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Indolizines

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The methods of synthesis and properties of indolizines—bicyclic condensed heterocylic compounds with a bridgehead nitrogen atom—are examined. The bibliography includes 201 references.

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I. INTRODUCTION

The studies on indolizines, which have been fairly vigorously prosecuted in recent years, are associated with the development of methods of synthesis and the investigation of this condensed system of pyridine and pyrrole with a bridgehead nitrogen atom as well as the search for physiologically active substances among indolizine derivatives.

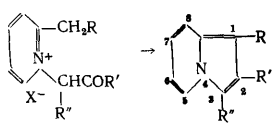
At the present time the chemistry of indolizines constitutes a fairly thoroughly investigated branch of the chemistry of heterocyclic compounds, which was founded by Scholtz and Chichibabin. Scholtz was the first to obtain 1,3-diacetylindolizine from α-picoline and acetic anhydride. He then converted it into indolizine (pyrrocoline).[1-4] Chichibabin elucidated the mechanism of this reaction[5,6]. He also developed one of the general and most convenient methods for the synthesis of indolizines from 2-methyl-*N*-β-oxoalkylpyridinium salts[7,8].

The chemistry of indolizines has been reviewed by Borrows and Holland[9] and a chapter in Mosby's monograph[10] is devoted to it. The present review surveys data on individual sections of indolizine chemistry and deals with recent studies which yielded new information both about the methods of synthesis and properties of indolizines.

II. SYNTHESIS OF INDOLIZINES

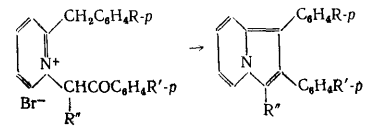
The Preparation of Indolizines from 2-Alkyl-*N*-(β-oxoalkyl)pyridinium Salts (The Chichibabin Method)

The closure of the five-membered ring of the indolizine system takes place on treating the salts formed from α-picoline (α-picoline substituted in the methyl group) and α-halogenoketones with sodium bicarbonate and certain other bases in aqueous, alcoholic, or acetone solutions:



Chichibabin obtained in this way 2-methyl, 2-phenyl, 2,5-dimethyl-, and 2-methyl-1-phenylindolizines[7,8].

This reaction was carried out both with and without isolation of the corresponding pyridinium salts. When α-bromoketones are used, substituted indolizines are formed in high yields—up to 90% for aryl-substituted derivatives[7,8,11-15]. A series of indolizines where the 2-position is occupied by a substituted phenyl or naphthyl group (with alkyl, halogeno-, nitro-, amino-, hydroxy-, alkoxy-, alkylthio-, phenylthio-, and other substituents)[16-26] as well as the *p*-arylphenyl[27], *p*-cyclohexylphenyl[28], 2-thienyl[29], 5-aryl-2-thienyl[30], *m*-(2,5-dimethylpyrrolyl)phenyl[31], 9-ethyl-3-carbazolyl[32], 2-dibenzofuryl[33], and 3-phenoxathiinyl[34] groups were obtained by this method, which was also used to synthesise 4,4-di-(2-indolizinyl)biphenyl from α-picoline and 4,4-di-(ω-bromoacetyl)biphenyl[35]. Indolizines with a methyl group in the 1-position were obtained from α-ethylpyridine[36,37]. α-Benzylpyridines with substituents in the benzene ring were used to synthesise 1,2-diaryl- and 1,2,3-triarylindolizines[38,39]:



In the synthesis of indolizines of this type quaternisation products were isolated[12,14]. It was not possible to isolate the quaternary salt formed from α-halogenoketones and 2-*p*-chlorobenzylpyridine, since it cyclises spontaneously to the corresponding substituted indolizine[38,40].

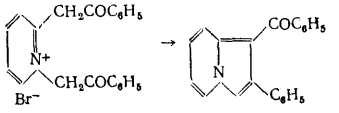
Only a limited number of studies have been made on the synthesis by this method of indolizines with substituents in the six-membered ring owing to the comparatively low availability of substituted α-picolines. 2,5-Dimethylindolizine was obtained by Chichibabin from αα′-lutidine and bromoacetone[7]. 2,6-Dimethyl-7-phenyl- and 6-methyl-2,7-diphenyl-indolizines[41], were obtained from 2,5-dimethyl-4-phenylpyridine[42]. 7-Benzyloxy-5-methyl-2-phenylindolizine was obtained in a very low yield from 4-benzyloxy-2,6-dimethyl-*N*-phenacylpyridinium bromide[43]. In the synthesis of 8-ethoxycarbonyl-2-methylindolizine (in 30% yield) ethyl 2-methylnicotinate and bromoacetone were used; the conversion of the resulting ester into 2-methylindolizine-8-carboxylic acid has been described[44].

Indolizines are formed from α′-substituted α-picolines in a lower yield than from α-picoline itself owing to steric hindrance due to the substituents at the $C_{(6)}$ atom of the pyridine ring[36]. A similar influence on the yield of indolizines was discovered for the sterically hindered

carbonyl group in halogenoketones[14,15,25]. The corresponding indolizine could not be synthesised from α-picoline and ω-bromo-4-(t-butyl)-2,6-dimethylacetophenone or ω-bromo-6-methoxy-2,4-dimethylacetophenone[25].

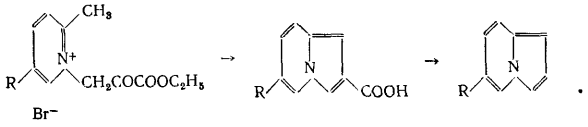
Vinylindolizines—2,3-dimethyl-6-vinyl- and 2-methyl-6-vinyl-derivatives—were obtained from 2-methyl-5-vinylpyridine and α-bromoethyl methyl ketone and bromoacetone respectively. The latter indolizine is resistant to polymerisation and oxidation in air[45,46]. 2-Methyl-5-vinylindolizine could not be isolated, because it polymerises during the reaction[47].

The synthesis of many indolizines with functional groups was achieved by the Chichibabin method. 1-Acetylindolizine could not be obtained from 2-acetonylpyridine and bromoacetophenone, because the corresponding quaternary salt is not formed[48]. However, 1,2-diphenacylpyridinium cyclises exclusively with formation of 1-benzoyl-2-phenylindolizine[49,50]:

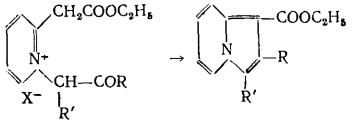


2-(*o*-Acetamidophenyl)-1-acetyl-indolizine was obtained in a yield of more than 40% by the cyclisation of 1-(*o*-acetamidophenacyl)-2-acetonyl-pyridinium salts[51]. 6-Ethoxycarbonyl(carbamoyl, cyano)-2-methyl- and 7-acetamidomethyl(cyano)-2-methyl-indolizines substituted in the six-membered ring were obtained by the cyclisation of 1-acetonyl-2-methylpyridinium bromides with the corresponding substituents in the pyridine ring[52].

Several versions of the synthesis of indolizinecarboxylic acids with carboxy-groups in the five-membered ring have been developed. The cyclisation of the quaternary salt formed from α-picoline and ethyl bromopyruvate gives a 30% yield of indolizine-2-carboxylic acid[14,53]. 6-Ethylindolizine-2-carboxylic acid was obtained in the same way from 5-ethyl-2-methylpyridine[54]. Indolizine[55,56] and 6-ethylindolizine were obtained by the decarboxylation of these acids[53]:



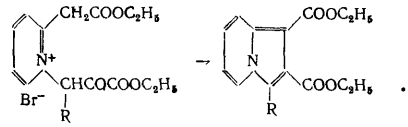
The cyclisation of the quaternary salts obtained from 2-ethoxycarbonylmethylpyridine and α-halogeno-substituted aldehydes and ketones leads to indolizine-1-carboxylic acids[57,58]. The above pyridine base and chloroacetone were used to synthesise 2-methylindolizine-1-carboxylic acid[59]. Salts obtained from the same pyridine base were used in the analogous condensation reaction with bromoacetaldehyde, α-bromopropionaldehyde, and bromophenylacetaldehyde. The corresponding indolizine-1-carboxylic acids are formed in comparatively low yields in the above reactions[49,57]:



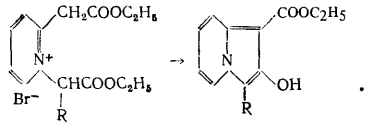
R=CH_3, R′=H; R=R′=H; R=H, R′=CH_3; R=H, R′=C_6H_5.

The synthesis of the methyl ester of 2-(*o*-acetamidophenyl)indolizine-1-carboxylic acid from 1-(*o*-acetamidophenacyl)-2-methoxycarbonylmethylpyridinium bromide has been described[60]. 1-Acetonyl-2-β-ethoxycarbonylethylpyridinium bromide and its analogue with a methoxy-group in the 4-position have been cyclised to 1-ethoxycarbonylmethyl-2-methyl- and 1-ethoxycarbonylmethyl-7-methoxy-2-methyl-indolizines. 1-(α-Ethoxycarbonylethyl)-2-methylindolizine was obtained from 2-(β-ethoxycarbonylpropyl)pyridine and bromoacetone in acetone, after which it was successively acetylated (benzoylated) at $C_{(3)}$ and then hydrolysed to 3-acetyl-(benzoyl)-1-(α-carboxyethyl)-2-methylindolizine[61]. The cyclisation of 2-(β-carbamoylethyl)-1-phenacylpyridinium bromide results in the formation of 1-carbamoylmethyl-2-phenylindolizine[43].

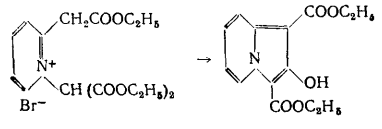
The diethyl ester of indolizine-1,2-dicarboxylic acid is formed in 95% yield in the Chichibabin cyclisation of the pyridinium salt obtained from 2-ethoxycarbonylmethylpyridine and bromopyruvic acid[49]. 2-Methoxycarbonylmethylpyridine was used in a similar condensation[58]. The esters of indolizine-1,2-dicarboxylic acids were also obtained with substituents in the 3-position[57]:



The reactions of quaternary salts formed from 2-ethoxycarbonylmethylpyridine and α-bromopropionate and bromophenylacetate esters are examples of syntheses of hydroxy-acids of the indolizine series. The ethyl esters of 2-hydroxy-3-methyl(phenyl)indolizine-1-carboxylic acids were obtained in this way[49].



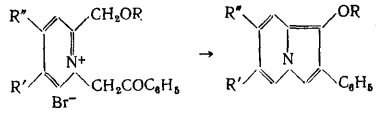
When the cyclisation is carried out in ether, the ethyl ester of 2-hydroxyindolizine-1-carboxylic acid is formed from 1,2-di(ethoxycarbonylmethyl)pyridinium bromide. When this reaction is carried out in the absence of a solvent, the ethyl esters of 3-ethoxycarbonylmethyl-2-hydroxyindolizine-1-carboxylic acid and 3-(1-ethoxycarbonyl-2-indolizinyl)-2-hydrozyindolizine-1-carboxylic acid are formed as a result of secondary reactions[49]. The diethyl ester of 2-hydroxyindolizine-1-carboxylic acid was obtained from 2-ethoxycarbonylmethylpyridine and bromomalonic ester[49]:



Indolizines with a cyano-group in the 1-position were obtained by the cyclisation of quaternary salts derived from 2-cyanomethylpyridine with α-bromoketones[49,62]. The ethyl ester of 3-cyano-2-methylindolizine-1-carboxylic acid was synthesised from 1-(α-cyanoacetonyl)-2-ethoxycarbonylmethylpyridinium bromide[63].

When 2-hydroxymethyl-1-phenacyl- or 2-acetoxymethyl-1-phenacyl-pyridinium bromide is treated with sodium bicarbonate, the product is 1-hydroxy-2-phenylindolizine—an unstable compound which rapidly darkens in air[63]. The cyclisation of 1-acetonyl(phenacyl)-2-ethoxymethyl-(phenoxymethyl)-5-methyl-4-phenylpyridinium bromide

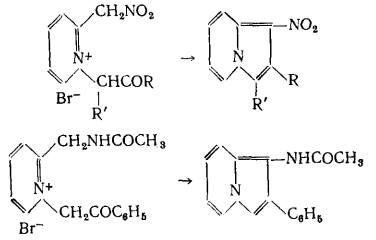
gave the corresponding substituted indolizines with an ethoxy- or phenoxy-group in the 1-position[41]:



R=R′=R″=H; R=C_2H_5, R′=CH_3, R″=C_6H_5; R′=CH_3, R=R″=C_6H_5.

An instance of the synthesis by the Chichibabin method of an indolizine with the hydroxymethyl group in the five-membered ring has been described. 1-Hydoxymethyl-2-methylindolizine was obtained in high yields by the cyclisation of 1-acetonyl-2-(β-hydroxyethyl)pyridinium bromide in sulpholan[52]. However, the cyclisation of 2-(β-hydroxypropyl)-1-phenacylpyridinium resulted in the formation of 2-phenylindolizine instead of the expected hydroxyalkylindolizine. It has been suggested that the hydroxyethyl group is split off during the reaction as a result of retro-aldol condensation[48].

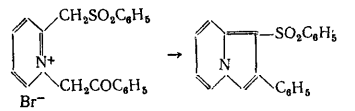
3-Nitroso-2-phenylindolizine is formed in the cyclisation of an α-picolinium salt with ω-chlorohydroxyimine-acetophenone[64]. The cyclisation of quaternary salts obtained from 2-nitromethylpyridine (hydrate) and bromoacetaldehyde, bromophenylacetaldehyde, bromoacetone, and bromoacetophenone results in the formation of 1-nitroindolizines in yields up to 50%.[63] 1-Acetamido-2-phenylindolizine was obtained in the same way from 2-acetamidomethyl-1-phenacylpyridinium bromide[63]:



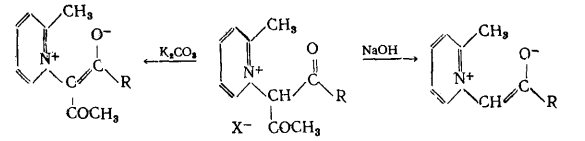
When 1-[2-(2-furyl)-1-isonitroso]-2-oxoethyl-2-picolinium chloride was treated with a 30% sodium hydroxide solution, 2-(2-furyl)-3-nitrosoindolizine was obtained in 87% yield[65].

A number of 1-aminomethyl-, 1-(β-aminoethyl)-, and 1-(γ-aminopropyl)-2-phenylindolizines with CH_3, $(CH_3)_2$, $COOC_2H_5$, and $CON(C_2H_5)_2$ substituents in the amino-group have been synthesised. The quaternary salts obtained from bromoacetophenone and the corresponding pyridines with ω-aminoalkyl-substituted amino-groups in the α-position were cyclised. Indolizines of this type with an alkylated amino-group were obtained by the reduction of an alkylcarbamoyl group with lithium tetrahydroaluminate after ring closure[50,66].

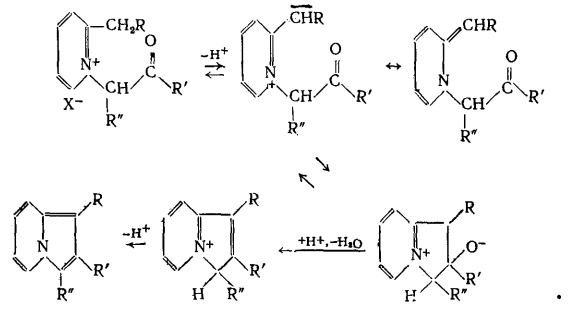
A sulphur-containing indolizine, phenyl 2-phenyl-1-indolizinyl sulphone, was synthesised from phenyl 2-picolinyl sulphone and bromoacetophenone[54,67]:



The mechanism of the formation of indolizines by the Chichibabin method has not as yet been fully elucidated. It has been discussed in detail by Bragg and Wibberley[49]. One of the initial factors serving as a basis for conclusions concerning the mechanism of this reaction was the difficulty encountered in the synthesis of certain indolizines by the Chichibabin method. It was not possible to cyclise salts obtained from α-picoline and α-chloroacetylacetone, α-bromobenzoylacetone, and ethyl α-bromobenzoylacetate[14,53]. Under the conditions of the cyclisation reaction, these salts, which are formed with difficulty, are converted into "enol-betaines". Then, depending on the nature of the salt and the base employed, either the acyl (ester) group splits off ("acid cleavage") or the enol-betaine is retained[68-72]:

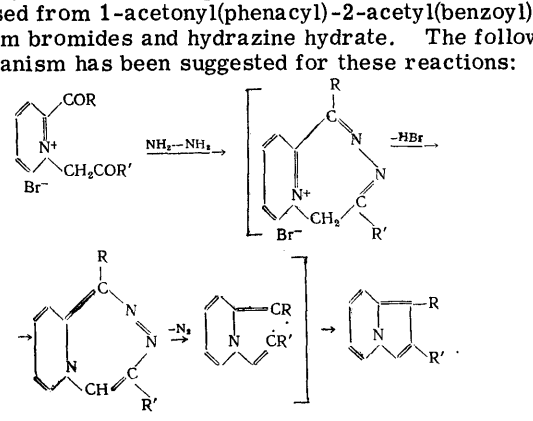


It has been suggested that fairly stable enol-betaines cannot cyclise and that indolizines are formed via a stage involving the condensation of the 1,3-ylid formed from the pyridinium salt when the latter is treated with a base[49]:



The formation of the ylid is facilitated when the substituent at the methyl group (at the carbon atom in the 2-position) has electron-accepting properties; it is also promoted by the use of sodium bicarbonate. The ylid cyclises intramolecularly via a reaction of the aldol type; the subsequent elimination of water from the betaine formed under these conditions followed by irreversible dehydrogenation of the 3*H*-indolizinium cation results in the formation of a substituted indolizine. Another hypothesis concerning the conversion of the ylid into a cyclic betaine has also been put forward: the methine obtained from the ylid cyclises[44].

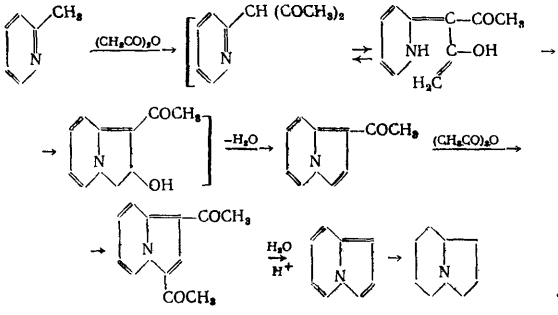
Hitherto the Chichibabin method has been one of the fundamental procedures for the synthesis of various indolizines. 1,2-Disubstituted indolizines, described by Kröhnke and Weis[73], were obtained by a different method from 2-acyl-1-(β-oxoalkyl)pyridinium salts. They were synthesised from 1-acetonyl(phenacyl)-2-acetyl(benzoyl)-pyridinium bromides and hydrazine hydrate. The following mechanism has been suggested for these reactions:



1,2-Disubstituted indolizines with a methyl or phenyl group in the 1-position and with a methyl or aryl group in the 2-position were synthesised by this method.

The Synthesis of Indolizines from α-Picoline (Substituted in the Methyl Group) and Acetic or Propionic Anhydride (the Scholtz Method)

The mechanism of the formation of 1,3-diacetylindolizine from α-picoline and acetic anhydride as well as the structure of the indolizine were elucidated by Chichibabin[1-7,74]:



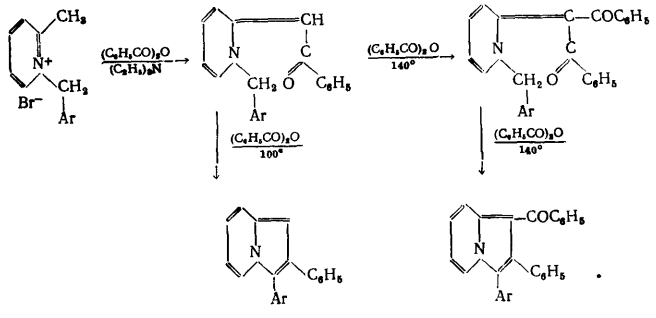
α-Picoline is acetylated to 2-diacetylmethylpyridine, the cyclisation of a tautomeric form of which gives rise to 1-acetyl-2-hydroxy-2,3-dihydroindolizine. Further dehydration leads to 1-acetylindolizine and the latter is acetylated to 1,3-diacetylindolizine. Deacetylation takes place on acid hydrolysis. Indolizine has been converted by catalytic hydrogenation into octahydroindolizine—δ-coniceine[55].

1,3-Diacetyl-5-methyl- and 1,3-diacetyl-5-phenylindolizines were obtained by the Scholtz method from the corresponding substituted α-picolines[3,75]. Only propionic anhydride as well as acetic anhydride can be used in this reaction[4,76]. The structure of the resulting 3-methyl-1-propionylindolizine was demonstrated by acetylating it to 3-methylindolizine[11].

The synthesis of 3-acetyl-1-(*p*-chlorophenyl)indolizine from 2-(*p*-chlorophenyl)methylpyridine by this method has been described[77]. 1-Acetyl-3-ethoxyindolizine were obtained by heating ethoxymethyl α-picolinyl ketone with acetic anhydride[78].

The Synthesis of Indolizines from 2-Alkyl-1-Benzylpyridinium Salts

When 1-benzyl-2-methylpyridinium salts are treated with acetic, propionic, or benzoic anhydrides in the presence of bases (for example triethylamine), the five-membered ring is closed at the $C_{(2)}-C_{(3)}$ bond, resulting in the formation of substituted indolizines. When the reaction is carried out at 100°C, 2,3-disubstituted indolizines are formed and at 140°C also 1,2,3-trisubstituted indolizines:



The pyridinium salt is benzoylated at the α-methyl group with simultaneous elimination of hydrogen bromide. This results in the formation of 2-benzoylmethylene-1-benzyl-1,2-dihydropyridine substituted in the benzene ring of the benzyl group. Its cyclisation at 100°C, which is an intramolecular aldol condensation, leads to the formation of 3-aryl-2-phenylindolizine. When the reaction is performed at 140°C, the methine derivative is benzoylated to 2-dibenzoylmethylene-1-benzyl-1,2-dihydropyridine, the cyclisation of which leads to 3-aryl-1-benzoyl-2-phenylindolizine. Since direct benzoylation of 3-aryl-2-phenylindolizine can be achieved only at 200°C, it is believed that a dibenzoylmethine derivative is formed as an intermediate in the above reactions[50,63,67,79,80]. In many cases monosubstituted methine derivatives were isolated and their conversion into indolizines was investigated. Methines are obtained on simultaneous acylation and dehydrohalogenation of 1-benzyl-2-methylpyridinium bromides[72,81,82].

1-Benzyl-2-phenacylidene-1,2-dihydropyridine was prepared in two ways: by the Schotten-Baumann benzoylation of 1-benzyl-α-picolinium bromide[81,83,84] and by the quaternisation of 2-phenacylpyridine[50,81]. On treatment with acetic anhydride in the presence of triethylamine, 2-benzoylmethylene- and 2-acetylmethylene-1-benzyl-1,2-dihydropyridine are converted in yields up to 90% into 1-acetyl-2,3-diphenyl- and 1-acetyl-2-methyl-3-phenylindolizines respectively[50,67]. Triethylamine can be successfully replaced in this reaction by sodium acetate[85]. When propionic anhydride was used in the first instance, the analogous indolizine with the propionyl group in the 1-position was obtained.

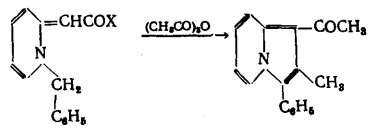
Methine derivatives are cyclised on being heated in formamide[79]. 6-Methyl-2,3,7-triphenylindolizine was obtained in this way from 1-benzyl-5-methyl-2-phenacylidene-4-phenyl-1,2-dihydropyridine; its cyclisation in the presence of acetic anhydride leads to its 1-acetyl-substituted analogue[82].

The corresponding indolizines with *p*-nitro- and *p*-chloro-phenyl groups in the 3-position were obtained, without the isolation of the methine derivatives, from 2-methyl-1-[*p*-nitro(*p*-chloro)]benzylpyridinium bromides and acetic or benzoic anhydride at 140°C with and without the acyl group in the 1-position in each case[79,80]. The influence on the yield of indolizines of the nature of the substituent in the *p*-position of the *N*-benzyl group which affects the reactivity of the *N*-methylene group was investigated. The following sequence of substituents in terms of increasing yields of indolizine caused by their introduction has been established: $p\text{-}NO_2C_6H_4 < C_6H_5 < p\text{-}CH_3OC_6H_4$.

1-Acetyl-2,3-dimethylindolizine was obtained in 9% yield from 1-ethyl-2-phenacylidene-1,2-dihydropyridine after heating for 12 h with acetic anhydride. The corresponding indolizine could not be obtained from 1-methyl-2-phenacylidene-1,2-dihydropyridine and benzoic anhydride. The product isolated in this case was 2-dibenzoylmethylene-1-methyl-1,2-dihydropyridine, which was also obtained by the direct benzoylation of 1-methyl-2-phenacylidene-1,2-dihydropyridine[80].

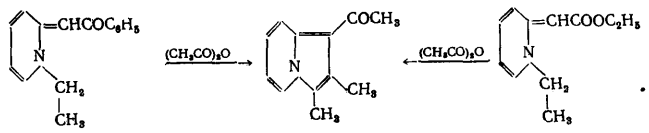
1,2,3-Triphenylindolizine[38] was synthesised by this method from 1,2-dibenzylpyridinium bromide and benzoic anhydride, while the use of acetic anhydride led to the isolation of 2-methyl-1,3-diphenylindolizine[79].

1-Acetyl-2-methyl-3-phenylindolizine is formed from 1-benzyl-2-cyanocarbonyl(carbamoyl, phenylcarbamoyl, acylcarbonyl)methylene-1,2-dihydropyridines and acetic anhydride[50]:

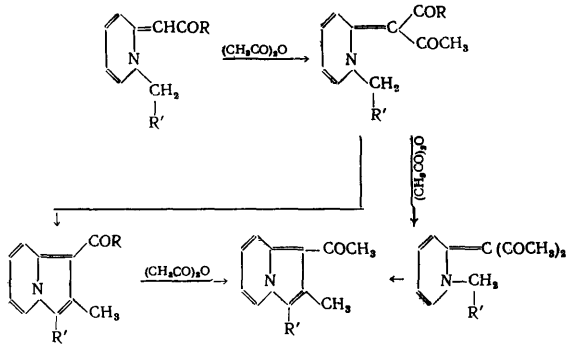


X=CN, NH_2, NHC_6H_5, COR.

1-Acetyl-2,3-dimethylindolizine was obtained similarly from 2-benzoyl(ethoxycarbonyl)methylene-1-ethyl-1,2-dihydropyridine:



It is believed that the first reaction stage is *C*-acetylation of the ketoenamine to a diacylmethine, which can then be converted into indolizine in two ways:



Initially the diacyl derivative undergoes transacylation and then cyclises. The second pathway involves the cyclisation of the diacylmethine derivative via the acetyl group followed by transacetylation at the 1-position. This is less likely because 1-ethoxycarbonyl- and 1-cyano-indolizines are stable in relation to acetic anhydride and ethoxycarbonyl and cyano-groups are not replaced by the acetyl group in these substances[50].

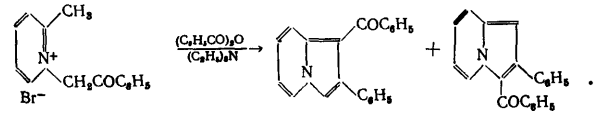
The occurrence of transacylation in the formation of indolizines from diacylmethines is confirmed to some extent by the following results obtained in the synthesis of indolizines from 1-benzyl-2-ethoxycarbonylmethylene-1,2-dihydropyridine[50,86]. When this methine was treated with acetic anhydride, 2-acetoxy-1-acetyl-3-phenylindolizine, 1-acetyl-2-methyl-3-phenylindolizine, and 1-ethoxycarbonyl-2-methyl-3-phenylindolizine were obtained in proportions of approximately 14 : 8 : 1. When this reaction was carried out in acetic acid, the ratios of the indolizines changed sharply and became 4 : 20 : 1. Thus the ethoxycarbonyl group is split off during the reaction (transacylation), which is promoted by an increase of the acidity of the medium[86].

Two methods have been described for the cyclisation of 1-(*p*-nitrobenzyl)-α-picolinium chloride to 3-(*p*-nitrophenyl)indolizine. This indolizine is formed in a low yield on heating the above picolinium salt with *s*-triazine in a pyridine–piperidine mixture; it is suggested that the intermediate in this reaction is 2-(β-aminovinyl)-1-(*p*-nitrobenzyl)pyridinium chloride. The second method involves heating the same picolinium salt in a pyridine–piperidine mixture with triethyl orthoformate: it is suggested that in this case the intermediate is 1-[β-ethoxy-α-(*p*-nitrophenyl)vinyl]-2-methylpyridinium chloride. 3-(*p*-Nitrophenyl)indolizine was obtained by the second method in 67% yield[87].

Synthesis of Indolizines from 2-Alkyl-1-(β-oxoalkyl)-pyridinium Salts and Acid Anhydrides

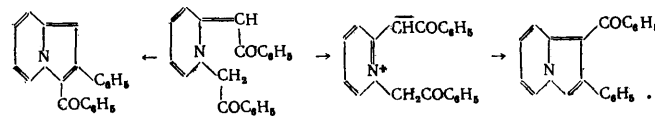
This method, as it were, combines two procedures for the synthesis of indolizines: their preparation by treating 2-alkyl-1-(β-oxoalkyl)pyridinium salts with bases and by treating 2-alkyl-1-benzylpyridinium salts with acid anhydrides, also in the presence of bases.

In one of these methods a 1-(β-oxoalkyl)pyridinium salt is treated with acetic anhydride in the presence of triethylamine. A mixture of 1-benzoyl-2-phenylindolizine and 3-benzoyl-2-phenylindolizine was obtained in this way in a satisfactory yield in proportions of 1 : 2 from 2-methyl-1-phenacylpyridinium bromide, benzoic anhydride, and triethylamine at 140°C.[44,79,80] The same indolizines were obtained in the same proportions when the initial pyridinium salt was treated with benzoic anhydride in the presence of sodium benzoate[44]:

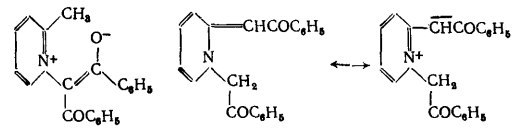


3-Acetyl-2-methylindolizine (58%) and 1,3-diacetyl-2-methylindolizine (27%) were obtained from 1-acetonyl-2-methylpyridinium bromide, acetic anhydride, and sodium acetate[44]. The synthesis of analogues of the same indolizines with substituents in the six-membered ring was achieved by the same procedure.

1-Ethoxycarbonyl-3-methylindolizine was obtained in 47% yield on heating 2-ethoxycarbonylmethylpyridine with α-bromopropionaldehyde in acetic anhydride[88]. The following syntheses of 1-benzoyl-2-phenyl- and 3-benzoyl-2-phenyl-indolizines, mentioned above, and also 2-phenylindolizine apparently constitute important evidence which can be used for the solution of problems concerning the mechanisms of the formation of indolizines from 2-alkyl-1-(β-oxoalkyl)pyridinium salts and acid anhydrides. The first two indolizines were formed (in proportions of 1 : 5) when 1-phenacyl-2-phenacylidene-1,2-dihydropyridine was treated with acetic anhydride. It was suggested that 3-benzoyl-2-phenylindolizine is formed directly from the methine derivative (ring closure at the 2–3 positions) and 1-benzoyl-2-phenylindolizine is formed from the intermediate ylid (ring closure at the 1–2 positions[49,50]:

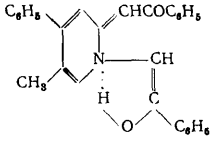


Different structures have been attributed to the product formed on benzoylation of 2-methyl-1-phenacylpyridinium bromide: enol-betaine[71,80] as well as 1-phenacyl-2-phenacylidene-1,2-dihydropyridine and its mesoform as the betaine-anion (ylid)[50]:



The enol-betaine was synthesised from α-picoline and dibenzoylmethyl bromide. It was established that hydrobromic acid cleaves it to benzoic acid and 2-methyl-1-phenacylpyridinium bromide.

An enolic structure with an intromolecular hydrogen bond was attributed to 5-methyl-1-phenacyl-2-phenacylidene-4-phenyl-1,2-dihydropyridine on the basis of its spectroscopic characteristics:

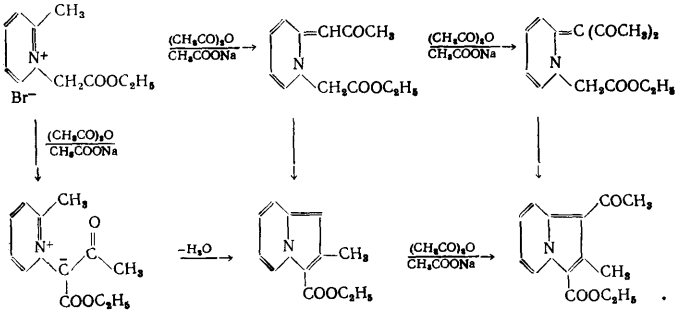


When this methine derivative was heated with acetic anhydride, 3-benzoyl-6-methyl-2,7-diphenyl-, 1-benzoyl-6-methyl-2,7-diphenyl-, and 1-acetyl-3-benzoyl-6-methyl-2,7-diphenyl-indolizines were obtained. The second indolizine is formed on cyclisation of the methine derivative in the presence of formamide[89]. 3-Benzoyl-2-phenyl- and 1-benzoyl-2-phenyl-indolizines were synthesised from the stable 2-methylpyridinium dibenzoylmethylid on brief heating with acetic anhydride[79,80].

Analysis of the type of substitution in the indolizines formed on treatment of 2-alkyl-1-(β-oxoalkyl)pyridinium salts with acid anhydrides in the presence of triethylamine or the sodium salt of the acid led Dainis[44] to the hypothesis that the first reaction stage involves the conversion of the pyridinium salt into ylids. The Table[44] illustrates examples of this reaction.

The method of synthesis of indolizines from 2-alkyl-1-(β-oxoalkyl)pyridinium salts with the aid of acetic anhydride and sodium acetate (as well as propionic anhydride and sodium propionate) has been used in the synthesis of indolizinecarboxylic acids. A mixture of the ethyl ester of 2-methylindolizine-3-carboxylic acid (the main product) and the ethyl ester of 1-acetyl-2-methylindolizine-3-carboxylic acid was obtained by this method in a good yield from 1-ethoxycarbonylmethyl-2-methylpyridinium bromide (3-cyanosubstituted analogues of these indolizines were also obtained from 1-cyanomethyl-2-methylpyridinium). The ethoxycarbonyl group in these indolizines is readily removed on acid hydrolysis[85].

The following explanation has been proposed for the formation of substituted indolizines by this method, which is illustrated by the syntheses of the above indolizines.

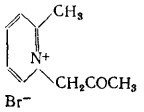
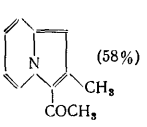
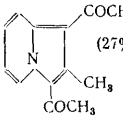
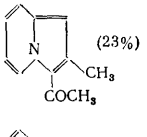
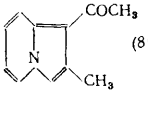
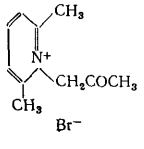
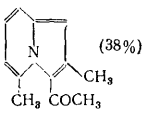
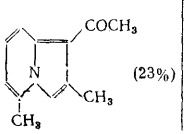
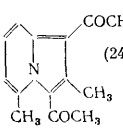
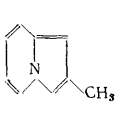


Bearing in mind that 3-ethoxycarbonyl-2-methylindolizine greatly predominates in the mixture of indolizines obtained and that direct acetylation of this indolizine with acetic anhydride in the presence of sodium acetate gives rise to 1-acetyl-3-ethoxycarbonyl-2-methylindolizine in a low yield (12%, the remainder consists of the initial indolizine), it is suggested that kinetically the rate-limiting stage is the formation of the diacylmethine[85]. Quantitative data for the synthesis of indolizines from 1-methoxycarbonylmethyldimethylpyridinium salts are consistent with this conclusion. When the methyl groups in the pyridine ring are in the 2,4- and 2,5-positions, a mixture of indolizines non-acylated and acylated at $C_{(1)}$ is formed; on the other hand, when the methyl groups are in the 2,3-positions, only 3-acetyl-2,8-dimethylindolizine is produced (70% yield). The explanation is that the methyl group at $C_{(3)}$ in the pyridine ring causes steric hindrance to the acylation of the intermediate acylmethine to the diacylmethine.

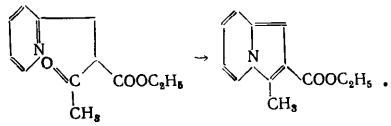
Cyclisation of 2-(γ-oxoalkyl)pyridines

The initial substituted pyridines of this type are obtained from 2-bromomethylpyridine and sodio-derivatives of acetoacetic and malonic esters as well as acetylactone[90]. The cyclisation is achieved by heating 2-(γ-oxoalkyl)pyridine with acetic anhydride for a short time[63].

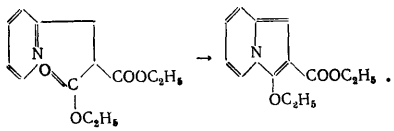
Indolizines obtained from 1-acetonyl-2-methyl(2,6-dimethyl)pyridinium bromides.

Starting compound	Method	Indolizines isolated			
	$(CH_3CO)_2O$ + CH_3COONa	 (58%)	—	 (27%)	—
	$(CH_3CO)_2O$ + $(C_2H_5)_3N$	 (23%)	 (8%)	—	—
	$(CH_3CO)_2O$ + CH_3COONa	 (38%)	 (23%)	 (24%)	

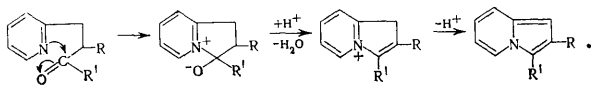
The condensation of 2-($\beta\beta$-diacetylethyl)pyridine leads to the formation of 2-acetyl-3-methylindolizine. The more active carbonyl group enters into cyclisations of this type, which has been shown in the conversion of 2-(β-acetyl-β-ethoxycarbonylethyl)pyridine into the ethyl ester of 3-methylindolizine-2-carboxylic acid:



As expected, bearing in mind the foregoing considerations, the cyclisation of 2-[$\beta\beta$-di(ethoxycarbonyl)ethyl]-pyridine to the ethyl ester of 3-ethoxyindolizine-2-carboxylic acid proceeds with greater difficulty and with a lower yield under comparable conditions:



It is believed that the cyclisation reaction begins with nucleophilic attack by the nitrogen atom on the carbonyl group in the side chain, which leads to ring closure with formation of a betaine. The protonation of the latter and subsequent dehydration result in the formation of an indolizinium cation, which is converted into a substituted indolizine by acid-catalysed dehydrogenation:

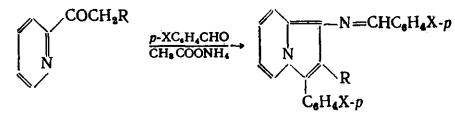


An indolizine is probably formed similarly (in 50% yields) from 3-(2-pyridyl)-1-propanol when it is heated in the presence of palladium on charcoal, since the intermediate should be 3-(2-pyridyl)propanol. 5-Methyl-2-phenylindolizine was obtained by the same procedure from 3-(6-methyl-2-pyridyl)-2-phenylpropanol[75]. It is suggested that 3-(2-pyridyl)indolizine is formed in the same way from 1,1-diacetoxy-1,3-di-(2-pyridyl)propane when it is heated *in vacuo*[91]. Pyrolysis of 2-($\alpha\gamma$-diacetoxypropyl)pyridine leads to the formation of indolizine[92]. 5-Methylindolizine was obtained similarly in a low yield by the pyrolysis of 2-($\beta\gamma$-diacetoxypropyl)-6-methylpyridine. The same indolizine was formed in 30% yield on pyrolysis (at 450°C) of 2-(α-acetoxypropenyl)-6-methylpyridine[75].

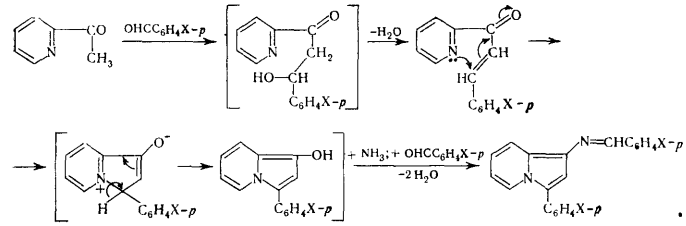
When 2-(γ-hydroxypropyl)pyridine *N*-oxide is treated with acetic anhydride, the product is 2-(γ-acetoxy-α-acetylpropyl)pyridine, which cyclises to an indolizine at 480°C with elimination of two acetic acid molecules[92]. On treatment with concentrated sodium hydroxide, 2-(γ-chloro-β-hydroxypropyl)pyridine, formed in a low yield on partial reduction of 2-(γ-trichloro-β-hydroxypropyl)pyridine with zinc in dilute sulphuric acid, is converted into an indolizine in a low yield[93]. The reaction of 2-pyridyl-lithium with epichlorohydrin leads to 2-hydroxy-3*H*-indolizinium chloride from which an indolizine was obtained on treatment with sodium hydroxide[94].

The Cyclisation of 2-Cinnamoylpyridines

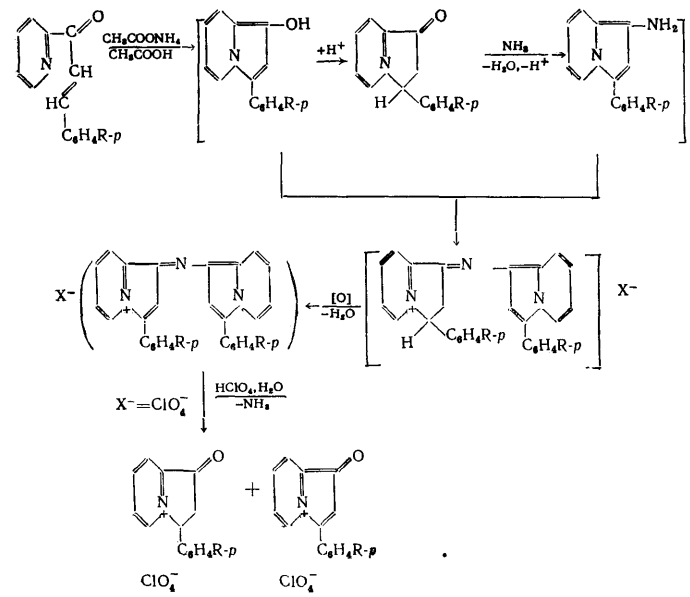
When 2-acetyl(propionyl, benzoyl)pyridines are heated with aromatic aldehydes in glacial acetic acid in the presence of ammonium acetate (with an acylpyridine : aldehyde ratio of 1 : 2), azomethines derived from 1-aminoindolizines are formed in yields up to 50%:[95-97]



The first stage of this reaction is the aldol condensation of 2-acylpyridine with the aromatic aldehyde, which results in the formation of 2-cinnamoylpyridine. Its intramolecular condensation leads to the formation of 3-aryl-1-hydroxyindolizine. On interaction of the latter with ammonia, the hydroxy-group is replaced by the amino-group and 1-amino-3-arylindolizine then condenses with the aromatic aldehyde[97-101]:



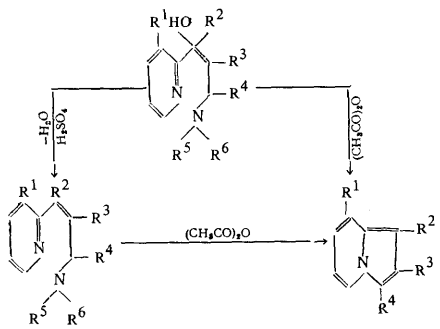
When 2-cinnamoylpyridines and ammonium acetate are heated in glacial acetic acid in the presence of air, the products are also azocyanines, but this time with two indolizine rings, which can be isolated in the form of salts. It is suggested that 3-aryl-1-hydroxyindolizine, whose salt has the 3-aryl-1-oxo-2,3-dihydro-1*H*-indolizinium structure, and 1-amino-3-arylindolizine formed from it condense. The intermediate dihydroazomethine is then oxidised further by atmospheric oxygen to the azomethine:



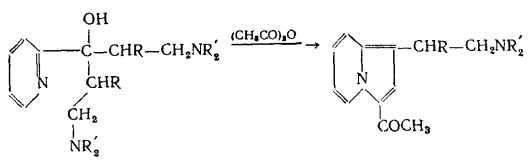
When the perchlorate of such an azomethine ($X^- = ClO_4^-$) is heated with 70% perchloric acid, it is cleaved with formation of 3-aryl-1-oxo-2,3-dihydro-1*H*-indolizinium and 3-aryl-1-oxo-1*H*-indolizinium perchlorates[102].

Deamination and Cyclisation of 2-(γ-dialkylamino-α-hydroxyalkyl)pyridines

On heating with acetic anhydride, the aminoalcohols formed from 2-lithiopyridines and β-dialkylaminoketones[103] are converted into substituted indolizines in yields up to 60%. The same indolizines are formed under the same conditions from the dehydration products of 2-(γ-dialkylamino-α-hydroxyalkyl)pyridines. When R^4 = H (see the reaction scheme), indolizines acetylated in the 3-position are obtained[77,104-106]:

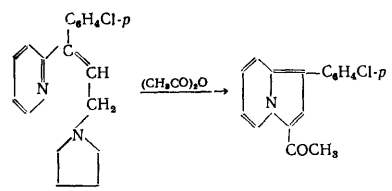


3-Acetyl-1-(*p*-chlorophenyl)indolizine together with a number of side products were obtained in this way from 1-(*p*-chlorophenyl)-1-(2-pyridyl)-3-(1-pyrrolidinyl)-1-propanol. The use of diaminomethanols (symmetric and asymmetric) in these reactions permitted the synthesis of aminoalkylindolizines[106]:



3-Acetyl-2-methyl(ethyl)-1-(β-dimethylaminoethyl)-indolizines, whose structure has been established by ultraviolet spectroscopy, were obtained from asymmetrically substituted carbinols of the following type: 2-methyl(ethyl)-1,5-bis(dimethylamino)-3-(2-pyridyl)-3-pentanols. The formation of the isomeric indolizines unsubstituted in the 2-position could not be observed.

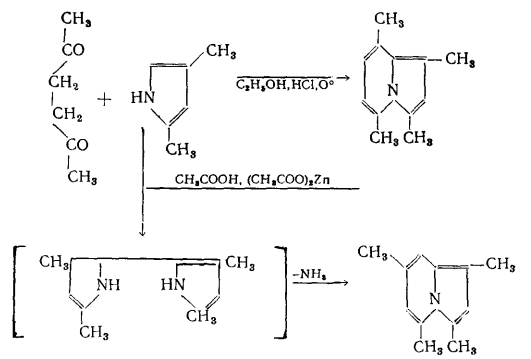
It is believed that the alkenylamines formed on dehydration of the aminomethanols are not intermediates in the conversion of the aminomethanols into indolizines, although they are converted into substituted indolizines under the same conditions. Thus 3-acetyl-1-(*p*-chlorophenyl)indolizine, mentioned above, was obtained from *cis*-1-(*p*-chlorophenyl)-1-(2-pyridyl)-3-(1-pyrrolidinyl)-prop-1-ene:



The *trans*-isomer does not cyclise under analogous conditions (refluxing for 30 min), more severe conditions being required for this purpose, and the yield of the substituted indolizine is low. In these reactions an appreciable amount of 3-acetoxy-1-(*p*-chlorophenyl)-1-(2-pyridyl)prop-1-ene is formed as a side product.

The Conversion of Alkylpyrroles into Indolizines

When 2,4-dimethylpyrrole is heated with acetonylacetone in acetic acid in the presence of zine acetate, 1,3,5,7- and 1,3,5,8-tetramethylindolizines are formed[107,108]. Later it was established that the second indolizine is formed from 2,4-dimethylpyrrole and acetonylacetone in alcoholic solution at 0°C in the presence of hydrogen chloride. It is suggested that the formation of 1,3,5,7-tetramethylindolizine proceeds via a pyrrolinylpyrrole stage[109]:

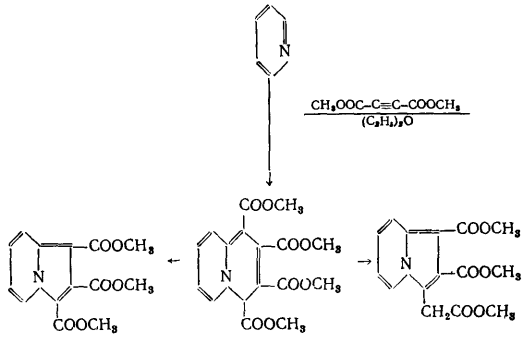


1,2,6,7-Tetraethylindolizine was obtained similarly in 24% yield from 3,4-diethylpyrrole in the presence of zinc acetate and the condensation of the same substituted pyrrole with acetonylacetone led to the isolation of 1,2-diethyl-5,8-dimethylindolizine. 3,4-Dimethylpyrrole was also converted into 1,2,6,7-tetramethylindolizine[110]. The interaction of pyrrole with hexane-2,5-dione in acetic acid containing zinc acetate leads to the formation of a mixture of various condensation products containing more than 10% of 5,8-dimethylindolizine and also substituted indole, carbazole, and other substances[111].

The Conversion of 1,2,3,4-Tetra(methoxycarbonyl)-4*H*-quinolizine into Indolizine-1,2,3-tricarboxylic Acid Esters

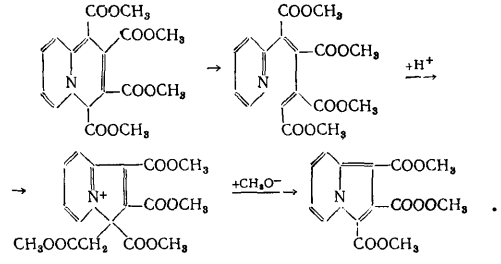
One of the substances formed in the interaction (in ethereal solution) of pyridine with acetylenedicarboxylic acid dimethyl ester is the tetramethyl ester of 4*H*-quinolizine-1,2,3,4-tetracarboxylic acid (the yellow "stable product") to which the structure of 1,2,3,4-tetra(methoxycarbonyl)-9*aH*-quinolizine was attributed previously. When this tetramethyl ester is treated with bromine and then hydrolysed, or when it is oxidised with dilute nitric acid or chromic acids, or when it is irradiated with light from a 450 W mercury lamp, the trimethyl ester of

indolizine-1,2,3-tricarboxylic acid is formed (on irradiation the yield is only 5%). When the above dihydroquinolizine is heated with phenol or formic acid, 1,2-di(methoxycarbonyl)-3-methoxycarbonylmethylindolizine is also formed[53,55,56,112-119]:

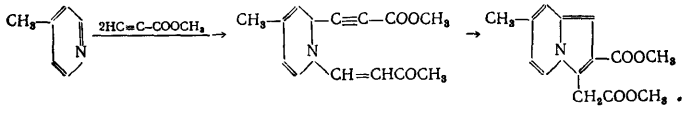


α-Picoline[120], β-picoline[115,121], isonicotinonitrile[122], and stilbazole[118,123] were introduced into the reaction with acetylenedicarboxylic acid dimethyl ester with the formation of tri(methoxycarbonyl)indolizines with the corresponding substituents in the six-membered ring.

It has been suggested that irradiation of a methanolic solution of 4*H*-quinolizine-1,2,3,4-tetracarboxylic acid tetramethyl ester (the experiment is carried out in a stream of nitrogen) leads to the opening of the 4*H*-ring with formation of a substituted α-pyridylbutadiene, which subsequently undergoes cyclisation[119]:



The substances formed in the interaction of 2-, 3-, and 4-methyl and 3,5-dimethylpyridines with methyl propiolate have been studied[124-126]. It was established (mainly by spectroscopic methods) that this involves the formation of compounds of two types: substituted cyclo-[3,2,2]azines and indolizines. The formation of 2-methoxycarbonyl-3-methoxycarbonylmethyl-7-methylindolizine from γ-picoline and a propiolate ester was observed:



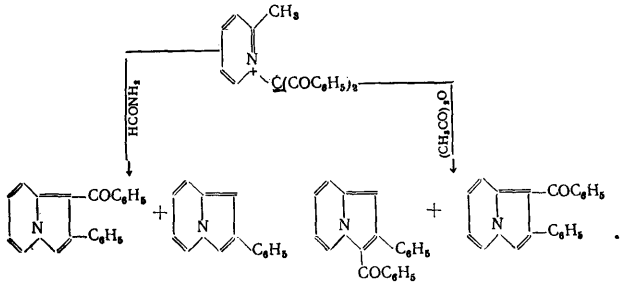
It is suggested that 2-(methoxycarbonylethynyl)-1-(β-methoxycarbonylvinyl)-4-methyl-1,2-dihydropyridine is formed as an intermediate. This method was extended to the synthesis of benzoindolizine systems[127].

The interaction of 2-phenylethynylpyridine with acetylenedicarboxylic acid dimethyl ester in acetonitrile leads to the formation of the tetramethyl ester of oxy-bis-(1-phenylmethyleneindolizine-2,3-dicarboxylic acid), whose treatment with bromine in chloroform led to a quantitative yield of 1-bromoindolizine-2,3-dicarboxylic acid dimethyl ester[128].

The Synthesis of Indolizines from Ylids

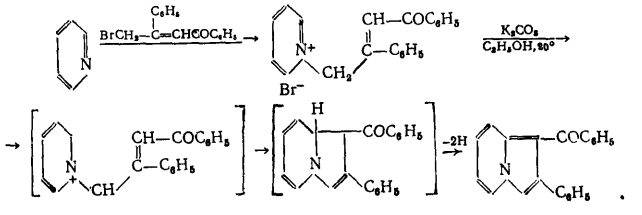
Ylids are converted into indolizines either by the cyclisation of the ylids themselves or by their interaction with acetylenic compounds, i.e. via 1,3-dipolar cycloaddition.

A mixture of 1-benzoyl-2-phenyl- and 3-benzoyl-2-phenyl-indolizines in proportions of 1 : 2 and a small amount of 2-phenylindolizine are formed from the stable 2-methylpyridinium dibenzoylmethylid when it is heated for a short time with acetic anhydride[44,79,80]. When the same ylid was refluxed in formamide, the main reaction product proved to be 1-benzoyl-2-phenylindolizine, but when the refluxing was continued only for a very short time (about 1 min), 2-phenylindolizine was obtained quantitatively:



3-Benzoyl-1-methyl-2-phenylindolizine and 3-benzoyl-1,2-diphenylindolizine were obtained in quantitative yields on refluxing 2-ethyl- and 2-benzyl-pyridinium dibenzoylmethylids respectively in acetic anhydride. The latter ylid was converted quantitatively into 3-benzoyl-1,2-diphenylindolizine when it was heated to the melting point (170–172°C) or to 200°C for 1 min in formamide[44].

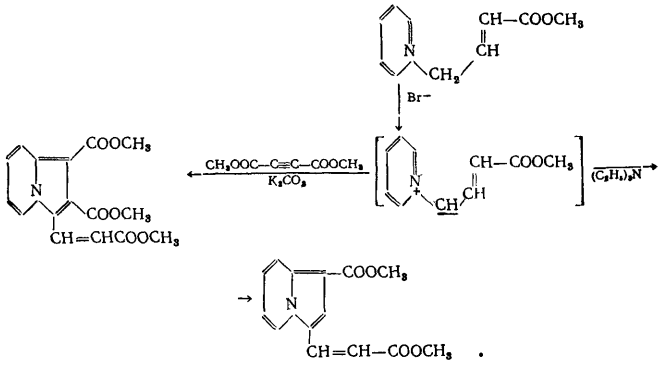
The syntheses of certain substituted indolizines where 4-bromo-1,3-diphenylbut-2-en-1-one was used for the preparation of pyridinium salts have been described. The synthesis of 1-benzoyl-2-phenylindolizine is illustrated below[129]:



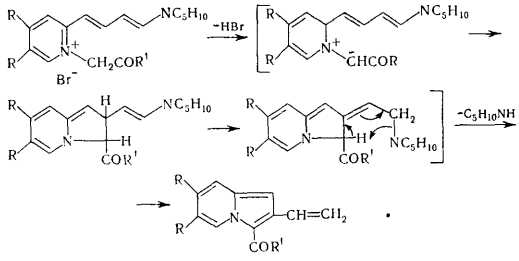
The ylid formed under the conditions of base catalysis cyclises with formation of dihydroindolizine, which is aromatised during the reaction with elimination of hydrogen.

The formation of a substituted indolizine from the analogous pyridinium salt—1-(γ-methoxycarbonylallyl)-pyridinium bromide—when the latter is heated with triethylamine apparently proceeds in a different way. Instead of the expected ester of indolizine-1-carboxylic acid, the product consisted of a 20% yield of 1-methoxycarbonyl-3-(β-methoxycarbonylvinyl)indolizine, the hydrogenation of which in the presence of palladium on charcoal led to its conversion into 1-methoxycarbonyl-3-(β-methoxycarbonylethyl)-indolizine. It is suggested that the reaction proceeds via a γ-methoxycarbonylallylid stage. This is confirmed indirectly by the formation of

1,2-di(methoxycarbonyl)-3-(β-methoxycarbonylvinyl)-indolizine from the same pyridinium salt and acetylenedicarboxylic acid dimethyl ester in dimethylformamide[88]:

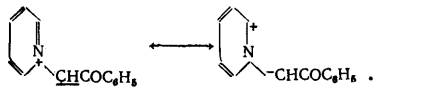


When 2,3-disubstituted quinolizinium bromide (with CH_3, C_6H_5, or H substituents) react with piperidine or morpholine, conjugated tetramethines are formed: 4,5-disubstituted 2-[4-piperidino(morpholino)buta-1,3-dienyl]pyridines. Their salts formed by reaction with bromoacetone or bromoacetophenone undergo intramolecular cyclisation when their chloroform solution is passed through a column containing alumina (Grade III activated alumina). This results in the formation of 6,7-disubstituted 3-acetyl(or benzoyl)-2-vinylindolizines[130]. The mechanism of this reaction is illustrated below:

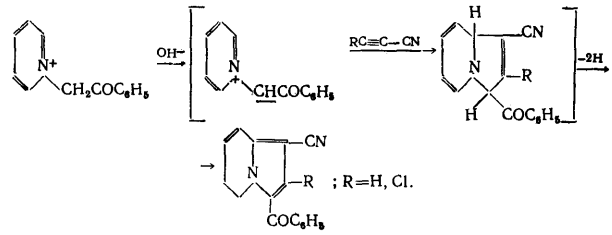


A mechanism similar to that described above was considered by Mörler and Krohnke for the formation of these indolizines[130]. The first indolizine is formed when *N*-vinylpyridine is split off from the intermediate dihydroindolizine and the second is formed via the acetylation of the dihydroindolizine in the 1-position and the elimination of piperidine. In the next communication, dealing with the study of the reactions of a salt of 4,5-disubstituted 2-(4-piperidinobuta-1,3-dienyl)piperidine and ethyl bromoacetate in the presence of acetic anhydride and triethylamine, two 6,7-disubstituted indolizines were reported: 1-(β-formylvinyl)-2-methyl- and 3-ethoxycarbonyl-1-(β-formylvinyl)-2-methylindolizines[131].

Pyridinium phenacylid[71, 132] in acetonitrile solution reacts exothermically with cyanoacetylene and also with chlorocyanoacetylene (with a 1 : 2 ylid : substituted acetylene reactant ratio), which results in the formation of substituted indolizines with a cyano-group at $C_{(1)}$ and a benzoyl group at $C_{(3)}$ in yields ranging from 5 to 25%.[133-135] Indolizines are formed from ylids and substituted acetylenes via a 1,3-dipolar cycloaddition reaction, owing to the presence of the stabilised mesomeric form of the 1,3-zwitterion of the ylid[136]:



The following explanation has been proposed for the formation of the indolizine system in the above reactions:

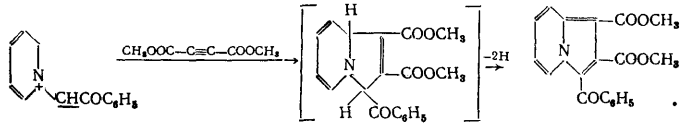


An intermediate in these reactions is an unstable dihydroindolizine, which is dehydrogenated to the final product. The substituted acetylene, which is introduced into the reaction in a molar excess, serves in this case as the hydrogen acceptor in the aromatisation of the dihydroindolizine. The formation of acrylonitrile and *trans*-β-chloroacrylonitrile as side products of these reactions was confirmed experimentally. The nitrile of 3-benzoyl-8-methylindolizine-1-carboxylic acid was obtained similarly in 10% yield from 3-methyl-1-phenacylpyridinium bromide.

3-Benzoyl-1-cyano-1,2,3,8*a*-tetrahydroindolizine, which is dehydrogenated at room temperature in the presence of palladium on charcoal to the similarly substituted 2,3-dihydroindolizine, was obtained from 1-phenacylpyridinium bromide via a stage involving the formation of an ylid. If the reaction of the ylid with acrylonitrile is carried out at an elevated temperature or for a long time, 3-benzoyl-1-cyanoindolizine, which was obtained also in the dehydrogenation of the corresponding 2,3-dihydroindolizine, is formed immediately[137].

The reaction of pyridinium phenacylid with acetylene dicarboxylic acid dimethyl ester has been investigated in fair detail. When this reaction is carried out in the presence of 5% of palladium on charcoal, 3-benzoylindolizine-1,2-dicarboxylic acid dimethyl ester is formed in 18% yield; its structure was demonstrated by converting it via acid hydrolysis and subsequent decarboxylation into indolizine-2-carboxylic acid[138]. It has been shown[139] that the use of a dehydrogenation catalyst in this reaction is not obligatory. The same indolizine was obtained in 32% yield when the reaction was performed in dimethylformamide in the presence of sodium hydride.

The intermediate in the reaction of pyridinium phenacylid with acetylene dicarbocylic acid dimethyl ester is also the corresponding dehydroindolizine, which is converted into a substituted indolizine via 1,4-elimination:



A similar mechanism has been proposed to account for the reaction of pyridine with acetylenedicarboxylic acid dimethyl ester, which leads to the formation of 1,2,3-tri(methoxycarbonyl)indolizine and 1,2-di(methoxycarbonyl)-3-[methoxy(methoxycarbonyl)methyl]indolizine[140].

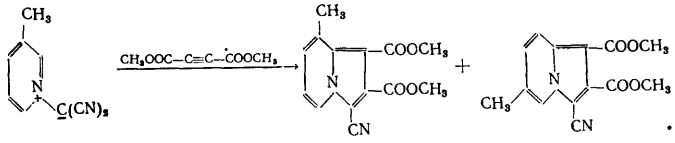
As expected, 3-substituted pyridinium phenacylids give rise to isomeric indolizines as regards the position of the substituent in the six-membered ring. 3-Benzoyl-1,2-di(methoxycarbonyl)-6-methyl(cyano)- and 3-benzoyl-1,2-di(methoxycarbonyl)-8-methyl(cyano)-indolizines were obtained in this way from 3-methyl(cyano)pyridinium phenacylids. Isomeric indolizines were also synthesised from 3,4-dimethylpyridinium phenacylid. However, as

was to be expected, 3-benzoyl-1,2,7-tri(methoxycarbonyl)-indolizine was obtained from 4-methoxycarbonylpyridinium phenacylid[135]. Ylids obtained from quaternary pyridinium salts and bromoacetone, bromoacetate esters, and bromoacetonitrile were also introduced into the reaction with acetylenedicarboxylic acid dimethyl ester. The indolizines thus obtained contain a group in the 3-position, which is linked to the methine carbon atom of the ylid. Indolizines are not formed by the above procedure from *N*-methyl(ethyl, allyl, benzyl)pyridinium salts.

When the reaction of pyridinium phenacylid with acetylenedicarboxylic acid dimethyl ester is carried out in the presence of iodine, 1,2,3-tribenzoylindolizine is formed. Bearing in mind the above mechanism, this mode of reaction has been explained by postulating the formation of dibenzoylacetylene during the reaction, although this could not be demonstrated experimentally[139]. Only 3-benzoyl-1,2-di(methoxycarbonyl)indolizine is formed from pyridinium dibenzoylmethylid and acetylenedicarboxylic acid dimethyl ester. The formation of 3-ethoxycarbonyl-1,2-di(methoxycarbonyl)indolizine from the corresponding di(ethoxycarbonyl)methylid proceeds with analogous elimination of the ethoxycarbonyl group[139].

Pyridinium dicyanomethylid is formed from pyridine and tetracyanoethylene and its interaction with acetylene dicarboxylic acid dimethyl ester at room temperature gives rise to a 48% yield of 3-cyanoindolizine-1,2-dicarboxylic acid dimethyl ester[141].

To elucidate the mode of the 1,3-dipolar cyclisation in the interaction of methylids with acetylenedicarboxylic acid dimethyl ester 3-methylpyridinium dicyanomethylid was also used:



It was established that 8- and 6-substituted indolizines are formed in this reaction in proportions of 3 : 1.[135,142]

The Synthesis of Indolizines from Heterocyclic Compounds in Their Catalytic Reactions

When furan and ammonia are passed over alumina at 350–400 °C, pyrrole and traces of indole, carbazole, and indolizine are formed[143–145]. Indolizine is also present in the products of the pyrolytic decomposition of pyridine. Octahydroindolizine could not be aromatised in the presence of palladium on charcoal or with the aid of selenium[146].

The Synthesis of a Substituted Indolizine from α-Picoline and Sulphur

Prolonged refluxing of α-picoline with sulphur leads to the formation of a substance $C_{36}H_{24}N_6S_2$, which is converted into 1,2-di(2-pyridyl)indolizine on reduction with hydriodic acid in the presence of phosphorus and into 3-nitro-1,2-di(2-pyridyl)indolizine on nitration[147].

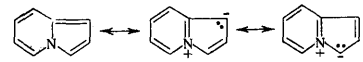
III. PROPERTIES OF INDOLIZINES

The physical and chemical properties of indolizine and its derivatives have been described fairly completely[9,10]. In the present review we shall consider mainly studies on the properties of indolizines carried out in recent years.

Electrophilic substitution reactions constitute a characteristic chemical feature of indolizines. Nucleophilic substitution—amination of indolizine with sodamide—could not be achieved[9].

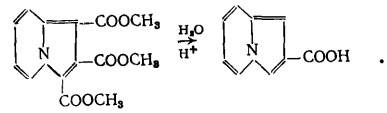
Electrophilic Substitution

Indolizine is more reactive than benzene with respect to electrophilic agents owing to the delocalisation of the lone electron pair of the nitrogen atom. An estimate of the distribution of π-electron density and of the bond orders in the indolizine molecule by the molecular orbital method[148] and also calculation of the frontal electron density in the molecule in relation to electrophilic substitution[149] have shown that its fundamental mesoforms consist of structures with maximum electron density in the 3-position and then in the 1-position[9]:



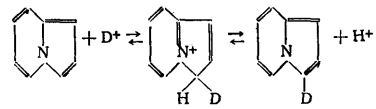
Therefore electrophilic substitution in the indolizine system should take place primarily in the 3-position and then in the 1-position; in the presence of substituents further substitution takes place in the 2-position. In electrophilic attack on indolizine substitution takes place only in the five-membered ring[150]. Substitution of the pyridine ring of indolizine cannot be achieved.

The enhanced electron density in the 3-position of the indolizine ring is indicated by the stepwise decarboxylation of indolizine-1,2,3-tricarboxylic acid. On hydrolysis (by heating with dilute hydrochloric acid) of its trimethyl ester, decarboxylation in the 1- and 3-positions takes place. Indolizine-2-carboxylic acid thus formed was decarboxylated by pyrolysing its calcium salt[53,56]:



Calculations by the LCAO-MO method[151] have shown that the 1- and 3-positions are almost equally effective in relation to electrophilic substitution with a slight preference for substitution in the 1-position. However, examination of resonance structures shows that electrophilic attack should take preferentially on the 3-position.

The calculated data were confirmed in a study of the deuteration reaction. It is suggested[152] that in the deuteration of indolizine the formation of a cation identical with a π complex constitutes an intermediate stage:



The rate of deuteration of indolizine itself in the 3-position is fives times faster than the rate of deuteration in the 1-position. Similar relative rates of deuteration in the 3- and 1-positions hold also for 2-methylindolizine. The reactivities of different positions of the

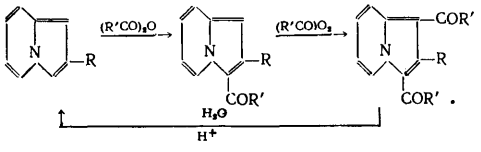
indolizine system were determined[153] with the aid of electrophilic hydrogen exchange and were compared with calculated data. The distribution of π-electron density agrees with the experimental reactivities of different positions in the indolizine system, which decrease in the sequence $3 > 1 \gg 2 > 5 \simeq 7 > 6 > 8$. Contradictions, which still remain controversial, were encountered when these results were compared with the calculated electron localisation energies.

Similar conclusions concerning the different reactivities of various positions in the indolizine ring in relation to electrophilic attack were reached on the basis of a determination by ^{1}H NMR of the degrees of protonation of the $C_{(1)}$ and $C_{(3)}$ positions in a number of methylindolizinium perchlorates in trifluoroacetic and hydrochloric acids. The protonation of indolizines without a methyl group at $C_{(3)}$ involves almost exclusively the 3-position[154]. 100% of the 3*H*-cations was detected in the protonation of 3,5-dimethyl-, 1,2,3-trimethyl-, and 1,3-dimethyl-2-phenyl-indolizines. The amounts of the 3*H*-cations and the 1*H*-cations in the case of 2,3-dimethylindolizine were 41 and 59% respectively[155].

Acylation of Indolines and the Reactions of Acylindolizines

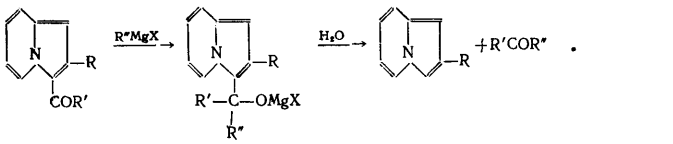
On heating with acid anhydrides in the presence of the sodium salts of the corresponding acids, indolizines are readily acylated to 3-acylindolizines[3-6,14,15,44,74,156,157]. When monoacyl derivatives are heated with the anhydride at a higher temperature, 1,3-disubstituted indolizines are formed. Acetylation of the nitrile of 2-methyl-(phenyl)indolizine-1-carboxylic acid also leads to the formation of the 3-acetyl derivative[5,14]. 3-Alkoxycarbonyl-2-methylindolizines are extremely resistant to acetylation; the yield of their 1-acetyl derivatives on acetylation with acetic anhydride in the presence of sodium acetate is only slightly more than 10%.[85]

Certain characteristic features are observed in the interaction of indolizines with acyl halides. 2-Methylindolizine is acetylated with difficulty by acetyl chloride (by the Friedel–Crafts reaction) in carbon disulphide to 1,3-diacetyl-2-methylindolizine. Acetylation of 3-acetyl-2-methylindolizine[158] and particularly 2-phenylindolizine (the phenyl group is partly acetylated)[14] proceeds more readily in the presence of aluminium chloride. In the absence of a catalyst 2-phenylindolizine does not react with acetyl chloride or bromide, but is benzoylated by benzoyl chloride in the 3-position and then in the 1-position under more severe conditions[38,44,69,79,157,159-161]. In the absence of a catalyst indolizine itself does not react with benzoyl chloride[4]:

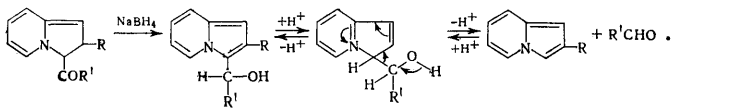


The reaction of aroylacetic acid esters with indolizine and also with 2-methylindolizine at 140°C leads to the formation of 3-(β-aryl-β-oxopropionyl)indolizines[162]. Substituted indolizines, obtained by treating indolizine with oxalyl chloride in benzene using different proportions of the reactants, have been described. 3-Carboxycarbonylindolizine and di-(3-indolizinyl)glyoxal were obtained in yields of 80% and 15% respectively[151]. 3-Ethoxycarbonyl-2-methylindolizine was synthesised from 2-methylindolizine and chlorocarbonic acid ester[85].

The acyl groups in the pyrrole ring of indolizine are readily removed by acid hydrolysis[1,3,5,14,50,76,105,106,134]. Diacyl derivatives are hydrolysed with greater difficulty than monoacyl derivatives. Acylindolizines with a nitro-[74,156] or nitroso-group[64] in the five-membered ring are not hydrolysed in this way. The acyl group is eliminated from 3-acylindolizines when they interact with organomagnesium compounds. The initial and deacylated indolizines and a ketone are present in the reaction products[48,163]:

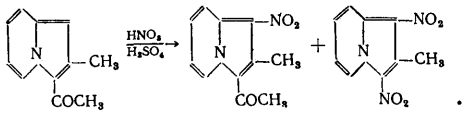


When the products of the reaction of 3-acetyl-2-methylindolizine with sodium tetrahydroborate were treated with D_2O in alcohol, 2-methylindolizine deuterated in the 3-position to an extent greater than 75% was obtained. Consequently the intermediate carbinols are readily protonated in the 3-position. These experimental findings were used to account for the mechanism of the elimination of the acetyl group from the 3-position in indolizines on treating the latter with sodium tetrahydroborate[164]:



It has been shown in many instances that the elimination of the acetyl group with the aid of sodium tetrahydroborate is selective. The acyl group is not split off from the 1-position under these conditions[164].

Nitration of acetylindolizines results in partial substitution of the acetyl group for the nitro-group. Thus nitration of 3-acetyl-2-methylindolizine in the presence of sulphuric acid leads to the formation of a mixture of 3-acetyl-2-methyl-1-nitroindolizine (59%) and 2-methyl-1,3-dinitroindolizine[156]:



3-Ethoxycarbonyl-2-methyl-1-nitroindolizine was obtained in a yield exceeding 30% by the nitration of 1-carboxymethyl-3-ethoxycarbonyl-2-methylindolizine[85]. When 3-acetyl-2-phenylindolizine is treated with iodine, the acetyl group is partly substituted by iodine and the reaction products contain 3-acetyl-1-iodo-2-phenylindolizine and 1,3-diiodo-2-phenylindolizine[48]. 3-Acylamino-2-methylindolizines are formed by the Schmidt reaction from 3-acyl-2-methylindolizines[157]. Several 1-acetamido-3-aryl-2-methylindolizines have been synthesised by this method from 1-acetyl-3-aryl-2-methylindolizines[97].

1- and 3-Acylindolizines are reduced by lithium tetrahydroaluminate to 1- and 3-alkylindolizines[67,78,82,157,165,166]. The reduction of 3-methoxycarbonyl indolizine with lithium tetrahydroaluminate leads to the formation of 3-hydroxymethylindolizine[52] and 2,3-dimethylindolizine was obtained from 3-methoxycarbonyl-2-methyl indolizine in a yield exceeding 70%.[164]

1- and 3-Acylindolizine behave differently in the reactions with hydroxylamine and phenylhydrazine. The corresponding derivatives involving the carbonyl group

are formed under the usual conditions only from 1-acylindolizines. In 1,3-diacylindolizines only the acyl carbonyl in the 1-position enters into these reactions[1,3-5,14,165]. The condensation (in the presence of alkali) of 1,3-diacetylindolizines with aromatic aldehydes leads to the formation of mono- and di-cinnamoylindolizines[1,3,14,15].

Nitrosation of Indolizines and the Reactions of Nitrosoindolizines

Direct nitrosation of indolizines with the 3-position free leads to 3-nitrosoindolizines. When the 3-position is occupied, 1-nitroso-derivatives are formed[14-16,25,27-29,64,79,167-169]. When 1-methyl-2-phenyl, 1-acetyl-5-methyl-2-phenyl-, 3-methyl-2-phenyl-, and 3-acetyl-2-phenylindolizines were nitrosated with sodium nitrite in concentrated hydrochloric acid to which glacial acetic acid or acetone had been added, the first two indolizines gave rise to 3-nitroso-derivatives and the last two gave rise to 1-nitroso-derivatives.

Careful oxidation of nitrosoindolizines with nitric, acetic, and peracetic acids converts them into nitroindolizines[64,156]. When 1-nitrosoindolizines are treated with nitric oxide in the cold, diazonium salts, stable in the solid state and in solutions, are formed in high yields. 3-Methyl-2-phenyl-1-indolizinyldiazonium nitrate was obtained in this way from 3-methyl-1-nitroso-2-phenylindolizine. After coupling it with β-naphthol, the corresponding azo-compound was isolated[168,170]:



3-Nitrosoindolizines do not react with nitric oxide even after prolonged treatment, which has not so far been explained[168]. Aminoindolizines are unstable in air and therefore cannot be used for diazotisation[50,63]. Azocyanine dyes are formed on condensation of nitrosoindolizines with heterocyclic compounds containing an active methylene group. Some of these azocyanines are used in the manufacture of photographic emulsions[171].

Formylation of Indolizines

Indolizines are formylated in the 3- and 1-positions by the Vilsmeier method using methyl- and dimethylformamides[157,165,166]. 3-Formyl-2-methylindolizine was obtained from 2-methylindolizine and then reduced by the Wolff–Kishner method to 2,3-dimethylindolizine[165]. When the formyl derivative is heated with hydrochloric acid, the formyl group is split off. 1,3-Diformyl-2-methylindolizine was obtained from 2-methylindolizine by the Reimer–Tiemann method and then reduced to 1,2,3-trimethylindolizine[165].

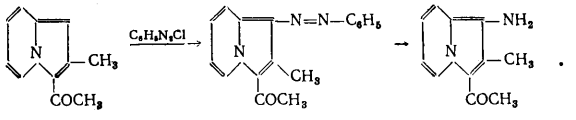
Formylation of indolizine in the presence of sodium hydrogen sulphide led to the formation of 3-thioformylindolizine[172].

Nitration of Indolizines

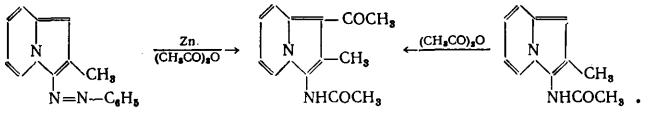
In order to suppress oxidation processes, substituted indolizines are nitrated in sulphuric acid at a reduced temperature or in nitric acid at an elevated temperature, but for a short period. Nitration results in a mixture of isomers. 2-Methyl-1-nitroindolizine and 2-methyl-3-nitroindolizine were obtained in 62 and 1.5% yields respectively by nitrating 2-methylindolizine in the presence of sulphuric acid[156]. 2-Methyl-1,3-dinitroindolizine is formed much more readily on nitration of 2-methyl-3-nitroindolizine than 2-methyl-1-nitroindolizine.

Indolizines in Azo-coupling Reactions

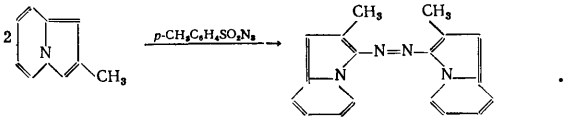
Azo-coupling of indolizine and 2-substituted indolizines involves the 3-position. When it is occupied, the 1-position is involved in azo-coupling[4,68-71,157,167]. 3-Acetyl-2-methyl-1-phenylazoindolizine was obtained by coupling phenyldiazonium chloride with 3-acetyl-2-methylindolizine and its catalytic reduction gave rise to 3-acetyl-1-amino-2-methylindolizine, which is unstable in air[167]:



The reduction of 2-methyl-3-phenylazoindolizine with zinc in acetic anhydride led to the isolation of 3-acetamido-1-acetyl-2-methylindolizine, which is resistant to acid and alkaline hydrolysis and which is formed also on acetylation of 3-acetamido-2-methylindolizine[120]:



3,3′-Azobis(2-methylindolizine) is formed in the reaction of 2-methylindolizine with tosyl azide[173]:

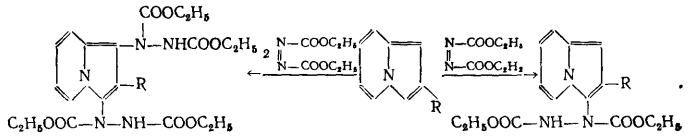


Similar azo-compounds coupled at the 1-position in the indolizine ring have been obtained from 2,5-dimethyl- and 3-methyl-2-phenyl-indolizines. 2-Phenylindolizine does not react with tosyl azide even on heating[174]. It has been confirmed[175] that 3,3′-azobisindolizines are formed from 2-methylindolizine and from 1,2-dimethylindolizine, both on treatment with tosyl azide and with picryl azide in ethyl acetate. Under the same conditions, 1,1′-azobis-(2,3-dimethylindolizine) is formed from 2,3-dimethylindolizine. This condensation takes place particularly readily with 2-methyl- and 1,2-dimethyl-indolizines. Fast dyes for polyamide and polyester fibre with tints ranging from yellow to violet have been found among 3-(1-indolizinylazo)-2-phenylindoles, 2,3-disubstituted in the indolizine ring, and 2-substituted 3-(3-indolizinylazo)-2-phenylindoles[176].

Condensation of Indolizines with Certain Dienophiles and with Azodicarboxylic Ester

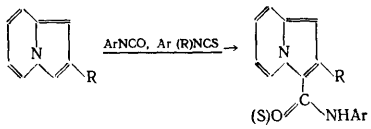
Adducts formed by indolizines with malic anhydride[123,177] and with quinone[4] have been described. 2-Phenyl(methyl)-indolizine is involved in a Diels–Alder type of reaction in benzene at room temperature with the diethyl ester of azodicarboxylic acid, forming a monoadduct—the diethyl

ester of [2-phenyl(methyl)-3-indolizinyl]hydroazodicarboxylic acid, while on refluxing a di-adduct is formed[178]:

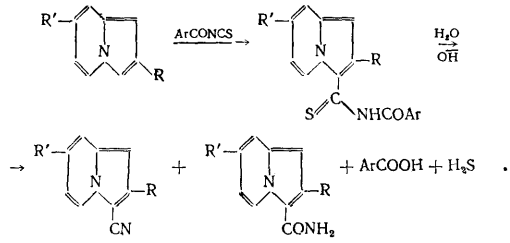


Similar addition products were obtained from 1-methyl-2-phenyl-, 3-methyl-2-phenyl-, and 2,3-dimethylindolizines. As a rule, the 3-adducts are formed more readily and in higher yields than the 1-adducts.

The carbamoylation and thiocarbamoylation of indolizines can be included among reactions of a similar type. When equimolar amounts of 2-methylindolizine and phenyl isocyanate, formed on decomposition of benzoyl azide under these conditions, are refluxed in toluene, the *N*-phenylamide of indolizine-3-carboxylic acid is obtained[179]. The thiocarbamoyl group is introduced similarly into the 3-position of 2-methyl- and 2,7-dimethyl-indolizines when these interact with isothiocyanates[180]:

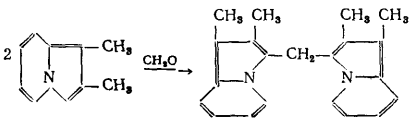


N-Aroylthioamides of the corresponding indolizine-3-carboxylic acids were synthesised from 2-methyl-, 2-aryl-, 2,7-dimethyl-, and 2-aryl-7-methyl-indolizines and aroyl isothiocyanates[181,182]; on being refluxed in an alkaline alcoholic solution, they give rise to nitriles and amides of indolizine-3-carboxylic acids (in yields up to 15%):[183]

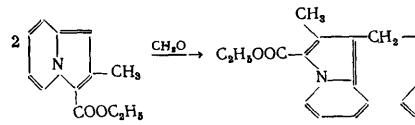


Alkylation of Indolizines

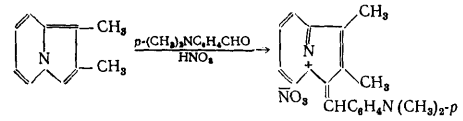
Alkyl groups, which may be substituted by functional groups, can be introduced into the 3- and 1-positions of indolizines in several ways. (3-Benzoyl-1-indolizinyl)-acetic acid was synthesised by the condensation of 3-benzoylindolizine with diazoacetic ester[184]. Condensation of indolizines containing free 1- or 3-positions with formaldehyde and other aldehydes leads to diindolizinylmethanes[1,3,4,93,105,157,165]. Di-(1,2-dimethyl-3-indolizinyl)-methane was obtained in a yield exceeding 90% from 1,2-dimethylindolizine and 40% formaldehyde solution[185]:



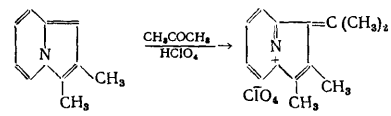
A similar condensation product involving the 1-positions of the indolizines rings was obtained from 2,3-dimethylindolizine[165]. The condensation of 3-ethoxycarbonyl-2-methylindolizine with formaldehyde gave a 75% yield of di-(3-ethoxycarbonyl-2-methyl-1-indolizinyl)methane[85]:



The condensation of 1,2- and 2,3-dimethylindolizines with *p*-dimethylaminobenzaldehyde in alcoholic solution in the presence of nitric acid led to the formation of 1,2-dimethyl-3-(*p*-dimethylaminobenzylidene)indolizinium and 2,3-dimethyl-1-(*p*-dimethylaminobenzylidine)-indolizinium nitrates respectively[37]:



A similar dye was synthesised by the condensation of 2-methylindolizine hydriodide with *p*-dimethylamino-benzaldehyde[36]. Methine derivatives of indolizines have been synthesised by condensing them with aromatic ketones containing the *p*-dimethylamino-group in one of the benzene rings[37] and also with aliphatic ketones. The condensation of 2,3-dimethylindolizine with acetone in the presence of perchloric acid led to the isolation of 1-isopropylidene-2,3-dimethylindolizinium perchlorate[165]:

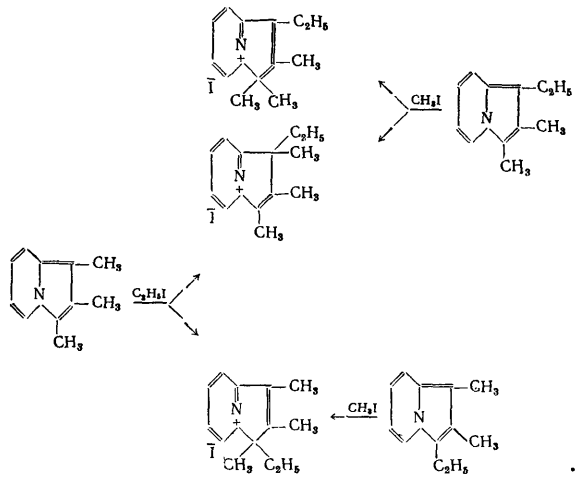


The products of the condensation of 2-aryl-1-methylindolizines with *p*-dimethylaminobenzaldehyde and with di-(*p*-dimethylaminophenyl) ketone were isolated as the perchlorates or the tetrafluoroborates[186].

The condensation of 5-methyl-2-phenylindolizine with *NN*-dimethylacetamide in the presence of phosphoryl chloride results in the formation of a mixture of 1- and 3-(α-dimethylaminoethylidene)indolizines, which were isolated as the perchlorates. After treating a mixture of these perchlorates with sodium hydroxide, 1-acetyl-5-methyl-2-phenylindolizine and an enamine [3(α-dimethylaminovinyl)-5-methyl-2-phenylindolizine] were obtained. If there is no substituent causing steric hindrance at $C_{(5)}$ in the indolizine ring, then condensation with *NN*-dimethylacetamide proceeds almost wholly with formation of the 3-(α-dimethylaminoethylidene) derivative[187].

The interaction of indolizines substituted by alkyl groups in the five-membered ring with certain alkyl iodides has been studied[10,36]. The alkyl halide adds to 1,2,3-trialkylindolizine with formation of an indolizinium salt, the alkyl group entering both the 3- and 1-positions.

In 2,3-dialkylindolizines the alkyl group enters the 3- and 1-positions:



3-Phenacyl-2-phenylindolizine was obtained from 2-phenylindolizine and bromoacetophenone semicarbazone in the presence of triethylamine[188]. The reaction of 2-methylindolizine with ethyl iodoacetate in the presence of aluminium chloride results in the formation of a mixture of 3-ethoxycarbonylmethyl-2-methylindolizine, 1,3-di(ethoxycarbonyl methyl)-2-methylindolizine, and the initial indolizine. The attempt to introduce the ethoxycarbonylmethyl group into 2-methylindolizine with the aid of bromoacetic and diazoacetic esters was unsuccessful[161].

2,3-Dimethylindolizine was aminomethylated via the Mannich reaction. On treatment with dimethylamine, 2,3-dimethyl-1-dimethylaminomethylindolizine was obtained[165]. A number of similar 3-aminomethyl-1,2-diphenylindolizines substituted in the amino-group have been described[189]. 1-Aminomethyl derivatives with dimethyl- and diethyl-amino-groups and also with an *N*-pyrrolidinyl substituent have been synthesised from 3-alkyl-2-phenylindolizines[190,191]. A number of 1,3-bis-(dialkylaminomethyl)-2-phenylindolizines were synthesised from 2-phenylindolizine for pharmacological study[192]. The synthesis of unsubstituted aminomethylindolizines is difficult. Reduction of the amide of indolizine-2-carboxylic acid (which was obtained by heating the methyl ester of this acid with ammonia in methanol at 155°C) with lithium tetrahydroaluminate led to the isolation of an unstable substance to which the structure of 2-aminomethylindolizine was attributed on the basis of infrared and NMR spectra[52]. 1-Aminomethylindolizine is also very unstable; it was characterised as the *N*-acetyl derivative[50]. 3-(1-Hydroxy-2-dimethylaminoethyl)-2-phenylindolizine was obtained in a low yield by the reduction of *NN*-dimethyl-(2-phenyl-3-indolizinyl)glyoxylamide with lithium tetrahydroaluminate[43]. The reduction of the nitrile of 2-methylindolizine-7-carboxylic acid with lithium tetrahydroaluminate led to the isolation of 7-aminomethyl-2-methylindolizine[52].

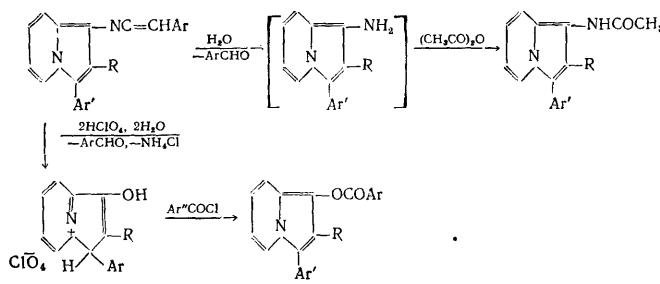
2-Hydroxymethyl-, 3-hydroxymethyl-, and 6-hydroxymethyl-2-methyl-indolizines were obtained in fairly high yields by the reduction of the corresponding indolizinecarboxylic acid esters with lithium tetrahydroaluminate[52]. However, the reduction of the ethyl ester of 2-methylindolizine-1-carboxylic acid with $LiAlH_4$ in tetrahydrofuran led to the isolation of only one product—1,2-dimethylindolizine[52].

The methyl group in the 5-position of the indolizine ring system is analogous to the methyl group of α-picoline. When 5-methylindolizine and 5-methyl-2-phenylindolizine are treated with butyl-lithium and then with a carbonyl compound, the corresponding 5-(β-hydroxyalkyl) derivatives are formed[193]. After treating 5-methyl-2-phenylindolizine with butyl-lithium and then with dimethylbenzamide, 5-phenacyl-2-phenyl-indolizine was obtained. 5-Formylmethyl-2-phenylindolizine was synthesised similarly using dimethylformamide. The same reactions were achieved also with 5-methylindolizine[194].

Amino- and Hydroxy-indolizines

1-Aminoindolizines, which are formed on reduction of 1-nitroso- and 1-nitroindolizines, could not be isolated since they are unstable in air[113,167]. 1-Amino-2-phenylindolizine hydrochloride, obtained by the reduction of 1-nitro-2-phenylindolizine with hydrogen in the presence of palladium on charcoal, is unstable like the base itself[63]. 3-Acetamido-1-acetyl-2-methylindolizine[157], 1-acetamido-(propionamido, benzamido)-2,3-dimethyl- and 1-acetamido-(propionamido, benzamido)-2,3-diphenyl-indolizines[67], and 1-acetamido-2-phenylindolizine were synthesised in various ways. The last compound is resistant to alkali, but on acid hydrolysis is readily converted into 1-hydroxy-2-phenylindolizine[50,63]. The unstable hydrochloride of 1-hydroxy-2,3-diphenylindolizine was obtained by the hydrolysis of 1-benzamido-2,3-diphenylindolizine in the presence of hydrochloric acid[50]. The conversion of 1-amino-2-phenylindolizine into 1-acetamido-2-phenylindolizine and the acid hydrolysis of both indolizines to the unstable 1-hydroxy-2-phenylindolizine have been described[63].

1-Azomethines, formed when 2-acylpyridines interact with aromatic aldehydes in acetic acid in the presence of ammonium acetate, are hydrolysed in the presence of acetic anhydride with formation of 1-acetamidoindolizines. After such 1-azomethines have been heated for a long time with 70% perchloric acid, 1-hydroxyindolizinium perchlorate can be isolated and then benzoylated by the Schotten–Baumann method at the hydroxy-group to give the benzoyl derivative[97,102]:



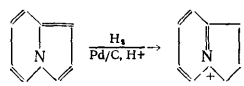
1-Hydroxy-3-phenyl-(*p*-chlorophenyl, *p*-anisyl)-indolizinium and 1-hydroxy-2-methyl-3-phenyl-(*p*-chlorophenyl, *p*-anisyl)indolizinium *p*-nitrobenzoates were obtained in this way.

Reduction and Oxidation of Indolizines

Indolizine[9] and substituted indolizines[66] are not reduced by zinc in acid[1] and on hydrogenation under the usual conditions in the presence of palladium on charcoal. Alkylindolizines are hydrogenated in the presence of

Raney nickel or the Adams catalyst at room temperature to 5,6,7,8-tetrahydro-derivatives and on heating to octahydroderivatives[9,11,14,15,25,54-56,66,92,109,114,195,196]. When 6-ethylindolizine was hydrogenated in glacial acetic acid on a platinum oxide catalyst (at 20°C and 7 atm), 6-ethyloctahydroindolizine was obtained in 80% yield[54]. The hydrogenation of 3-acetyl-2-methyl(phenyl)indolizines in the presence of the Adams catalyst at room temperature also stops at the stage of the 5,6,7,8-tetrahydroderivatives[15,196]. 1-(ω-Aminoalkyl)-2-phenylindolizines are not hydrogenated on a palladium catalyst, while on Raney nickel the reduction also involves the six-membered ring and yields the tetrahydroderivatives[66].

However, in 2*N* hydrobromic acid in the presence of palladium on charcoal indolizine is hydrogenated in the five-membered ring with formation of 1,2-dihydro-3*H*-indolizinium bromide in 85% yield:



It is suggested that in an acid solution there exists a mesomeric form of indolizine, which contains a pyridine ring conjugated with a double bond in the five-membered ring and that this species is hydrogenated[197].

Alkylindolizines are readily oxidised even by atmospheric oxygen[1,2]. Electrophilic substituents in the five-membered ring stabilise indolizines with respect to oxidants; indolizine-1,2,3-tricarboxylic acid is not oxidised by either nitric or chromic acid[48,55,56]. The final product of the oxidation of indolizines by peracetic acid or hydrogen peroxide in acetic acid is picolinic acid *N*-oxide or its homologues[55].

Physiological Properties of Indolizines

The research on indolizines is to a great extent concerned with the study of their physiological properties in addition to synthetic and theoretical investigations of this heterocyclic system. The hydrogenated indolizine system is contained in strychnine, securinine, and veratrine alkaloids: cevine, germine, and protoverine. There are some similarities between indolizines and serotonine.

It has been reported that certain alkylindolizines resemble convulsants in their physiological action; they paralyse muscular and respiratory activity[198]. Mannich bases obtained from 1,2-diphenylindolizine, formaldehyde, and ephedrine as well as a deoxy-analogue of the last compound have a depressant effect on the central nervous system[199]. 3-Dialkylaminomethyl-1,2-diphenylindolizines[192,200] and 1-aminoalkyl-2-phenylindolizines[66,190,191] also influence the central nervous system. 2-Furylindolizines exhibit antimicrobial activity[169]. Indolizine-1-acetic acid is an analgesic. 3-Acetyl(benzoyl)-1-(α-carboxyethyl)indolizines have been patented as analgesic and anti-inflammation agents[61].

3-Benzoylindolizine-1-acetic acid (the structural analogue of heteroauxin) exhibits an auxin-like activity[184]. β-(1-Indolizinyl)alanine is a tryptophan antimetabolite[201]. 1-Carboxymethyl-3-(*p*-chlorobenzoyl)-7-methoxy-2-methylindolizine and 3-carboxymethyl-1-(*p*-chlorobenzoyl)-6-methoxy-2-methylindolizine exhibit anti-inflammatory activity but are less effective than indomethacin [1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole] although less toxic than the latter[161]. It has been established that 2-arylindolizines are not carcinogenic[28].

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