 28:** Reagents (i) piperidine

**Table 1:** Percentage composition of protonated 3-substituted indolizines in trifluoroacetic acid

Compound	3H-cation	1H-cation
3-methylindolizine	21	79
2,3-dimethylindolizine	41	59
3-methyl-2-phenylindolizine	72	28
3-methyl-2-methylindolizine	78	22
1,2,3-trimethylindolizine	100	
1,3-dimethyl-2-phenylindolizine	100	
3,5-dimethylindolizine	100	

the indolizine nucleus was achieved for the first time in 1946, by Borrows *et al.*,<sup>[67]</sup> who showed that while the action of nitric acid on 2-methyl and 2-phenylindolizines at moderate temperatures resulted mainly in oxidation, rapid reaction at higher temperatures gave the respective 1,3-dinitro indolizines in low yields. Furthermore, nitration of 2-methylindolizine (92) in sulfuric acid has been shown to afford the 1-nitro-2-methylindolizine (93) as the main product, accompanied by small quantities of the 3-nitro derivative (95) and the 1,3-dinitro derivative (94) [Scheme 29]. A similar treatment of the 2-phenylindolizine (96) resulted in the phenyl ring being attacked first, giving the 2-*p*-nitrophenylindolizine (97) [Scheme 30]. This reaction shows that the indolizine system is closely allied to pyrrole in its properties, for similar treatment of *N*-phenylpyrrole yields *N-p*-nitrophenylpyrrole. Compound (97) on further nitration affords 1-nitro-2-*p*-nitrophenylindolizine (98) [Scheme 30]. Nitration of 3-acetyl-2-methylindolizine proceeds readily in concentrated sulfuric acid to yield the 1-nitro derivative along with a small quantity of the 1,3-dinitro compounds. On the other hand, nitration of the 3-acetyl-2-phenylindolizine under similar conditions affords a mixture of nitrated products.

## Physical properties of indolizines

The parent indolizine (2) and its alkyl derivatives are either low-melting solids or high-boiling liquids. It is sensitive to air, light and volatile in steam. However, when a phenyl group is attached at the 2<sup>nd</sup> or 5<sup>th</sup> position, the indolizines are found to be stable solids and nonvolatile in steam. Most indolizines are highly fluorescent and show feeble basic properties.<sup>[1]</sup>

## Chemical properties of indolizines

Reference has already been made to the structure of indolizines and, in particular, to its delocalized orbitals. Indolizines readily undergo electrophilic substitution and show resistance to nucleophilic attack. In their chemical reactivity, indolizines resemble pyrroles, indoles, and isoindoles. The following section deals with reactions of indolizines with electrophiles, oxidation, reduction, and other miscellaneous reactions.

## Reactions with electrophiles

Electrophilic substitution in indolizines occurs preferentially at the 3-position and then at the 1-position but sometimes at both 3 and 1 positions simultaneously.<sup>[65]</sup> The enhanced susceptibility to electrophilic attack at C-3 and C-1 is consistent with the MO calculations, which indicate C-3 to be the most reactive site for electrophilic attack, followed by C-1.

## Protonation

Fraser<sup>[66]</sup> studied the protonation of indolizines using NMR spectroscopy. Protonation of indolizines occurs preferentially at position 3. In three-substituted indolizines, the site of protonation was found to be dependent on the nature of the C-3 substituent as well as the substituent's at positions 1, 2, and 5. Indolizines which have the same substituents at position 1 and 3 are exclusively protonated at position 3. Similarly, protonation of 3,5-disubstituted indolizines occurs preferentially at position 3. Fraser argued that in the 3,5-disubstituted indolizines, intramolecular overcrowding encourages protonation at site 3. In general, protonation of the 3-substituted indolizines affords a mixture of the 3H- and 1H-cations [Table I]. It was found that the ratio of the 3H: 1H cations could be increased by introducing substituents at position 2. As indicated above, the resulting steric interaction between the C-3 and C-2 substituents is relieved by protonation at C-3. The relief in steric strain may be attributed to the consequent change in the hybridization state of C-3. Protonation of most of the aza indolizines is found to occur at the nonbridgehead nitrogen. Surprisingly, protonation of the 5-azaindolizines occurs preferentially at the 3-position, followed by the 1-position.<sup>[32]</sup>

## Nitration

Nitration of the indolizine nucleus often results in oxidation of the substrate with little evidence of nitration. Successful nitration of

## Nitrosation

Direct nitrosation of the indolizine nucleus was first achieved by Konde and Nischizawa, in 1937, when they treated 3-acetyl-2-methylindolizine with nitrous acid to give the 1-nitroso derivative. In indolizines, which have their 3-position unsubstituted, nitrosation takes place at the 3-position. The preferential nitrosation at position 3 is in marked contrast to the preferential nitration at position 1, as discussed above.

## Halogenation

Not much work has been done on the halogenation of indolizines. Attempts to prepare stable bromo derivatives have not always been successful. However, preparation of stable iodo derivatives has proved possible. For example, iodination of 3-acetylindolizine in alcohol proceeds readily to give the 1,3-diiodo derivative and in the presence of sodium acetate, the 1-iodo derivative.

## Acylation

acylation of indolizines takes place preferentially at position 3 and less readily at position 1. Indolizines can be acylated simply by treating with acid chlorides, anhydrides, and even esters. One of the most convenient methods for acylating the indolizine nucleus is by heating the indolizine with acid anhydrides in the presence of sodium salt of the corresponding acid. In 1912, Scholtz<sup>[1]</sup> synthesized for the first time, the 3-acetyl derivative of the indolizine and the 7-methylindolizine using this approach. Tschitschibabin<sup>[1]</sup> in 1929 and Borrows *et al.* in 1946<sup>[40]</sup> extended this approach to the preparation of 3-acetyl derivatives of 2-methyl and 2-phenylindolizine and the 3-benzoyl derivative of 2-phenylindolizine. The monoacetyl indolizines, on further treatment with acetic anhydride at higher temperatures, were found to yield the respective 1,3-diacetylindolizines. In 1940, Ochai, a Japanese researcher, reported the preparation of 1,3-diacetyl-2-methylindolizine (100) from

a Friedel–Crafts reaction in  $\text{CCl}_4$  on 3-acetyl-2-methylindolizines (99) using acetyl chloride and a large excess of aluminum chloride as catalyst [Scheme 31]. Acylation of 2-methylindolizine (101) under similar conditions but using carbon disulfide as solvent afforded the diacetyl derivative (100) in very low yield [Scheme 32]. With 2-phenylindolizine, however, Friedel–Crafts acylation proceeds readily in carbon disulfide to give a mixture of 1,3-diacetyl-2-phenylindolizine and 2-*p*-acetylphenylindolizine. It was found that acetyl chloride and bromide failed to react in the absence of a catalyst. This is in marked contrast to the facile mono benzylation of indolizine when treated with benzoyl chloride even in the absence of a catalyst.

## Reactions with diazonium electrophiles

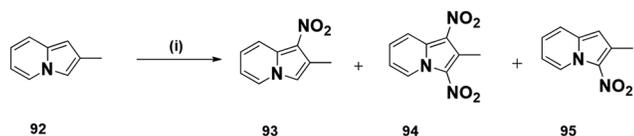
The preparation of azo derivatives of indolizines can be easily achieved using arene diazonium ion as an electrophile. Diazo coupling occurs normally at position 3, however if this position is already occupied, position 1 is attacked resulting in the formation of the 1-azo derivatives. In 1913, Scholtz and Fraude achieved the first synthesis of a 3-azo derivative of indolizine. Similar treatment of 3-acetyl-2-methylindolizine by Kondo *et al.*<sup>[1]</sup> in 1936, yielded the 1-phenylazo derivative.

## Oxidation reactions

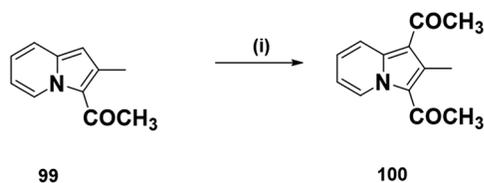
Indolizines undergo oxidation very easily. Ring fission is a rather common phenomenon observed in oxidation of indolizines. In the past, this reaction was used for structural elucidation.<sup>[68]</sup> A typical example is  $\text{H}_2\text{O}_2$ -induced oxidation outlined in Scheme 33. However, some cases of oxidation where ring fission does not occur have been reported. A classic example is the potassium ferricyanide oxidation of the indolizine (104), which afforded compound (105) as the oxidation product [Scheme 34].<sup>[69]</sup>

## Reduction reactions

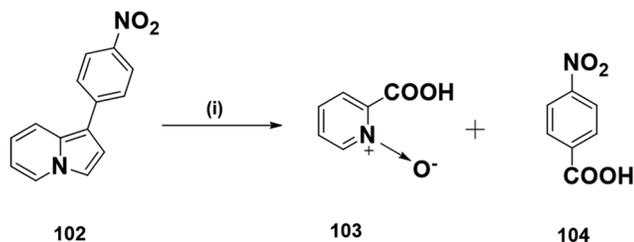
Reduction of the indolizine nucleus was first achieved in 1912 by Scholtz,<sup>[1]</sup> when he treated the parent indolizine (2) with sodium



**Scheme 29:** Reagents (i)  $\text{HNO}_3/\text{H}_2\text{SO}_4$



**Scheme 31:** Reagents (i)  $\text{CH}_3\text{COCl}/\text{AlCl}_3$  in  $\text{CCl}_4$



**Scheme 33:** Reagents (i)  $\text{H}_2\text{O}_2$

and alcohol. Scholtz presumed the structure of the reduction product to be the ring opened system (107). In 1946, Borrows and Holland<sup>[1]</sup> proposed the product of the sodium-alcohol reduction as, in fact, the dihydro derivative (108). Several reports on the complete hydrogenation of the six-membered ring of the indolizine system have been published. Although the above results indicate that the six-membered ring of the indolizine nucleus is more susceptible to hydrogenation than the five-membered ring, Diels and Meyer reported hydrogenation of the five-membered ring in the reduction of dimethyl 1-(methoxy carbomethoxy methyl) indolizine-2,3-dicarboxylate (109) in the presence of platinum oxide, the isolated product being the tetrahydro compound (110) [Scheme 35]. Under more drastic conditions, e.g., in the presence of Raney nickel at high temperature and pressure, complete reduction of the indolizine nucleus has been reported.<sup>[1]</sup>

## Reactions with nucleophiles and bases

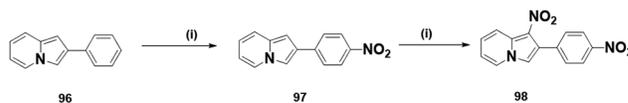
Indolizines and aza indolizines with electron withdrawing groups undergo nucleophilic attack. Thus, treatment of 8-nitro indolizines with secondary amines and oxygen was found to give 5-amino-8-nitro indolizines. Similarly, 1-azaindolizine (111), on treatment with ethyl thioglycolate anion in DMF, afforded the thio derivative (112) [Scheme 36]; 6-azaindolizine (113), on treatment with phosphoryl chloride, gave the bis-nitrogen bridged annulene (114) [Scheme 37].<sup>[70]</sup>

## Industrial applications of indolizines

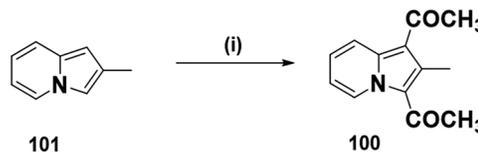
Indolizines find use as fabric brightening agents and as photographic sensitizers.<sup>[71]</sup> Some indolizines have been successfully used as dyes which show great resistance to light and heat.<sup>[72]</sup>

## Pharmacological properties

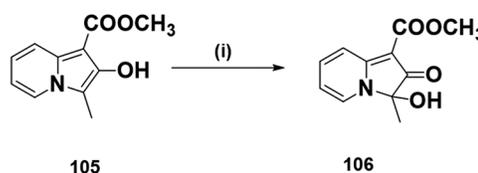
In 1960, James M. Price<sup>[73,74]</sup> of Wisconsin Medical School suggested the possibility of preparing pharmacologically active indolizine derivatives by replacing the indole ring of biologically active indoles with the indolizine ring system. The striking structural similarity between the indole and indolizine nucleus prompted this speculation. Most of the naturally occurring pharmacologically active indoles such as reserpine (115),



**Scheme 30:** Reagents (i)  $\text{HNO}_3/\text{H}_2\text{SO}_4$

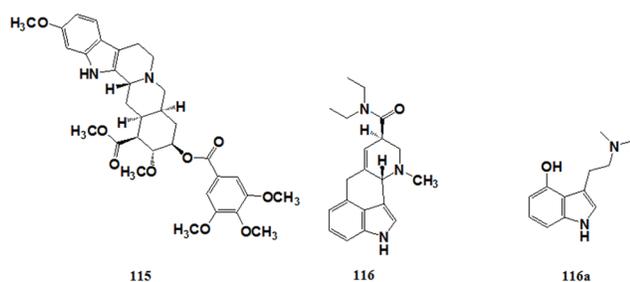


**Scheme 32:** Reagents (i)  $\text{CH}_3\text{COCl}/\text{AlCl}_3$  in  $\text{CS}_2$



**Scheme 34:** Reagents (i)  $\text{K}_3\text{Fe}(\text{CN})_6$

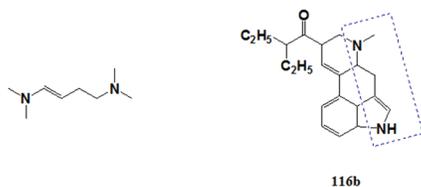
lysergic acid diethylamide (116), and psilocin (116a) have the indole nitrogen and the extra indole nitrogen separated by four carbons.<sup>[75]</sup>



115

116

116a



116b

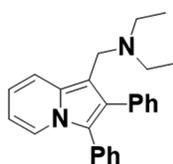
117

117a

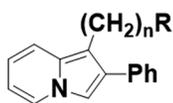
Research on these compounds suggested that their biological activity is partly dependent on the separation between the indole nitrogen and the extra indole nitrogen (116b). This hypothesis provided the lead for developing indolizine analog of biologically active indoles. In 1961, Carbon and Brehm<sup>[76,77]</sup> prepared  $\beta$ -(1-indolizyl) alanine (117a) as an analog of tryptophan (117), an essential amino acid present in relatively small amounts in proteins. Tryptophan is the precursor of several physiologically important metabolites but is completely destroyed during acid hydrolysis of proteins. Compound (117) is considered to be a potential tryptophan antimetabolite.

### Central nervous system-depressant activity

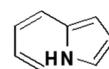
By the late sixties, medicinal chemists in several laboratories had recognized the importance of preparing aminoalkyl indolizines for pharmacological studies. 1-(Diethylaminomethyl)-3-methyl-2-phenylindolizine (118), prepared in 1966, showed depressant activity on the central nervous system (CNS).<sup>[78]</sup> The  $LD_{50}$  was found to be in the range 70–100 mg/kg. A year later, 2-phenylindolizines (119a-m) and their derivatives were synthesized and screened for their effects on the CNS in mice and in some cases in cats [Table 2]. Many of these compounds (e.g., 119b, d, g, h, l) were stimulants at low doses, depressants at higher doses, and lethal at even higher doses. Although compound (119c), at doses of 30–100 mg/kg, produces slight CNS depression, it was found to be nonlethal at dosages as high as 1000 mg/kg, while compound (119e) led to a loss of aggression in rats. Compound (119f), however, showed locomotor depression at low doses, which become worse with increased dosage.



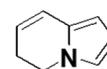
118



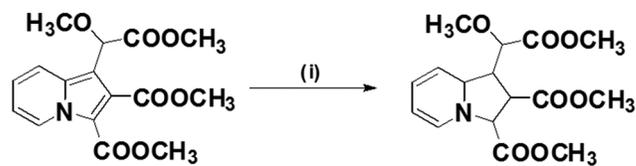
(119a-m)



107



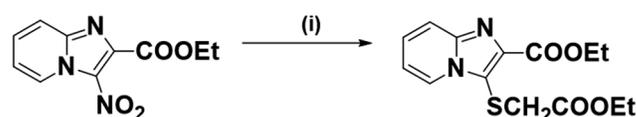
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109

110

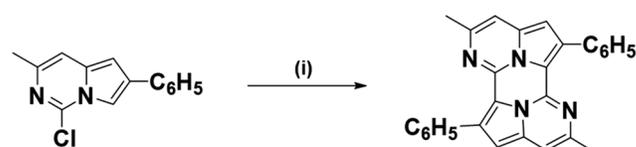
Scheme 35: Reagents (i) catalyst platinum oxide



111

112

Scheme 36: Reagents (i) ethyl thioglycolate anion in dimethyl fumarate



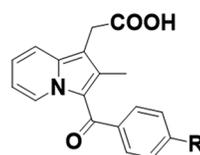
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114

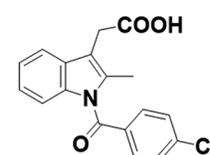
Scheme 37: Reagents (i) phosphoryl chloride

### Analgesic and anti-inflammatory activities

In 1971, certain indolizine-1-acetic acids (120) that exhibited analgesic and anti-inflammatory activities<sup>[79-81]</sup> were developed. The resemblance between the structure and pharmacological properties of these indolizines to indomethacin (121), a potent anti-inflammatory agent (introduced in 1963), suggested that the elementary constitution necessary for anti-inflammatory action was not destroyed by the shift of the “indole nitrogen” (in indomethacin) to the bridgehead position.<sup>[82]</sup> This encouraged the development of a range of indolizine analogs with anti-inflammatory properties.



120

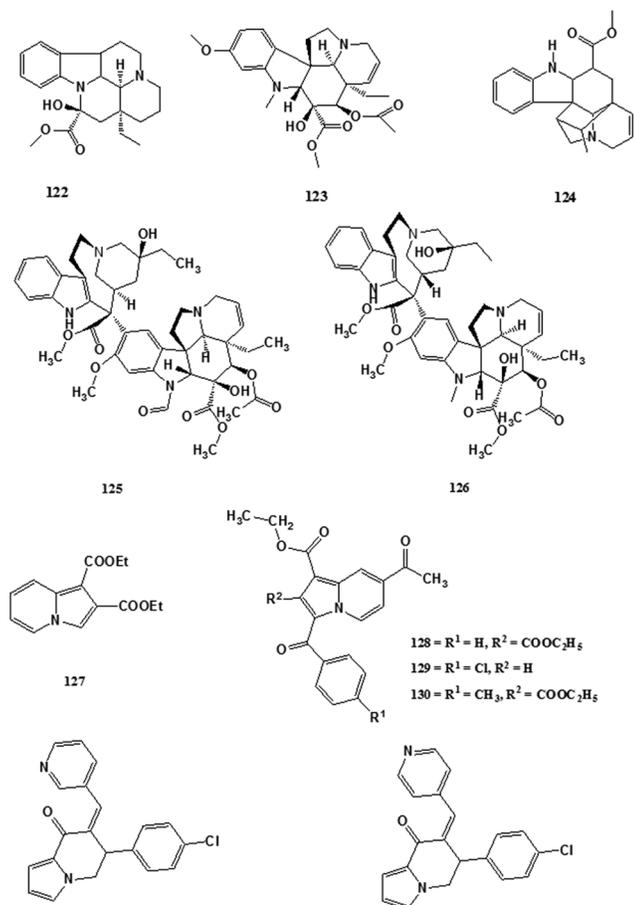


121

### Anticancer activity

The occurrence of the indolizine ring system (2) in natural products is not very common. However, alkaloids of the Vinca group, such as vincamine (122), vindoline (123), and vindolinine (124), contain several ring systems including the indolizine system.<sup>[83]</sup> Certain indolizines were also screened for anti-neoplastic activity based on

an extension of the rationale that some carcinolytic Vinca alkaloids, such as vincristine (125) and vinblastine (126) (used in cancer chemotherapy). However, sporadic attempts in developing carcinolytic indolizines met with little and only one indolizine derivative, *viz.*, diethyl indolizine-1, 2-dicarboxylate (127) showed significant anticancer activity.<sup>[84,85]</sup> Sandeep *et al.* reported dose-dependent anticancer activity of indolizine analogs (128–130) against human cervix cancer cell line SiHa at 10, 20, 40, and 80 µg/mL.<sup>[86]</sup> Inhibitors of the cytochrome P450 aromatase are therapeutic agents for the treatment of estrogen-dependent diseases such as breast cancer.<sup>[87]</sup> Several inhibitors of aromatase have been reported and are either clinically available or under clinical evaluation; however, many of these inhibitors are not as potent as expected *in vivo* or have terrible side effects.<sup>[87]</sup> Thus, the synthesis and development of more powerful and specific aromatase inhibitors are of great importance for the treatment of breast cancers.<sup>[87]</sup> Molecular modeling studies carried out by Sonnet *et al.* led to the design of a novel hypothetical aromatase inhibitor.<sup>[87]</sup> The group synthesized an array of indolizine compounds based on the indolizine pharmacophore and were tested for aromatase inhibition in 30 human placental microsomes. The *in vitro* biological evaluation of these compounds led to the identification of two new and potent nonsteroidal aromatase inhibitors MR 20494 (131) and MR 20492 (132) which are undergoing clinical development.



### Antibacterial activity

There are approximately 1.6 million deaths annually worldwide due to tuberculosis (TB). Current treatments for TB must be taken for 6–9 months and due to the lengthy period many patients stop taking the drugs leading to the growing problem of

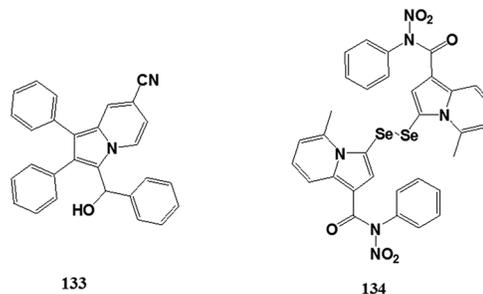
**Table 2:** Compounds (119a–m) tested for central nervous system-depression activity

	<b>N</b>	<b>R</b>
a	1	NCH <sub>3</sub> (COOC <sub>2</sub> H <sub>5</sub> )
b	1	N(CH <sub>3</sub> ) <sub>2</sub>
c	2	NHCOOC <sub>2</sub> H <sub>5</sub>
d	2	NHCH <sub>3</sub>
e	2	NCH <sub>3</sub> (COOC <sub>2</sub> H <sub>5</sub> )
f	2	N(CH <sub>3</sub> ) <sub>2</sub>
g	2	CON(CH <sub>3</sub> ) <sub>2</sub>
h	3	N(CH <sub>3</sub> ) <sub>2</sub>
i	2	N(CH <sub>3</sub> ) <sub>3</sub> BR
j	2	N(CH <sub>3</sub> ) <sub>3</sub> I
k	2	NHCOOC <sub>2</sub> H <sub>5</sub>
l	2	NHCH <sub>3</sub> HCL
m	2	N(CH <sub>3</sub> ) <sub>2</sub> HCL

multidrug-resistant strains of TB.<sup>[88]</sup> The increased resistance of the microorganism against antibacterial compounds calls for research and development into producing novel TB agents which are effective against the drug-resistant TB strains.<sup>[88]</sup> Gundersen *et al.* began screening indolizine derivatives which had been previously studied for their antioxidant properties and came across the antimycobacterial properties of (±)-1-(hydroxy phenylmethyl)-2,3-diphenylindolizine-7-carbonitrile (133). The indolizine compound was screened against *M. tuberculosis* H37Rv and showed excellent results *in vitro* and with continued development may prove to be a potent and selective antimycobacterial agent.

### Antioxidant activity

Narajji *et al.*<sup>[89]</sup> synthesized series of indolizine compounds and reported 3,3'-diselanediybis (5-methyl-N-nitro-N-phenyl-indolizine-1-carboxamide) (134) for antioxidant activity at IC<sub>50</sub> of 4.11 ± 0.05 mmol L<sup>-1</sup>.

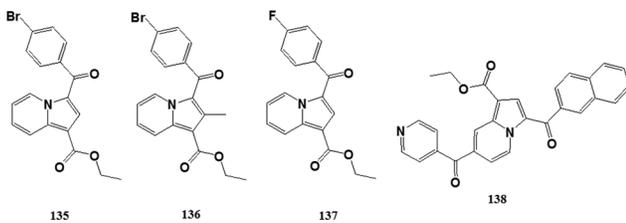


### Larvicidal activity

Sandeep *et al.*<sup>[90]</sup> reported greener synthesis of a series of novel indolizine analogs by the cyclization of aromatic cycloimmonium ylides with electron deficient alkynes in the presence of water as the base and solvent at 80°C. Characterized title compounds were evaluated for larvicidal activity against *Anopheles arabiensis* by the standard WHO larvicidal assay using Temephos as standard at 4 µg/mL. Title compounds (135), (136), and (137) exhibited promising larvicidal activity at 93%, 81%, and 95%, respectively.

### Anti-HIV activity

Huang *et al.*<sup>[91]</sup> reported compound (138) exhibited promising anti-HIV-1 activity, at IC<sub>50</sub> value of 11 µM. This information provides new information to develop highly potent small-molecule HIV-1 virion infectivity factor inhibitors.



## CONCLUSIONS

Indolizine pharmacophore has become an important synthetic target in the development of novel synthetic analogs with various pharmacological properties such as CNS depressant, analgesic and anti-inflammatory, anticancer, antibacterial, antioxidant, larvicidal, and anti-HIV.

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## Conflicts of interest

There are no conflicts of interest.

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